SCOTTISH HOSPITALS INQUIRY

Bundle of documents for Oral hearings commencing from 19 August 2025 in relation to the Queen Elizabeth University Hospital and the Royal Hospital for Children, Glasgow

Bundle 44 – Documents in respect of NHS GGC - Expert Report by Prof Peter Hawkey, Dr Samir Agrawal and Dr Lydia Drumright - The evidence of risk of infection from water and ventilation systems at QEUH and RHC - 24 July 2024 ("HAD Report")

Volume 1

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Table of Contents

1.	A49396252	NHS GGC - Expert Report by Prof Peter Hawkey, Dr Samir Agrawal and Dr Lydia Drumright - The evidence of risk of infection from water and ventilation systems at QEUH and RHC - 24 July 2024 (“HAD Report”)	Page 5
2.	A52270095	Glasgow 4 - Inventory of Documents - Submitted by NHSGGC in relation to the HAD Report	Page 224
3.	A51839146	CLO for NHS GGC - Letter of Instruction - Dr Samir Agrawal - 21 November 2022	Page 234
4.	A49404308	CLO for NHS GGC - Letter of Instruction - Prof. Peter Hawkey - 21 November 2022	Page 239
5.	A49404313	CLO for NHS GGC - Letter of Instruction - Dr Lydia Drumright - 21 November 2022	Page 244
6.	A51839185	Re Antibiotic Data Email Sean MacBride-Stewart - 11 July 2023	Page 246
7.	A51839158	Public Inquiry Analysis of Antimicrobial Prescribing	Page 248
8.	A51839162	Summary analysis refreshed	Page 297
9.	A51837795	BMT 100 005 02 Antibiotic Prophylaxis Policy - 30 April 2007	Page 304
10.	A51837798	BMT 100 005 03 Antibiotic Prophylaxis Policy - 21 June 2010	Page 311
11.	A51837787	BMT 100 005 04 Antibiotic Prophylaxis Policy - 08 August 2012	Page 319
12.	A51837784	BMT 100 005 05 Antibiotic Prophylaxis Draft - 08 January 2019	Page 326
13.	A51837793	BMT 100 005 06 Antibiotic Prophylaxis Draft	Page 331
14.	A51837808	BMT 100 006 01 Antibiotic Treatment Policy - 28 November 2007	Page 336

15.	A51837813	BMT 100 006 02 Antibiotic Treatment Policy - 06 November 2008	Page 350
16.	A51837816	BMT 100 006 03 Antibiotic Treatment Policy - 21 September 2018	Page 369
17.	A51837806	BMT 100 006 04 Antibiotic Treatment Guideline - 04 July 2018	Page 382
18.	A51837811	BMT 100 006 05 Antibiotic Treatment Guideline	Page 390
19.	A51837802	BMT 100 006 06 Antibiotic Treatment Guideline dapto update	Page 398
20.	A51837818	BMT 100 008 02 Antifungal Policy - 19 December 2006	Page 406
21.	A51838224	BMT 100 008 03 Antifungal Policy - 19 May 2008	Page 440
22.	A51837820	BMT 100 008 04 Antifungal Policy - 31 March 2009	Page 477
23.	A51838170	BMT 100 008 05 Antifungal Policy - 04 August 2011	Page 505
24.	A51837817	BMT 100 008 06 Antifungal Policy - 27 April 2015	Page 522
25.	A51838075	BMT 100 008 07 Antifungal Policy - 16 April 2018	Page 536
26.	A51838073	BMT 100 008 08 Antifungal Policy - 16 April 2018	Page 550
27.	A51838047	BMT 100 008 09 Antifungal policy	Page 564
28.	A51838348	BMT 100 041 01 Assessment of Infection in the Immuno Pt - 3 November 2009	Page 576
29.	A51838345	BMT 100 041 02 Assessment of Infection in the Immuno Pt - 29 July 2019	Page 582
30.	A51838349	BMT 100 041 03 Assessment of Infection in the Immuno Pt - 10 January 2019	Page 586
31.	A51838346	BMT 100 041 04 Assessment of Infection in the Immuno Pt - 1 April 2020	Page 590
32.	A51838350	BMT 100 041 05 Assessment of Infection in the Immuno Pt	Page 594
33.	A51838447	Febrile Neutropenia Final - V1 - Aug 2010	Page 597

34.	A51838550	Febrile Neutropenia Policy - V2 Final - Dec 2015	Page 609
35.	A51838470	Febrile Neutropenia Policy - V3 Final - Jan 2017	Page 621
36.	A51838552	HAEM-ONC-003 - Febrile Neutropenia Policy - V4 Final - Mar 2020	Page 634
37.	A51838668	HAEM-ONC-003 - Febrile Neutropenia Policy - V5 final - Nov 2021	Page 647
38.	A51839140	HPS Summary - Review of NHSGG&C paediatric haemato-oncology data - October 2019	Page 661
39.	A51838352	Methodology of obtaining Admissions Data	Page 666
40.	A51839132	Glasgow Hospitals Case Note Review D3 - notes and commentary on Environmental Bacteria – Draft 3 - 05 October 2023	Page 667
41.	A51839142	Initial bullet point thoughts on Executive Summary for Report - Prof Peter Hawkey	Page 700
42.	A43570900	PPP 5 - QEUH Campus - History of Infection Concerns (HOIC) - Counsel's note	Page 701
43.	A51839066	Cupriavidus environmental samples	Page 703
44.	A51839118	Enterobacter tree	Page 704
45.	A51839081	Stenotrophomonas tree with CHI numbers	Page 705
46.	A51839220	Timeline - Ward moves & MALDI	Page 706

Expert Report for the Scottish Hospitals Inquiry on the evidence of risk of infection from the water and ventilation systems at the Queen Elizabeth University Hospital and Royal Hospital for Children, Glasgow

Professor Peter M Hawkey BSc PhD DSc MB BS MD FRCPath FFPath FRCPI

Professor Emeritus of Clinical & Public Health Bacteriology, University of Birmingham & Consultant Clinical Microbiologist, Grampian Health Board

Dr Samir G Agrawal BSc MB ChB FRCP FRCPath PhD

Consultant Haematologist and Senior Lecturer, Barts Cancer Centre, Department of Haemato-oncology, St Bartholomew's Hospital; and Immunobiology, Blizard Institute, Queen Mary University of London

Dr Lydia N Drumright PhD MPH

Research Assistant Professor, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington

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Executive Summary

Introduction

1. This report considers the question of whether there is objective evidence that patients were exposed to a greater risk of infection than would be expected due to alleged widespread contamination of the water system and/or inadequate ventilation systems in the Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC).
2. This risk would not manifest itself equally across the hospital. The greatest impact would be in severely immunocompromised patients. Hence, this report is targeted on patients with haematological, and other, cancers undergoing intensive chemotherapy and/or haematopoietic stem cell transplants (HSCT) at QEUH.
3. Infection risk is multifactorial and varies depending on: a micro-organisms ability to cause disease (pathogenicity), its natural habitat (source), ability to spread (mode of transmission), susceptibility of the host to infection (opportunity). If an increase in infection rates is observed, this is not necessarily attributable to the built environment given this complexity.
4. To assess if there is an increased risk of infection, a normal level of risk must be established.
5. What is an outbreak? In clinical practice, an outbreak is suspected if there is an increase beyond the normally expected numbers of infections due to a specific bacterium. Relatedness of these infections in time and space provide circumstantial evidence for cross infection. A strict definition is the occurrence of two or more cases of infection caused by genetically indistinguishable micro-organisms.
6. **The primary source for bacteria causing bloodstream infection (BSI) in neutropenic patients is the patient's own gut**, particularly for Gram-negative bacteria.

Environment and Non-Environmental Micro-Organisms

7. Environmental micro-organisms are widely distributed in the natural, home and hospital environments, as well as other sites: plants, soil, water, taps, sink traps, shower heads, waste-water, surfaces and medical equipment, food, the human and animal gut, and skin.

8. There is continuous exposure to these micro-organisms in and outside of the hospital environment. These bacteria rarely cause infection but can do so in immune-compromised patients.
9. Pathogenic environmental bacteria (e.g. *Pseudomonas aeruginosa, Klebsiella spp., Stenotrophomonas maltophilia*[1] etc.) can colonise the gut, nasopharynx and skin of patients' and cause a BSI in the same patient.
10. Bacteria that are part of our normal flora living in harmony with us are referred to as commensal bacteria. In some situations, commensal bacteria can cause overt disease (e.g. *Escherichia coli* carried in the gut causing a urinary infection).
11. The patient's own commensal (or colonising) flora (principally of the gut) is well-recognised as being the commonest source of BSIs in the target population for this report.
12. Attributing the source of a BSI pathogen to the built environment of the hospital can only be shown if: the strains identified are indistinguishable, a source is present, and a route of transmission and a portal of entry are identified.

Water Systems

13. Water distribution systems are never sterile, hospital systems being no exception. Potable water must not contain any detectable *Escherichia coli* or *Enterococcus* spp. as these are indicators of faecal pollution. However, bacteria from soil, decaying plants etc. are permitted and the presence of these bacteria is well recognised.
14. A study of the Glasgow municipal drinking water collected from domestic taps showed the most frequently encountered Gram-negative bacteria were: *Cupriavidus, Blastomonas, Acidovorax* and *Burkholderia*[1]. These bacteria cause no harm to the vast majority of individuals both in the community and in hospitals
15. In studies of water outlets in ICUs in hospitals in England and France, rates of Pseudomonas aeruginosa detection were significantly higher than at QEUH – ranging from 4.8-28% of taps versus 1.1% in high-risk areas at QEUH.
    - **The available data does not support an opinion that the water system at QEUH had widespread contamination.**

[1] These organisms were identified as of significance by the Queen Elizabeth University Hospital and Royal Hospital for Children Case Note Review Overview Report (Stevens, Evans and Wilcox, 2021) [CNR]

Ventilation Systems

16. A previous report (by Dr Agrawal, 18/05/2021) highlighted that the QEUH ventilation system for high-risk areas (such as the BMT service) did not meet the Scottish Health Technical Memorandum (SHTM) 03-01 Ventilation for healthcare premises guidance.
17. There is a theoretical risk of increased (airborne) infection with a SHTM 03-01 non-compliant system. However, this is not supported by the literature, nor in clinical practice, nor from QEUH data on relevant airborne infections (see below).

Infection At QEUH – Bacteraemia in Adults

18. From available GGC data (Adult Haematology 2013-2023), the overall incidence of BSI due to environmentally relevant microorganisms in adult haemato-oncology patients at QEUH compared to other hospitals in the GGC are statistically the same, as are incidence broken down by epidemiological clustering; suggesting no differences between hospitals.
19. The pattern observed in incidence of BSI due to environmentally relevant microorganisms is largely the same as that of BSI caused by microorganisms that are not environmentally transmitted, suggesting that peaks and troughs in incidence reflect the normal pattern of BSI in this patient population in GGC.
20. Following the move of the BMT service (Adults) from North sector to QEUH, the incidence of bacteraemia attributable to environmental organisms decreased with the move to QEUH.
21. *S. maltphilia* is an example of a potentially environmentally derived bacteraemia that caused BSIs. 45 BSIs were due to *S. maltophilia* - 19 from patients at QEUH and 26 from patients at other hospitals. WGS data for 3 of the adult QEUH cases showed that none were linked to each other or environmental samples. Among all of the isolates of *S. maltophilia* from human samples, that were subject to WGS, there was no evidence of clustering of indistinguishable strains.
22. There is neither an elevated number of cases of *S. maltophilia* at QEUH versus other hospitals in GGC, nor is there sufficient evidence of environmental contamination and transmission to patients.
    - **This data does not support the hypothesis that the environment at QEUH is playing a significant role in harbouring and transmitting pathogens to adult patients.**

Infection at QEUH – Bacteraemia in Paediatrics

23. Paediatric haematology and oncology data was available from 2005 to 2022 which allowed comparisons between infection rates both at QEUH and when the service was located at Yorkhill.
24. At the time of the move to QEUH in 2015, the incidence of environmentally relevant bacteraemia cases at QEUH is similar to that observed for the prior 10 years at Yorkhill, but then steadily declines from ~2018 onward. The same pattern is seen for total bacteraemia cases.
25. Of 23 cases of *Acinetobacter baumannii*, more than two thirds occurred at Yorkhill. The pattern of occurrence – namely, sporadic - was the same at Yorkhill and QEUH.
26. All but 2 of the 28 *Burkholderia cepacian* cases occurred at Yorkhill, with the two at QEUH being sporadic (occurring in 2017 and 2018). In contrast, most of the cases at Yorkhill were suggestive of clustering.
27. There were 3 cases of *Cupriavidus pauculus* bacteraemia. Two occurred at QEUH and appear both epidemiologically (i.e., related to space and time) and genetically (i.e., based on WGS) to be sporadic and unrelated.
28. Epidemiological data shows that QEUH has a statistically lower number of cases versus Yorkhill, as well as a lower number of potential clusters.
29. The pattern observed in incidence of BSI due to environmentally relevant microorganisms is largely the same as that of BSI caused by microorganisms that are not environmentally transmitted, suggesting that peaks and troughs in incidence reflect the normal pattern of BSI in this patient population in the GGC.
    - **This data does not support the hypothesis that the environment at QEUH is playing a significant role in harbouring and transmitting pathogens to paediatric patients.**

Infection at QEUH – in Relation to Ventilation

30. A key indicator for an increased rate of infection related to an "inadequate or insufficient" ventilation system in the haemato-oncology population is infections due to *Aspergillus* species (*Aspergillus* spp.).
31. The difficulties of case definition of invasive fungal diseases led us to count any microbiological evidence of infection with *Aspergillus* spp. as a case. This approach will tend to inflate the number of cases but avoid missing true cases.

32. From 2013 to 2023, there is no indication of increased cases of infections with *A.* spp. in the Adult BMT service, including after the permanent move to QEUH from the Beatson Unit in June 2018.
33. From 2013 to 2023, there is no indication of increased cases of infections with *A.* spp. in the Adult Haematology South service, including after the permanent move to QEUH May 2015.
34. The case numbers from 2013-2023 in the Adult Haematology North service - which did not move to QEUH - show the expected variation over time.
35. From 2018-2023, the total numbers of cases in the Adult BMT unit at QEUH were 17, as compared to 19 cases in the same time period for the Adult Haematology North service.
36. The annual total number of paediatric cases show the low level variation from 2005-2022 before and after the move to RHC in June 2015, which is the expected pattern.
37. During the various relocations of paediatric services on the QEUH campus, there are no marked differences in case numbers by site (RHC versus Wards 4B and 6A).
    - **For both the paediatric and adult services, the variations in annual total cases over time, by location and during the period of co-location of the services on the QEUH wards, do not indicate the built environment is determining case rates, rather patient-related factors are the key drivers.**

Inquiry's Key Questions

38. In Direction 5, the Inquiry set out 4 Key Questions. These are set out below, with our opinion based on the evidence set out in this report and summarised above:
39. From the point at which there were patients within the QEUH/RHC was the water system (including drainage) in an unsafe condition, in the sense that it presented an additional risk of avoidable infection to patients?
    - **The data does not support the hypothesis that the water system at the QEUH/RHC was in an "unsafe condition".**
40. From the point at which there were patients within the QEUH/RHC was the ventilation in an unsafe condition, in the sense that it presented an additional risk of avoidable infection to patients?
    - **The data does not support the hypothesis that the ventilation system at the QEUH/RHC was in an "unsafe condition".**

41. Are the water and ventilation systems no longer in an unsafe condition in the sense that they now present no additional avoidable risk of infection?

- **The data does not support the hypothesis that the water or ventilation systems at the QEUH/RHC present an additional avoidable risk of infection.**

42. Is there a link, and if so in what way and to what extent, between patient infections and identified unsafe features of the water and ventilation systems?

- **The data does not demonstrate a link between the water or ventilation systems and patient infections.**

Contents

Executive Summary 1

Contents 7

1. Introduction 11

2. Micro-organisms 13

2.1. How bacteria are named 13

2.2. What is meant by an outbreak 15

3. Clinical significance and epidemiology of the most common groups of presumed environmental bacteria selected for inclusion by the CNR 18

3.1 Order Enterobacterales 18

3.1.1. *Klebsiella* spp. (30) 18

3.1.2. *Enterobacter* spp. (27) 21

3.1.3. *Serratia marcescens* (7) 22

3.1.4 *Citrobacter* spp. (5) 23

3.2. Order Pseudomonales 23

3.2.1. Pseudomonas spp. (17) - P. aeruginosa (9), P. putida (7) and P. stutzeri (1) 23

3.2.2. *Acinetobacter* spp. (11) 25

3.2.3 Stenotrophomonas maltophilia (23) 25

3.3. Other more rarely reported bacteria in the CNR selected by the panel. 27

3.3.1. *Pantoea* spp. (3) 28

3.3.2. *Raoultella* spp. (2) 28

3.3.3. Elizabethkingia spp. (6) 29

3.3.4. Chryseobacterium spp. (5) 30

3.4. Order Burkholderiales 30

3.4.1. *Burkholderia* spp. (2) 30

3.4.2. *Delftia* spp. (3) 31

3.4.3. *Cupriavidus* spp. (2) 31

3.4.4. *Achromobacter* spp. (1) 32

3.4.5. *Herbaspirillum* spp. (1)....32

3.4.6. *Aeromonas* spp. (2) 33

3.4.7. *Sphingomonas* spp. (1)....33

3.4.8. Roseomonas spp (1)....33

3.4.9. Rhizobium spp (1)....33

3.4.10. *Brevundimonas* spp. (1) 34

4. Case Note Review....35

5. Water....41

5.1. Are hospital water systems sterile?....41

5.2. What constitutes a contaminated hospital water system? 41

5.3. If there was "widespread contamination" of the hospital water system (whether this was due to ingress contamination, regressional contamination, or contamination at installation and/or commissioning): 43

5.3.1. Would this be evident through water testing (routine testing required by guidance or additional testing not contained in guidance)? 43

5.3.2. If so what would be the expected findings that would demonstrate that there is "widespread contamination"? 44

5.4. If patients were at an increased risk of infection from the water system as a result:....45

5.4.1. Which types of organisms would be it be expected to see an increased rate of infection?....45

5.4.2. Are there any particular organisms that will be an indicative marker of there being an increased risk of infection from the water system?....46

5.4.3. Would it become evident by way of an increased rate of infection in the patient population as a whole?....47

6. Ventilation....49

6.1. If the ventilation system in the hospital was inadequate or insufficient for patients:...55

6.1.1. How would this manifest itself in terms of an increased risk of infection?....55

6.1.2. Which types of organisms would it be expected to see an increased rate of infection from an inadequate or insufficient ventilation system? 55

6.1.3. Would this become evident by way of an increased rate of infection in the patient population as a whole or are there particular vulnerable patient groups where this may be more evident? 56

7. Water - analysis of infection rates and data from QEUH & RHC 57

7.1 Are the water testing results consistent with there being “widespread contamination”? 57

7.2 Is there an increased level of infections consistent with there being “widespread contamination” of the water system? 59

7.2.1 Epidemiological review of incidence of bacteraemia by environmentally relevant species from available GGC data (Adults 2013-2023; Paediatric 2005-2022) 59

7.2.2 Methods for analysing GGC bacteraemia data 62

7.2.3 Bloodstream infections in adult patients in GGC January 2013-June 2023 64

7.2.3 Bacteraemia in adult patients in GGC January 2013-June 2023 with Potential Environmental Relevance 68

7.2.3 Bacteraemia with potential environmental relevance in adult patients in the GGC by species type 70

7.2.6 Assessment of potential epidemiological clusters of BSIs 79

7.2.5 Comparison of BSI from organisms of potential environmental relevance to all others organisms isolate in BSIs among adult patients in the GGC 82

7.2.6 Assessment of adult bone marrow transplant patients only 87

7.2.7 Bacteraemia in paediatric patients in GGC 89

7.2.8 Bacteraemia attributable to environmentally relevant microorganisms in paediatric patients in GGC 90

7.2.9 Bacteraemia attributable to environmentally relevant microorganisms compared to those that are not among paediatric patients in GGC 110

7.2.10 Evidence of environmental contamination, particularly the water supply, based on bacteraemia data from haemato-oncology patients in the GGC 113

7.3 What does the available sequencing data show? 114

8. Ventilation - analysis of infection rates and data from QEUH & RHC 118

8.1 Is there an increased rate of airborne infections in QEUH consistent with a failure of the ventilation system? 118

8.1.1 Results – Adults 119

8.1.2 Interpretation – Adults 121

8.1.3 Results – Paediatrics 122

8.1.4 Interpretation - Paediatrics 124

8.1.5 Summary 125

9. List of Tables and Figures 127

10. References 132

11. Declaration 146

12. Authors 148

12.1 Professor Peter M Hawkey BSc, PhD, DSc, MBBS, MD, FRCPath, FFPath, FRCPI 148

12.2 Dr Samir G Agrawal BSc, MB ChB, FRCP, FRCPath, PhD 179

12.3 Dr Lydia N Drumright PhD, MPH 191

1. Introduction

This independent expert report is instructed by the Central Legal Office, on behalf of Greater Glasgow Health Board (NHSGGC).

Since the Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC) opened in 2015, issues have been identified with the design and construction of the buildings and concerns have been raised about whether patients have contracted infections from the hospital built environment, including a report of "widespread contamination of the water system" (HPS, 2018).

The purpose of this instruction is to consider the question of risk, specifically whether there is objective evidence/data that would support the proposition that since the QEUH and RHC opened in 2015 patients were exposed to a greater risk of infection than would be expected due to a widespread issue with the water and ventilations systems.

We live in a microbiological world with micro-organisms on our bodies, in air, in water and on surfaces around us. We are being exposed to micro-organisms continuously. Infection risk is multifactorial and varies depending on, for example, a micro-organisms ability to cause disease (pathogenicity), the organisms natural habitat (source), its ability to spread (mode of transmission), and susceptibility of the host to infection (opportunity). The time period between exposure to a micro-organism and the development of an infection varies significantly. Not all infections are avoidable. Surveillance is carried out in hospitals in order to identify whether infection risk issues are arising.

The occurrence of a particular infection does not mean that the built environment poses an increased risk. As the hospital environment is not sterile, it will always pose a certain level of risk of infection. If the built environment poses an increased risk of infection, then this would manifest in an increased rate of infection. Therefore, the approach taken in this report is to: (i) identify the types of infections that would arise from a widespread issue with the water and ventilation systems (i.e. which micro-organisms and which patient groups would be affected); and (ii) analyse the data on infections for these micro-organisms and patient groups in the QEUH and RHC to determine whether these rates are in line with what would be expected.

A comparative exercise is essential, as before it can be said that there is an increased (i.e. abnormal) risk of infection it must first be understood what a normal level of risk is. If an

increase in infection rates is observed, this does not necessarily mean that it is attributable to the built environment, as the causes of infection are multifactorial. Further investigation would be required to establish if the built environment was linked to any detected infections. However, if there is no increase in infection rates then it can be concluded that there is no increased level of risk from the built environment or other potential factors.

A significant reliance appears to have been placed on the Queen Elizabeth University Hospital and Royal Hospital for Children Case Note Review Overview Report (Stevens, Evans and Wilcox, 2021) (CNR) in relation to whether the built environment at the QEUH and RHC posed an increased risk of infection. However, we do not consider that the CNR is of assistance in determining this for the reasons set out below.

2. Micro-organisms

In order to be able to identify the sources of particular micro-organism that can cause infection, a number of factors need to be understood including, the natural habitats of that micro-organism, the route of transmission by which micro-organisms get to the patient and enter the body. The identification of micro-organisms and what constitutes an outbreak must also be understood.

2.1. How bacteria are named

Living organisms are classified according to the binomial system established by Carl Linnaeus in the 18th century. He came up with the concept of a species which represented animals and plants that had a very high degree of similarity (e.g. flower structure) and bred between themselves. Those species that were similar to each other he grouped together into a genus. The first name of a living organism is that of the genus and the second the species. These names are derived from Latin and Greek roots and often refer to characteristics of the organisms or the person that first named them. Hence modern man is *Homo sapiens:* genus *Homo* (meaning man), species *sapiens* (meaning wise). The two other human species now extinct were *Homo erectus* and *Homo neanderthalensis* (Neanderthal man) who were the other members of the genus *Homo*. The species name is always set in italics. The first mention of a species in text has the full name spelt out e.g., *Escherichia coli* and thereafter the genus is usually shortened to a single letter *E. coli*.

Bacteria (singular bacterium) were not properly visualised by microscopy and staining until the latter part of the 19th century because of their small size (1-5 micrometres (µm) - 1 µm is a thousandth of a millimetre). It was then noted that bacteria had different shapes: round balls-cocci and rods-bacilli being the most common. They were also divided by the Gram stain into positive: staining purple and negative: staining red. Whilst the microscopic appearance of bacteria was useful in trying to classify them it was limited in its ability to differentiate bacteria, so species and genus assignment was not easy. Subsequently once bacteria could be cultured on artificial media (nutrient containing agar in Petri dishes) a particular bacterium's ability to ferment different sugars, produce different enzymes and other biochemical properties enabled a much more accurate classification which broadly forms the current taxonomy (the science of naming organisms). The big advance was the use of genotypic data which is based on DNA sequence which initially in the 1980s measured the relatedness of the different bacterial

genomes. Bacteria do not have chromosomes, just one small double stranded piece of DNA. Relatedness was initially determined by allowing different single stranded pieces of genomic DNA to hybridise between each other and the amount of hybridization of identical sequences being determined by a radiochemical method. More recently the actual sequence of different DNA bases can be compared giving much more information.

Bacteria are single celled organisms which have much simpler cell structures than higher organisms (e.g., plants, mammals etc.). Bacteria are divided up into major groups called phyla (singular phylum), these are further subdivided into classes. The Gram stain reflects fundamental chemical differences in the bacterial cell wall and does broadly divide bacteria. There is one large phylum of Gram-positive bacteria called the Firmicutes (now sometimes referred to as the Bacillota). This phylum includes the medically important Gram-positive bacteria such as *Staphylococcus aureus*, *Clostridium* spp. (abbreviation referring to all the species in this genus), *Lactobacillus* spp. and *Bacillus anthracis* (cause of anthrax). This phylum contains mainly Gram-positive bacteria which can be both bacilli and cocci in shape. There are a number of other clades in the Firmicutes of which both Gram-positive and negative bacteria exist in the environment and have no medical significance. Another phylum consisting mainly of Gram-negative bacteria of considerable medical importance is the Pseudomonata.

Two classes within Pseudomonata are important in medical bacteriology. These are the Betaproteobacteria and Gammaproteobacteria. The Betaproteobacteria includes the genus *Neisseria* which causes gonorrhoea and meningitis and plant pathogens such as *Ralstonia* spp. and *Burkholderia* spp. and *Xylophilus* spp. that are common and widely distributed in the natural environment to which we are exposed all of the time. These bacteria very rarely, and only in immune-compromised patients, cause infection often associated with intravascular lines (tubes inserted into veins to provide fluids). Bacteria cannot easily be classified as pathogens or non-pathogens as a continuum exists from rare highly pathogenic bacteria which almost invariably cause disease e.g. (*Yersina pestis* - causes plague) to bacteria that are part of our normal flora living in harmony with us, often referred to as commensal bacteria, but in certain situations can cause overt disease (e.g. *Escherichia coli* - causing urinary tract infections). In individuals with greatly impaired immune systems the environmental bacteria which frequent live on and in plants and the soil can rarely cause infection (e.g. *Delftia* spp. in bone marrow transplant patients). The other class of Gammaproteobacteria are Gram-negative bacteria with a range of morphologies bacilusi, coccus, spirals and filaments. The

Gammaproteobacteria class contains over 250 genera of bacteria making it the most genus rich taxonomic group of the prokaryotes. These bacteria live in both marine and terrestrial environments including extreme ones such as hydrothermal vents. As might be expected they have a range of metabolisms both aerobic (requiring oxygen) and anaerobic. Although the Gammaproteobacteria are mainly environmental (e.g., *Methylococcus* that feed on methane) they include many important human adapted pathogens as well as free living bacteria which do not require a mammalian host. A number of these bacteria can cause disease in humans particularly those with immuno-compromise.

The order Pseudomonales (next grouping below class) contains the genera *Pseudomonas* and *Acinetobacter* both important hospital acquired pathogens, but many members also are pure environmental bacteria and/or plant pathogens. Another order of the class Gammaproteobacteria, Xanthomonales contains the genus *Stenotrophomonas*, most species of which are soil plant associated, however one species *S. maltophilia*, in addition to being a plant associated bacterium can cause hospital acquired infections. Arguably the most important from a medical perspective order in the class Gammaproteobacteria is the order Enterobacterales. This comprises genera which are plant pathogens such as *Erwinia* but also the key family of Enterobacteriaceae. This family has the genera: *Salmonella. Shigella, Klebsiella, Enterobacter, Citrobacter* and *Escherichia* which are predominantly human pathogens. The genus *Escherichia* contains the world's most well characterised bacterium *E. coli*. Many of the Enterobacterales bacteria are described as opportunistic pathogens. They surround us, colonise our gut and are in our food outside of the hospital environment. Some strains (a subdivision of a specific species (e.g. *E. coli* 0157) have special disease causing properties that make them more likely than the "ordinary" strains to cause disease in normal people.

2.2. What is meant by an outbreak

The term outbreak is both emotive and superficially well understood, but on detailed consideration is somewhat nebulous. A strict definition is the occurrence of two or more cases of infection caused by genetically indistinguishable micro-organisms. Practically, precise genetic subtyping of microorganisms rarely identifies the outbreak as it is a relatively slow and complicated process and therefore typically carried out retrospectively. More often it is an increase beyond the normally expected numbers of a specific infection. Usually the causative

bacterium is known to species level and therefore draws attention rather than a general increase in different species and or genera of bacteria. This is described as an exceedance beyond the normally expected number of cases of infection and this is what often draws attention to the possibility of an outbreak occurring. Frequently such exceedances occur in patients that are related in time and space providing further circumstantial evidence for cross infection and therefore potentially an outbreak.

When defining a putative outbreak it is necessary to identify 3 features: the source of the infecting organisms, the route of transmission and the portal of entry into the patient. When considering bloodstream infections in haematology oncology patients the source is variable. Although there are many reports of outbreaks of bloodstream infections (BSI), the majority of episodes are single episodes. One reason for this not being obvious is that when the scientific literature is examined it is dominated by reports of outbreaks, which causes publication bias. This is a situation where peer review journals generally are more interested in publishing reports that identify controllable sources with a clear understanding of the routes of transmission and portals of entry, rather than accepting reports with lots of single sporadic unrelated cases of infections.

The widely recognised source for BSI in neutropenic patients, particularly for Gram-negative bacteria is the gut (Rolston et al. 2014). The frequent administration of antibiotics to neutropenic patients also induces a gut microbiome dysbiosis with colonisation by multi resistant Gram-negative bacteria. This has been supported by a recent study in a cohort of 63 patients with acute myeloid leukaemia (AML) and BSI, using whole genome sequencing based strain typing on the BSI isolates and digital drop PCR (a method of amplifying DNA from individual bacterial cells) combined with 16S rRNA sequencing to identify matching species in oral and gut microbiome. The authors found a highly significant correlation between BSI and oral/faecal carriage of the same bacterial strain compared to other BSI cases where there was no colonisation. The effect was particularly marked for *E. coli*, *Pseudomonas aeruginosa* and viridans streptococci (McMahon et al. 2023). In another study, using powerful metagenomic refers to DNA from bacteria which includes bacteria not normally culturable) tools, further explored the relationship between prior gut colonisation with BSI pathogens in bone marrow transplant (BMT) recipients (Tamburini et al. 2018). The authors compared the role of translocation of gut bacteria versus non enteric commensal and environmental bacteria accessing the bloodstream through intravenous lines or breaks in the skin. They prospectively

studied 30 BMT patients with 32 episodes of BSI in 18 months in a major USA cancer hospital. As might be expected pathogens regarded as gut derived such as *E. coli, Klebsiella pneumoniae, Enterococcus faecium* and *Streptococcus mitis* were identified at strain level in both gut flora and blood. In opposition to current dogma which states that environmental bacteria such a *Pseudomonas aeruginosa* are not generally found in the gut, this study documented that both *P.aeruginosa* and *Staphylococcus epidermidis* were found as indistinguishable strains in the patient's gut metagenome and BSI (Tamburini et al. 2018). The importance of patient infection with *Klebsiella pneumoniae* developing from their own strain carried in the gut was recently reaffirmed by a study of ICU patients in which 45% of admission rectal swab culture positive patients had a subsequent infection caused by the same often unique strain as determined by whole genome sequencing. This was in contrast to only 12% percent of episodes being attributable to spread amongst hospital patients (Gorrie et al. 2017). Whilst quite correctly there is a focus on identifying environmental sources of nosocomial infection in haematology oncology units, the “environmental” bacteria as will be seen from the detailed descriptions below, occur widely in the general environment. An example would be a recent study of Glasgow municipal tap water which demonstrated bacteria such as *Cupriavidus* spp., and *Burkholderia* spp. etc can be found at low levels in the drinking water (Khan et al. 2016).

3. Clinical significance and epidemiology of the most common groups of presumed environmental bacteria selected for inclusion by the CNR

As a significant reliance appears to have been placed by the CNR on particular bacterial species, for the purposes of this report, the micro-organisms considered by the CNR are detailed here.

3.1 Order Enterobacterales

This order comprises genera which are plant pathogens such as *Erwinia* but also the key family of Enterobacteriaceae. This family has the genera: *Salmonella. Shigella, Klebsiella, Enterobacter, Serratia, Citrobacter* and *Escherichia* which are predominately gut commensals which can be human pathogens. The genus *Escherichia* contains the world's most well characterised bacterium *E. coli*.

Three genera referred to sometimes as the KES (*Klebsiella, Enterobacter, Serratia*) bacteria are most commonly associated with nosocomial (hospital acquired) infections and generally are multiply drug resistant (MDR). *Klebsiella* together with the closely related genus Enterobacter are arguably the most common causes of nosocomial infection within the family Enterobacteriaceae. *Serratia* which has some special antibiotic resistance genes s are also included in the KES group.

The numbers of positive blood cultures featured in the CNR are shown in brackets in the header.

3.1.1. *Klebsiella* spp. (30)

This genus of bacteria belong to the order Enterobacteriales which is a member of the class Gammaproteobacteria which contain most of the Gram-negative bacilli that cause human infections. The natural habitat of *Klebsiella* spp. is the mammalian gut. In common with *E. coli* and other members of the Enterobacteriales, there are many individuals in the community with asymptomatic gut carriage of *Klebsiella* spp.. A European study showed that between 5-35% of healthy individuals carry *Klebsiella* in their gut flora (Calderon-Gonzalez et al. 2021). Rarely, in certain situations, infection in these individuals will develop. Carriage rates in

hospitalised patients are often higher and not confined to the gut but also include the naso-pharynx and skin which then acts as a source for spread to other patients often by transfer on staff hands. There are two species: *K pneumoniae* which is the most frequently encountered and *K. oxytoca* which has become more common in recent times and has a similar epidemiology and pathogenicity to *K .pneumoniae* (Neong et al. 2021).

K. pneumoniae has a more extensive literature compared to *K.oxytoca* and the usual source for nosocomial infection is the patient with faecal colonisation. As described above, community carriage can be a source and was detected at a rate of 6% in ICU admissions from the community (19% for those with previous healthcare contact) (Gorrie et al. 2017). Those patients found to be colonised on admission had a statistically higher rate of subsequent infection (16% V 3% OR 6.9) with 80% of infections having a genetically matched between colonising and infecting strains (Gorrie et al. 2017).

This colonisation in ward patients is most frequently acquired from another patient usually due to transfer on staff hands or contact with contaminated surfaces in the ward, food/drink and from additional wet sources in which the *Klebsiella* can survive and multiply. This route of transmission was identified nearly 50 years ago together with an effective control of transmission by using hand wash containing Chlorhexidine (Casewell et al. 1977). At the time resistance to the newly developed and very important antibiotic gentamicin drove a major problem with serious infections in hospitals which was easily identifiable because of the antibiotic resistance marker of gentamicin resistance. Faecally colonised patients also had significant numbers of *K. pneumoniae* on their skin and in their nasopharynx. This resulted in spread on nurses and doctors hands to colonise other patients in the ward. Control was achieved by using Chlorhexidine hand washing gel with rigorous attention to hand washing together with screening for identification of those patients with faecal colonisation (Casewell et al.1977).

These careful early studies of the epidemiology of *Klebsiella* are often forgotten and the importance of the colonised patient is underestimated. Careful investigation of outbreaks of infection nowadays can reveal lapses in hand hygiene which probably represents the most common route of transmission in hospital wards.

In some cases there have been reports of sink traps and drains, bowls, cloths and other stagnant wet materials which have been implicated as a source of infection when molecular typing to

trace infecting bacteria to individual patient infections has been undertaken (Kizny-Gordon et al. 2017). This review focused on carbapenem resistant organisms (CRO) but the basic bacterial epidemiology is unaffected by the antibiotic resistance genes carried. Sink traps (U bends or P traps) which always contain water and therefore large bacterial populations, usually in a biofilm, are sometimes seen as the most important source of Gram-negative infections in wards with vulnerable patients (e.g. haematology/oncology, intensive care units, burns units etc.). It is important to maintain a balanced view, as just because bacteria of the same species can be found in those sites they are not necessarily the source of infection.

Klebsiella spp. together with *Pseudomonas* spp., *Acinetobacter* spp. and *Enterobacter* spp. are the bacteria most often suggested to cause infections related to sink traps (Kizny-Gordon et al. 2017). A recent review reported that *Pseudomonas aeruginosa* was the most frequently reported bacterium in such studies (41%) (Kizny-Gordon et al. 2017). The authors drew attention to the various limitations of their work: failure in 60% of studies to undertake admission screening to detect existing colonisation, publication bias (focus on discrete outbreaks) and the use of poorly discriminatory strain typing techniques.

A recent review reported that there are relatively few reports of environmental sources for multi-resistant *Klebsiella pneumoniae*, as the majority involved *Pseudomonas aeruginosa* (41% of studies) (Kizny-Gordon et al. 2017). The authors concluded that *Pseudomonas* spp. and *Acinetobacter* spp. are environmental colonisers surviving in low nutrient conditions whereas the Enterobacteriales are predominantly of human origin and their concentration in drains may represent a different ecosystem and inoculation from human waste.

A detailed study using whole genome sequencing (WGS) of a collection of 250 *K. pneumoniae* strains from UK and Ireland were compared to 10 WGS databases of globally distributed strains. WGS data correlated very closely with multilocus sequence type (MLST) that defines highly related clones of *Klebsiella* by a sequence type (ST) (Moradigaravand et al.2017). The UK hospital isolates had representatives from all of the major global ST's, the most common being ST15. The authors were able to conclude that the UK *Klebsiella pneumoniae* population was highly diverse and that some clones have emerged and spread across the country with potential links to European hospitals. They also stated that as a commensal opportunistic pathogen *K. pneumoniae* has the potential to rapidly spread between hospitals via carriage in patients transferring between countries (Moradigaravand et al. 2017).

To summarise Klebsiella are important nosocomial pathogens, the most common sources are the community colonised patients admitted to hospital and a colonised hospital patient with transfer to colonise other patients via contact with contaminated surfaces, hands of medical/nursing staff and sometimes food. On occasions wet sources such as sink traps, drains, medical equipment and cleaning cloths can act as primary sources for infection having been contaminated by material from colonised patients.

3.1.2. *Enterobacter* spp. (27)

After *Klebsiella pneumoniae*, *Enterobacter cloacae* was the next most frequently isolated pathogen from blood in the CNR. *E. cloacae* has a complex taxonomy but most human infections are caused by *E. cloacae* or very closely related bacterial species referred to as the *Enterobacter cloacae* complex. The next most common species encountered in hospitals is *E. hormaechie* which used to be classified as *E.cloacae* and is still often misidentified as *E.cloacae* by conventional biochemical identification techniques (Davin-Regli et al. 2019). The epidemiology is very similar to *Klebsiella pneumoniae* with the colonised patient as the most common source which can then rarely lead to contamination of the environment particularly drains (Denissen et al. 2022).

Most infections are endogenous and outbreaks from a single environmental source would typically be with genetically indistinguishable strains. When outbreaks of *Enterobacter cloaceae* involving environmental sources occur molecular typing using WGS usually demonstrates a clear cluster of a specific strain type. A good example is the outbreak described by Nurjadi et al. 2021, in a 58 bed haematology unit between 2018 and 2020 involving *E cloacae* producing OXA-48 carbapenemase, a distinctive antibiotic resistance marker. They used WGS, assigning isolates to different sequence types (ST) which is a highly discriminative subtyping method. A total of 41 patients over the time period were colonised in the gut and nine patients developed BSI. There was no clear epidemiological link between the patients. Sequence typing of all *E. cloaceae* isolates across the hospital revealed many ST types (ST 66, ST 231, ST27,ST90, ST 96) with a notable excess of ST66 isolates in the haematology wards. The wastewater traps in 20 of 38 patients rooms were positive for OXA-48 *E cloacae* most of which were ST66. Disinfection of traps with acetic acid and the use of an autoclavable shower insert to reduce splash from the waste outlet terminated the outbreak completely. This study shows that when sink traps are a significant source then WGS typing readily identifies a number of indistinguishable isolates which are found in both patients and the environment. As with *K.*

pneumoniae certain clones of *E. cloacae* are highly adapted and successful in the hospital setting. They usually carry important antibiotic resistance genes such as those for the carbapenemases e.g. KPC (Kneckt et al. 2022). The use of antibiotics in hospital wards therefore has a strong influence on the occurrence of these nosocomial bacteria, particularly third generation cephalosporins (Eichel et al. 2020). In some cases *E. cloacae* outbreaks when investigated over an extended time show a diversity of strains are causing infection which suggests there is no constant single environmental source but rather introduction by individual faecally colonised patients. Such a study over 6 years in a major neonatal unit using WGS strain typing which is very sensitive and reliable showed waves of different diverse clones occurred, suggesting introduction from different sources (Ferry et al. 2020). The authors commented that the infant gut was the most likely source with spread via hands and contaminated objects.

3.1.3. *Serratia marcescens* (7)

Serratia marcescens is by far the most common species of the genus *Serratia* causing human infections, particularly in neonatal and immunocompromised patients. That said, it is a rare cause of human infection, most cases being sporadic. Publication bias has led to hospital outbreaks being reported more commonly. It is a member of the Enterobacterales and is common in the neonatal microbiome whereas in adults it is rare (Lewis et al. 1983). In a study of pre term neonates the presence of *Serratia* in the faecal microbiome was strongly associated with a high degree of immaturity as well as antibiotic therapy and mechanical ventilation (Moles et al. 2020). Whilst environmental sources for nosocomial outbreaks are described those sources tend to be equipment such as bronchoscopes, scalp vein needles or disinfectants (Knowles et al. 2000).

Numerically the most important source for both sporadic cases and outbreaks is the colonised patient (predominantly faecal) which then leads to general environmental contamination and transfer on staff hands from that environment and/or the patient (Lewis et al. 1983; Knowles et al. 2000; Montanaro et al. 1984). Because *S. marcescens* has intrinsic resistance to a range of antibiotics, antibiotic usage in the ward is reported to be associated with outbreaks (Knowles at al. 2000; Lewis et al. 1983). *S. marcescens* is the only species of *Serratia* which can carries the *aac* 6'-Ic gene conferring resistance to aminoglycosides, all strains carry the gene thus explaining perhaps its dominance in causing human infections under antibiotic selection (Snelling et al. 1993). The *aac6'-Ic* gene is normally not expressed, so isolates are sensitive to a aminoglycoside antibiotics when not exposed to aminoglycosides. However, if a patient is

treated with an aminoglycoside (e.g. gentamicin, netilmicin or amikacin) the gene is derepressed. This process results in the full expression of resistance. That strain will often retain expression of resistance even after no longer being exposed to the aminoglycoside antibiotic and therefore pass as a resistant strain from patient to patient (Snelling et al. 1993).

S. marcescens should not be viewed as an environmental bacterium in the way non-fermenters such as *Stenotrophomonas*, *Cupriavidus*, *Rhizobium* etc. are, as the colonised patient is the common source of outbreaks. *S.marcescens* should however be seen as a commensal of the paediatric gut which under antibiotic selection leads to heavy faecal colonisation in the patient which in turn acts as a source for nosocomial transmission.

3.1.4 *Citrobacter* spp. (5)

This bacterium is another member of the order Enterobacterales and in the CNR only represented 3.2% of isolates, so not in the top 6 number of isolates. It is much less frequently encountered in nosocomial infection compared to *Klebsiella* and *Enterobacter* but has a similar epidemiology to *E. coli* that was excluded from consideration by the CNR.

3.2. Order Pseudomonales

3.2.1. Pseudomonas spp. (17) - P. aeruginosa (9), P. putida (7) and P. stutzeri (1)

These bacteria belong to a different order to the Enterobacteriales to which the above bacteria belong, namely, Pseudomonales. This means that although they are Gram-negative bacilli they have different properties to the Enterobacteriales. The main difference is that they are not normally animal gut commensals, but live in association with plants and soil. The most common human pathogen is *Pseudomonas aeruginosa* which belongs to the family Pseudomonadaceae. This is a very large family of bacteria of mainly environmental and plant associated bacteria some of which are capable or fixing atmospheric nitrogen to the benefit of the plant host. The genus *Pseudomonas* has 313 species most of which are plant pathogens.

P. aeruginosa is probably the most common environmental derived pathogen seen almost exclusively in immunocompromised, burns, ICU and cystic fibrosis patients. Faecal colonisation can occur even in healthy individuals in the community one study reporting a

carriage rate of 8.2% (Estepa et al. 2014). Higher rates of colonisation are seen in hospital patients. Colonisation may lead to the development of infection by invasion from the bowel in immunocompromised patients subsequently making it difficult to define exactly the original source for infection. This accords with the relative infrequency of infection derived directly from the environment. As reported in the study of *P. aeruginosa* environmental epidemiology in four very large critical care units using WGS typing, in only 5.1% of colonised patients was the *P. aeruginosa* definitely acquired from a water outlet in the unit. This is in the background where in the largest unit 25-28% of the 231 outlets sampled on three separate occasions were positive for *P. aeruginosa* carriage (Halstead et al. 2021).

P. aeruginosa is capable of successful colonisation of biofilms in most wet environments particularly if there is plastic or rubber present as the bacteria can use these as a nutritional source. It is the most important bacterium when considering colonisation of hospital water systems which then can lead to infection in susceptible patients (Kinzy- Gordon et al. 2017). Thermostatic mixer valves contaminated when tested following manufacture have been particularly implicated as sources and certain clones of the *P. aeruginosa* have been identified as causing both colonisation and infection in augmented care units (ICU/burns) (Halstead et al. 2021). *P. aeruginosa* is the main bacterium colonising water supplies as opposed to waste traps when other bacteria such as *Klebsiella* and *Enterobacter* tend to colonise hand washing sink traps potentially from the disposal of patient materials (urine, washing water with traces of faeces etc.) (Hayward et al. 2022). A recent study looked intensively at an intensive care unit over a long time using highly discriminative WGS typing to assess the role of sink traps in *Pseudomonas aeruginosa* infections (Couchoud et al. 2023). They concluded “that genome based typing revealed the contamination of patients by *P. aeruginosa* originating from sink traps to be infrequent (1.5%) and that only 7.75% of patients acquired *P. aeruginosa* from another patient” suggesting that endogenously acquired infections are much more significant. In summary although sink traps have a diverse bacterial population which is enriched repeatedly by human derived materials being poured into the sink they are not necessarily the dominant source of BSI when compared to gut/oral microbiomes of patients.

Pseudomonas putida is a plant associated bacterium whose ecological niche is to act as a growth stimulant for plants in the rhizosphere (the microbial community surrounding plant roots) (Costa-Gutierrez et al.2022). Because of its very widespread distribution outside of hospitals it can colonise compromised patients at home as well as in the hospital environment.

Although rarer than *P. aeruginosa* in causing infections it's frequency appears to be increasing and it is now regarded as the next most common species of pseudomonas after *P. aeruginosa* causing outbreaks in hospital associated with patient colonisation and wet sources in high dependency areas (Baykal et al.2022).

3.2.2. *Acinetobacter* spp. (11)

Bacteria of the genus *Acinetobacter* are important soil organisms frequenting the rhizosphere. They belong to the order Pseudomonales like pseudomonas but are in the family Moraxellaceae being very different in their metabolism and epidemiology. There are a very large number of species found in the general environment but only a very small number associated with hospital infections, the most common being *Acinetobacter baumannii* and more rarely *A. ursingii* and *A. pittii* (Kiyasu et al. 2020). The reason for their success is thought to be their high levels of antibiotic/disinfectant resistance, metabolic flexibility and desiccation resistance allowing survival for long periods on surfaces contaminated by colonised patients (Jawad et al. 1998). The epidemiology of *Acinetobacter* is therefore rather different to *Pseudomonas* and *Klebsiella* in that although there are reports of contamination of wet medical equipment together with isolates from sink traps as outbreak sources, surface contamination and resistance to drying is the most important source (Cruz- Lopez 2022). This difference in epidemiology was illustrated by the successful control of a long term outbreak in a neurosurgical unit by increased environmental and surface cleaning rather than controlling any wet sources (Denton et al. 2004).

3.2.3 Stenotrophomonas maltophilia (23)

The natural habitat of *Stenotrophomonas maltophilia* is the rhizosphere (microbial community surrounding plant roots) (Mukherjee and Roy 2016). It belongs to the order Xanthomonales and is therefore not closely related to either Enterobacterales or Pseudomonales. Although an aerobic bacterium it has the ability to use nitrate as a terminal electron acceptor in the absence of oxygen so can grow in an anaerobic environment. It can utilise a wide range of organic molecules as an energy source including toxic solvents (trichloroethylene, chloroform etc) and plastics (Mukherjee and Roy 2016). The ability to survive in a low nutrient, wet and anaerobic environments combined with high levels of intrinsic antimicrobial resistance means that it can cause a range of nosocomial infections.

Despite low pathogenicity, infections in ventilated ICU, immunocompromised and patients with cystic fibrosis are moderately common (Brooke, 2021). A wide range of wet environmental potential sources of infection in hospital have been reported such as sink traps, plastic medical equipment, taps etc. (Brooke, 2013). Because *S. maltophilia* is so widely encountered in the environment microbiological monitoring often finds this bacterium in wet/moist hospital sites. When outbreaks are investigated these environmental isolates do not always correspond to those causing the patient's infection (Kampmeier et al. 2017). In many outbreaks one or two specific strains from the greater number present in the ward environment contaminate a particular niche where they can multiply and critically have access to either the bloodstream (via CVC lines etc.) or the respiratory tract (e.g. ventilator equipment). Strain typing then reveals a cluster of indistinguishable isolates in the infected patients with isolates from the specific equipment. A good example of such an outbreak is described in the contamination of a needleless blood sampling syringe system and subsequent contamination from it of ECMO equipment leading to an outbreak of bacteraemia caused by *S. maltophilia* (Menekse et al. 2023). These outbreak investigations also identify isolates from the environment of different strain types to the clinical isolates and which do not match the outbreak isolates. These patients have most probably been colonised from other sources and particularly in immunocompromised patients the colonisation is often driven by the frequent administration of antibiotics as shown by the work of Aitken et al. (2021). Recent studies of the genetic diversity of *S.maltophilia* has shown that some genetic subgroups (referred to as clades) occur only in the environment with some other clades only causing infections in humans with others occurring in both groups (Steinmann et al. 2018). More recent work using WGS confirms this and shows that animal strains can also be identified in human infections suggesting that animals such as pets could be a source (Mercier-Darty et al. 2020). When hospital outbreaks occur and are carefully investigated with WGS strain typing which usually only identifies one or two strains in a number of patients along with a larger number of highly divergent strains. Investigation of the environment reveals a large number of environmental isolates of which only a small number are derived from the putative source and match those found in the infected patients. An example of this is an outbreak of bacteraemia in four patients who were ultimately shown to be infected by two clades of *S. maltophilia* (3 patients by ST361, 1 by ST138). The environmental source was identified as a calorimeter moisture trap which had become colonised with these strains probably from an environmental source within the ward. Widespread environmental sampling (54 samples) yielded 13 positive for *S. maltophilia*, but only a sink trap and two plastic buckets were positive for the outbreak strain (Gideskog et

al. 2020) This emphasises the fact that *S. maltophilia* can be found very widely in the hospital environment but comparatively rarely causes infections, even in the immune-compromised and careful strain typing is needed to identify any actual environmental source. Acquisition of *S. maltophilia* from environments other than the hospital such as the home have been reported, an example being that of cystic fibrosis patients (Denton et al. 1998). Every isolate of *S. maltophilia* carries a chromosomal beta-lactamase (L1) which confers resistance to carbapenem antibiotics. The use of carbapenems has been demonstrated to be significantly associated with patient colonisation in a cohort and subsequent development of infection caused by *S. maltophilia* in vulnerable patients (Aitken et al. 2021). Patients with hematologic malignancy who develop infection usually have prior colonisation and dominance in their faecal microbiome by the infecting bacterium. In the case of Enterobacterales the infection is generally primary bacteraemia following gastrointestinal translocation which was preceded by colonisation often driven by antibiotic administration (Velden et al. 2014). In contrast Aitken et al. (2021) found that colonisation with *S. maltophilia* was mainly oral rather than faecal as seen with other Enterobacterales which could fit with the predominance of respiratory and catheter related blood stream infections in this population. The acquisition of multi drug resistant Gram-negative bacilli may be from environmental sources but can also be from sources outwith the hospital or from the patients indigenous microbiome.

3.3. Other more rarely reported bacteria in the CNR selected by the panel.

Very small numbers of a wide range of different species of Gram-negative bacteria were reported from cases of bacteraemia over the extended time period. Most of these bacteria are associated with plant/soil and can therefore be acquired by immunocompromised patients in a non-hospital setting as well as in hospital. Some such as *Elizabethkingia* spp. have been reported as colonising wet hospital environments and causing single environmental source outbreaks as determined by molecular typing. Many of the other species are very common in the general environment and can very rarely cause infection in immune-compromised patient. These short descriptions provide background on the most common habitats and their association with human disease.

3.3.1. *Pantoea* spp. (3)

This genus was comparatively recently established and involved the transfer of *Enterobacter agglomerans* (a bacterium well recognised as a human pathogen) into the genus with about 20 other species which are most commonly associated with plants (Walterson and Stavrinides, 2015). As a member of the order Enterobacteriales, *Pantoea* forms a mono-phyletic group (highly related) with the genera *Tatumella* and *Erwinia* which mainly consist of plant pathogens (Walterson and Stavrinides, 2015).

A number of species have been found in clinical samples, WGS studies suggest that environmental and clinical isolates do not form distinct clusters. This implies colonisation, mainly from general environmental sources plants soil etc, occurs and then very rarely infection develops in both immunocompetent and immune- compromised patients (Walterson and Stavrinides, 2015). Recent genomic studies have demonstrated that this genus has two major clades (groups which are highly genetically related). One of them contains *Enterobacter agglomerans*, renamed *Pantoea agglomerans* which is well recognised as a rare pathogen in humans. The genus has been considerably expanded and now has 21 species. While some other species such as *P. septica*, *P. calida* and *P. dispersa* have been isolated from both human immune-compromised and immunocompetent patients, the majority of species are associated either with plant disease or act as endosymbionts (symbiotic bacteria that grow within a plant). They do not have any particular association with aquatic environments. The closely related genus of *Erwinia* is a well-recognised plant pathogen consisting of very many species as are the other genera in the Enterobacteriales which are plant pathogens (*Tatumella*, *Dickeya*, *Brenneria*, *Pectobacterium* and *Sodalis*).

3.3.2. *Raoultella* spp. (2)

Raoultella is another member of the Enterobacteriales which is rarely encountered causing human disease and is most commonly isolated from plants (Sekowska, 2017). It was formerly classified in the genus *Klebsiella* and similarly has the ability to colonise the human gut (Sekowska, 2017). The epidemiology of infections is very similar to *Klebsiella*, with infections occurring in intensive care, haematology-oncology units in patients with comorbidities but also in non-immunocompromised patients usually following broad spectrum antibiotic treatment and/or implanted devices (Appel et al. 2021).

3.3.3. Elizabethkingia spp. (6)

Although these appear to be a newly recognised species of bacteria, however it is the result of the reclassification of *Flavobacterium meningosepticum*. This bacterium was recognised by Miss Elizabeth O King in the USA in the late 1950s as causing clusters of neonatal meningitis (Jean et al 2014). A new genus was created and named in her honour which has eight species including *E. meningosepticum* (which is phylogenetically distinct from the others) and of which *E. anopheles*, *E. ursingii* are the most frequently encountered other species in clinical settings (Zajmi et al. 2022). The genus belongs to the very large order Flavobacteriales which are environmental bacteria of which only *Elizabethkingia* and *Capnocytophaga* are associated with human disease.

From their first description these bacteria have been frequently reported causing nosocomial outbreaks of bacteraemia, meningitis, soft tissue and line infections (Lin al 2019; Jean et al 2014). There are a number of reports which have wet sources such as sink traps, taps, humidification systems and contaminated aqueous solutions (e.g. saline or Chlorhexidine disinfectant) act as sources (Jean et al. 2014; Moore et al. 2016). *Elizabethkingia* spp. are ubiquitous in general aquatic environments and can colonise both domestic and healthcare water systems. They carry multiple resistance genes often conferring resistance to broad spectrum antimicrobials such as carbapenems and 3rd generation cephalosporins (Hem et al. 2022; Moore et al. 2016). Identification by conventional phenotypic biochemical methods does not allow reliable species differentiation and even MALDI-TOF does not reliably differentiate some species e.g. *E. meningosepticum* and *E. anopheles* (Lin et al. 2019). Highly discriminatory strain typing has to be applied to link patient isolates with any environmental isolates as it is a common bacterium in aquatic systems.

Most frequently infected patients are those receiving intensive care, paediatric/ neonatal and immunocompromised often because of the proximity to sources and the multiple portals of entry for the bacteria (Moore et al 2016; Lim et al 2019). Infected and colonised patients become prolific sources of the bacteria which can then contaminate surfaces such as keyboards, locker tops and medical equipment leading to further cases (Moore et al. 2016; Jean et al. 2014).

3.3.4. Chryseobacterium spp. (5)

This is a very widely distributed bacterium in the general environment with over 100 species recognised. Originally known as *Flavobacterium* (on account of the production of yellow orange pigmented colonies on agar) the most important human pathogen *C. meningosepticum* was reclassified to another genus *Elizabethkingia*. The vast majority of *Chryseobacterium* together with *Flavobacterium* spp. are the most abundant bacteria in the plant rhizosphere (Nishioka et al 2016). *Chryseobacterium* have plant growth promoting properties, protect plants from infection by producing antifungal/antibacterial compounds and releasing nutrients by secreting biodegrading enzymes such as chitinase as well as degrading aromatic hydrocarbon pollutants (e.g. 2-4 dinitro toluene) (Nishioka et al. 2016). Therefore, only two species are rare causes of human infection namely *Chryseobacterium indologenes* and *Chryseobacterium gleum*, which were recognised when an expanded MALDI-TOF databases was used (Lin et al .2018). They have a propensity to be associated with intra-venous lines, intra-cerebral and plastic shunt infections as well as bacteraemia in immune-compromised patients (Lin et al. 2018; Ozcan et al. 2013). Environmental nosocomial sources such as sink traps have rarely been reported as sources so acquisition from contact with soil and plants or other infected patients with subsequent gut colonisation and invasion across the gut wall seems to be the most common source of infections (Hsueh et al. 1996; Mukerji et al. 2016).

3.4. Order Burkholderiales

This large order of bacteria is dominated by families of bacteria found in soil and water with a very few that can cause human disease even in immunocompromised patients. I have grouped them together because they have similar properties, particularly in that they cannot ferment sugars to provide energy unlike the order Enterobacteriales. The following genera belong to the order Burkholderiales and are represented in the CNR bacteraemia series.

3.4.1. *Burkholderia* spp. (2)

The species of the genus *Burkholderia* (part of the Burkholderaceae family) most frequently encountered in human infections is *B. cepacia* formerly known as *Pseudomonas cepacia* which causes colonisation and pneumonia in patients with cystic fibrosis (CF). There are now 24 other species of which are those encountered in human infections are dominantly in CF patients,

being *B. cenocepacia* and *B. multivorans* (Tavares et al. 2020). Unlike Enterobacteriales and some other Gram-negative bacteria, commensal gut carriage is not common and infections are acquired in hospital settings or directly from the environment (soil and water). In the case of *B. cenocepacia* (formerly *B. cepacia genomovar III*) in CF patients, the strains of the species found in soil and water and in patients homes are indistinguishable from the infecting bacteria (Tavares et al. 2020). Spread amongst patients in hospitals is associated with intravenous and urinary catheters, endotracheal tubes, human dialysis and long periods of hospitalisation. Spread is thought to occur by aerosols and direct or indirect contact (via surfaces) with infected patients (Tavares et al. 2020). Another quite commonly reported source for nosocomial infection caused by *Burkholderia* is contaminated water based pharmaceutical and cleaning products, where it is recognised as the most commonly identified causative bacterium (Tavares et al. 2020).

3.4.2. *Delftia* spp. (3)

This bacterium used to be called *Pseudomonas acidovorans* and has been recognised since the late 1960s as an extremely rare cause of infection in patients with comorbidities or immunocompromise (Bhat et al. 2022). Its normal habitat is a wide range of environmental sites as it is part of the rhizosphere (microbial community surrounding plant roots) microbiome. It is capable of fixing nitrogen and also acts as a plant growth promoting bacterium when it is described as an endophytosphere bacterium growing within plant cells inside the plant. It is also capable of removing heavy metals so is found in a wide range of aquatic environments and is used in bioremediation of metal contaminated soils (Bhat et al. 2022). Infections have been reported from both immune-competent and immunocompromised patients but low numbers of cases appear in the literature (Bilgin et al. 2022). Colonisation of wet sites such as sink traps is possible as the bacterium has been reported to have the ability to coaggregate with other bacteria and provide nutritional support for those bacteria to form biofilms (Afonso et al. 2023).

3.4.3. *Cupriavidus* spp. (2)

These bacteria belong to the family Burkholderaceae (as do *Ralstonia*) which are very widely distributed in soil and water with 17 species currently recognised. *C. pauculus* has been identified as a rare cause of bacteraemia in immunocompromised patients (Inkster et al. 2021). Three cases were identified over a five-year period, molecular typing was undertaken and all

isolates were distinguishable suggesting a common source was unlikely, there was no mention of correlation with environmental isolates in the report. *C. pauculus* has been identified as being present in water collected from 5/10 hospitals in the UK, although *Acidovorax*, *Blastomonas*, *Brevundimonas*, *Pseudomonas aeruginosa* and *Sphingomonas* were identified at a greater number of hospital sites (Inkster et al 2022). Patients are likely to come into contact with *Cupriavidus* outside of hospital because of its widespread distribution in water, soil and plants. A recent study has shown that together with *Ralstonia* and *Pseudomonas* they were the most commonly isolated bacteria from final rinse water used to prepare lettuce and spinach (Gu et al. 2020). The authors postulated that resistance to the sanitizer (chlorine) added to the rinse water increased counts of these bacteria. As these foods are eaten without cooking this represents a significant risk for colonisation in the compromised patient.

3.4.4. *Achromobacter* spp. (1)

Another genus in the Burkholderaceae which contains *Achromobacter xylosoxidans* which has been reported as a rare cause of human infection. It most is most frequently encountered in patients with cystic fibrosis, probably selected by repeated courses of broad spectrum antibiotics (Isler et al. 2020). It is rarely encountered as a nosocomial pathogen, although older outbreaks have been associated with contamination of disinfectant solutions such as aqueous Chlorhexidine to which it is resistant.

3.4.5. *Herbaspirillum* spp. (1)

Like other members of the Burkholderaceae this genus are endophytes, many being able to fix nitrogen and are very common in soil and vegetation. Reports of human infections are mainly confined to single case reports in patients with immune-compromise or cystic fibrosis (Dhital et al. 2020). There is a report of a hospital based cluster of eight cases, seven with bacteraemia, of *Herbaspirllum* infections at the M D Anderson Cancer Center, Texas (Chemaly et al. 2015). Five cases were hospitalised between 19- 28 July 2011 so were tightly clustered in time and four of those isolates had indistinguishable pulse field gel electrophoresis (PFGE) typing patterns, however all the patients were on different wards and floors of the hospital. Despite extensive investigation of the environment including water sink traps etc. no environmental source was found. It was concluded that it could have been spread on hands of staff resulting in colonisation of central venous lines or ingestion of a common uncooked plant based food (Chemaly et al. 2015)

3.4.6. *Aeromonas* spp. (2)

These bacteria have a natural habitat of surface waters and are well recognised as causing local soft tissue infections and gastroenteritis which can evolve into septicaemia particularly in elderly patients (Pinto-Cora et al. 2023). Hospital outbreaks are unusual and when reported usually relate to the consumption of unchlorinated tap water by compromised patients (Fernandez-Bravo and Figueras 2020; Picard & Goullet 1987). Most compromised patients probably acquire the bacterium from water or food in the general environment (Pinto-Cora et al. 2023).

3.4.7. *Sphingomonas* spp. (1)

These are plant associated bacteria that can be acquired from environmental sources such as water and food. Most reports are of sporadic hospital acquired outbreaks often in immunocompromised patients (Aşkın et al. 2022). However, these reports are subject to reporting bias and a very large population-based survey in Australia over a 20 year time frame showed 134 of 282 episodes of bloodstream infection caused by Sphingomonas were community associated and the overall mortality was only 6% (Laupland et al. 2022).

3.4.8. Roseomonas spp (1)

This is a group of bacteria of which many species have been found in water and soil. Therefore when there are rare reports of infections they are often related to intravascular catheters and compromised patients, an environmental source such as water is often hypothesised as the cause (Shao et al. 2019). This assumption has been challenged as a genomic study demonstrated that the skin microbiome is the source of *Roseomonas mucosa*, the most commonly encountered species in humans (Romano-Bertrand et al. 2016).

3.4.9. Rhizobium spp (1)

These bacteria are one of the most important nitrogen fixing bacteria for plants and are therefore obligate plant endosymbionts. Human infections are rare usually community acquired and associated with indwelling plastic devices (Tiwari and Beriha, 2015).

3.4.10. *Brevundimonas* spp. (1)

This is a large genus consisting of 34 species of plant growth promoting and plant pathogenic bacteria. They are rare pathogens of compromised patients with a total of 49 cases found in the world literature up until 2018, the majority being *B. vesicularis* (Ryan and Pembroke, 2018). The bacterium has been identified as an important component of biofilm communities and provides nutrients to enable *Legionella pneumophila* to grow (Koide et al. 2014). Although capable of colonising low nutrient wet environments in healthcare facilities it is very widely distributed in the general environment as evidenced by its frequent occurrence in plant debris on beaches in numbers sufficient to raise concerns for human safety (Suzuki et al. 2021).

4. Case Note Review

The CNR regards many of the bacteria reviewed in the previous section as being acquired from a ward environmental source and to have "possibly" caused BSI in 70% of cases. They further identified a group of 34% of cases given the designation of "most likely" suggesting an even greater confidence in acquisition from the environment. Patients spend long periods at home when there is ample opportunity for colonisation by these environmental bacteria as has been demonstrated in cystic fibrosis patients for *Stenotrophomonas maltophilia* (Denton et al. 1998) and also for *Burkholderia* spp. (Tavares et al. 2020) It is therefore reasonable, particularly in the light of the metagenomic studies above, to assume that a smaller percentage of the BSI in the CNR are derived from a hospital environmental source than the 34% categorised as being "most likely" derived from the hospital environment. It is a matter of opinion but we would regard a figure that is significantly lower (e.g. 20% or less) as being reasonable. This opinion is supported by studies such as that of a 15 bed MICU over a 10-month period (Couchoud et al. 2023). They used WGS typing of 519 isolates of *Pseudomonas aeruginosa* from sink traps and only identified 1.5% of patients acquiring indistinguishable strains from a sink traps. In contrast person to person cross colonisation was much more common with 7.7% patients acquiring an indistinguishable strain from other patients. The authors opined that this transfer most probably occurred on hands of staff and via contaminated surfaces from colonised patients (Couchoud et al. 2023). Another study of augmented care units (ICU, burns units, etc.) located in four major teaching hospitals over 16 weeks sampled all water outlets for *Pseudomonas aeruginosa* on three occasions. Whole genome sequencing was used to match all clinical isolates with all the environmental isolates. Overall, only 5.1% of patient infections had a definite match with a water isolate. In the hospital with the greatest number of matches 15% of patient clinical isolates had a match with an environmental isolate. This hospital had exceptionally high levels of isolation of *P. aeruginosa* from water outlets. If isolates with a much lower probability of matching by WGS were included then overall only 19.2% patient isolates had a low probability match with an environmental isolate (Halstead et al. 2021). Broad spectrum antibiotics, of which haematology oncology patients receive a large number, also select for gut carriage of multi resistant Gram-negative bacteria which are often of the "environmental" type because these bacteria possess high levels of intrinsic resistance to broad spectrum antibiotics. The patients are frequently exposed to them and, as the bacteria are resistant, they become dominant in the gut flora because the more sensitive bacteria are killed. This is eloquently illustrated by the study of both colonisation and infection by

Stenotrophomonas maltophilia in haematology oncology patients in the USA (Aitken et al. 2021). These authors showed that in following a cohort of 90 patients receiving remission induction chemotherapy for acute myeloid leukaemia (AML) there was a statistically significant association of both oral colonisation and subsequent systemic infection (BSI) from *Stenotrophomonas maltophilia* with the prior administration of carbapenem antibiotics (e.g. meropenem) to which the bacterium is intrinsically resistant.

When reading the CNR it is not clear exactly how many cases of BSI occurred in the time period studied and what the causative bacteria were in terms of species type. The report states (at paragraph 3.2) that the cases for review were selected on the basis of a protocol referenced as #27. This reference document is not available, so it is not clear that all or only some cases of BSI caused by bacterial species regarded as having an environmental origin were included or not. It seems that all *E. coli* were excluded but it is not clear if all cases of the other Gram-negative bacteria were included. This is important as there is a description at 3.6.6 that a variety of patient clinical and epidemiological (location and clustering) data for each case was used to assign a relative likelihood that the infection was acquired from an environmental source in the hospital.

The term cluster is a very loose one, as most people see it as being defined as a number (two or more) of isolates of the same bacterial species (sometimes further characterised by preliminary strain typing) occurring in a short time period and in a setting where they may be arising as the result of cross infection. We do not think it is appropriate to group different species of bacteria as a cluster despite the CNR panel suggesting that the putative environmental sources had multiple types of many different species and therefore, they believed there was a high probability these sites were the sources of the BSI.

There are multiple locations in all clinical areas in which water is present which result in the growth of environmental bacteria (mostly Gram-negative) for instance: in sink traps, tap nozzles, drains etc. as discussed in detail above under each bacterial species. The fact that such bacteria can be isolated in spatial and temporal association with a patient that has a BSI caused by one of the component species from the environmental site does not prove it as a source. Critically a route of transmission and portal of entry into the patient needs to be identified to help support the probability of such a site acting as a source for BSI. The only conclusive proof arises from strain typing the environmental and clinically infecting isolates and demonstrating that they are indistinguishable.

The most powerful modern method which is used is whole genome sequencing (WGS). Bacteria only have a simple single "chromosome" which is referred to as the genome which is composed of a circle of double stranded DNA with between 5 and 15 million nucleotide bases (adenosine, thymine, guanine and cytosine abbreviated to A T G C). The order of these bases carries the information to enable the cell to function and replicate. In the process of sequencing a bacterial genome the genomic DNA is fragmented and amplified in a DNA sequencer machine. The precise nucleotide sequence of the majority of an individual bacterial genome can then be determined. Because amino acids (the building blocks of all proteins and therefore the whole bacterial cell) are encoded by three base codes (e.g. ATC, AGC etc.) providing 64 unique codes, but only 20 amino acids are found in proteins. It is this codon redundancy that allows for single nucleotides to be substituted and not affect the final amino acid makeup of the protein. These changes are called single nucleotide polymorphisms (SNPs). SNP analysis is highly accurate, discriminatory and a very well validated method for strain characterization of bacteria. Although there may be a number of strains of the same bacterial species in the environmental site and the key infecting strain may not have been selected when that site was cultured, studies of outbreaks using WGS will show some matches thus identifying the sources involved (Kampmeier et al. 2017; Halstead et al. 2021). No such matches were found with exception of a pair of isolates of *Cupravidus spp*. The CNR panel's method of "defining" outbreaks/clusters in our experience is an unusual, suboptimal and a limited method of investigation. As they did not wish to consider the WGS strain typing data (section 8.3.1) from patient isolates and appropriate environmental isolates some of which were made at the time of the infection in the patient in which the reported BSI occurred, the methodology is probably the only possible but flawed approach.

The generally accepted epidemiological definition for acquisition is that indistinguishable bacterial types are found in the source and the patient (defined by the group as definite). The CNR panel accepted this definition but had to report that none of the BSI episodes satisfied this criterion (p.68 and Table 5.3). The next category of degree of association with a putative environmental source was "probable" to which 28% of cases are allocated, including just three 3% being assigned to "strong probable" The criteria used for "probable" and a larger weaker category "possible and strong possible" was based on an opinion that "the environment was likely to be the source (on the grounds of probability), using a standard infection prevention and control assessment of the available data/information" (p.44). The CNR panel decided that the two probable categories and the strong possible category represented the group with "the

closest likelihood of a link to the hospital environment" (p.69), which they are referred to as the "Most likely" group. This group consisted of 37 episodes (31% of all episodes). These three groups were pulled out as a single category into a comparative table (Table 5.4, p.69). The comment is made that "There is a striking excess of *Stenotrophomonas* spp. in the 'Most likely' group", and application of the Chi squared test showed this general excess to be statistically significant compared to other bacterial species. It seems that there is likely to be too much reliance placed on the occurrence of episodes of BSI caused by the same bacterial species in a certain time and place frame, which can easily arise by chance. Without molecular typing and characterisation of the repeated occurrence of the same strain and it being actively identified in the environment this methodology seems highly speculative.

It is it is notable and commented on by the CNR panel that the two most frequently encountered genera of bacteria causing BSI are *Stenotrophomonas* and *Klebsiella*. *Stenotrophomonas* is particularly highlighted by the CNR panel to be over represented in a particular timeframe and there is speculation that this has come from the environment. However, the *Stenotrophomonas* cluster could equally be derived by the use of carbapenem antibiotics in the same manner as reported by Aitken et al. (2021) (see 3.2.3 of this report and below). If the categorisation was made purely on the basis of the occurrence of a particular species of bacterium in a certain time frame then endogenous infections rather than environmentally acquired is more likely as typically this can occur in cases of infection with *Klebsiella* and some other species of Enterobacteriales.

As described at 3.1.1 above *Klebsiella* can be spread from an environmental source but the colonised patient is most often the source in ward transmission events. The CNR panel is dismissive of the WGS typing data as a tool for refuting the clusters of *Stenotrophomonas maltophilia* BSIs (8.3.1 p.96) on the grounds of poor strain representation. However, isolates from 15/23 total infections were typed together with 59 environmental isolates and 10 other clinical isolates none of which were indistinguishable and therefore not related. In our opinion this is a reasonable sample and should be compared to the findings of a cluster investigation of BSIs caused by *Stenotrophomonas maltophilia* in a large German haematology unit (Kampmeier et al. 2017). They identified 4 cases of BSI between February and July 2016, a clear exceedance from their 0.5 cases/year. WGS showed no relationship between the isolates, typing of environmental isolates only identified one of the four BSI isolates to be indistinguishable from a shower head isolate. Using the CNR panel's criteria this would be

classified as an outbreak of 4 cases, whereas WGS demonstrated that this was not an outbreak but a single acquisition from an environmental source.

E. coli BSI is completely excluded from consideration by the CNR panel with no explanation. Most infections in immunocompromised patients with *E.coli* are likely to arise following gut colonisation in the community followed by translocation across the gut mucosa into the bloodstream. Careful molecular typing studies have occasionally shown that *E. coli* is capable of ward based transmission including environmental contamination, this being particularly apparent when strains are multi resistant or have an unusual antibiotic resistance marker (Woodford et al. 2007). It may be that the CNR panel made this generalisation due to a desire to simplify the investigation but it does in our opinion reflect a lack of detailed understanding of the epidemiology of infections caused by Gram-negative bacteria.

Although fleetingly mentioned (bottom of p.68) that environmental pathogens in immunocompromised patients can be acquired outside of hospital, no allowance for this appears to be made in the analysis. The review of the literature around all of the selected bacterial species (see above) shows that this is not an uncommon occurrence and this is a significant shortcoming in the report. Despite this the CNR panel classify 76 (70%) episodes of BSI as possible and 33 (30%) as probable from being acquired from a hospital environmental source.

The CNR panel draw attention to two clusters of *Stenotrophomonas maltophilia* BSI in January-September 2018 and April-September 2019 (p.56). They tested with Chi squared for statistical significance of all of the *S.maltophilia* isolates in the "Most likely" category as being an excess compared to other bacterial species and found the result to be statistically significant (p.70) whereas none of the other species were significant. It is our understanding that none of these isolates were indistinguishable by strain typing which if a single source was considered to be likely then it would be expected that at least some of the isolates would be indistinguishable. The report draws attention to the cluster of *Stenotrophomonas maltophilia* cases in 2018 as being significant. The inclusion of these strains as having an environmental source greatly boosts the number presumed to have come from the environment as they have ignored the WGS typing data which by analogy with the Kampmeier et al. (2017) study would mean that there was no environmental source outbreak. There is also good evidence that the use of carbapenem antibiotics results in colonisation with *Stenotrophomonas maltophilia* as it is always resistant to carbapenems (Aitken et al. 2021). Due to a shortage of piperacillin-

tazobactam at this time, NHSGGC, like many other units had an increased usage of meropenem.

It is also not necessarily true that colonisation with *Stenotrophomonas* always comes from the hospital, as there are as many home environmental sources which have been shown in CF patients to be the source of colonisation (Denton et al. 1998). It is our opinion that this apparent increase in cases of BSI caused by *Stenotrophomonas maltophilia* does not represent an outbreak. The WGS typing which was performed on a significant number of BSI and environmental isolates showed that all the isolates were genetically distinct. As no BSI isolates were related to environmental isolates or even each other, then this is not what would be expected to be seen in an outbreak.

In 2017-18 there was a worldwide shortage of piperacillin/tazobactam which resulted in many units switching to carbapenem antibiotics. Piperacillin-tazobactam was used in the unit for empirical therapy of neutropenic sepsis and was therefore sometimes substituted by Meropenem. This resulted in an increased usage of meropenem around the time of the increase occurrence of *S. maltophilia*. The work of Aitken et al. (2021) provides a highly plausible explanation for the apparent increase in *S. maltophilia* BSI caused by unrelated strains as the patients will have acquired isolates from the environment in the home, gardens, food etc. as a result of being given meropenem. Meropenem exerts a strong selective pressure for colonisation with *S. maltophilia* because all isolates are resistant to the antibiotic. Because *S. maltophilia* is so widely distributed in the domestic and general environment the causative strains would not match those from the hospital environment as they are most likely to have been acquired from elsewhere.

There is no comparison of the overall rates of infection with other similar institutions which is very important. Comments about there being an excess of specific species associated with the environment would then be set in context as well as understanding whether there was actually an increase in infections during the period relative to other establishments. This is analysed in detail later in this report. The CNR report appears to be written from a preconceived view that environmental sources in the hospital resulted in most if not all of cases of BSI caused by Gram-negative bacteria which by virtue of their identification are presumed almost automatically to come from the environment. This is a dangerous assumption and, as shown above, is not supported by the literature and represents a flawed approach.

5. Water

5.1. Are hospital water systems sterile?

Hospital water systems are not sterile. In some specialist areas such as renal dialysis high quality water with low counts of environmental bacteria are supplied and necessary to prevent nosocomial infection. More recently it has become recognised that in intensive care units, operating theatres etc., generally referred to as augmented care areas, there should be a standard applied to reduce the number of *Pseudomonas aeruginosa* present in the water. Other bacteria are not as yet recognised by either legislation or guidance.

5.2. What constitutes a contaminated hospital water system?

All water distribution systems have bacteria present in them of varying numbers and species. Mains water as supplied to hospitals has to meet potable water standards as defined in the Public Water Supplies (Scotland) Regulations 2014. From a bacteriological perspective, water must contain zero colony forming units (CFU) per 100MLs of both *Escherichia coli* and *Enterococcus* spp.. These bacteria are used as indicators of human or animal faecal pollution of the water. The potential presence of these bacteria is used as a marker for the presence of dangerous human pathogens spread by faecal contamination such as *Salmonella typhi*, *Vibrio cholerae*, enterohemorrhagic *E. coli* etc.

Presence of other bacteria from soil, decaying plants etc. is permitted in potable water. Generally, these bacteria cause no harm to the vast majority of individuals in the population both in the community and in hospitals. The widespread presence of these bacteria is well recognised as evidenced by a study of Glasgow municipal drinking water collected from domestic taps (Khan et al. 2014). The investigators showed that the most frequently encountered genera of Gram negative bacteria (number of isolates) were: *Blastomonas* (9), *Acidovorax* (8), *Burkholderia* (6), and *Cupriavidus* (14).

These bacteria are not uniformly distributed in the hospital water system. They often rely on forming communities with other bacteria. Extracellular carbohydrates produced by the bacteria form a matrix called a biofilm, which protects the bacteria particularly from being washed away or dried out. This biofilm is macroscopically visible as a jelly-like coating particularly on surfaces such as rubber and plastic which act as a source of nutrients for the bacteria living in

the biofilm. It is often coloured green or black and to the untutored eye is dismissed as dirt. Water tanks and pipe work where flow rates are low tend to have more biofilm build up.

Water outlets in the clinical environment can be contaminated by bacteria arising from the supply (i.e. from water supplied by the water company) which is referred to as ingress contamination. Contamination which is brought into contact with the outlets of taps and shower heads is referred to as regression contamination Probably the most common method of the regression type of contamination occurs when the tap outlet is contaminated by immersion in water containing human derived material (e.g. wash water from a patient which may contain small amounts of urine, faeces, or worse, infected urine being emptied into a sink). Hospitals have strict rules on the disposal of such waste to prevent colonisation of water outlets in clinical areas, but under pressure they may not always be followed. The bacteria encountered in this setting are gut bacteria and sometimes skin bacteria although skin bacteria such as *Staphylococcus aureus* do not survive well in the environment whereas *E. coli*, *Klebsiella* spp. and other such organisms may survive as transient colonisers of the biofilm on the tap nozzle. The significance of this is that the tap in turn can act as a source to contaminate water that is drawn from the tap for use on patients or staff hands during hand washing. Exposure to the types of bacteria responsible for this colonization by healthy individuals carries no risk and indeed these bacteria almost invariably form part of the gut microbiome of such people. Furthermore, taps in domestic premises and non-clinical areas of hospitals are usually colonised. However, some groups of patients (such as those with neutropenia, immunosuppression, long term indwelling intravascular cannulas, respiratory tract intubation with mechanical ventilation, etc.) can infrequently become infected from these sources. It should be remembered that though one can find a source in a hospital environment of potentially pathogenic bacteria, without a route of transmission and a portal of entry into the patient these sources are of little consequence.

Sinks and their waste traps to prevent back flow of sewer gasses (usually referred to as U bends or P traps) always contain water and therefore large bacterial populations usually in a biofilm are present. Sometimes they are seen as the most important source of infections caused by Gram negative bacteria in wards with vulnerable patients (e.g. haematology, oncology, intensive care, neonatal and burns units). It is important to maintain a balanced view as just because bacteria of the same species can be found in these sites they are not necessarily the source of a bacteraemia caused by the same bacterial species in a patient located on the same

ward. *Klebsiella* spp. together with *Pseudomonas aeruginosa* and *Enterobacter* spp. are the bacteria most often identified as potential causes of outbreaks derived from sink traps. A recent review reported that *Pseudomonas aeruginosa* was the most frequently reported bacterium in studies involving presumed or positively identified environmental sources causing infection in hospital patients (41%) of studies (Kizny-Gordon et al. 2017). The authors drew attention to various limitations of the studies that they reviewed: failure in 60% of studies to identify prior admission colonisation, publication bias with focus on unusual organisms causing outbreaks and use of poorly discriminating strain typing techniques which potentially show erroneous identity of strains, so called pseudo-outbreaks. A recent study looked exhaustively at an intensive care unit over a two year time period. Using highly discriminatory Whole Genome Sequencing (WGS) strain typing to assess the role of sink traps as a source for *Pseudomonas aeruginosa*, the study concluded that "genome based typing revealed the contamination of patients by Pseudomonas aeruginosa originating from sink traps to be infrequent (1.5%) and that only 7.7% patients acquired *Pseudomonas aeruginosa* originating from another patient, suggesting that endogenously acquired infections are much more significant than those acquired from the environment" (Couchoud et al. 2023). In summary, although sink traps have a diverse and sometimes profuse bacterial population which is enriched sometimes by human derived materials and consequently bacteria associated with human colonisation or infection, they are not the dominant source of bloodstream infection when compared to gut and or oral microbiomes of immune compromised patients themselves.

5.3. If there was "widespread contamination" of the hospital water system (whether this was due to ingress contamination, regressional contamination, or contamination at installation and/or commissioning):

5.3.1. Would this be evident through water testing (routine testing required by guidance or additional testing not contained in guidance)?

In our experience significant problems of increased rates of infection caused by bacteria capable of coming from an environmental source are identified when intensive testing of water is undertaken when an outbreak is suspected, rather than from routine or prospective testing. In fact, routine testing in terms of guidance has only been recommended recently and is confined to looking for *E. coli*, *Legionella* and *Pseudomonas aeruginosa*. In addition, the total viable count bacteria identified in 100 mL of a water sample is also quantified. These

recommendations apply only to augmented care areas (ICU, neonatal ITUs etc.) and are essentially being used to ascertain whether this sort of testing in the longer term is going to be helpful in identifying environmental sources of infection in these highly vulnerable patients.

5.3.2. If so what would be the expected findings that would demonstrate that there is "widespread contamination"?

It has hopefully become clear from the explanation above when a water system is a source of environmental contamination and when there is spread to vulnerable patients it is generally not the whole system which has a high bacterial load. It is rather specific outlets such as tap outlets and sink traps which can be heavily colonised and therefore represent a potential source for spread to patients. One of the biggest problems is that almost all traps and very often tap outlets/shower heads have a positive culture for bacteria of the type referred to above, but it is the linking by strain typing (molecular being the most sensitive method) of that source with specific infections that is necessary to prove an association. The definitive evidence for linkage is to demonstrate that the DNA sequences (or part thereof - see below) of a micro-organism causing a BSI in a patient is indistinguishable to that of the same species of micro-organism found in the built microenvironment. This is not only essential for the understanding/identifying of an environmental source of risk to patients but also for ensuring there is not an overreaction to these possible sources of infection. The patient's own microflora in the gut is most frequently the source of the infection. Confusingly, patients may become colonised in the gut from various environmental sources not only in the hospital but also at home and in the general community.

When outbreaks involving a potential environmental source occur, molecular typing particularly using whole genome sequencing (WGS) and single nucleotide polymorphism (SNP) analysis usually demonstrate a clear cluster of a specific strain known as a sequence type (ST). A good example is the outbreak described by Niranjani et al. (2021) around a 58 bedded haematology oncology ward between 2018 and 2020 involving carbapenem resistant *Enterobacter cloacae* which produced the carbapenemase OXA-48. The presence of such a distinctive antibiotic resistance marker often draws attention in surveillance to a problem with clusters of infection. The authors used WGS assigning isolates to sequence types which is a highly discriminatory subtyping method which also permits further differentiation by looking at single nucleotide polymorphisms within other genes if necessary although usually sequence type fits very well with the epidemiology of the outbreak. A total of 41 patients over the time

period were colonised in the gut and nine of those patients developed bloodstream infection. There was no clear epidemiological link between the patients with OXA-48 producing *Enterobacter cloacae*, despite many having indistinguishable isolates. The typing of both patient and environmental isolates across the hospital revealed many ST types (ST66, ST231, ST27, ST90, and ST96) with a noticeable excess of ST66 isolates associated with the haematology oncology ward. The wastewater traps in 20 of 38 patients rooms were positive for OXA-48 producing Enterobacter cloacae, most being ST66. Disinfection of traps with the acetic acid and use of an autoclavable shower insert to reduce splashing from the water trap in showers was introduced as a control measure. Interventions terminated the outbreak and no further clusters of ST66 *Enterobacter cloacae* were detected. This study shows that when water traps are a significant source then WGS typing readily identifies a number of indistinguishable isolates in the traps. These isolates may be related to putative environmental sources with the potential of patient to patient transfer. In our experience, when clusters of infection occur caused by potentially environmentally sourced bacteria in immune supressed patients, investigation with detailed typing very often reveals a homogeneous cluster of strains and helps tremendously in identifying the source and introducing control measures.

5.4. If patients were at an increased risk of infection from the water system as a result:

5.4.1. Which types of organisms would be it be expected to see an increased rate of infection?

Generally, immunocompromised patients' infections are autogenous i.e. derived from their own microbiome. As described above, the types of bacteria derived from water systems seen causing infections in immunocompromised patients are of two types. The first group of bacteria that have a natural habitat of wet environmental sites and are often associated with plants, particularly roots (the microbial community intimately associated with plant rootlets is called the rhizosphere) and decaying vegetation and soil. This group of bacteria very rarely, if ever, cause infections in people with a normal immune system. The second group are bacteria, which although capable of surviving and growing in environmental sites, are also particularly well adapted to be human opportunistic pathogens. Some species such as *Pseudomonas aeruginosa*

are widely distributed in the general environment and are well recognised as plant pathogens. Recent WGS studies have demonstrated that the species consists of five separate sub-groups which are genetically distinct and represent evolutionary subdivisions known as clades (Freschi et al. 2019). However, all members of *Pseudomonas aeruginosa* can in the right setting cause disease in humans (Quiroz-Morales et al. 2023)

5.4.2. Are there any particular organisms that will be an indicative marker of there being an increased risk of infection from the water system?

Arguably the most reliable bacteria that are indicative of a contaminated water system are those that are highly associated with water as their natural habitat. The study of Glasgow domestic water supplies by Khan et al. (2014) cited above lists such bacteria, two genera of which were identified in the Case Note Review i.e. *Cupriavidus* and *Burkholderia*. In each case only two episodes of blood stream infections (BSI) were found in the entire time period of the Case Note Review. One of the *Cupriavidus* isolates was matched using WGS strain typing to an environmental isolate. This was the only example of highly probable transmission from the water system to a patient with subsequent development of infection. Another bacterial species belonging to this group would be *Stenotrophomonas maltophilia*. This bacterial species is most frequently found in soil and associated with plants, it is often a symbiote providing nutrients for the plant and sometimes protection from pathogens. It can rarely cause human infections, most notably in the immunocompromised and cystic fibrosis patients. The bacterium is intrinsically resistant to many antibiotics which is thought to particularly result in colonisation and subsequent infection when susceptible patients are given antibiotics.

The second group of bacteria, which although capable of surviving and multiplying in wet environmental sites, are more frequently seen as opportunistic bacterial pathogens and in some cases represent part of the normal gut microbiome of humans. Although frequently seen causing infections in immunocompromised patients they also can occur in a much wider range of patients, sometimes in those with normal immune systems. Commonly carried in the human, gut either as an indigenous member or transient coloniser the episodes of infection are either orthologous (arise from the patient's own flora) or by contamination of the ward environment from faecal carriage and subsequent spread by person to person transmission often on hands. Commonly encountered genera and species of these bacteria are *Pseudomonas aeruginosa*, *Klebsiella*, *Enterobacter* and *Serratia*.

5.4.3. Would it become evident by way of an increased rate of infection in the patient population as a whole?

We do not usually see an increase in infection rates across the whole of a hospital population. Invariably one sees local rises in particular physical locations or amongst particular groups of patients when there is nosocomial infection occurring. The most frequently used method in infection control of identifying a problem with hospital acquired infection, whether it be acquired from the environment or transmission amongst colonised or infected patients, is looking for unusual rises in the incident rate of infection. They are often described as clusters or exceedances from an expected average number of cases over a defined time period. Such clusters are seen with all of the common hospital acquired pathogens such as MRSA, *Clostridioides difficile*, *Klebsiella* etc.

The CNR made special note of the occurrence of two time periods when there appeared to be an increased frequency of bacteremia caused by *Stenotrophomonas maltophilia* in 2018 and 2019. During this time period, 16 of the total of 23 BSI cases which occurred during the whole five years were observed. They stated that 12 episodes occurred between Jan 2018 and Sept 2018 followed by none until 5 between April 2019 and Sept 2019 (there is a discrepancy as Table 4.3 only shows 4 cases in the second period). The review suggested that these infections were derived from an environmental source. A very similar episode, also initially thought to be ascribed to an environmental source, is reported in the literature from an allogeneic stem cell transplant unit in Germany (Kampmeier et al. 2017). In this case there were two 10 bed wards affected over a just a six month period. Four cases of BSI caused by *S. maltophilia* were reported. The yearly average for the unit was 0.5 BSI infections by *S.maltophilia*. Routine testing of the environment normally focused on aqueous sources for *Pseudomonas aeruginosa* and because of this increase in *S. maltophilia* testing was expanded to include that bacterium. Using WGS strain typing by identifying multi-locus sequence types (MLST; a form of ST typing) all the patient isolates were found to be very different unrelated types. This suggested that there was not a single environmental source for the cluster. However, one environmental isolate from a shower outlet was indistinguishable from a patient's isolate who had had an infection and had occupied the same room thus proving a route of transmission. The authors concluded that WGS MLST could be used to refute a large scale outbreak and also identify potential transmission events from the environment to patients.

The important lesson here is that not all clusters of *S. maltophilia* infections in immunocompromised patients are necessarily spread from an environmental source. It also demonstrates the power of WGS typing to identify highly related clusters of organisms coming from single sources. The reason for the relatively high rate of occurrence of *S. maltophilia* infections in haematology oncology patients is suggested by a large scale prospective study of bone marrow transplant patients over a substantial time (Aitken et al. 2021). The authors showed the progressive colonisation of AML patients during their induction treatment phase as a consequence of exposure to antibiotics, particularly carbapenems, the association being demonstrated to be statistically significant. The patients were often colonised in the nasaopharynx and developed infections with their own strains [autologous infection]. It seems most likely that as the patients spent substantial amounts of time at home as well as in the unit other sources in a domestic environment may well have resulted in their colonisation with *S. maltophilia*. Current understanding of the colonisation of patients by Antimicrobial Resistant (AMR) bacteria would suggest that their microbiome was damaged by the broad spectrum carbapenem antibiotics with loss of colonisation resistance. Indeed it has been shown in the case of cystic fibrosis patients that the same types of *S. maltophilia* causing their infection can be found both in domestic water outlets in their homes as well as in hospital water outlets (Denton et al. 1998).

In the case of *Pseudomonas aeruginosa* the CNR has classified it as a waterborne environmental pathogen with an estimated 70% of all Pseudomonas aeruginosa BSI infections derived from a ward environmental source. Unlike infections caused by Enterobacteriales and vancomycin resistant enterococci (VRE), which most frequently arise from prior gut colonisation (Liss et al. 2012), those caused by *P. aeruginosa* are less often preceded by gut colonisation (Nesher et al. 2015). The study looked at 794 allogenic haematopioetic stem cell transplant patients over a two year period. Of those patients 58/736 (7.3%) were colonised with 19 (32%) developing infection with an indistinguishable strain of *P. aeruginosa*. On the other hand, 37/736 non-colonised patients developed an infection with a presumed non-gut source, perhaps environmental. However, 19 of the total of 56 (34%) patients with *P. aeruginosa* infection during the study had a gut rather than an environmental source for their infection. In conclusion although *P. aeruginosa* may be found in the environment, often quite frequently, it is not always the sole source of infection which in itself is a relatively infrequent occurrence.

6. Ventilation

Ventilation refers to specific provision in a hospital to control the quality of the air, particularly in terms of airborne pathogens and air flow. This may vary from no specific intervention to specialised ventilation systems with filters and pressure gradients to direct air flow to minimise the burden of airborne pathogens, for example, high efficiency particulate air (HEPA) systems.

To understand the potential infection risk from an "inadequate or insufficient" ventilation system, it is first necessary to consider the various sources of pathogens that patients are exposed to. The major sources of infection are:

i. Patients themselves. Commensal skin and gut organisms can cause serious infections in the neutropenic setting. Gut translocation of Gram-negative organisms occurs due to damage to the lining of the bowel by chemotherapy, which is potentially life-threatening in a neutropenic patient. Normally harmless skin flora can enter the bloodstream via intravenous catheters.
ii. Airborne pathogens. These include viral, bacterial and fungal infections. Fungal spores, most notably *Aspergillus species* (*A. spp.).*, can be normal airway commensals and patients may come into hospital with such spores already present in the lung.
iii. Transmission of pathogens from visitors, other patients or healthcare workers.

In view of the key sources of infection, the management of risk is based on the following parameters:

i. Isolation – ideally in single rooms with *en suite* facilities (NICE Guideline 47).
ii. Infection control policies – use of handwashing, personal protective equipment (such as facemasks), restricted access to persons essential to the care of the patient, appropriate waste disposal etc.
iii. Clean air – requires a ventilation system with filters to remove airborne particles, including micro-organisms.
iv. Antimicrobial prophylaxis – use of antibiotics, antifungals, antivirals to prevent infection. There is a large body of data and guidelines addressing antimicrobial prophylaxis, particularly for the use of prophylactic antibiotics and antifungals (summarised in NICE Guideline CG151, Tissot F et al.). With respect to airborne pathogens, antifungals are most relevant, and a randomised controlled clinical trial has

shown the efficacy of Posaconazole in decreasing fungal infections in patients treated for AML (Cornely O et al. 2007).

v. Clinical monitoring – regular review by medical staff, multiple daily review by nursing staff/healthcare assistants.

vi. Use of laboratory tests and imaging modalities to aid in the early diagnosis of infection and allow early antimicrobial treatment.

vii. Screening - certain laboratory tests can be used as screening assays as an early warning to potential infection before the patient has clinical signs or symptoms.

viii. Guidelines – specifically, a written policy for "febrile neutropenia" (management of patients who are, or are expected to become, severely neutropenic – and who have developed a fever) and a system to ensure all relevant persons are aware of the guidelines. This is particularly relevant to patients with haematological cancers receiving intensive chemotherapy and/or haematopoietic stem cell transplantation (HSCT).

ix. Audit and microbiological monitoring – ongoing, continuous monitoring of laboratory-identified micro-organisms to follow changing epidemiological patterns and antimicrobial resistance. This data is centre-specific and informs the local febrile neutropenia guidelines.

Although it is self-evident, it is important to recognise that any ventilation system only offers protection against the airborne transmission of infectious diseases while the patient remains in the specially ventilated area. However, patients are frequently required to leave this protective environment, for example:

i. Investigations may require the patient to leave the isolation room (e.g. imaging, radiological and surgical procedures).

ii. Clinical deterioration may require the patient to move to another area for ongoing care (critical care, surgery).

iii. Imbalance between patient numbers and the availability of beds. It is frequently the case that patients must be managed for variable periods of time in wards/rooms not designed to HTM 03-01 specifications.

iv. Ambulatory care is routine in many centres in the UK and around the world. This involves managing patients, including those with AML who have received intensive chemotherapy, in Day Unit and hostel/hotel facilities (Halpern and Walter, 2020). By

intention, there is no provision with ambulatory care for an environment meeting HTM 03-01 specifications.

Further limiting the utility of hospital ventilation systems is the ubiquitous nature of some airborne infectious agents in the environment, namely, fungal spores of *A. spp.*, such that we all breathe in *A. spp..* spores every day. Therefore, all patients will already have such spores in the airways prior to coming into hospital and are re-exposed once they are discharged. The clinical relevance of this is only for the most immunocompromised patients, as other patients and healthy individuals do not develop infections from these fungal spores due to their intact immune defences.

Aspergillus infections can also be acquired from water sources. Drinking water is not sterile and contains *A. spp.* and individuals can be directly exposed to these organisms either through bioaerosols and water, after ingestion, inhalation, and skin contact, and through mucous membranes (Douglas et al. 2023; Richardson and Rautemaa-Richardson, 2019).

General guidance on building standards for inpatient facilities in the UK is covered by the Department of Health (DH) document Health Building Note 04-01. Specific guidance with respect to ventilation for healthcare facilities is covered in Scotland by SHTM 03-01 (parts A and B), which acknowledges the parent DH document HTM 03-01 (parts A and B). The relevant guidance for air-change rates and filters is found in Appendix 2 HTM 03-01 Part A. With respect to wards with neutropenic patients, the specifications are: air-change rate of 10/hour, a positive pressure gradient of +10Pa compared to the 'outside' ward/corridor, and HEPA filters (H12).

NICE Guideline 47 does not mandate the requirement for such standards: "Consider installing clean-air systems into isolation facilities for adults and young people who have haematological malignancies and are at risk of more than 7 days of neutropenia of $0.5x10^9$/litre or lower."

Joint Accreditation Committee ISCT-EBMT (JACIE) is the international authority that inspects and certifies all haematopoietic stem cell transplant (HSCT) centres. JACIE provides "minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures". The scope of JACIE inspection is broad and includes both inpatient and outpatient care. In practice, JACIE accreditation extends beyond HSCT activities alone and effectively is an indication of the whole activity of a haemato-oncology unit. Of particular relevance is JACIE standard B2.1, which is quoted in full below:

B2.1 There shall be a designated inpatient unit of appropriate location and adequate space and design that minimizes airborne microbial contamination.

Explanation:

Clinical unit facilities may vary among centers. Variability may be based on a number of factors, including the number and type (autologous or allogeneic) of transplants performed, the patient case mix, the cell source, epidemiological factors influencing the prevalence of opportunistic infections, and economic considerations.

This standard does not require that every clinical unit have laminar airflow availability, but HEPA filtration with positive pressure is recommended for high-risk patients. If non-HEPA filtered rooms are used for lower risk patients or if there is a shortage of HEPA filtered rooms, the SOP(s) on infection control, biosafety, and chemical and radiological safety should indicate how allocation of rooms is prioritized. Further, auditing of airborne microbial infections in non-HEPA rooms should be performed as part of the QM Program.

Evidence:

The inspector will tour the inpatient unit during the on-site inspection. Because different patients have different infection control needs, the Clinical Program must have policies and SOPs that define infection control requirements based upon differing patient conditions and room configurations. The type of air handling should be documentable from a facilities management office. An SOP detailing alternatives in case there is a shortage of isolation rooms; steps for preventing and controlling specific health care-associated infections, such as MRSA, C. Difficile, and community respiratory virus infections; and procedures for monitoring airborne infections will provide evidence of compliance.

Signs posted around the clinical unit and the behaviour of the staff consistent with expectations for the type of infection control described in the policies and procedures demonstrate compliance with this standard. If there are renovation or construction projects underway, the appropriate environmental controls must be present. The risk of spread of communicable disease agents must be minimized in any setting where patients could reasonably be expected to be (including dialysis or intensive care units). Care should be taken that the ventilation from other isolation rooms (where infected patients may reside) does not pass through the rooms used for recipients. Evidence of compliance with this

standard will require preinspection documentation of infection control policies, specifications of air handling, and floor plans.

When an accredited Clinical Program is to be relocated, qualification and validation must be performed to confirm the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT accreditation policies, which are available on the FACT website. The Clinical Program is expected to submit a description and floor plans of the new facility, QM documents, and an expected relocation date. If a JACIE-accredited facility intends to relocate, the program should submit plans and descriptions of the relocation to the JACIE office. Most relocations will be assessed during regularly scheduled inspections or interim audits; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):

If HEPA filtration with positive pressure is not available, single patient rooms should be located on a patient care unit where infection control policies can be implemented. Alternatively, portable, industrial-grade HEPA filters may be available to accommodate vulnerable patients in case of a shortage of rooms.

Visitors should receive information concerning communicable infections. Signs posted to inform the public about visitation restrictions could also include information about incubation periods and risks of live vaccines.

In ambulatory settings, patients may be accommodated in a hostel, hotel, or home-based setting for periods of the transplant with frequent day case review and potential rapid inpatient admission. Clinical Programs should share criteria with these facilities regarding practices to prevent the spread of communicable infections.

There are number of points to note:

i. No specifications are given for ventilatory requirements.
ii. HEPA filtration and positive pressure are recommended, but not mandated.

iii. Provision is made for the use of non HEPA rooms and/or a shortage of HEPA-filtered rooms. “If HEPA filtration with positive pressure is not available, single patient rooms should be located on a patient care unit where infection control policies can be implemented.”

iv. The on-site inspection includes assessment of infection control policies and air handling performance.

The value of protective room ventilation, such as HEPA filtration and positive pressure–directed airflow for haemato-oncology patients is unclear. A systematic review in 2006 reported on 16 trials (9 with death as an outcome and 10 with fungal infection as an outcome) that compared HEPA filtration with non-HEPA filtration. No significant advantages of HEPA filtration were found in the prevention of death among patients with haematological malignancies with severe neutropenia (Eckmanns T et al. 2006).

With respect to autologous HSCT, recent guidelines from the German Society of Hematology and Medical Oncology concluded that “The value of protective room ventilation such as high efficiency particulate air (HEPA) filtration, positive pressure–directed airflow or laminar airflow is not well established…” (Christopeit M et al. 2021). The authors cite the decreasing use of air-filtered rooms for such patients “as the incidence of filamentous fungal infections is extremely low” (Hicheri Y et al. 2013) and a prospective trial with 400 autologous HSCT patients that showed, “no significant impact of HEPA filtration on the incidence of pneumonia, including IFD*, or mortality…” (Vokurka S et al. 2014). [*IFD: invasive fungal disease]

It is clear that there remains uncertainty about the overall benefits of ventilation and filtration systems in the haemato-oncology patient group. While HTM 03-01 guidance standards are used in many centres, these are not mandated by NICE nor JACIE. While theoretically a SHTM 03-01 compliant ventilation system offers more protection against airborne pathogens than a non-compliant system, there is no clear evidence in the literature to support this in clinical practice. SHTM 03-01 specifications represent only one factor amongst many for managing the risk of infection. Furthermore, the impact of an “inadequate or insufficient” ventilation system on the risk of infection has to be considered in the context of the broad and complex approaches to minimise the risk of infection.

6.1. If the ventilation system in the hospital was inadequate or insufficient for patients:

6.1.1. How would this manifest itself in terms of an increased risk of infection?

It is clear that a ventilation system providing clean air is only one element that impacts on the risk of infection in the hospital environment. An "inadequate or insufficient" ventilation system could increase the risk of infection by airborne pathogens. While there is ample evidence that aerosol disease transmission occurs for viruses, bacteria and fungal spores (Aliabadi et al. 2011), it is the main route for diseases, such as tuberculosis (TB) and aspergillosis. In the context of hospitalised immunocompromised paediatric and adult patients with haematological, and other, cancers, the key concern is with respect to invasive aspergillosis (IA) involving the lungs – invasive pulmonary aspergillosis – as *Aspergillus* spores are ubiquitous in the environment.

For infections due to *A. spp.*, an increase in rates attributable to the ventilation system would suggest a failure in filtration and would manifest as a greater number of cases of invasive pulmonary aspergillosis or disseminated IA versus the expected number over time - measured in months to years - or alternatively, as an outbreak, or cluster, of cases in a specific location (i.e. a specific at-risk population) and time period.

For respiratory viral infections and TB, increased numbers of cases attributable to the ventilation system would suggest a failure in pressure gradients (i.e. not maintaining negative pressure) for infected patients admitted to hospital. However, infection control measures (see above) are far more important for limiting the spread of these infections in hospital.

6.1.2. Which types of organisms would it be expected to see an increased rate of infection from an inadequate or insufficient ventilation system?

No airborne pathogens were addressed in the Case Note Review.

The key indicator for an increased rate of infection related to an "inadequate or insufficient" ventilation system is infections due to *Aspergillus* species, and in particular invasive pulmonary aspergillosis. While viral and bacterial organisms can be brought into the hospital environment by patients, visitors and healthcare workers, fungal spores are ubiquitous in the environment. *Aspergillus* spores are well adapted to airborne dissemination and can be transported great

distances as airborne particles (Talento et al. 2019). The respiratory tract is the most common portal of entry and invasive pulmonary aspergillosis may then develop following inhalation of airborne fungal spores. A number of outbreaks of IA have been documented in healthcare settings from 1976 to 2022 (Vonberg and Gastmeier, 2006; Douglas et al. 2023) with haematology-oncology patients being the most commonly affected population. Fungal spore transmission via the airborne route is typical, with skin and soft tissue infections far less frequent. *Aspergillus fumigatus* followed by *Aspergillus flavus* are the most frequently encountered species. Hospital-acquired outbreaks of IA are a well-recognized complication of building work in or near hospital wards housing immunocompromised patients. However, there is no defined threshold for the airborne concentration of *Aspergillus* spores to indicate a protective environment and even very low concentrations have been associated with outbreaks (Vonberg and Gastmeier, 2006).

Therefore, the filtering of airborne organisms and air exchange functions of a ventilation system play a role in reducing the airborne burden of fungal spores, however, cannot eliminate the risk. While other pathogenic fungal species are also transmitted as airborne spores – for example, mucor species, *Fusarium* species – they are far less frequent than *Aspergillus spp.* as a cause of infection (at least in the UK).

6.1.3. Would this become evident by way of an increased rate of infection in the patient population as a whole or are there particular vulnerable patient groups where this may be more evident?

The risk of infection resulting from an "inadequate or insufficient" ventilation system would not be equal across all patient populations. Within a large hospital serving many different types of patients, the impact would be greatest in patients with the greatest degree of immunocompromise, either because of their underlying medical condition, the treatments they are receiving, or both. Therefore, any increase in infection rates due to airborne transmissible diseases would be most visible in these patients and one of the highest-risk populations is the group of patients with haematological, and other, cancers undergoing intensive chemotherapy and/or HSCT.

7. Water - analysis of infection rates and data from QEUH & RHC

7.1 Are the water testing results consistent with there being "widespread contamination"?

We have been provided with a comprehensive and detailed summary of the water testing results (Chaput DL, 2023). In assessing the level of contamination of the QEUH and RHC in relation to the BSI's recorded in the haematology-oncology patients we have focused on results relating to the following bacterial species: Enterobacteriales, *Pseudomonas aeruginosa* and other Gram negative bacilli as described in detail in the clinical significance and epidemiology section above. The reason for this is that these particular bacteria have been described as causing infections arising from an environmental source in highly vulnerable patients. It is important to distinguish between water testing that is mandated and that which is performed to explore water or wet sites such as sink drains sink traps etc as a possible source for presumed outbreaks relating to the environment. In trying to assess whether there is widespread contamination of the water system we are faced with the problem that all water systems have a bacterial load and there is no published and accepted threshold value for contamination that correlates with the development of an outbreak. This concept has been explained in detail in earlier sections of this report. However, *Pseudomonas aeruginosa* has been recognised as causing problems in augmented care units and following a number of outbreaks in such units, including a high profile episode in a Belfast neonatal unit the Department of Health produced recommendations for acceptable levels of *P. aeruginosa* in water on such units. These recommendations were adopted in Scotland and are described in an addendum to SHTM 04-01 (*Pseudomonas aeruginosa* routine water sampling in augmented care areas for NHS Scotland 2019). The interpretation of the counts of *Pseudomonas aeruginosa* colony forming units (CFU) per 100ml of water which has been membrane filtered and placed on a selective/differential agar medium and then incubated are as follows: <1 CFU/100 ml pass no action; 1-10 CFU/100 ml (pre flush) action to be taken and check post flush counts; >10 CFU/100ml re-test and risk assess taking out that outlet out of service; >100 CFU/ml remove outlet from service and institute remedial action.

Inspection of water testing results for *Pseudomonas aeruginosa* should give a good indication as to whether there was extensive contamination of the hospital water system and particularly in the high risk areas which includes the paediatric haematology-oncology wards. At the

QEUH, low level (frequency) testing for *Pseudomonas aeruginosa* of approximately an average of 20 samples per month was undertaken over the whole time only in the high risk areas. There was intensive sampling in December 2015 to March 2016 with 450 samples taken. Due to a transcription error for these sample results they suggested much higher counts than actually occurred, this was corrected in the report with the false results being shown in red. In November 2018 much higher rates of sampling were instituted with an average of 200 samples per month in high risk areas. Also basement tanks and 100 to 200 outlets in the general hospital were sampled as well. In the general areas only three samples of 3758 (0.08%) were positive using a threshold for positivity of 10 CFU/100 ml. In the high risk areas with a much tighter threshold of 1 CFU/100 ml only 69/6042 samples were positive (1.1%). In our experience this is a reassuringly low rate of colonisation of the water system with *Pseudomonas aeruginosa*.

In order to reach a conclusion as to whether there was widespread contamination we have looked at published studies in situations where monitoring for infections caused by environmental bacteria in vulnerable populations was undertaken in parallel with water testing. There are very few such studies, but two prospective research studies are helpful in reaching a conclusion in this area. The first is a French study of 10 ICU's (each with eight to 16 beds, average 9.9 beds) studied over a five month period (Coppry et al. 2020). Water samples were taken weekly from 233 taps and cultured for *P. aeruginosa* by filtration of 100 ml with a positive threshold of >1 CFU/100 ml. At the first sampling 51/233 (22%) taps were positive and 81/233 (35%) were positive at anytime during the study. At the QEUH the overall positivity rate for high risk areas was 69/6042 (1.1%). When the key wards data is examined of the 3985 samples taken only 64 (1.6%) were positive. This result is not consistent with there being widespread contamination of the water system with *Pseudomonas aeruginosa* in either the general hospital environment or the wards of special interest in haematology-oncology.

The other study that helps put the QEUH results into context is that by Halstead et al. 2021. The augmented care units (ACU) in four large English teaching hospitals (W, X, Y, Z) with a total of 23 distinct units were sampled three times in a 16 week study period. The hospital with lowest number of positive outlets for Pseudomonas aeruginosa was hospital Y (4.8-9.0%), the highest was W (25-28%). All of these values for positivity are well above those of QEUH. None of the hospitals in the study were described as having an ongoing outbreak of environmentally *Pseudomonas aeruginosa* infections. We conclude that the water testing

results for *Pseudomonas aeruginosa* in the QEUH do not support an opinion that the water system had widespread contamination.

7.2 Is there an increased level of infections consistent with there being "widespread contamination" of the water system?

As the environmental bacterial species discussed in this report generally only infect immunocompromised patients, we would not expect to see an increase in infections in the general hospital population.

7.2.1 Epidemiological review of incidence of bacteraemia by environmentally relevant species from available GGC data (Adults 2013-2023; Paediatric 2005-2022)

It is difficult, and often inappropriate, to compare numbers of cases of a possible healthcare associated infections (HCAI) between different hospitals, locations and/or wards without taking into account the volume of activity in a given hospital/location/ward. While incidence rates, which epidemiologically take into account number of people at risk for a health problem, use people as the denominator when we examine populations at risk as whole, for example when looking at incidence of seasonal influenza or COVID-19 infection; for HCAIs bed days have been deemed to be a better denominator for incidence. Bed days not only take into account numbers of people but also duration of stay and percent bed occupancy, which are also important factors in HCAI transmission either from person to person or the environment. For example, two comparable units could have the same number of people attend the unit in a given month, but the mean length of stay could be 1 day for unit A and 20 days for unit B, which would mean that unit B has both substantially more people in the unit on any given day, i.e., higher person density, and each person has a higher risk of coming into contact with a pathogen from the environment or another person due to duration of exposure. Therefore, bed days are the most appropriate denominator for incidence rates when examining HCAIs.

Examination of HCAI incidence is further complicated by a test's ability to detect an organism, clinical definitions of infection, organism properties, route of transmission, and general health status of the patient population. Haemato-oncology patients have a very high risk of infection

due to both health condition and treatment reducing the efficacy of normal immune functioning. Furthermore, growth of pathogens in blood samples, i.e., bacteraemia, is not always a true indicator of a bloodstream infection (BSI), as contamination of the blood culture can occur when collecting or processing samples. Therefore, retrospective analyses of blood cultures are not confirmatory of a BSI, and may overestimate true numbers of infections, which is most often true for microorganisms commonly found on human skin. Additionally, antimicrobial prophylaxis and treatment, if given prior to taking blood samples, may mask the growth of microorganisms resulting in failure to detect an infection that was originally present. Ineffective antimicrobial treatment could also result in the impression of repeated infections of the same organism in the same individual even though it could be the same infection that has never been cleared. Additionally, only some microorganisms that are detected in bacteraemia can survive, thrive and transmit through the environment, as opposed to human-to-human contact or infection in the bloodstream of an organism that normally resides in another isolated area on a human, such as the skin. Table 1 provides a list of organisms of environmental concern and possible sources (summarised from section 3 of the report) detected at NHS GGC Hospitals included in our analyses.

We reviewed all potential bacteraemia in adults and paediatric settings in the NHS GGC for Queen Elizabeth University Hospital (QEUH) and comparable hospitals, including all available data to examine bacteraemia incidence and compare any differences in trends. Paediatric and adult care settings were examined separately.

Table 1: Microorganisms grown in blood samples reported by the clinical laboratory between 2008-2023 for adult and paediatric patients at NHS GGC Hospitals that could be environmentally transmitted

ORGANISM OF ENVIRONMENTAL TRANSMISSION CONCERN			
Organism	**Potential Sources of Infection**	**Adult**	**Paediatric**
Achromobacter spp.	Contaminated liquids/ cleaning supplies	✓	✓
Acinetobacter spp.	Fomites, water, sink traps	✓	✓
Aeromonas spp	Water, food	✓	✓
Brevundimonas spp	Plants, drinking water	✓	✓
Burkholderia spp.	Plants, water, catheters	✓	✓
Cellulosimicrobium cellulans	Water, soil, fomites, person-to-person	✓	X
Chryseobacterium spp.	Plants, water, soil	✓	✓
Chryseomonas spp	Plants, water, soil damp environments	✓	✓
Citrobacter spp	Gut, soil, water, waste-water, surfaces	✓	✓
Comamonas spp.	Soil, water, waste-water, sludge, animal intestine	✓	X
Cryptococcus spp.	Plants, food, drinking water	X	✓
Cupriavidus spp	Soil, water, sink traps	✓	✓
Delftia spp	Soil, water, sink traps	✓	✓
Elizabethkingia spp.	Contaminated equipment, water	✓	✓

Enterobacter spp.	Sink traps, hospital environments	✓	✓
Klebsiella spp.	Intestine, sink traps, person-to-person	✓	✓
Leclercia adecarboxylata	Food, water, general environment	✓	✓
Morganella morganii	Intestine, person-to-person, fomites	✓	✓
Ochrpbactrum anthropi	Water sources	X	✓
Pantoea spp.	Soil, plants, water	✓	✓
Proteus spp.	Soil, water, urinary catheters	✓	✓
Pseudomonas spp.	Intestine, sink traps	✓	✓
Psychrobacter phenylpyruvicus	Ice, water, animal faeces, fish	✓	X
Ralstonia pickettii	Water, plants, soil	X	✓
Raoultella spp.	Water, soil, fish	✓	✓
Rhizobium radiobacter	Plants, agricultural soil	✓	✓
Rosemonas spp.	Water, soil, skin, hospital environments	✓	✓
Scopulariopsis brevicaulis	Vegetation, soil	X	✓
Serratia spp.	Intestine, hospital environments	✓	✓
Sphingomonas spp.	Water soil, shower heads, fomites	✓	✓
Stenotrophomonas maltophilia	Plants, soil, hospital environments	✓	✓

Table 2: Microorganisms grown in blood samples reported by the clinical laboratory between 2008-2023 for adult and paediatric patients at NHS GGC Hospitals that are not usually associated with an environmental source

ORGANISMS THAT ARE NOT ENVIRONMENTALLY TRANSMITTED					
Organism/Grouping	**Adult**	**Paediatric**	**Organism/Grouping**	**Adult**	**Paediatric**
Abiotrophia spp.	✓	✓	Gram-positive cocci	✓	✓
Actinomyces spp	✓	X	*Granulicatella spp.*	✓	✓
Aerococcus spp	✓	✓	*Haemophilus spp.*	✓	✓
Alliococcus spp.	✓	X	*Halfnia spp*	✓	✓
Bacillus spp	✓	✓	*Kocuria spp.*	✓	✓
Bacteriodes spp	✓	✓	*Lactobacillus spp.*	✓	✓
Bordetella spp.	X	✓	*Leptotrichia spp.*	✓	✓
Brevibacterium spp	✓	✓	*Leuconostoc spp.*	✓	✓
Campylobacter spp.	✓	✓	*Listeria spp.*	✓	✓
Candida spp	✓	✓	*Microbacterium spp.*	✓	X
Capnocytophaga spp.	X	✓	*Micrococcus ssp.*	✓	✓
Clostridium spp	✓	✓	Mixed coliforms/ coliforms	✓	✓
Corynebacterium spp.	✓	✓	Mixed organisms	✓	X
Cutibacterium spp	✓	X	*Moraxella spp.*	✓	✓
Dermabacter spp.	✓	X	Moulds	✓	X
Dermacoccus spp.	✓	✓	*Mycobacterium spp.*	✓	✓
Dietzia spp	✓	X	*Neisseria spp.*	✓	✓
Diphtheroid spp.	✓	✓	*Paenibacillus spp.*	✓	✓
Eggerthella lenta	✓	X	*Prevotella oris*	✓	X
Enterococcus spp.	✓	✓	*Propionibacterium spp.*	✓	✓
Escherichia spp.	✓	✓	*Rhodotorula mucilaginosa*	X	✓
Exophiala spp.	✓	X	*Rothia spp.*	✓	✓
Fusobacterium spp	✓	✓	*Salmonella spp.*	✓	✓
Gemella spp.	✓	✓	*Staphylococcus spp.*	✓	✓
Geotrichum spp.	✓	X	*Streptococcus spp.*	✓	✓
Globicatella spp.	✓	X	*Turicella otitidis*	✓	X
Gordonia spp.	✓	✓	*Veillonella parvula*	✓	X
Gram-positive baciili	✓	✓	*Weissella spp.*	✓	✓
Gram-negative baciili	✓	✓	Yeasts	✓	✓

7.2.2 Methods for analysing GGC bacteraemia data

Data on organism detections by patient, differentiated by coded identification number with name suppressed, and bed days was provided by NHS GGC for both adult and paediatric patients. To account for repeat testing, which is common in healthcare settings, especially to determine impact of treatment, organism detection by species were considered a new case if the patient had not had a positive detection for that organism within the prior 14 days. Counts of new organism cases were collated by month and year by species. Total case counts, as well as total counts of organisms with potential environmental transmission were added from individual organism counts. To generate incidence rates, monthly bacteraemia counts by species and total were divided by the bed days per month and year and multiplied by 1,000 to provide incidence rates by 1,000 bed days, which is a standard incidence for HCAIs.

For all organisms that had potential to be environmentally transmitted (Table 1), we examined potential epidemiological clusters by species, dates and locations and reported on these. Organisms that are not environmentally transmitted (Table 2) were only used to demonstrate relative abundance and patterns of bacteremia detected in this patient population. Possible clusters were examined by looking at all available data including bacterial species identified, hospital, consultant area, ward, and dates. Assessment of epidemiological clusters were identified as follows (Table 3):

- Did not cluster if they were from different hospitals or were ≥ 1 year apart in time even if they were from the same ward;
- Unlikely to cluster if they were from the same ward and ≥ 5 months apart or from different wards in the same hospital and ≥ 2 months apart in time;
- Possibly cluster if they are from the same ward in the same hospital and are >1-4 months apart in time or are from different wards in the same hospital and are ≤ 2 months apart in time; and
- Probably cluster if the cases are from the same ward and are ≤ 1 month apart in time.

While we understand that water systems are of concern to the inquiry, epidemiological evidence of clustering is still stronger based on ward location as environmental microorganisms tend to find niches where they thrive in micro-environments, such as a given location in a building complex e.g., a particular sink or drain trap. Generally widespread contamination is

more indicative of the larger environment, such as high levels of the microorganism circulating in the general environment or overall water supply.

Note "probable" epidemiological cluster is a qualitative definition; without molecular evidence, there is no way to confirm that two cases are a related as speciation of a microorganism is not sufficient evidence for clustering. These would be clusters that we would recommend investigating. Where available, all whole genome sequencing (WGS) data on microorganisms was reviewed to determine if qualitatively defined epidemiological clusters had further evidence of clustering.

Epidemiological clustering taxations were further assessed by looking at the (1) number per clustering category by hospital; (2) rate per clustering category by hospital using bed days as the denominator; and (3) score based on clustering category where did not cluster=0, unlikely to cluster=1, possibly clusters=2, and probably cluster=3. Denominators were taken into account to examine clustering burden over bed days occupied. Incidence per month of clusters (i.e., unlikely, possible, probable) were also calculated and graphed to demonstrate trends over time and comparisons to background historical data, as well as other hospitals. Differences in overall incidence of BSI attributable to environmentally relevant organisms, as well as incidence based on epidemiological clustering were statistically assessed using negative binomial regression models, which robustly assesses counts of cases controlling for bed days and can accommodate overdispersion in the data.

Table 3: Criteria for ranking clusters

Clustering Certainty	Definition
Probable	≥ 2 cases from the same ward ≤1 month apart in time or ≥ 2 cases from the same hospital but different wards in the same month
Possible	≥ 2 cases from the same ward between 2-4 months apparat in time or ≥ 2 cases from the same hospital but different wards ≤ 2 months apart
Unlikely	≥ 2 cases from the same ward ≥ 5 -11 months apart in time ≥ 2 cases from the same hospital but different wards ≥3 -11 months apart
Not clustered	Cases are from different hospitals or are ≥ 12 months apart in time even on the same ward

Adult Patients

For adult patients, data were examined both by consultant sector, BMT, North and South, and by months and years in which consultant section was assigned to either the QEUH or all other locations. Consultant sectors of South and BMT were attributed to QEUH as follows: the South sector became QEUH in May 2015 and remained part of QEUH through 2023 where data provided stops; BMT became part of QEUH for a period of approximately one and a half months across the months of June and July in 2015 and then from June 2018 onward. As bed days were only available by month and year all months where ½ or more of the days could be attributed to QEUH were included with QEUH and those months with less than half of the days attributable to QEUH were attributed to other hospitals. In order to examine differences in the transplant patients by hospital, incidence of bacteremia in BMT were also examine alone.

Paediatric Patients

For paediatric patients we compared the historic Yorkhill hospital data from 2005- May 2015 with more current data from the Royal Hospital for Children (RHC; June 2015-2022). Paediatric services moved from Yorkhill to the the QEUH site on 10 June 2015. As there were more patients at QEUH than Yorkhill in June 2015, that month was assigned to QEUH.

7.2.3 Bloodstream infections in adult patients in GGC January 2013-June 2023

Figures 1 and 2 show incidence of bloodstream infection (BSIs), both bacterial and fungal, in adult patients by month and year by consultant sector (Figure 1) or QEUH vs other hospitals in NHS GGC (Figure 2). These figures demonstrate overall high incidence of BSI, to be expected in a haemato-oncology population of patients, regardless of sector or hospital. Between the two figures we observe large spikes in incidence in September 2016, November 2019, and January 2023 corresponding to an uncharacteristically low number of bed days in each of those months reported by the South sector (Table 3). It is not clear if the low number of bed days is an error or real. Indeed, when we adjust the denominator for those that are unrealistically small in sensitivity analyses by taking the mean value of that month in every year and imputing it as the value for the unrealistically small number of bed days, we see those extreme peaks subside (Figure 3).

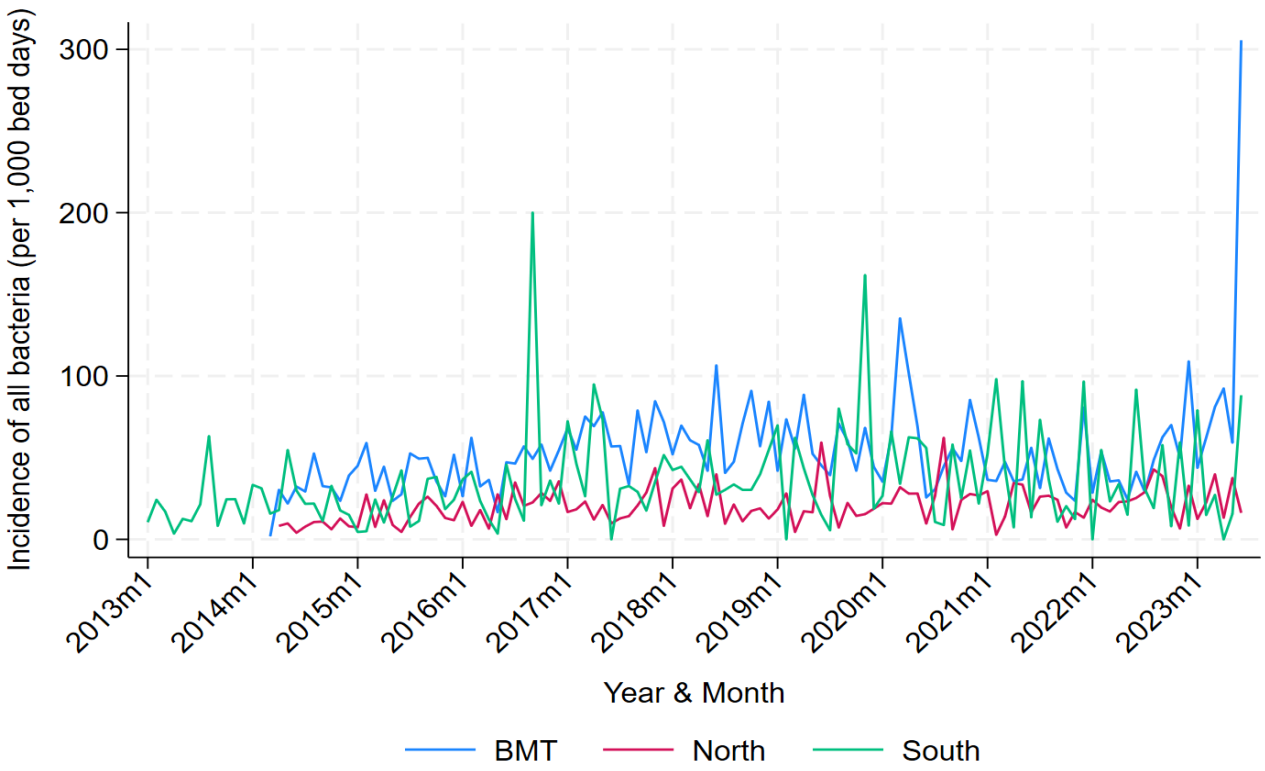


Figure 1: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by Consultant Sector

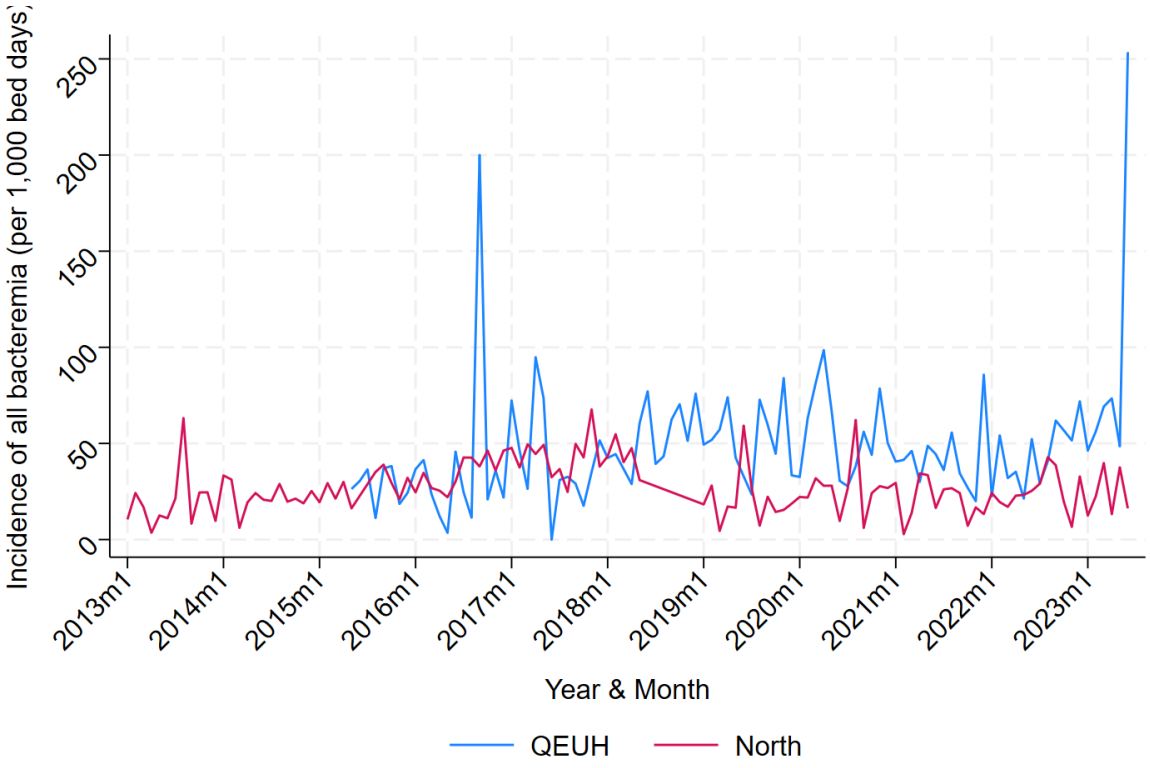


Figure 2: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by QEUH vs other hospitals in NHS GGC

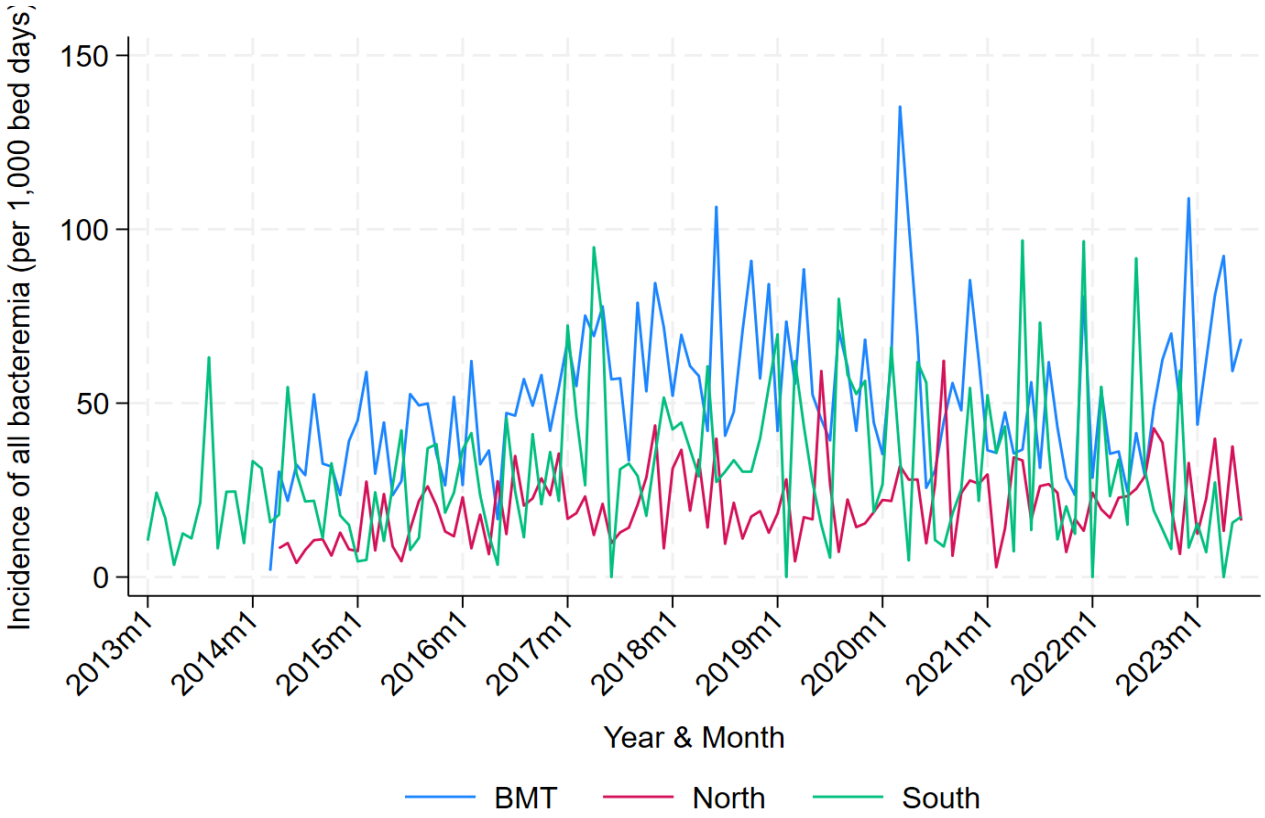


Figure 3: **Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by Consultant Sector with adjusted denominators based on average of other years for those denominators presented in red in Table 4**

Table 4: Bed days reported by sector and derived for hospital by month and year

	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec
Year	**BMT**											
2013	505	225	332	441	364	355	405	398	399	552	584	452
2014	457	405	558	429	502	526	478	476	491	472	764	563
2015	444	356	471	405	467	725	456	385	541	649	569	444
2016	454	467	617	522	481	424	668	527	487	482	523	440
2017	456	419	399	433	424	475	455	597	431	599	529	556
2018	576	402	544	519	738	310	689	547	381	451	508	368
2019	714	422	486	339	458	287	611	480	364	642	337	428
2020	481	638	207	187	188	741	555	515	466	584	328	321
2021	439	504	528	563	491	589	637	421	511	981	509	310
2022	490	260	536	360	651	435	554	577	368	457	619	404
2023	502	466	518	455	591	**108**						
Year	**North**											
2013	443	316	339	489	389	396	460	450	300	379	383	461
2014	385	398	277	363	307	495	386	472	460	488	548	251
2015	672	328	392	335	455	221	292	411	460	438	382	427
2016	523	483	390	304	472	404	316	341	354	317	255	338
2017	299	381	388	331	428	513	390	493	433	454	390	604
2018	417	328	524	385	491	377	522	562	271	402	422	314
2019	437	356	442	407	422	287	374	552	314	418	519	321
2020	406	366	282	250	214	206	301	193	327	331	288	410
2021	305	353	358	494	328	364	306	262	454	416	299	527

2022	495	308	587	438	258	355	379	257	388	456	451	244
2023	401	266	377	452	293	**185**						
Year	**South**											
2013	286	165	177	284	319	180	514	95	483	204	244	205
2014	210	96	254	447	183	234	230	365	267	214	226	334
2015	222	408	452	193	228	166	257	178	189	157	216	206
2016	191	145	170	246	283	197	162	262	**45**	191	167	137
2017	83	108	265	116	245	**12**	129	245	172	341	199	155
2018	212	135	109	173	99	183	99	238	99	231	251	146
2019	258	176	161	161	294	200	538	125	189	209	**68**	320
2020	225	106	235	**16**	97	143	94	114	69	119	92	137
2021	153	**51**	231	135	124	222	82	136	185	246	241	145
2022	130	128	215	207	332	120	98	209	**52**	124	118	236
2023	**38**	67	147	117	192	**34**						

Of note, overall bacteraemia is higher among QEUH patients compared with the Beatson and SGH GGC hospitals. As Figure 2 includes all bacteraemia, rather than just those caused by organisms that could be of environmental significance, this may be an indication of QEUH having patients with greater immune compromised status, as observed by the large drop in incidence at the other hospitals in 2018 when the bone marrow transplant unit moved to QEUH. However, it could also be an indication of greater testing for bloodstream infections or other policy differences at QEUH, such as antimicrobial polices that can have a significant impact on BSIs, particularly with specific organisms. Similar to results observed in Figure 3, we can also adjust the extremely small denominators observed in Table 4 by taking the mean of that month over all years and reduce the elevated peak in incidence (Figure 4), demonstrating a similar, yet higher incidence of overall bacteraemia among haemato-oncology patients at QEUH compared to other GGC hospitals over time.

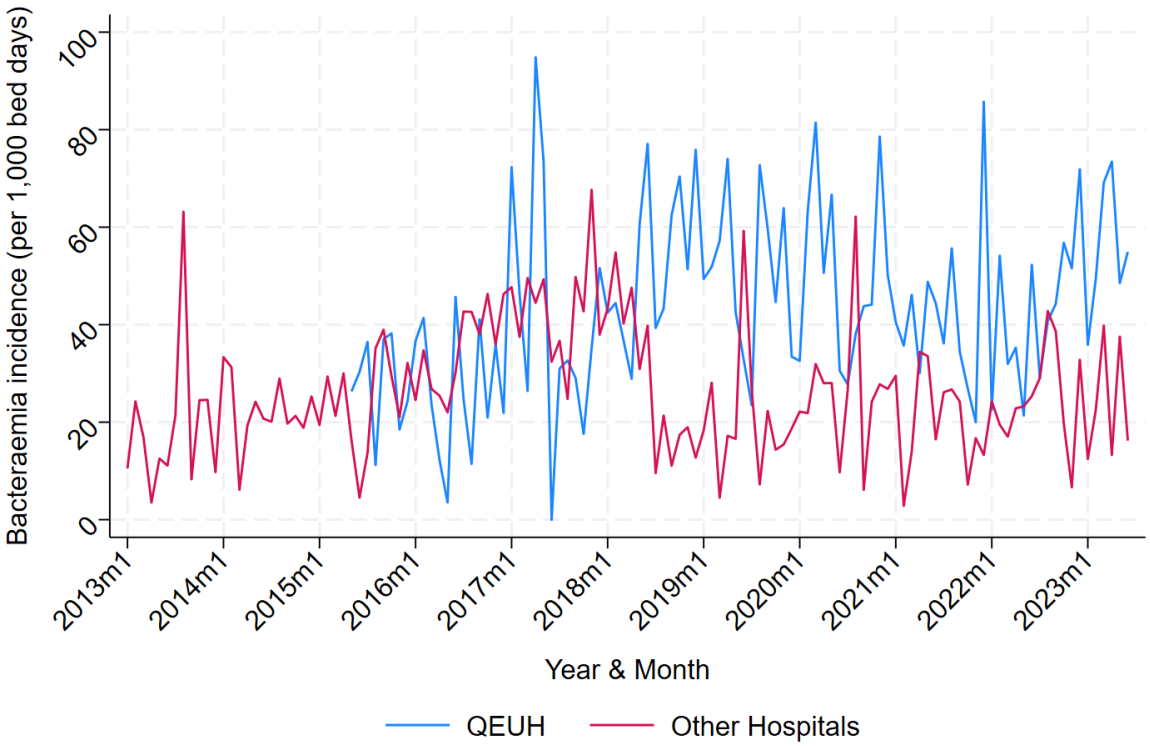


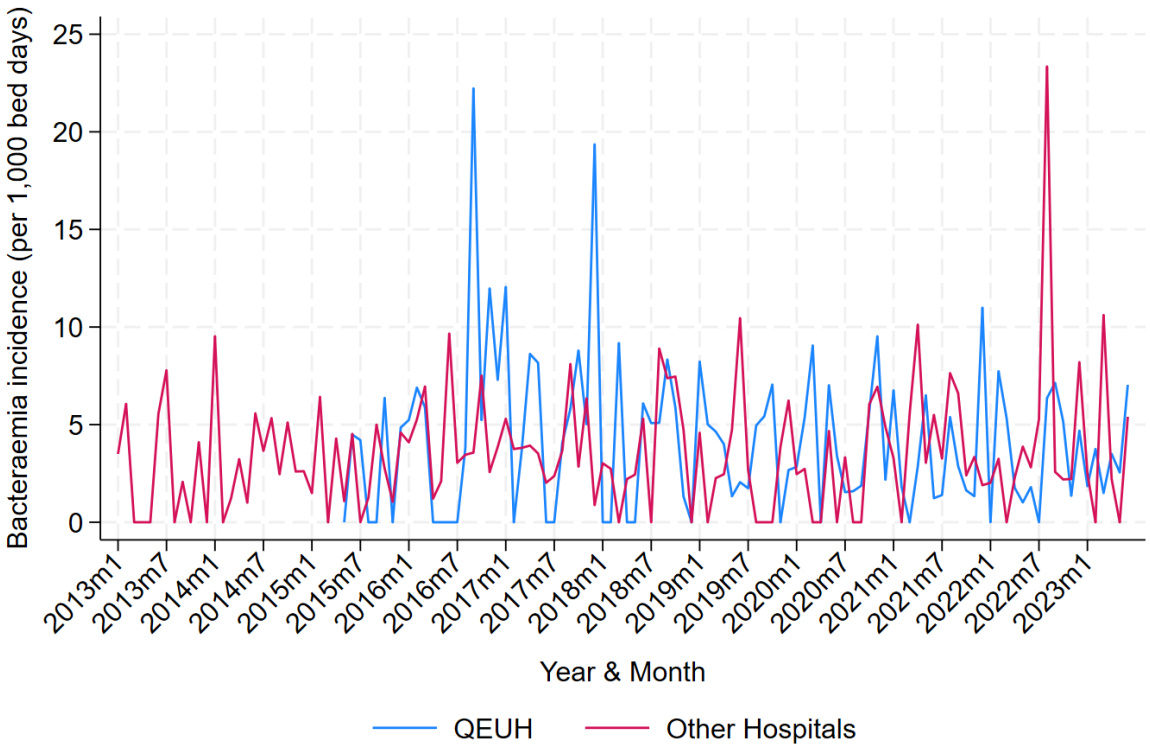
Figure 4: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by QEUH vs other hospitals in NHS GGC with adjusted denominators based on average of other years for those denominators presented in red in Table 4

7.2.3 Bacteraemia in adult patients in GGC January 2013-June 2023 with Potential Environmental Relevance

Organisms presented in Table 1 represent those of environmental interest, as they can survive in the environment, including water, and can subsequently be transmitted to patients or others in the environment, such as healthcare professionals. Consistent with section 3, while these organisms persist in the environment, many can also be found in the intestine of patients and in outbreaks are often transmitted between patients by healthcare professionals and via fomites (i.e., contaminated objects), due to inadequate infection control practices including insufficient hand hygiene. When observed contaminating the environment, these organisms are often found in niche locations, such as sink traps, rather than posing a risk to the overall environment.

Incidence of environmentally relevant organisms by QEUH vs other GGC hospitals (Figure 5) demonstrates similar incidence by month per year of environmentally relevant organisms, with the exception of both QEUH and other hospitals in GGC having period spikes in incidence. Of note, from mid-2016 to mid-2018, there appear to be a series of spikes in incidence at QEUH, however by mid-2018, incidence rates in both QEUH and other hospitals are similar, if not slightly higher at other hospitals. When we adjust for unrealistically small denominators,

predominantly from the South Sector, which moved to QEUH in May 2015 (Figure 6), we see a dampening effect in the spikes, with a single possible true spike in incidence at QEUH in early 2018 followed by significantly lower incidence for the remainder of the time period. This suggests that there may have been an overall brief spike in incidence compared to background at QEUH at this time, with constant and relatively low incidence following, and even a possible reduction in incidence from 2022 onward of bacteraemias attributable to microorganisms that can persist in the environment. In comparison, incidence of these microorganisms at other GGC hospitals (i.e., Beatson and SGH), occasional spikes are also observed.



<u>Figure 5</u>: Incidence of bacteraemia from organisms that could be environmentally transmitted by QEUH vs other NHS GGC hospitals

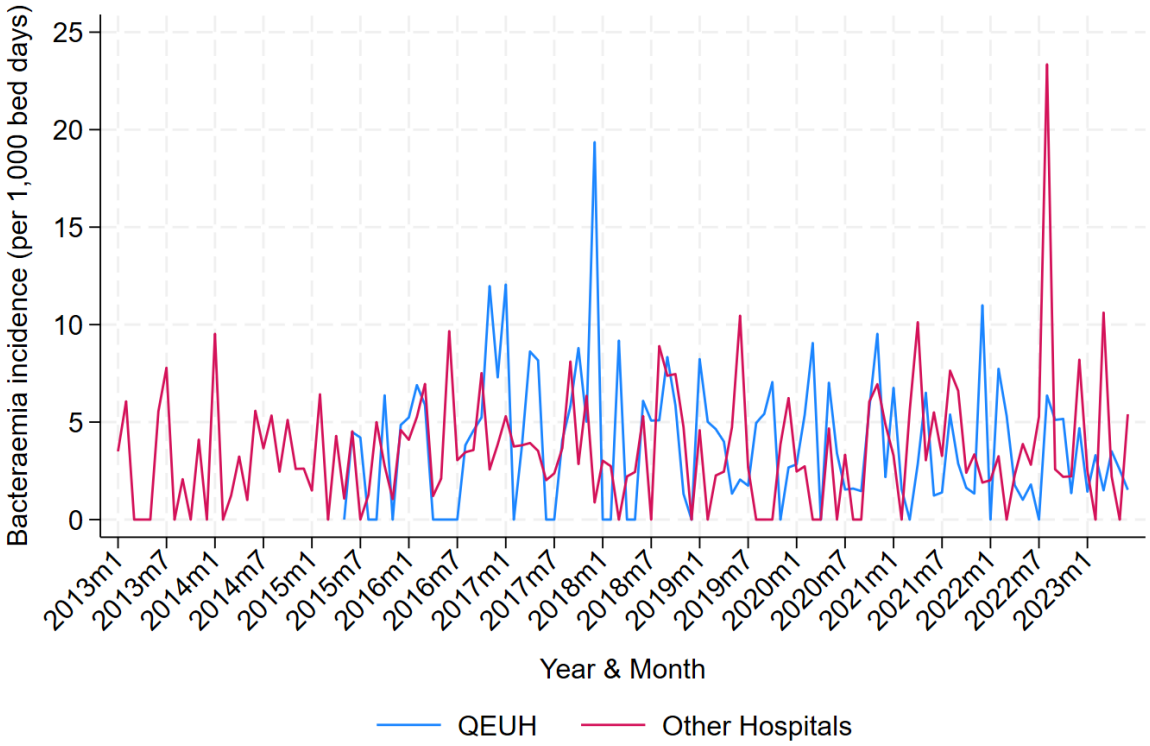


Figure 6: Incidence of bacteraemia from organisms that could be environmentally transmitted by QEUH vs other NHS GGC hospitals with adjusted denominators based on Table 4

7.2.3 Bacteraemia with potential environmental relevance in adult patients in the GGC by species type

When we examine organisms of environmental interest by species to determine the presence of clustering using epidemiological criteria presented in Table 3, we did not observe a consistent pattern of potential clustering, although we did identify small potential clusters in both QEUH and other hospitals in NHS GGC (Tables 5A-D, 6, 7, and 8). Growth of *Achromobacter spp., Aeromonas spp., Brevundimonas spp., Burkholderia spp., Cellulosimicrobium spp., Chryseobacterium spp.,* and *Chryseomonas spp.* were uncommon in blood cultures and none of these organisms appeared at unexpected incidence by consultant sector or hospital. Patients from the bone marrow transplant unit represented a large proportion of cases attributable to these types of bacteraemia, which is not unexpected given their immune compromised state (Table 5A).

While there were 28 incident bacteraemias with *Acinetobacter spp.* isolated, these represented 6 different species and some unspecified. These were distributed across QEUH vs other hospitals with near equal number of cases (Table 5A). *A. ursingii* was the most commonly

isolated from blood cultures, occurring at near equal numbers over time between QEUH and other GGC hospitals.

Table 5A: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location

Species	# Cases	Consultant Sector	QEUH	Year	Month	Location	Cluster
Achromobacter xylosoxidans	1	BMT	✓	2016	Feb	Ward B8 Beatson	No
Achromobacter spp. (undefined)	1	BMT	✓	2019	Mar	Bone Marrow Transplant	No
Acinetobacter baumanni	2	South	X	2013	July	Ward 24 SGH	Unlikely
		South	X	2014	Jan	Haematology Day Unit	Unlikely
Acinetobacter calcoaceticus	1	South	✓	2022	Feb	Haematology Day Unit	No
Acinetobacter haemolyticus	1	South	✓	2021	Jan	Ward 4CH	No
Acinetobacter lwoffii	4	BMT	X	2017	July	Ward B9 Beatson	Unlikely
		BMT	X	2018	Apr	Ward B8 Beatson	Unlikely
		BMT	✓	2018	Oct	Bone Marrow Transplant	No
		BMT	✓	2021	Oct	Bone Marrow Transplant	No
Acinetobacter radioresistens	1	BMT	✓	2023	Jun	Bone Marrow Transplant	No
Acinetobacter ursingii	13	South	✓	2015	Oct	Ward 4B2	No
		BMT	X	2016	Oct	Ward B8 Beatson	Unlikely
		BMT	X	2017	Jun	Ward B9 Beatson	Possible
		BMT	X	2017	Aug	Ward B8 Beatson	Possible
		BMT	✓	2018	Aug	General OP	Possible
		South	✓	2018	Aug	Ward 4CH	Possible
		North	X	2018	Aug	Ward B6 Beatson	Unlikely
		BMT	✓	2019	Jan	Bone Marrow Transplant	Possible
		North	X	2019	Jan	Oncology Assessment	Unlikely
		BMT	✓	2019	July	Bone Marrow Transplant	Possible
		BMT	✓	2019	Sept	Bone Marrow Transplant	Possible
		Norh	X	2021	Apr	Ward B7 Beatson	No
		BMT	✓	2023	Aug	Bone Marrow Transplant	No
Acinetobacter spp. (undefined)	6	North	X	2015	Oct	McMillan DCU	Possible
		North	X	2015	Dec	Ward B7 Beatson	Possible
		BMT	✓	2018	Aug	Haematology Day Unit	Unlikely
		BMT	✓	2019	Mar	Bone Marrow Transplant	Possible
		BMT	✓	2019	Aug	Bone Marrow Transplant	Possible
		BMT	✓	2022	Mar	Bone Marrow Transplant	No
Aeromonas hydrophila/ caviae	1	BMT	✓	2022	Oct	Bone Marrow Transplant	No
Brevundimonas vesicularis	2	BMT	X	2016	Sept	Ward B8 Beatson	Unlikely
		BMT	X	2017	Mar	Ward B8 Beatson	Unlikely
Burkholderia cepacia	2	South	X	2014	Jun	Ward 24 SGH	No
		BMT	✓	2019	July	Bone Marrow Transplant	No
Cellulosimicrobium cellulans	1	BMT	✓	2020	Feb	Bone Marrow Transplant	No
Chryseobacterium spp.	1	BMT	✓	2015	July	Ward B9 Beatson	No
Chryseomonas indologenes	4	BMT	X	2014	Jun	Ward B8 Beatson	No
		North	X	2017	Oct	Ward B7 Beatson	No
		BMT	✓	2018	July	Haematology Day Unit	No
		BMT	✓	2022	Aug	Bone Marrow Transplant	No

Table 5B: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Species	# Cases	Consultant Sector	QEUH	Year	Month	Location	Cluster
Citrobacter freundii	1	South	✓	2021	Jan	Ward 4CH	No
Citrobacter koseri	5	South	✓	2017	Dec	Ward 4B	No
		BMT	X	2018	Jan	Ward B9 Beatson	No
		BMT	✓	2020	Aug	Bone Marrow Transplant	No
		North	X	2020	Nov	Ward B7 Beatson	No
		North	X	2022	May	Haematology Day Unit	No
Citrobacter werkmanii	1	North	X	2019	Nov	Ward B6 Beatson	No
Comamonas spp.	1	BMT	✓	2019	Oct	Bone Marrow Transplant	No
Cupriavidus pauculus	3	North	X	2015	Dec	Oncology Assessment	No
		South	✓	2015	Dec	Haematology Day Unit	No
		North	X	2020	Jan	Ward B7 Beatson	No
Delftia acidovorans	6	BMT	X	2016	Feb	General OP	No
		BMT	X	2017	Apr	General OP	Unlikely
		BMT	X	2017	July	Ward B6 Beatson	Unlikely
		BMT	X	2017	Dec	Ward B9 Beatson	Unlikely
		South	✓	2018	Mar	Ward 4B	Unlikely
		BMT	✓	2019	Feb	Bone Marrow Transplant	Unlikely
Elizabethkingia miricola	2	North	X	2018	Oct	Ward B6 Beatson	No
		North	X	2021	Oct	Ward B7 Beatson	No
Enterobacter aerogenes	2	BMT	X	2015	Jan	Ward B9	Probable
		BMT	X	2015	Feb	Ward B9	Probable
Enterobacter hormaechei	2	South	✓	2017	Sept	Ward 4C1H	Possible
		South	✓	2017	Nov	Haematology Day Unit	Possible
Klebsiella oxytoca	27	South	X	2013	Feb	Ward 24	Possible
		South	X	2013	July	Ward 24	Possible
		BMT	X	2014	Aug	Ward B9	Probable
		BMT	X	2014	Aug	Ward B9	Probable
		North	X	2014	Nov	HaemOnc Secreta	No
		BMT	X	2015	Sept	Ward B5	No
		BMT	X	2016	Mar	General OP	Probable
		BMT	X	2016	Mar	General OP	Probable
		BMT	X	2016	Mar	Ward B8	Possible
		North	X	2016	May	Ward B5	Possible
		BMT	X	2016	Jun	Ward B8	Possible
		BMT	X	2016	Jun	Ward B9	Possible
		South	✓	2016	Dec	Ward 4CH	Unlikely
		South	✓	2017	May	Ward 4CH	Unlikely
		North	X	2018	Aug	Ward B6	No
		BMT	✓	2018	Oct	Bone Marrow Transplant	No
		South	✓	2020	Nov	Ward 4CH	Possible
		South	✓	2021	Jan	Ward 4CH	Possible
		BMT	✓	2021	May	Bone Marrow Transplant	Probable
		BMT	✓	2021	Jun	Bone Marrow Transplant	Probable
		North	X	2021	Jun	Ward B7	No
		BMT	✓	2021	July	Bone Marrow Transplant	Probable
		BMT	✓	2021	Aug	Bone Marrow Transplant	Probable
		BMT	✓	2021	Sept	Bone Marrow Transplant	Probable
		North	X	2023	Mar	Haematology Day Unit	No
		BMT	✓	2023	July	Bone Marrow Transplant	Probable
		BMT	✓	2023	July	Bone Marrow Transplant	Probable
Klebseilla varicola	1	BMT	✓	2022	Oct	Bone Marrow Transplant	No

Table 5C: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Species	# Cases	Consultant Sector	QEUH	Year	Month	Location	Cluster
Leclercia adecarboxylata	1	BMT	X	2015	July	Ward B8 Beatson	No
Morganella morganii	3	North	X	2016	May	Ward B7	Unlikely
		BMT	X	2016	Aug	Ward B8	Unlikely
		BMT	✓	2020	Nov	Bone Marrow Transplant	No
Pantoea agglomerans	12	South	✓	2016	Jan	Ward 4B2	No
		BMT	X	2017	May	Ward B8	No
		BMT	X	2018	Apr	Ward B8	Possible
		North	X	2018	May	Ward B7	Possible
		South	✓	2018	Jun	Ward 4B	Unlikely
		BMT	✓	2018	Sept	Bone Marrow Transplant	Unlikely
		South	✓	2020	Jan	Ward 4CH	Possible
		North	X	2020	Feb	Ward B5	No
		South	✓	2020	Mar	Ward 4CH	Possible
		North	X	2021	Apr	Haemophilia Unit	Possible
		North	X	2021	Apr	Ward B5	Possible
		BMT	✓	2022	Sept	Bone Marrow Transplant	No
Proteus mirabilis	2	South	✓	2018	Nov	Ward B7	No
		North	X	2019	Oct	Ward 4CH	No
Proteus vulgaris / penneri	1	BMT	X	2016	Jun	Ward B9	No
Pseudomonas fluorescens	3	North	X	2016	Jun	Oncology Assessment	No
		North	X	2021	Apr	Ward B7	No
		BMT	✓	2021	Dec	Bone Marrow Transplant	No
Pseudomonas luteola	1	North	✓	2023	Mar	Ward B7	No
Pseudomonas oryzihabitans	7	South	X	2015	Apr	Ward 24 SGH	No
		BMT	✓	2018	Aug	Bone Marrow Transplant	Possible
		BMT	✓	2018	Sept	Haematology Day Unit	Possible
		BMT	✓	2019	Jan	Bone Marrow Transplant	Possible
		South	✓	2019	Jan	Ward 4CH	Possible
		BMT	✓	2019	Oct	Bone Marrow Transplant	Unlikely
		North	X	2021	July	Haematology Day Unit	No
Pseudomonas putida	5	South	X	2014	June	Ward 24 SGH	No
		BMT	X	2014	July	Ward B8 Beatson	No
		North	X	2021	May	Ward B7	No
		South	✓	2022	June	Ward 4CH	Unlikely
		South	✓	2023	Mar	Ward 4CH	Unlikely
Pseudomonas stutzeri	1	BMT	X	2017	May	Ward B8	No
Psychrobacter phenylpyruvicus	1	BMT	✓	2023	Feb	Bone Marrow Transplant	No
Raoultella ornithinolytica	2	BMT	X	2016	Jan	Bone Marrow Transplant	No
		North	X	2020	Mar	MacMillan DCU	No
Raoultella planticola	1	BMT	X	2015	Sept	Ward B9	No
Raoultella terrigena	1	BMT	✓	2019	Jan	Bone Marrow Transplant	No
Rhizobium radiobacter	2	BMT	✓	2017	Aug	General OP	Unlikely
		BMT	✓	2018	May	Ward B8	Unlikely
Roseomonas gilardii	3	BMT	X	2016	Jan	Ward B9	Unlikely
		BMT	X	2016	Oct	Ward B8	Possible
		BMT	X	2016	Nov	Ward B9	Possible

Table 5D: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Species	# Cases	Consultant Sector	QEUH	Year	Month	Location	Possible Cluster
Roseomonas mucosa	10	North	X	2017	Aug	Ward B7	Possible
		BMT	X	2017	Oct	General OP	Possible
		BMT	X	2017	Nov	Ward B8	Possible
		BMT	✓	2018	Aug	Bone Marrow Transplant	Probable
		BMT	✓	2018	Sept	Bone Marrow Transplant	Probable
		North	X	2019	Dec	Ward B7	No
		BMT	✓	2021	Apr	Bone Marrow Transplant	Unlikely
		BMT	✓	2022	Dec	Bone Marrow Transplant	Unlikely
		BMT	✓	2023	Apr	Bone Marrow Transplant	Possible
		BMT	✓	2023	Aug	Bone Marrow Transplant	Possible
Serratia grimesii	2	North	X	2021	Apr	Ward B7	No
		BMT	✓	2023	Apr	Bone Marrow Transplant	No
Serratia liquefaciens	4	BMT	X	2014	Aug	Ward B9	Unlikely
		North	X	2015	June	MacMillam DCU	Unlikely
		BMT	✓	2020	Feb	Bone Marrow Transplant	No
		North	X	2023	Mar	Ward B7	No
Serratia marcescens	9	North	X	2016	Nov	Ward B7	No
		North	X	2018	Oct	Ward B6	Unlikely
		North	X	2019	Jan	Oncology Assessment	Unlikely
		BMT	✓	2019	May	Bone Marrow Transplant	No
		North	X	2019	Dec	Ward B4	Unlikely
		North	X	2020	Nov	Haematology Day Unit	Unlikely
		North	X	2021	Aug	Ward B7	Unlikely
		North	X	2022	Dec	Haematology Day Unit	Unlikely
		North	X	2023	July	Ward B7	Unlikely
Serratia plymuthica	1	BMT	X	2016	June	Ward B8	No
Sphingomonas paucimobilis	4	BMT	X	2014	Aug	Ward B9	No
		BMT	X	2017	Sept	Ward B8	No
		BMT	✓	2018	July	Bone Marrow Transplant	No
		BMT	✓	2020	Feb	Bone Marrow Transplant	No

Bacteraemia with growth of *Citrobacter spp., Comamonas spp., Cupriavidus spp., Delftia spp., Elizabethkingia spp., Enterbacter spp.* were uncommon among adult haemato-oncology patients across hospitals, with no apparent clustering by hospital (Table 5B). As *Cupriavidus spp.* were considered important as potential environmental pathogens that may have contaminated the QEUH, these were investigated via whole genome sequencing (WGS). One of the three *Cupriavidus* adult bloodstream infections was sequenced, demonstrating that a paediatric case on another ward two years prior was the closest match, but these were 144 SNPs apart, so were not related (Table 9). There were 28 cases of bacteraemia with *Klebsiella spp.* growth, predominantly *Klebsiella oxytoca*, with nearly equal representation by QEUH vs other hospitals.

Similarly, *Leclercia spp., Morganella spp., Proteus spp., Psychrobacter spp., Roultella spp.* and *Rhizobium spp*. were uncommonly detected among bacteraemia cases (Table 5C) and with

no apparent pattern by QEUH vs other hospitals. In contrast there were 12 bacteraemias attributed to *Pantoea agglomerans*, occurring in all sectors and at both QEUH and other hospitals. There were 17 bacteraemias attributable to *Pseudomonas spp*. across six different species and while fairly evenly distributed across QEUH vs other hospitals, QEUH had more *Pseudomonas oryzihabitans* bacteraemias, while the North Sector had more *Pseudomonas putida* and *Pseudomonas fluorescens* bacteraemias; however, with such small numbers of bacteraemia attributed to these organisms a significant pattern could not be established.

There were 13 bacteraemias with *Rosemonas spp*. detected (Table 5C & 5D), with all cases of *Roseomonas gilardii* identified in the North Sector bone marrow transplant unit while it was at a hospital prior to QEUH and a near equal representation of *Roseomonas mucosa* between North/BMT at another hospital and BMT at the QEUH. Among the 16 cases of bacteraemia attributed to *Serrati spp.* all but three occurred at a hospital other than QEUH, however, according to qualitative assessment of clustering, these were mostly unlikely to cluster (Table 5D). *Sphingomonas paucimobilis* was uncommon among bacteraemias.

The three most common organisms of environmental relevance detected in bacteraemias were *Enterobacter cloacae* (N=33), *Pseudomonas aeruginosa* (N=32), *Stenotrophomonas maltophilia* (N=45), which is consistent with organisms identified among haemato-oncology patients. Examining bacteraemia attributed to *Enterobacter cloacae/cloacae complex*, 17 cases occurred at QEUH and 16 at other GGC hospitals (Table 6). For cases isolated at QEUH, two had no cluster identified by epidemiological criteria, 6 were unlikely to cluster, 5 had a possible cluster assignment and 4 a probable cluster assignment. In comparison, for the 16 cases from other hospitals (i.e., Beatson and SGH), 4 had no cluster assignment, 2 were unlikely, 8 were possible and 2 were probable. There were no whole genome sequencing (WGS) or other data comparing any of these *Enterobacter cloacae/cloacae complex* cases with the environment or one another (Table 9); however, WGS data for *Enterobacter spp.* did demonstrate a lack of evidence of clustering except for two cases in adjacent paediatric wards, with no sufficient evidence an environmental source of infection for the two cases (see report on Enterobacter related infections by Professor T Evans). Without additional evidence, cases of bacteraemia attributable to *Enterobacter cloacae* appear to be similar over time between QEUH and Beatson or SGH hospitals, suggesting an expected presentation of cases, which is consistent with the incidence data in Figure 5 that includes all bacteraemia from environmentally relevant samples.

Among bacteraemia cases attributed to *Pseudomonas aeruginosa* 13 were isolated from patient at QEUH and 19 were isolated from patients at other GGC hospitals (Table 7). Among cases from QEUH 2 were not assigned clustering, 4 were unlikely, 5 were possible, and 2 were probable. In contrast among those from other hospitals 8 were classified as unlikely, 9 possible and 2 probable. These data demonstrate both a slightly higher number of cases from outside of QEUH and with a greater likelihood of clustering. No WGS data were available for *Pseudomonas spp.* limiting our ability to determine if qualitative likelihood of clustering is indicative of true clusters. These data suggest that there is no evidence of elevated contamination of the environment by pseudomonas compared to other GGC hospitals at QEUH.

Table 6: *Enterobacter cloacae* bacteraemia by consultant sector, hospital, date and location (N=33)

Consultant Sector	QEUH	Year	Month	Location	Cluster
BMT	X	2014	Mar	Ward B9 Beatson	Unlikely
South	X	2014	Apr	Ward 24 SGH	No
BMT	X	2014	July	Ward B8 Beatson	Possible
BMT	X	2014	Sept	Ward B8 Beatson	Probable
BMT	X	2014	Oct	Ward B8 Beatson	Probable
BMT	X	2014	Dec	Ward B8 Beatson	Possible
BMT	X	2015	Feb	Ward B9 Beatson	Possible
BMT	X	2015	Feb	Ward B8 Beatson	Possible
South	✓	2015	July	Ward 42B	No
BMT	X	2016	Jan	Ward B8 Beatson	Possible
BMT	X	2016	Mar	General OP	Possible
South	✓	2016	Sept	Ward 4CH	Probable
South	✓	2016	Oct	Ward 4CH	Probable
BMT	X	2017	Feb	Ward B8 Beatson	Unlikely
South	✓	2017	May	Ward 4CH	Unlikely
South	✓	2017	Oct	Ward 4C1H	Possible
South	✓	2017	Dec	Ward 4B	Possible
BMT	✓	2018	June	Ward B8 Beatson	Unlikely
South	✓	2019	Jan	Ward 4CH	Unlikely
North	X	2019	Mar	Ward B6 Beatson	No
BMT	✓	2019	Apr	Bone Marrow Transplant	Possible
BMT	✓	2019	Aug	Bone Marrow Transplant	Possible
BMT	✓	2019	Dec	Bone Marrow Transplant	Possible
North	X	2020	May	Ward B6 Beatson	No
BMT	✓	2020	June	Bone Marrow Transplant	Unlikely
South	✓	2020	Oct	Haematology Day Unit	No
South	✓	2021	Jan	Ward 4CH	Unlikely
North	X	2021	Sept	Ward B7 Beatson	No
South	✓	2021	Oct	Ward 4CH	Unlikely
South	✓	2022	Mar	Ward 4CH	Probable
South	✓	2022	Apr	Ward 4CH	Probable
North	X	2022	July	Ward B7 Beatson	Possible
North	X	2022	Aug	Oncology Assessment	Possible

Table 7: *Pseudomonas aeruginosa* bacteraemia by consultant sector, hospital, date and location (N=32)

Consultant Sector	QEUH	Year	Month	Location	Cluster
South	X	2013	June	Ward 24 SGH	Unlikely
South	X	2014	Oct	Ward 24 SGH	Unlikely
BMT	X	2014	Oct	Ward B9 Beatson	Possible
BMT	X	2015	Jan	Ward B9 Beatson	Possible
BMT	✓	2015	June	Ward 4B2	No
BMT	X	2015	Aug	Ward B9 Beatson	Possible
North	X	2015	Oct	Ward B7 Beatson	Possible
BMT	X	2016	Oct	Ward B9 Beatson	Unlikely
South	✓	2016	Nov	Ward 4CH	No
BMT	X	2017	Jan	Ward B8 Beatson	Unlikely
BMT	X	2017	Apr	Ward B9 Beatson	Unlikely
BMT	X	2017	Sept	Ward B8 Beatson	Possible
BMT	X	2017	Nov	Ward B8 Beatson	Probable
BMT	X	2017	Nov	Ward B8 Beatson	Probable
North	X	2017	Nov	Ward B7 Beatson	Possible
North	X	2018	Jan	Oncology Assessment	Possible
BMT	X	2018	June	Ward B6 Beatson	Unlikely
BMT	✓	2018	July	Bone Marrow Transplant	Possible
BMT	✓	2018	Oct	Bone Marrow Transplant	Possible
South	✓	2019	Oct	Ward 2A	Unlikely
BMT	✓	2020	Mar	Bone Marrow Transplant	Unlikely
North	X	2020	July	Ward B6 Beatson	Unlikely
BMT	✓	2021	Feb	Bone Marrow Transplant	Possible
North	X	2021	Mar	Ward B7 Beatson	Possible
North	X	2021	Mar	Oncology Assessment	Possible
BMT	✓	2021	Apr	Bone Marrow Transplant	Possible
South	✓	2021	May	Ward 4CH	Probable
South	✓	2021	May	Ward 4CH	Probable
South	✓	2021	Aug	Ward 4CH	Possible
BMT	✓	2022	Dec	Bone Marrow Transplant	Unlikely
North	X	2023	Jan	Ward B5 Beatson	Unlikely
BMT	✓	2023	Aug	Bone Marrow Transplant	Unlikely

Finally, the largest number of bacteraemia cases among adult haemato-oncology patients in the provided GGC data were attributed to *Stenotrophomonas maltophilia.* Among these, 19 were isolated from patients at QEUH and 26 were isolated from patients at other hospitals (Table 8). Among QEUH cases, 5 were classified as unlikely to cluster, 8 possible, and 6 probable. Among cases from other GGC hospitals, 1 did not cluster, 2 were unlikely, 17 possible and 6 probable. There was WGS for 3 of the adult QEUH cases, of which none were linked to other cases or environmental samples (Table 9). Among all of the human samples that were subject to WGS, there was no evidence of clustering among them by *Stenotrophamonas spp.* and it was reported that human environment pairs were also unlikely. Again, this suggests that there is neither an elevated number of cases of *Stenotrophomonas maltophilia* between QEUH and other hospitals in GGC, nor is there sufficient evidence of environmental contamination and transmission to patients.

Table 8: *Stenotrophomonas maltophilia* bacteraemia by consultant sector, hospital, date and location (N=45)

Consultant Sector	QEUH	Year	Month	Location	Cluster
South	X	2013	July	Ward 24 SGH	Possible
South	X	2013	Nov	Ward 24 SGH	Possible
South	X	2014	Jan	Ward 24 SGH	Possible
BMT	X	2014	May	Ward B9 Beatson	Probable
BMT	X	2014	June	Ward B9 Beatson	Probable
BMT	X	2014	Aug	Ward B8 Beatson	Possible
BMT	X	2014	Sept	Ward B9 Beatson	Probable
BMT	X	2014	Oct	Ward B9 Beatson	Probable
BMT	X	2015	Apr	Ward B9 Beatson	Unlikely
BMT	✓	2015	June	Ward 4B2	Unlikely
BMT	X	2015	Sept	General OP	Possible
North	X	2015	Sept	Ward B7 Beatson	Possible
BMT	X	2015	Dec	Ward B8 Beatson	Possible
South	✓	2016	Feb	Haematology Day Unit	Unlikely
BMT	X	2016	Mar	Ward B9 Beatson	Possible
North	X	2016	May	Oncology Assessment	Possible
BMT	X	2016	July	Ward B9 Beatson	Probable
BMT	X	2016	Aug	Ward B9 Beatson	Probable
BMT	X	2016	Oct	Ward B8 Beatson	Possible
BMT	X	2017	June	Ward B9 Beatson	Possible
BMT	X	2017	Aug	Ward B8 Beatson	Possible
North	X	2018	June	Ward B7 Beatson	Possible
North	X	2018	Sept	Ward B7 Beatson	Possible
North	X	2018	Oct	Ward B6 Beatson	Possible
BMT	✓	2019	Jan	Bone Marrow Transplant	Possible
BMT	✓	2019	Mar	Bone Marrow Transplant	Probable
BMT	✓	2019	Apr	Bone Marrow Transplant	Probable
BMT	✓	2020	June	Bone Marrow Transplant	Possible
South	✓	2020	Sept	Ward 4CH	Probable
South	✓	2020	Oct	Ward 4CH	Probable
South	✓	2020	Oct	Haematology Day Unit	Possible
North	X	2020	Dec	Ward B7 Beatson	No
BMT	✓	2021	May	Bone Marrow Transplant	Unlikely
BMT	✓	2021	Dec	Bone Marrow Transplant	Possible
South	✓	2021	Dec	Medical Day Unit	Possible
North	X	2022	Feb	Haematology Day Unit	Unlikely
South	✓	2022	Feb	Ward 4CH	Probable
South	✓	2022	Mar	Ward 4CH	Probable
BMT	✓	2022	May	Bone Marrow Transplant	Unlikely
North	X	2022	Aug	Oncology Assessment	Possible
North	X	2022	Aug	Ward B7 Beatson	Possible
South	✓	2022	Aug	Ward 4CH	Unlikely
BMT	✓	2022	Oct	Bone Marrow Transplant	Possible
BMT	✓	2022	Dec	Bone Marrow Transplant	Possible
BMT	✓	2023	Feb	Bone Marrow Transplant	Possible

Table 9: Summary of adult whole genome sequencing (WGS) data available compare with epidemiological clustering data

Years Samples for WGS	# WGS Patient Clusters (Non-Confirmatory)	# WGS Patient Environment Clusters	# Epidemiological Clusters	Total # of Haemato-oncology Patients with WGS	Individual Case Month/ Year Overlap	Findings
Cupriavidus spp.						
2016-2021	1	1	0	1	Jan 2020	Closest sequence from paediatric case (144 SNP difference), not epidemiologically linked
Overall *Cupriavidus pauculus* information from WGS reports: No evidence of clustering Two human cases with 144 SNP difference across 3yrs/5mos – no evidence for common origin Human and environmental sample with 102 SNPs difference – environmental samples were collected after patient sample						
Enterobacter spp.						
2016-2019	0	0	1 (unlikely) 1 (possible)	0	NA	
Overall *Enterobacter spp.* information from WGS reports: Samples from only 7 adult patients were sequenced, none of who were haemato-oncology patients.						
Stenotrophomonas spp.						
2015-2018	0	0	3	3	June 2015	No patient or environmental clustering
					Apr 2019	No patient or environmental clustering
					June 2020	No patient or environmental clustering
Overall *Stenotrophomonas spp.* information from WGS reports: While 3 patients from 3 epidemiological clusters were sequenced, there were no person-to-person or person-environmental clusters identified in WGS of Stenotrophomonas spp., even though environment-environment clusters were identified.						

7.2.6 Assessment of potential epidemiological clusters of BSIs

Examining number of clusters by type, incidence by type, qualitative summary score and summary score over bed days and clustering score (Table 10), we observe a greater number of every type of clustering in other hospitals when compared to QEUH, with marked differences in possible clusters, which were almost twice at other hospitals than at QEUH. QEUH, however, had about two thirds of the bed days as other hospitals over the data period (January 2013 – June 2023). Therefore, when the number of bed days are considered, QEUH has slightly higher incidence than the other hospitals, but these numbers are not statistically significantly different.

Table 10: Summary of epidemiological clustering assessment for adult patients by hospital

	QEUH	Other Hospitals	p-value*
Summary Score	153	248	NA
Incidence by Summary Score (per 1000 bed days)	3.27	2.87	0.199
Cases			
No Cluster	43	46	NA
Unlikely Clustering	33	42	NA
Possible Clustering	38	64	NA
Probable Clustering	22	26	NA
Total Cases	136	178	NA
Overall Incidence (per 1,000 bed days)			
All Cases	2.91	2.06	0.488
Any Cluster	1.99	1.53	0.784
Possible & Probable Clusters	1.28	1.04	0.266
Probably Clusters	0.47	0.30	0.126

*p ≤0.05 was considered statistically significant

Indeed, if we look at incidence of those that cluster (unlikely, possible or probable) by month and year (Figure 7), with the exception of the spike in incidence at QEUH in late 2016, which largely corresponds to months with unrealistically low denominators, QEUH has a similar monthly incidence of bacteraemia attributable to environmentally relevant organisms as other GGC hospitals. Conversely the other GGC hospitals have a series of spikes in incidence in mid-2022 and early 2023, that cannot be attributed to unusually small numbers of bed days. When we adjust the denominator based on small numbers of bed days observed in Table 4 (Figure 8), the spike in incidence in late 2016 goes away, with comparable incidence between QEUH and other hospitals until mid-2022 when other GGC hospitals have significant spikes sin incidence. Taken together these data suggest that the pattern observed at QEUH in environmentally relevant bacteraemia is indicative of the norm in the GGC area.

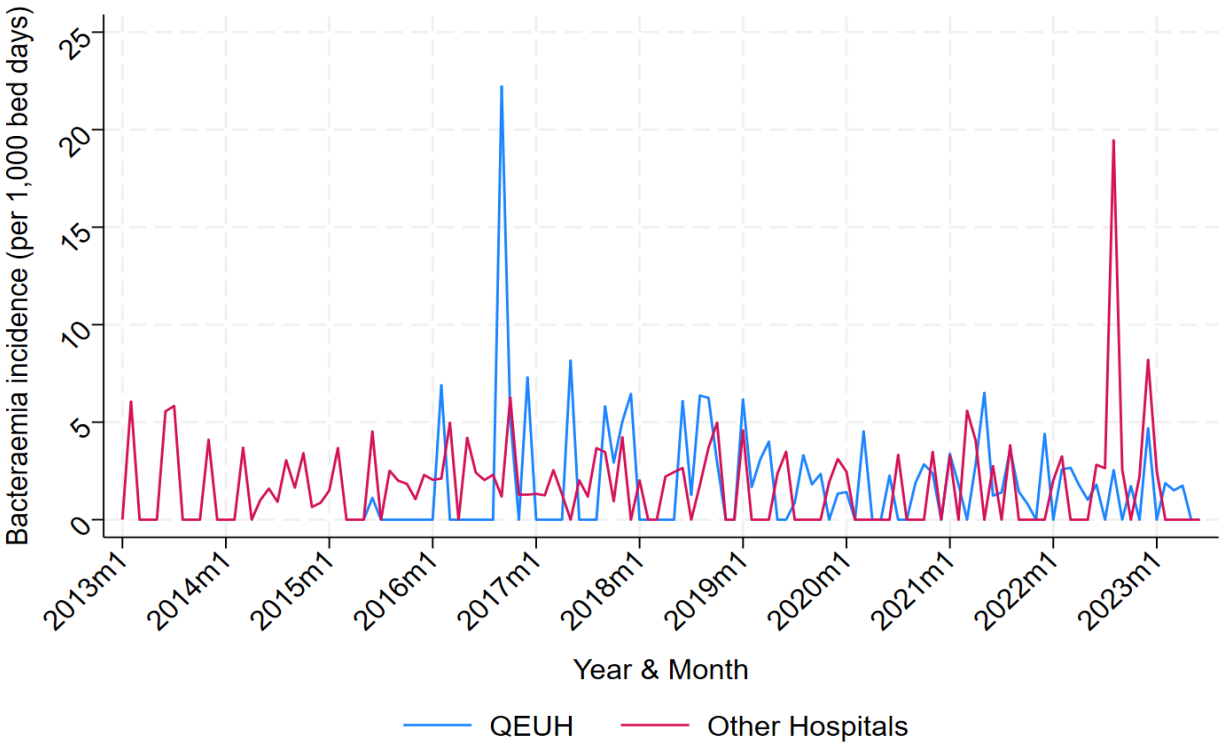


Figure 7: **Clusters (unlikely, possible, probable) of bacteraemia of environmental significance by hospital and date**

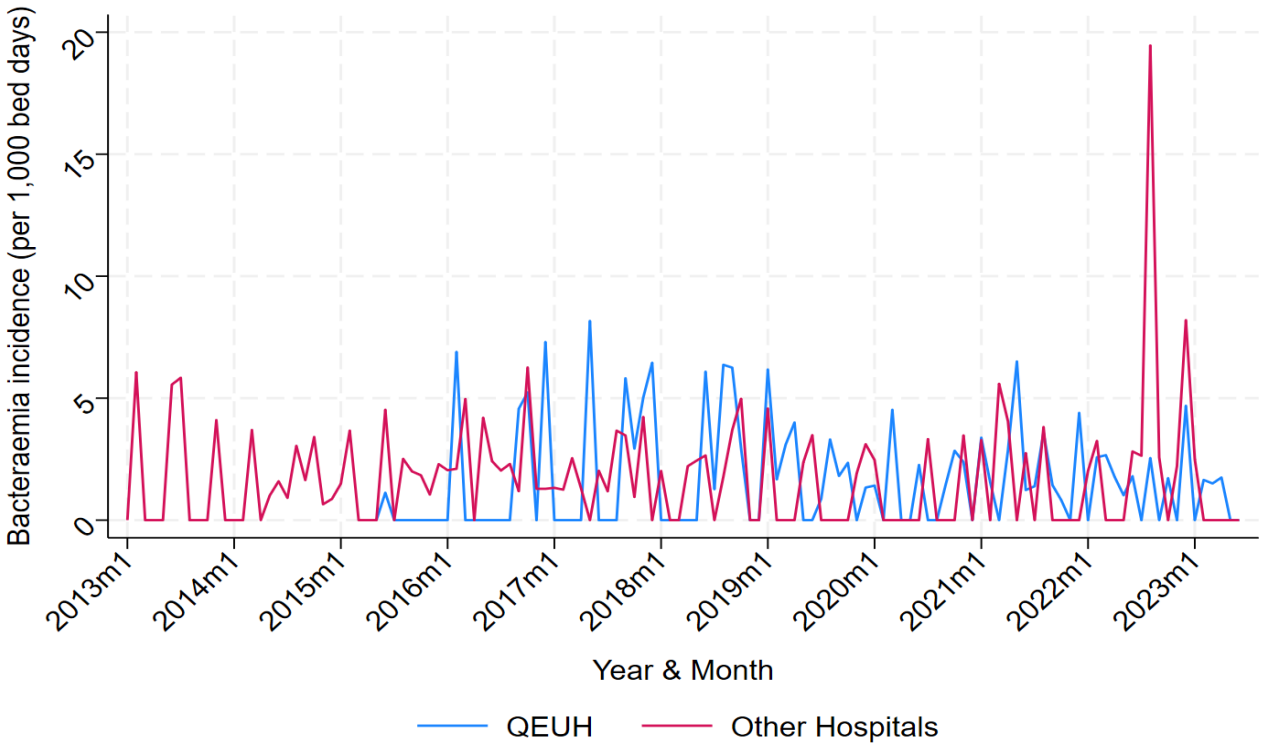
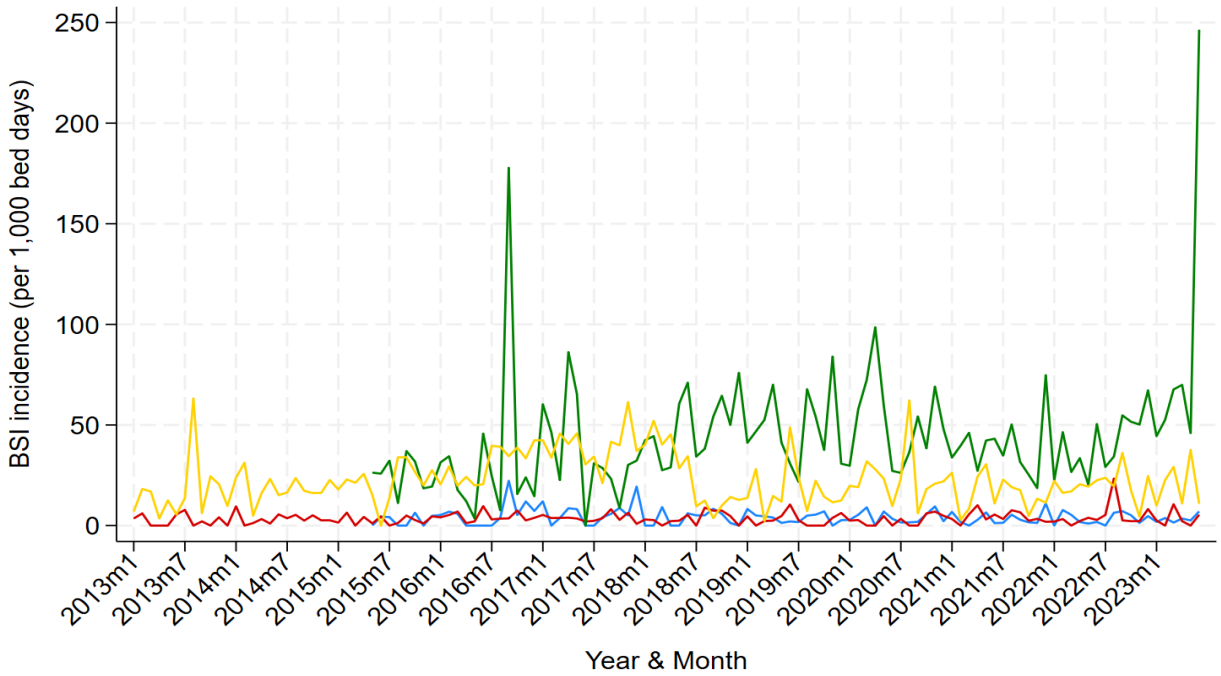


Figure 8: **Clusters (unlikely, possible, probable) of bacteraemia of environmental significance by hospital and date with denominator adjustments based on Table 4**

7.2.5 Comparison of BSI from organisms of potential environmental relevance to all others organisms isolate in BSIs among adult patients in the GGC

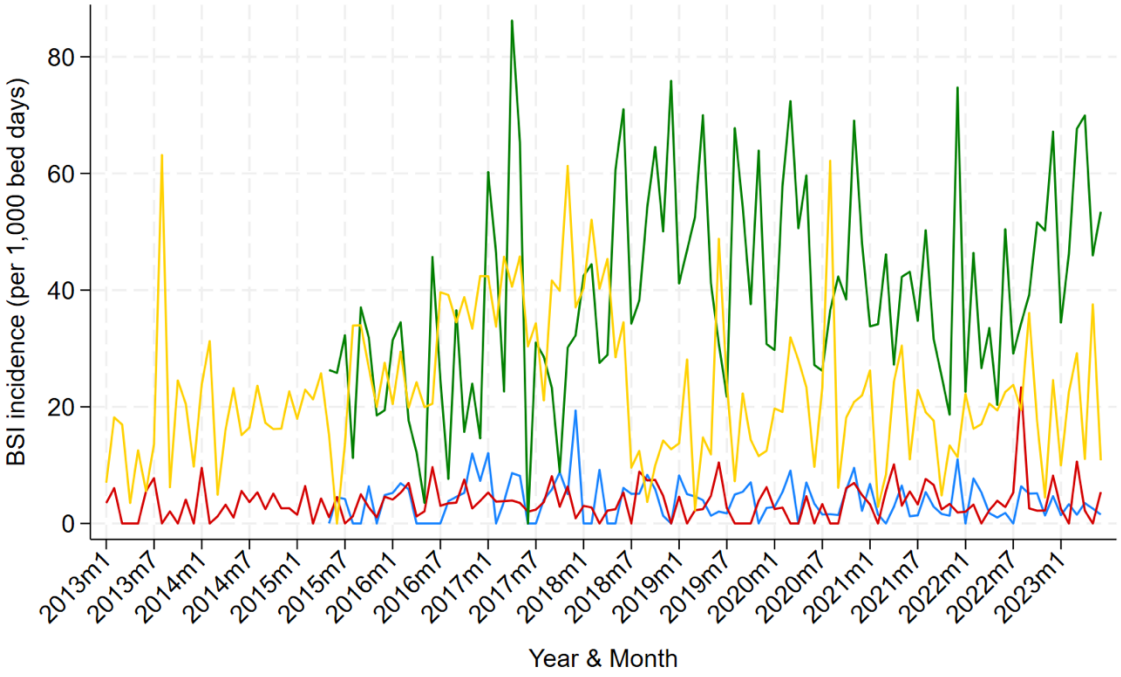
In order to address concerns regarding an apparent increase in cases of BSI at QEUH in 2017-2018, followed by continuous decline from 2020, we examined BSI by organisms that could exist in the environment and infect patients (presented in Table 1) and those that normally do not, such as gram-positive microorganisms and those that are normally human commensal microorganisms (presented in Table 2). Examining incidence of these organisms by hospital (Figure 9), we first observe that incidence rates of BSI attributed to non-environmentally significant microorganisms far exceeds that of BSI attributed to environmentally relevant organisms. There are also a series of peaks in 2016-2017, that are largely attributable to the unusually small denominators noted in Table 4, and then again a sustained increase is observed starting in mid-2018 when the bone marrow transplant patients transitioned from Beatson in the North Sector to QEUH, accompanied by reductions in incidence in other GGC hospitals from North and South Sectors, with the greatest contribution from the Beatson. This trend is even more pronounced when we adjust the unrealistically small number of bed days in the denominator with the average number of bed days for that month over many years (Figure 10). We observe both levelling of the unrealistically high peaks and that there is an increasing incidence of BSI attributable to microorganisms that are not environmentally significant in other hospitals until the move of bone marrow transplant unit from the Beatson to the QEUH in June 2018, when we see incidence for BSI attributable to microorganisms that are not environmentally significant increase at QEUH. BSI attributed to environmentally relevant organisms at both QEUH and other hospitals maintain a consistently low and similar incidence with periodic small spikes at different points in time.

These data highlight both the general pattern of BSI among haemato-oncology patients across hospitals in GGC and the relative contribution that microorganisms that are not environmentally significant have on the overall number of cases and incidence patterns observed. It is clear from these data that BSIs attributable to microorganisms that are not environmentally significant could artificially inflate the number and incidence of BSI in comparison to organisms that could be environmentally relevant, and that the burden of BSIs attributable to microorganisms that are not environmentally significant are likely to be carried by bone marrow transplant patients.



<u>Figure 9:</u> BSI incidence among adult haemato-oncology patients in the GGC by hospital and whether or not the organism isolated in culture is of environmental significance or not.

*Green - BSI with non-environmentally significant organisms among QEUH patients
*Yellow – BSI with non-environmentally significant organisms among patients from other GGC hospitals
*Blue - BSI with environmentally relevant organisms among QEUH patients
*Red – BSI with environmentally relevant organisms among patients from other GGC hospitals



<u>Figure 10:</u> BSI incidence among adult haemato-oncology patients in the GGC by hospital and whether or not the organism isolated in culture is of environmental significance or not including adjusted denominators

*Green - BSI with non-environmentally significant organisms among QEUH patients
*Yellow – BSI with non-environmentally significant organisms among patients from other GGC hospitals
*Blue - BSI with environmentally relevant organisms among QEUH patients
*Red – BSI with environmentally relevant organisms among patients from other GGC hospitals

A linear trend line for increasing, decreasing, or stable incidence can be statistically fitted to these incidence plots using logistic regression. When we apply these trend lines to data on BSI incidence attributable to non-environmentally significant microorganisms (Figure 11), we see a suggested increase in incidence of this type of BSI at QEUH over the time period of data, but no increase at other hospitals in the GGC. When we adjust for the outliers created by the unrealistically low denominators identified in Table 4, this increasing trend in incidence cases persists (Figure 12). The increase in incidence of BSI attributable to non-environmentally significant microorganisms at QEUH is expected given the transfer of the bone marrow transplant patients to QEUH, who carry a disproportionate burden of BSI among all patients given that they are severely immune compromised. This also serves as an expected pattern of all BSI in the QEUH patients, including BSI attributed to environmentally relevant organisms.

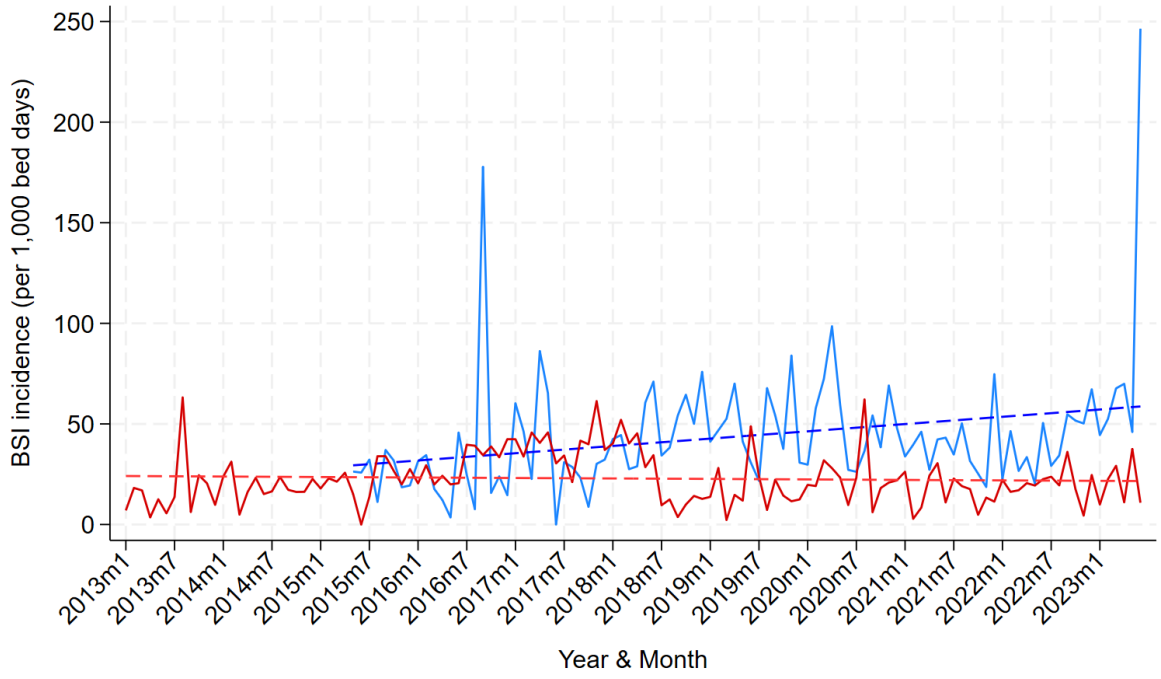


Figure 11: BSI incidence attributable to non-environmentally significant microorganisms among adult haemato-oncology patients in the GGC by hospital
*Blue - BSI with non-environmentally significant organisms among QEUH patients
*Red – BSI with non-environmentally significant organisms among patients from other GGC hospitals
*Fitted linear trend lines from linear regression models are shown in dashed lines

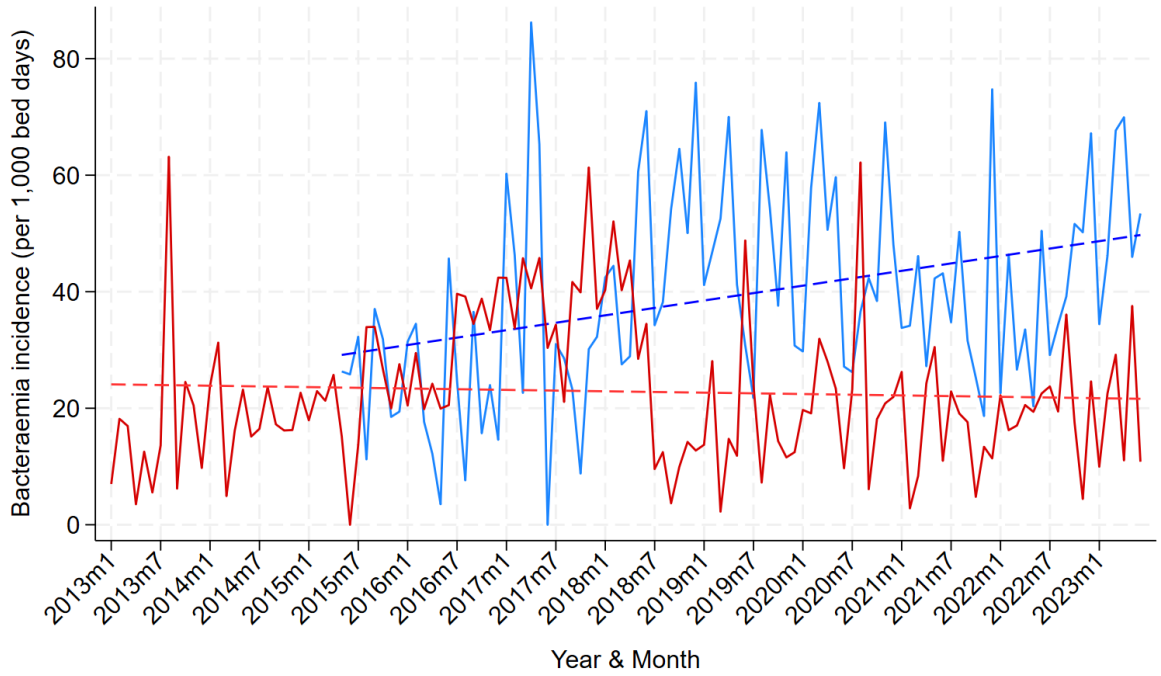


Figure 12: BSI incidence attributable to non-environmentally significant microorganisms among adult haemato-oncology patients in the GGC by hospital including adjusted denominators
*Blue - BSI with non-environmentally significant organisms among QEUH patients
*Red – BSI with non-environmentally significant organisms among patients from other GGC hospitals
*Fitted linear trend lines from linear regression models are shown in dashed lines

When we fit linear trend lines to data on BSI attributable to environmentally relevant organisms, we observe a slightly decreasing trend at QEUH, with a relatively stable trend at other hospitals (Figure 13). When we fit trend lines to denominator adjusted data, this trend persists (Figure 14); which is relevant as outliers can have a significant impact on trend lines. These data suggest that despite a background of increasing incidence of BSI generally in the adult QEUH patient population, BSI attributable to environmentally relevant organisms may be decreasing slightly, which may be due to positive changes in policy or clinical practice or even patient behaviours outside of the hospital setting. These patterns do not support the notion of a common, persistent source of environmental contamination in the hospital.

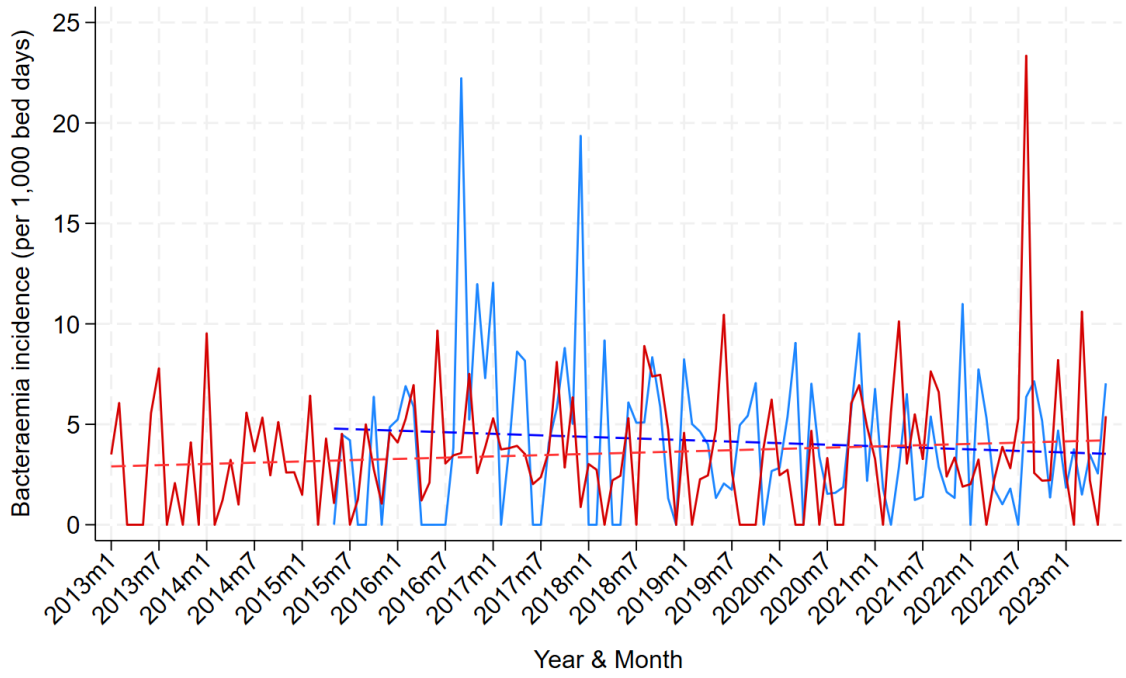


Figure 13: BSI incidence attributable to environmentally relevant microorganisms among adult haemato-oncology patients in the GGC by hospital

*Blue - BSI with environmentally relevant organisms among QEUH patients

*Red – BSI with environmentally relevant organisms among patients from other GGC hospitals

*Fitted linear trend lines from linear regression models are shown in dashed lines

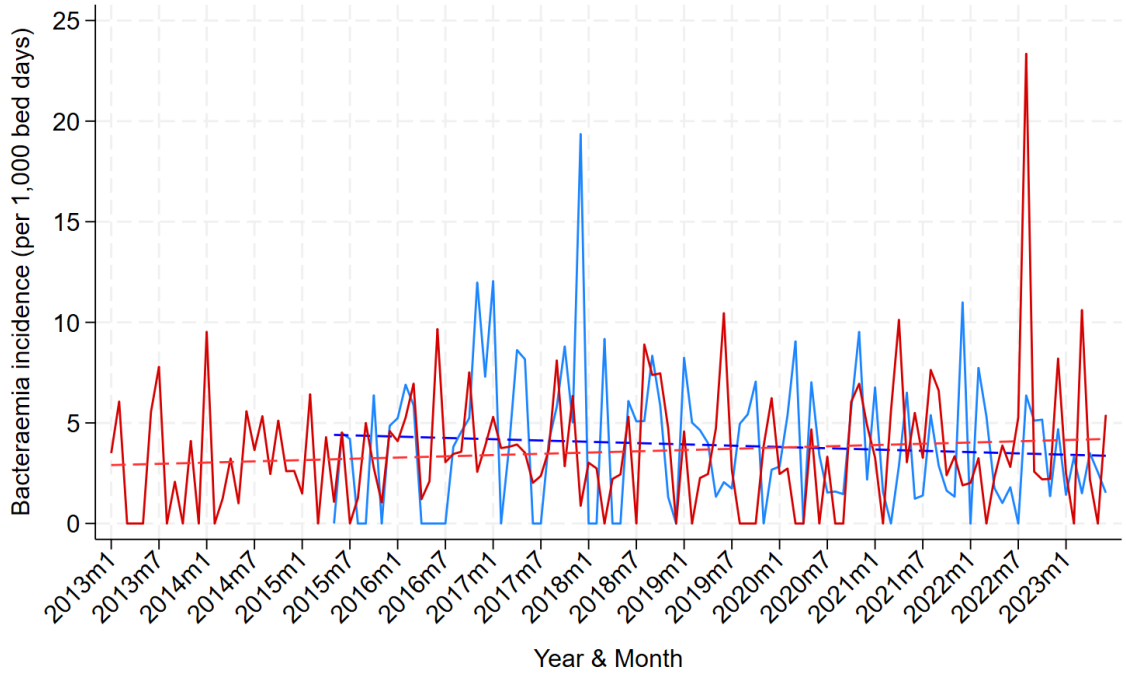


Figure 14: BSI incidence attributable to environmentally relevant microorganisms among adult haemato-oncology patients in the GGC by hospital including adjusted denominators

*Blue - BSI with environmentally relevant organisms among QEUH patients

*Red – BSI with environmentally relevant organisms among patients from other GGC hospitals

*Fitted linear trend lines from linear regression models are shown in dashed lines

7.2.6 Assessment of adult bone marrow transplant patients only

We were interested in examining single patient populations as services transitioned from another hospital to QEUH to determine if there was an increase in number of cases of environmentally relevant bacteraemias, which could be indicative of environmental sources of infection. As bone marrow transplant patients are at exceptionally high risk of bacteraemia and the BMT is a sector within the GGC, we examined data over time for only patients in BMT.

Figure 15 shows the incidence of bacteraemia attributable to environmentally relevant organisms over time, revealing that incidence decreased from when BMT was located in the North Sector at the Beatson to when BMT moved to QEUH. There is also a slight, but possibly relevant trend in decreasing incidence at QEUH. A similar, and possibly more pronounced trend in reduction of incidence following the move to QEUH is observed when we look at bacteraemias that could cluster in space and time (Figure 16). These data further suggest that incidence of bacteraemia attributable to environmentally relevant organisms may be occurring at lower rates at QEUH than the norm for the GGC area, although these findings should be interpreted in light of other factors that could influence incidence over time.

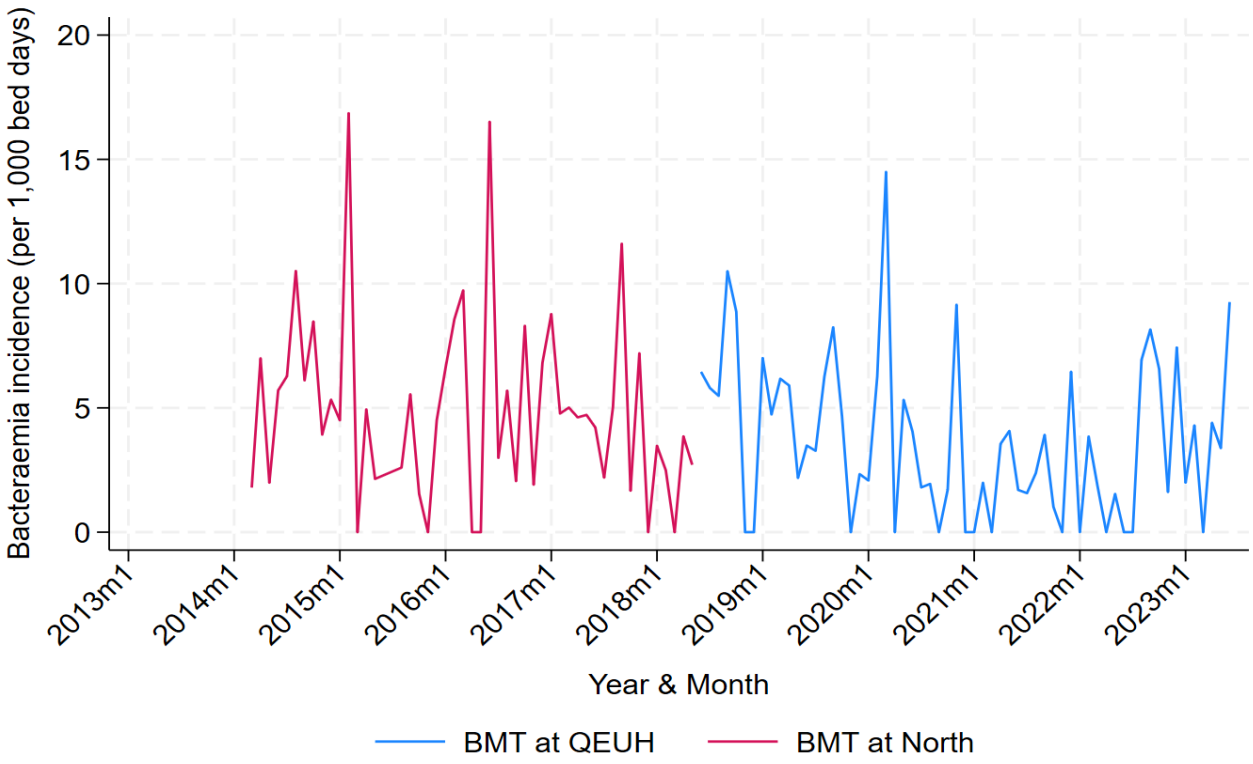


Figure 15: Incidence of environmentally relevant bacteraemia within BMT patients only over time

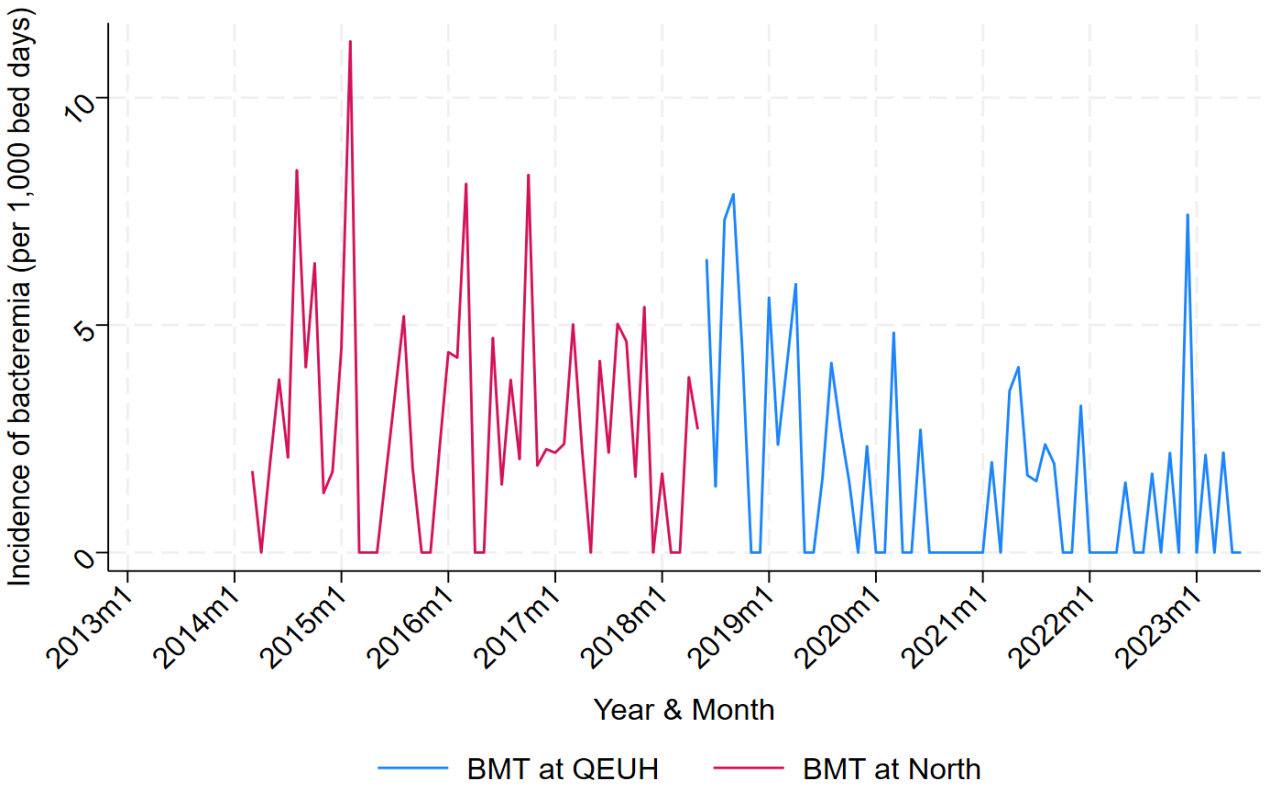


Figure 16: Incidence of bacteraemia that may cluster (unlikely, possible probable) within BMT patients only over time

7.2.7 Bacteraemia in paediatric patients in GGC

The Royal Hospital for Children (RHC) resided at Yorkhill in 2005 and moved to QEUH in 2015, data on bed days and bacteraemia were available from January 2005-Dec 2022 for RHC. Figure 17 show the incidence of all bacteraemia over this time period. At the time of the move to QEUH, bacteraemia incidence was similar to rates at Yorkhill, but steadily declined from early 2018 onward. As these are cases of all bacteraemia, this suggests infection control, antimicrobial, or other policy changes at QEUH that have been influencing positive reductions in bacteraemia collectively.

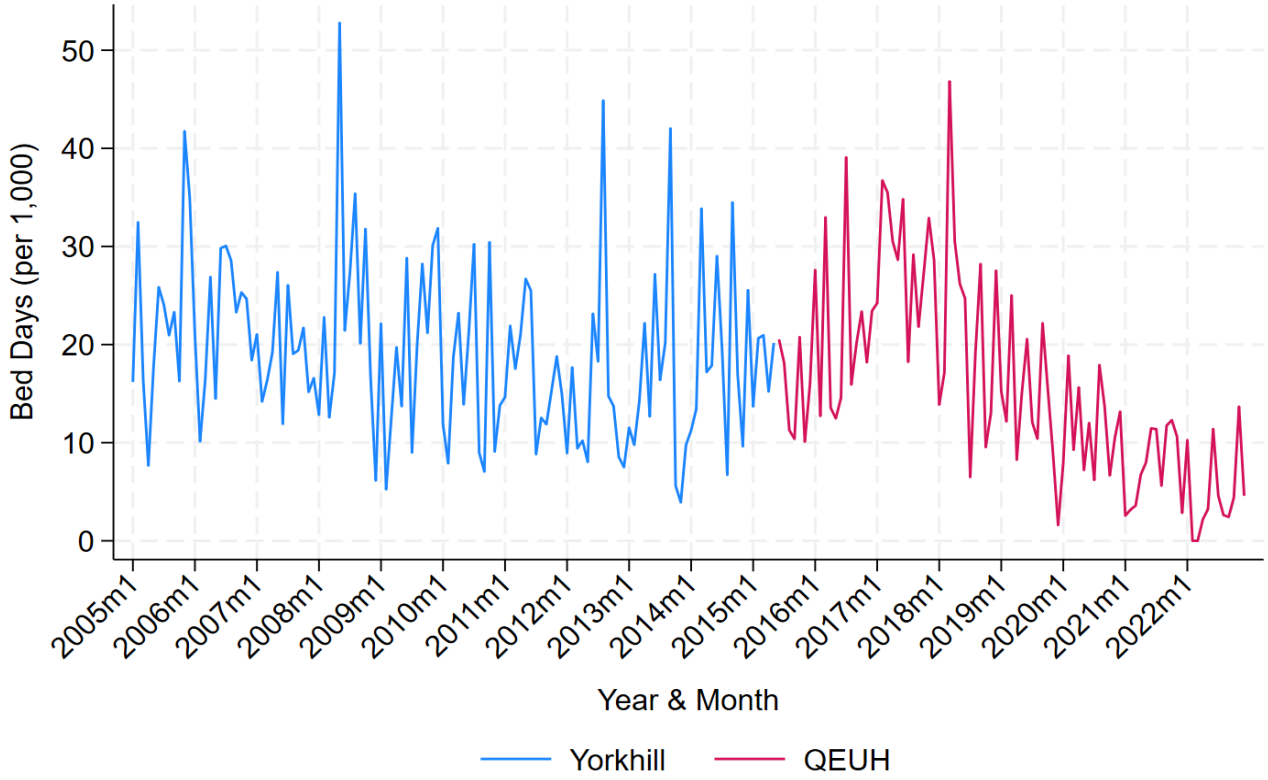
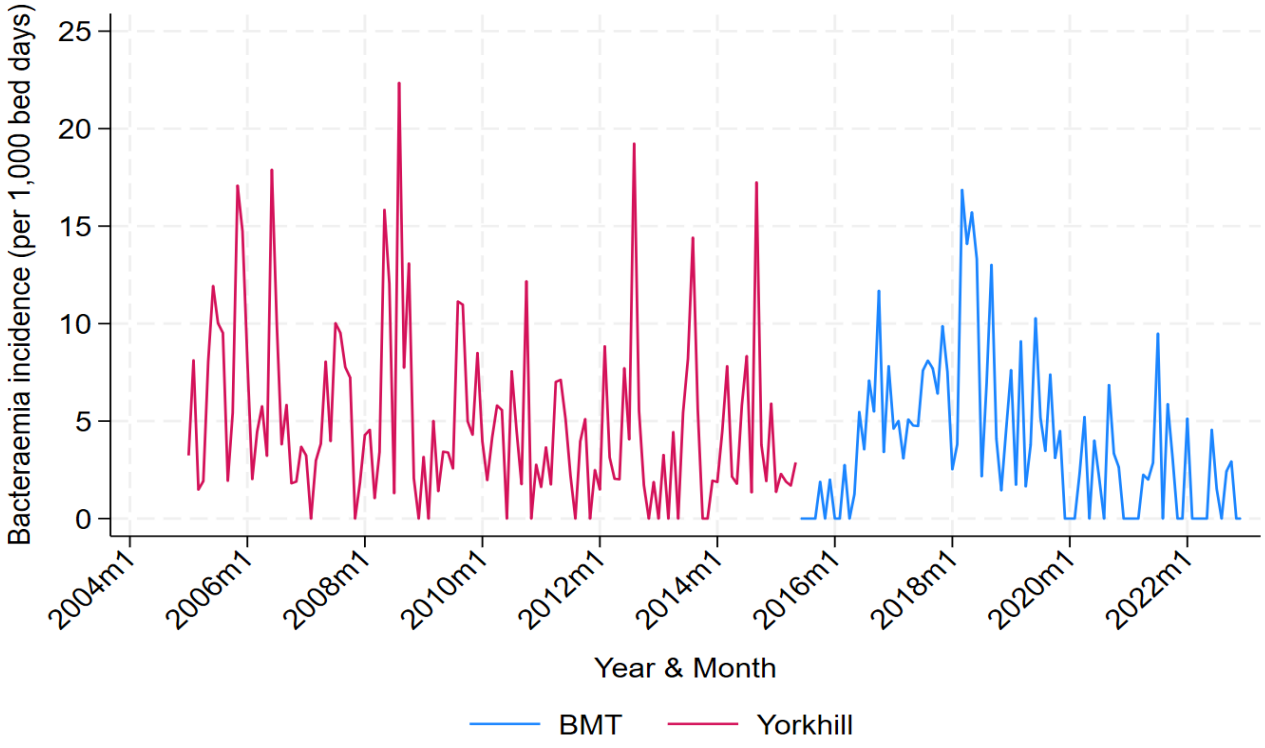


Figure 17: Incidence of all cases of bacteraemia among paediatric patients over the study period

7.2.8 Bacteraemia attributable to environmentally relevant microorganisms in paediatric patients in GGC

A similar, but less pronounced pattern of incidence is observed when looking at incidence of environmentally relevant bacteraemia cases (Figure 18). Incidence starts off at QEUH similar to that observed for the prior 10 years at Yorkhill, but then steadily declines from ~2018 onward. This suggests that whatever factors are influencing bacteraemia incidence overall are also having an impact on bacteraemia attributable to environmentally relevant pathogens, further suggesting that the environment is unlikely to be playing a significant role in harbouring and transmitting pathogens to paediatric patients.



<u>Figure 18:</u> Incidence of bacteraemia from organisms of potential environmental concern among paediatric patients over the study period

Examination of individual cases of bacteraemia attributable to environmentally relevant microorganisms indicated that cases attributable to *Achromobacter spp., Aeromonas spp.,* and *Brevundimonas spp.* were infrequently observed, however, 44 cases were attributed to

Acinetobacter spp. (Table 11A). *Acinetobacter baumanni* was most frequently grown (N=23), with >2/3 occurring at Yorkhill. While cases were sporadic at QEUH, there were a handful occurring in different months and on different wards in 2017 at QEUH, however this pattern was the norm at Yorkhill, suggesting that this may be usual presentation in this population, rather than a large environmental source of contamination. There were 7 cases of *Acinetobacter ursingii* mostly occurring at QEUH, but sporadically across years. Yorkhill reported 7 of the 8 cases of unspeciated *Acinetobacter* and both *Acinetobacter lwoffii* cases. It is important to note that some of the differences observed in *Acinetobacter spp.* maybe attributable to changes in diagnostic tools to speciate these organisms; in example, matrix assisted laser deabsorbtion/ionization (MALDI) technology became available at QEUH, allowing for better identification of *A. baumanii* than with previous techniques that would have been available at Yorkhill. Inspite of this, these data suggest that *Acinetobacter spp.* was historically a far larger problem at Yorkhill than currently at QEUH, which has had a modest number of cases for this population.

Burkholderia cepacian (N=28) and *Chryseomonas spp.* (N=12) and to a lesser extent *Chryseobacterium spp.* (N=6) were also represented within the pathogens identified in bacteraemias among paediatric patients (Table 11B). All but 2 of the *Burkholderia cepacian* cases occurred at Yorkhill, with those at QEUH sporadically occurring in 2017 and 2018. In contrast, most of the cases at Yorkhill were suggestive of clustering, highlighting what we might expect of concerning data related to an ongoing source of infection for this pathogen, although without wider Glasgow regional environmental surveillance and sequencing data it is difficult to speculate where or not there was a common source for infections in the Yorkhill hospital environment. *Chryseomonas indologenes* and *Chryseomonas meningosepticum* bacteraemia cases were also predominantly reported at Yorkhill, with only 4 cases occurring sporadically at QEUH over a 4-year period. All 4 cases were judged to not cluster or to be unlikely to cluster given location and time frame of occurrence relative to one another. Similarly, 4 of the 6 *Chryseobacterium spp.* bacteraemia cases that occurred at Yorkhill and the 2 occurring at QEUH were separated in time by ~3 years and occurred on separate wards, suggesting qualitatively that they were unlinked.

Table 11A: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Achromobacter xylosoxidans	1	Yorkhill	2010	May	Schiehallion Ward	No
Achromobacter spp.	1	QEUH	2019	Sept	Ward 6A	No
Acinetobacter baumanni	23	Yorkhill	2005	Nov	Schiehallion DCU	Possible
		Yorkhill	2005	Nov	Schiehallion Ward	Probable
		Yorkhill	2005	Dec	Schiehallion Ward	Probable
		Yorkhill	2006	June	Schiehallion Ward	Unlikely
		Yorkhill	2007	Apr	Schiehallion Ward	Possible
		Yorkhill	2007	July	Schiehallion Ward	Possible
		Yorkhill	2008	Feb	Schiehallion DCU	Unlikely
		Yorkhill	2008	Aug	Schiehallion Ward	Probable
		Yorkhill	2008	Sept	Schiehallion Ward	Probable
		Yorkhill	2008	Oct	Schiehallion Ward	Probable
		Yorkhill	2009	Jan	A&E	Unlikely
		Yorkhill	2009	Sept	Schiehallion Ward	Possible
		Yorkhill	2009	Dec	Schiehallion Ward	Possible
		Yorkhill	2010	Aug	Schiehallion Ward	Unlikely
		Yorkhill	2011	Sept	Schiehallion Ward	No
		Yorkhill	2014	Aug	Schiehallion Ward	No
		QEUH	2016	Aug	Ward 2A	Possible
		QEUH	2017	Jan	Ward 2A	Possible
		QEUH	2017	Apr	Emergency Department	Unlikely
		QEUH	2017	June	Ward 2B Day Care Unit	Unlikely
		QEUH	2017	Oct	Ward 2B Day Surgery	Unlikely
		QEUH	2022	June	Ward 2B Day Care Unit	Unlikely
		QEUH	2022	Oct	Ward 2B Day Surgery	Unlikely
Acinetobacter lwoffii	2	Yorkhill	2005	Feb	Schiehallion Ward	No
		Yorkhill	2006	Sept	Schiehallion Ward	No
Acinetobacter ursingii	7	Yorkhill	2013	Apr	Schiehallion Ward	Unlikely
		Yorkhill	2015	Feb	Schiehallion DCU	Unlikely
		QEUH	2016	Dec	Ward 2A	No
		QEUH	2017	Dec	Ward 2A	Unlikely
		QEUH	2018	Jun	Ward 2A	Possible
		QEUH	2018	Jun	Ward 3C	Possible
		QEUH	2019	Nov	Day Unit 6A	No
Acinetobacter spp.	8	Yorkhill	2006	Jan	Schiehallion DCU	No
		Yorkhill	2008	Jan	Schiehallion DCU	No
		Yorkhill	2010	Mar	Schiehallion Ward	Possible
		Yorkhill	2010	May	Schiehallion Ward	Possible
		Yorkhill	2010	Oct	Schiehallion DCU	Unlikely
		Yorkhill	2011	Oct	Ward 7A	No
		Yorkhill	2012	Feb	Schiehallion DCU	No
		QEUH	2017	Dec	Ward 2A	No
Aeromonas hydrophila/ caviae	4	Yorkhill	2005	Nov	Schiehallion DCU	No
		Yorkhill	2009	Oct	Yorkhill OP	No
		Yorkhill	2013	August	Schiehallion Ward	No
		QEUH	2016	May	Ward 2B	No
Brevundimonas spp.	1	QEUH	2017	Apr	Ward 2A	No

Table 11B: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients (continued)

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Burkholderia cepacia	28	Yorkhill	2005	May	Schiehallion Ward	Probable
		Yorkhill	2005	June	Schiehallion Ward	Probable
		Yorkhill	2005	Aug	Schiehallion Ward	Probable
		Yorkhill	2005	Sept	Schiehallion Ward	Probable
		Yorkhill	2005	Oct	Schiehallion Ward	Probable
		Yorkhill	2006	Jan	Schiehallion Ward	Possible
		Yorkhill	2006	June	Schiehallion Ward	Probable
		Yorkhill	2006	July	Schiehallion DCU	Probable
		Yorkhill	2006	July	Schiehallion Ward	Probable
		Yorkhill	2006	Aug	Schiehallion Ward	Probable
		Yorkhill	2006	Sept	Schiehallion Ward	Probable
		Yorkhill	2009	July	Schiehallion Ward	Probable
		Yorkhill	2009	Aug	Schiehallion Ward	Probable
		Yorkhill	2009	Sept	Schiehallion Ward	Probable
		Yorkhill	2010	Mar	Schiehallion Ward	Probable
		Yorkhill	2010	Apr	Schiehallion Ward	Probable
		Yorkhill	2010	Apr	Schiehallion Ward	Probable
		Yorkhill	2011	Feb	Schiehallion Ward	Possible
		Yorkhill	2011	Apr	Schiehallion Ward	Probable
		Yorkhill	2011	May	Schiehallion DCU	Possible
		Yorkhill	2011	May	Schiehallion Ward	Probable
		Yorkhill	2011	June	Schiehallion Ward	Probable
		Yorkhill	2011	Oct	Schiehallion Ward	Possible
		Yorkhill	2012	Sept	Schiehallion Ward	Possible
		Yorkhill	2012	Oct	Ward 5A	Possible
		Yorkhill	2014	Sept	Schiehallion Ward	No
		QEUH	2017	May	Ward 2A	No
		QEUH	2018	June	Ward 2A	No
Chryseobacterium spp.	6	Yorkhill	2005	June	Schiehallion Ward	No
		Yorkhill	2008	Aug	Yorkhill OPs	Possible
		Yorkhill	2008	Sept	Yorkhill ITU	Possible
		Yorkhill	2009	Dec	Schiehallion Ward	No
		QEUH	2018	May	Ward 2A	No
		QEUH	2022	Jan	Clinical Decision Unit	No
Chryseomonas indologenes	10	Yorkhill	2005	Nov	Yorkhill OP	No
		Yorkhill	2008	April	Schiehallion Ward	Probable
		Yorkhill	2008	May	Schiehallion Ward	Probable
		Yorkhill	2008	June	Schiehallion Ward	Probable
		Yorkhill	2014	Apr	Schiehallion Ward	Unlikely
		Yorkhill	2014	Nov	Schiehallion DCU	Unlikely
		QEUH	2016	Dec	Ward B2 Day Surgery	Unlikely
		QEUH	2017	May	Ward 2A	Unlikely
		QEUH	2018	Aug	Clinical Decisions Unit	No
		QEUH	2019	July	Ward 6A	No
Chryseomonas meningosepticum	2	Yorkhill	2006	June	Schiehallion Ward	No
		Yorkhill	2009	Sept	Schiehallion Ward	No

There was only a single case of *Cryptococcus neoformans,* 3 cases of *Cupriavidus pauculus* and 5 cases of *Delftia acidovorans* bacteraemia over the timeperiod covered by data (Table 11C). We are aware that *Cupriavidus spp.* were of particular concern in the paediatric patients

to the inquiry. Two paediatric QEUH cases of *Cupriavidus pauculus* were included in the WGS based on samples from Hickman lines. The Sept 2017 case had a distant sequence match (144 single nucleotide difference) to another sample from a different case 3 years and 5 months apart, however this was deemed unrelated (see Report on Cupriavidus Related Infections by Professor T Evans). No environmental or other patient samples were associated with the Jan 2018 case according to WGS. These data suggest that the pattern of *Cupriavidus spp.* bacteraemia cases appear both epidemiologically (i.e., related to space and time) and genetically (i.e., based on WGS) to be sporadic and unrelated. While 4 of the 5 *Delftia acidovorans* cases occurred in patients at QEUH, they are also unlikely to be epidemiologically clustered given distances in time and space.

In contrast *Citrobacter spp.* (N=12) *and Elizabethkingia spp.* (N=9) contributed a larger number of bacteraemia cases within the paediatric data (Tables 11C). The most frequently isolated *Citrobacter spp.* was *C. freundii* of which 6 of the 8 cases were identified at Yorkhill, mostly in 2007 and 2012. The two cases that occurred at QEUH were separated both by location and time, suggesting that they were not epidemiologically linked. QEUH also had 3 sporadic cases of other species of *Citrobacter* including *C. braakii, C. koseri,* and *C. youngae* of which none are related as they are different species. Thus, suggesting no common source for *Citrobacter spp.* bacteraemia cases at QEUH. Two-thirds of the bacteraemia cases attributed to *Elizabethkingia spp.* occurred at QEUH. Three cases of *E. meningoseptica* bacteraemia occurred at Yorkhill, all close in time during 2014. No prior cases may suggest that this is a more recently observed infection in paediatrtic haemato-onology patients within GGC, although complete data on all bacteraemia cases among paediatric patients across Scotland would be relevant to substantiate this hypothesis. The remaining 3 cases of *E. meningoseptica* occurred at QEUH between September 2016 and January 2017, with 2 additional cases with unidentified *Elizabethkingia spp.* occurred in 2017. While we cannot rule out a possible small cluster of *E. meningoseptica* at QEUH between September 2017 – August 2017, lack of speciation, along with gaps in time and different ward locations makes it difficult to draw any conclusions about epidemiological linkage of cases with qualitative clustering assignment of two cases possibly clustered and five unlikely to be clustered.

Table 11C: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients (continued)

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Citrobacter braakii	2	Yorkhill	2009	Apr	Schiehallion Ward	No
		QEUH	2017	Nov	Ward 2A	No
Citrobacter freundii	8	Yorkhill	2005	Oct	Schiehallion Ward	No
		Yorkhill	2007	May	Schiehallion Ward	Unlikely
		Yorkhill	2007	Aug	Schiehallion DCU	Unlikely
		Yorkhill	2012	Feb	Schiehallion DCU	Unlikely
		Yorkhill	2012	Aug	Schiehallion DCU	Possible
		Yorkhill	2012	Aug	Schiehallion Ward	Possible
		QEUH	2017	Mar	Ward 2A	No
		QEUH	2018	Nov	Ward 6A	No
Citrobacter koseri	1	QEUH	2018	Sept	Ward 2A	No
Citrobacter youngae	1	QEUH	2017	April	Ward 2A	No
Cryptococcus neoformans	1	QEUH	2018	Dec	Ward 1D PCC	No
Cupriavidus pauculus	3	Yorkhill	2012	Mar	Schiehallion DCU	No
		QEUH	2017	Sept	Ward 2B Day Surgery	Unlikely
		QEUH	2018	Jan	Ward 3C	Unlikely
Delftia acidovorans	5	Yorkhill	2013	Feb	Schiehallion DCU	No
		QEUH	2017	Feb	Ward 2B DSU	Unlikely
		QEUH	2017	June	Ward 2B DCU	Unlikely
		QEUH	2019	Oct	Day Unit 6A	Unlikely
		QEUH	2020	July	Clinical Decision Unit	Unlikely
Elizabethkingia meningoseptica	6	Yorkhill	2014	May	Schiehallion Ward	Possible
		Yorkhill	2014	June	Schiehallion DCU	Possible
		Yorkhill	2014	July	Schiehallion Ward	Possible
		QEUH	2016	Sept	Ward 1B Day Surgery	Unlikely
		QEUH	2016	Dec	Ward 2A	Possible
		QEUH	2017	Jan	Ward 2A	Possible
Elizabethkingia miricola	1	QEUH	2019	July	Ward 6A	No
Elizabethkingia spp (Unidentified)	2	QEUH	2017	Mar	Ward 2A	Unlikely
		QEUH	2017	Aug	Ward 2B Day Surgery.	Possible
Enterobacter aerogenes	1	QEUH	2019	Jan	Neonatal ICU	No
Enterobacter cancerogenus	1	QEUH	2021	July	Ward 6A	No
Enterobacter hormaechei	2	QEUH	2017	July	Ward 2B Day Surgery	No
		QEUH	2018	Oct	Ward 6A	No
Enterobacter sakazakii	1	Yorkhill	2007	May	Schiehallion Ward	No
Klebsiella oxytoca	24	Yorkhill	2005	Jan	Schiehallion Ward	Probable
		Yorkhill	2005	Feb	Schiehallion Ward	Probable
		Yorkhill	2005	Feb	Day Surgery DSU	Possible
		Yorkhill	2005	June	Schiehallion Ward	Probable
		Yorkhill	2005	July	Schiehallion Ward	Probable
		Yorkhill	2005	Dec	Schiehallion Ward	Unlikely
		Yorkhill	2007	Sept	Schiehallion Ward	Unlikely
		Yorkhill	2008	Apr	Schiehallion Ward	Unlikely
		Yorkhill	2008	Oct	Schiehallion DCU	Unlikely
		Yorkhill	2009	Mar	Yorkhill OPs	Possible
		Yorkhill	2009	June	Unlikely	Possible
		Yorkhill	2010	Dec	Schiehallion Ward	No
		Yorkhill	2012	Mar	Schiehallion DCU	No
		Yorkhill	2013	Apr	Schiehallion DCU	Possible
		Yorkhill	2013	July	Schiehallion Ward	Probable
		Yorkhill	2013	Aug	Schiehallion Ward	Probable
		QEUH	2015	Dec	Ward 2B Day Surgery	No

Enterobacter spp. (N=75) was one of the more commonly detected organisms in bacteraemia cases among paediatric patients in the available data. Sporadic cases of *E. aerogenes* (N=1)*, E. cancerogenus* (N=1)*, and E. hormaechei* (N=2) were isolated from blood samples at QEUH (Table 11C) and one case of bacteraemia attributed to *E. sakazakii* was isolated from a blood sample at Yorkhill. The two *E. hormaechi* cases were not epidemiologically linked in time and space, nor were samples from these patients sequenced, however, given that they occurred >1 year apart and were from patients on different wards there is little concern of clustering. *E. cloacae* was the most commonly isolated *Enterobacter spp.* with 70 bacteraemia cases across both hospitals (Table 12). Fifty-six percent of cases were reported at Yorkhill and 44% at QEUH. Among the 39 cases at Yorkhill, 2 were deem unlikely for epidemiological clustering, 23 possible and 14 probable. Among the 31 cases at QEUH, one was considered unlinked epidemiologically, 15 possible and 15 probable. At Yorkhill there were a number of cases in 2005, 2006, 2008, 2009, and 2012 which predominately occurred in patients on the Schienhallion Ward and Day Care Units. It is, however, unclear if this is indicative of a pattern of normal *E. cloacae/ cloacae complex* bacteraemia in these patients or indicative of a common environmental source, especially given that no WGS data were available from Yorkhill. At QEUH most cases were detected in 2017, 2018 and 2019, predominantly on Wards 2A and 6A. These overlapped with WGS data, which included samples from 15 of the 22 with *E. cloacae/cloacae complex* bacteraemias during this time period (Tables 15A & 15B). Two cases from 2017, occurring in August and September, on separate wards were identified as a cluster by WGS, but were not linked to any environmental samples (see 3.8 in the Report on Enterobacter Related Infection by Professor T Evans & Whole Genome Sequencing Report by Prof Leanord), suggesting that cases of *E. cloacae/cloacae complex* bacteraemia that are epidemiologically linked may be more likely transmitted from person-to-person than from environmental sources, although data are very limited. Indeed, the other 13 additional human samples were not clustered or were too many single nucleotide polymorphisms (SNPs) apart to be considered clustered with any other samples or environmental sample in WGS, suggesting that epidemiological definitions of clustering are likely to over-estimate clusters of cases. Additionally, further microbiological analysis of the two patient samples that appeared to cluster revealed different antimicrobial resistance patterns, which were unlikely in a cluster and therefore they were deemed not to cluster.

Klebsiella spp. (N=109) were the most common isolates from bacteraemia samples. Twenty-four of these were due to *Klebsiella oxytoca* (Table 11C and 11D) while 85 were due to

Klebsiella pnemoniae (Table 13). One third of *Klebsiella oxytoca* cases were from QEUH while 2/3 were from Yorkhill. Half (N=4) of the QEUH cases occurred in 2016, with 3 occurring in October on Ward 2A, suggesting epidemiological clustering. Although no WGS data were available to determine if this was a true cluster. Historical data from Yorkhill suggests that it is not uncommon to have cases close together in time on the same ward, as observed in 2005 and 2013, and a large number of cases with twice as many occurring at Yorkhill as at QEUH. Similarly, 1/3 of *Klebsiella pnemoniae* cases were from QEUH and 2/3 were from Yorkhill. While most cases at QEUH occurred between June 2016 and Oct 2018 on Ward 2A, Yorkhill demonstrated a similar pattern where most cases were detected on Schiehallion Ward between Jan 2006 and Oct 2008, with another distinct large set of cases occurring from May 2010-August 2012, and again, but in a smaller number between March 2014 and Apr 2015. Without WGS data, including environmental samples, it is difficult to determine if such cases are unrelated and typically high-burden within this patient population, human-to-human transmission clusters, or are due to an environmental contamination. Indeed, the most common source of *Klebsiella pnemoniae* infection in healthcare settings is person to person transmission, followed by contaminated intraveneous catheters, which point to infection control practices rather than environmental concerns; improved infection control may be why we have seen a reduction in cases at QEUH compared Yorkhill. Additionally, as noted in Section 3.1.1 many patients are colonized with *Klebsiella pnemoniae* and intestinal or skin colonies match blood stream infection strains in 80% cases. Antimicrobial prescribing polices often drive both colonization and infection of microorganisms, which may also be a reason for more recent reductions in incidence. Whatever the drivers for reduction in incidence of *Klebsiella pnemoniae*, existing data and information in the literature suggest that cases are not likely to be due to environmental sources.

Bacteraemia cases attributable to *Proteus spp.* (N=8) and *Pantoea spp.* (N=8) were more common than those attributed to *Morganella morganii* (N=1) or *Ochrobactrum anthropic* (N=1) (Table 11D). Bacteraemia cases of *Proteus mirabilis* almost exclusively occurred in patients at Yorkhill, with one case from QEUH. This suggests that not only are these pathogens not environmental contaminants at QEUH, current policies and practices (e.g., antimicrobial prescribing, infection control) at QEUH may be actively preventing cases of bacteraemia attributable to the organisms from occurring given the historical presentation expected from Yorkhill. *Proteus spp.* bacteraemia case data from both Yorkhill and QEUH suggest a sporadic pattern of cases unrelated to a local or environmental contamination or person-to-person

transmission with the exception of two possibly linked *Pantoea agglomerans* cases at Yorkhill in 2005.

There were 45 bacteraemia cases with *Pseudomonas spp.* detected (Tables 11D & 11E). The majority of these were attributed to *Pseudomonas aeruginosa* (N=34), with just over 1/3 from QEUH and the remaining ~2/3 from Yorkhill. Most Yorkhill cases occurred between November 2005 and December 2010, with epidemiological clustering probable due to occurrence close together in time on the same ward, which was most often Schiehallion Ward followed by Schiehallion Day Care Unit. Cases at QEUH were more sporadic, with small potential clusters of 2-3 cases occurring between Feb 2018 and September 2020, with the exception of April-June 2018, these all occurred on separate wards. These could be unrelated cases or due to periodic contamination of sink areas, as is common with *Pseudomonas* in health care settings, that is well managed preventing extensive transmission, however additional data would be required to determine this. There were 9 cases of *Pseudomonas putida* over the period covered by the data, of which 3 occurred at Yorkhill and 6 occurred at QEUH (Table 7E). At both sites, cases were mostly sporadic with little epidemiological evidence of clustering. There was only one case each of *Pseudomonas fluorescens* (Yorkhill) and *Pseudomonas stutzeri* (QEUH), which by definition cannot be part of a cluster within the hospital setting.

There were only one case each of *Ralstonia pickettii* (Yorkhill)*, Raoultella planticola* (QEUH)*,* and *Roseomonas mucosa* (QEUH) and two cases of *Scopulariopsis brevicaulis* (Yorkhill) in the same patient (Table 11E). Single cases of a bacteraemia caused by a given microorganism are indicative of opportunistic infections observed in this patient population that do not have a common source. There were 9 cases of bacteraemia attributed to *Rhizobium radiobacter* (Table 7E). Eight of nine *Rhizobium radiobacter* cases occurred at Yorkhill and all cases were consistent with possible or probable epidemiological clustering. The QEUH case occurred in 2016 and appears to be an isolated case, leaving little concern about going environmental contamination from this microorganism.

Table 11D: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients (continued)

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Klebsiella oxytoca (continued)	24	QEUH	2016	Mar	Ward 2A	Possible
		QEUH	2016	Oct	Ward 2A	Probable
		QEUH	2016	Oct	Ward 2A	Probable
		QEUH	2016	Oct	Ward 2A	Probable
		QEUH	2017	Sept	Ward 2A	Possible
		QEUH	2017	Nov	Ward 2B Day Surgery	Possible
		QEUH	2018	Aug	Ward 2B Day Surgery	Unlikely
Leclercia adecarboxylata	1	Yorkhill	2005	October	Schiehallion Ward	No
Morganella morganii	1	Yorkhill	2011	May	Ward 3A	No
Ochrobactrum anthropi	1	Yorkhill	2012	Feb	Schiehallion Ward	No
Pantoea agglomerans	3	Yorkhill	2005	Nov	Schiehallion Ward	Possible
		Yorkhill	2005	Dec	Yorkhill OPs	Possible
		Yorkhill	2014	Feb	Schiehallion Ward	No
Pantoea species	5	Yorkhill	2007	May	Schiehallion DCU	No
		Yorkhill	2015	Jan	Schiehallion Ward	No
		QEUH	2017	Jan	Ward 2A	No
		QEUH	2018	May	Ward 2A	No
		QEUH	2022	June	Ward 2B DCU	No
Proteus mirabilis	8	Yorkhill	2005	Feb	Short Stay Ward	No
		Yorkhill	2006	June	Schiehallion Ward	Possible
		Yorkhill	2006	Nov	Schiehallion Ward	Probable
		Yorkhill	2006	Dec	Schiehallion Ward	Probable
		Yorkhill	2010	Jan	Schiehallion Ward	Unlikely
		Yorkhill	2010	Oct	Schiehallion DCU	Unlikely
		Yorkhill	2012	Dec	Schiehallion Ward	No
		QEUH	2018	Mar	Clinical Decision Unit	No
Pseudomonas aeruginosa	34	Yorkhill	2005	Nov	Schiehallion DCU	Probable
		Yorkhill	2005	Dec	Schiehallion DCU	Probable
		Yorkhill	2006	Jan	Schiehallion DCU	Probable
		Yorkhill	2007	Jan	Schiehallion Ward	Possible
		Yorkhill	2007	Mar	Schiehallion Ward	Possible
		Yorkhill	2007	July	Schiehallion Ward	Probable
		Yorkhill	2007	July	Schiehallion Ward	Probable
		Yorkhill	2007	July	Schiehallion DCU	Possible
		Yorkhill	2008	May	Schiehallion Ward	Probable
		Yorkhill	2008	Jun	Schiehallion Ward	Probable
		Yorkhill	2008	Aug	Schiehallion Ward	Possible
		Yorkhill	2009	Jan	Schiehallion Ward	Possible
		Yorkhill	2009	May	Yorkhill OPs	Possible
		Yorkhill	2009	Aug	Schiehallion Ward	Possible
		Yorkhill	2009	Oct	Schiehallion Ward	Probable
		Yorkhill	2009	Nov	Schiehallion Ward	Probable
		Yorkhill	2009	Dec	Schiehallion Ward	Probable
		Yorkhill	2010	Apr	Schiehallion Ward	Possible
		Yorkhill	2011	June	Schiehallion Ward	No
		Yorkhill	2013	Aug	Schiehallion Ward	Possible
		Yorkhill	2013	Dec	ITU	Possible
		Yorkhill	2014	July	Schiehallion Ward	Unlikely
		QEUH	2017	May	Ward 2A	Unlikely

Table 11E: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients (continued)

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Pseudomonas aeruginosa (continued)	34	QEUH	2018	Feb	Ward 2B Day Surgery	Possible
		QEUH	2018	Mar	Clinical Decision Unit	Possible
		QEUH	2018	Apr	Ward 2A	Probable
		QEUH	2018	May	Ward 2A	Probable
		QEUH	2018	June	Ward 2A	Probable
		QEUH	2019	Mar	Clinical Decision Unit	Possible
		QEUH	2019	Mar	Day Unit 6A	Possible
		QEUH	2020	Sept	Clinical Decision Unit	Possible
		QEUH	2020	Sept	Day Unit 6A	Possible
		QEUH	2021	Sept	Ward 2C	No
		QEUH	2022	Sept	Clinical Decision Unit	No
Pseudomonas fluorescens	1	Yorkhill	2007	Oct	Schiehallion Ward	No
Pseudomonas putida	9	Yorkhill	2007	Aug	Schiehallion Ward	Possible
		Yorkhill	2007	Oct	Schiehallion Ward	Possible
		Yorkhill	2013	Sept	Schiehallion Ward	No
		QEUH	2015	Oct	Emergency Department	Unlikely
		QEUH	2016	July	Ward 2A	Possible
		QEUH	2016	Nov	Ward 2A	Possible
		QEUH	2017	Aug	Ward 2A	Unlikely
		QEUH	2018	May	Ward 2A	Unlikely
		QEUH	2019	June	Emergency Department	No
Pseudomonas stutzeri	1	QEUH	2017	Oct	Ward 2A	No
Ralstonia pickettii	1	Yorkhill	2008	June	Schiehallion Ward	No
Raoultella planticola	1	QEUH	2017	Nov	Ward 2B Day Surgery	No
Rhizobium radiobacter	9	Yorkhill	2007	Dec	Schiehallion Ward	Probable
		Yorkhill	2008	Jan	Schiehallion Ward	Probable
		Yorkhill	2009	July	Schiehallion DCU	Possible
		Yorkhill	2009	Aug	Schiehallion Ward	Possible
		Yorkhill	2012	Mar	Schiehallion Ward	Possible
		Yorkhill	2012	July	Schiehallion Ward	Possible
		Yorkhill	2014	Feb	Schiehallion Ward	Probable
		Yorkhill	2014	Mar	Schiehallion Ward	Probable
		QEUH	2016	Nov	Ward 2A	No
Roseomonas mucosa	1	QEUH	2017	Sept	Ward 2A	No
Scopulariopsis brevicaulis	2	Yorkhill	2005	Apr	Schiehallion Ward	Probable
		Yorkhill	2005	May	Schiehallion Ward	Probable
Serratia liquefaciens	4	Yorkhill	2005	Mar	Schiehallion Ward	No
		Yorkhill	2008	May	Schiehallion Ward	No
		Yorkhill	2011	Sept	Schiehallion DCU	No
		QEUH	2018	Mar	Ward 2A	No

There were three cases of bacteraemia attributed to *Sphingomonas paucimobilis* and 24 attributed to *Serratia spp.* (Tables 11E and 11F). All *Sphingomonas paucimobilis* cases appeared to be sporadic in time and space with one occurring at QEUH and 2 at Yorkhill, suggesting no environmental source contributing to infections. There were 4 cases of bacteraemia attributed to *Serratia liquefaciens* (Table 11E), of which 3 occurred at Yorkhill and one at QEUH. None of these cases had epidemiological evidence of clustering. Among the 21 cases of bacteraemia attributed to *Serratia marcescens,* 6 occurred at QEUH and 15

occurred at Yorkhill (Table 11F). Two of the QEUH cases did not have sufficient evidence for epidemiological clustering, 2 were unlikely to cluster and 2 possibly clustered based on occurrence close in time. Conversely, 6 of the Yorkhill cases demonstrated probable epidemiological clustering, 6 demonstrated possible cluster, 2 had unlikely clustering and one had no evidence of epidemiological clustering. With very little clustering evidence and no WGS data on a historical background of more extensive epidemiological clustering evidence at Yorkhill, these data suggest that there is little evidence that *Serratia marcescens* is a source of environmental contamination an QEUH.

Table 11F: Microorganism species of environmental concern detected in low abundancy per year by hospital, year, month and location for paediatric patients (continued)

Species	# Cases	Hospital Location	Year	Month	Ward	Cluster
Serratia marcescens	21	Yorkhill	2005	Aug	Schiehallion Ward	Unlikely
		Yorkhill	2006	May	Ward 7A	Unlikely
		Yorkhill	2008	Aug	Schiehallion Ward	Possible
		Yorkhill	2008	Aug	Schiehallion DCU	Possible
		Yorkhill	2008	Oct	Schiehallion DCU	Possible
		Yorkhill	2008	Oct	Yorkhill OPs	Possible
		Yorkhill	2009	Sept	Schiehallion Ward	Probable
		Yorkhill	2009	Oct	Schiehallion Ward	Probable
		Yorkhill	2010	Oct	Schiehallion Ward	Probable
		Yorkhill	2010	Oct	Schiehallion Ward	Probable
		Yorkhill	2012	Aug	Schiehallion Ward	Possible
		Yorkhill	2012	Sept	Day Surgery Unit	Possible
		Yorkhill	2013	July	Schiehallion Ward	Probable
		Yorkhill	2013	Aug	Schiehallion Ward	Probable
		Yorkhill	2014	Dec	Schiehallion Ward	No
		QEUH	2016	June	Ward 2A	Unlikely
		QEUH	2017	Feb	Ward 2B Day Surgery	Unlikely
		QEUH	2018	Sept	Ward 3B	No
		QEUH	2019	Sept	Ward 6A	Possible
		QEUH	2019	Nov	1D Paed CritCare	Possible
		QEUH	2020	Oct	Ward 6A	No
Sphingomonas paucimobilis	3	Yorkhill	2005	Dec	Schiehallion Ward	No
		Yorkhill	2007	Sept	Yorkhill OPs	No
		QEUH	2017	Jan	Ward 2B Day Surgery	No

Table 12: Cases of *Enterobacter cloacae* by hospital, ward, date, and clustering potential (N=70)

Hospital	Year	Month	Ward	Cluster
Yorkhill	2005	May	Schiehallion DCU	Possible
Yorkhill	2005	May	Schiehallion Ward	Probable
Yorkhill	2005	June	Schiehallion Ward	Probable
Yorkhill	2005	June	Schiehallion Ward	Probable
Yorkhill	2005	July	Schiehallion DCU	Possible
Yorkhill	2005	July	Schiehallion Ward	Probable
Yorkhill	2005	Aug	Schiehallion Ward	Probable
Yorkhill	2005	Dec	Schiehallion Ward	Possible
Yorkhill	2006	Mar	Schiehallion Ward	Possible
Yorkhill	2006	Apr	Schiehallion DCU	Possible
Yorkhill	2006	May	Schiehallion Ward	Possible
Yorkhill	2006	June	Schiehallion Ward	Possible
Yorkhill	2006	July	Schiehallion Ward	Possible
Yorkhill	2006	July	Day Surgery Unit	Possible
Yorkhill	2006	Aug	Schiehallion Ward	Possible
Yorkhill	2006	Sept	Yorkhill OPs	Possible
Yorkhill	2007	May	Schiehallion Ward	Possible
Yorkhill	2007	July	ITU	Possible
Yorkhill	2008	May	Schiehallion Ward	Possible
Yorkhill	2008	June	Schiehallion DCU	Possible
Yorkhill	2008	Aug	Schiehallion DCU	Possible
Yorkhill	2008	Sept	Schiehallion Ward	Possible
Yorkhill	2008	Sept	ED	Possible
Yorkhill	2009	Mar	Schiehallion Ward	Probable
Yorkhill	2009	Mar	Schiehallion Ward	Probable
Yorkhill	2009	June	Schiehallion Ward	Possible
Yorkhill	2009	Oct	Schiehallion Ward	Possible
Yorkhill	2010	July	Schiehallion Ward	Possible
Yorkhill	2010	Aug	Schiehallion Ward	Possible
Yorkhill	2012	Jan	Schiehallion Ward	Possible
Yorkhill	2012	Feb	Schiehallion DCU	Possible
Yorkhill	2012	Apr	Schiehallion Ward	Possible
Yorkhill	2012	June	Schiehallion Ward	Probable
Yorkhill	2012	June	Schiehallion Ward	Probable
Yorkhill	2012	Aug	Schiehallion Ward	Possible
Yorkhill	2013	Sept	Schiehallion Ward	Unlikely
Yorkhill	2014	June	Schiehallion Ward	Possible
Yorkhill	2014	Sept	Schiehallion Ward	Possible
Yorkhill	2014	Dec	Schiehallion DCU	Unlikely
QEUH	2016	Dec	Ward 2A	Possible
QEUH	2016	Dec	Ward 2B DSU	Possible
QEUH	2017	Jan	Ward 2A	Possible
QEUH	2017	July	Ward 2A	Probable
QEUH	2017	Aug	Ward 2A	Probable
QEUH	2017	Aug	Ward 2B DSU	Possible
QEUH	2017	Sept	Ward 2A	Probable
QEUH	2017	Nov	Ward 2A	Possible
QEUH	2017	Dec	ED-Major	Possible
QEUH	2018	Apr	Ward 2A	Probable
QEUH	2018	Apr	Ward 2A	Probable
QEUH	2018	May	Ward 2A	Possible
QEUH	2018	May	Ward 2B DSU	Possible
QEUH	2018	Jun	Ward 2A	Probable
QEUH	2018	July	Ward 2A	Probable
QEUH	2018	Aug	Ward 2B DSU	Possible
QEUH	2018	Oct	Ward 6A	Possible
QEUH	2019	Jan	Clinic 1 OP	Possible
QEUH	2019	Feb	Ward 6A	Probable
QEUH	2019	Mar	Ward 6A	Probable
QEUH	2019	May	Ward 6A	Probable
QEUH	2019	Jun	Ward 6A	Probable
QEUH	2019	Jun	Day Unit 6A	Possible
QEUH	2019	July	Ward 6A	Probable
QEUH	2020	Apr	Ward 6A	Possible
QEUH	2020	June	Ward 6A	Possible
QEUH	2021	July	Ward 6A	Probable
QEUH	2021	July	Ward 6A	Probable
QEUH	2021	Sept	CDS	Possible
QEUH	2021	Oct	Ward 6A	Possible
QEUH	2022	Oct	Schienhall DSU	No

Table 13: Cases of *Klebsiella pnemoniae* bacteremia by hospital, location, date and clustering potential (N=85)

Hospital	Year	Month	Ward	Cluster
Yorkhill	2005	Jan	Schiehallion DCU	Possible
	2005	May	Schiehallion DCU	Possible
	2005	Nov	Schiehallion Ward	Probable
	2005	Nov	Schiehallion Ward	Probable
Yorkhill	2006	Jan	Schiehallion Ward	Probable
	2006	Feb	Schiehallion Ward	Probable
	2006	Mar	Schiehallion Ward	Probable
	2006	Apr	Schiehallion Ward	Probable
	2006	Apr	Schiehallion Ward	Probable
	2006	June	Schiehallion Ward	Probable
	2006	June	Schiehallion Ward	Probable
	2006	July	Schiehallion Ward	Probable
	2006	Nov	Schiehallion Ward	Possible
	2006	Dec	Schiehallion DCU	Possible
Yorkhill	2007	Mar	Schiehallion DCU	Possible
	2007	June	Schiehallion Ward	Probable
	2007	June	Schiehallion Ward	Probable
	2007	Aug	ITU	Possible
	2007	Aug	Schiehallion Ward	Probable
	2007	Aug	Schiehallion Ward	Probable
	2007	Sept	Schiehallion DCU	Possible
	2007	Sept	Schiehallion Ward	Possible
	2007	Oct	Schiehallion Ward	Probable
	2007	Oct	Schiehallion Ward	Probable
Yorkhill	2008	Jan	Schiehallion Ward	Probable
	2008	Jan	Schiehallion Ward	Probable
	2008	Feb	Schiehallion Ward	Probable
	2008	Mar	Schiehallion Ward	Probable
	2008	May	Schiehallion Ward	Probable
	2008	Jun	Schiehallion Ward	Probable
	2008	Aug	Schiehallion Ward	Probable
	2008	Aug	Schiehallion Ward	Probable
	2008	Aug	Schiehallion Ward	Probable
	2008	Oct	Yorkhill OPs	Possible
Yorkhill	2009	Aug	Schiehallion DCU	Possible
	2009	Sept	Schiehallion Ward	Possible
Yorkhill	2010	May	Schiehallion Ward	Possible
	2010	July	Schiehallion Ward	Probable
	2010	Aug	Schiehallion Ward	Probable
Yorkhill	2011	Mar	Schiehallion DCU	Possible
	2011	Apr	Schiehallion Ward	Probable
	2011	Apr	Schiehallion Ward	Probable
	2011	May	Schiehallion DCU	Possible
Yorkhill	2011	July	Schiehallion DCU	Possible
	2011	Dec	Schiehallion DCU	Possible
Yorkhill	2012	May	Schiehallion Ward	Possible
	2012	May	Ward 7A	Possible
	2012	July	Schiehallion Ward	Possible
	2012	Aug	Schiehallion DCU	Possible
Yorkhill	2014	Mar	Schiehallion Ward	Probable
	2014	Mar	Schiehallion Ward	Probable
	2014	July	Schiehallion Ward	Possible
	2014	Sept	Schiehallion Ward	Possible
	2014	Oct	Schiehallion DCU	Possible
Yorkhill	2015	Mar	Schiehallion Ward	Possible
	2015	Apr	Schiehallion DCU	Possible
QEUH	2016	June	Ward 2A	Possible
	2016	July	Ward 2B DSU	Possible
	2016	Aug	Ward 2A	Probable
	2016	Aug	Ward 2A	Probable
	2016	Oct	Ward 2A	Possible
	2016	Nov	Ward 2B DSU	Possible
QEUH	2017	Apr	ED-Major	Unlikely
	2017	July	Ward 2A	Probable
	2017	Aug	Ward 2A	Probable
	2017	Oct	Ward 2A	Probable
	2017	Oct	Ward 2A	Probable
	2017	Nov	Ward 2A	Probable
	2017	Nov	Ward 2A	Probable
	2017	Dec	Ward 2A	Probable
QEUH	2018	Jan	Ward 2A	Possible
	2018	Mar	Ward 2A	Probable
	2018	Mar	Ward 2A	Probable
	2018	Mar	Ward 3C	Possible
	2018	May	Ward 2A	Possible
	2018	Oct	Ward 6A	Unlikely
QEUH	2019	Jan	CDU	Possible
	2019	Mar	Ward 6A	Possible
QEUH	2020	Mar	CDU	Unlikely
	2020	Nov	Ward 6A	Unlikely
QEUH	2021	Apr	Ward 6A	Possible
	2021	Jun	Ward 2C	Possible
	2021	July	Ward 6A	Probable
	2021	July	Ward 6A	Probable
QEUH	2022	Jan	Ward 6A	Unlikely

Among 66 bacteraemia cases attributed to *Stenotrophomonas maltophilia,* 1/3 were from QEUH and 2/3 were from Yorkhill (Table 14). Among case at QEUH 1 demonstrated unlikely epidemiological cluster while 15 were possible, and 6 were probable. In contrast, among cases from Yorkhill 1 provide no evidence of epidemiological clustering, 2 were unlikely, 26 were possible, and 15 probable. Cases persisted year on year from June 2005-June 2014 at Yorkhill, suggesting either a common source or high burden among the patient population. At QEUH

cases persisted for a shorter period of time, from April 2017 until September 2019; no new cases are observed after September 2019. Samples from 13 of the 21 cases at QEUH between 2017-2019 were sent for WGS revealing that the two samples from July 2017 from Ward 2A classified as having probable epidemiological clustering, were unrelated to one another (Table 15C). Similarly, cases from March, April and May 2018, April and July 2017, and May, August and September 2019, which were epidemiologically classified as possibly clustering, were all genomically unrelated, and unrelated to environmental samples according to WGS analyses. These data suggest that (1) epidemiological clustering may over-estimate clustering for *Stenotrophomonas maltophilia*; (2) this patient population may carry a high persistent burden of *Stenotrophomonas maltophilia* bacteraemia unlinked to hospital-related environmental sources; and (3) recent changes, possibly due to practices or policies in antimicrobial prescribing or other healthcare management may be reducing the incidence of *Stenotrophomonas maltophilia* in more recent years.

The summary of the epidemiological clustering data (Table 16) reiterates the significantly higher number of cases observed historically when the haemato-oncology paediatrics service was located at Yorkhill compared with QEUH cases. There were 1.9 times more bacteraemia cases attributable to potential environmentally transmitted pathogens at Yorkhill compared to QEUH (163 vs 309), including a 2.87 times higher number of epidemiological clusters classified as probable and 2.07 times higher number of possible clusters. When we take into account the denominator of number of bed days from which cases were drawn, this corresponds to 1.44 time greater incidence of any epidemiological clustering, 1.63 times greater incidence of possible or probable clusters, and 1.98 greater incidence of probable clusters at Yorkhill as compare to QEUH. All differences were statistically significant.

Table 14: Cases of bacteremia attributed to *Stenotrophomonas maltophilia* by hospital, date and location with possible clustering assessment (n=66)

Hospital	Year	Month	Ward	Cluster
Yorkhill	2005	June	Schiehallion Ward	Possible
	2005	July	Unknown	Possible
	2005	Aug	DSU	Possible
	2005	Aug	Schiehallion Ward	Probable
	2005	Nov	Schiehallion Ward	Probable
	2005	Dec	Schiehallion Ward	Probable
	2005	Dec	Ward 7A	Possible
Yorkhill	2006	Mar	Schiehallion Ward	Possible
	2006	June	Schiehallion Ward	Probable
	2006	June	Schiehallion Ward	Probable
Yorkhill	2007	Jan	Schiehallion Ward	Unlikely
	2007	Apr	Yorkhill OPs	Possible
	2007	May	Schiehallion DCU	Possible
Yorkhill	2008	May	Schiehallion DCU	Possible
	2008	June	ITU	Possible
	2008	June	Schiehallion Ward	Probable
	2008	June	Schiehallion Ward	Probable
	2008	Aug	Schiehallion Ward	Probable
	2008	Aug	Schiehallion DCU	Probable
	2008	Aug	Yorkhill OPs	Possible
	2008	Oct	Schiehallion Ward	Possible
	2008	Oct	ITU	Possible
Yorkhill	2009	Mar	Schiehallion Ward	Possible
	2009	Aug	Schiehallion Ward	Possible
	2009	Nov	Schiehallion Ward	Possible
	2009	Dec	Schiehallion Ward	Probable
Yorkhill	2010	Jan	Schiehallion Ward	Probable
	2010	Feb	ITU	Possible
	2010	July	Schiehallion Ward	Probable
	2010	Aug	Schiehallion Ward	Probable
	2010	Sept	DSU	Possible
	2010	Oct	Schiehallion DCU	Possible
	2010	Dec	Schiehallion Ward	Possible
Yorkhill	2011	Jan	Schiehallion DCU	Possible
Yorkhill	2012	Feb	Schiehallion Ward	Unlikely
	2012	Jun	Ward 7A	Possible
	2012	Aug	Schiehallion Ward	Probable
	2012	Sept	Schiehallion Ward	Probable
Yorkhill	2013	June	Schiehallion DCU	Possible
	2013	June	Schiehallion Ward	Possible
	2013	Aug	Schiehallion Ward	Possible
Yorkhill	2014	Jan	Schiehallion Ward	Possible
	2014	June	Schiehallion Ward	Possible
Yorkhill	2015	May	Schiehallion Ward	No
QEUH	2016	June	Ward 2A	Unlikely
QEUH	2017	Apr	Ward 2A	Possible
	2017	May	Ward 2A	Possible
	2017	June	2B DCU	Possible
	2017	July	Ward 2A	Probable
	2017	July	Ward 2A	Probable
	2017	Sept	Ward 2A	Possible
QEUH	2018	Mar	CDU	Possible
	2018	Mar	Ward 2A	Probable
	2018	Mar	Ward 2A	Probable
	2018	Apr	Ward 2B- DSU	Possible
	2018	May	ED-Major	Possible
	2018	May	Ward 2A	Probable
	2018	June	Ward 2A	Probable
	2018	Aug	CDI	Possible
	2018	Sept	Ward 2B- DSU	Possible
	2018	Sept	ED-Major	Possible
	2018	Sept	Ward 2A	Possible
QEUH	2019	Apr	Ward 6A	Possible
	2019	May	Day Unit 6A	Possible
	2019	Aug	Ward 6A	Possible
	2019	Sept	4BCH BMTU	Possible

Table 15A: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Month/Year WGS	# WGS Patient Clusters (Non-Confirmatory)	# WGS Patient Environment Clusters	# Epi Clusters (type)	Total # of Haemato-oncology Patients with WGS	Individual Case Month/ Year Overlap	WGS Findings
Cupriavidus spp.						
02/2018-08/2019	1	1	1 (unlikely)	2	Sept 2017	Not clustered with any other sequence
					Jan 2018	Closest sequence from paediatric case (114 SNP difference), not epidemiologically linked
Overall *Cupriavidus pauculus* information from WGS reports: No evidence of clustering Two human cases with 144 SNP difference across 3yrs/5mos – no evidence for common origin Human and environmental sample with 102 SNPs difference – environmental samples were collected after patient sample						
Enterobacter spp.						
01/2016-09/2019	5	0	15 (all possible/probable)	15	Jan 2017	Not clustered with other patients or environment samples
					July 2017	115 SNP difference with May 2018 case, no evidence of common source
					Aug 2017	421 SNP difference with 2 isolates from a sink in the same ward isolated 13 months after the case, no evidence of a common source
					Aug 2017	56 SNP difference with the Sept 2017 case, but each organism had marked difference in antibiotic sensitivities, not related
					Sept 2017	56 SNP difference with the Aug 2017 case, but each organism had marked difference in antibiotic sensitivities, not related
					May 2018	115 SNP difference with July 2017 case, no evidence of common source
					May 2018	Not clustered with other patients or environment samples

Table 15B: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Years WGS	# WGS Patient Clusters (Non-Confirmatory	# WGS Patient Environment Clusters	# Epi Clusters (type)	Total # of Haemato-oncology Patients with WGS	Individual Case Month/ Year Overlap	WGS Findings
Enterobacter spp.						
2016-2019	2	0	15 (all possible/probable)	15	June 2018	236 SNP difference with a non-haemato-oncology patient from Mar 2016, no evidence of common source
					July 2018	117 SNIP difference with Oct 2018 case in the same patient, no evidence of common source
					Aug 2018	Not clustered with other patients or environment samples
					Oct 2018	117 SNIP difference with July 2018 case in the same patient, no evidence of common source new infection
					Jan 2019	Not clustered with other patients or environment samples
					Feb 2019	Not clustered with other patients or environment samples
					Mar 2019	Not clustered with other patients or environment samples
					May 2019	Not clustered with other patients or environment samples
					June 2019	Not clustered with other patients or environment samples
					July 2019	Not clustered with other patients or environment samples
Overall *Enterobacter spp.* information from WGS reports: There were some differences in interpretation between the two different WGS reports, specifically with the differences between the Aug and Sept 2017 cases, however, across 15 possible or probable epidemiologically clustered cases, there was 1 or 0 (depending on if one discounts the antibiotic resistance data) that were true human-human clusters; and no environmental samples clustered with human samples.						

Table 15C: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Years WGS	# WGS Patient Clusters (Non-Confirmatory	# WGS Patient Environment Clusters	# Epi Clusters (type)	Total # of Haemato-oncology Patients with WGS	Individual Case Month/ Year Overlap	WGS Findings
Stenotrophomonas spp.						
2017-2019	0	0	13	13	April 2017	No patient or environmental clustering
					May 2017	No patient or environmental clustering
					June 2017	No patient or environmental clustering
					July 2017	No patient or environmental clustering
					July 2017	No patient or environmental clustering
					Sept 2017	No patient or environmental clustering
					Mar 2018	No patient or environmental clustering
					Apr 2018	No patient or environmental clustering
					May 2018	No patient or environmental clustering
					June 2018	No patient or environmental clustering
					Sept 2018	No patient or environmental clustering
					Sept 2018	No patient or environmental clustering
					May 2019	No patient or environmental clustering
					Aug 2019	No patient or environmental clustering
					Sept 2019	No patient or environmental clustering
Overall *Stenotrophomonas spp.* information from WGS reports: While 13 patients from 13 epidemiological clusters were sequenced, there were no person-to-person or person-environmental clusters identified in WGS of Stenotrophomonas spp., even though environment-environment clusters were identified.						

Table 16: Summary of epidemiological clustering assessment for paediatric patients by hospital

	QEUH	Yorkhill	p-value*
Summary Score	270	617	NA
Incidence by Summary Score (per 1000 bed days)	5.75	9.01	0.001
Cases			
No Cluster	39	44	NA
Unlikely Clustering	29	25	NA
Possible Clustering	62	128	NA
Probable Clustering	39	112	NA
Total Cases	169	309	NA
Incidence (per 1000 bed days)			
Any BSI	3.60	4.51	0.042
Any Cluster	2.77	3.87	0.019
Possible & Probable Clusters	2.15	3.50	0.002
Probable Clusters	0.83	1.64	0.009

*$p \leq 0.05$ considered statistically significant

Furthermore, incidence of bacteraemia cases attributable to environemntally relevant microorganisms that may cluster epidemiologically by month and year (Figure 13), highlights the ~2 fold lower incidence of cases at QEUH compared to historical cases at Yorkhill. They also demonstrate a potential decreased incidence over time at QEUH.

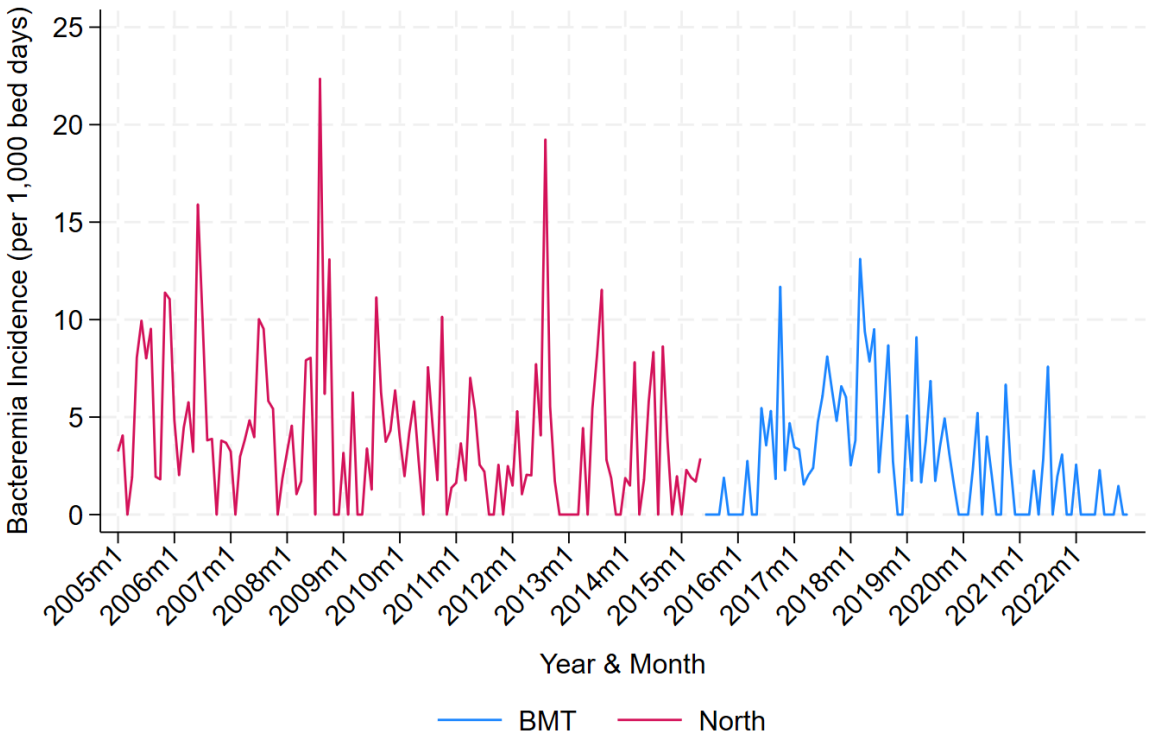


Figure 19: Incidence of bacteraemia cases attributable to environemntally relevant microorganisms that may cluster edpidemiologically among haemato-oncology paediatric patients in GGC

7.2.9 Bacteraemia attributable to environmentally relevant microorganisms compared to those that are not among paediatric patients in GGC

In order to develop a better understanding of the patterns of BSI among paediatric haemato-oncology patients in the GGC, we examined all BSIs and compared the patterns in those that were and were not environmentally relevant (please consult Tables 1 and 2 and see section 3 for further explanation). Figure 20 shows all BSIs broken down by hospital and environmental relevance. By hospital, BSIs attributable to environmentally relevant organisms largely follow the same pattern as BSIs attributable to organisms that do not persist in the environment/are human commensal organisms, meaning that they infect the blood of the immune compromised individual they are living on when an opportunity presents, for example surgery, indwelling catheters, etc. We can observe two exceptions to this where in late 2006/early 2007 at Yorkhill there appears to be a more significant reduction in environmentally relevant organism than those that are not environmentally attributable and again in 2015/early 2016 when the patients are moved from Yorkhill to QEUH, however, this does follow the pattern that is observed at Yorkhill directly before the move in early 2015. This type of difference in BSI pattern could

be attributable to a wide range of factors, including changes in antimicrobial policy, capacity of laboratory services, policies on testing for BSI, and natural patterns of microorganism attributable to environmental factors, as well as many others. In historical data without an extensive volume of additional information, it would be difficult to determine a likely cause. While it is unclear what may be driving these two lower troughs in environmentally relevant BSIs compared to other types of BSIs at these timepoints, it is clear that environmentally relevant BSIs largely follow the same pattern as those that cannot be attributable to the environment over time, suggesting a natural pattern of BSI among these immune compromised patients, rather than some sort of widespread environmental contamination.

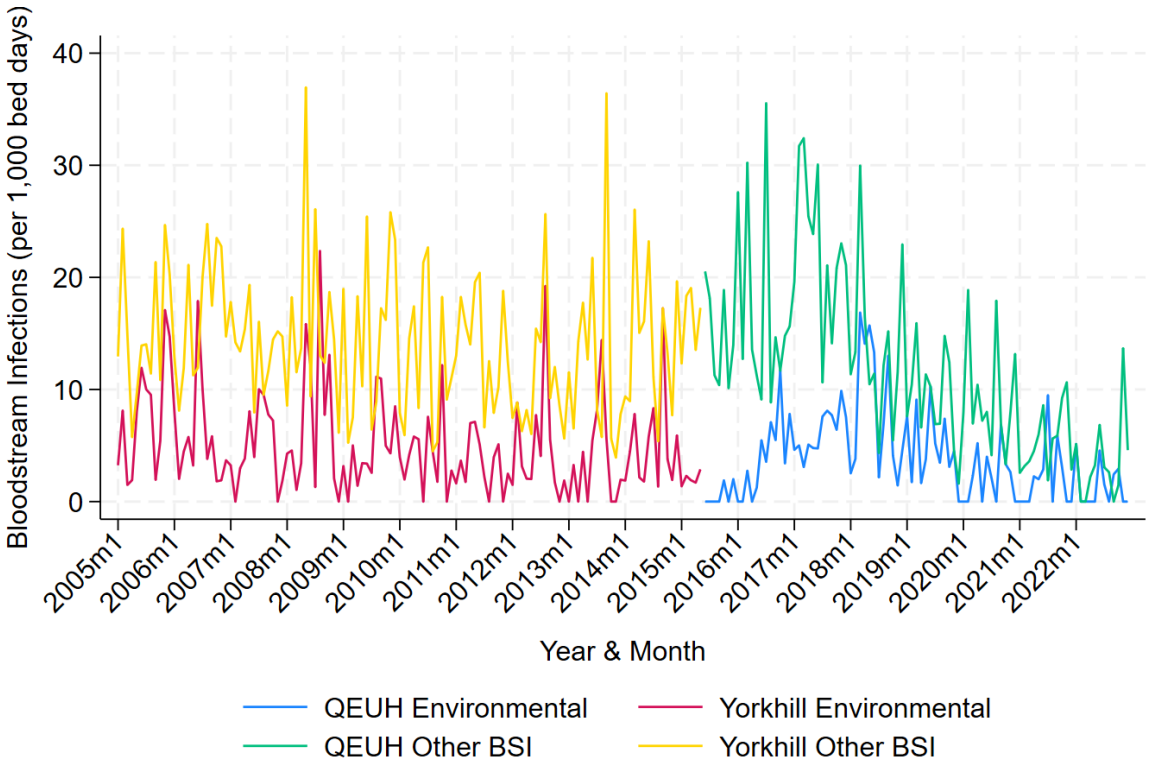


Figure 20: Bloodstream infections over time by hospital and relevance to environmental survival and transmission

Breaking these data down further, and fitting a predicted trend line, we observe a very slightly decreasing pattern of BSI that cannot be attributed to the environment over time at Yorkhill, and a much more steeply decreasing pattern of BSI at QEUH (Figure 21). Given that data from each hospital covers different periods of calander time, and QEUH is more recent, this is not surprising. As we learn more about the impact of antimcrobial prophylais and prescribing on patient risk and treatments for haemato-oncological conditions improve, management of the

whole patient population has improved over time, which could result in reductions in BSI over time. These data do demonstrate, though that prevention of BSI is has significantly improved at QEUH.

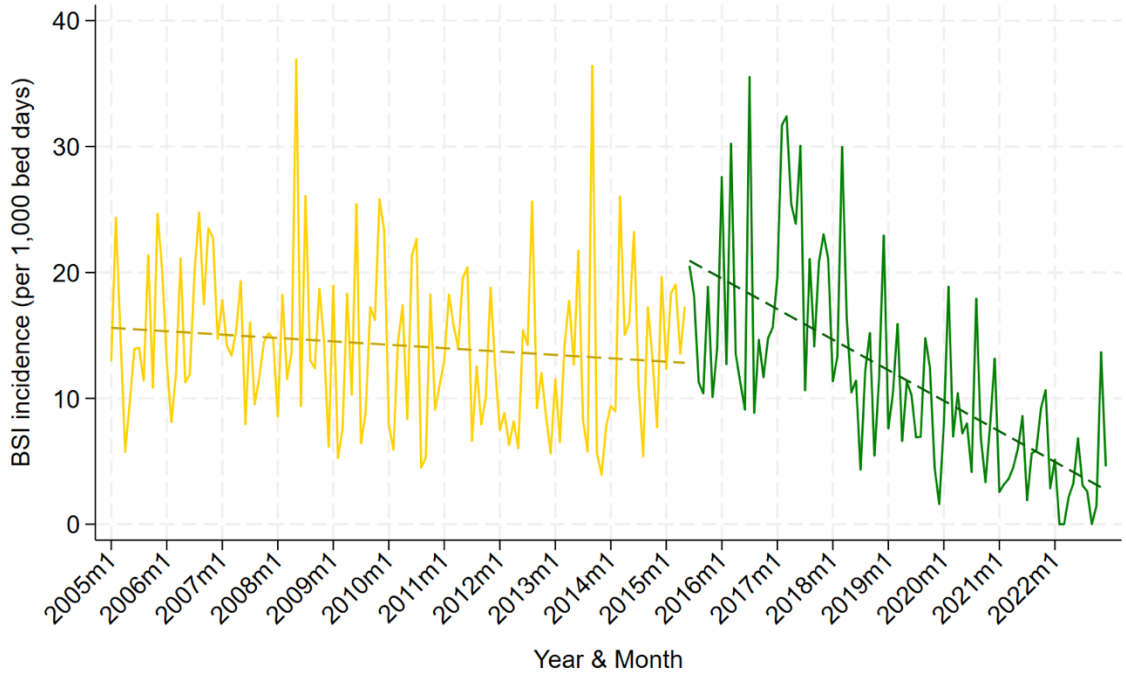


Figure 21: Bloodstream infections attributable to organisms with no environmental relevance at Yorkhill and QEUH with a fitted line showing change over time

Similarly, when we fit a trend line to the data on BSIs that are environmentally relevant, we note that Yorkhill started with a slightly higher incidence of envirnmentally relevant BSIs and show a decrease in these over time (Figure 22), as would be predicted by the pattern observed in overall BSI as shown in Figure 21. QEUH started with an overall average lower incidence of BSI from environmentally relevant organisms and has show a slightly more dramatic decrease in these BSIs over time (Figure 22), as expected from the patterns observed in Figure 21 based on BSIs that are not attributable to envirnmentally relevant organisms. Overall, this highlights that BSIs with environmentally relevant organisms are following the same pattern as BSIs overall and that significant reduction in BSIs, both environmentally relevant and others, continues to occur at QEUH.

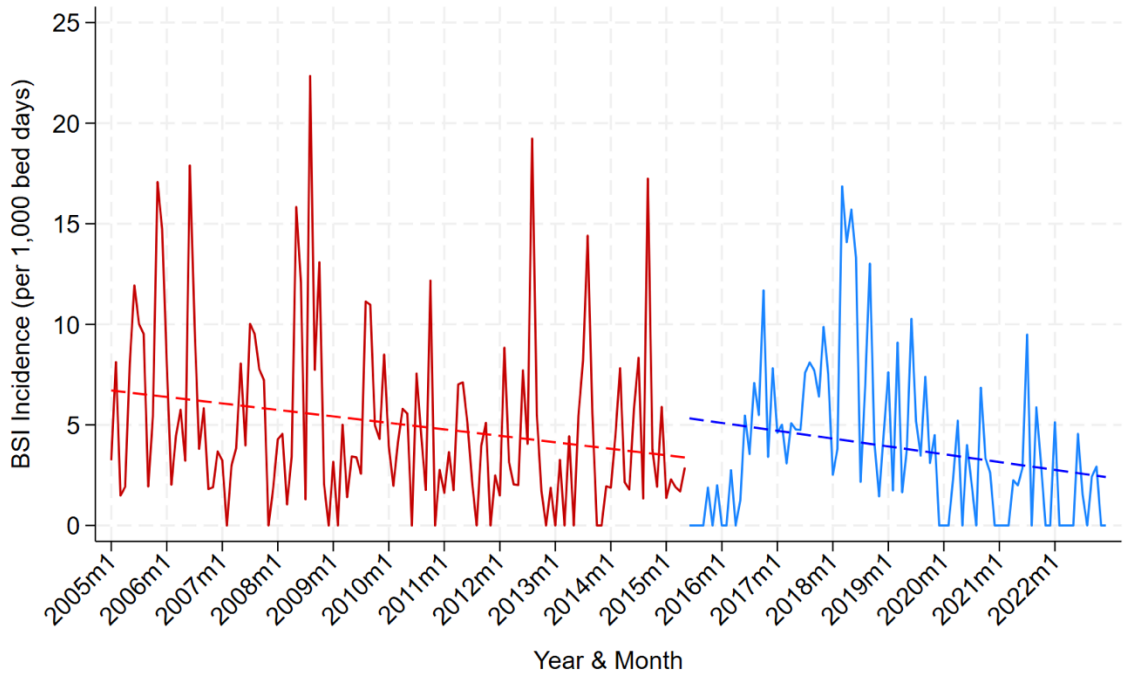


Figure 22: Bloodstream infections attributable to organisms with environmentally relevant at Yorkhill and QEUH with a fitted line showing change over time

7.2.10 Evidence of environmental contamination, particularly the water supply, based on bacteraemia data from haemato-oncology patients in the GGC

In summary, the historical data from the GGC haemato-oncology services provides a background into prior incidence and cases of bacteraemia attributable to microorganisms that could be environmentally relevant. This allows us to evaluate cases and incidence at QEUH relative to the same or equivalent services for haemato-oncology patients within the local Glasgow region, which is particularly important for comparing like with like. These data reveal a number of important facts in considering risk of infection to patients from purported environmental reservoirs as follows.

- Haemato-oncology patients across services have an expected, yet very high risk of bacteraemia and cases are common in this patient population.
- Among adult haemato-oncology patients, including comparison of both historical and current services, both incidence and cases of bacteraemia attributed to environmentally relevant microorganisms individually or taken together are statistically similar between QEUH and other GGC hospitals.

- Examining the most vulnerable adult patients in this service, bone marrow transplant patients, alone there is a continued decrease in incidence overtime following transfer of these services from the Beatson Hospital in the North Sector to QEUH.
- Among paediatric haemato-oncology patients, we see an ~2 fold decrease in incidence and cases of bacteraemia attributed to environmentally relevant microorganisms following transfer of services from Yorkhill to QEUH; lower incidence at QEUH was statistically significant.
- While we can identify a number of probable and possible epidemiological clusters based on microorganism species, date and location of sampling, where available WGS data suggest that these epidemiological clusters are a high over-estimate of true clusters.
- For most cases of bacteraemia attributed to specific species of microorganisms we observed a decrease in cases over time since patients moved to QEUH.
- Overall, patterns of BSI attributable to microorganisms that are environmentally relevant follow the same pattern as BSIs attributable to microorganisms that cannot be attributed to environmental contamination, suggesting that all BSIs are following a natural pattern.
- There have been large reductions in incident BSI overall and by microorganisms environmental attribution at QEUH overtime, suggesting overall increasingly effective prevention strategies.

Taken together, these data provide little to no evidence for environment sources of bacteraemia in patients at QEUH and conversely suggest that policies and procedures for patient management over time could be decreasing incidence of bacteraemia attributable to environmentally relevant microorganisms, as well as all BSIs, although this is speculative and the patient population still has significant bacteraemia burden overall.

7.3 What does the available sequencing data show?

We have described in Section 3 above the properties of the bacteria selected by the CNR panel as potentially causing infection with an environmental source in a highly vulnerable patient population. It is tempting to speculate that most of the infections caused by these very divergent bacterial species come from the ward environment as a number of them have been identified in environmental samples. However, as explained above patients can acquire these bacteria from environments other than the hospital such as their home and in the general community as

well as cross colonisation from other patients. The study by Coppry et al. (2020), which looked at *Pseudomonas aeruginosa* infections in ICU patients, is an example. They found that only 170/1515 isolates were regarded as having an exogenous origin (i.e. not already being carried by the patient on admission). When considering the origin of these exogenous isolates the smallest number of 29 originated from taps as determined by PFGE; in 55 isolates the origin could not be determined and a total of 86 were acquired from another patient. It should be remembered that in this study 35% of all water outlets were positive for *Pseudomonas aeruginosa* at some point in the study. This represents a much heavier level of colonisation in the environment than that seen at QEUH. This demonstrates that acquisition from the hospital environment even in a setting where there is substantial environmental contamination does occur but is relatively rare.

Whilst some possible clusters of potentially water derived bacteria were noted by the CNR panel at the QEUH, when analysed these were confined to *Stenotrophomonas* and *Klebsiella*. As described above while some cases may have been acquired from the environment there are other potential reasons for patients to become colonised with these bacteria in particular selection by administration of carbapenem antibiotics particularly in the case of *Stenotrophomonas*.

If there is a persisting environmental source causing infection in patients then in almost all reported studies environmental isolates are closely related to or indistinguishable from the clinical isolates when sensitive strain typing methods are applied. A good example of this situation is the study by Nurjadi et al. (2021) of carbapenem resistant *Enterobacter cloacae* in a haematology unit between 2015 and 2021 using WGS strain typing. Although only occurring relatively infrequently one to two isolates/month a peak of infections occurred in 2018 raising the suspicions in the team of an outbreak. This prompted a prospective investigation and WGS strain typing of both the contemporaneous isolates and historical isolates. This showed the majority to be highly clonal belonging to the ST66 sequence type. Sampling the environment revealed 50% of sinks and water outlets to be positive for ST66 *E. cloacae*. Typing of earlier isolates showed them also to be ST66. The isolates were highly related as the maximum number of snips between all of the ST66 isolates over the six year was 48 SNPs, which would be consistent where there is chronological evolution of a clone. Allowing for the time period this is consistent with a clonal outbreak with an extensive water source. Shower drain traps were eventually identified as the most likely persisting source and fitting autoclavable shower tray

inserts terminated the outbreak. When such environmentally based outbreaks occur there is a clear increase in cases of infection caused by the environmental bacterium. This is a very different pattern of environmental isolations and clinical infections compared to QEUH.

This typical outbreak pattern of infections arising from the environment is also illustrated in the report of an outbreak of *Sphingomonas paucimobilis* infections in a paediatric haematology-oncology unit (Aşkın et al. 2022). The authors describe a sudden substantial increase in the infection rate represented by a cluster of 25 cases of infection over a five month time frame. Sampling of hot water taps identified 4 hot water taps with growth of *Sphingomonas paucimobilis* thus identifying the source.

We do not believe in the face of the published experience and the levels of infection with marker organisms seen at QEUH that the environment was a significant source of infection. We conclude that whilst some infections may have been acquired from the hospital environment, acquisition of colonisation in other settings can be considered as the probable cause for many of the infections encountered.

In considering the molecular typing data on the QEUH isolates we recognise that not all clinical and environmental isolates have been subjected to WGS strain typing. However, a reasonable sample has been sequenced bearing in mind the investigation of the wards was not a funded prospective research study. The detailed reports by Professor Tom Evans does not identify any matching isolates between the environment and patients for *Stenotrophomonas*. In the case of *Enterobacter* spp. all 29 blood culture isolates were typed together with 60 environmental isolates. The only paired indistinguishable isolates in the clinical collection were from isolates obtained at different times from the same patient. This confirms the sensitivity and specificity of WGS SNP typing. No patients shared indistinguishable strains which is what would be expected if a common environmental source was potentially responsible. Compare this finding to that of Nurjadi et al. (2021).

In the case of *Cupravidus* spp., which is a very common bacterium in all water supplies, unsurprisingly large numbers isolates were collected. The extensive collection of these isolates despite the fact they very rarely cause infection even in compromised patients was presumably due to a local interest in the bacterium. A total of 127 environmental isolates and six human isolates were subjected to WGS SNP analysis. As two of the human isolates were obtained prior to 2018 and therefore were not contemporaneous with the intensive environmental

sampling for *Cupravidus* which occurred in February and March 2018, it is therefore difficult to come to any conclusion as to their likely source. No evidence was found that the four human isolates obtained post March 2018 matched any of the environmental isolates.

An argument could be advanced that due to a very diverse population individual matching isolates of *Cupravidus* could be missed. The WGS data showed environmental populations of *C. pauculus*, the most common species, *C. gilardii* and *C. metalodurans* were highly clonal with only 1-30 SNPs between representatives of each species. The human isolates differed very substantially suggesting that they came from a different population. It should be noted that sampling was not uniform during the time period of interest 191/485 total isolates being obtained in February and March 2018. However, it seems probable that elements of this highly clonal population structure would have persisted over time ensuring that they were sampled.

It could be suggested that this uneven sampling strategy resulted in an isolate being missed. We concur fully with the conclusion of Professor Evans expressed in his conclusion paragraph 4.5 as follows: "One important consideration is whether the sampling 'missed' a water organism that spread directly to a patient. The water sampling strategy showed that out of 10,311 samples, only 485 such samples grew *Cupriavidus* species. Of these 10,311 water samples, 6,183 looked specifically for Cupriavidus of which 275 (4.4%) were positive for this genus. For human isolates obtained after March 2018, the water sampling was more intense and more *Cupriavidus* isolates were stored and sequenced. In this period, therefore, the sequence data are highly representative of the *Cupriavidus* species isolated in environmental samples. It is therefore unlikely that during this period the sampling did not capture a significant presence of *Cupriavidus* strains, unless they were extremely transitory. For the 2 human cases isolated prior to this date, the sampling was not so intense and sequences are not available for any 6 Cupriavidus that might have been isolated. It is not possible, therefore, to comment on whether there were closely related environmental isolates to these human samples".

8. Ventilation - analysis of infection rates and data from QEUH & RHC

A key indicator for an increased rate of infection related to an "inadequate or insufficient" ventilation system in the haemato-oncology population is infections due to *Aspergillus* species (*A. spp.*).

8.1 Is there an increased rate of airborne infections in QEUH consistent with a failure of the ventilation system?

Definitions of invasive fungal disease

Internationally accepted criteria (Donnelly et al. 2020) for invasive fungal diseases, including IA, define three categories with decreasing certainty of a case representing true infection:

- Proven. Microscopic visualisation of tissue damage by, and/or culture of, *A.*spp. from a normally sterile tissue.
- Probable. A combination of a susceptible host PLUS clinical features (principally, findings on a CT chest scan suggestive of an invasive fungal disease) PLUS mycological culture from sputum or broncho-alveolar lavage (BAL) and/or biomarker positivity (see below) with galactomannan (GM), PCR for *A. spp*, and/or Beta-D-glucan (BDG).
- Possible. Cases that meet the criteria for a host factor and a clinical feature but for which mycological evidence is lacking.

Laboratory data

The NHS GGC laboratory services take samples from other health boards and primary care, so data was filtered based on allocation to either a haematology/haemato-oncology consultant or location.

All microbiological data that could indicate infection due to *A. spp*. were analysed. As *A. spp*. are never (with only vanishingly rare exceptions) cultured form blood, we looked at data from sputum and BAL with any *A. spp*. growth detected. In addition, three biomarkers that can indicate the presence of *A. spp*. were analysed:

- Galactomannan (GM), which is specific for *A. spp*.

- PCR for *A. spp*, which is also specific for *A. spp*.
- Beta-D-glucan (BDG), which can support a diagnosis of invasive aspergillosis, even though it is not *A. spp*. specific, but is a pan-fungal marker.

Case definitions for this report

In this patient population, Proven cases of aspergillosis are exceptionally rare (as obtaining sterile tissue for diagnosis requires invasive procedures in an unwell patient). Outside of Proven cases, objective evidence for invasive aspergillosis comes from mycological data - culture or biomarkers – which is part of the Probable case definition but not Possible. Also, if BDG is the only mycological criterion, this is not indicative of an invasive aspergillosis as it is a pan-fungal marker.

Given these challenges of case definition, for the purposes of this evaluation, *any evidence of infection with A. spp. was counted as a suspected case (regardless of host and imaging factors)*. This approach may inflate the number of cases as mycological data alone is not regarded as a case by the EORTC/MSGERC criteria. On the other hand, Possible cases will be lost, as this category is based on host plus imaging criteria, but as explained above, Possibles lack any objective evidence of infection with an *A. spp*.

Time period

Results were available from 2013 to 2023 for the adult haemato-oncology service and from 2005 to 2022 for the paediatric service.

De-duplication

Where the same patient had multiple positive tests for the same admission episode, this was classified as one case.

8.1.1 Results – Adults

Figure 23 shows the total adult cases with evidence of infection with *A. spp*. by year and with respect to location in the different sectors of QEUH and haemato-oncology services of NHS GGC. The Adult BMT results are shown as green bars in the histogram while the horizontal green bars above the histogram represent when the Adult BMT services were in QEUH. The

blue and orange bars represent cases in the other sites across Glasgow serving haemato-oncology (Adult South and Adult North).

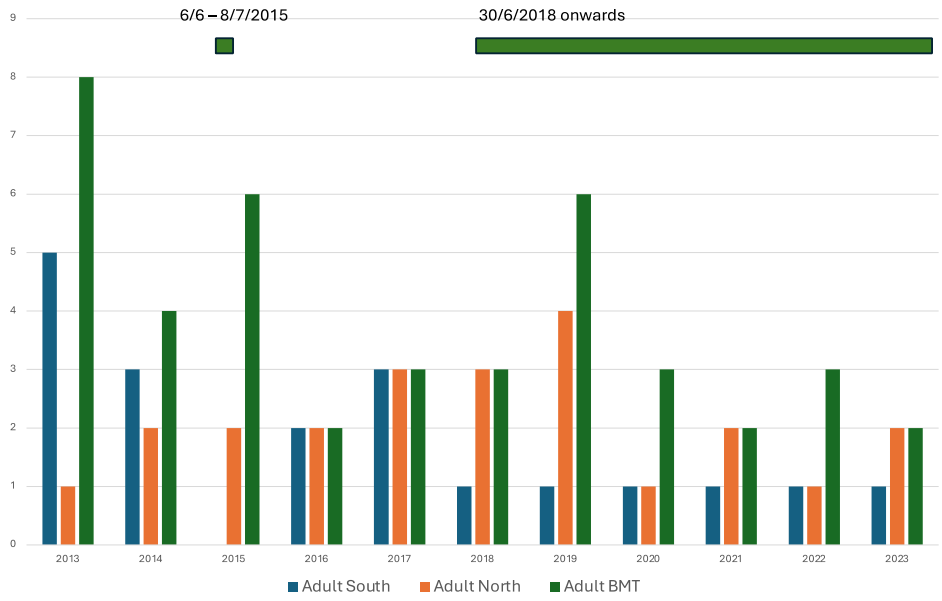


Figure 23: Total number of adult cases with evidence of infection with *Aspergillus species* by year and location. The horizontal green bars above the histogram indicate when the Adult BMT service was located in QEUH.

The Adult BMT service moved from the Beatson Institute to Ward 4B QEUH on 6th June 2015 but then returned to the Beatson Wards B8/9 on 8 July 2015. Adult BMT was then permanently placed at QEUH 4B from 30 June 2018. The distribution of cases in the Adult BMT service in the split site years of 2015 and 2018 between the Beatson and QEUH was: six versus none, and 2 versus 1, respectively.

The Adult haematology (South) service moved to Ward 4C QEUH between 1-3 May 2015, while Adult haematology (North) was never on the QEUH campus.

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
QEUH	-	-	0	-	-	1	6	3	2	3	2
Beatson	8	4	6	2	3	2	-	-	-	-	-

Table 17: Cases over time in the Adult BMT service by site: QEUH (Queen Elizabeth University Hospital) or the Beatson

Table 17 shows variation over the decade from 2013 to 2023 in cases with evidence of infection due to *A. spp.* in the Adult BMT service. The low-level variation over time is the expected pattern with no trends visible. There is no indication of increasing numbers of cases following the permanent move to QEUH on the 30th June 2018 – 17 cases (2018-2023) versus 25 (Beatson Adult BMT, 2013-2018).

Table 18 below shows the data for the other haemato-oncology services in Glasgow with low-level variation in case numbers, as seen in the Adult BMT data, with no trends visible over time or location. Although data for only two full calendar years was available prior to the Adult South service relocating to the QEUH, there is no suggestion of increased rates of *Aspergillus* infections in the QEUH: pre-move, 8 cases in 2 years (2013-2014) versus 10 cases in 7 years (2016-2022; data for 2023 was only to March and so not counted) in QEUH.

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Adult South	5	3	0	-	-	-	-	-	-	-	-
Adult South QEUH	-	-	0	2	3	1	1	1	1	1	1
Adult North	8	4	6	2	3	3	6	3	2	3	2

Table 18: Cases over time in the Adult Haematology South and Adult Haematology North services. Adult South data is shown pre- and post the move to QEUH (Queen Elizabeth University Hospital) in May 2015.

8.1.2 Interpretation – Adults

The methodology used for case definition would be predicted to inflate numbers. Despite this, total numbers of cases across the adult haemato-oncology services are low. For comparison, a study from the adult Haemato-Oncology Unit at St Bartholomew's Hospital, London, looked at 589 patient-episodes between September 2005 and June 2009 (Tsitsikas et al. 2012). Fungal biomarker testing was with GM testing alone and only performed for 9 months of the study. Despite the markedly limited diagnostic testing in the study, 17 cases were identified with evidence of *Aspergillus* infection, not including 4 proven cases. The St Bartholomew's BMT

Unit covers a population half the size of the population served by the Adult BMT QEUH service: approximately 2.1 million versus 5.5 million.

- The total number of cases with evidence of infection with *A. spp.* is low across the different sectors of QEUH and haemato-oncology services of NHS GGC.
- From 2013 to 2023, there is no indication of increased cases of infections with *A. spp.* in the Adult BMT service, including after the permanent move to QEUH from the Beatson Unit in June 2018.
- From 2013 to 2023, there is no indication of increased cases of infections with *A. spp.* in the Adult Haematology South service, including after the permanent move to QEUH May 2015.
- The case numbers from 2013-2023 in the Adult Haematology North service - which did not move to QEUH - show the expected variation over time.
- Total numbers of cases in the Adult BMT unit at QEUH (2018-2023) were 17, as compared to 19 cases in the same time period for the Adult Haematology North service.

8.1.3 Results – Paediatrics

Data was available for the paediatric haematology and oncology service from 2005 to 2022. The service moved to the RHC site on 10th June 2015, with subsequent movements to different areas of the QEUH campus, coming back to RHC Wards 2A and 2B in March 2022. These movements and the total number of cases over time are shown in Figure 24. Of note, on 26th September 2018, paediatric BMT patients moved to QEUH Ward 4B, and the other inpatient/day care to 6A at QEUH - the Adult BMT and non-BMT/haemato-oncology wards, respectively. The inpatient service moved to RHC CDU on 22nd January 2019 before returning to 6A on 11th February 2019.

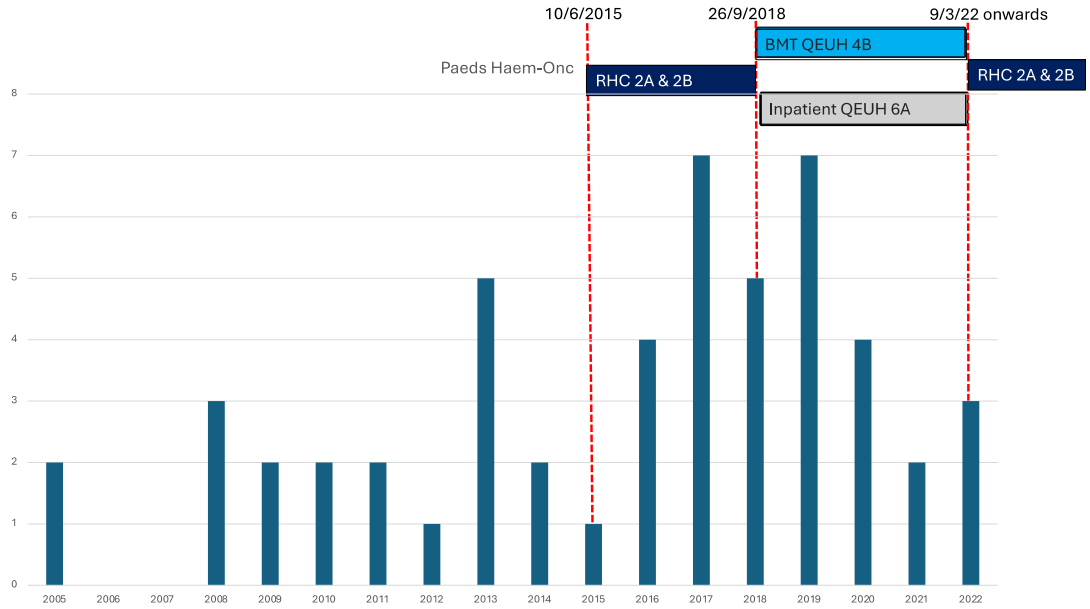


Figure 24: Total number of paediatric cases with evidence of infection with *Aspergillus species* by year and location. The horizontal bars above the histogram indicate the different locations of the service on the QEUH campus. Dark blue bar: paediatric haematology and oncology. Light blue bar: paediatric BMT. Grey bar: inpatient and day care.

The number of cases with evidence of infection with *A. spp.* in the paediatric haematology and oncology service following the move to RHC in 2015 varied from 1 to 7 per annum from 2016-2022, as compared to 0 to 5 from 2005-2014.

Table 19 shows the breakdown of cases by location throughout the period the paediatric service was based on Wards 2A/B, RHC, and during the time of relocation to QEUH 4B and 6A. The annual total number of cases for the paediatric services varied from 1-7 (2015-2022) compared to 0-5 cases per year prior to 2015. No trends are seen over time for the number of cases by location when the service was split between QEUH 4B and 6A.

	2015	2016	2017	2018	2019	2020	2021	2022
QEUH 4B BMT	-	-	-	0	0	1	0	0
QEUH 6A	-	-	-	1	5	2	2	0
RHC 2A and 2B	1	2	6	3	-	-	-	2
Annual Total	1	4♣	7♦	5♥	7*	4#	2	3**

Table 19: Distribution of paediatric cases with evidence of infection with *Aspergillus species* by year and location in RHC or QEUH (ie, after relocation of the service in June 2015). Diagnostic samples were sent from: ♣ - 2 cases in Ward 1D Paeds critical care, RHC; ♦ - 1 case in CritCar Un6 HDU50-59 QEUH; ♥- 1 case in Ward 2B Day CareUnit RHC; * - 1 case in Clinical decision Unit RHC; 1 case in Ward 1D Paeds critical care, RHC; # - 1 case in CritCar Un4 HDU31-40 QEUH; ** - 1 case in Schiehall DaySur Wd2B RHC.

8.1.4 Interpretation - Paediatrics

The annual total number of cases show low level variation from 2005-2022 before and after the move to RHC in June 2015. This variation over time is expected. The repeated relocation on the QEUH campus, with the associated disruption, would be a risk factor for increased rates of invasive aspergillosis. However, there are no marked differences in case numbers by location (namely, RHC versus Wards 4B and 6A in QEUH, see Figure 24 and Table 19), with similar variations seen over time regardless of the location or the specific population (BMT versus non BMT).

	2015	2016	2017	2018	2019	2020	2021	2022
Paeds QEUH 4B BMT	-	-	-	0	0	1	0	0
Adult BMT	0	-	-	1	6	3	2	3
Paeds QEUH 6A	-	-	-	1	5	2	2	0
Adult South QEUH	0	2	3	1	1	1	1	1

Table 20: Paediatric and adult cases with evidence of infection with *Aspergillus species* over time on the QEUH/RHC sites. Co-location of paediatric and adult BMT services are highlighted in red and the non BMT services are highlighted in green.

It is useful to look at both the paediatric and adult services – both BMT and non BMT data – during the period of co-location of services between 26/09/2018 to March 2022 on QEUH 4B and 6A (Table 20). In the same built environment, there is low level variation over time between the two patient groups based on location. This variation is expected and, along with the overall low absolute numbers of cases, there is no evidence of increased infection rates associated with the ventilation system. The data is most in keeping with patient-related factors being the key drivers: the underlying haematological condition, myelosuppression and immunosuppression associated with the cancer and treatments given, treatment-related toxicities and the commensal carriage of *A. spp.* spores in the airways.

8.1.5 Summary

The question posed was: "Is there an increased rate of airborne infections in QEUH consistent with a failure of the ventilation system?"

In the context of hospitalised immunocompromised patients with haematological, and other, cancers, a key concern is invasive aspergillosis involving the lungs. An increase in infections due to *A. spp.* attributable to the ventilation system would manifest as trends over time - measured in months to years - or as an outbreak, or cluster, of cases in a specific location.

For both the paediatric and adult services, the observed number of cases and variations over time do not show evidence of the built environment increasing infection rates.

- With the low absolute numbers of cases, and the expected variation over time, there is no indication of the ventilation system increasing infections with *A. spp.* in either RHC or QEUH.
- From 2013 to 2023, there is no indication of increased cases of infections with *A. spp. in the* Adult BMT service, including after the permanent move to QEUH from the Beatson Unit in June 2018.
- From 2013 to 2023, there is no indication of increased cases of infections with *A. spp. in the* Adult Haematology South service, including after the permanent move to QEUH May 2015.

- The case numbers from 2013-2023 in the Adult Haematology North service, which did not move to QEUH, show the expected variation over time and are comparable with cases in the Adult BMT service at QEUH (19 versus 17, respectively, 2018-2023).

- For both the paediatric and adult services, the variations in annual total cases over time, by location and during the period of co-location of the services on the QEUH wards, do not indicate the built environment is determining case rates, rather patient-related factors are the key drivers.

9. List of Tables and Figures

Tables

Table 1: Microorganisms grown in blood samples reported by the clinical laboratory between 2008-2023 for adult and paediatric patients at NHS GGC Hospitals that could be environmentally transmitted

Table 2: Microorganisms grown in blood samples reported by the clinical laboratory between 2008-2023 for adult and paediatric patients at NHS GGC Hospitals that are not usually associated with an environmental source

Table 3: Criteria for ranking clusters

Table 4: Bed days reported by sector and derived for hospital by month and year

Table 5A: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location

Table 5B: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Table 5C: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Table 5D: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location (Continued)

Table 6: Enterobacter cloacae bacteraemia by consultant sector, hospital, date and location (N=33)

Table 7: Pseudomonas aeruginosa bacteraemia by consultant sector, hospital, date and location (N=32)

Table 8: Stenotrophomonas maltophilia bacteraemia by consultant sector, hospital, date and location (N=45)

Table 9: Summary of adult whole genome sequencing (WGS) data available compare with epidemiological clustering data

Table 10: Summary of epidemiological clustering assessment for adult patients by hospital

Table 11A: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients

Table 11B: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients (continued)

Table 11C: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients (continued)

Table 11D: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients (continued)

Table 11E: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients (continued)

Table 11F: Microorganism species of environmental concern detected in low abundancy per year by consultant sector and hospital by month, year and location paediatric patients (continued)

Table 12: Cases of Enterobacter cloacae by hospital, ward, date, and clustering potential (N=70)

Table 13: Cases of Klebsiella pnemoniae bacteremia by hospital, location, date and clustering potential (N=85)

Table 14: Cases of bacteremia attributed to Stenotrophomonas maltophilia by hospital, date and location with possible clustering assessment (n=66)

Table 15A: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Table 15B: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Table 15C: Summary of paediatric whole genome sequencing (WGS) data available compare with epidemiological clustering data

Table 16: Summary of epidemiological clustering assessment for paediatric patients by hospital

Table 17: Cases over time in the Adult BMT service by site: QEUH (Queen Elizabeth University Hospital) or the Beatson

Table 18: Cases over time in the Adult Haematology South and Adult Haematology North services. Adult South data is shown pre- and post the move to QEUH (Queen Elizabeth University Hospital) in May 2015.

Table 19: Distribution of paediatric cases with evidence of infection with Aspergillus species by year and location in RHC or QEUH (ie, after relocation of the service in June 2015).

Table 20: Paediatric and adult cases with evidence of infection with Aspergillus species over time on the QEUH/RHC sites.

Figures

Figure 1: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by Consultant Sector

Figure 2: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by QEUH vs other hospitals in NHS GGC

Figure 3: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by Consultant Sector with adjusted denominators based on average of other years for those denominators presented in red in Table 4

Figure 4: Incidence of all bacteraemia by month and year (incidence/1,000 bed days) by QEUH vs other hospitals in NHS GGC with adjusted denominators based on average of other years for those denominators presented in red in Table 4

Figure 5: Incidence of bacteraemia from organisms that could be environmentally transmitted by QEUH vs other NHS GGC hospitals

Figure 6: Incidence of bacteraemia from organisms that could be environmentally transmitted by QEUH vs other NHS GGC hospitals with adjusted denominators based on Table 4

Figure 7: Clusters (unlikely, possible, probable) of bacteraemia of environmental significance by hospital and date

Figure 8: Clusters (unlikely, possible, probable) of bacteraemia of environmental significance by hospital and date with denominator adjustments based on Table 4

Figure 9: BSI incidence among adult haemato-oncology patients in the GGC by hospital and whether or not the organism isolated in culture is of environmental significance or not.

Figure 10: BSI incidence among adult haemato-oncology patients in the GGC by hospital and whether or not the organism isolated in culture is of environmental significance or not including adjusted denominators

Figure 11: BSI incidence attributable to non-environmentally significant microorganisms among adult haemato-oncology patients in the GGC by hospital

Figure 12: BSI incidence attributable to non-environmentally significant microorganisms among adult haemato-oncology patients in the GGC by hospital including adjusted denominators

Figure 13: BSI incidence attributable to environmentally relevant microorganisms among adult haemato-oncology patients in the GGC by hospital

Figure 14: BSI incidence attributable to environmentally relevant microorganisms among adult haemato-oncology patients in the GGC by hospital including adjusted denominators

Figure 15: Incidence of environmentally relevant bacteraemia within BMT patients only over time

Figure 16: Incidence of bacteraemia that may cluster (unlikely, possible probable) within BMT patients only over time

Figure 17: Incidence of all cases of bacteraemia among paediatric patients over the study period

Figure 18: Incidence of bacteraemia from organisms of potential environmental concern among paediatric patients over the study period

Figure 19: Incidence of bacteraemia cases attributable to environemntally relevant microorganisms that may cluster edpidemiologically among haemato-oncology paediatric patients in GGC

Figure 20: Bloodstream infections over time by hospital and relevance to environmental survival and transmission

Figure 21: Bloodstream infections attributable to organisms with no environmental relevance at Yorkhill and QEUH with a fitted line showing change over time

Figure 22: Bloodstream infections attributable to organisms with environmentally relevant at Yorkhill and QEUH with a fitted line showing change over time

Figure 23: Total number of adult cases with evidence of infection with Aspergillus species by year and location.

Figure 24: Total number of paediatric cases with evidence of infection with Aspergillus species by year and location.

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11. Declaration

We, Professor Peter Hawkey, Dr Samir Agrawal and Dr Lydia Drumright declare that:

1. We understand that our duty in providing written reports and giving evidence is to help the Inquiry, and that this duty overrides any obligation to the party by whom we are engaged or the person who has paid or is liable to pay us. We confirm that we have complied and will continue to comply with our duty.

2. We confirm that we have not entered into any arrangement where the amount or payment of fees is in any way dependent on the outcome of the Inquiry.

3. We know of no conflict of interest of any kind, other than any which we have disclosed in this report.

4. We do not consider that any interest which we have disclosed affects our suitability as expert witnesses on any issues on which we have given evidence.

5. We will advise the party by whom we are instructed if, between the date of this report and the evidential hearing, there is any change in circumstances which affects the evidence provided in this report.

6. We have shown the sources of all information relied upon.

7. We have exercised reasonable care and skill in order to be accurate and complete in preparing this report.

8. We have endeavoured to include in this report those matters, of which we have knowledge or of which we have been made aware, that might adversely affect the validity of our opinion. We have clearly stated any qualifications to my opinion.

9. We have not, without forming an independent view, included or excluded anything which has been suggested to us by others, including my instructing lawyers.

10. We will notify those instructing us immediately and confirm in writing if, for any reason, this report requires any correction or qualification.

11. We understand that:

11.1 This report may form part of the evidence to be given under oath or affirmation;

11.2 Questions may be put to us in writing for the purposes of clarifying this report and that our answers shall be treated as part of this report and covered by our statement of truth;

11.3 The Inquiry may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues;

11.4 The Inquiry may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;

11.5 We may be required to attend an evidential hearing to provide oral evidence;

11.6 We are likely to be the subject of public adverse criticism by the Chair if the Inquiry concludes that we have not taken reasonable care in trying to meet the standards set out above.

12. We have read the Code of Practice produced by The Law Society of Scotland entitled "Expert Witnesses Engaged by Solicitors" and we have complied with its requirements.

STATEMENT OF TRUTH

We confirm that we have made clear which facts and matters referred to in this report are within our own knowledge and which are not. Those that are within our own knowledge we confirm to be true. The opinions we have expressed represent our true and complete professional opinions on the matters to which they refer.

12. Authors

12.1 Professor Peter M Hawkey BSc, PhD, DSc, MBBS, MD, FRCPath, FFPath, FRCPI

Current Posts	Emeritus Professor of Clinical and Public Health Bacteriology (appointed Emeritus 2020) The Medical School, University of Birmingham, Edgbaston, Birmingham, U.K
	Locum NHS Consultant Microbiologist, Grampian Health Board with special responsibility for Shetland Health Board, NHS Scotland 2020-
	Retired Visiting Professor of Microbiology, Xiangya University Hospital, South Central University, Changsha, Hunan, PRC
2001-2020	Professor of Clinical and Public Health Bacteriology and Honorary Consultant, The Medical School, University of Birmingham, Edgbaston, Birmingham, U.K and Honorary Consultant Microbiologist, Queen Elizabeth Hospital, Birmingham 2016-2020, previously Honorary Consultant Microbiologist, Heartlands Hospital, Birmingham (2001-2016).
2004-2018	West Midlands Regional Microbiologist, Public Health England & Director,Birmingham Public Health Laboratory, Heartlands Hospital, Birmingham.
1993-2001	Professor of Medical Microbiology , Department of Microbiology, University of Leeds and Honorary Consultant Leeds General Infirmary
1991-1993	Reader and Honorary Consultant, University of Leeds
1985-1991	Lecturer/Senior Lecturer and Honorary Consultant, University of Leeds
1979-1985	Lecturer and Honorary Senior Registrar, University of Bristol

Professor Peter Hawkey has published over 300 research papers in the areas of molecular evolution and epidemiology of antibiotic resistance, Clostridium difficile, tuberculosis and molecular diagnostics for infectious diseases. One current research focus is on the use of Faecal Microbiome Transplant (FMT) for treating severe Clostridium difficile infection. This work has been expanded to encompass the effect of FMT on inflammatory bowel disease and the patient microbiome. He is a regular speaker at international conferences and advisory boards on these topic areas. Peter has edited two widely used clinical microbiology post graduate textbooks: Principles and Practice of Clinical Bacteriology (Wiley) and Medical Bacteriology (OUP). His research support has come from the Department of Health NIHR, PHE, NERC, Wellcome Trust and the pharmaceutical industry. For the last 25 years Peter has

researched extensively on the subject of antibiotic resistance in S.E. Asia particularly through collaborative projects with colleagues in China particularly at Chinese University of Hong Kong. He was visiting Professor at Xiangya Hospital, South Central University, Changsha for 10 years. He is currently locum consultant microbiologist for NHS Grampian. Peter has a longstanding practice (35 years) in medico-legal litigation as an expert witness. He was involved in shaping UK national policy on nosocomial infection control and antibiotic resistance by chairing and participating in expert groups and committees in the UK and Europe. Most notably being a founding member of the DoH's main advisory committee for hospital infection control and antimicrobial resistance (ARHAI). In total he was invited to serve 3 five-year terms. He is cited in Who's Who. He was awarded the prestigious Garrod Medal from the British Society for Antimicrobial Chemotherapy in 2017.

Qualifications

- FFPath, FRCPI, Royal College of Physicians of Ireland
- FRCPath Royal College of Pathologists
- MD, University of Bristol
- MB BS, University of London (Kings College Hospital), 1978
- DSc, University of Leeds
- PhD University of Birmingham
- BSc (Hons) Microbiology, University of East Anglia

Biography

Peter Hawkey started his scientific career as a plant pathologist working on Gleosporium perrenans a fungal storage pathogen of pathogen in apples at East Malling Research Station. A longstanding attraction to medical microbiology following a research post in 1971 at Kings College Hospital prompted enrolment for a medical degree. Experience as a junior doctor looking after patients with the superbug of the 1970's, gentamicin resistant, Klebsiella pneumoniae kindled a life-long interest in the mechanism and evolution of plasmid mediated resistance to antibiotics in gram negative bacteria.

Recruitment as a lecturer at the University of Bristol to work on gentamicin resistant Providencia stuartii resulted in a higher degree studying transposition immunity and composite transposon formation in vivo mediated by Tn3. This thesis supervised by Peter Bennett and Sir Mark Richmond, the MRCPath being obtained concurrently.

Due to lack of promotion opportunities in Bristol a move to work with Richard Lacey in Leeds as Senior Lecturer and subsequently a personal chair in 1992 facilitated the development of his research group which worked on molecular evolution of plasmids and antibiotic resistance genes in Enterobacteriaceae, Neisseria gonorrhoeae and acinetobacter. The early application in 1989 of PCR to M. tuberculosis led

to a further research area resulting in the development of clinical diagnostics for TB using PCR and rapid PCR-based typing techniques for M. tuberculosis.

An invitation to run a workshop in Guangzhou, China in 1997 led to the characterisation and first description of the gene encoding second most common CTX-M Extended Spectrum Beta Lactamase (ESBL) in the world, CTX-M-14. His longstanding interest in the evolution and development of antibiotic resistance in China and the Far East has resulted in a number of important publications in the arena of molecular epidemiology of antibiotic resistance. A move to the chair of public health and clinical bacteriology, which was newly established jointly by the University of Birmingham, HPA and Heart of England Foundation Trust, enabled more extensive development of research on the molecular epidemiology of M. tuberculosis, the environmental flow and evolution of antibiotic resistance genes in collaboration with the University of Warwick and the antibiotic research group founded by

Laura Piddock. Peter's group was the first to describe the existence of variable number tandem repeat DNA elements within the Staphylococcus aureus genome and to exploit those variable elements for rapid molecular typing to identify cases of cross-infection in patients. The application of the same technology to Clostridium difficile has led to research work on sub-typing of the dominant clones of Clostridium difficile in the UK and to chairing the Department of Health working party producing the definitive guidance on the control and management of Clostridium difficile infections for England. A similar role has been filled in relation to ESBL and carbapenemase producing Enterobacteriaceae for the DoH through the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections (ARHAI) of which Peter was a founder member.

He has developed the largest UK centre for faecal microbiome transplantation (FMT) which holds the only MHRA specials licence for third party provision of FMT, treating over 200 patients with CDI to date. Several projects involving the use of shotgun metagenomics and SNP polymorphism typing are on-going in relation to CDI and the use of FMT. He is now undertaking a large scale trial of the use of FMT in ulcerative colitis in collaboration with Professor Tariq Iqbal (University of Birmingham), funded by NIHR.

He lectures extensively internationally with invited key note lectures delivered at major medical microbiology conferences. As an experienced consultant to all the major pharmaceutical companies involved in antimicrobial development he has a unique insight into the future pipelines of agents as well as an understanding of the threats to human and animal health posed by AMR.

In December 2017 Peter was awarded the highly prestigious Garrod medal by the British Society for Antimicrobial Chemotherapy.

Teaching

Peter was the course convenor for infection teaching for the MBChB and BMedSci (intercalated) up until 2019. He still teaches on a wide range of Postgraduate teaching programmes with a number of invited lecturers at regional, national and international level.

Postgraduate supervision

Peter has supervised over 40 PhD/MD doctorates.

RESEARCH

Research Themes

Antimicrobial resistance, molecular epidemiology, rapid diagnostics for infection, clinical trials.

Peter's work focuses on the following 3 areas:

Novel resistance mechanisms

Peter's research work studies widely dispersed and clinically very important mechanisms of resistance to Extended Spectrum cephalosporins and carbapenem antibiotics. Most of this work is conducted with the University of Warwick and internationally in China. Current work involves characterising the molecular basis and genetic mobility of newly emerging and emerged resistance genes to these antibiotics.

Molecular epidemiology

Peter has been involved in developing novel molecular characterisation techniques for nosocomial (hospital acquired) bacteria for over 30 years.

Novel interventions to reduce nosocomial infection

Currently studied approaches include the introduction of clinical care systems to enhance control of nosocomial infection. Development and research on the use of Faecal Microbiome Transplant (FMT) for treating severe Clostridium difficile infection. This work has been expanded to encompass the effect of FMT on inflammatory bowel disease and the patient microbiome. He was employed up to August 2020 employed to develop the IMI's Ref Impact case on the R&D that led to the delivery of a national service for FMT. He is a member of the multidisciplinary team that produced the 2024 guidelines for faecal transplantation in the UK.

Current Grants

NIHR-EME Stop Colitis co-I with Prof Tariq Iqbal UoB £3.1 million 2017-23

OTHER ACTIVITIES

National Committees and Advisory Groups:

Member of:

PHE HCAI & AMR Programme Board (2009-2014)

Chairman of UK NEQAS national microbiology steering committee 2009-2018

Department of Health's Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections (ARHAI) [previously Specialist Advisory Committee on Antimicrobial Research (2001-6)] (2006-2016), and the ARHAI sub-committee on Healthcare-associated Infection Research Network (HAIRN) (2008 -2016)

Chairman of DoH working party on the control and management of Clostridium difficile infections (2009-!5), and member of the DoH MRSA working party (2015)

Defra Antimicrobial Resistance Co-ordination Group (DARC) (2005-2020) and chair of the DARC group's sub-committee on ESBLs (2008-2020)

Council of the British Society of Antimicrobial Chemotherapy (2001-7), chairman of Grants Committee (from 2005-8), and member of Education Committee (1995-9)

Examinerships

Examiner for Royal College of Pathologists, chair of RCPath Regional Training committee (1995-2001), member of RCPath examination review group (1999-2003) and RCPath specialty advisor (1999-2001). Hong Kong College of Pathologists for fellowship examination

Formerly external Examiner to:

- University of Cambridge,
- University of London (Queen Mary College)
- University of London (University College)
- University of Malaya
- Chinese University of Hong Kong (CUHK)*

Currently (2021-2024):

- Chinese University of Hong Kong (CUHK)
- University College London Medical School(end 2023)

International Committees and Advisory Groups

Chairman of the European Committee on Antimicrobial Sensitivity Testing (EUCAST) Sub-Committee on Molecular Testing (1998-2002)

Advisor and trainer for SEARO to the WHO Antimicrobial Resistance

Monitoring Programme (1997-2006)

Submission as a medical & technical expert to the NICE MTEP on use of Faecal Microbiome Transplant for treatment of recurrent Clostridium difficile infection 2021

Expert advisor to Eumedica, Menarini, Merck & Co, Novartis, Pfizer, Roche & Shionogi on development of new antimicrobials. Pfizer, Roche, Shionogi

Invited Lectures

In the last 10 years Professor Hawkey has been invited and delivered over 200 seminars/lectures and presentations for organisations including:

- Pasteur Institute
- Imperial College London
- University College London
- University of Cambridge
- All India Institute of Medical Sciences
- University of Queensland
- University of Western Australia
- Chinese University of Hong Kong
- University of Leiden
- European Congress of Clinical Microbiology and Infectious Diseases
- Australian Society for Microbiology
- Infectious Disease Society of America Annual Meeting
- Asia Pacific Congress of Clinical Microbiology and Infection (APCCMI)
- RCP London & Glasgow
- RCPath

Editorships

- Reviews in Medical Microbiology (1989 to date)
- Clinical Microbiology and Infection (2002 to 2014)
- Bugs & Drugs (2008 to 2015)
- Journal of Antimicrobial Chemotherapy (1992 – 1997)
- Editor of two of the leading postgraduate text books in medical microbiology:
    - Medical Bacteriology – a Practical Approach, 2nd Edition. (P.M. Hawkey and D. Lewis, editors), University Press, Oxford, (2004)
    - Principles and Practice of Clinical Bacteriology, 2nd Edition (S.G. Gillespie and P.M. Hawkey, editors), Wiley, (2006)

AWARDS

Garrod Medal from British Society for Antimicrobial Chemotherapy 2017

JD Williams Lecture 1999

PUBLICATIONS

1. Ng RW, Dharmaratne P, Wong S, Hawkey P, Chan P, Ip M. Revisiting the donor screening protocol of faecal microbiota transplantation (FMT): a systematic review. Gut 2023;.2023-329515. doi: 10.1136/gutjnl-2023-329515.
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12.2 Dr Samir G Agrawal BSc, MB ChB, FRCP, FRCPath, PhD

QUALIFICATIONS

B.Sc Pharmacology (Hons) 2.1	1985, University of Bristol
Bachelor of Medicine and Surgery	1988, University of Bristol
MRCP (London)	1991, Member, Royal College of Physicians
PhD in Immunology (« 1st class »)	1999, University of Paris (XII)
MRCPath	2000, Member, Royal College of Pathologists
Specialist in Haematology	1.9.2000, Accreditation with the Dept. of Health
FRCPath	2007, Fellow, Royal College of Pathologists
FRCP (London)	2011, Fellow, Royal College of Physicians

Professional memberships

British Society of Haematology
Royal College of Pathologists
UK CLL Forum – former CTC member
UK MDS Forum – former Trustee and CTC member

Patient Group Support

Former trustee for CLL Support Association (Registered Charity No 1113588, www.cllsupport.org.uk). Renamed, CLL Support in 2019 – my role became medical advisor.

CURRENT POST **Senior Lecturer and Hon. Consultant in Haematology (from Nov 2001).**

Queen Mary University Medical and Dental School and London and Barts Health NHS Trust

- Director of the Stem Cell Laboratory (GMP Facility)
- Head of Diagnostic Immunophenotyping
- Clinical Lead for CLL
- **Clinical Lead for infection management**
- Audit Lead for Haemato-Oncology
- Chair of Tumour Board for Haemato-Oncology, North East London Cancer Network (2009 - 2012)
- London Cancer (2012)
  - Deputy Chair, Haemato-Oncology Pathway Board

- Lead for the Cancer follow up re-design sub group
- Lead of the CLL subgroup

Managerial roles:

- My current roles at Barts include Audit lead, Lead for infection management and supportive care, Lead for remote patient care.
- I have developed and implemented new management pathways for sepsis, including novel diagnostics and strategies for invasive fungal diseases.
- I developed, funded and implemented the "remote Patient Monitoring Programme", which went live in 2015. Patient feedback is overwhelmingly positive.
- Deputy Chair for the London Cancer Haem-Onc Pathway Board (2012 – 2014). Goals: to define best practice and reconfigure services across North Central, North East London; population ~ 4.5M. This work led to reduction of BMT services from 3 to 2 providers (Barts and UCLH) and acute leukaemia centres to 3 (Barts, UCLH and one regional centre).
- Chair of Tumour Board for Haemato-Oncology, North East London Cancer Network. Remit: with all relevant healthcare professionals, to agree and disseminate guidelines for patient management. Audits of compliance were performed asking, for example, "Was the patient discussed at a multidisciplinary meeting?" – target 100%. This work was incorporated into London Cancer.
- Director of the Stem Cell Laboratory (2002 – 2015)
  I managed the transformation of services through several major changes: the EU directives on tissue processing for human therapeutic purposes; two relocations and rebuilds (in 2003, £0.7M; and 2011, £1.5M investment); new accreditation inspections by the MHRA and the Human Tissue Authority in 2007, 2009, 2011, 2014; and a JACIE inspection in 2012. I this role, I promoted clinical research with Cancer, Renal medicine and, most notably, cardiology (see publications)
- Group leader for several research projects supervising BSc, MSc, PhD and postgraduates. These individuals have gone to careers in the NHS, academia and industry. I was directly responsible for staff, as their line manager, for career progression, annual appraisal, training and personal development.

- I chaired the multidisciplinary Leukaemia Diagnostic Unit meetings (Southampton). At Barts, I am a core member of the MDT.

SERVICE DELIVERY and AUDITS

In addition to the clinical service (transplantation, the "Lymphoma Team" and infection lead), I was lead for two regional services providing cutting edge facilities for local and referring physicians. The first department at Barts Health to have a Human Tissue Authority inspection.

- Clinical service

  Major developments in the clinical service have been (a) the remote monitoring programme, which puts patients' needs at the centre of their care, rather than the needs of the hospital. (b) The introduction of novel diagnostic tests and approaches to infection management. (c) Introduction of regular antimicrobial stewardship rounds.

  Audits

- rh-EPO in the management of cancer chemotherapy induced anaemia.

  I designed, funded, produced clinical guidelines and implemented this service. Audits show excellent outcomes (the best reported worldwide) and led to publications and oral presentations at international meetings. Outputs: reductions in red cell transfusions, improvements in QOL, protocols for IV iron supplementation (Funding £0.17M 2004 – 2007).

- Introduction of biosimilar G-CSF across Haemato-Oncological practice.

  In 2011, Barts switched to biosimilar G-CSF, Zarzio. Extensive audit of this switch has shown the successful transition to the biosimilar G-CSF and its safety. (See publications).

- Anti-fungals in high-risk haemato-oncology patients.

  Invasive fungal disease remains a challenging problem in haemato-oncology. With an annual budget of ~£1M spent on anti-fungal drugs. Retrospective audits since 2003 have led to updating of our protocols. In 2012, a diagnostic-driven strategy was introduced and audited, showing a dramatic reduction in anti-fungal usage.

  A highly successful interaction with the small university fungal research group, that I have set up, is ongoing. This has led to new diagnostics in the clinic, development of new assays to be validated for clinical use, publications (see below) and international recognition. A web site – Fungal Update (https://mycologyconference.co.uk/) showcases the annual Fungal Update meeting, which is now in its 20th year.

  I have also developed a web-based audit tool to support antimicrobial stewardship.

INTERNATIONAL ROLES

Collaborator on ERA-NET biomix group aspergillus programme (AspBiomics)
Member of EAPCRI – European initiative on diagnostic PCR assays for invasive aspergillosis, 2010.
ECIL5/6 - European Conference for Infections in Leukaemia; member of the aspergillus treatment subgroup, 2013 (see publications).
INSERM – I was an external, independent assessor for an INSERM programme assessment for the "Programme du Conseil Scientifique de l'Institut Jean-Godinot" Reims, France, 2012.
AmBiGuard Steering Committee Meeting (at ECCMID, Berlin, 2013) – multinational, multicenter RCT of fungal prophylaxis in acute lymphoblastic leukaemia (see publications)

NICE, NATIONAL ROLES AND GUIDELINES

English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Fungal Subgroup member, 2015 – ongoing.
Chair for the British Committee for Standards in Haematology subgroup to rewrite the Guidelines for the Management of Invasive Fungal Disease. BCSH 2103 - ongoing.
British Society of Haematology representative on NICE scoping panel for the Technology Appraisal of Obinutuzumab for previously untreated chronic lymphocytic leukaemia [ID650]. NICE 2013.
Critical review of guidelines for the management of invasive fungal disease in patients with haematological malignancy for the Pan-London BMT Consortium – review paper and Commisioner audit tool. (See publications – 2011)
Haemato-Oncology expert on the emergency government Dept. of Health Committee for the production of IVIg use guidelines – development of a national monitoring programme; plus annual review process (2008).
Update April 2009 . "DH – National Immunoglobulin Database Update"
Royal College of Physicians and Pathologists expert Haematology representative on the Topic Expert Group (TEG) for Quality Standards in chronic kidney disease. 2010
Royal College of Physicians and Pathologists expert Haematology representative on the Guideline Development Group (GDG) for Management of the anaemia of chronic kidney disease. (http://www.nice.org.uk/nicemedia/pdf/Anaemia_Management_full_guideline.pdf)
Royal College of Physicians and Pathologists expert Haematology witness to the NICE health technology assessment of the use of erythropoietic agents for the management of cancer treatment-induced anaemia.
Evidence reviewer for the Systematic Review supporting the NHS Centre for Reviews and Dissemination COG guidelines for « Guidance on commissioning cancer services - improving outcomes in haemato-oncology ». Status – published by NICE 2003.

AWARDS

1. **British Medical Journal** 2018 – finalist in the "Cancer Care Team of the Year" awards
2. **Royal Society of Medicine** 2017 – runner-up in "Telemedicine and eHealth Innovation"
3. **NHS Innovations** 2006 - Innovator Award 2006: for introduction of new diagnostic tests for the diagnosis of human leukaemias - especially, CD160
4. **NHS Health and Social Care**, Innovative Technology Award 2007: one of 3 finalists for translation of research to routine NHS laboratory providing cheaper, faster and more accurate diagnosis of haematological cancers.
5. **Barts Health Trust-wide audit competition** 2005 - winner; introduction of rh-EPO in the management of cancer chemotherapy induced anaemia (for implementation, guidelines and funding)

PUBLICATIONS

1. Paschalis Vergidis, Ryan W. Stevens, Samir G. Agrawal. Antifungal Stewardship Interventions in Patients with Hematologic Malignancies. Current Fungal Infection Reports. 2023. https://doi.org/10.1007/s12281-023-00465-1
2. Samir Agrawal, Neil Gow, Duncan Wilson and Lewis White. Guest editor and Editorial for: Invasive Fungal Disease in the Immunocompromised Host/Research. Topic Proceedings of the Mycology 2021 Meeting", Front. Cell. Infect. Microbiol., 2022. DOI: 10.3389/fcimb.2022.1033739
3. Caldwell L…Agrawal S. Cessation of ciprofloxacin prophylaxis in haemato-oncology patients. Clin Infect Diseases. 2021 https://doi.org/10.1093/cid/ciab1000
4. Aries JA et al. Clinical Outcome of Coronavirus Disease 2019 in Haemato-oncology Patients. Br J Haematol. 2020;190(2):e64-e67. doi: 10.1111/bjh.16852. Epub 2020 Jun 10.
5. Farren T, Sadanand K, Agrawal S. Highly Sensitive and Accurate Assessment of Minimal Residual Disease in Chronic Lymphocytic Leukemia Using the Novel CD160-ROR1 Assay. Front Oncol. 2020 Dec 3;10:597730. doi: 10.3389/fonc.2020.597730. eCollection 2020.
6. Muhsen IN et al. Worldwide Network for Blood and Marrow Transplantation (WBMT) perspective: the role of biosimilars in hematopoietic cell transplant: current opportunities and challenges in low- and lower-middle income countries. (2019) Bone Marrow Transplantation. https://doi.org/10.1038/s41409-019-0658-2
7. Samir G Agrawal, Paul E Pfeffer, P Lewis White. 13th Fungal Update Congress, Special Supplement with editorial, Medical Mycology. 2019. https://doi.org/10.1093/mmy/myz065
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Book Chapters :

1. Schiavon V, Agrawal S, Boumsell L, Bensussan A. Does BY55 monoclonal antibody identify a novel NK receptor? (Section: Signal transduction- NK receptors and function). In Genetic diversity of HLA. Functional and medical implications. Edited by D. Charron. Published by EDK, Paris, France.

12.3 Dr Lydia N Drumright PhD, MPH

OVERVIEW

I am an epidemiologist and health informatician with an interdisciplinary background centering on innovative use of routinely collected health data, clinical decision support (CDS), evaluation of health interventions, substance use epidemiology, HIV and aging, and the dynamics between behavioral, social, biological, and environmental factors for disease. My research has taken a multidisciplinary approach to data science with an emphasis on utilizing modern technologies to understand significant human health issues. My early career focused on the intersections between substance use and HIV and HCV, with a strong emphasis on individual, partnership and network-level risk assessment. Following my relocation to the UK, I developed my skills in data science and health informatics, leading to an Alan Turing Fellowship and position as University Lecturer in Clinical Informatics at the University of Cambridge. I established the ethical and computing infrastructure to harness electronic medical data for research from the UK's first fully integrated electronic health record system for tertiary and acute care (Epic at Cambridge University Hospitals NHS Foundation Trust). From this platform, I developed clinical informatics tools, novel surveillance methods, large research studies, and decision support. Throughout my career I have led teams across large research consortia, bridging interdisciplinary elements. Much of my research has been directly translational, supporting policy, surveillance and health interventions. My current research activities include understanding rapid aging among people with HIV, using technology to support better clinical outcomes, and harnessing high-tech solutions to support research and surveillance in low- and middle-income settings. In addition to my research experience, I have a wealth of experience in mentoring pre- and post-doctoral trainees and have contributed to university leadership through chairing university and national ethics committees, co-directing an interdisciplinary research center and serving on other executive and regulatory committees.

EDUCATION

03/2006	**Doctorate of Philosophy in Epidemiology and Public Health** University of California, San Diego (UCSD), School of Medicine and San Diego State University (SDSU), Graduate School of Public Health. Dissertation: Illicit Substance Use and Risk of HIV Transmission among Men who have Sex with Men (MSM)
08/1999	**Master of Public Health, Community Health and Health Education,** California State University, Northridge Thesis: Identification of Additional Risk Factors for Acute Hepatitis A Infection
12/1995	**Bachelor of Science, Biochemistry and Cell Biology** University of California, San Diego

PROFESSIONAL EXPERIENCE

01/24-current	**Research Assistant Professor, University of Washington**, School of Nursing, Department of Biobehavioral Nursing and Health Informatics, WA, USA.
02/21-12/23	**Clinical Assistant Professor, University of Washington**, School of Nursing, Department of Biobehavioral Nursing and Health Informatics, WA, USA.
09/20-12/23	**Research Scientist, University of Washington,** Department of Medicine, CFAR Network of Integrated Clinical Systems (CNICS), WA, USA.
04/20-12/21	**Lecturer in Clinical Informatics, University of Cambridge**, School of Clinical Medicine, Department of Medicine (*Equivalent to Adjunct Assistant Professor in US*), UK.
06/18 - 12/21	**Turing Fellow, The Alan Turing Institute,** London, UK.

08/14 – 03/20 **University Lecturer in Clinical Informatics, University of Cambridge,** School of Clinical Medicine, Department of Medicine (*Equivalent to tenured assistant professor in US*), UK.

09/15 – 09/20 **Deputy Vice President (2017), Fellow (2015) of Hughes Hall,** College of the University of Cambridge, UK.

06/15 - 12/20 **Co-Head, Cambridge Infectious Diseases Interdisciplinary Research Centre,** University of Cambridge, UK.

08/14 – 09/20 **Co-Director, Cambridge Clinical Informatics**, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, UK.

05/10- 07/14 **University Lecturer in Infectious Diseases and Epidemiology**, **Imperial College London**, Division of Infectious Diseases and Immunity, Department of Medicine

04/09- 04/10 **Epidemiologist**, **Health Protection Agency,** Tuberculosis Division, Department of Respiratory and Systemic Infections, Center for Infections, London, UK.

03/06-12/08 **Postdoctoral Fellow**, **University of California, San Diego**, Department of Family and Preventive Medicine, Division of International Health and Cross-Cultural Medicine, USA.

1/00 – 12/05 **Research Associate, University California, Los Angeles,** Department of Epidemiology**.** Doctoral student researcher / project manager for two NIH (NIAID) funded studies.

ADDITIONAL BIOLOGICAL LABORATORY EXPERIENCE

11/99 - 04/00 **Research Associate, Althea Technologies**

09/96- 08/97 **Research Associate**, **University of California, San Diego**, Department of Psychiatry, School of Medicine

07/95- 09/96 **Research Assistant, Salk Institute for Biological Studies**, Infectious Disease Laboratory

ADDITIONAL PUBLIC HEALTH EXPERIENCE

09/99 – 03/00 **Field Epidemiology, San Quintin, Mexico.** Developed study materials, conducted field work, analyzed data and made recommendations focused on understanding health issues of migrant farm laborers.

07/98 – 08/99 **Los Angeles County Department of Health and Human Services**, Acute Communicable Disease Control. Conducted outbreak investigations, supported CDC investigations lead by the EIS officer in post and developed an independent study to examine new risk factors for hepatitis A infection.

HONOURS & AWARDS

2018 Alan Turing Personal Fellowship Recipient

2014 UK NIHR Leadership Programme Recipient

2011 UK NIHR Personal Fellowship Recipient

2007 Scholarship for Conference on Retroviruses and Opportunistic Infections

2006 Scholarship for International AIDS Society Meeting

2006 Scholarship for HIV Drug Resistance Conference

2001 San Diego County Epidemiology Exchange Conference

2000 Scholarship for University of Washington 2000 STD Training Course

1998 James R. Simpson Scholarship Recipient

1998 Charlotte Ann Resnick Memorial Scholarship Recipient

1991 Presidential Academic Fitness Award for Outstanding Achievement

CAREER ACCOMPLISHMENTS

- Secured significant research funding in the US and internationally as a principal investigator or co-investigator since 2001, including as a doctoral student.
- Collaborated on ten multi-million dollar research consortia leading to ground-breaking science in HIV, HCV, respiratory infections, HCAI, antimicrobial prescribing, and other infectious and chronic diseases.
- Provided consultancy for 11 years to various industrial and government partners in order to support, vaccines, medications, healthcare delivery, and other medically beneficial products.
- Successful collaborative working across research, public health and clinical services with Public Health England in the UK, State and County Health Departments in the US, the Ministry of Health and WHO in Uganda, NHS trusts in the UK, outpatient clinics in the USA, and hospitals in Kenya and the Philippines.
- Built a clinical informatics research platform to harness routinely collected data from the first fully integrated electronic health record system in the UK's National Health Service, enabling multiple risk and outcomes studies.
- Developed the first known synthetic data generation model that maintains the joint distribution of the original dataset with world-renowned artificial intelligence (AI) scientists for the ethical and widespread use of patient-similar clinical data.
- Developed and applied methods for studying gastrointestinal illness, surgical site infections, healthcare associated infections, liver disease, cancer care pathways, HIV, sexually transmitted infections, hepatitis C, tuberculosis, hepatitis A, influenza, norovirus, and malaria.
- Completed numerous, novel analytic studies across HCV outcomes, antimicrobial prescribing, influenza surveillance, gastrointestinal illness and HIV risk and outcomes that have changed policy and lead to interventions for prevention and surveillance.
- Co-led work on a clinical decision support platform for controlled substance prescribing that has been successfully adopted by three healthcare facilities, was shortlisted for the American Medical Informatics Association FHIR Competition and continues to receive support from Office of the National Coordinator (ONC) and CDC for further development.
- Supported diversity, equity, and inclusion (DEI) throughout my career including training a diverse team of students, healthcare professionals and postdoctoral fellows; conducting human-centered research with a focus on impact of inequities; conducting extensive public and patient involvement and engagement; and supporting ethical research through my work as member and chair of ethical review committees.

RESEARCH EXPERIENCE: LEADERSHIP IN LARGE RESEARCH CONSORTIA

2023-current **HIV SUCCESS (*HIV and Substance Use Cohort Coordinating Center (CC) for Emerging and High Impact Scientific Cross Cohort Studies)*** – MPI and director of a coordinating center for the 9 NIDA HIV and substance use cohorts. Responsible for maintaining, collating, and harmonizing data between HIV and substance use cohorts to answer critical questions around the dynamics of substance use and HIV and HIV progression. Includes cross-cohort analyses, data discovery platforms, supporting future scientific agenda in HIV and substance use, and mentoring the next generation of HIV/ substance use researchers. I am part of the MPI team of HIV SUCCESS and oversee day-to-day running of the coordinating center, including leadership in working and writing groups, data analysis, and mentoring.

2021-current **CFAR Network of Integrated Clinical Systems (CNICS).** CNICS is a network of ten large HIV treatment clinics across the United States that collects patient reported outcomes and measures and electronic clinical data of people living with HIV in treatment. It is one of the largest and longest running HIV cohorts still active today. Across the network, investigators work together to develop unparalleled understanding

of unique issues among people living with HIV (PLWH), which in turn can be used to deliver care uniquely tailored to the needs of the population. Within CNICS I am leading research focused on understanding the dynamics of substance use patterns on health behaviors and outcomes of PWH.

2021-current **Clinical Informatics Research Group (CIRG).** CIRG is one of the University of Washington's School of Nursing research centers, focusing on collaborative faculty activities to develop, build and deliver health informatics tools for healthcare, public health and research. Within CIRG I engage in identifying and securing funding; project design, implementation and evaluation; management; and scholarly presentation and publication.

2010-2020 **Chair/Member National and University Research Ethics Committees (REC).** I served as a member on the West London REC (specializing in: gene therapy, stem cell and phase I-III clinical trials and research involving children) from 2010-2014. I was the chair of the Cambridge Central REC (specializing in: phase I-III clinical trials, medical device trials, databases, tissue banks and research involving adults lacking capacity) from 2005-2020. I was a member (2016-2018) and chair (2018-2020) of the University of Cambridge REC, which was established to provide guidance and policy for research ethics and integrity across the University of Cambridge.

2014-2020 **Cambridge Biomedical Research Centre (BRC).** Biomedical Research Centres are supported by the UK National Institute for Health Research (NIHR) to bring together leading Universities and NHS organizations to support translational research in healthcare and public health. Within the BRC, my centre, Cambridge Clinical Informatics, supported research across all BRC health-focus themes and industrial collaborators by providing clinical data and informatics support, as well as developing methods and producing exemplar research studies. The Centre currently leads the UK in its ability to retrieve and utilize clinical data collected on patients within an NHS trust.

2014-2020 **NIHR Health Informatics Collaborative (HIC)** – The NIHR HIC is a UK Department of Health Funded project to bring together data on key therapeutic areas across five NHS hospital trusts. Within the HIC there are 10 themes, five cancer-related, intensive care, renal transplant, coronary artery disease, viral hepatitis and infection. I led the infection theme and co-led the viral hepatitis theme for Cambridge.

RESEARCH EXPERIENCE: INVOLVEMENT IN LARGE RESEARCH CONSORTIA (CONTINUED)

2011-2014 **Mechanisms of Severe Acute Influenza Consortium (MOSAIC).** This Wellcome Trust funded study aimed to elucidate the mechanisms of pathogenesis H1N1 influenza, involving 47 investigators worldwide. I directed clinical data extraction of 10,000 variables and data consolidation, centralization, validation, management and analysis for clinical data, virology, bacteriology, immune mediators, immune response, genetics, and transcriptomics.

2010-2014 **Centre for Infection Prevention and Management (CIPM).** CIPM was one of seven UK-CRC funded Centres to focus on disease prevention within the NHS. I led research, collaboration and funding activities in the behavioral and surveillance workstreams.

2005-2009 **Study to Reduce Intravenous Exposure (STRIVE).** This was a National Institutes of Drug Abuse (NIDA) funded intervention trial to reduce onward transmission of HCV in three urban centers in the USA. I led data analysis and reporting for the secondary intervention endpoints (influencing access to healthcare and reduction in alcohol consumption).

2000-2009 **Acute Infection and Early Disease Research Program (**AIEDRP). This was a 10-year NIH National Institutes of Allergy and Infectious Diseases (NIAID) funded research program to understand the biological and behavioral dynamics of early HIV infection. I implemented, oversaw and managed all aspects of the behavioral arm of this study.

RESEARCH EXPERIENCE: CURRENT GRANTS AND CONTRACT

2023-2028 **NIDA R01 DA058938**
Understanding Health Inequities at the Intersection of the HIV and substance use across racial/ethnic and other underserved populations Role: Co-investigator

2023-2028 **NIDA 1U24DA058307**
Title: HIV and Substance Use Cohort Coordinating Center for Emerging and High Impact Scientific Cross Cohort Studies: HIV SUCCESS Role: MPI

2022-2025 **Office of the National Coordinator/ CDC contract via Security Risk Solutions**
Title**:** Scaling and Dissemination of Open-Source Electronic Clinical Decision Support Tool for Opioid Prescribing Role: MPI

2021-2024 **ViiV Healthcare**
Title: Internalized HIV Stigma, Age and Gender related outcomes among people with HIV (HIV StAGe Outcomes) Role: MPI/Lead Investigator

2021-2026 **NIAAA P01AA029544**
Title: Alcohol Research Consortium in HIV Role: Co-investigator

2021-2026 **NIA R33AG067069**
Title: AIDS and Aging Research Platform Role: Co-investigator

RESEARCH EXPERIENCE: COMPLETED GRANTS

2019-2021 **Medical Research Council** **£194K**
Title: Assessing the potential for transforming health in Uganda through an electronic health data sharing platform
Role: MPI and UK Lead Investigator

2017-2020 **National Institute for Health Research (NIHR) UK- £114M** **£114M**
Title: Cambridge Biomedical Research Centre
Role: Co-Investigator on the Population and Quantitative Sciences Theme and the Infection Theme

RESEARCH EXPERIENCE: COMPLETED GRANTS (CONTINUED)

2018-2021 **Alan Turing Research Fellowship** **£45K**
Title: Generation of Synthetic Data from Routine Clinical Care
Role: Principal investigator

2017-2020 **Economic and Social Science Research Council -** **£300K**
Title: ExISE
Role: Co-Investigator

2017-2019 **Alborada Trust** **£20K**
Title: An assessment of etiology and co-infections in African children admitted with acute diarrhea after introduction of rotavirus vaccination
Role: Co-Investigator

2016 **Engineering and Physical Science Research Council (EPSRC) UK -** **£9M**
Title: Peta-5: A National Facility for Petascale Data Intensive Computation and Analytics
Role: Co-Investigator and Theme Lead for Health Informatics

2014-2019 **NIHR Health Protection Research Unit UK** **£3.95M**
Title: Healthcare Associated Infections (HCAI) and antimicrobial resistance (AMR)
Role: Co-investigator for data linkage, syndromic surveillance and modelling theme

2015-2017 **Isaac Newton Trust / Wellcome Trust ISSF UK** **£80K**

	Title: Epidemiological dynamics of infectious intestinal disease among hospitalised patients Role: Principal Investigator	
2015-2020	**University of Cambridge Research Strategy Office Small Grant Scheme (7 awarded grants)** Role: Co-Principal Investigator (MPI) - Title: Fostering an international culture of convergence in research: An Israel- Cambridge bi-national workshop - Title: Interdisciplinary workshop on antimicrobial resistance (£4000) - Title: Understanding the biological basis of persistent nasal carriage of *Staphylococcus aureus* (£77,576) - Title: Biomedical Early Career Interdisciplinary Research Networking Programme (£7450) - Title: Early Career Interdisciplinary Seed Fund (ISF) (£5000) - Title: Developing an interdisciplinary cookbook of infectious disease models: an IDHackathon (£5000) - Title: Big Data in Medicine: Interdisciplinary approaches to technologies for transforming health (£10,000) - Title: Infectious Diseases NeXt: Special Interest Research Networks (£4500)	**£120K**
2011-2015	**National Institutes for Health Research, Career Development Fellowship UK** Title: Preventing Healthcare Related Norovirus Outbreaks and Ward Closures through Identification of Reservoirs in Healthcare Settings: Viral, Host, and Environmental Determinants Role: Principal Investigator	**£570K**

RESEARCH EXPERIENCE: COMPLETED GRANTS (CONTINUED)

2012-2014	**British Society for Antimicrobial Chemoprophylaxis UK** Title: Optimising antibiotic prescribing through a novel junior doctor-centered short course: development of a needs-based educational module and assessment of acceptability and efficacy Role: Principal Investigator	**£25K**
2012-2014	**Wellcome Trust UK** Title: Mechanisms of Severe Acute Influenza Consortium (MOSAIC) Role: Co-Investigator and lead of data management, quality control and analysis	**£2.7M**
2011-2013	**Imperial College Healthcare NHS Trust BRC UK** Title: Analysis of norovirus and C. difficile co-carriage, co-infection and outcomes (Causal or Casual?) Role: Principal Investigator	**£356K**
2009-2010	**European Center for Disease Prevention and Control** Title: Evaluation results of enhancing of the TB-HIV co-infection surveillance at EU level Role: Co-Investigator	**£50K**
2009-2013	**UK CRC** Title: Centre for Infection Prevention and Management Role: Lecturer in Infectious Diseases Epidemiology	**£5M**
2009-2010	**NIHR HTA UK** Title: Review and Meta-Analysis of the Duration of Protection from Tuberculosis Conferred by BCG Vaccination	**£1.5M**

	Role: Lead epidemiologist and study manager	
2007-2009	**National Institutes of Health US, Loan Repayment Research Scheme** Title: HIV Transmission probabilities among MSM Role: Principal Investigator	**$90K**
2007-2009	**University of California, San Diego: Center for AIDS Research Developmental Grant** Title: Examining the role of venues in structuring social and sexual networks among MSM Role: Co-investigator	**$30K**
2006-2008	**State of California Universitywide AIDS Research Program (UARP) Grant US** Title: HIV Transmission Probabilities among MSM Role: Principal Investigator	**$90K**
2005-2008	**National Institutes of Health (NIAID) US (5 T32 AI07384) -** Title: AIDS Training Grant Role: Post-doctoral fellow/ trainee in infectious diseases and HIV	**$5M**
2003-2005	**State of California Universitywide AIDS Research Program (UARP)** Title: Redefining "high-risk" among high-risk individuals Role: Principal Investigator	**$50K**
2001-2005	**National Institutes of Health (NIAID) US (U01 AI43638)** Title: The Southern California Primary Infections Program Role: Doctoral Research Assistant	**$10M**

RESEARCH EXPERIENCE: CONSULTATION

Note per consultancy agreements names of companies and individuals cannot be provided.

2024-current	Consulting with UK Government Agency on evidence of increased incidence of blood stream infections across hospitals over a 10 -year period.
2017-2021	Consulted with healthcare trusts and organization on design, implementation, and use of clinical informatics platforms based on electronic health records.
2017-2021	Conducted assessments of Norovirus symptomatology and burden by population characteristics. Provided design recommendations on clinical trials to test novel norovirus vaccines.
2011-2021	Provide written and telephone consultations regarding areas of expertise in Epidemiology, Biological Sciences, and Health Informatics for clients from across the international sector.
2015-2020	Provided consultation and recommendations on ethical recruitment, design, conduct and evaluation of human research studies.
2018	Designed, conducted, and analyzed a study examining risk for chronic kidney disease among patients in the UK.
2011-2013	Designed, conducted and evaluated an intervention trial for a new personalized hand sanitizer dispenser product.
2011-2013	Provided epidemiological and scientific advice on clinical trials for a novel surgical site infection prevention product.

RESEARCH EXPERIENCE: PUBLICATIONS: PEER REVIEWED

1. Fredericksen RJ. Mixson LS. **Drumright LN**. Nance RM. Delaney JAC. Ruderman SA. Whitney BM. Hahn A. Ma J. Mayer KH. Christopoulos KA. Willig AL. Napravnik S. Bamford L. Cachay E. Eron JJ. Saag M. Jacobson J. Kitahata MM. Crane HM. Intimate partner violence, including

psychological partner violence, in a multisite U.S. cohort of people in HIV care. *Accepted to AIDS and Behavior*.

2. **Drumright LN**, Short D, Cachay E, Ruderman SA, Whitney BM, Crawford TN, Christopoulos K, Neilands T, Ma J, Moffatt E, Dai M, Mixson LS, Johnson MO, Mayer KH, Keruly JC, Chander G, Lober WB, Saag MS, Kitahata MM, Moore RD, Willig AL, Eron JJ, Napravnik S, Nance RM, Hahn AH, Bamford L, Fredericksen RJ, Delaney JAC, Crane HM. Differences in internalized HIV stigma across subpopulations of people living with HIV in care at eight US sites. *In press at AIDS*
3. Ruderman SA, **Drumright LN**, Delaney JAC, Webel AR, Fitzpatrick AL, Whitney BM, Nance RM, Hahn AW, Ma J, Mixson LS, Eltonsy S, Willig AL, Mayer KH, Napravnik S, Greene M, McCaul M, Cachay E, Kritchevsky SB, Austad SN, Landay A, Saag MS, Kitahata MM, Lau B, Lesko C, Chander G, Crane HM, Odden MC. Evaluating the sick quitting hypothesis for frailty status and reducing alcohol use among people with HIV in a longitudinal clinical cohort study JANAC. 2024: 35(1): 5-16.
4. Crane HM, Nance RM, Ruderman SA, Haidar L, Tenforde MW, Heckbert SR, Budoff MJ, Hahn AW, **Drumright LN**, Ma J, Mixson LS, Lober WB, Barnes GS, McReynolds J, Attia EF, Peter I, Moges T, Bamford L, Cachay E, Mathews WC, Christopolous K, Hunt PW, Napravnik S, Keruly J, Moore RD, Burkholder G, Willig AL, Lindstrom S, Saag MS, Kitahata MM, Crothers KA, Delaney JAC. Venous thromboembolism among people with HIV: Design, implementation, and findings of a centralized adjudication system in clinical care sites across the United States. J Acquir Immune Defic Syndr 2024 1;95(2):207-214. doi: 10.1097/QAI.0000000000003339.
5. Ma J, Luu B, Ruderman SA, Whitney BM, Merrill JO, Nance RM, **Drumright LN**, Hahn AH, Fredericksen RJ, Chander G, Lau B, McCaul ME, Safren S, O'Cleirigh C, Cropsey K, Mayer KH, Mathews WC, Moore RD, Napravnik S, Christopoulos K, Willig A, Jacobson JM, Webel A, Burkholder G, Mugavero MJ, Saag MS, Kitahata MM, Crane HM, Delaney JAC. Alcohol and drug use severity are independently associated with antiretroviral adherence in the current treatment era. *AIDS Care*. 2024: 36(5): 618-630. doi: 10.1080/09540121.2023.2223899
6. Haidar L, Crane HM, Nance RM, Webel A, Ruderman SA, Whitney BM, Willig AL, Napravnik S, Mixson LS, Leong C, Lavu A, Aboulatta L, Dai M, Hahn A, Saag MS, Bamford L, Cachay E, Kitahata MM, Mayer KH, Jacobson J, Moore RD, Delaney JAC, **Drumright LN**, Eltonsy S. Weight loss associated with Semaglutide treatment among people with HIV. AIDS 2023 Nov 17. doi: 10.1097/QAD.0000000000003791. Online ahead of print.
7. Nabukenya J, **Drumright L**, Egwar Alunyu A, Semwanga AR. Critical risk and success factors for sustainability of an electronic health data capture, processing and dissemination platform for Uganda. *Health Informatics Journal*. 2023: 29(2). doi:10.1177/14604582231180576
8. Ruderman SA, Odden MC, Webel AR, Fitzpatrick AL, Crane PK, Nance RM, **Drumright LN**, Whitney BM, Mixson LS, Ma J, Willig AL, Haidar L, Eltonsy S, Mayer KH, O'Cleirigh C, Cropsey K, Eron JJ, Napravnik S, Greene M, McCaul M, Chander G, Cachay E, Lober WB, Kritchevsky SB, Austad S, Landay A, Pandya C, Cartujano-Barrera F, Saag MS, Kamen C, Hahn AW, Kitahata MM, Delaney JAC, Crane HM. Tobacco Smoking and Pack-years are Associated with Frailty Among People with HIV**.** *JAIDS*. 2023. 26. doi: 10.1097/QAI.0000000000003242.
9. **Drumright LN**, Nance RM, Delaney JAC, Hahn A, Fredericksen RJ, Ruderman S, Whitney BM, Ma J, Luu B, Lober WB, Willig A, Moore RD, Christopoulos K, Saag MS, Matthews WC, Eron JJ, Mayer KM, Kitahata MM, Crane HM. Effects of alcohol and cigarette use on myocardial infarction among people living with HIV (PLWH)**.** *HIV Medicine.* 2023. 24(6): 703-715. doi:10.1111/hiv.13466
10. Nabukenya J, Egwar A A, **Drumright L**, Semwanga A, Kasasa S. Feasibility and utility of Point-of-Care electronic clinical data capture in Uganda's healthcare system: a qualitative study. *Journal Am Med Informatics Assoc.* 2023. 30(5): 932-942. doi:10.1093/jamia/ocad034
11. Ruderman SA, Nance RM, **Drumright LN**, Whitney BM, Hahn AW, Ma J, Haidar L, Eltonsey S, Mayer KH, Eron JJ, Greene M, Matthews WC, Webel A, Saag MS, Willig AL, Kamen C, McCaul M, Chander G, Cachay E, Lober WB, Pandya C, Cartujano-Barrera F, Kritchevsky SB, Austad SN, Landay A, Kitahata MM, Crane HM, Delaney JAC. Development of Frail RISC-HIV: a Risk Score for Predicting Frailty Risk in the Short-term for Care of People with HIV. *AIDS.* 2023. 37(6): 967-975. doi:10.1097/QAD.0000000000003501

12. Fredericksen RJ. Fitzsimmons E. Loo S. Pearce J. Dougherty S. Brown S. Nance RM. Whitney BW. Ruderman S. **Drumright LN**. Delaney JAC. Mayer KH. Mugavero MJ. Crane HM. Hahn A. Vaporized nicotine use among patients in HIV care who smoke tobacco: perceived health effects and effectiveness for smoking cessation. *AIDS Care.* 2023. Mar:1-8. doi:10.1080/09540121.2023.2180476
13. Fredericksen R, Fitzsimmons E, Sigal M, Dougherty S, Pearce J, Powell M, Nguyen J, Ruderman S, Whitney B, **Drumright L**, Ma J, Nance R, Mixson S, Delaney J, Mayer K, Willig A, Crane H, Hahn A. Changes in marijuana use and associated attitudes and health behaviors among patients in HIV care in the U.S. in the post-legalization era: a qualitative study. *J AIDS and HIV Research.* 2023. 15(1): 1-9.
14. Hahn AW, Ruderman SA, Nance RM, Whitney BW, Eltonsy S, Haidar L, Delaney JAC, **Drumright LN**, Ma J, Mayer KH, O'Cleirigh C, Napravnik S, Eron JJ, Christopoulos K, Bamford L, Cachay E, Jacobson JM, Willig A, Cropsey K, Chander G, Crane HM, Fredericksen RJ. Vaporized Nicotine (E-cigarette) and Tobacco Smoking Among People with HIV: Use Patterns and Associations with Depression and Panic Symptoms. *JAIDS.* 2023. 92(3):197-203. doi:10.1097/QAI.0000000000003132
15. Ruderman SA, Webel AR, Willig, AL**, Drumright LN**, Fitzpatrick AL, Odden MC, Cleveland JD, Burkholder G, Davey CH, Fleming J, Buford TW, Jones R, Nance RM, Whitney BM, Mixson LS**,** Hahn AW, Mayer KH, Greene M, Saag, MS, Kamen C, Pandya C, Lober WB, Kitahata MM, Crane PK, Crane HM, Delaney JAC. Validity Properties of a Self-reported ModifiedFrailty Phenotype Among People With HIV in Clinical Care in the United States. *J Assoc Nurses in AIDS Care.* 2023. 34(4): 158-170. doi:10.1097/JNC.0000000000000389
16. Fredericksen RJ, Fitzsimmons E, **Drumright LN**, Loo S, Dougherty S, Brown S, Pearce J, Nance RM, Whitney BW, Ruderman S, O'Cleirigh C, Cropsey K, Mayer KH, Mugavero MJ, Delaney JAC, Crane HM, Hahn A. Vaporized nicotine use among patients in HIV care who smoke tobacco: perceived health effects and effectiveness as a smoking cessation tool. *AIDS Care*. 2023 35(11):1741-1748.
17. Crane HM, Ruderman SA, Whitney BM, Nance RM, **Drumright L**, Webel AR, Willig AL, Saag MS, Christopoulos K, Greene M, Hahn AW, Eron JJ, Napravnik S, Mathews WC Chander G, McCaul ME, Cachay ER, Mayer KH, Landay A, Austad S, Ma J, Kritchevsky SB, Pandya C, Achenback C, Cartjujano-Barrera F, Kitahata MM, Delaney JAC, Kamen C. Associations between drug and alcohol use, smoking, and frailty among people with HIV across the United States in the current era of antiretroviral treatment. *Drug and Alcohol Dependence.* 2022. 240: 109649. doi:10.1093/cid/ciab1000
18. Agoti CN, Curran MD, Murunga N, Ngari M, Muthumbi E, Lambisia AW, Frost SDW, Blacklaws B, Nokes DJ, **Drumright LN**. Differences in epidemiology of enteropathogens in children pre- and post- rotavirus vaccine introduction in Kilifi, coastal Kenya. *Gut Pathogens.* 2022 14(1):32: 1-12. doi:10.1186/s13099-022-00506-z
19. Short CA, Woods AW, **Drumright L**, Zia R, Mingotti N. An alternative approach to delivering safe, sustainable surgical theatre environments. *Buildings and Cities.* 2022 3(1): 316-33. doi:10.5334/bc.154.
20. Luu B*, Ruderman S, Nance R, Delaney JAC, Ma J, Hahn A, Heckbert SR, Budoff MJ, Crothers K, Mathews WC, Christopolous K, Hunt PW, Eron J, Moore R, Keruly J, Lober WB, Burkholder GA, Willig A, Chander G, McCaul ME, Cropsey K, O'Cleirigh C, Peter I, Feinstein M, Tsui JI, Lindstroem S, Saag M, Kitahata MM, Crane HM, **Drumright LN**, Whitney BM. Tobacco smoking and binge alcohol use are associated with incident venous thromboembolism in an HIV cohort. *HIV Medicine*. 2022. 23: 1051-1060. doi:10.1111/hiv.1330
21. Crane HM, **Drumright LN**. HIV, Aging, and Comorbidities Research in Clinical Cohorts: 3 lessons learned using examples from the CNICS cohort. *J Acquir Immune Defic Syndr*. 2022 Feb 1;89(Suppl 1):S10-S14. doi:10.1097/QAI.0000000000002836
22. Woods AC, Short CA, Mingotti N, Schoefert K, **Drumright LN**, Zia, R**.** Innovative practice in the manufacture of aseptic surgical environments in the late Nineteenth Century. *Journal of Architectural Conservation*. 2021 27(3):225-241. doi:10.1080/13556207.2021.1982541

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24. Konig KMK, Jahun AS, **Drumright LN**, Zilbauer M, Goodfellow I, Hosmillo M. Design, development, and validation of a strand-specific RT-qPCR assay for GI and GII human Noroviruses. *Wellcome Open Research*. 2021 6:245. doi:10.12688/wellcomeopenres.17078.1
25. Hosmillo M, Chaudhry Y, Nayak K, Sorgeloos F, Koo BK, Merenda A, Lillestol R, **Drumright L**, Zilbauer M, Goodfellow I. Norovirus replication in human intestinal epithelial cells is restricted by the interferon-induced JAK/STAT signalling pathway and RNA Polymerase II mediated transcriptional responses. *mBio*. 2021 11(2): e00215-20. doi:10.1128/mBio.00215-20
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29. Banerjee A, **Drumright LN**, Mitchell ARJ. Can the NHS be a learning health system in the age of digital technology? *BMJ Evidence Based Medicine*. 2018 23(5):161-165 doi:10.1136/bmjebm-2018-110953
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49. **Drumright LN**, Hagan H, Thomas DL, Latka MH, Golub ET, Garfein RS, Clapp JD, Campbell JV, Bonner S, Kapadia F, Thiel TK, Strathdee SA. Predictors and effects of alcohol use on liver function among young HCV-infected injection drug users in a behavioral intervention. *J Hepatol*. 2011 55(1):45-52.
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55. Gorbach PM, **Drumright LN**, Javanbakht M, Pond SL, Woelk CH, Daar ES, Little SJ. Antiretroviral drug resistance and risk behavior among recently HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr*. 2008 47(5):639-43. doi:10.1097/QAI.0b013e3181684c3d. PMID:18285715
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62. Gorbach PM, **Drumright LN**, Holmes KK. Discord, discordance, and concurrency: comparing individual and partnership-level analyses of new partnerships of young adults at risk of sexually transmitted infections. *Sex Transm Dis*. 2005 32(1):7-12. PMID:15614115
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RESEARCH EXPERIENCE: PUBLICATIONS: PEER REVIEWED GROUP AUTHORSHIP PUBLICATIONS

65. Dunning J, Blankley S, Hoang LT, Cox M, Graham CM, James PL, Bloom CI, Chaussabel D, Banchereau J, Brett SJ; **MOSAIC Investigators**, Moffatt MF, O'Garra A, Openshaw PJM. Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza. *Nature Immunology*. 2018 19(6):625-635.
66. Everitt AR, Clare S, Pertel T, John SP, Wash RS, Smith SE, Chin CR, Feeley EM, Sims JS, Adams DJ, Wise HM, Kane L, GouldingD, Digard P, Anttila V, Baillie JK, Walsh TS, Hume DA, Palotie A, Xue Y, Colonna V, Tyler-Smith C, Dunning J, Gordon SB, The GenISIS Investigators, **The MOSAIC Investigators**, Smyth RL, Openshaw PJ, Dougan G, Brass AL, Kellam P. IFITM3 restricts the morbidity and mortality associated with influenza. *Nature*. 2012 484(7395):519-23. doi:10.1038/nature10921. PMID: 22446628
67. Elderfield RA, Watson SJ, Godlee A, Adamson WE, Thompson CI, Dunning J, Fernandez-Alonso M, Blumenkrantz D, Hussell T; **MOSAIC Investigators**., Zambon M, Openshaw P, Kellam P, Barclay WS. Accumulation of human-adapting mutations during circulation of A(H1N1)pdm09 influenza virus in humans in the United Kingdom. *J Virol*. 2014 88(22):13269-83. doi:10.1128/JVI.01636-14.PMID:25210166

RESEARCH EXPERIENCE: PUBLICATIONS: BOOK CHAPTER PUBLICATIONS

68. **Drumright LN**, Colfax GN. HIV risk and prevention for non-Injection substance users (chapter 13). HIV Prevention: a comprehensive approach. Mayer KH and Pizer HF, editors. Burlington, MA: Academic Press 2009.

RESEARCH EXPERIENCE: PUBLICATIONS: MANUSCRIPTS UNDER REVIEW

1. Ma J, Delaney JAC, Ruderman SA, Nance RM, Hahn AW, **Drumright LN**, Whitney BM, Fredericksen RJ, Mixson LS, Kitahata MM, Crane HM, Williams EC. Substance use severity and number are independently associated with antiretroviral therapy adherence over time among people with HIV in the current treatment era. *Under review at AIDS and Behavior.*
2. Ruderman SA, Hunt PW, Beck-Engeser G, Ambayec G, Willig AL, Saag MS, Napravnik S, Cachay E, Bamford L, Landay A, **Drumright LN**, Mixson LS, Whitney BM, Nance RM, Kitahata MM, Crane HM, Delaney JAC, Hahn AW. Biomarkers of Microbial Translocation and Generalized Inflammation are Associated with Frailty among People with HIV. *Under review at AIDS.*
3. Crawford TN, Neilands TB, **Drumright LN**, Fredericksen RJ, Johnson MO, Mayer KH, Bamford L, Batchelder AW, Crane HM, Elopre L, Gripshover BM, Moore RD, Rosengren-Hovee L, Christopoulos K. Internalized HIV Stigma and Viral Suppression: Examining the Mediating and Moderating Roles of Social Support, Substance Use, and Depressive Symptoms. *Under review at AIDS.*
4. Crane HM, Ruderman SA, Nance RM, **Drumright LN**, Whitney BM, Mixson LS, Mayer KH, Eron JJ, Napravnik S, Christopoulos K, Cachay ER, Bamford L, Chander G, Webel A, Saag MS, Willig AL, Burkholder G, Pandya C, Cartujano-Barrera F, Kamen C, Hahn AW, Ma J, Kitahata MM, Lober WB, Delaney JAC. Approaches to optimally target frailty screening among people with HIV in clinical care: findings from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). *Under review at JAIDS.*
5. Ruderman SA, Nance RM, Crane HM, Cachay E, Kitahata MM, Napravnik S, Whitney BM, Heckbert SR, Attia E, Longenecker CT, Hoffmann A, Budoff MJ, Ma J, Christopolous K, Hunt PW, Moore RD, Keruly JC, Burkholder G, Bamford L, Willig AM, Chander G, Saag MS, **Drumright LN**, Feinstein MJ, Crothers K, Delaney JAC. Cumulative HIV Viral Load and Lower CD4 Cell Count are Associated with Incident Venous Thromboembolism in People with HIV. *Under review at AIDS.*
6. Bapat A/ **Drumright LN** (shared first authorship), Caldwell L, Jimenez-England F, Lambourne J, Agrawal S. Ending fluoroquinolone prophylaxis in haemato-oncology patients is associated with reductions in antimicrobial resistance and increased survival. *Under review at Lancet ID*

RESEARCH EXPERIENCE: PUBLICATIONS: MANUSCRIPTS IN PREPARATION

1. Dai M, Willig AL, Whitney BM, Ma J, Mixson SL, Ruderman SA, Nance RM, Hahn AH, Fredericksen RJ, Haidar L, Mayer KH, Jacobson J, Christopoulos K, Cachay E, Bamford L, Saag MS, Kitahata MM, Napravnik S, Eron JJ, Lesko C, Moore RD, McCaul ME, Delaney JAC, Webel AR, Chander G, Crane HM**, Drumright LN**. Alcohol use disorder diagnosis, but not current alcohol use is associated with falls among people with HIV in care in the US. *Draft circulating with coauthors target journal JAIDS.*
2. **Drumright LN**, Fredericksen RJ, Crawford TN, Ma J, Moffatt E, Dai M, Christopoulos K, Neilands T, Cachay E Mayer KH, Keruly JC, Chander G, Johnson MO, Lober WB, Saag MS, Kitahata MM, Moore RD, Willig AL, Eron JJ, Napravnik S, Nance RM, Hahn AH, Bamford L, Ruderman SA, Delaney JAC, Crane HM. Internalized HIV stigma is longitudinally associated with poorer HIV antiretroviral therapy (ART) adherence among people with HIV (PWH) *Draft revisions being made in preparation for submission to JAIDS.*
3. **Drumright LN**, Willig AL, Ruderman SA, Whitney BM, Nance RM, Hahn AW, Mixson LS, Ma J, Fredericksen R, Jacobson JM, Christopoulos K, Napravnik S, Cachay E, Mayer KH, Eron JJ, Delaney JAC, Kitahata MM, Saag M, Webel AR, Crane HM. Illicit substance use and falls among people with HIV in care in the United States. *Draft revisions in preparation for submission to AIDS.*

4. Fredericksen RJ, Nance RM, **Drumright LN**, Mixson LS, Ruderman SA, Whitney BM, Christopoulos KA, Napravnik S, Cachay E, Mayer KH, Keruly J, Moore R, Eron J, Burkholder G, Rodriguez A, Safren S, Jacobson J, Delaney JAC, Crane HM, Hahn A. Differences in methamphetamine use, self-reported impact, and HIV-related outcomes by gender and sexual orientation in a multisite U.S. cohort of people with HIV in care. *Circulating draft with coauthors, target journal AIDS and Behavior.*
5. Hahn AW, Ruderman SA, Nance RM, Delaney JAC, Whitney BW, Eltonsy S, Haidar L, Drumright LN, Ma J, Mayer KH, O'Cleirigh C, Christopoulos K, Bamford L, Cachay E, Willig A, Cropsey K, Chander G, Crane HM, Fredericksen RJ.Cannabis Use Patterns Among People with HIV Before and After Legalization. *Circulating draft with coauthors, target journal AIDS Care.*

RESEARCH EXPERIENCE: PRESENTATIONS: INVITED ORAL

1. **Leveraging health informatics to facilitate cohesiveness in research, healthcare, and public health.** Biomedical and Health Informatics Lecture Series, University of Washington, School of Medicine. 10 February 2022.
2. **Harnessing routine health data for epidemiological research in the UK**. Biomedical and Health Informatics Lecture Series, University of Washington, School of Medicine. 28 May 2020.
3. **Harnessing routinely collected data for human and planetary health in Uganda**. University of Cambridge Planetary and Human Health Symposium. 21 May 2020
4. **Tales of the unexpected: natural language processing of free text electronic health records (EHR).** Linguamatics Natural Language Processing Seminar. 16 January 2020.
5. **Mathematical and Statistical Modeling in Clinical Settings**. Congress of the Brazilian Society of Tropical Medicine. 28th-30th July 2019. Belo Horizonte, Brazil.
6. **Intelligent use of Routinely Collected Data to Inform Healthcare Associated Infection Risk and Hospital Architecture**. Zhejiang University Visiting Scholar Programme. 23rd July 2019. Clare Hall, Cambridge, UK.
7. **Using Clinical Informatics to Transform Healthcare**. Shanghai Medical Innovation & Development Foundation Training Programme in Health Innovation and Quality Management in the Era of Big Data. 15th May 2019.
8. **Identifying surgical site infections (SSI) using mixed assessment of free text and structured data in electronic health records.** Linguamatics Spring Text Mining Conference. 21st March 2019.
9. **Understanding surgical site infection (SSI) control in UK hospitals within ExISE.** LoHCool & ExISE Sounding Panel Meeting. 29th March 2019.
10. **Enabling Artificial Intelligence in the NHS**. Health Data Research UK Seminar Series. 4th August 2018.
11. **The role of the built environment on contact networks, human flow, and infection transmission**. Cambridge University Antimicrobial Resistance Seminar, July 2018.
12. **Patient Care Delivery through Informatics Solutions**. IQVIA Digital Solutions Conference. June 2018.
13. **Enabling AI in the Clinical Setting**. Putting AI to Work in the NHS by PredictX. 23rd May 2018.
14. **Advancing Healthcare Delivery through an Integrated Research Electronic Health Record Model**. INFORMS Healthcare 2017. 27th-29th July 2017.
15. **Intelligent Use of Routinely Collected Data (and Samples): Increasing Research Efficiency and Transforming Medical Care**. CBBI Symposium. 17th May 2017.
16. **Overcoming Barriers and Realising Opportunities for Advancing Healthcare using Artificial Intelligence: Legal, Ethical and Social Considerations**. Realising the Potential of AI in the UK Healthcare Sector. 10th May 2017.

17. **Changing Healthcare and Policy with Data**. Farr Institute Learning Health Systems Day. April 28, 2017.
18. **Harnessing new Technologies to Understand Norovirus & Other Gastrointestinal Infections**. East of England Microbiology Development Group. 27th February 2017.
19. **Adoption and evolution of a fully electronic medical record system.** Cambridge Institute of Public Health Annual Conference. 23rd November 2016.
20. **Adoption & Evolution of a Fully Electronic Medical Record System: the Cambridge University Hospitals NHS Foundation Trust Experience**. Northern, Yorkshire and Humberside NHS Directors of Informatics Forum. 10th-11th November 2016.
21. **Ethical Considerations in Child Health Research**. East of England Paediatric Registrars Seminar. 14th September 2016.
22. **Implementing Bioinformatics for Infectious Diseases into Clinical Service.** ECCB 2016, Clinical Bioinformatics as a Service Workshop. 4th September 2016.
23. **Ethics of Interdisciplinary Research**. Cambridge University Research Ethic Committee Annual Ethics Series. 13th June 2016.
24. **Changing Healthcare and Policy with Data**. Farr Institute Learning Health Systems Day. 27th April 2016.
25. **Ethics of Big Data in Practice: Patient Record Linkage in Hospitals**. Cambridge Ethics of Big Data Lecture Series. 27th January 2016.
26. **Understanding Gastrointestinal Infection Dynamics using Clinical Informatics.** Cambridge Infectious Diseases Strategic Research Initiative Annual Meeting. 15th November 2015.
27. **Clinical Informatics**. University of Cambridge SCM/ EMBL-EBI Strategic Partnership Retreat. 30 October 2015.
28. **New Developments in Gastrointestinal Pathogen Screening and their Application**. Public Health England Detection for Gastrointestinal Pathogens Meeting. 5 August 2015.
29. **Changing What We Do: An Update on the Cambridge University Hospitals NHS Foundation Trust's Adoption of a Fully Electronic Health Record System**. NHS-Higher Education Forum. 4th June 2015.
30. **Intelligent use of Routinely Collected Samples & Data for Understanding Gastrointestinal Infections in Acute Care Settings: Successes and Challenges in Clinical Informatics, Big Data and Health**. UCL Research Symposium. April 2015.
31. **Ethical Review**. East of England ENT Clinical Seminar. 18th March 2015.
32. **Infectious Diseases and Collaborative Opportunities with the University of Cambridge**. MRC UK-Philippines Infectious Diseases Research Workshop. 12th March 2015.
33. **Use of Hospital Staff Absences for Influenza Surveillance: Difficulties and Benefits of Harnessing a Novel Source of Big Data for Syndromic Surveillance.** Big Data and Google Flu Conference, Warwick Data Science Institute. 15th December 2014.
34. **Expanding our Knowledge of Norovirus Infection, Transmission and Evolution**. CIPM Annual Scientific Research Meeting. 19th June 2014.
35. **Harnessing Molecular and Social Networks for HIV Prevention**. Division of Virology and Immunology, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention. Beijing. 16 October 2013.
36. **Healthcare Worker Illness Absence for Influenza Surveillance and Hospital Preparedness**. Imperial Centre for Respiratory Infections Annual Meeting. 10th April 2011.
37. **Surveillance of illness in HCWs in the Imperial College Healthcare NHS Trust.** REACT Meeting, Berlin Germany. 29 January 2011.
38. **Methamphetamine use and risks for HIV transmission and acquisition**. Imperial College London; November 2006.
39. **Methamphetamine use among MSM**. UNC Infectious Disease Rounds; November 3, 2006**.**

40. **Methamphetamine use among MSM: risks for HIV transmission and acquisition.** UCSD AIDS Rounds; July 14, 2006.
41. **Partnership types in primary HIV and changes post-diagnosis**. UCSD Community Advisory Board Meeting; April 5, 2004.
42. **Concurrency and HIV transmission: beyond overlapping partnerships**. UCSD AIDS Rounds; November 21, 2003.

RESEARCH EXPERIENCE: PRESENTATIONS: PEER-REVIEWED ORAL & POSTER

1. **Drumright LN**, Delaney JAC, Whitney BM, Mayer KM, Heinke D, Dai M, Fredericksen R, Ruderman SA, Mixson LS, Haidar L, Moore RD, Napravnik S, McCaul ME, Peter I, Christopoulos K, Cachay E, Bamford L, Jacobson J, Kitahata MM, Saag MS, Chander G, Crane HM. Polysubstance use is associated with a 4.8-fold greater prevalence of non-fatal overdose than single substance use among PWH in care 2019-2023. Poster presentation. College on Problems of Drug Dependence (CPDD), June 15-19, 2024, Montréal, Quebec.
2. Crane HM, Whitney BM, Moore RD, Napravnik S, McCaul ME, Peter I, Christopoulos K, Cachay E, Bamford L, Jacobson J, Kitahata MM, Saag MS, Delaney, **Drumright LN**. Demographic and mental health characteristics among PWH in in the USA care who reported non-fatal overdose (2019-2023). College on Problems of Drug Dependence (CPDD), June 15-19, 2024, Montréal, Quebec.
3. Mixson LS, Whitney BM, Ruderman SA, **Drumright LN**, Pho M, Jenkins W, Westergaard R, Seal D, Go V, Miller W, Zule W, Korthuis PT, Friedmann P, Smith G, Feinberg J, Cooper H, Young A, Tsui JI, Crane HM, Delaney JAC. Behavioral and Health Outcome Differences by Heroin or Methamphetamine Preference among People in Rural Us Communities who Use both Substances. College on Problems of Drug Dependence (CPDD), June 15-19, 2024, Montréal, Quebec.
4. Fredericksen RJ. Nance RM. Hahn A. **Drumright LN**. Ruderman SA. Mixson LS. Whitney BM. Christopoulos K. Napravnik S. Cachay E. Mayer KH. Keruly J. Moore R. Eron J. Willig A. Rodriguez A. Safren S. Jacobson J. Delaney JAC. Crane HM. Differences in methamphetamine use and self-reported impact by gender and sexual orientation in a multisite U.S. cohort of people with HIV in care. Oral presentation. College on Problems of Drug Dependence, June 15-19, 2024, Montréal, Quebec.
5. **Drumright LN**, Chander G, Whitney BM, Mixson SL, Dai M, Pho M, Young A, Zule W, Stopka T, Miller W, Go V, Korthuis T, Seal D, Feinberg J, Delaney JAC, Tsui J, Crane HM. Heay episodic alcohol use and differences in overdose experiences and naloxone access among rural people who use drugs. Research Society on Alcohol (RSA) Conference, June 22-26, 2024, Minneapolis, MN.
6. Dai M, **Drumright LN**, Burkholder G, Heath S, Moore R, Lesko C, Kalayjian R, Bamford L, Christopoulos K, Mayer K, Commanday A, Whitney B, Fretts A, Willig A, Delaney J, Crane H, Chander G. Alcohol use patterns stratified by level of kidney damage among people living with HIV in care in the United States. Research Society on Alcohol (RSA) Conference, June 22-26, 2024, Minneapolis, MN.
7. Whitney BM, **Drumright LN**, Ruderman SA, Mixson LS, Nance RM, Willig AL, Napravnik S, Mayer KH, Bamford L, Cachay E, Jacobson J, Fredericksen RJ, Delaney JAC, Crane HM. Housing instability is associated with decreased viral suppression among people with HIV in the United States. Society for Epidemiological Research (SER) Conference, June 18-21, 2024; Austin, TX.
8. Whitney BM, Crane HM, Heinke D, Ruderman SA, Mixson LS, Nance RM, Willig AL, Napravnik S, Mayer KH, Bamford L, Cachay E, Jacobson J, Fredericksen RJ, **Drumright LN**, Delaney JAC. Housing instability is associated with higher prevalence of methamphetamine, cocaine, and opioids among people with HIV in the US. Society for Epidemiological Research (SER) Conference, June 18-21, 2024; Austin, TX.
9. Heinke D, Kyle RP, Delaney JAC, Whitney BM, Mixon S, Fredericksen RJ, Kipke M, Lesko C, Mayer KH, Li M, Goldbach J, Mustanski B, Parra L, Chander G, Crane HM, **Drumright LN.** Are you positive? Outcome-dependent positivity violations in small populations: an example study of substance use by gender identity. Society for Epidemiological Research (SER) Conference, June 18-21, 2024; Austin, TX.

10. **Drumright LN**, Chapman Lambert C, Willig A, Nance RM, Ruderman SA, Whitney BM, Napravnik S, Christopoulos K, Cachay E, Bamford L, Mixson LS, Hahn A, Haider L, Dai M, Fredericksen R, Ma J, Mayer KH, Kitahata MM, Saag MS, Johnson M, Webel AR, Delaney JAC, Crane HM. Frailty and Health-Related Quality of Life in an Aging Cohort of People with HIV 2012-2022. 2024 Conference on Retroviruses and Opportunistic Infections (CROI) March 3-6, Denver, CO.
11. Ruderman SA, Hunt PW, Beck-Engeser G, Ambayec G, Willig AL, Saag MS, Napravnik S, Cchay E, Bamford L, Landay A, **Drumright LN**, Mixson LS, Whitney BM, Nance RM, Kitahata MM, Crane HM, Delaney JAC, Hahn AW. Biomarkers of Microbial Translocation and Generalized Inflammation are Associated with Frailty among People with HIV. 2024 Conference on Retroviruses and Opportunistic Infections (CROI) March 3-6, Denver, CO.
12. Ma J, Nance RM, **Drumright LN**, Tirschwell D, Chow F, Delaney JAC, Crane HM. Associations between depressive symptom severity and incident stroke in people with HIV.2024 Conference on Retroviruses and Opportunistic Infections (CROI) March 3-6, Denver, CO.
13. Haidar L, Crane HM, Nance RM, Webel A, Chander G, Whitney BM, Willig AL, Mixson LS, Lavu A, Aboulatta L, Dai M, Hahn A, Cachay E, **Drumright LN**, Eltonsy S. Impact of Semaglutide on Weight Change Among People with HIV: A Stratified Analysis by Baseline BMI. 2024 Conference on Retroviruses and Opportunistic (CROI) March 3-6, Denver, CO.
14. Dai, M, **Drumright LN**, Fredericksen R, Delaney JAC, Nance RM, Mixson LS, Whitney BM, Lober WB, Kitahata MM, Mayer KH, Webel A, Willig AL, Jacobson J, Cachay E, Bamford L, Christopoulos K, Moore R, Napravnik S, Saag Ms, Crane HM. Routine Collection of Patient-Reported Outcomes in HIV Clinics: Findings After >100,000 Assessments. 2024 Conference on Retroviruses and Opportunistic Infections (CROI) March 3-6, Denver, CO.
15. **Drumright LN**, Crane HM, Whitney BM, Napravnik S, Willig A, Christopoulos K, Ruderman SA, Haidar L, Cachay E, Mayer KH, Jacobson J, Moore R, Kitahata MM, Saag MS, Delaney JAC. Increases in quality-of-life among people with HIV in the US from 2012-2022 and impact of antiretroviral therapy class. Oral presentation. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2024, March 21-23, Vilamoura, Portugal.
16. Whitney BM, **Drumright LN**, Ruderman SA, Mixson LS, Nance RM, Willig AL, Napravnik S, Mayer KH, Bamford L, Cachay E, Jacobson J, Fredericksen RJ, Delaney JAC, Crane HM. Housiong instability is associated with decreased viral suppression among people with HIV in the United StatesPoster presentation. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2024, March 21-23, Vilamoura, Portugal.
17. Ruderman SA, Webel AR, Willig AL, Cleveland JD, Horvat Davey C, Fleming J, Buford TW, Burkholder G, Katundu M, Whitney BM, **Drumright LN**, Delaney JA, Crane HM. Food insecurity is associated with increased frailty among people with HIV in care in the United States. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2024, March 21-23, Vilamoura, Portugal.
18. Crane HM, Whitney BM, Nance RM, Safren SA, Mayer KH, Kitahata MM, Delaney JAC, Webel AR, Willig AL, Saag MS, Napravnik S, Christopoulos K, Lober WB, **Drumright LN.** Identification of the best PHQ-2 cut-point to identify depression and minimize burden among people with HIV in the United States. Poster presentation. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2024, March 21-23, Vilamoura, Portugal.
19. Haidar L, Crane HM, Nance RM, Webel A, Ruderman SA, Whitney BM, Willig A, Napravnik S, Mixson LS, Lavu A, Aboulatta L, Dai M, Hahn A, Saag MS, Bamford L, Cachay E, Kitahata MM, Mayer KH, Jacobson J, Moore RD, Delaney JAC, **Drumright LN**, Eltonsy S. Weight Loss Associated with Semaglutide Treatment Among People with HIV. International conference for Pharmacoepidemioloogy 2023. August 23-27. Halifax, Nova Scotia, Canada
20. **Drumright, LN**, Ruderman SA, Dai M, Willig A, Whitney B, Hahn A, Mayer KH, Napravnik S, Lesko C, McCaul ME, Moore R, Jacobson J, Chrstopoulos K, Cachay E, Delaney JAC, Webel A, Chander G, Crane H. Alcohol use disorder diagnosis, but not current alcohol use is associated with falls among people with HIV in care in the US. 46th Annual Research Society on Alcohol Meeting, 2023, June 24-28. Bellevue, Washington, USA.
21. **Drumright LN**, Willig AL, Ruderman SA, Whitney BM, Nance RM, Hahn AW, Mixson LS, Ma J, Fredericksen R, Jacobson JM, Christopoulos K, Napravnik S, Cachay E, Mayer KH, Eron JJ,

Delaney JAC, Kitahata MM, Saag M, Webel AR, Crane HM. Illicit substance use and falls among people with HIV in care in the United States. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2023, March 23-25, Athens Greece.

22. Ruderman SA, Short D, Whitney BM, Ma J, Hahn A, Moffatt E, Willig A, Cachay E, Napravnik S, Nance RM, Fredericksen RJ, Webel AR, Delaney JAC, Crane HM, **Lydia N Drumright**. Internalized HIV stigma is associated with current and future frailty among people with HIV. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2023, March 23-25, Athens Greece.
23. Hahn AW, Nance RM, Ruderman SA, **Drumright LN**, Whitney BM, Ma J, Haidar L, Eltonsy S, Mayer KH, Christopoulos K, Saag MS, Kitahata MM, Kamen C, Lober WB, Jacobson J, Cropsey K, Willig A, Cachay E, Webel AR, Bamford L, Eron JJ, Napravnik S, Kritchevsky S, Austad S, Landay A, Fredericksen RJ, Chander G, Crane PK, Delaney JAC, Crane HM. Association between baseline blood glucose and progression to frailty is modified by access to glycemic control agents among people with HIV. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2023, March 23-25, Athens Greece.
24. Whitney BM, Nance RM, Misxon LS, Ruderman SA, **Drumright LN**, Heckbert SR, Feinstein MJ, Budoff MJ, Eron JJ, Moore RD, Chander G, Delaney JAC, Crane HM. Impact of smoking parameterization on modeling Type 1 and Type 2 Myocardial Infarction Risk among People with HIV. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2023, March 23-25, Athens Greece.
25. **Drumright LN**, Whitney BM, Duncan Short, Sonia Napravnik, Edward Cachay, Ellie Moffatt, Katerina Christopoulos, Torsten B Neilands, Kenneth H Mayer, Mallory O Johnson, Jimmy Ma, Andrew Hahn, Robin M. Nance, Timothy Crawford, Geetanjali Chander, Rob J Fredericksen. Internalized HIV Stigma and Mental Health/Substance Use Over Time**.** Conference on Retroviruses and Opportunistic Infections (CROI) 2023, February 19-22, Seattle, WA.
26. **Drumright LN**, Ruderman SA, Willig AL, Whitney BM, Nance RM, Hahn AW, Mixson LS, Ma J, Fredericksen R, Jacobson JM, Christopoulos K, Napravnik S, Cachay E, Webel AR, Crane HM. Comorbidities AND Symptoms Associated with Falls from 2020-2021. Conference on Retroviruses and Opportunistic Infections (CROI) 2023, February 19-22, Seattle, WA.
27. Fredericksen RJ, **Drumright LN**, Mixson S, Nance RM, Whitney B, Ruderman S, Ma J, Hahn A, Napravnik S, Jacobson J, Christopoulos K, Bamford L, Cachay E, Kitahata M, Crane HM. Intimate partner violence in a cohort of persons with HIV in care. Conference on Retroviruses and Opportunistic Infections (CROI) 2023, February 19-22, Seattle, WA.
28. Ruderman SA, Webel AR, Willig AL, **Drumright LN**, Fitzpatrick AL, Odden MC, Cleveland JD, Davey CH, Fleming J, Buford TW, Jones R, Greene M, Kamen C, Pandya C, Crane HM. Validity of a self-reported, modified frailty phenotype among people with HIV. Conference on Retroviruses and Opportunistic Infections (CROI) 2023, February 19-22, Seattle, WA.
29. **Drumright LN**, Short D, Fredericksen RJ, Ma J, Ruderman SA, Moffatt E, Christopoulos K, Cachay E, Mayer KH, Keruly JC, Chander G, Johnson MO, Lober WB, Nance RM, Hahn A, Moore RD, Willig A, Eron JJ, Napravnik S, Kitahata MM, Saag MS, Delaney JAC, Crane HM. Internalized HIV stigma is longitudinally associated with lower HIV medication adherence. IAPAC Adherence 2022, November 7-9, Washington DC.
30. Lober WB, **Drumright LN.** Clinical Opioid Summary with Rx Integration (COSRI): A Clinical Decision Support (CDS) Tool for Increasing Safety in Prescribing Controlled Substance. American Medical Informatics Association (AMIA) FHIR Competition (S72) 2022, AMIA Annual Symposium, November 5-9, Washington DC.
31. Fredericksen RJ, **Drumright LN,** Short D, Ruderman SA, Whitney BM, Nance RM, Ma J, Hahn A, Cachay E, Willig A, Mayer K, Napravnik S, Eron J, Chander G, Jacobson J, Delaney JAC, Crane HM. Longitudinal factors associated with quality of life (EQ-5D-3L) in a U.S. cohort of people with HIV (PWH) in routine care in the current treatment era. 29th Annual International Society for Quality of Life Research (ISOQOL) Conference 2022, October 19-22, Prague, Czech Republic.
32. **Drumright LN,** Short D, Whitney BM, Ruderman SA, Ma J, Haidar L, Nance RM, Hahn A, Moffatt E, Mayer KM, Christopoulos K, Johnson MO, Saag MS, Kitahata MM, Lober WB, Moore RD, Keruly JC, Willig A, Cachay E, Eron JJ, Napravnik S, Chander G, Crane HM, Delaney JAC, Crane PK, Fredericksen RJ. Differences in Burden of Internalized HIV Stigma (IHS) by Race/Ethnicity

among People with HIV (PWH) Living in the US. # EPD 404. AIDS 2022, July 28- August 2, Montreal, Canada.

33. Ruderman SA, Nance RM, **Drumright LN**, Whitney BM, Mayer KH, Eron JJ, Napravnik S, Christopoulos K, Greene M, Mathews WC, Cachay ER, Webel A, Saag MS, Willig AL, Pandya C, Cartujano-Barrera F, Kamen C, Hahn AW, Kitahata MM, Lober WB, Delaney JAC, Crane HM. Approaches to optimally target frailty screening among people with HIV in clinical care#EPB 133 AIDS AIDS 2022, July 28- August 2, Montreal, Canada.
34. Fredericksen RJ, Fitzsimmons EF, Sigal M, Dougherty S, Pearce J, Powell M, Nguyen J, Ruderman SA, Whitney BM, **Drumright L**, Ma J, Nance RM, Delaney JAC, Mayer KH, Willig AL, Crane HM, Hahn A. Marijuana use goals, patterns, and perceptions of health impact among persons with HIV in care in the era of state-level legalization. AIDS 2022, July 28- August 2, Montreal, Canada.
35. **Drumright LN**, Lober WB. Implementing the Clinical Opioid Summary with Rx Integration (COSRI) CDS Tool in Washington State. AMIA Clinical Informatics Conference 2022, May 24-26, Houston, TX.
36. Ma J, Ruderman SA, Whitney BM, Fredericksen RJ, Scott JD, Nance RM, Reisner S, Mayer KH, Robinson JR, Delaney JA, Cachay ER, Chander G, Kim HN**, Drumright LN**. The hepatitis C care continuum in the DAA era among transgender women with HIV. # ID 405. CROI 2022, February 13-16, 2002, Boston, MA.
37. Fredericksen RJ, Nance RM, **Drumright LN**, Whitney BM, Ruderman SA, Ma J, Hahn AW, Cachay ER, Chander G, Jacobson J, Mayer KH, Napravnik S, Willig A, Crane HM. Impact of methamphetamine use on viral load by gender among people with HIV. #ID 1322. CROI 2022, February 13-16, 2002, Boston, MA.
38. Fredericksen RJ. Nance RM. Nash P. Schnarrs PW. Ruderman S. Whitney B. **Drumright L**. Ma J. Potter J. Mathews W. Mayer K. Jacobson J. Napravnik S. Eron J. Willig A. Mugavero M. Delaney JAC. Crane HM. Impact of childhood household violence on antiretroviral adherence and health outcomes among people living with HIV. 16th International Conference on HIV Treatment and Prevention Adherence, Orlando FL November 7-9 , 2021.
39. Fredericksen R, Fitzsimmons E, Brown S, Loo S, Dougherty S, **Drumright L**, Pearce J, Whitney B, Nance R, Ruderman S, Mayer K, Mugavero M, Crane H, Hahn A. Vaporized nicotine use among current and former tobacco-smoking patients in primary HIV care: initiation, patterns of use, and perceived health effects. Quality of Life Research. 2021. 30 (S1): S119-S120.
40. Ruderman SA, Ma J, Delaney JAC, Nance RM, Luu B, **Drumright LN**, Whitney BM, et al. High HIV viral load is associated with incident venous thromboembolism. International workshop on HIV and Aging. 23-24 September, 2021.
41. Ruderman SA, Delaney JAC, Nance RM, Fredericksen RJ, **Drumright LN**, Whitney BW, et. Al. Vaporized nicotine (e-cig) use among people with HIV in care in the US. International Conference on Pharamcoepidemiology. 23-25 August, 2021.
42. Luu B, Ruderman S, Nance R, Delaney J, Ma J, Whitney B, **Drumright L**, Heckbert S*, et al.* Tobacco smoking and binge alcohol use are associated with incident venous thromboembolism in an HIV cohort. 11th IAS Conference on HIV Science. 18-21 July, 2021.
43. Fredericksen RJ. Fitzsimmons E. Brown S. Loo S. Dougherty S. **Drumright L.** Pearce J. Whitney B. Nance R. Ruderman S. Mayer K. Mugavero M. Crane H. Hahn A. Vaporized nicotine use among current and former tobacco-smoking patients in primary HIV care: initiation, patterns of use, and perceived health effects. 28th Annual Conference of the International Society of Quality of Life Research. October 2021 (virtual).
44. Lester J, Sze-To W, Brown N, **Drumright LN**. Candidemia trends and risk factors for mortality over 23 years (1995-2018) within the Cambridge University Hospitals NHS Foundation Trust (CUH): clinical informatics solutions to real-time, continuous surveillance. Fungal Update, London, UK 15-16 March 2019.
45. Sze-To W, Lester J, Brown N, Enoch D, **Drumright LN**. Prevalence of Invasive Fungal Infection (IFI) among hospital patients in the East of England (1995-2018). Fungal Update, London, UK 15-16 March 2019.

46. Marks WH, Slater NKH, D'Arcy DM, **Drumright LN**. Novel Drug Release Test Using USP4 Flow Through Cell and CFD Simulations for Nipple Shield Delivery System. Pacific Southwest Conference for Engineering. Irvine, CA April 6-8 2017.
47. Marks WH, **Drumright LN**, Slater NKH, D'Arcy DM. Novel Imaging Platform for Predicting Efficacy of Nipple Shield Delivery System Designs via High-Speed Photography. IEEE International Symposium on Biomedical Imaging. Melbourne, Australia 18-21 April 2017.
48. Marongiu L, Curran M, Parmar S, Lillestol R, **Drumright LN**. TaqMan Array Card (TAC) Assay: Increased Sensitivity over Conventional RT-qPCR for Norovirus Detection. 2016 Norovirus Conference, Lubeck, Germany. 16-19 March 2016.
49. Lillestøl R, Frost SDW, O'Masta B, **Drumright LN**. Complex epidemiology of hospital norovirus cases revealed through intensive sampling. 2016 Norovirus Conference, Lubeck, Germany. 16-19 March 2016.
50. Marongiu L, Shain E**, Drumright LN**, Lillestøl R, Somasunderam D, Curran MD. Assumption-free improvement of the maxRatio algorithm increases the accuracy of qPCR assays targeting viruses. Presentation at ESCV 2016.
51. **Drumright LN,** Frost SDW. Long distance distribution of GII.3 and GII.4 norovirus worldwide. 21st Conference on HIV Dynamics and Evolution, Tucson, Arizona, USA. 6-11 May 2014.
52. SDW Frost, **LN Drumright.** Automated genotyping and recombination analysis of norovirus strains. Fifth International Calicivirus Conference, Beijing, China, 12-15 October 2013
53. **Drumright LN,** Frost SDW. Long distance distribution of GII.3 and GII.4 norovirus worldwide. Fifth International Calicivirus Conference, Beijing, China, 12-15 October 2013.
54. Davis G, Sevadalis N, **Drumright LN**. Three-dimensional Geographic Imaging of Hospital Environments: A novel technique to analyse, model and predict Healthcare Associated Infections. ECCMID 2013
55. Castro Sanchez E, Charani E, **Drumright LN**, Sevdalis N, Shah N, Holmes AH. Fragmentation of Care, Frustration and Ambiguity: Healthcare Professionals' Narratives on Peripheral Vascular Access. ECCMID 2013
56. Davis G, Sevdalis N, **Drumright LN**. Spatio-temporal distribution of *Clostridium difficile* in two London hospitals. HPA Annual Conference 2012
57. Castro Sanchez E, Charani E, **Drumright LN**, Sevdalis N, Shah N, Holmes AH. "Broken lines: Fragmentation of care in peripheral vascular access" . Infection Prevention Society Annual Conference 2012.
58. Shah N, Edwards R, **Drumright LN**, Charani E, Castro Sanchez E, Sevdalis N, Holmes AH. "Understanding non-compliance with infection prevention practices". Infection Prevention Society Annual Conference 2012
59. Charani E, Shah N, Edwards R, **Drumright LN**, Holmes AH. "The barriers and facilitators to optimal antimicrobial prescribing: a qualitative study ECCMID 2012
60. **Drumright LN,** Frost SDW, Catchpole M, Harrison J, Atkins M, Parker P, Elliot AJ, Holmes AH. Improving ILI Surveillance using NHS Hospital Staff Influenza Like Absence (ILA). 2012 ISDS Conference, San Diego, California; December 2012.
61. **Drumright LN,** Holmes AH. Healthcare Worker Illness Absence for Influenza Surveillance and Hospital Preparedness. Centre for Respiratory Infections Conference 2011.
62. **Drumright LN**, Weir SW, Frost SDW. "The Role of Venues in Structuring STI and Risk Networks among Men Who Have Sex With Men". 2011 International Society for Sexually Transmitted Disease Research, July, Quebec City, Canada
63. Edwards R, E Charani, N Sevdalis, B Alexandrou, E Sibley, D Mullett, HP Loveday, **LN Drumright**, A Holmes. Optimising infection prevention and control practice using behavior change: a systematic review. International Conference on Prevention & Infection Control (ICPIC 2011) Geneva, Switzerland. 29 June- 2 July 2011

64. Kruijshaar ME, Pimpin L, Ködmön C, Lipman M, Delpech V, Rice B**, Drumright LN**, Manissero D, Abubakar I. P170 TB-HIV co-infection: how does the UK compare to Europe? 2010 Union World Conference on Lung Health, 11-15 November, Berlin Germany.
65. **Drumright LN,** Abubakar I. "Immigration status and HIV in tuberculosis infection: diverging trends in the United Kingdom and United States". 2009 Union World Conference on Lung Health, December 3-7, Cancun, MX.
66. **Drumright LN,** Frost SDW. "Bars, social networks, and HIV/STI risk among MSM in San Diego, CA, USA". 2008 Epidemics Conference, December 1-3, 2008, Asilomar, CA. Abstract # EPID2008 344
67. **Drumright LN,** Gorbach PM, Strathdee SA, Cachay ER, Morris SR, Little SJ. "Unprotected receptive, but not insertive, anal Intercourse & recent syphilis infection are associated with incident HIV infection among MSM." 2007 International Society for STD Research Conference, July 29 – August 1, 2007, Seattle, WA. Abstract # 521.
68. White PJ**, Drumright LN,** Fox J, Gorbach PM, Macdonald N, Daar ES, Fidler S, Little SJ, Ward H. "Preventing onward transmission of HIV from MSM with primary HIV Infection through early diagnosis, counseling, and treatment: comparison of UK and USA studies using a stochastic, individual-based model". 2007 International Society for STD Research Conference, July 29 – August 1, 2007, Seattle, WA.
69. **Drumright LN**, Little SJ, Richman DD, Frost SDW. Using social network methods to analyze phylogenetic clustering of HIV among recently-infected MSM in San Diego, California. 2007. Sunbelt Social Network Conference, Corfu, Greece, May 1- May 5, 2007.
70. **Drumright LN,** Little SJ, Richman DD, Frost SDW. "Age discordance predicts clustering of HIV among recently-infected MSM in San Diego". 2007 Conference on Retroviruses and Opportunistic Infections, February 27- March 1, 2007, Los Angeles, CA. Abstract # 654.
71. **Drumright LN**, Strathdee SA, Little SJ, Araneta MRG, Slymen DJ, Malcarne VL, Daar ES, Gorbach PM. "Associations between unprotected anal intercourse and substance use before and after HIV diagnosis among recently HIV-infected men who have sex with men". Conference of the International AIDS Society; August 13-18, 2006, Toronto, Canada. Abstract WEPE0299.
72. **Drumright LN**, Gorbach PM, Frost SDW, Strathdee SA, Woelk C, Kosakovsky Pond SL, Daar ES, Richman DD, Little SJ. "Transmitted HIV drug resistance is associated with methamphetamine use among recently HIV infected MSM in southern California, USA". 2006 HIV Drug Resistance Conference, June 13-17, 2006, Sitges, Spain.
73. **Drumright LN**, Gorbach PM, Daar ES, Little SJ. Drug use and unprotected anal intercourse among men who have sex with men who were recently infected with HIV. 2005. The 16th Biennial Meeting of the International Society for Sexually Transmitted Diseases Research (ISSTDR); July 10-13, 2005; Amsterdam, The Netherlands. Abstract MP-049.
74. Gorbach PM, **Drumright LN**, Daar ES, Little SJ. "Transmission behavior following HIV diagnosis". Poster # 981; 2005 Conference on Retroviruses and Opportunistic Infections, Boston, MA February 22-26.
75. Frost SDW, Cheng WS, **Drumright LN**, Leigh Brown AJ, Richman D, Little SJ, Gorbach PM. "Bath-houses, bars, and bridges: patterns of sexual partner recruitment in a cohort of MSM with recent HIV infection." 2005. Paper # 169, 2005 Conference on Retroviruses and Opportunistic Infections, Boston, MA February 22-26.
76. **Drumright LN**, Gorbach PM, Daar ES, Little SJ. Risk reduction and partnerships patterns of MSM with recent HIV infection. 2004. 2nd International Workshop on Acute HIV-1 Infection, Washington, DC, May 3-5.
77. Gorbach PM, **Drumright LN**, Garnett GP, Holmes KK. "The natural history of new sexual partnerships: a niche for bacterial STDs" 2004. Abstract # CDC National Sexually Transmitted Disease Conference, Philadelphia, PA, March 7-11.

78. **Drumright LN**, Gorbach PM, Little SJ. "Sexually transmitted diseases and sildenafil use: risks for HIV transmission among MSM" 2004. Poster #P20, 2004 Universitywide AIDS Research Program Conference Los Angeles, CA February 21.
79. **Drumright LN**, Gorbach PM, Holmes KK. Partnership concurrency and sexually transmitted diseases. 2003. International Society for Sexually Transmitted Disease Research Congress, Ottawa, ON July 27-30. Abstract # 474.
80. Gorbach PM, **Drumright LN**, Daar ES, Little SJ. "Partnership types among men with recent HIV infection". 2003. International Society for Sexually Transmitted Disease Research Congress, Ottawa, ON July 27-30. Abstract # 545.
81. **Drumright LN**, Gorbach PM, Holmes KK. Discord, discordance and concurrency in partnerships. Present by Drumright LN at CDC 2002 National STD Conference San Diego, CA March 4-7.
82. Gorbach PM, **Drumright LN**, Holmes KK. "Concurrency and STD in new sexual partnerships." Poster #P29, CDC 2002 National STD Conference San Diego, CA March 4-7.
83. Yasuda J, Gorbach PM, **Drumright LN**, Holmes KK. "Health protective sexual communication scale in STD Clinics." Poster #P93, CDC 2002 National STD Conference San Diego, CA March 4-7.
84. Gorbach PM, **Drumright LN**, Leigh-Brown AJ, Frost SDW, Little S. "Partnership types and primary HIV infection and transmission." Poster #P20, 2002 Universitywide AIDS Research Program Conference Sacramento, CA February 22.
85. **Drumright LN**, Barrett-Connor E, Garland C, Kritz-Silverstien D, Morton D. Is calcium intake associated with reduced blood pressure? Presented by Drumright LN at 2001 San Diego County Epidemiology Exchange Conference, San Diego, CA May 11.

MEDIA, PRESS & PUBLIC FORUMS

1. **Innovative use of electronic medical records.** Cambridge Science Festival. Summer 2018. https://www.youtube.com/watch?v=jHdLIPm07CM
2. **Big Data in Healthcare**. Reform Big Data Conference. 21st February 2017.
3. **Making changes through clinical informatics.** Cambridge Biomedical Research Center Spotlight. https://cambridgebrc.nihr.ac.uk/spotlight-lydia-drumwright/
4. **Medical Informatics & the Transformation of Healthcare**. Cambridge Alumni Festival, Hughes Hall Alumni Lecture. 24th September 2016.
5. **eHospital Consent for Contact Consultations**. Cambridge University Health Partners Patient and Public Involvement Oversight Committee Meeting. 30th November 2015.
6. **The Researcher's Perspective: How can Organisations in EoE Improve Support to Researchers**. East of England Patient and Public Involvement Annual Meeting. 30th September 2015.
7. **Using big data to improve healthcare**. Naked Scientists Interview. July 13, 2015. https://www.thenakedscientists.com/articles/interviews/using-big-data-improve-healthcare
8. **The Big Dating Game.** Research Horizons, Big Data Spotlight. Issue 27 pages 24-25, June 1, 2015. https://issuu.com/uni_cambridge/docs/issue_27_research_horizons
9. **From Tropical to Urban Jungles: Emerging Infections in a Connected World.** Cambridge Pint of Science, Bugs to Drugs. 18 May 2015.
10. **The 'cutting edge' of science at the Cambridge Biomedical Campus.** Cambridge Institute of Public Health. March 22, 2015. https://www.cambridgenetwork.co.uk/news/cutting-edge-science-cambridge-biomedical-campus
11. **How does norovirus spread.** The Naked Scientists Radio show. 23 February 2014. https://www.thenakedscientists.com/articles/interviews/how-does-norovirus-spread
12. **Novel surveillance in acute care settings**. Infection Control and Emergency Planning – Preparing for the Challenge of Pandemic Influenza. Public Policy Exchange. 23 April 2013.
13. Center for Prevention and Management (CIMP) Surveillance Workstream. Imperial YouTibe. https://www.youtube.com/watch?v=5TjpUb97p1M

SERVICE: PROFESSIONAL AND COMMUNITY

2014 - 2019 **Creator/ Organizer, Big Data in Medicine Annual Conference**, University of Cambridge, UK

2015 – 2020 **Cambridge Theme Lead, Infection Theme, NIHR Health Informatics Collaborative**, Cambridge University NHS Hospitals Foundation Trust, UK

2015 - 2020 **Cambridge Theme Co-Lead, Viral Hepatitis Theme, NIHR Health Informatics Collaborative,** Cambridge University NHS Hospitals Foundation Trust, UK

2015 - 2019 **Organizer, UK Health Data Analytics Network,** University of Manchester, UK

2016 - 2020 **Academic Lead School of Clinical Medicine, University Information Services**, Schools Engagement Committee, University of Cambridge, UK

2008 **Reviewer, abstracts for the International AIDS Society Conference meeting**

2004- current **Journal reviewer**: *Drug and Alcohol Dependence, Journal of Acquired Immunodeficiency Syndromes*, *AIDS and Behavior*, *AIDS*, *Health Psychology*, *Current Drug Abuse Reviews*, *Culture Health, and Sexuality*, *AIDS Care*, *Perspectives on Sexual and Reproductive Health*, *Sexually Transmitted Infections*, *Addiction Research and Theory*, *Public Health, Annals of Epidemiology*, *Journal of Infectious Diseases*, *Lancet, BMC Public Health, Lancet Infectious Diseases, Bulletin of the WHO, HIV Medicine*

SERVICE: ADMINISTRATIVE AND ACADEMIC

2016 – 2020 **Member, Executive and Steering Committee**, Cambridge Big Data Strategic Research Initiative

2016 – 2019 **Chair (2018), Member (2016),** University of Cambridge Research Ethics Committee

2015 – 2019 **Chair, Cambridge Central Research Ethics Committee**, National Research Ethics Service, Health Research Authority, UK

2014 – 2017 **Chair (2016/2017), Secretary (2015/2016), Member (2014), University of Cambridge Board of Scrutiny**, University of Cambridge, UK

2010 – 2014 **Member, West London National Research Ethics Committee**, National Research Ethics Service, Health Research Authority, UK

2010 – 2014 **Member, Management Committee, MSc in Infection Management for Pharmacists**, Department of Medicine, Imperial College London

2011 – 2014 **Member, Steering and Management Committee, MSc in Infection for Health Professionals**, Department of Medicine, Imperial College London

2006 – 2008 **Member, Steering Committee, Joint Doctoral Program in Global Health**, University of California, San Diego and San Diego State University

TEACHING EXPERIENCE: STUDENT & INTERN SUPERVISION AND MENTORSHIP

Years	Name *(Institution)*	Training	Research Project
2023-curr	Mindy Dai *(University Washington)*	MPH	Impact of alcohol use on outcomes among people living with HIV
2024-curr	Mary Wingerson *(University Washington)*	MedSTAR	Understanding unhealthy alcohol use risk in gender diverse people
2018-2021	Charlotte Milbank ESRC Scholar *(Cambridge University)*	Doctoral / MPhil	Health outcomes of wild food consumption
2016-2018	William Marks Gates Scholar *(Cambridge University)*	Doctoral	Mechanistic analysis and optimisation of nipple shield drug delivery devices

2010-2017	Grahame Davis MRC Scholar *(Imperial College London)*	Doctoral	Spatial mapping to understand healthcare associated infection transmission and prevention
2015-2018	Wai Wen 'Vivian' Sze-To MRC Sackler Scholar *(Cambridge Universty)*	MPhil	Use of clinical informatics to understand the epidemiology of invasive fungal infections (IFIs)
2011-2012	Frank Hamill *(Imperial College London)*	MSc	Does monitoring of Infection Prevention and Control practices help improve the quality of clinical care?
2012-2013	Liquin Ren *(Imperial College London)*	MSc	Factors influencing prescribing knowledge and behaviors among junior doctors.
2012-2014	Sally Pearce *(Imperial College London)*	Personal Tutor	MSc in Infection for Pharmacists
2011-2013	Amy Lee *(Imperial College London)*	Personal Tutor	MSc in Infection for Pharmacists
2010-2012	Jeannette Bennett *(Imperial College London)*	Personal Tutor	MSc in Infection for Pharmacists
2011-2012	Xuanxiang Li *(Imperial College London)*	Undergraduate Thesis	Contributing factors to the increase in annual burden of human norovirus infection
2013-2014	Judy Lieber *(Imperial College London)*	Intern	Epidemiological and statistical analysis of asthma in respiratory infection
2012-2013	Dr Nidhi Gupta *(Imperial College London)*	Intern - Acute Admissions Resident	Risk factors for carbapenem resistant bacterial infections
2012-2014	Siddharth Mookerjee *(Imperial College London)*	Intern	Novel surveillance of existing hospital databases
2011-2013	Nisha Shah *(Imperial College London)*	Intern	Qualitative/quantitative study of healthcare worker HCAI prevention attitudes/behaviors
2010	Sarneet Singh *(Imperial College London)*	Intern – Medical Student	Understanding how perceptions of healthcare workers influence HCAI risk

TEACHING EXPERIENCE: POSTDOCTORAL AND PROFESSIONAL SUPERVISION

Years	**Name**	**Researcher**	**Research Projects**
2024-curr	Ryan Kyle	Postdoctoral	HIV SUCCESS
2023-curr	Dominique Heinke	Postdoctoral	HIV SUCCESS
2019-2021	Rabiya Zia	Postdoctoral	ExISE – Operating theatre design & infection risk
2016-2021	James Lester	Postdoctoral	Clinical Informatics infrastructure & epidemiology
2014–2018	Reidun Lillestol	Postdoctoral	Norovirus sequencing & epidemiology
2014-2016	Joao Bettencourt-Silva	Postdoctoral	Clinical Informatics infrastructure & epidemiology

2014-2016	Luigi Marongiu	Postdoctoral	Taqman array cards & gastrointestinal epidemiology
2012-2014	Enrique Castro-Sanchez	Research Nurse	Intervention for care of peripheral vascular cannulae, health literacy and medication outcomes in HIV/ TB
2012-2014	Mindy Gore	Postdoctoral	Norovirus research associate
2012-2014	Beth Pamba (Kangwana)	Postdoctoral	CIPM and MOSAIC Research Fellow
2010-2014	Laura Garcia Alvarez	Postdoctoral	CIPM and MOSAIC Research Fellow
2012-2014	Shelby Yamamoto	Postdoctoral	CIPM Research Fellow
2012-2012	Xiao Si 'Selena' Wang	Postdoctoral	MOSAIC data analyst
2010-2011	Rachel Edwards	Research Nurse	Social marketing in the NHS; hand hygiene compliance; antimicrobial stewardship

TEACHING EXPERIENCE: MODULE LEADERSHIP AND DIDACTIC TEACHING

09/17-11/20 **Lecturer, Routine Data Sources, MPhil in Epidemiology and Public Health, University of Cambridge.** Four hours of interactive lecture annually to graduate students in Epidemiology and Public Health focusing on clinical informatics, surveillance and use of routine data sources in Epidemiology.

09/13–07/14 **Lecturer, Ethics in Science, BSc Gastroenterology & Master Class for Postgraduate Students, Imperial College London.** Six hours of lecture annually to undergraduate and graduate students focusing on ethics in scientific research. Lectures cover a broad range of topics including ethical data collection and results reporting, use of public and charity funding, involvement of human research participants, use of human tissues, conducting research on animals, reporting of findings, peer review, data protection, and the place of ethics in science.

07/10– 07/14 **Module Leader/Lecturer, Epidemiology and Biostatistics, Department of Medicine, Imperial College London.** Developed and lectured annually a 25 hour week-long module to pharmacists and other health professionals (primarily nurses) completing their MSc in Infection. Lectures focus on fundamentals of epidemiology and biostatistics and how to apply these to their everyday work routines, Masters research project, and reading of the scientific literature

01/12 –07/14 **Lecturer, Epidemiology, MRes in Clinical Research, Imperial College London.** Two hours of lectures annually to Masters in Research students focusing on Epidemiology. Lectures cover a range of epidemiological topics including study design, testing, bias, confounding, and causal inference.

05/12 – 07/14 **Tutor, Statistical Surgeries for MSc in Infection and MSc in Infection for Pharmacists Theses.** 16 hours of tutoring in statistics annually to pharmacists and other health professionals (primarily nurses) completing a MSc in Infection. Sessions focused on teaching the use of SPSS in statistical analysis and how to interpret outputs. These sessions were tailored to individual's research questions and datasets.

06/10 – 06/11 **Lecturer, Epidemiology, Study Design and Biostatistics, Department of Medicine, Imperial College London.** Six hours of lecture bi-annually to Pharmacists completing a MSc in Infection Prevention. Lectures focus on fundamentals of epidemiology and biostatistics and how to apply these to their everyday work routines, Masters research project, and reading of the scientific literature.

9/09 – 04/10 **Lecturer, Tuberculosis Surveillance and Control Practical, Health Protection Agency, Center for Infections, Respiratory and Systemic Infections Division, Tuberculosis Section.** Institutes and dates in which the practical has been taught: 10/09: Heath Protection Agency- introductory course in epidemiology and disease surveillance;11/09: Oxford University – School of Public Health. This was a one-hour

interactive discussion and problem solving session to enhance epidemiological and medical concepts presented in the corresponding lecture.

9/07 – 12/08 **Course Instructor, Emerging and Re-Emerging Infectious Diseases, School of Medicine, UCSD.** Developed curriculum for new graduate and medical student level course examining emerging and re-emerging infectious diseases of global importance. Responsibilities included: course development and approval, organization, development of assignments and exams, grading.

8/06 – 12/08 **Lecturer, Epidemiology for Medical Students, School of Medicine, UCSD** Teaching medical students in small groups how to read, interpret, and understand epidemiological and statistical concepts in peer-reviewed, published manuscripts.

9/02 – 5/06 **Course Instructor, Sexually Transmitted Diseases, Graduate School of Public Health, SDSU.** Teaching to undergraduate students of all majors. Duties included preparing and conducting lectures; teaching students biological, social and epidemiological aspects of STD transmission and symptomatology; presentation techniques; organizing members of the community to speak to the class; and grading of students presentation and exams.

9/02 – 12/03 **Course Instructor, SPSS Laboratory, Graduate School of Public Health, SDSU.** SPSS programming and output interpretation course to graduate students in Epidemiology, Environmental Health and other biological sciences. Duties include preparing and conducting lectures; teaching students programming of the SPSS statistical package and interpretation of their data output; and grading of students projects.

2/02 – 12/03 **Course Instructor, SAS Laboratory, Graduate School of Public Health, SDSU.** SAS programming and output interpretation course to graduate students in Epidemiology, Environmental Health and other biological sciences. Duties include preparing and conducting lectures; teaching students programming of the SAS statistical package and interpretation of their data output; and grading of students projects.

9/01 – 9/02 **Course Instructor, Community Health Education, Graduate School of Public Health, SDSU.** Teaching evaluation of health education programs course to undergraduate students. Duties include preparing and conducting lectures; teaching students theoretical concepts in evaluation, data collection techniques and basic statistical analyses; and grading of students projects and exams.

8/00 – 6/02 **Teaching Assistant, Epidemiology, Graduate School of Public Health, SDSU.** Graduate level epidemiology course. Duties include conducting lectures, assisting professor in conducting lectures, review material covered in class, tutor graduate students and grading of students projects and exams.

8/98 – 9/99 **Teaching Assistant, Biostatistics Laboratory, Health Sciences Department, California State University, Northridge.** Graduate teaching assistant. Duties included preparing lectures, teaching technical skills, reviewing general biostatistics information and grading student projects.

PATIENT & PUBLIC INVOLVEMENT / POLICY & GOVERNMENT ENGAGEMENT

- **2014-2020** Within Cambridge Clinical Informatics, I ran an active patient and public involvement and engagement strategy. This program focused on ethical of de-identified patient records, using a qualitative focus group approach to capture evidence for and against different strategies. I supported policy translation through active engagement with the Cambridge Centre for Science and Policy (CSaP) and their government fellows, as well as active participation with organizations that work in conjunction with the government to address policy, such as Reform in the UK. In addition to these activities, I participated in regular community engagement about the work of my Centre, including the annual science festivals, popular radio and print news, and presentations in public locations (e.g., Pint of Science).

- **2010 -2014** At Imperial College London, I developed community involvement events, conducted a number of Community forums for healthcare workers (a main participant groups) and engaged in science festivals.
- **2000-2008** During my doctoral and postdoctoral training at UCSD in HIV Research, I regularly conducted AIDS Rounds for the medical staff across the county and gave presentations to the Community Advisory Board for the HIV Research Centre. Thus, I began my training with the breadth of ability in communicating with medical staff, public and patients, as well as other scientists.

SPECIALIST RESEARCH SKILLS

- Statistical Analysis: Univariate analyses for parametric and non-parametric/ independent and non-independent data; linear regression; regression diagnostics; ANOVA, ANCOVA, and MANOVA; logistic regression, including polychotomous, ordinal and conditional; Other generalized linear models, including general estimating equations, generalized linear and latent mixed models, generalized linear mixed effects models; survival analyses including Cox modeling; Markov change state modeling; cluster analysis; principal components analysis; surveillance analyses.
- Natural Language Processing: query building; performance assessment; gold standard development.
- Phylogenetic Analysis (virology data): sequence alignment; BLAST searches; phylogenetic inference using nucleotide substitution models, distance-based methods, maximum likelihood and Bayesian approaches; cluster analysis based on distance and phylogeny approaches; recombination analysis; phylogeography.
- Study Design: cross-sectional, case-control, nested case-control, and prospective study design; qualitative and observational studies; surveillance; sensitivity and specificity testing.
- Intervention Trial Design: behavioral interventions and low risk device trials; quasi-experimental designs including behavior change in healthcare settings using interrupted time series; software device trials for medical settings.
- Development of Quantitative Assessment Tools: extensive experience in development of new questionnaires to capture behavioral, medical symptom and social data; validity and reliability testing: capture of information on recall methods.
- Qualitative Research: interview schedule development; interview; and thematic code analysis.
- Patient and Public Involvement and Engagement.
- Wet Laboratory Techniques: nucleic acid extraction, PCR, qPCR, plasmid construction, sanger sequencing, MiSeq

SPECIALTY WORKSHOPS & TRAINING

- **BUILD PODER Critical Race Theory-Based Mentoring**. California State University, Northridge. March-May 2024.
- **Mentoring the Mentors Program**. University of California, San Francisco. October 2022.
- **NIHR Leadership Programme.** Ashridge Business School. February 2014 - March 2015
- **Methods of Cost Effectiveness Analysis.** University of Oxford. 30 June- 2 July 2014.
- **Bayesian Modeling, Inference and Prediction**. University of Reading. 25-29 November 2014.
- **Introduction to Health Economics**. University of Oxford. 14 March 2014.
- **Molecular Epidemiology of Viruses in R**. University of Cambridge, May1-3 2013.
- **Introduction to Python**. Imperial College London, March 2013.
- **VEME** (17th International BioInformatics Workshop on Virus Evolution and Molecular Epidemiology). 27 - 31 August 2012, Belgrade, Serbia. – Phylogenetic Inference Module.
- **Introduction to Bayesian Analysis Using WinBugs**. University of Cambridge MRC Biostatistics Unit. October 2011.

COMPUTER & LANGUAGE SKILLS

- Statistical packages: STATA, SAS, SPSS, R, EpiInfo, WinBUGS
- Interviewing Software: Sawtooth Software Ci3, SNAP, Adobe Acrobat Forms, QDS, EpiCollect, Survey Monkey
- Other Analytic Software: BEAST, MEGA, SeaView, PHYML, PHYLIP, RDP4, Python, MatLab, ATLAS.ti
- Word, Word Perfect, PowerPoint, Access, Adobe Acrobat Professional, Adobe Photoshop, Adobe Illustrator, Open Office
- Languages: Beginning French, Beginning Spanish

EXAMINATION & SCHOLARSHIP COMMITTEE ACTIVITIES

Masters Level Examination

- Internal Examiner – Imperial College London
- External Examiner – Imperial College London
- External Examiner - Swansea University

PhD Level Examination

- External Examiner – Swansea University
- External Examiner – University College London

PhD & Masters Level Scholarship Committees

- Gates International Scholars Program
- Gates United States Scholars Program
- Cambridge Trust Scholars Program
- Experimental Medicine Training Initiative

CITATION & ACADEMIC STATISTICS & INTERNET PRESENCE

Citations

- **Total Citations:** 3643
- **H-index:** 28 **i10 index:** 38

Other Academic Internet Presence

- **LinkedIn: https://www.linkedin.com/in/lydiadrumright/**
- **ResearchGate:** https://www.researchgate.net/profile/Lydia_Drumright2
- **Google scholar:** https://scholar.google.co.uk/citations?user=fdss0dkAAAAJ&hl=en
- **ORCID:** https://orcid.org/0000-0002-1255-1681
- Included in 2014 (impact years 2008-2013) REF at Imperial College London

Doc No.	Document Name	Comments	Date From DD/MM/YYYY	Date to DD/MM/YYYY	Patient/Staff Identifiable Data
1	Copy of Public Inquiry Data DRAFT v5 (20230330)	Not included in the bundle as it contains patient identifiable information.	01/07/2010	01/02/2023	Yes
2	Public Inquiry Analysis of Antimicrobial Prescribing	Included in this bundle (This document is the attachment appended to Document 4 of this inventory) – at Document 7 in this Bundle.	31/01/2024		No
3	Public Inquiry Data v11 (20240126)	Not included in the bundle as it contains patient identifiable information.			Yes
4	Re Antibiotic Data Email Sean MacBride-Stewart 2023-07-11	Included in this bundle (attachment is at Document 2 of this inventory) – at Document 6 in this Bundle.	11/07/2023		No
5	Summary analysis refreshed	Included in this bundle – Document 8			No
6	COMPLETE ASPERGILLUS POSITIVES, ADULTS 2013-2023 & PAEDS 2005 - 2022	Not included in the bundle as it contains patient identifiable information.			Yes
7	RHC Diagnostic Imaging Report No. 1	Not included in the bundle as it contains patient identifiable information.	30/07/2021	11/08/2021	Yes
8	RHC Diagnostic Imaging Report No. 2	Not included in the bundle as it contains patient identifiable information.	05/12/2022	16/12/2022	Yes
9	RHC Diagnostic Imaging Report No. 3	Not included in the bundle as it contains patient identifiable information.	07/12/2017	15/12/2017	Yes

10	RHC Diagnostic Imaging Report No. 4	Not included in the bundle as it contains patient identifiable information.	02/01/2014	29/03/2017	Yes
11	RHC Diagnostic Imaging Report No. 5	Not included in the bundle as it contains patient identifiable information.	22/02/2019	04/03/2019	Yes
12	RHC Diagnostic Imaging Report No. 6	Not included in the bundle as it contains patient identifiable information.	12/12/2022	24/12/2022	Yes
13	RHC Diagnostic Imaging Report No. 7	Not included in the bundle as it contains patient identifiable information.	10/11/2020	20/11/2020	Yes
14	RHC Diagnostic Imaging Report No. 8	Not included in the bundle as it contains patient identifiable information.	23/09/2018	04/10/2018	Yes
15	RHC Diagnostic Imaging Report No. 9	Not included in the bundle as it contains patient identifiable information.	12/10/2013	28/10/2013	Yes
16	RHC Diagnostic Imaging Report No. 10	Not included in the bundle as it contains patient identifiable information.	11/06/2018	29/06/2018	Yes
17	RHC Diagnostic Imaging Report No. 11	Not included in the bundle as it contains patient identifiable information.	15/04/2018	27/04/2018	Yes
18	RHC Diagnostic Imaging Report No. 12	Not included in the bundle as it contains patient identifiable information.	26/08/2018		Yes
19	RHC Diagnostic Imaging Report No. 13	Not included in the bundle as it contains patient identifiable information.	22/11/2019	13/11/2019	Yes

20	RHC Diagnostic Imaging Report No. 14	Not included in the bundle as it contains patient identifiable information.	18/11/2019	29/11/2019	Yes
21	RHC Diagnostic Imaging Report No. 15	Not included in the bundle as it contains patient identifiable information.	21/04/2017	26/04/2017	Yes
22	RHC Diagnostic Imaging Report No. 16	Not included in the bundle as it contains patient identifiable information.	12/03/2014		Yes
23	RHC Diagnostic Imaging Report No. 17	Not included in the bundle as it contains patient identifiable information.	07/03/2021	13/03/2021	Yes
24	RHC Diagnostic Imaging Report No. 18	Not included in the bundle as it contains patient identifiable information.	21/12/2014	02/01/2015	Yes
25	RHC Diagnostic Imaging Report No. 19	Not included in the bundle as it contains patient identifiable information.	30/08/2022	19/09/2022	Yes
26	RHC Diagnostic Imaging Report No. 20	Not included in the bundle as it contains patient identifiable information.	30/11/2016	24/01/2020	Yes
27	RHC Diagnostic Imaging Report No. 21	Not included in the bundle as it contains patient identifiable information.	20/10/2019	23/10/2019	Yes
28	RHC Diagnostic Imaging Report No. 22	Not included in the bundle as it contains patient identifiable information.	01/02/2019	04/02/2019	Yes
29	RHC Diagnostic Imaging Report No. 23	Not included in the bundle as it contains patient identifiable information.	18/12/2015	14/01/2016	Yes

30	RHC Diagnostic Imaging Report No. 24	Not included in the bundle as it contains patient identifiable information.	10/11/2017	28/07/2018	Yes
31	RHC Diagnostic Imaging Report No. 25	Not included in the bundle as it contains patient identifiable information.	15/06/2013	26/06/2013	Yes
32	RHC Diagnostic Imaging Report No. 26	Not included in the bundle as it contains patient identifiable information.	07/12/2016		Yes
33	RHC Diagnostic Imaging Report No. 27	Not included in the bundle as it contains patient identifiable information.	05/08/2022		Yes
34	RHC Diagnostic Imaging Report No. 28	Not included in the bundle as it contains patient identifiable information.	24/06/2020	02/07/2020	Yes
35	RHC Diagnostic Imaging Report No. 29	Not included in the bundle as it contains patient identifiable information.	28/03/2013	30/12/2013	Yes
36	RHC Diagnostic Imaging Report No. 30	Not included in the bundle as it contains patient identifiable information.	02/08/2022	26/08/2022	Yes
37	RHC Diagnostic Imaging Report No. 31	Not included in the bundle as it contains patient identifiable information.	17/10/2017	14/02/2018	Yes
38	RHC Diagnostic Imaging Report No. 32	Not included in the bundle as it contains patient identifiable information.	28/10/2020	15/12/2020	Yes
39	RHC Diagnostic Imaging Report No. 33	Not included in the bundle as it contains patient identifiable information.	22/08/2022		Yes

40	RHC Diagnostic Imaging Report No. 34	Not included in the bundle as it contains patient identifiable information.	16/02/2017	22/03/2017	Yes
41	RHC Diagnostic Imaging Report No. 35	Not included in the bundle as it contains patient identifiable information.	13/08/2019	20/09/2019	Yes
42	RHC Diagnostic Imaging Report No. 36	Not included in the bundle as it contains patient identifiable information.	09/09/2022	14/09/2022	Yes
43	RHC Diagnostic Imaging Report No. 37	Not included in the bundle as it contains patient identifiable information.	26/09/2022	03/10/2022	Yes
44	RHC Diagnostic Imaging Report No. 38	Not included in the bundle as it contains patient identifiable information.	20/12/2017	29/12/2017	Yes
45	RHC Diagnostic Imaging Report No. 39	Not included in the bundle as it contains patient identifiable information.	12/12/2013	20/12/2013	Yes
46	RHC Diagnostic Imaging Report No. 40	Not included in the bundle as it contains patient identifiable information.			Yes
47	Barts Haem Onc overnight spells analysis June 2024	Not included in the bundle as it contains patient identifiable information.	Apr-17	Jun-24	Yes
48	Adult HaemOnc 2013-31Aug23 - matched GMC	Not included in the bundle as it contains patient identifiable information.			Yes
49	Final Combined GGC Paeds Onc CHI only 01.01.05 - 31.12.22	Not included in the bundle as it contains patient identifiable information.			Yes

50	COMPLETE YKH ONC BC-HISTORIC TPATH v2 1.1.05-9.5.12 BY CHI ONLY	Not included in the bundle as it contains patient identifiable information.			Yes
51	GGC RHC HAEMONC BC & ADD PATIENTS 9.5.12-31.12	Not included in the bundle as it contains patient identifiable information.			Yes
52	Appendix B to Case Note Review Overview Report.pdf	Bundle 6, Doc 38, Page 1105			No
53	Queen-elizabeth-university-hospital-royal-hospital-children-case-note-review-overview-report	Bundle 6 , Doc 38	Mar-21		No
54	Appendices-d	Bundle 6, Doc 38, Pages 1105 - 1111			No
55	nhs-ggc-qeuh-oversight-board-timeline-incidents-period-2015-2019	Bundle 6, Doc 37	2015	2019	No
56	queen-elizabeth-university-hospital-nhs-greater-glasgow-clyde-oversight-board-final-report	Bundle 6, Doc 36	Mar-21		No
57	BMT 100 005 05 Antibiotic Prophylaxis Draft	Included in this Bundle – Document 12	08/01/2019		No
58	BMT 100 005 06 Antibiotic Prophylaxis Draft	Included in this Bundle – Document 13			No
59	BMT 100 005 02 Antibiotic Prophylaxis Policy	Included in this Bundle – Document 9	30/04/2007		No
60	BMT 100 005 03 Antibiotic Prophylaxis Policy	Included in this Bundle – Document 10	21/06/2010		No
61	BMT 100 005 04 Antibiotic Prophylaxis Policy	Included in this Bundle – Document 11	22/08/2012		No
62	BMT 100 006 01 Antibiotic Treatment Policy	Included in this Bundle – Document 14	28/11/2007		No
63	BMT 100 006 02 Antibiotic Treatment Policy	Included in this Bundle – Document 15	06/11/2008		No
64	BMT 100 006 03 Antibiotic Treatment Policy	Included in this Bundle – Document 16	06/10/2011		No
65	BMT 100 006 04 Antibiotic Treatment Guideline	Included in this Bundle – Document 17	04/07/2018		No
66	BMT 100 006 05 Antibiotic Treatment Guideline	Included in this Bundle – Document 18	Undated		No
67	BMT 100 006 06 Antibiotic Treatment Guideline dapto update	Included in this Bundle – Document 19	Undated		No
68	BMT 100 008 02 Antifungal Policy	Included in this Bundle – Document 20	19/12/2006		No
69	BMT 100 008 03 Antifungal Policy	Included in this Bundle – Document 21	19/05/2008		No

70	BMT 100 008 04 Antifungal Policy	Included in this Bundle – Document 22	31/03/2009		No
71	BMT 100 008 05 Antifungal Policy	Included in this Bundle – Document 23	04/08/2011		No
72	BMT 100 008 06 Antifungal Policy	Included in this Bundle – Document 24	27/04/2015		No
73	BMT 100 008 07 Antifungal Policy	Included in this Bundle – Document 25	16/04/2018		No
74	BMT 100 008 08 Antifungal Policy	Included in this Bundle – Document 26	16/04/2018		No
75	BMT 100 008 09 Antifungal policy	Included in this Bundle – Document 27	Undated		No
76	BMT 100 041 02 Assessment of Infection in the Immuno Pt	Included in this Bundle – Document 28	29/07/2010		No
77	BMT 100 041 01 Assessment of Infection in the Immuno Pt	Included in this Bundle – Document 29	03/11/2009		No
78	BMT 100 041 03 Assessment of Infection in the Immuno Pt	Included in this Bundle – Document 30	10/01/2009		No
79	BMT 100 041 04 Assessment of Infection in the Immuno Pt.pdf	Included in this Bundle – Document 31	01/04/2020		No
80	BMT 100 041 05 Assessment of Infection in the Immuno Pt	Included in this Bundle – Document 32	Undated		No
81	Febrile Neutropenia Final - V1 (Aug 2010)	Included in this Bundle – Document 33	01/08/2010		No
82	Febrile Neutropenia Policy - V2 final (Dec 2015)	Included in this Bundle – Document 34	01/12/2015		No
83	Febrile Neutropenia Policy - V3 final (Jan 2017)	Included in this Bundle – Document 35	01/01/2015		No
84	HAEM-ONC-003 - Febrile Neutropenia Policy - V4 final (Mar 2020)	Included in this Bundle – Document 36	01/03/2020		No
85	HAEM-ONC-003 - Febrile Neutropenia Policy - V5 final (Nov 2021)	Included in this Bundle – Document 37	01/11/2021		No
86	HPS Review of NHSGCC Paediatric Haemato-oncology Data (Oct 2019)	Bundle 7, Doc 6	01/10/2019		No
87	HPS Summary - Review of NHSGG&C paediatric haemato-oncology data (October 2019)	Included in this Bundle – Document 38	01/10/2019		No
88	IP Haem Onc selected consultants from 2013 by sector	Not included in the bundle as it contains patient identifiable information.			Yes

89	Methodology of obtaining admissions data	Included in this bundle – Document 39			No
90	Copy of RHC Haem onc adms from 2008 with monthly figures 2024-01-09	Not included in the bundle as it contains patient identifiable information.			Yes
91	RHC Haem onc adms by Episode Subtype	Not included in the bundle as it contains patient identifiable information.			Yes
92	Appendix 3 to Closing Statement by Counsel to the Inquiry	Can be found on the Inquiry website.			Yes
93	Closing Statement by Counsel to the Inquiry (Dec 2021)	Can be found on the Inquiry website.	20/09/2021	05/11/2021	No
94	Counsel - Alistair Duncan and Victoria Arnott - Closing Statement - 21 July 2023_1	Can be found on the Inquiry website.	12/06/2023	23/06/2023	No
95	Directions - 5 - in respect of the Hearing Commencing 19 August 2024	Bundle 21 vol (6), Doc 5	19/08/2023		No
96	FINAL Complete Report on the Water System WALKER - 21 FEB 2024 (1) - External copy	Bundle 21 vol (1), Doc 5	21/01/2014		No
97	PPP 5 - QEUH Campus - History of Infection Concerns (HOIC) - Counsel's note	Included in this bundle – Document 42	28/04/2023		No
98	PPP 5 - QEUH Campus - History of Infection Concerns (HOIC) - external version	Can be found on the Inquiry website.			No
99	Qualitative Infection Link Expert Report by Sara Mumford and Linda Dempster - 10 May 2024 - External version	Bundle 21 vol (1), Doc 4	24/05/2024		No
100	Quantitative Infection Link Expert Report by Sid Mookerjee - 9 May 2024 - External version	Bundle 21 vol (1), Doc 1	09/05/2024		No
101	QEUH New buildings Water and Environmental Testing Summary Report by D Chaput (Mar 2023)	Bundle 18 vol (1), Doc 2	03/03/2023		No
102	QEUH Whole Campus Water Testing Summary Report by D Chaput (Mar 2023)	Bundle 19, Doc 18	03/03/2023		No

103	Summary of legislation and guidance for routine microbiological water tests - D Chaput (9 Dec 2022)	Bundle 19, Doc 54	09/12/2022		No
104	Information request for Prof Thomas Evans with annotated responses	Bundle 19, Doc 20			No
105	Phylogenetic Trees	Illegible therefore not included in the bundle.	Undated		No
106	Report on Cupriavidus Related Infections by Prof T Evans (March 2023)	Bundle 8, Doc 44	05/03/2023		No
107	Report on Enterobacter Related Infections by Prof T Evans (March 2023)	Bundle 8, Doc 45	05/03/2023		No
108	Report on Stenotrophomonas Infections by Prof T Evans (March 2023)	Bundle 8, Doc 46	05/03/2023		No
109	Technical Appendix to Reports by Prof T Evans (March 2023)	Bundle 8, Doc 47			No
110	Whole Genome Sequencing Report by Prof Leanord 18.01.23	Bundle 6, Doc 40	18/01/2023		No
111	Cupriavidus environmental samples	Included in this Bundle – Document 43			No
112	Cupriavidus human samples	Not included in the bundle as it contains patient identifiable information.			Yes
113	Enterobacter Sequencing (updated)	Not included in the bundle as it contains patient identifiable information.			Yes
114	Enterobacter tree	Included in this Bundle – Document 44			No
115	Stenotrophomonas tree with CHI numbers	Included in this Bundle – Document 45			Yes
116	GGC Expert Report - FINAL (24 July 2024)	Included in this Bundle – Document 1	24/07/2024		No
117	Glasgow Hospitals Case Note Review D3 - notes and commentary on environmental bacteria	Included in this Bundle - Document 40	05/10/2023		No
118	Initial bullet point thoughts on executive summary for report	Included in this Bundle – Document 41			No

120	Letter of Instruction - Dr Agrawal	Included in this Bundle – Document 3	21/11/2022		No
121	NHS GGC Positioning Paper on Infection FINAL (5 Apr 2023)	Bundle 25, Doc 10			No
122	Ward moves & MALDI	Included in this Bundle – Document 46			No

Please note: ***Document 119 is the inventory itself; all the documents are listed in the order they were received by the Inquiry. Please also note that Letters of Instruction for Prof Peter Hawkey & Dr Lydia Drumright were not a part of this batch of documents submitted by NHS GGC/CLO.***

SENT BY E-MAIL ONLY

Dr S. G. Agrawal Bsc, FRCP, FRCPath, PhD
Senior Lecturer and Honorary Consultant
Barts Health NHS Trust;
and Blizard Institute,
Queen Mary University of London.

Division of Haemato-Oncology
St Bartholomew's Hospital
London EC1A 7BE

E-mail: [redacted]

Date 21 November 2022
Your Ref
Our Ref GB1/787 AR/DBC
Direct Line [redacted]
Email [redacted]

Dear Dr Agrawal

SCOTTISH HOSPITALS INQUIRY

The Central Legal Office (CLO) is instructed on behalf of NHS GGC in respect of a number of concurrent legal processes which are in progress in relation to the Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC) in Glasgow.

As you are aware, a public inquiry, known as the Scottish Hospitals Inquiry (the Inquiry) is underway concerning issues which have arisen in relation to ventilation and water safety and other matters at the QEUH & RHC. The Inquiry has heard evidence from patients and families who have alleged that infections occurred as a result of the hospital environment at the QEUH & RHC.

There is also an investigation conducted by Police Scotland in respect of issues relating to water and ventilation at the QEUH & RHC campus. Also a number of civil legal claims have been raised against NHS GGC where it is alleged that patients have contracted infections as a result of the hospital environment at the QEUH & RHC.

This instruction is requested in order for the CLO to provide legal advice to NHS GGC in respect of the police investigation, for the Inquiry and NHS GGC's defence to the civil claims.

Thank you for confirming that you are able to assist and that you are content to produce a joint report with Professor Peter Hawkey.

Background

To date the focus of the Inquiry, and the Police investigation, has been on the patients treated in Wards 2A/2B of the RHC and Wards 6A, 4C, and 4B of the QEUH. A short summary of the background is set out below. However, currently there have been indications that their interest is widening to be QEUH & RHC wide. It should be noted that the QEUH and RHC have a shared water system, but that individual wards have differing ventilation provision.

The QEUH & RHC opened in April 2015 with services being migrated to the new hospitals over the subsequent months. The campus is one of the largest healthcare facilities in Europe and is unique in the Scottish context in terms of scale, volume of activity, patient acuity and clinical specialism. Since the QEUH & RHC opened, a number of issues have been identified with the design and construction of the buildings and a number of these are the subject of an ongoing civil legal claim by NHS GGC against the contractor. For example, one of these issues relates to Ward 4B (the adult bone marrow transplant unit) where the installed ventilation system, even with significant remedial works having been undertaken, does not meet the contractual requirements or HTM 03-01 and required a derogation.

From March to June 2018 there was a perceived increase in gram negative infections in Wards 2A/2B RHC (the paediatric haematology/oncology unit which includes inpatients, paediatric bone marrow transplants, and the day unit), and one of the working hypotheses of the IMT was that there was “widespread contamination” of the hospital water system. The principal mitigation measures that were implemented were the installation of point of use filters and subsequently the installation of a chlorine dioxide system to dose the water (which began in November 2018 for RHC and March 2019 for QEUH).

In September 2018 there was a perceived recurrence of an increase in gram negative infections in Wards 2A/2B RHC. At this time, the working hypothesis was that this was due to the drains. This resulted in the decision to decant these wards to Wards 6A and 4B QEUH to allow further investigation of the drains to take place due to the disruption this work would cause.

In November and December 2018 there were 2 cases of *Cryptococcus neoformans*. One was a paediatric patient who had been treated on Wards 2A RHC, 6A QEUH, and PICU. One was an adult haematology patient who had been treated on Ward 4C QEUH, the adult haemato-oncology (but not bone marrow transplant) and renal transplant ward. As pigeon guano was found on the floor of one of the plantrooms, the working hypothesis was that spores could get into the Air Handling Unit during maintenance and be spread through the ventilation system. Wards 6A and 4C do not have HEPA terminal filtered air supply. Portable HEPA filters were introduced into these wards, and recirculating en-suite ceiling mounted HEPA filters air scrubbers were installed.

In June 2019 there was again a perceived recurrence of an increase in gram negative infections in this same population group who are now in Ward 6A QEUH. Although multiple hypotheses were considered, no clear hypothesis emerged with the main hypothesis being that chilled beams were either leaking or dripping condensation onto patients.

Wards 2A/2B underwent a full refurbishment, which included the ventilation system, and the paediatric haematology/oncology patients moved back to Wards 2A/2B on 9 March 2022.

Separately, from early 2017 onwards a quality improvement group was established to look at improving CLABSI rates. Through this a number of changes to practice were implemented including changes to line insertion techniques, line access and maintenance, the type of line cap used, and training for patients, families and staff.

Instructions

All of these infections have been the subject of intensive investigations, both by NHS GCC, and by external bodies (such as HPS/ARHAI and the Case Note Review). The focus of these have been on whether the infections were because of the hospital environment (i.e. causation). Our understanding is that typing of the patient infections were all reported as being unique strains, and only two cases (one in 2016 and one in 2019) did typing of environmental water samples from the hospitals confirm that those isolates were closely related to the patient infections.

As we know hospital water systems, and hospital air, is not sterile and that the risk of hospital acquired or healthcare associated infections can be mitigated against but not eliminated. Although there are issues with the construction of the hospitals, it is not accepted that this resulted in patients having been exposed to a materially increased risk of infection.

The purpose of this instruction is to consider the question of risk, specifically whether there is objective evidence/data that would support the proposition that since the QEUH & RHC opened in 2015 patients were exposed to a greater risk of infection than would be expected due to a widespread issue with the water and/or ventilations systems. Whilst this may not necessarily be a straightforward question to answer, we understand following our discussions with you that it should be possible to address this at a high level.

The intended approach, as set out in the question set that has been discussed with you and is appended to this letter, is broadly as follows:

(i) If there is a widespread problem with water or ventilation, to set out what that should look like in terms of water testing results and patient infections in order to define the parameters of the data that need to be reviewed. Given the interest in the particular wards and patient groups detailed above we would suggest that they be included as part of this data set.

(ii) Review this data for NHS GGC and determine whether this does or does not support the position that there is an increased risk of infection or whether NHS GGC falls within what would be expected.

In addition, we would ask that you specifically comment on the standards/requirements for water testing set out in existing legislation and guidance and how water contamination can be defined in that context.

The next step would be for you and Prof Hawkey to meet in order to discuss and define the scope of the data that needs to be reviewed. Once you have determined this, we will ask NHS GGC to provide this information.

Timescale

We understand that this will involve a significant amount of work which may take several months, and would appreciate it if you will provide regular updated on the estimated completion.

Please mark your draft report as “Confidential and subject to Legal Professional Privilege” and once ready please provide it only to the CLO. The report will not be shared with any third party until it is in an agreed and final form. In due course, you may be asked to give evidence in relation to your report in more than one legal forum (i.e. in criminal court, civil court and/or the public inquiry).

If you require any further assistance, please let me know.

Yours sincerely

[redacted]

Ash Rebello
Senior Solicitor

Appendix – Questions

Water

1) Are hospital water systems sterile?
2) What constitutes a contaminated hospital water system (particularly in reference to existing legislation and guidance)?
3) If there was "widespread contamination" of the hospital water system (whether this was due to ingress contamination, regressional contamination, or contamination at installation and/or commissioning[1]):
    a) Would this be evident through water testing (routine testing required by guidance, or additional testing not contained in guidance)?
    b) If so what would be the expected findings that would demonstrate that there is "widespread contamination"?
4) If patients were at an increased risk of infection from the water system as a result:
    a) Which types of organisms would it be expected to see an increased rate of infection?
        i) Are there particular organisms that would be an indicative marker of there being an increased risk of infection from the water system?
    b) Would this become evident by way of an increased rate of infection the patient population as a whole?
    c) Are there particular vulnerable patient groups where this may be more evident and if so which ones?
5) Looking at the data for the QEUH/RHC:
    a) Is the water testing results consistent with there being "widespread contamination"?
    b) Is there an increased level of infections consistent with there being "widespread contamination" of the water system:
        i) Evidenced by an increased level of infections from these 'marker organisms'?
        ii) In the patient population as a whole?
        iii) In those particular vulnerable groups?

Ventilation

6) If the ventilation system in the hospital was inadequate or insufficient for patients:
    a) How would this manifest itself in terms of an increased risk of infection?
    b) Which types of organisms would it be expected to see an increased rate of infection?
        i) Are there particular organisms that would be an indicative marker of there being an increased risk of infection from an inadequate or insufficient ventilation system?
    c) Would this become evident by way of an increased rate of infection the patient population as a whole?

[1] HPS Report dated 20 Dec 2018 - Summary of Incident and Findings of the NHS Greater Glasgow and Clyde: Queen Elizabeth University Hospital/Royal Hospital for Children water contamination incident and recommendations for NHSScotland.

d) Are there particular vulnerable patient groups where this may be more evident and if so which ones?

7) Looking at the data for the QEUH/RHC:

a) Is there an increased level of infections consistent with there being an inadequate or insufficient ventilation system:

i) Evidenced by an increased level of infections from these ‘marker organisms’?

ii) In the patient population as a whole?

iii) In those particular vulnerable groups?

SENT BY E-MAIL ONLY
Professor Peter Hawkey
[redacted]

E-mail: [redacted]

Date 21 November 2022
Your Ref
Our Ref GB1/787 AR/DBC
Direct Line [redacted]
Email [redacted]

Dear Professor Hawkey

SCOTTISH HOSPITALS INQUIRY

The Central Legal Office (CLO) is instructed on behalf of NHS GGC in respect of a number of concurrent legal processes which are in progress in relation to the Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC) in Glasgow.

As you are aware, a public inquiry, known as the Scottish Hospitals Inquiry (the Inquiry) is underway concerning issues which have arisen in relation to ventilation and water safety and other matters at the QEUH & RHC. The Inquiry has heard evidence from patients and families who have alleged that infections occurred as a result of the hospital environment at the QEUH & RHC.

There is also an investigation conducted by Police Scotland in respect of issues relating to water and ventilation at the QEUH & RHC campus. Also a number of civil legal claims have been raised against NHS GGC where it is alleged that patients have contracted infections as a result of the hospital environment at the QEUH & RHC.

This instruction is requested in order for the CLO to provide legal advice to NHS GGC in respect of the police investigation, for the Inquiry and NHS GGC's defence to the civil claims.

Thank you for confirming that you are able to assist and that you are content to produce a joint report with Dr Samir Agrawal.

Background

To date the focus of the Inquiry, and the Police investigation, has been on the patients treated in Wards 2A/2B of the RHC and Wards 6A, 4C, and 4B of the QEUH. A short summary of the background is set out below. However, currently there have been indications that their interest is widening to be QEUH & RHC wide. It should be noted that the QEUH and RHC have a shared water system, but that individual wards have differing ventilation provision.

The QEUH & RHC opened in April 2015 with services being migrated to the new hospitals over the subsequent months. The campus is one of the largest healthcare facilities in Europe and is unique in the Scottish context in terms of scale, volume of activity, patient acuity and clinical specialism. Since

the QEUH & RHC opened, a number of issues have been identified with the design and construction of the buildings and a number of these are the subject of an ongoing civil legal claim by NHS GGC against the contractor. For example, one of these issues relates to Ward 4B (the adult bone marrow transplant unit) where the installed ventilation system, even with significant remedial works having been undertaken, does not meet the contractual requirements or HTM 03-01 and required a derogation.

From March to June 2018 there was a perceived increase in gram negative infections in Wards 2A/2B RHC (the paediatric haematology/oncology unit which includes inpatients, paediatric bone marrow transplants, and the day unit), and one of the working hypotheses of the IMT was that there was "widespread contamination" of the hospital water system. The principal mitigation measures that were implemented were the installation of point of use filters and subsequently the installation of a chlorine dioxide system to dose the water (which began in November 2018 for RHC and March 2019 for QEUH).

In September 2018 there was a perceived recurrence of an increase in gram negative infections in Wards 2A/2B RHC. At this time, the working hypothesis was that this was due to the drains. This resulted in the decision to decant these wards to Wards 6A and 4B QEUH to allow further investigation of the drains to take place due to the disruption this work would cause.

In November and December 2018 there were 2 cases of *Cryptococcus neoformans*. One was a paediatric patient who had been treated on Wards 2A RHC, 6A QEUH, and PICU. One was an adult haematology patient who had been treated on Ward 4C QEUH, the adult haemato-oncology (but not bone marrow transplant) and renal transplant ward. As pigeon guano was found on the floor of one of the plantrooms, the working hypothesis was that spores could get into the Air Handling Unit during maintenance and be spread through the ventilation system. Wards 6A and 4C do not have HEPA terminal filtered air supply. Portable HEPA filters were introduced into these wards, and recirculating en-suite ceiling mounted HEPA filters air scrubbers were installed.

In June 2019 there was again a perceived recurrence of an increase in gram negative infections in this same population group who are now in Ward 6A QEUH. Although multiple hypotheses were considered, no clear hypothesis emerged with the main hypothesis being that chilled beams were either leaking or dripping condensation onto patients.

Wards 2A/2B underwent a full refurbishment, which included the ventilation system, and the paediatric haematology/oncology patients moved back to Wards 2A/2B on 9 March 2022.

Separately, from early 2017 onwards a quality improvement group was established to look at improving CLABSI rates. Through this a number of changes to practice were implemented including changes to line insertion techniques, line access and maintenance, the type of line cap used, and training for patients, families and staff.

Instructions

All of these infections have been the subject of intensive investigations, both by NHS GCC, and by external bodies (such as HPS/ARHAI and the Case Note Review). The focus of these have been on whether the infections were because of the hospital environment (i.e. causation). Our understanding is that typing of the patient infections were all reported as being unique strains, and only two cases (one in 2016 and one in 2019) did typing of environmental water samples from the hospitals confirm that those isolates were closely related to the patient infections.

As we know hospital water systems, and hospital air, is not sterile and that the risk of hospital acquired or healthcare associated infections can be mitigated against but not eliminated. Although there are issues with the construction of the hospitals, it is not accepted that this resulted in patients having been exposed to a materially increased risk of infection.

The purpose of this instruction is to consider the question of risk, specifically whether there is objective evidence/data that would support the proposition that since the QEUH & RHC opened in

2015 patients were exposed to a greater risk of infection than would be expected due to a widespread issue with the water and/or ventilations systems. Whilst this may not necessarily be a straightforward question to answer, we understand following our discussions with you that it should be possible to address this at a high level.

The intended approach, as set out in the question set that has been discussed with you and is appended to this letter, is broadly as follows:

(i) If there is a widespread problem with water or ventilation, to set out what that should look like in terms of water testing results and patient infections in order to define the parameters of the data that need to be reviewed. Given the interest in the particular wards and patient groups detailed above we would suggest that they be included as part of this data set.

(ii) Review this data for NHS GGC and determine whether this does or does not support the position that there is an increased risk of infection or whether NHS GGC falls within what would be expected.

In addition, we would ask that you specifically comment on the standards/requirements for water testing set out in existing legislation and guidance and how water contamination can be defined in that context.

The next step would be for you and Dr Agrawal to meet in order to discuss and define the scope of the data that needs to be reviewed. Once you have determined this, we will ask NHS GGC to provide this information.

Timescale

We understand that this will involve a significant amount of work which may take several months, and would appreciate it if you will provide regular updated on the estimated completion.

Please mark your draft report as “Confidential and subject to Legal Professional Privilege” and once ready please provide it only to the CLO. The report will not be shared with any third party until it is in an agreed and final form. In due course, you may be asked to give evidence in relation to your report in more than one legal forum (i.e. in criminal court, civil court and/or the public inquiry).

If you require any further assistance, please let me know.

Yours sincerely

[redacted]

Ash Rebello
Senior Solicitor

Appendix – Questions

Water

1) Are hospital water systems sterile?
2) What constitutes a contaminated hospital water system (particularly in reference to existing legislation and guidance)?
3) If there was "widespread contamination" of the hospital water system (whether this was due to ingress contamination, regressional contamination, or contamination at installation and/or commissioning[1]):
    a) Would this be evident through water testing (routine testing required by guidance, or additional testing not contained in guidance)?
    b) If so what would be the expected findings that would demonstrate that there is "widespread contamination"?
4) If patients were at an increased risk of infection from the water system as a result:
    a) Which types of organisms would it be expected to see an increased rate of infection?
        i) Are there particular organisms that would be an indicative marker of there being an increased risk of infection from the water system?
    b) Would this become evident by way of an increased rate of infection the patient population as a whole?
    c) Are there particular vulnerable patient groups where this may be more evident and if so which ones?
5) Looking at the data for the QEUH/RHC:
    a) Is the water testing results consistent with there being "widespread contamination"?
    b) Is there an increased level of infections consistent with there being "widespread contamination" of the water system:
        i) Evidenced by an increased level of infections from these 'marker organisms'?
        ii) In the patient population as a whole?
        iii) In those particular vulnerable groups?

Ventilation

6) If the ventilation system in the hospital was inadequate or insufficient for patients:
    a) How would this manifest itself in terms of an increased risk of infection?
    b) Which types of organisms would it be expected to see an increased rate of infection?
        i) Are there particular organisms that would be an indicative marker of there being an increased risk of infection from an inadequate or insufficient ventilation system?
    c) Would this become evident by way of an increased rate of infection the patient population as a whole?

[1] HPS Report dated 20 Dec 2018 - Summary of Incident and Findings of the NHS Greater Glasgow and Clyde: Queen Elizabeth University Hospital/Royal Hospital for Children water contamination incident and recommendations for NHSScotland.

d) Are there particular vulnerable patient groups where this may be more evident and if so which ones?

7) Looking at the data for the QEUH/RHC:

a) Is there an increased level of infections consistent with there being an inadequate or insufficient ventilation system:

i) Evidenced by an increased level of infections from these ‘marker organisms’?

ii) In the patient population as a whole?

iii) In those particular vulnerable groups?

PRIVATE & CONFIDENTIAL

Dr Lydia Drumright
[redacted]

Date 08 February 2024
Your Ref
Our Ref GB1/787 AAR/LEW
Direct Line [redacted]
Email [redacted]

Dear Dr Drumright

PUBLIC INQUIRY
QUEEN ELIZABETH UNIVERSITY HOSPITAL

The Central Legal Office (CLO) is instructed on behalf of NHS Greater Glasgow and Clyde (NHS GGC) in respect of a number of concurrent legal processes which are in progress in relation to the Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC) in Glasgow.

As we discussed at our meeting on 2 February 2024, a public inquiry, known as the Scottish Hospitals Inquiry (the Inquiry) is underway concerning issues which have arisen in relation to ventilation and water safety and other matters at the QEUH & RHC. The Inquiry has heard evidence from patients and families who have alleged that infections occurred as a result of the hospital environment at the QEUH & RHC.

There is also an investigation conducted by Police Scotland in respect of issues relating to water and ventilation at the QEUH & RHC campus. Also a number of civil legal claims have been raised against NHS GGC where it is alleged that patients have contracted infections as a result of the hospital environment at the QEUH & RHC.

Dr Samir Agrawal (whom you know) and Professor Peter Hawkey have been instructed to provide a report to the CLO in order for the CLO to provide legal advice to NHS GGC in respect of the Inquiry, the police investigation, and for NHS GGC's defence to the civil claims. A copy of the original letter of instruction to Dr Agrawal and Professor Hawkey is appended which details the background and scope of their instruction. The purpose of your instruction is to provide assistance with the statistical analysis of data for the report (e.g. rates, tends, statistical significance of variations, comparison with data from Dr Agrawal's hospital etc.). Thank you for confirming that you are able to assist and please liaise with Dr Agrawal and Professor Hawkey as to the specifics of the statistical analysis required.

The relevant documentation and data is held on a Microsoft Teams site, which you will be provided access to.

disability confident COMMITTED

Anderson House, Breadalbane Street, Edinburgh, EH6 5JR
Telephone: 0131 275 7800
www. www.nss.nhs.scot

NHS National Services Scotland is the common name of the Common Services Agency for the Scottish Health Service

If you require any further assistance, please let me know.

Yours sincerely



Dr Ash Rebello
Senior Solicitor

From:	MacBride-Stewart, Sean
To:	Neilson, Jillian; Ash Rebello
Cc:	Kinnaird, Fiona
Subject:	Re: Antibiotic Data
Date:	11 July 2023 08:05:09
Attachments:	Public-Enquiry.html Summary analysis.xlsx

Hi Ash/Jillian,

We've made good progress with the analysis of the prescribing trends.

Fiona pulled together the prescribing by

1. class - aminoglycosides, carbapenems and piperacillin with tazobactam
2. location - North is ‘Adult North excluding BMT’, South is ‘Adult South & BOC BMT’ and Paed is RHC

I then analysed the prescribing trends looking for statistically significant changes in the mean values. The output from R is provided it includes a plot of the raw prescribing trends, the change point analysis, the means for each segment, and a decomposition to visually assess seasonality and randomness. A narrative summary of the changes in trend has been added.

I've taken the change points and mean values and plotted them in Excel with the key dates to segment the data also lotted so that the relationship between these key dates and significant changes in the use of these three classes of antibiotic in these three locations can be assessed.

I haven't yet done any segmented regression analysis for a couple of reasons. Firstly, is a very practical reason and that is because I have managed to "break" RStudio which is the app I use to work with R and I'm waiting for IT to get it back up and running. Secondly, it was to confirm with you the timing of the change points. You might argue that the change point for modelling a change in antibiotic use could be set to be earlier than February 2018 (the start of the "water incident") if it is assumed the change in prescribing trends was better linked to any underlying change in infection rate.

Kind regards,

Seán
Dr Seán MacBride-Stewart
PhD FRPharmS GPhC(IP)
Lead Pharmacist Medicines Management Resources
Pharmacy Services | NHSGGC |Book time with Sean
Normal Working Hours: 13:00-17:30 Mon, 8:00-17:30 Tues to Fri

Public Inquiry Analysis of Antimicrobial Prescribing

Sean MacBride-Stewart

2024-01-31

Background

This is an analysis of prescribing trends for selected antimicrobial agents and selected wards/locations within NHSGGC.

For each group of antibiotics and location the following analysis was undertaken 1. the identification of statistically significant changes in trends (i.e. change point analysis) 2. the statistical test of change relating to pre-determined times (i.e. segmented regression analysis)

The key dates for the segmentation of the data are:

- June 2015 - services moved into QEUH/RHC
- Feb 2018 to Sep 2018 – the “water incident” period
- Oct 2018 to Feb 2022 – 2A/B decanted to 6A/4B (with period in CDU)
- Mar 2022 to present – 2A/B re-opened

The dates of the various ward moves are set out below:

Adult haematology (South):

· Moved from Ward 24 SGH to Ward 4C QEUH between 1-3 May 2015

Adult BMT:

· Moved from Beatson B8/9 to Ward 4B QEUH on 6 June 2015
· Moved from Ward 4B QEUH to Beatson B8/9 on 8 July 2015
· Moved from Beatson B8/9 to QEUH 4B on 30 June 2018

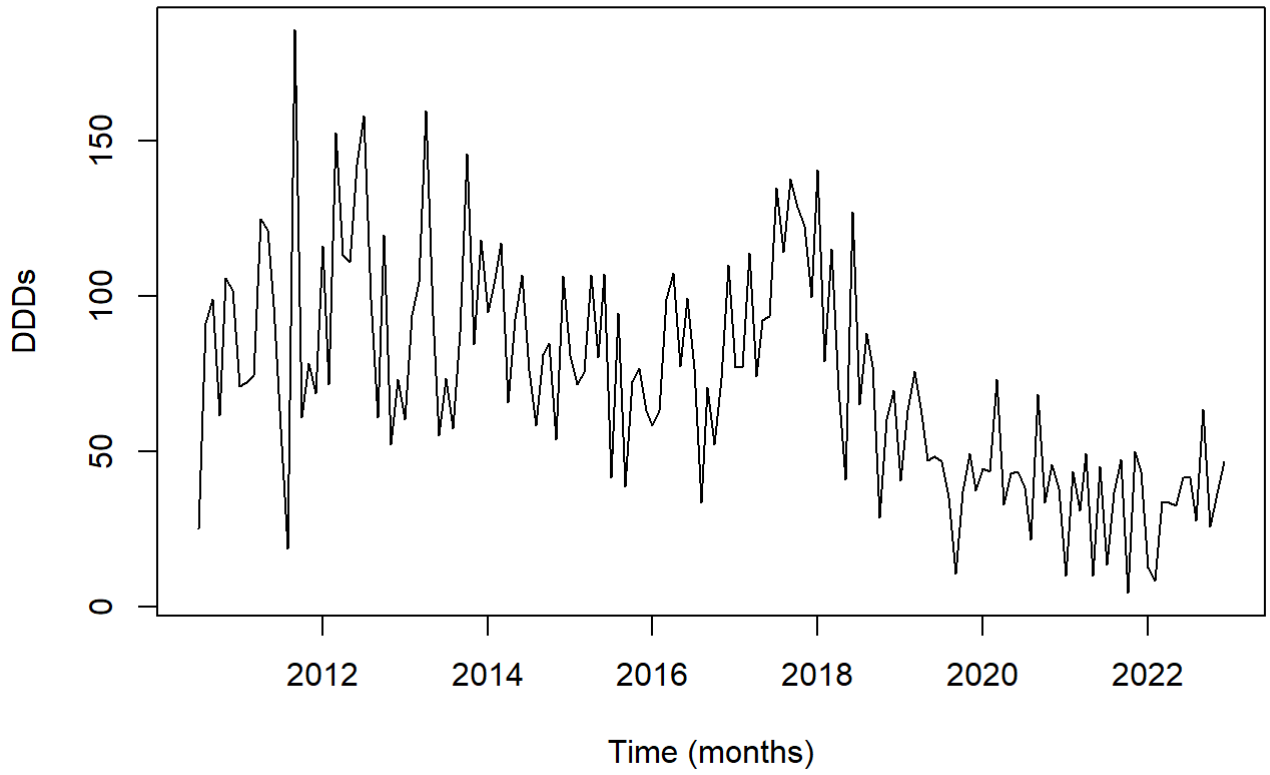
Paediatric haematology and oncology

· Moved from Yorkhill Schiehallion/DCU to RHC Wards 2A & 2B on 10 June 2015
· Moved from RHC Wards 2A (inpatients) & 2B (day care) to QEUH Wards 4B (paediatric BMT patients) and 6A (inpatients and day care) on 26 September 2018
· Moved from QEUH 6A to RHC CDU on 22 Jan 2019 (the move to CDU was for the 6A inpatients – day care attendance for 6A patients took place in RHC 1A during this decant period)
· Moved from RHC CDU to QEUH 6A on 11 Feb 2019
· Moved from QEUH 6A and 4B to RHC 2A & 2B on 9 March 2022

Change Point Analysis guided by: https://www.r-bloggers.com/2013/08/changepoint-analysis-of-time-series/ (https://www.r-bloggers.com/2013/08/changepoint-analysis-of-time-series/) Binary Segmentation with minimum number of observations between changes of 6.

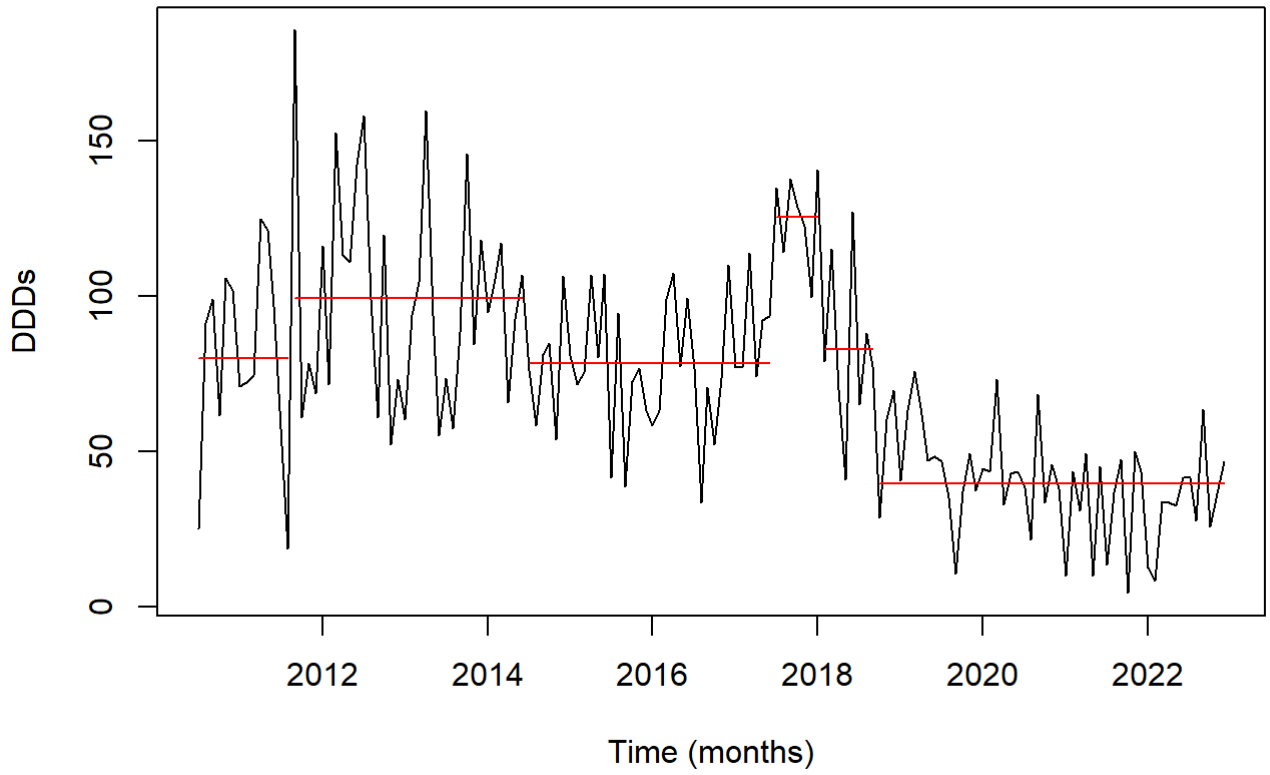
Paediatrics - Aminoglycosides

Prescribing Trends



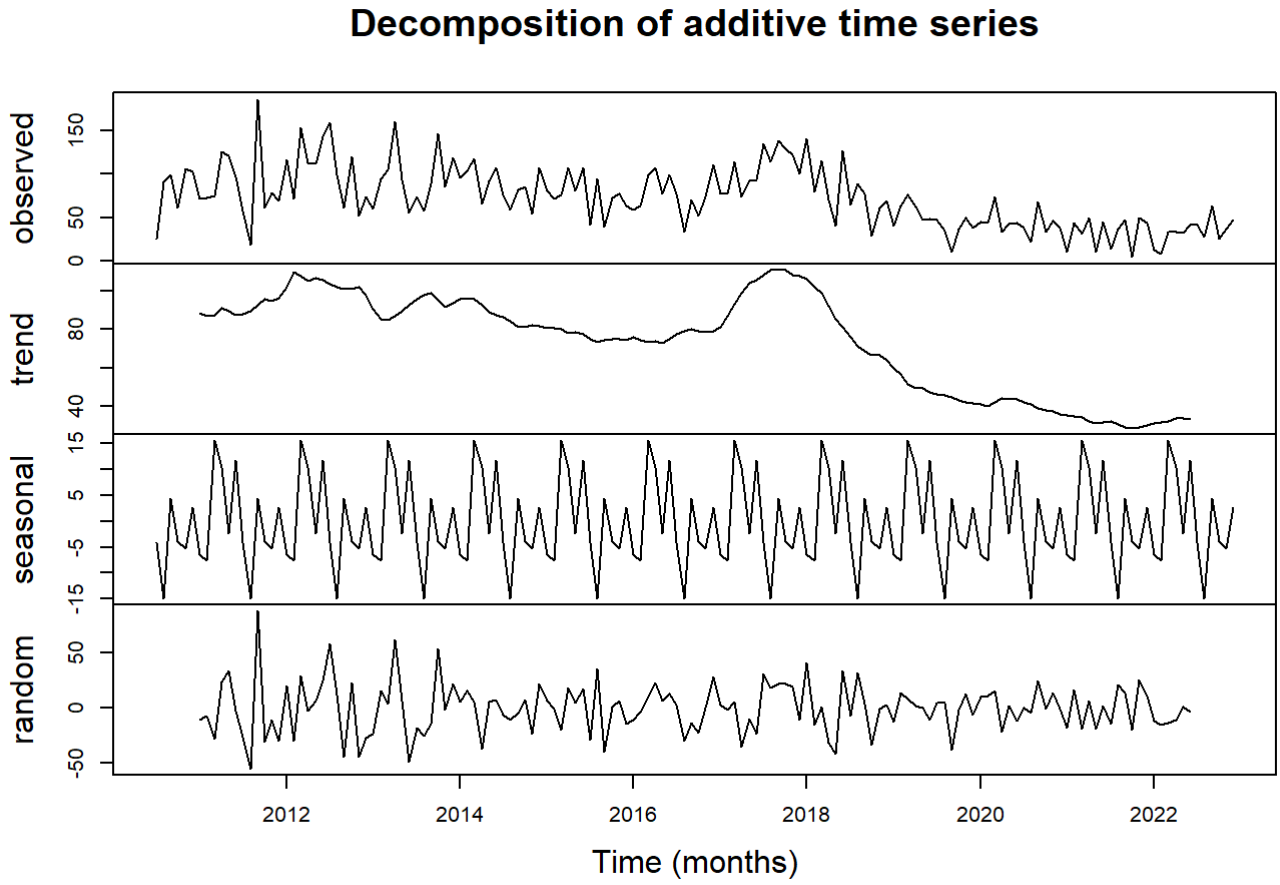
Change point analysis

```
## [1] 14 48 84 91 99
```



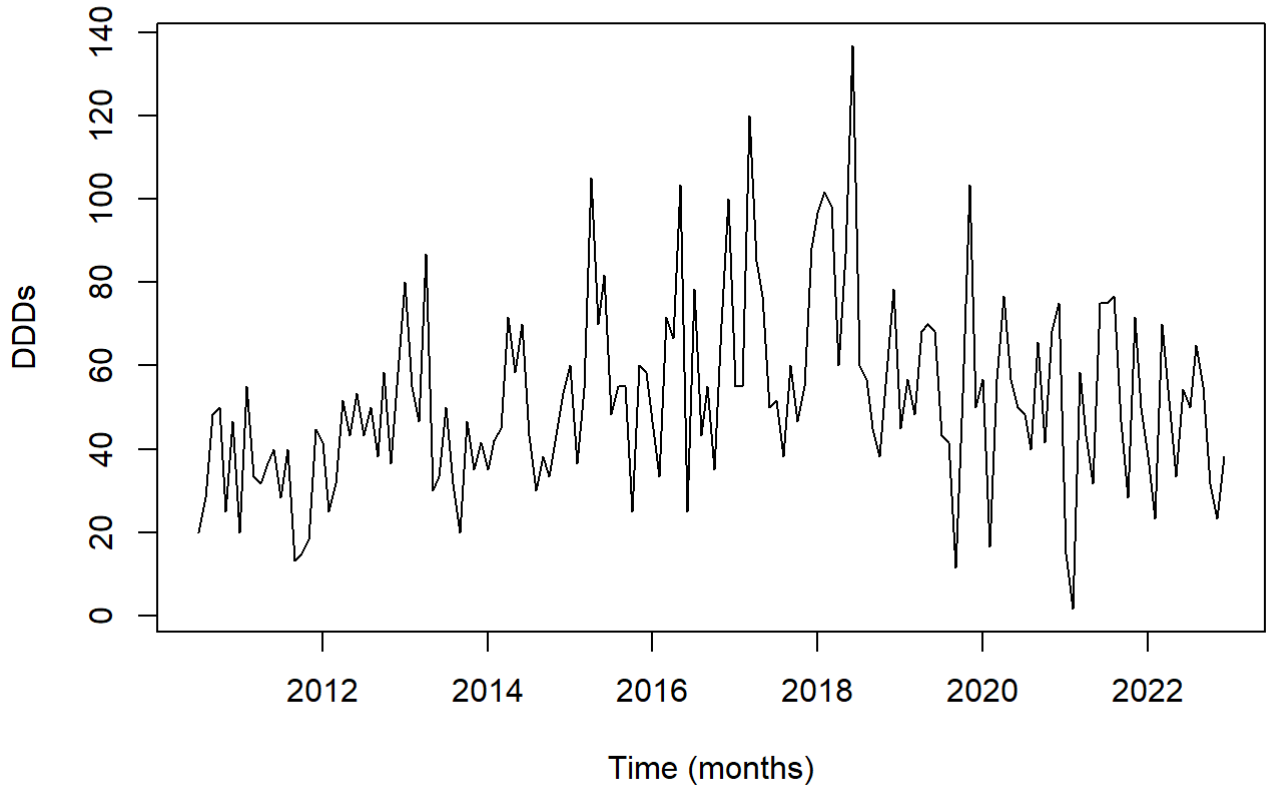

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Decomposed into trend, seasonality, random component



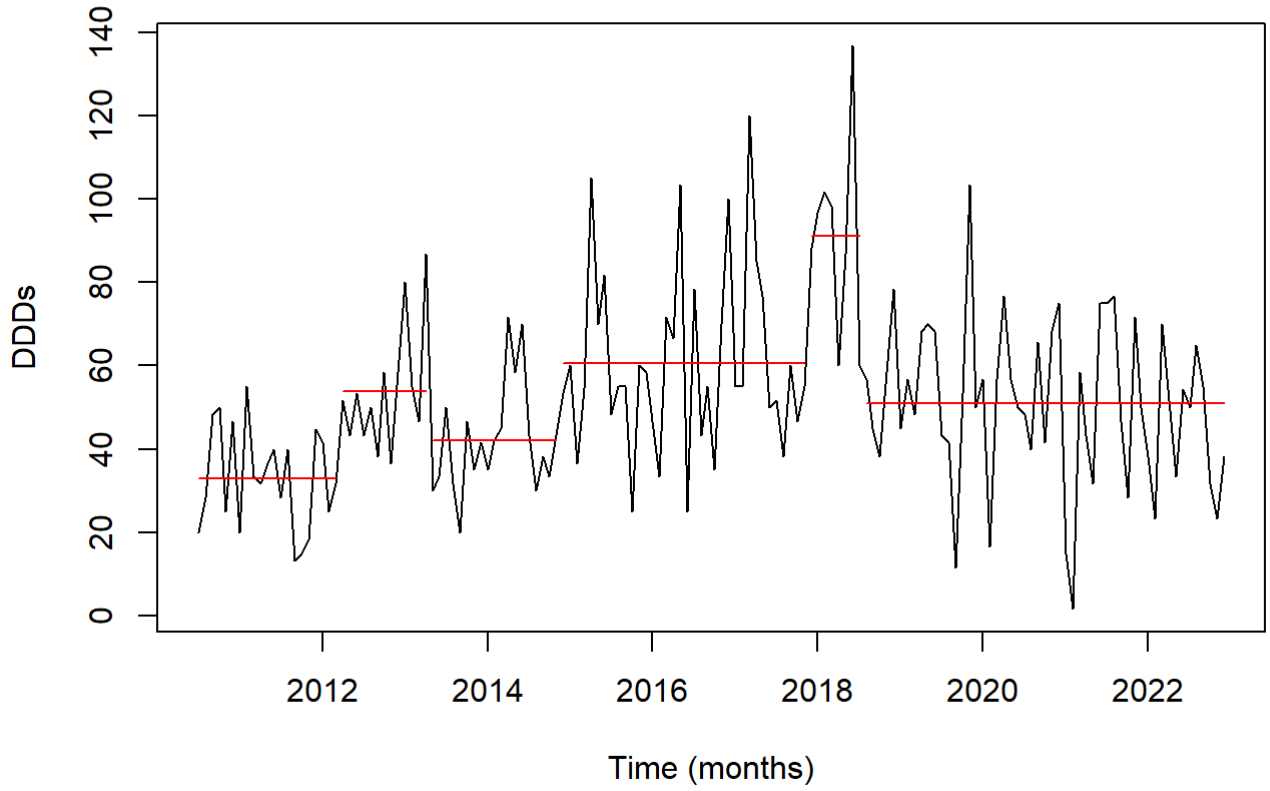
Paediatrics - Carbapenems

Prescribing Trends



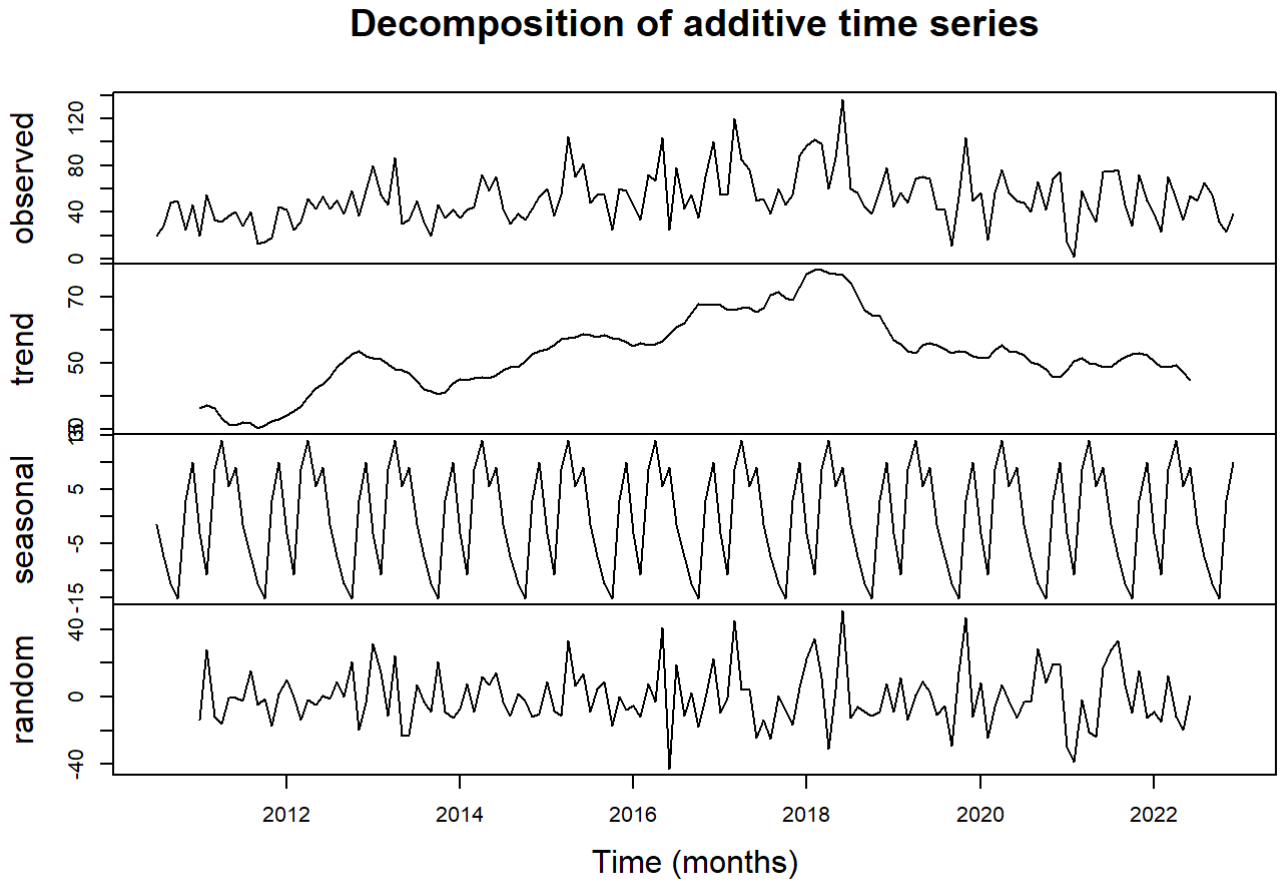
Change point analysis

```
## [1] 21 34 53 89 97
```



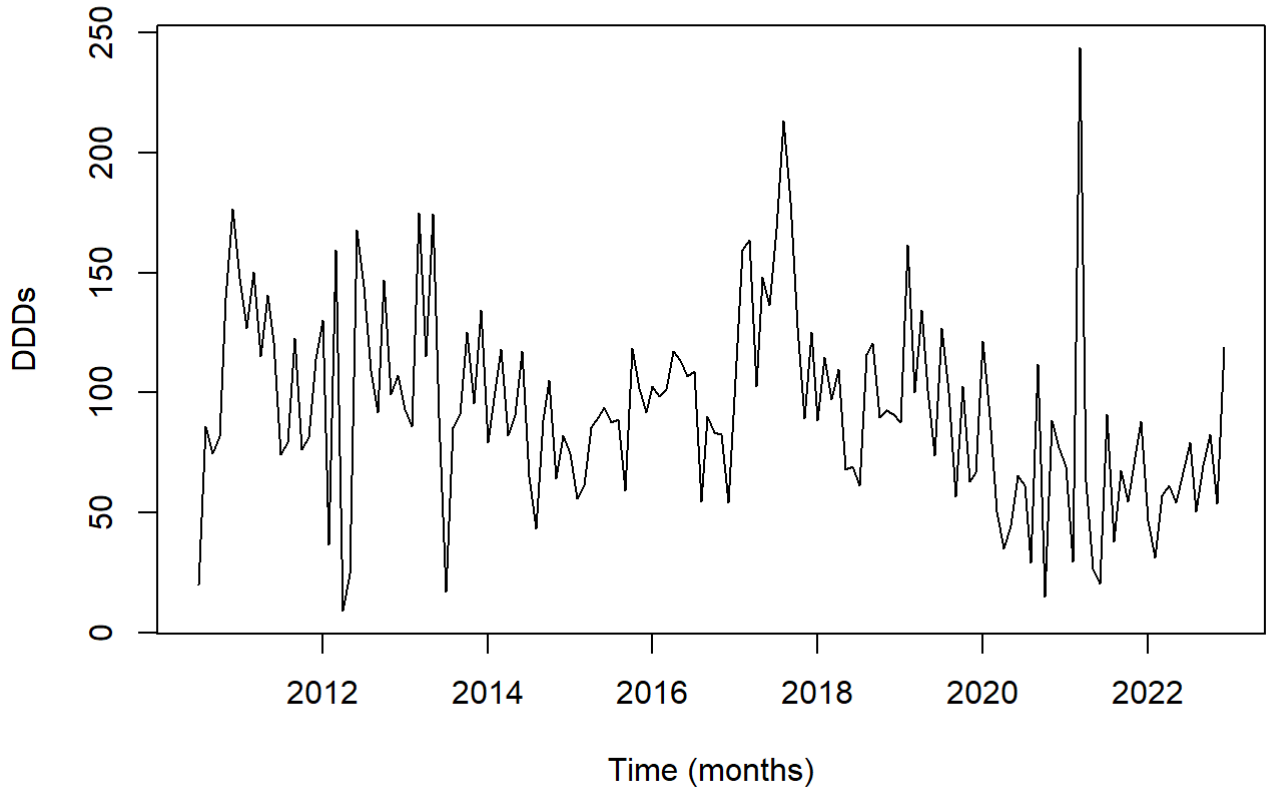

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```

Decomposed into trend, seasonality, random component



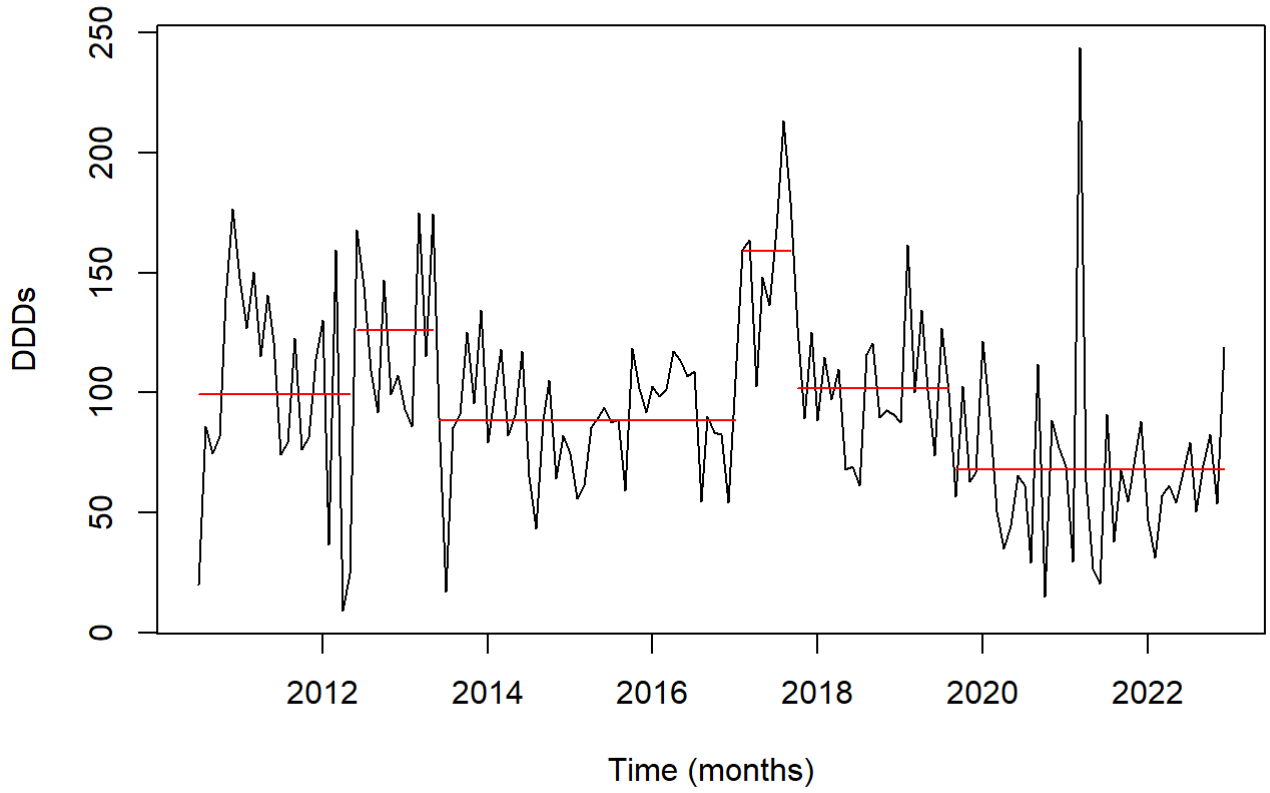
Paediatrics - Piperacillin with tazobactam

Prescribing Trends



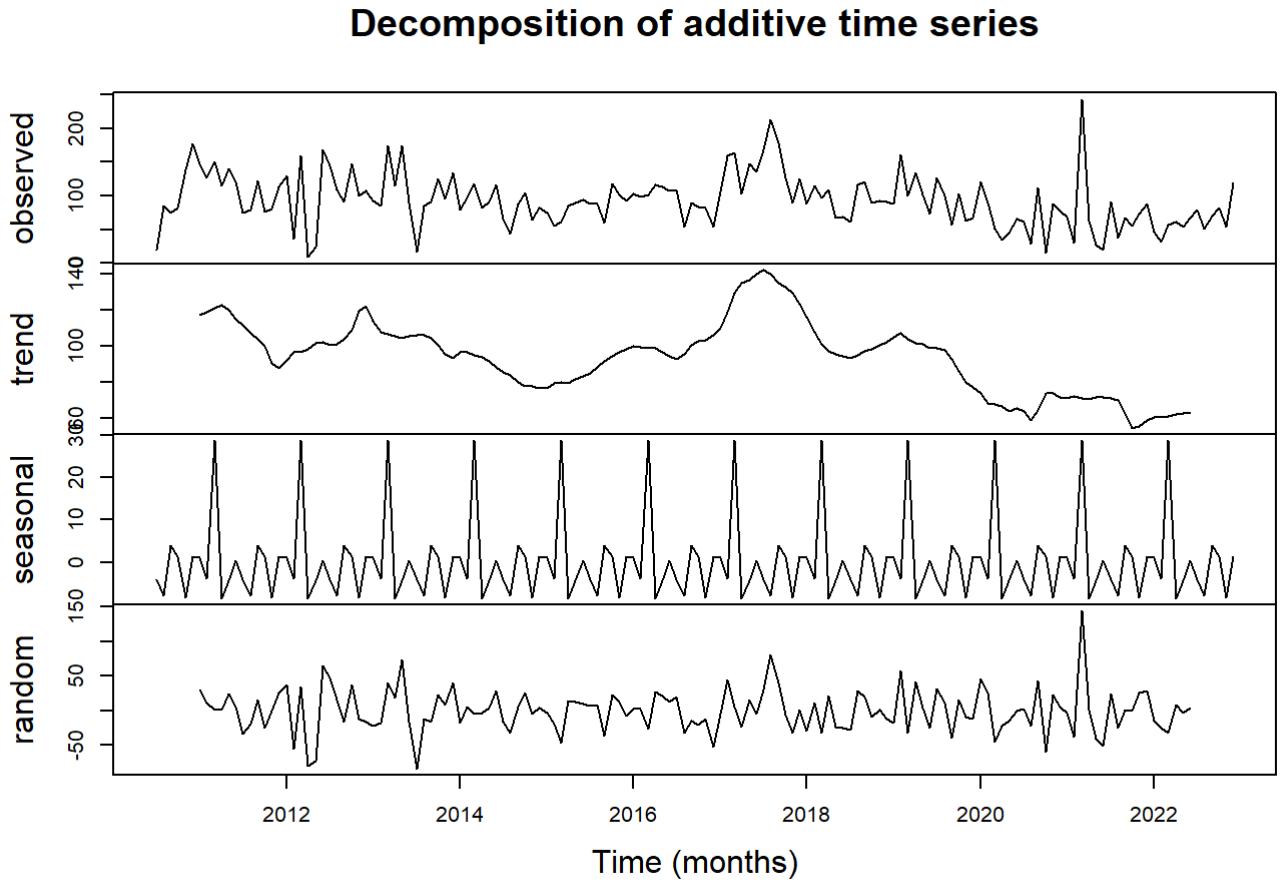
Change point analysis

```
## [1]  23  35  79  87 110
```




```
## $mean
## [1]  99.52795 125.86905  88.70130 158.94643 101.99379  67.96607
```

Decomposed into trend, seasonality, random component



Paediatrics - Summary

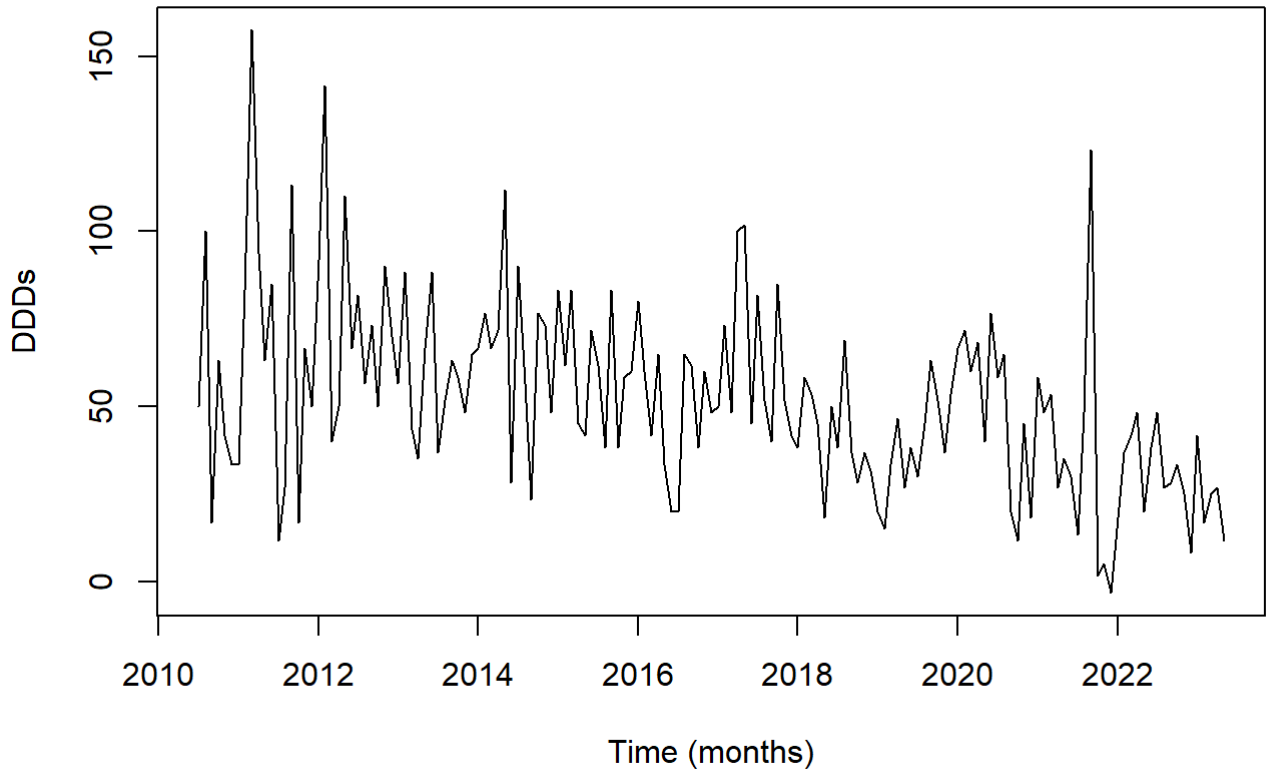
Prior to the opening of the RHC on the QEUH campus there was an increase in the use of carbapenems (mean DDDs rose from 33.00 to 60.68); a fall in piperacillin with tazobactam (mean DDDs 99.52 fell to 88.70 - after a temporary rise in 2012/13 to 125.87) and a smaller fall in aminoglycosides (mean DDDs fell from 80.11 to 76.45 after a longer rise from later 2011 to mid 2014 to 99.43).

At around the same time in late 2016 to early 2017 use rose in both piperacillin with tazobactam and aminoglycosides; carbapenems rose in late 2017. Piperacillin with tazobactam use was the first to fall back (to levels slightly higher than before the 2016/2017 rise) and this was in later 2017 just prior to the rise in carbapenems; their use fell away further in the autumn of 2019. In early 2018 aminoglycoside use fell back (to levels slightly higher than before the 2016/2017 rise); use fell away further in the end of 2018. Carbapenem use fell in mid-2018 to lower levels that before the 2017 rise.

More recently mean DDDs have been stable since late 2019 for all three classes of antibiotics.

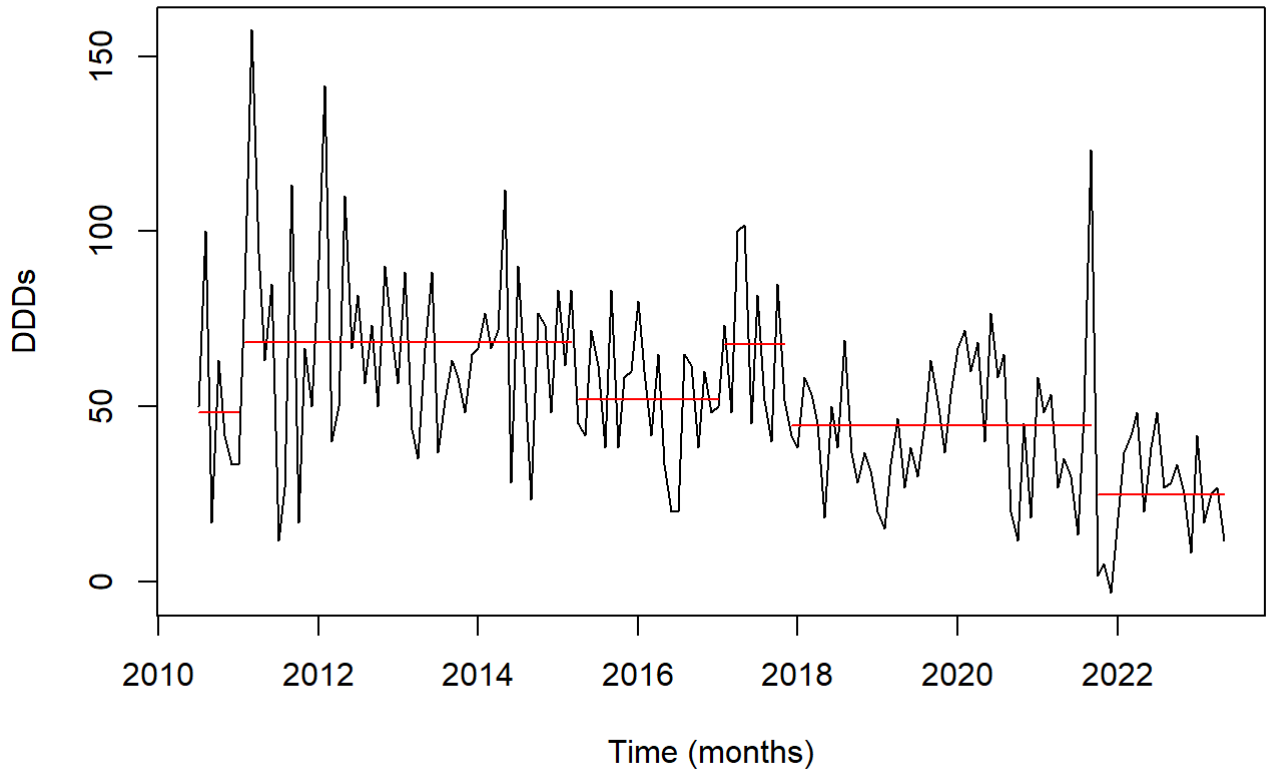
North Sector - Aminoglycosides

Prescribing Trends



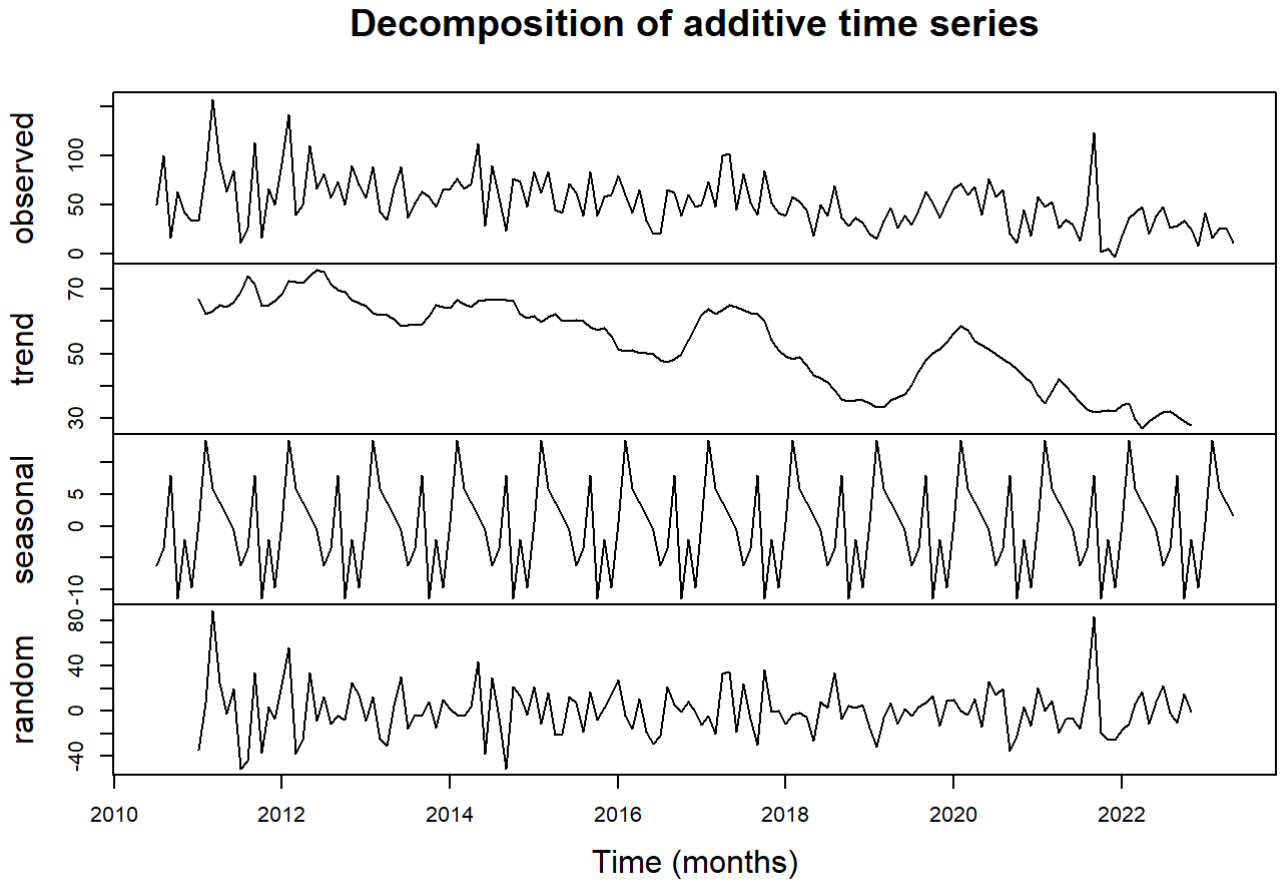
Change point analysis

```
## [1]   7  57  79  89 135
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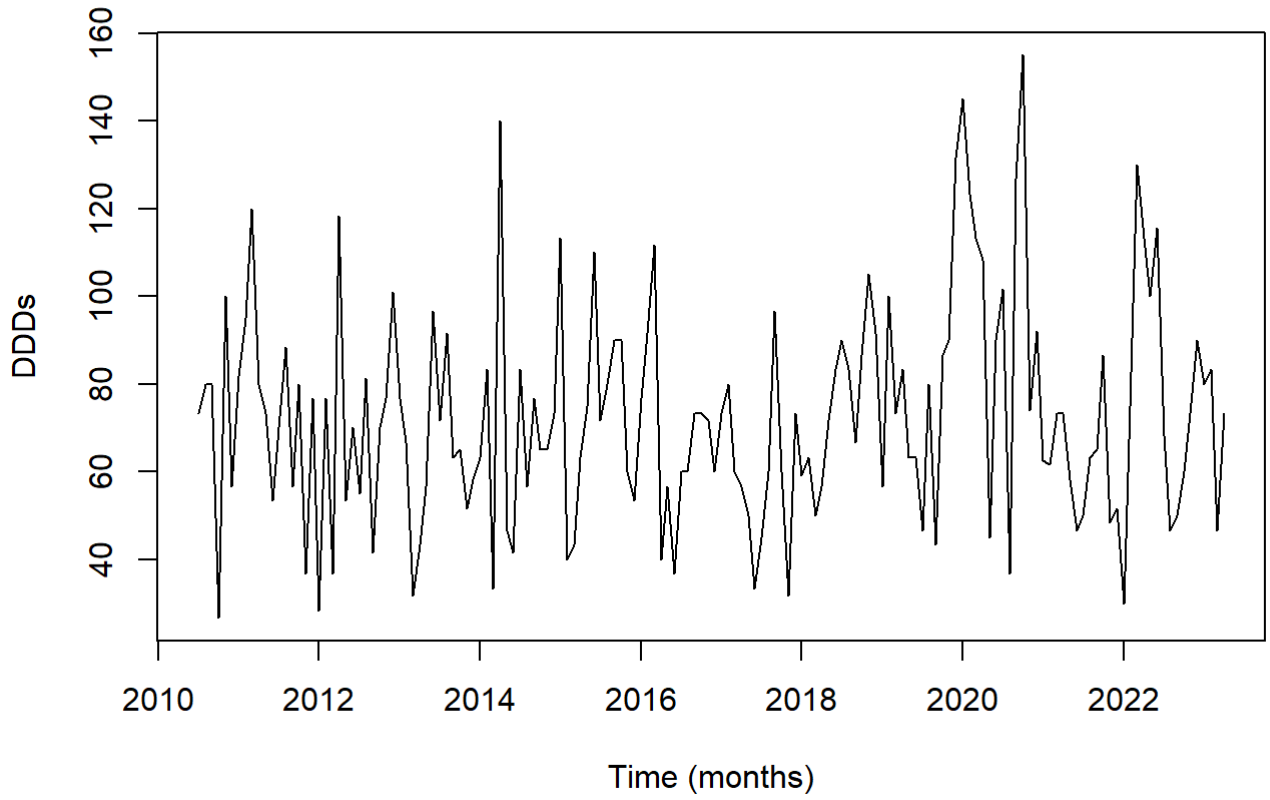

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## $mean
## [1] 48.32857 68.19600 51.89091 67.84000 44.43043 24.92000
```

Decomposed into trend, seasonality, random component



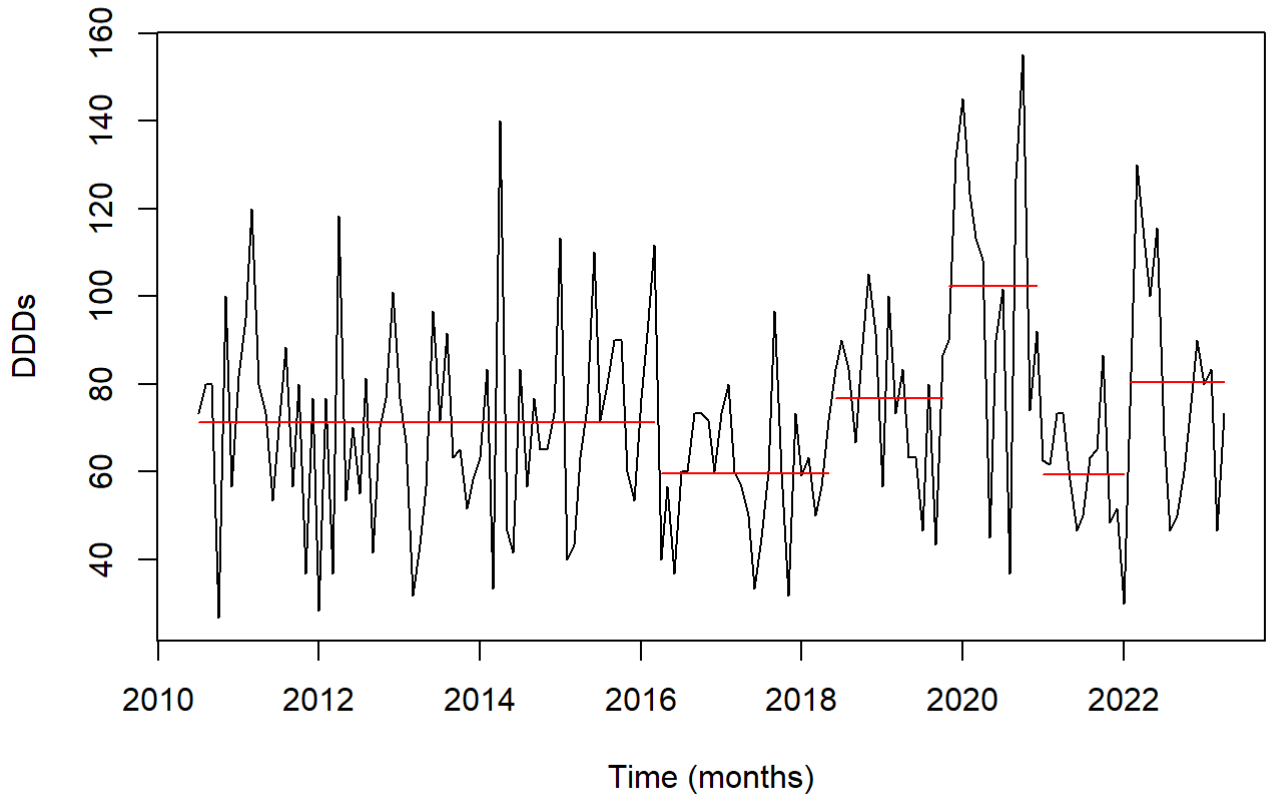
North Sector - Carbapenems

Prescribing Trends



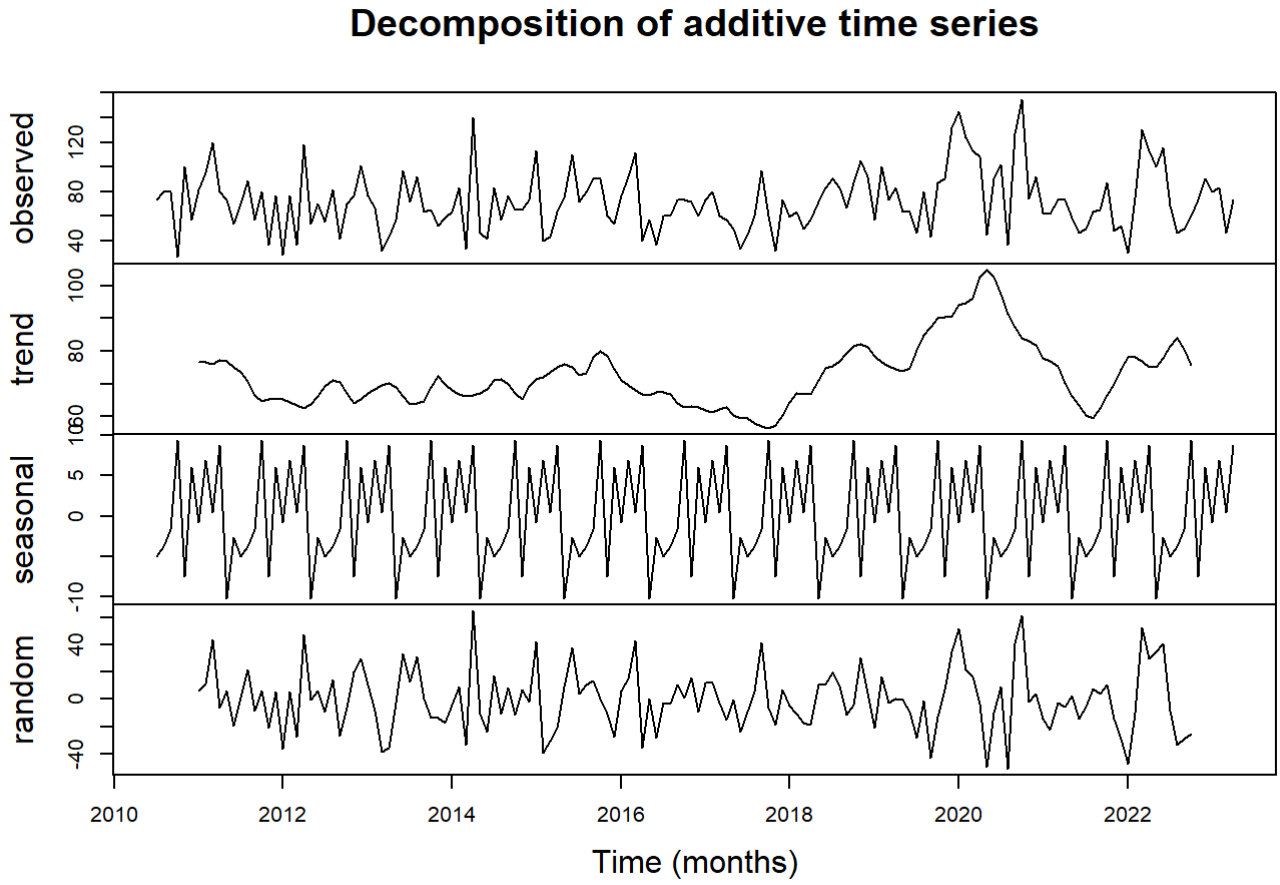
Change point analysis

```
## [1]  69  95 112 126 139
```



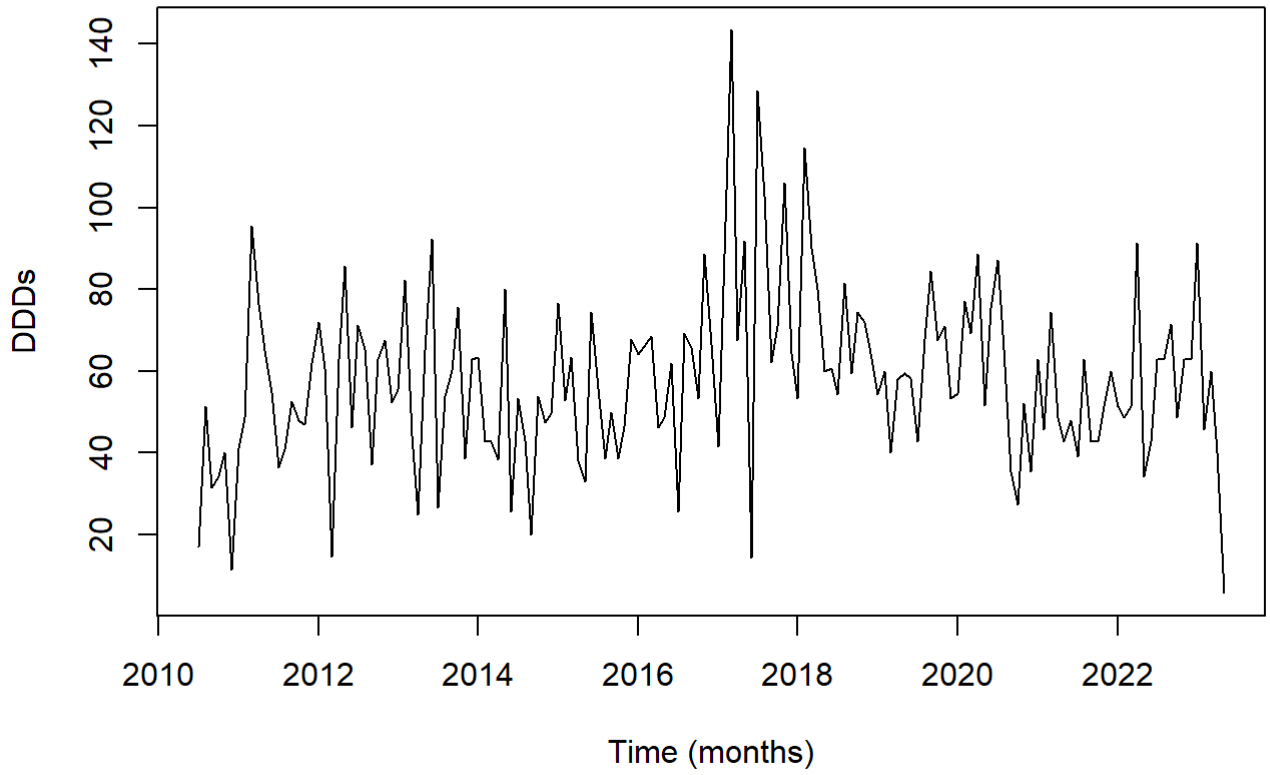

```
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```

Decomposed into trend, seasonality, random component



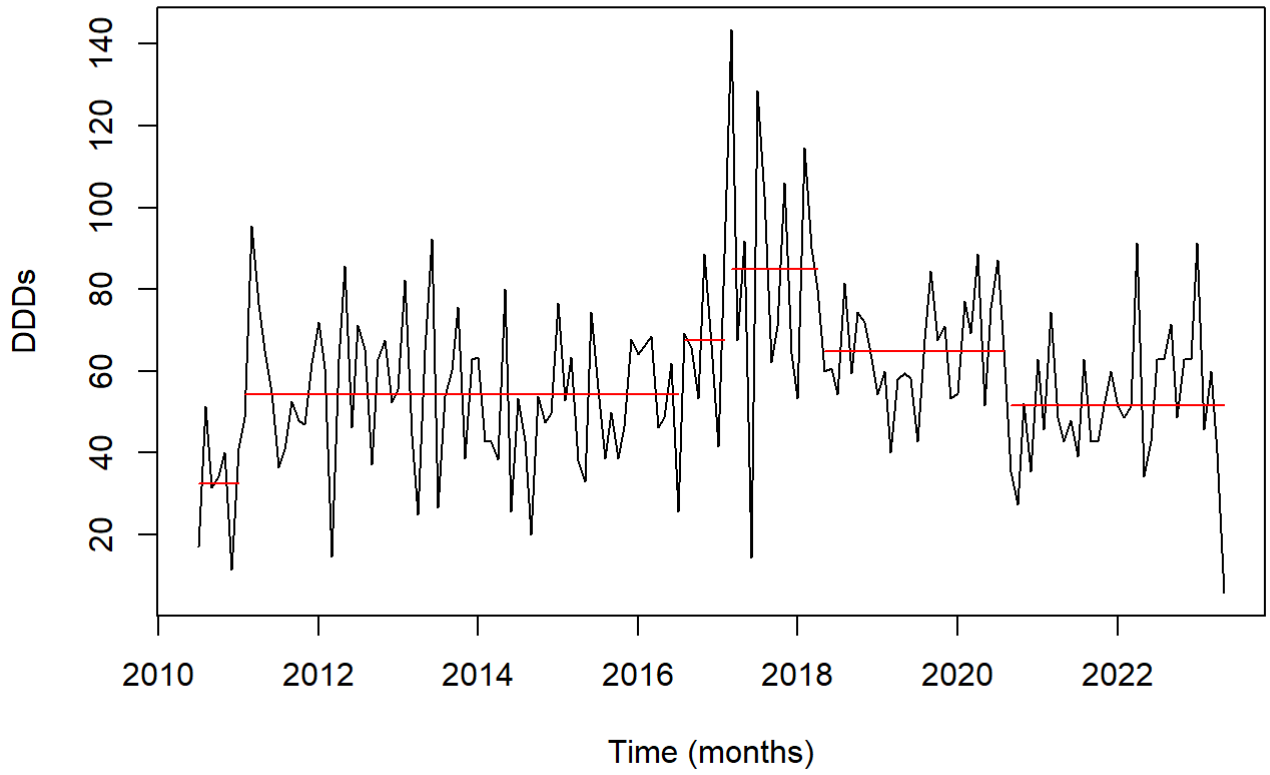
North Sector - Piperacillin with tazobactam

Prescribing Trends



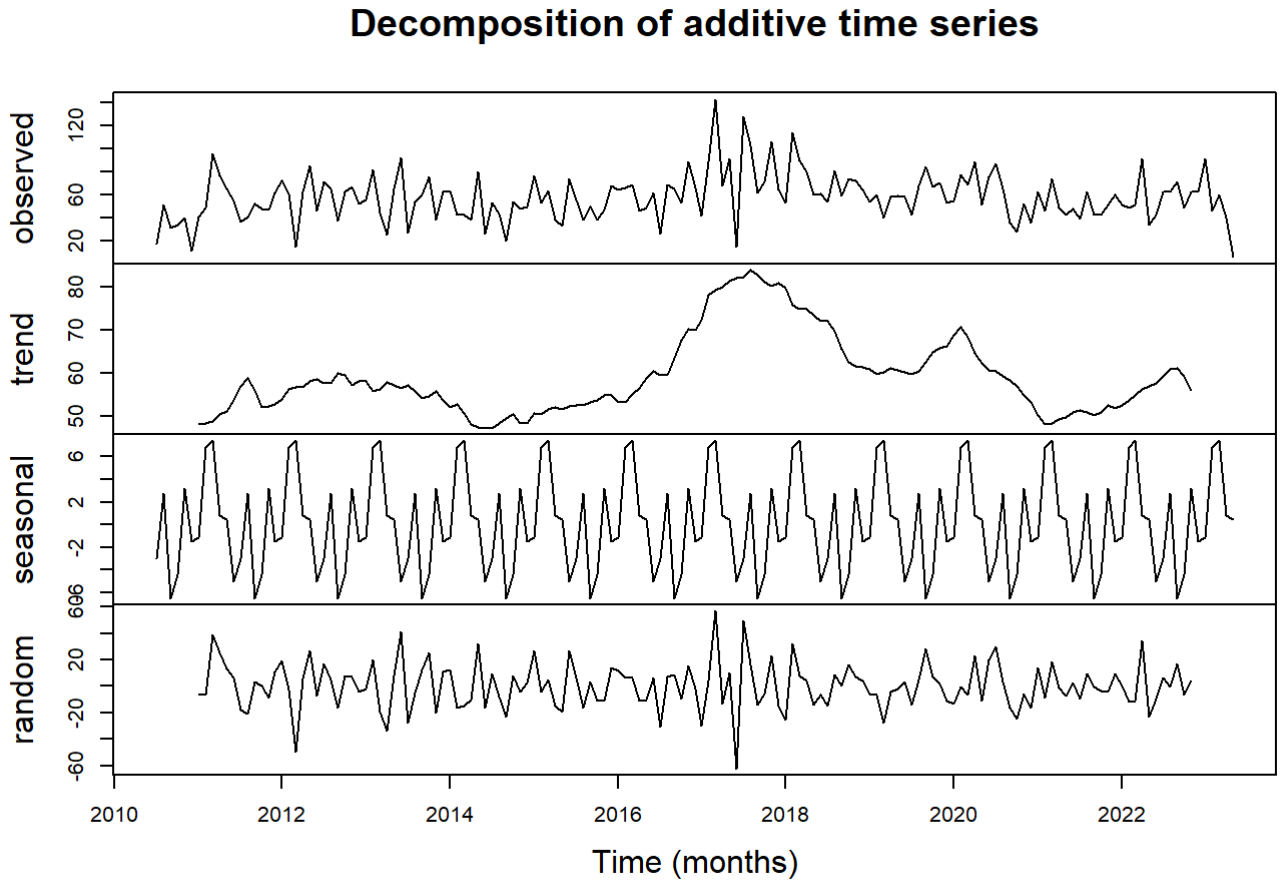
Change point analysis

```
## [1]   7  73  80  94 122
```




```
## $mean
## [1] 32.40816 54.30303 67.63265 85.00000 64.71939 51.70130
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Decomposed into trend, seasonality, random component



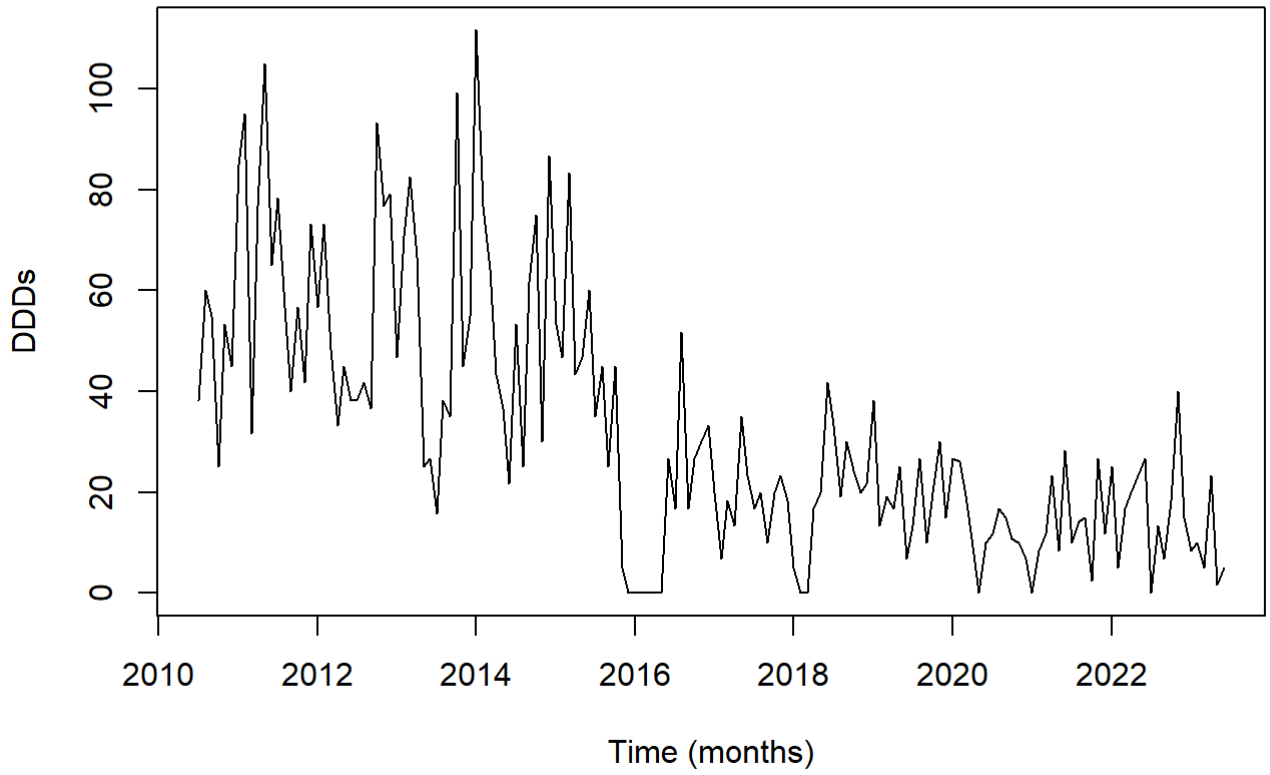
North Sector - Summary

Compared to Paediatrics the mean DDDs for piperacillin with tazobactam and aminoglycosides are lower. Over the entire timeframe piperacillin with tazobactam use increased in 2016/17 and then return to earlier levels by 2020. Aminoglycosides use fell over the timeframe.

Carbapenem mean DDDs are slightly higher that for paediatrics; they rise in late 2019 to be followed by a fall in late 2020 and a return to previous levels in late 2021.

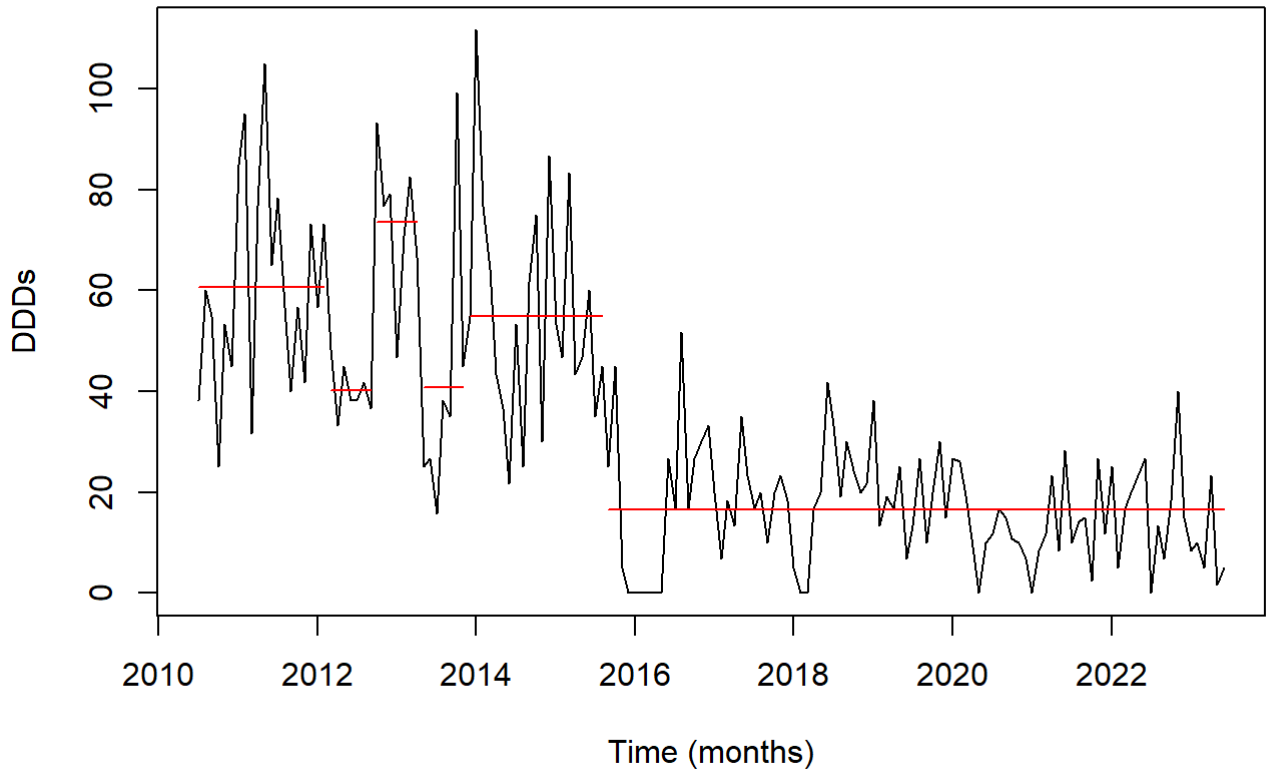
South Sector - Aminoglycosides

Prescribing Trends



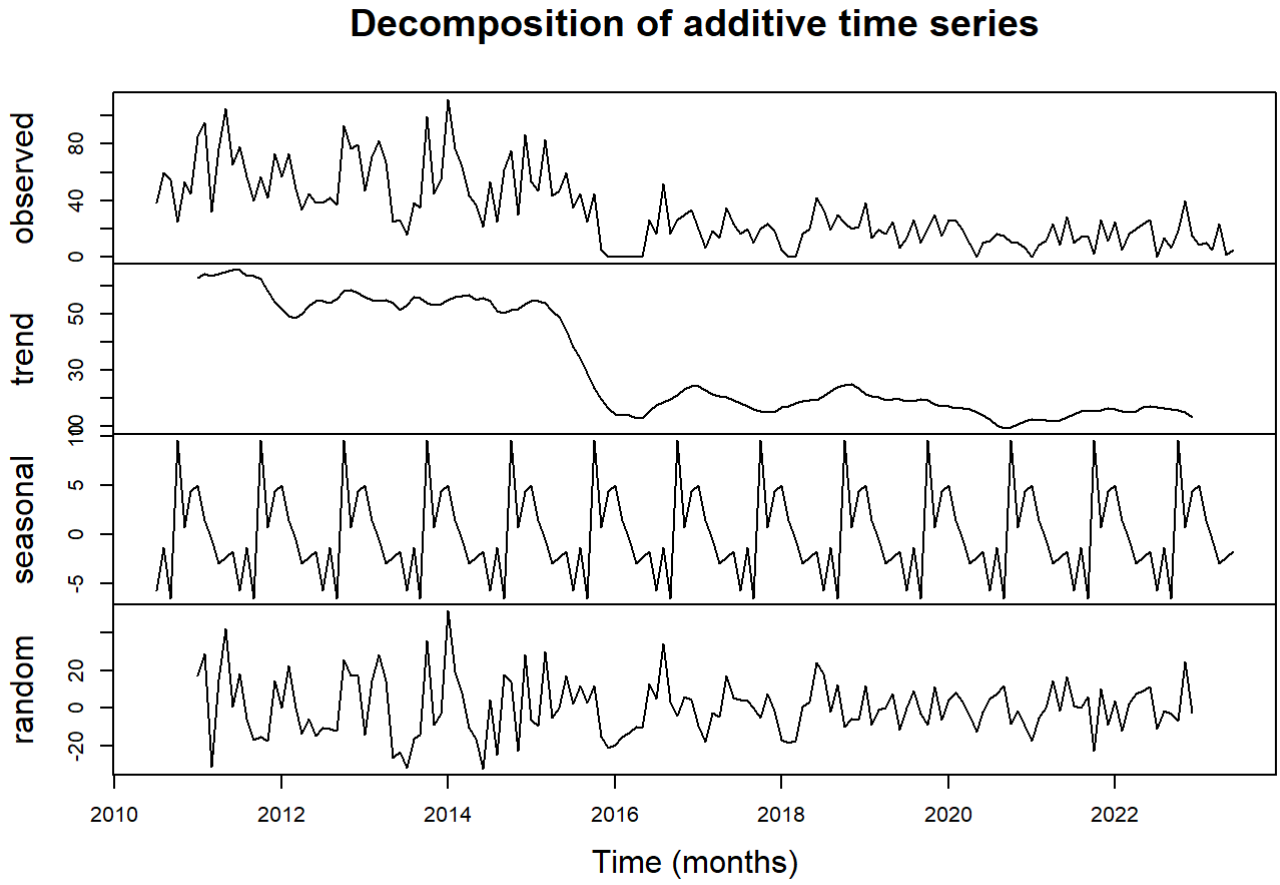
Change point analysis

```
## [1] 20 27 34 41 62
```



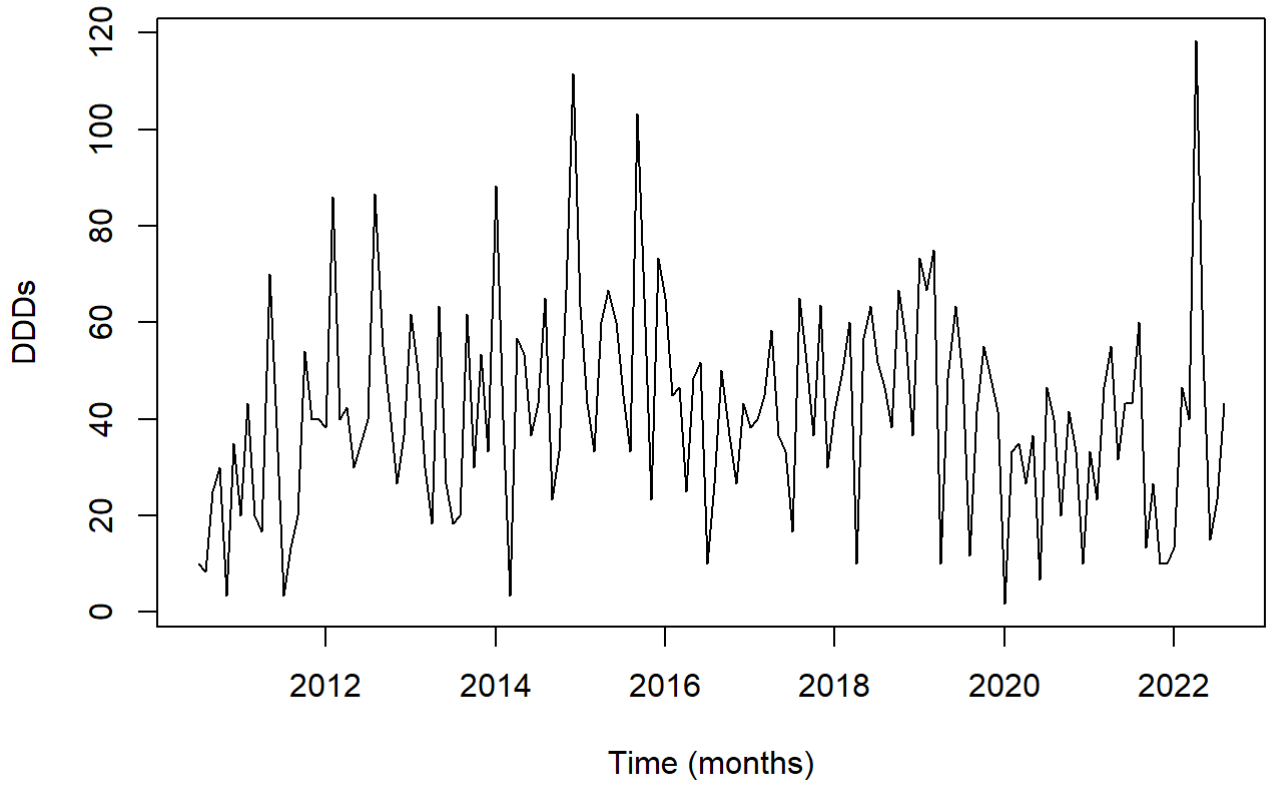

```
## $mean
## [1] 60.58500 40.22857 73.70000 40.71429 54.96667 16.52234
```

Decomposed into trend, seasonality, random component



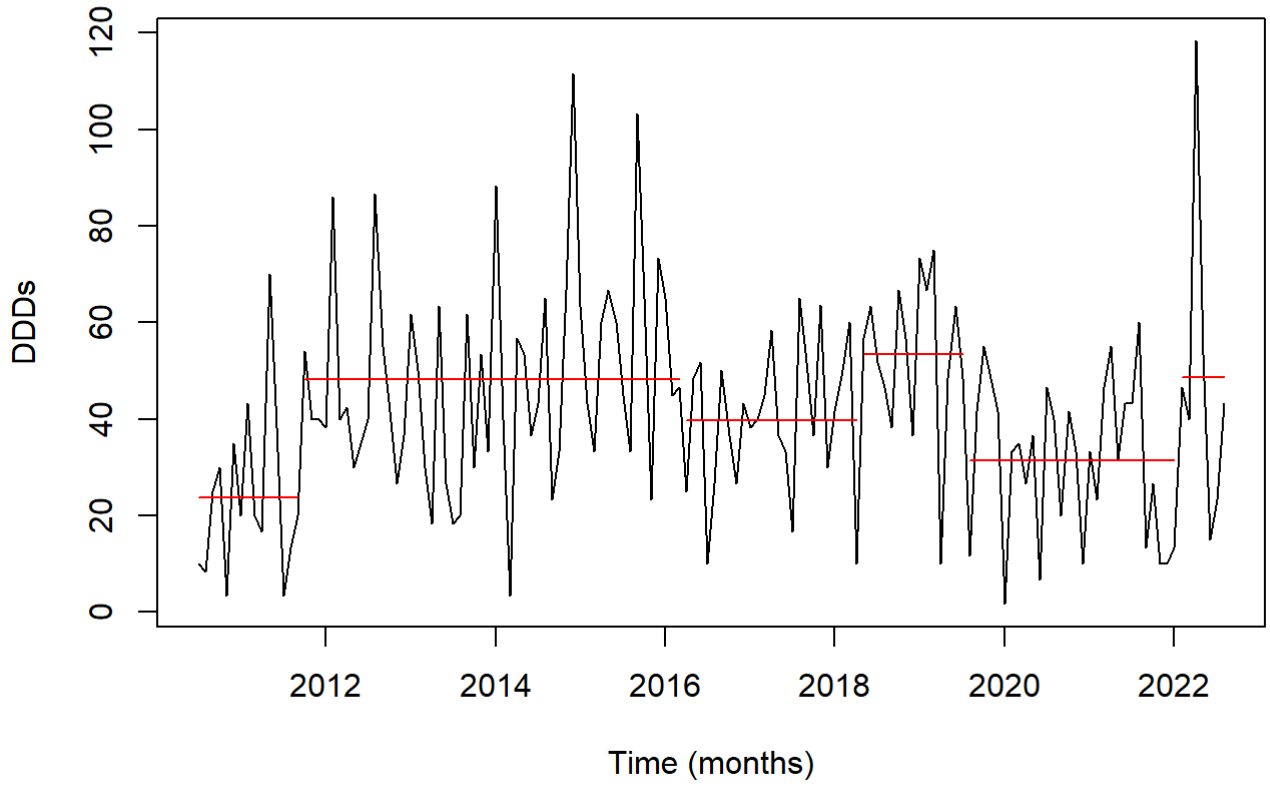
South Sector - Carbapenems

Prescribing Trends



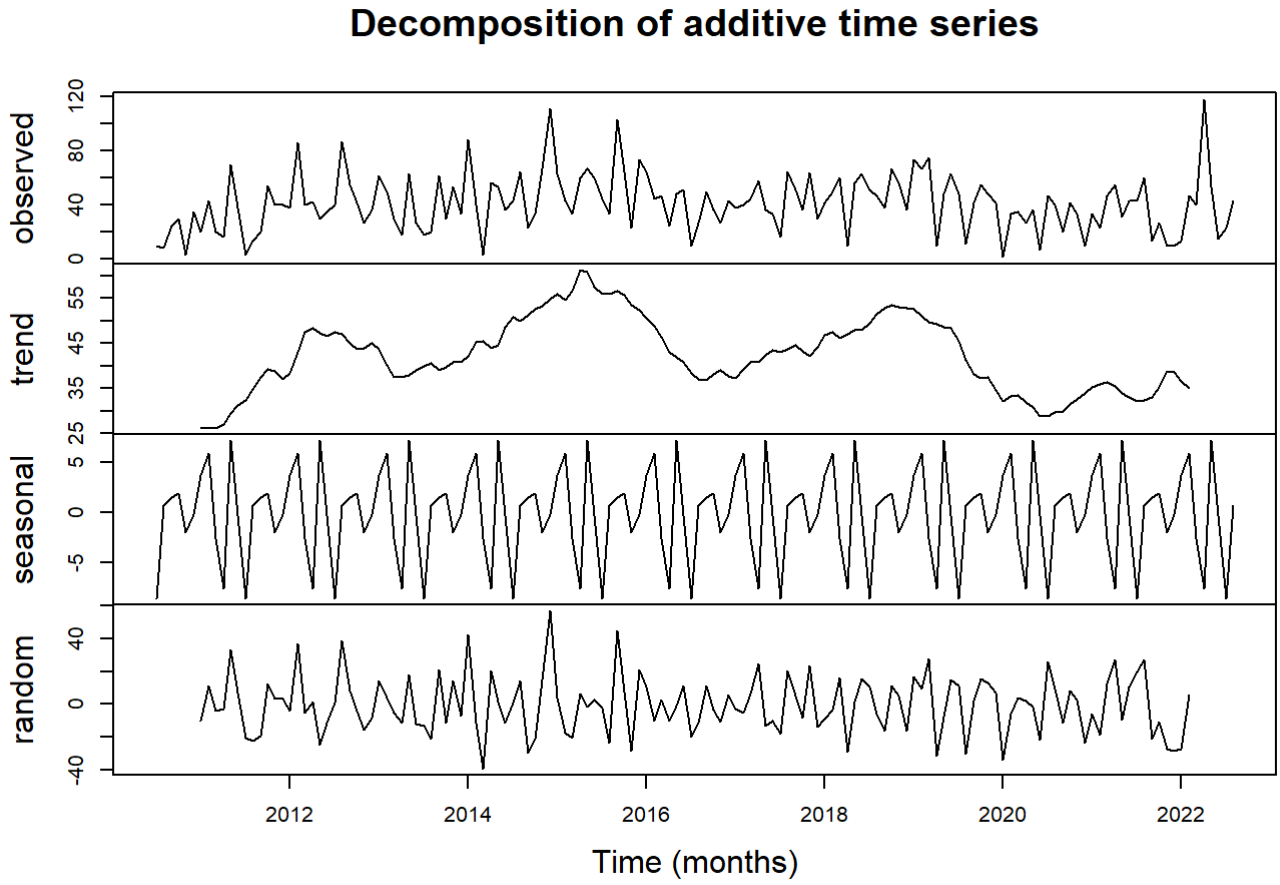
Change point analysis

```
## [1]  15  69  94 109 139
```



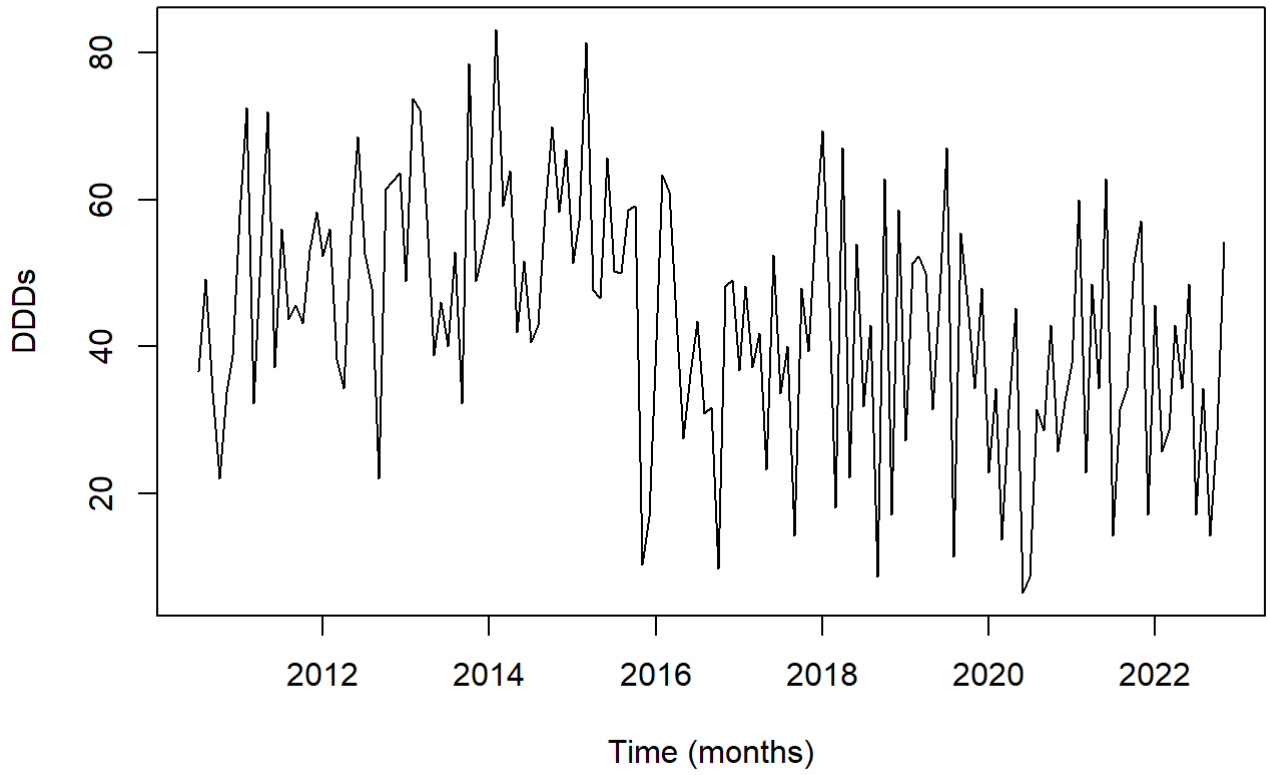

```
## $mean
## [1] 23.77778 48.28395 39.81333 53.44444 31.33333 48.57143
```

Decomposed into trend, seasonality, random component



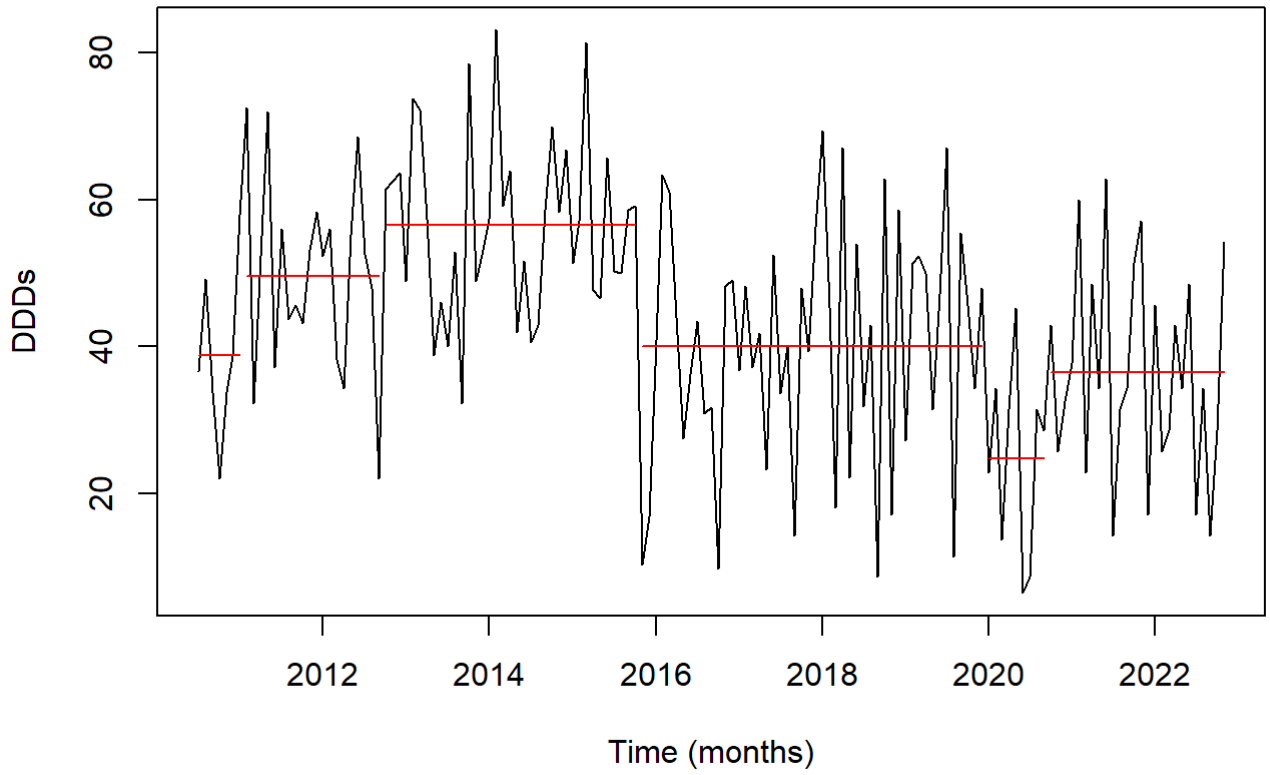
South Sector - Piperacillin with tazobactam

Prescribing Trends



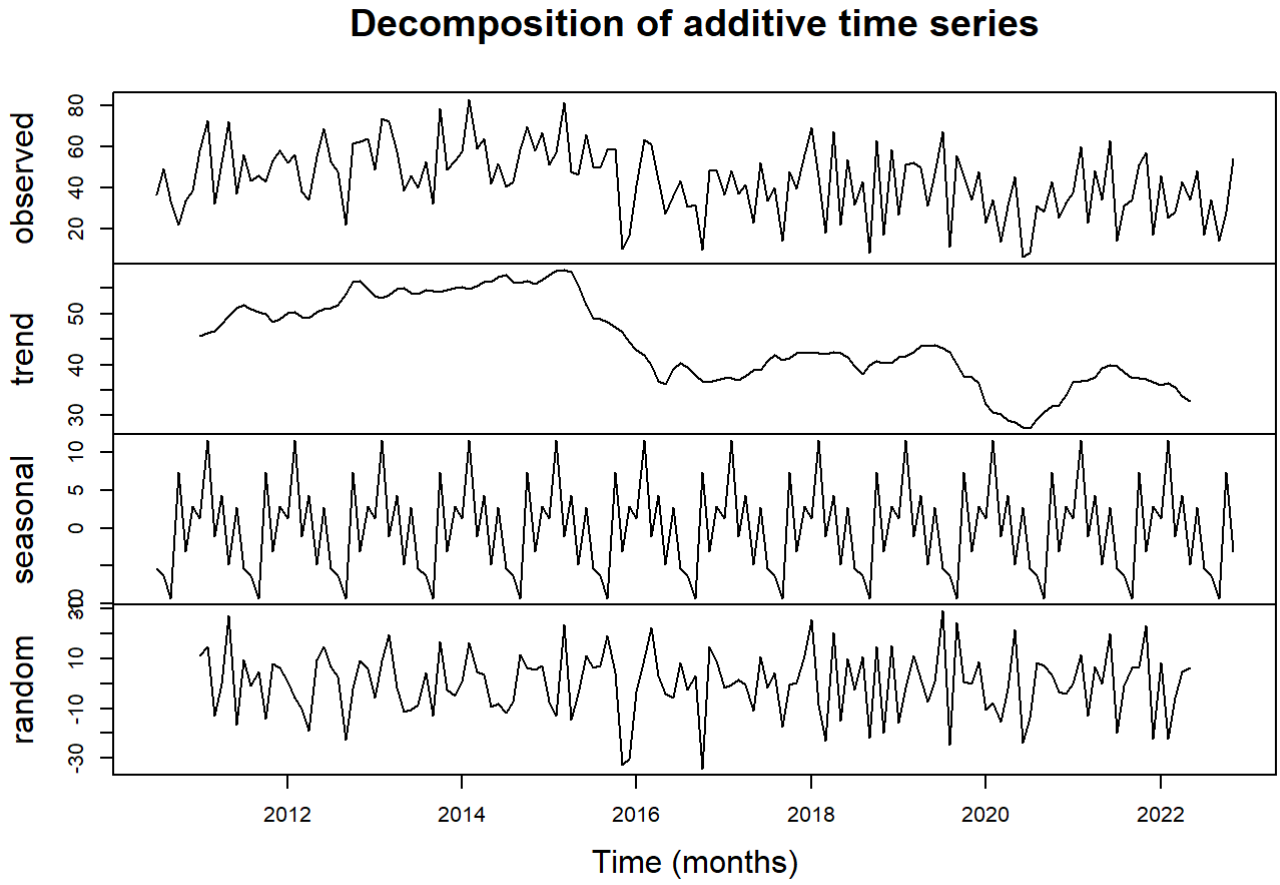
Change point analysis

```
## [1]   7  27  64 114 123
```




```
## $mean
## [1] 38.85714 49.67143 56.57143 40.07286 24.73016 36.43956
```

Decomposed into trend, seasonality, random component



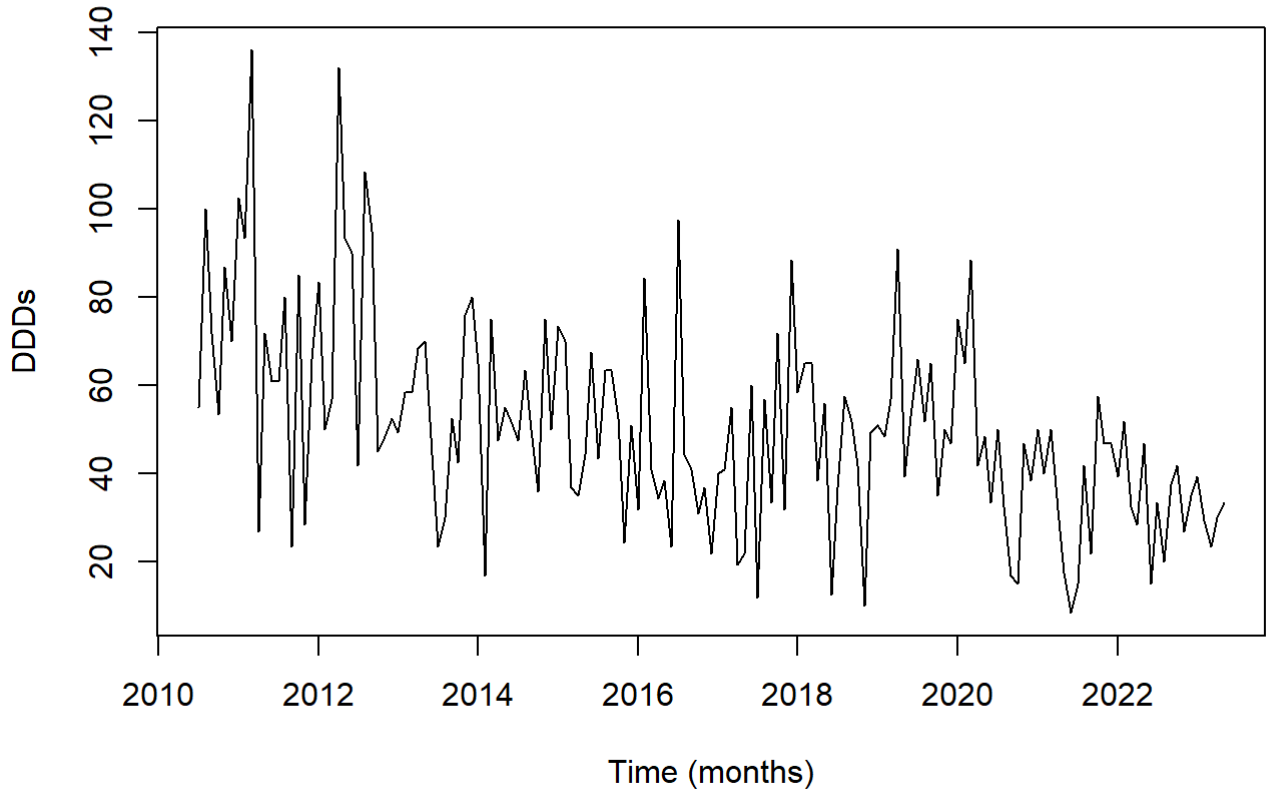
South Sector - Summary

Compared to Paediatrics the mean DDDs for carbapenems are initally similar and lower for animoglycosides and piperacillin with tazobactam. Over the entire timeframe use of aminoglycosides declines (a mean of 55.3 per month in 2011 falls to 15.9 in 2018 onwards).

Mean DDDs of carbapenem and piperacillin with tazobactam are lower that for paediatrics and North sector; they rise in the first third of the timeframe and fall back in the last third with the highest levels from 2011 to 2016.

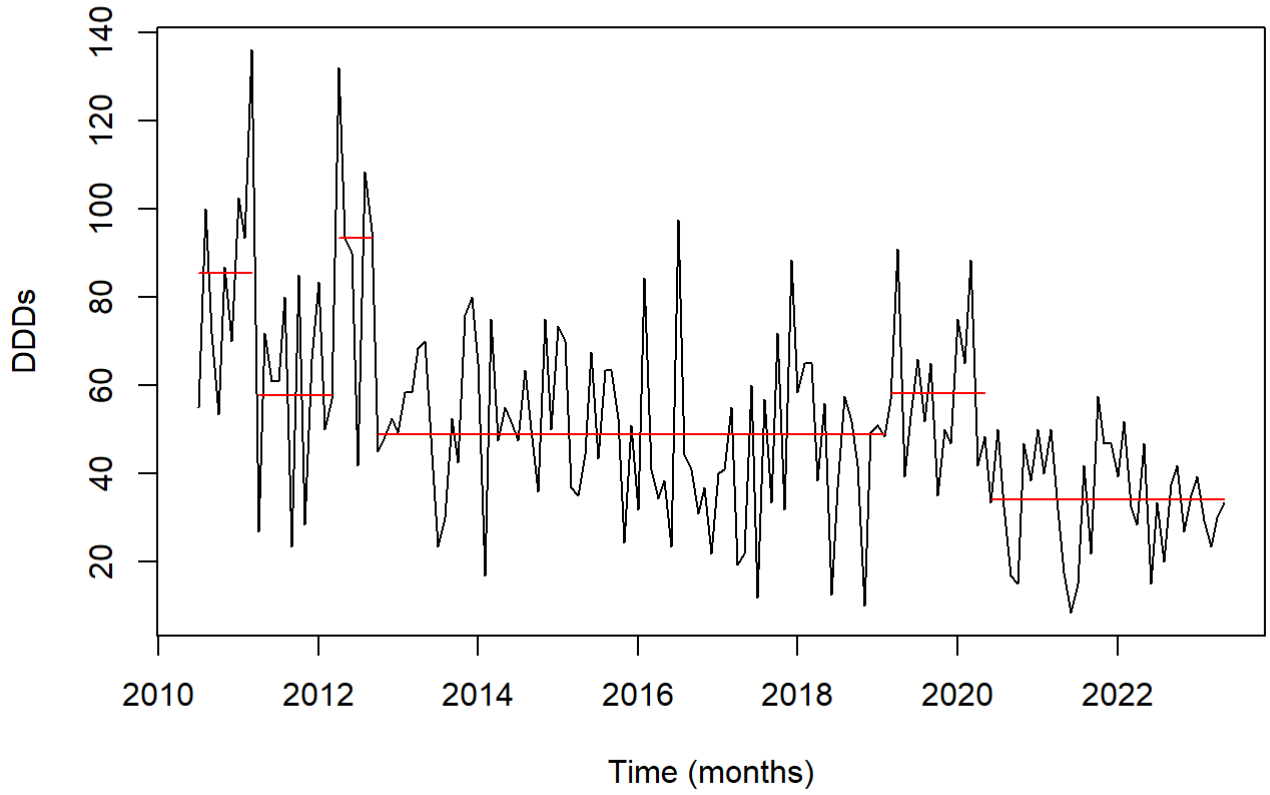
Bone Marrow Transplant Unit - Aminoglycosides

Prescribing Trends



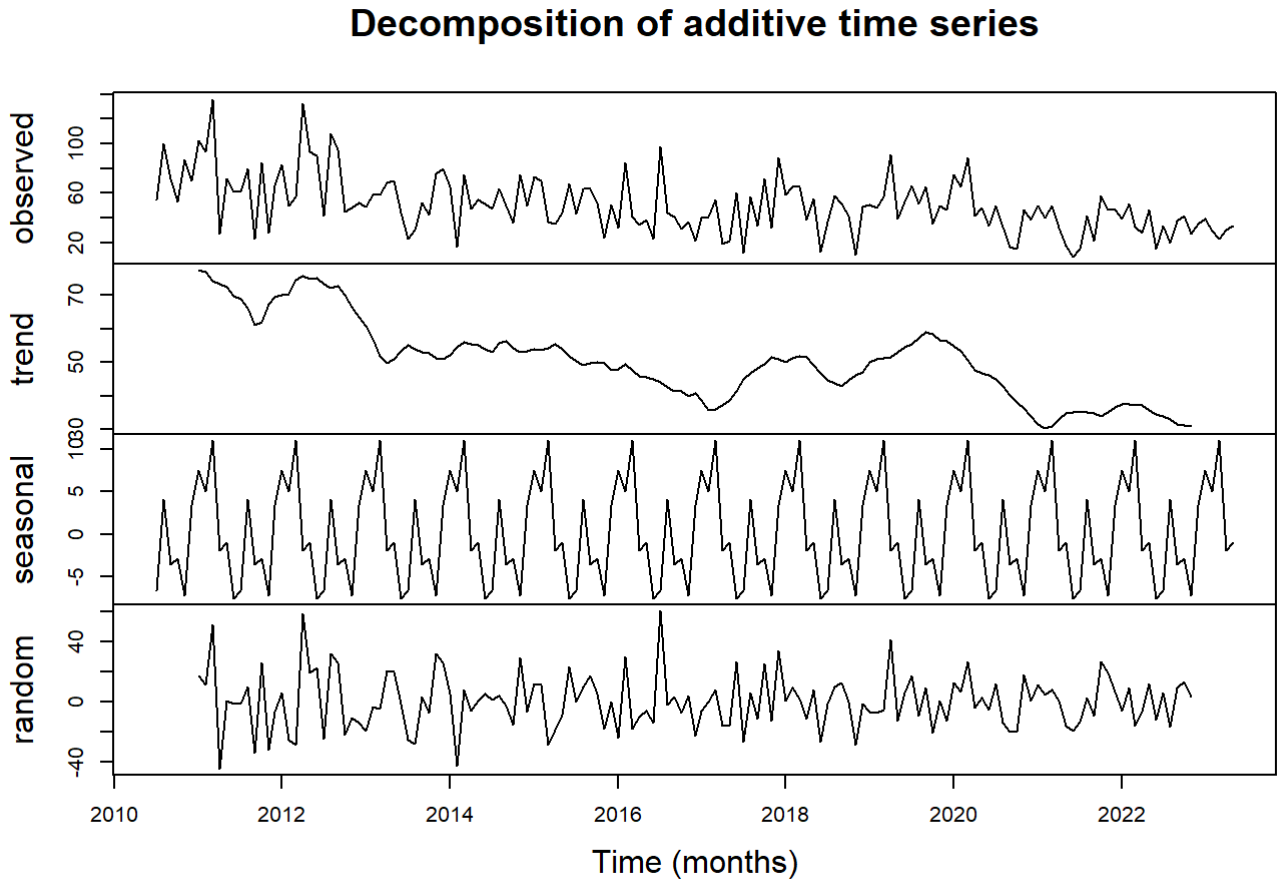
Change point analysis

```
## [1]   9  21  27 104 119
```



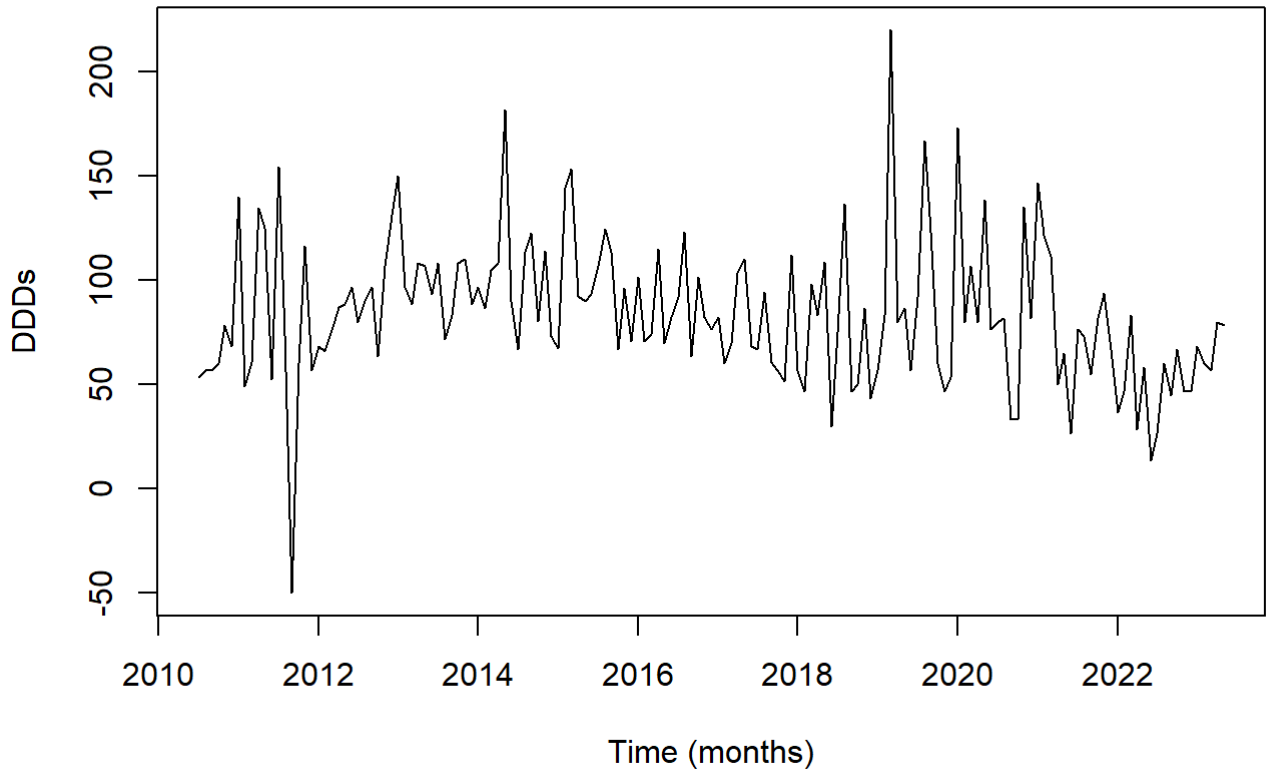

```
## $mean
## [1] 85.38889 57.70000 93.38333 48.70000 58.14667 33.94167
```

Decomposed into trend, seasonality, random component



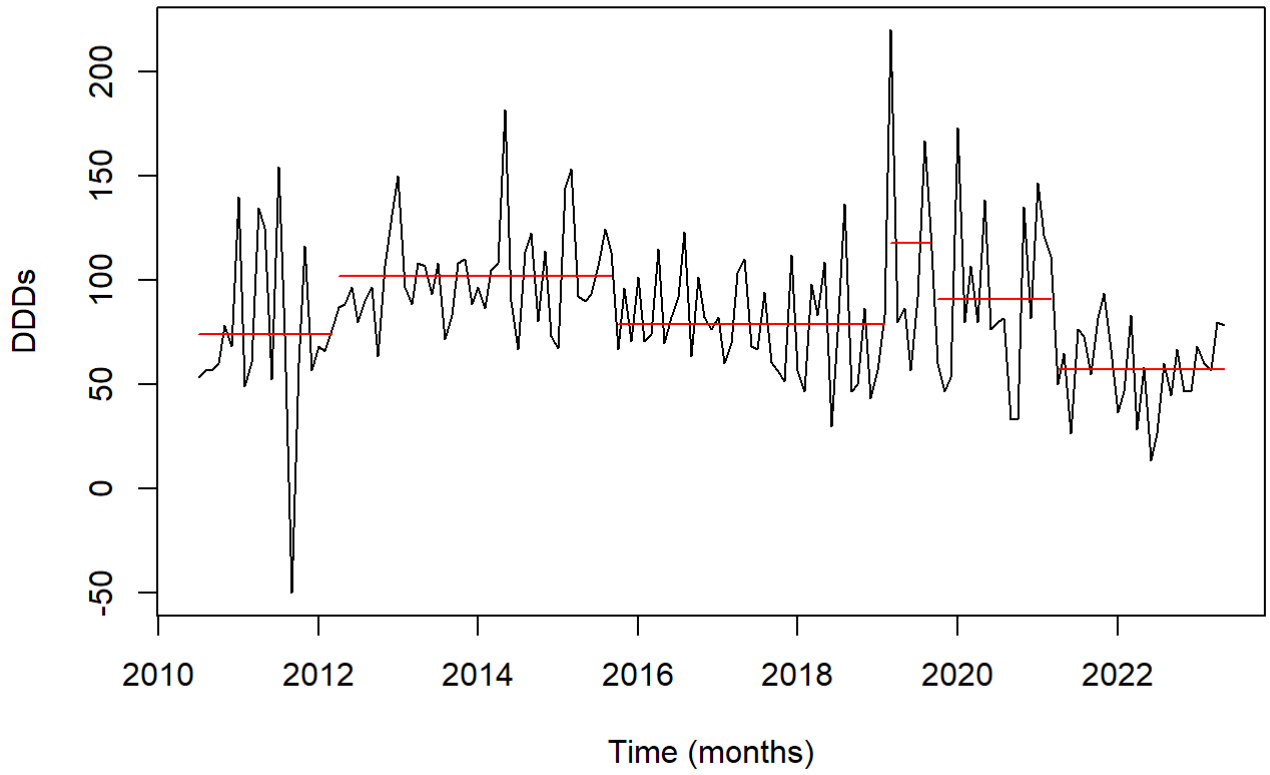
BMT Sector - Carbapenems

Prescribing Trends



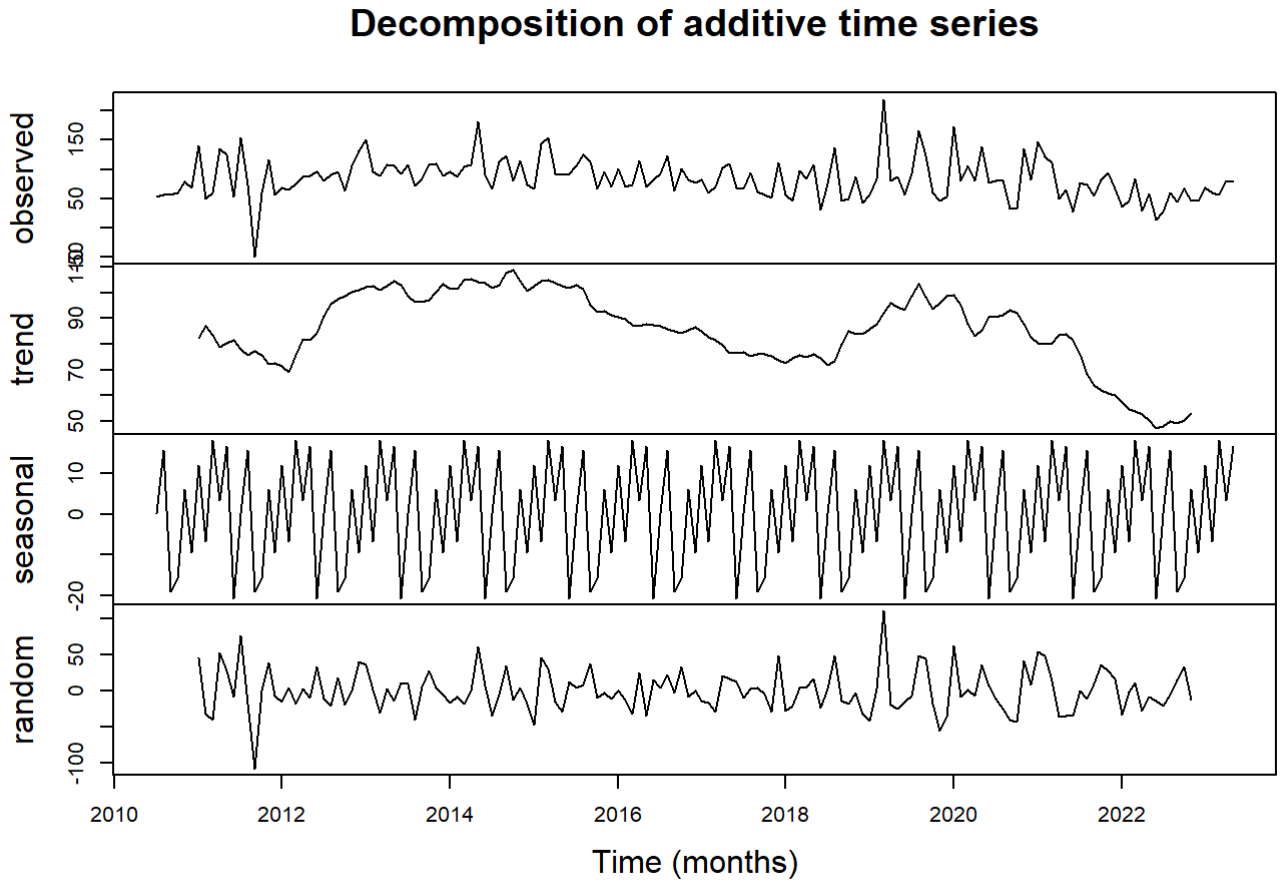
Change point analysis

```
## [1]  21  63 104 111 129
```



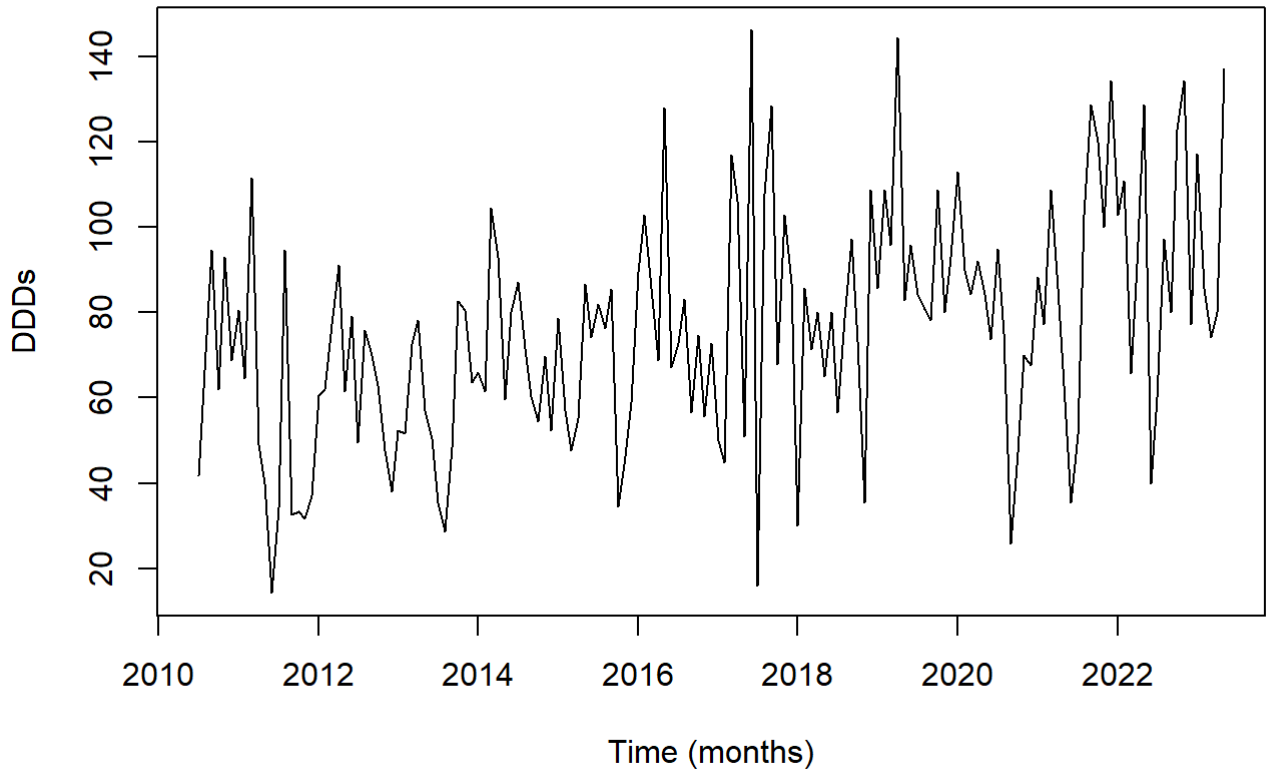

```
## $mean
## [1]  74.11905 101.85516  78.66463 117.85714  91.11111  57.33333
```

Decomposed into trend, seasonality, random component



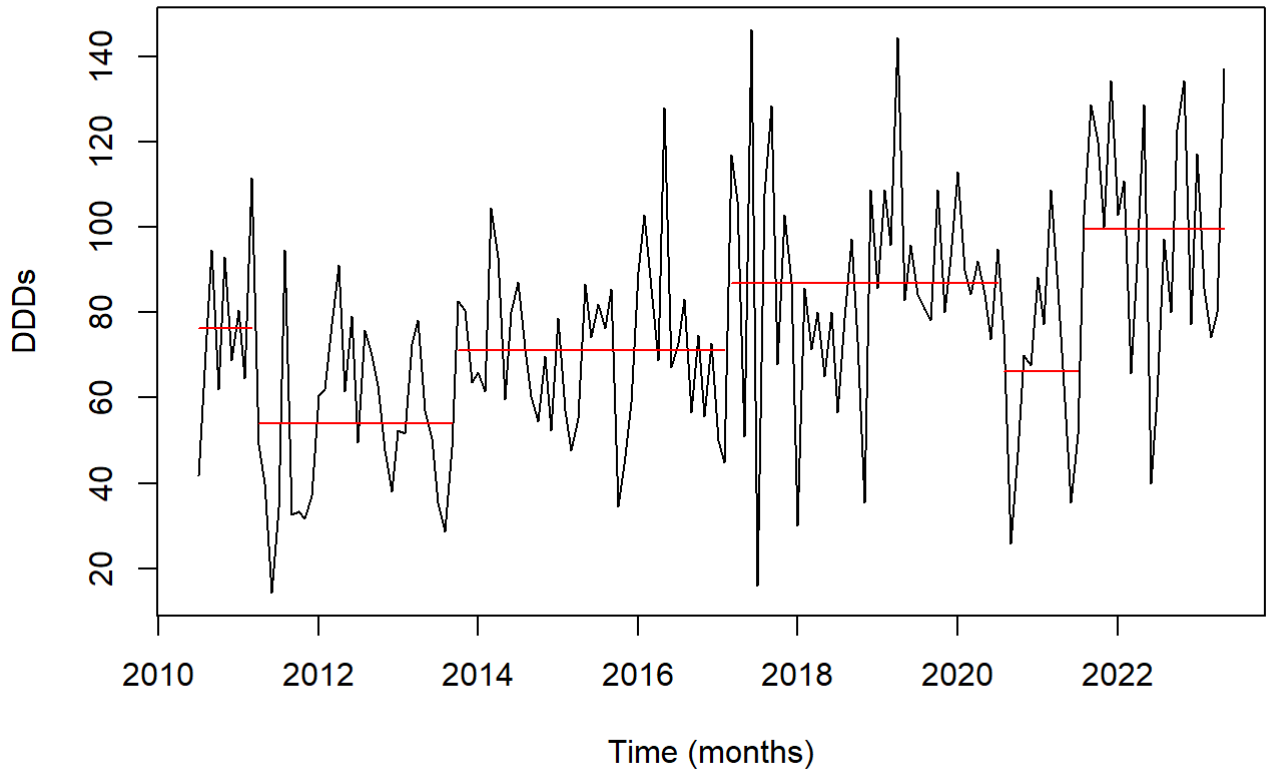
BMT Sector - Piperacillin with tazobactam

Prescribing Trends



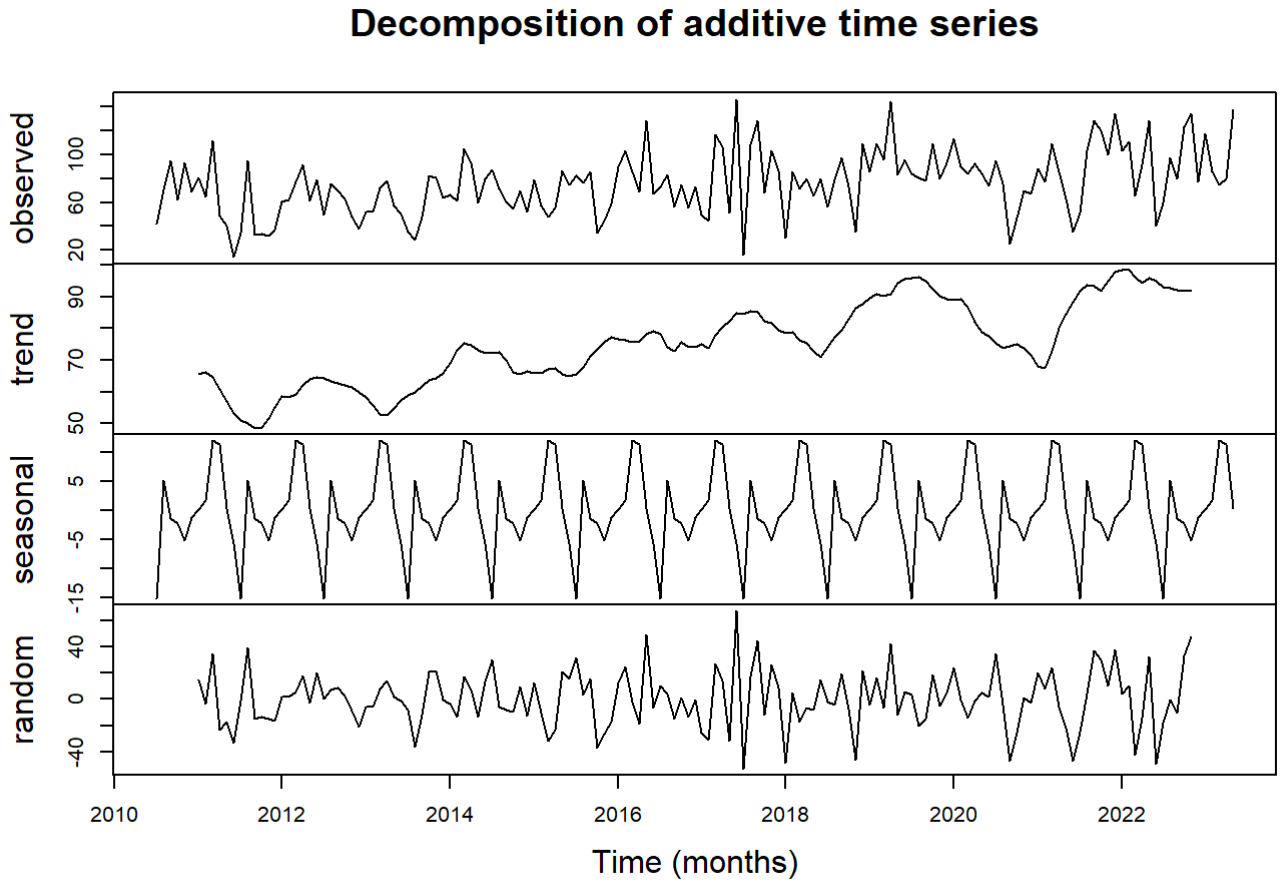
Change point analysis

```
## [1]   9  39  80 121 133
```




```
## $mean
## [1] 76.34921 53.90476 71.23345 86.85192 66.23810 99.57792
```

Decomposed into trend, seasonality, random component



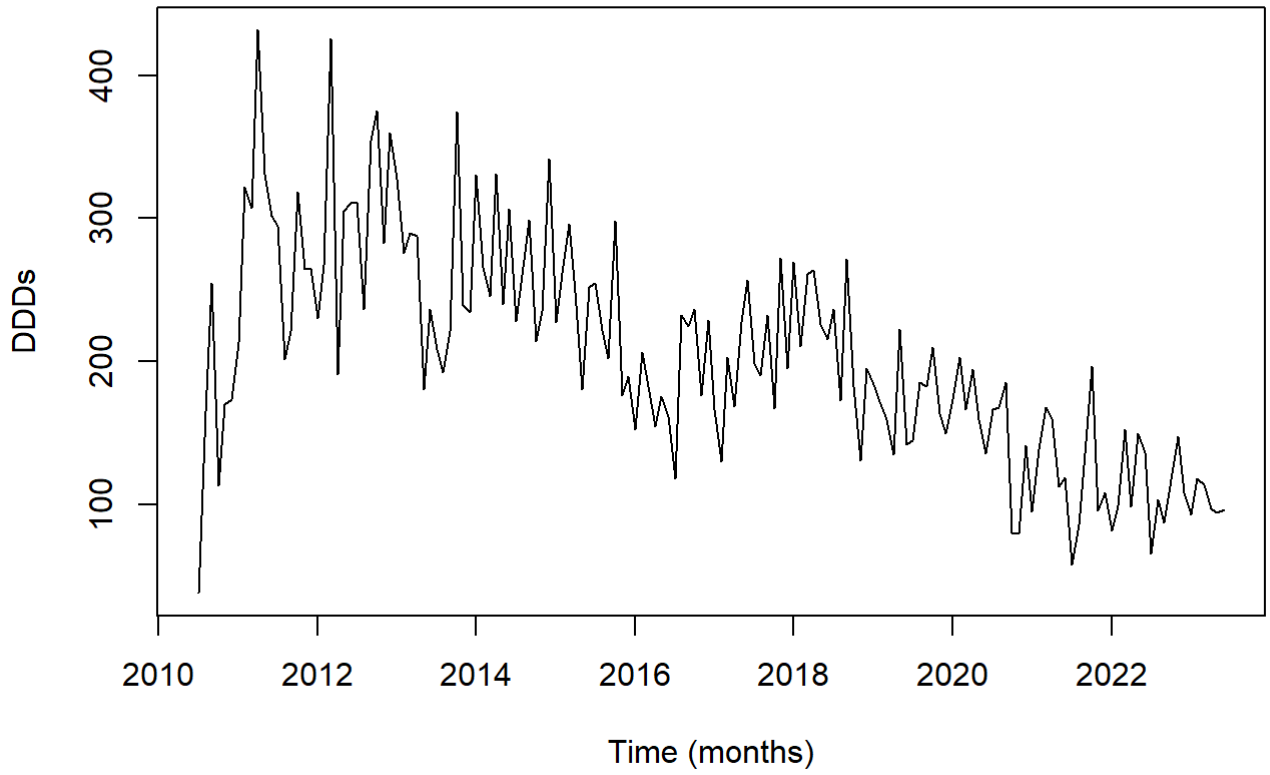
Bone Marrow Transplant Unit - Summary

Compared to Paediatrics the mean DDDs for carbapenems is initially higher; this remains relatively constant and declines in 2021. Aminoglycoside use declines over the timeframe from a peak mean monthly DDDs of 110.1 to a mean monthly DDDs of 33.9.

The mean monthly DDDs of piperacillin with tazobactam increases from a low of 53.9 in 2012 and 2013 to 99.6 toward the end of the timeframe (2022).

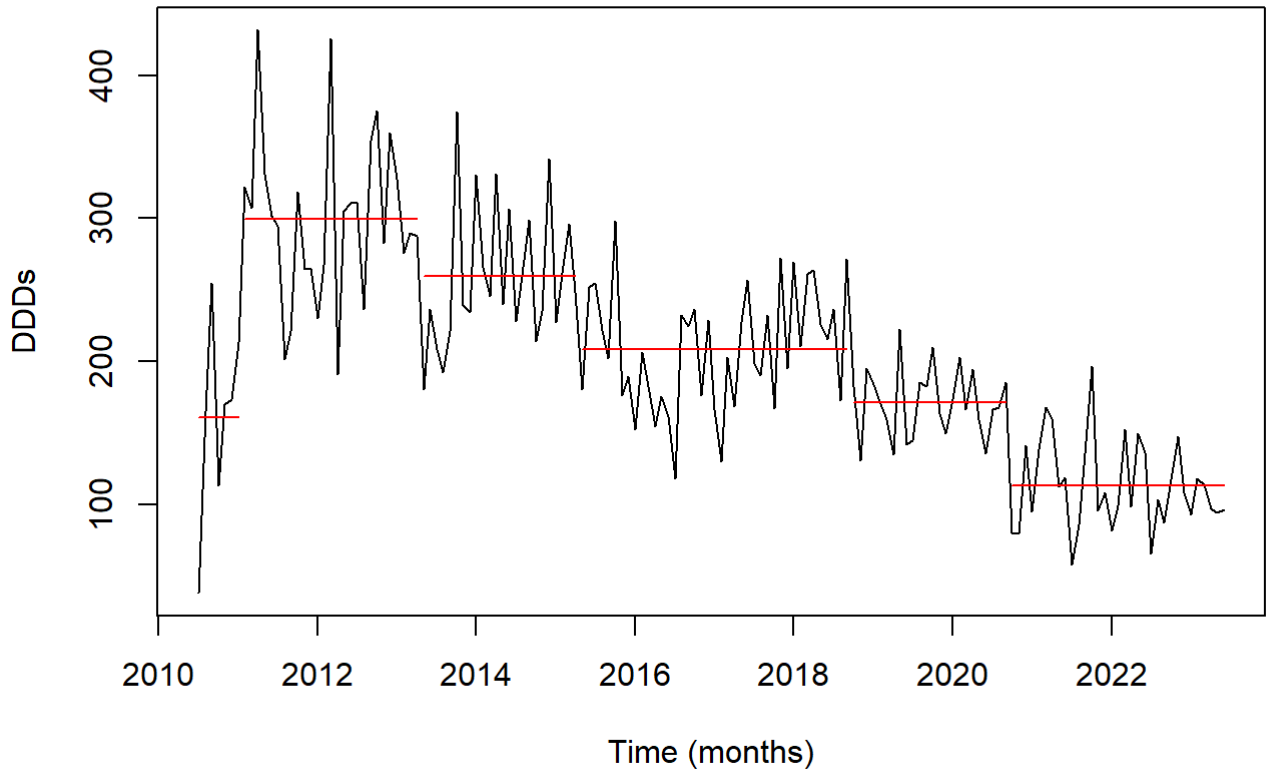
Overall total - Aminoglycosides

Prescribing Trends



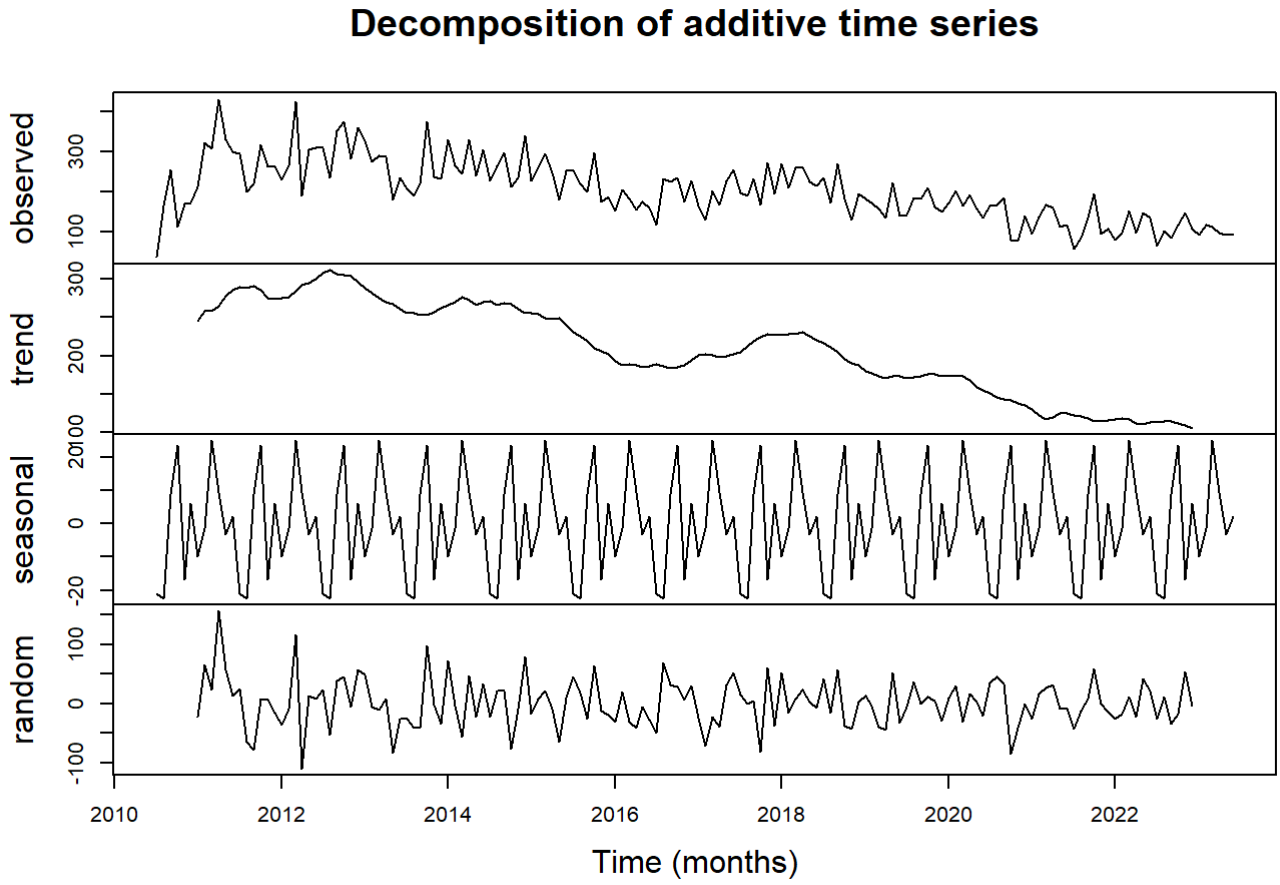
Change point analysis

```
## [1]   7  34  58  99 123
```



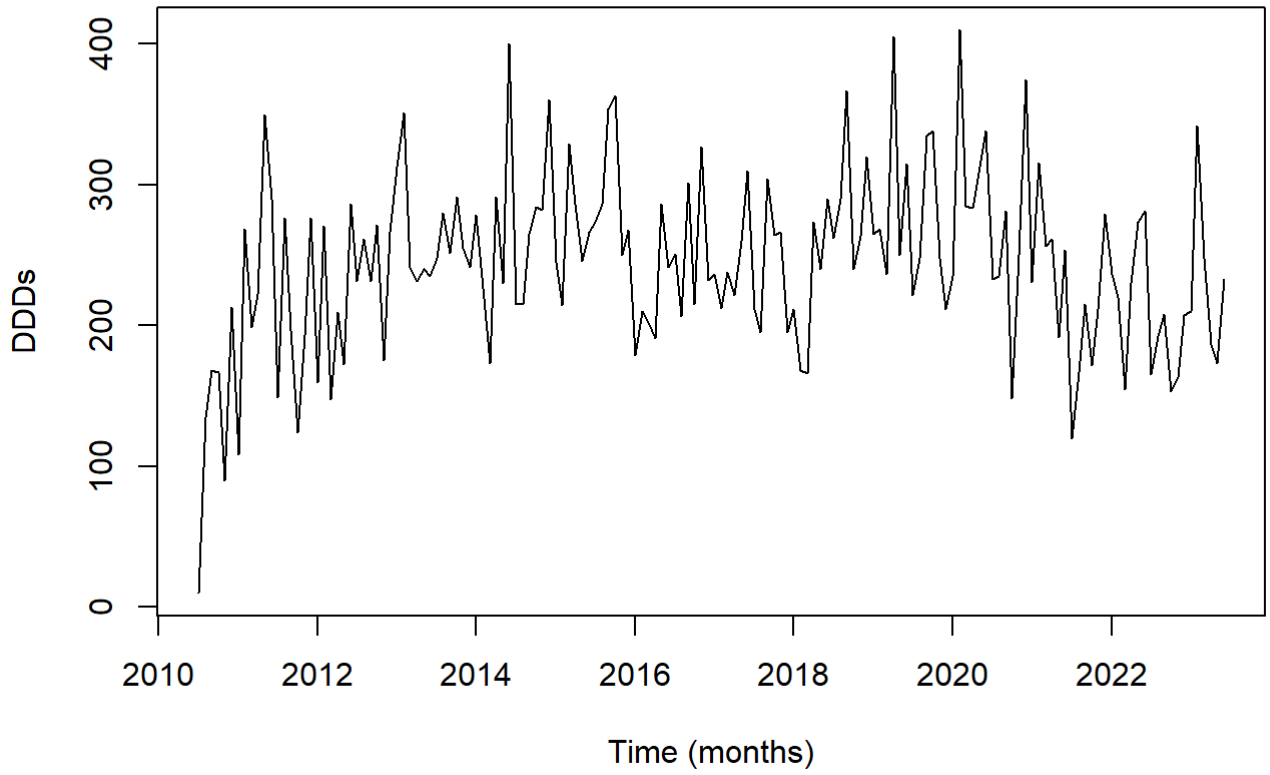

```
## $mean
## [1] 161.1905 299.6728 259.3889 208.9431 171.4556 113.2929
```

Decomposed into trend, seasonality, random component



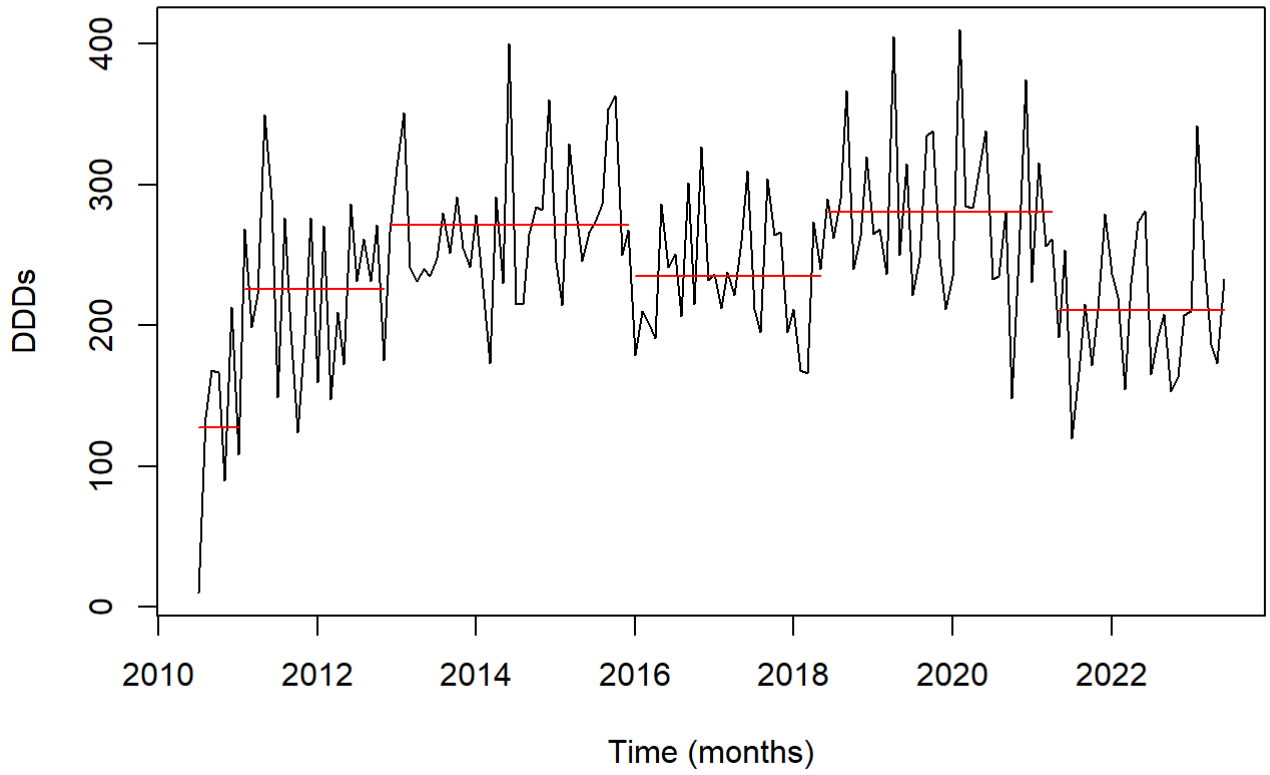
Overall total - Carbapenems

Prescribing Trends



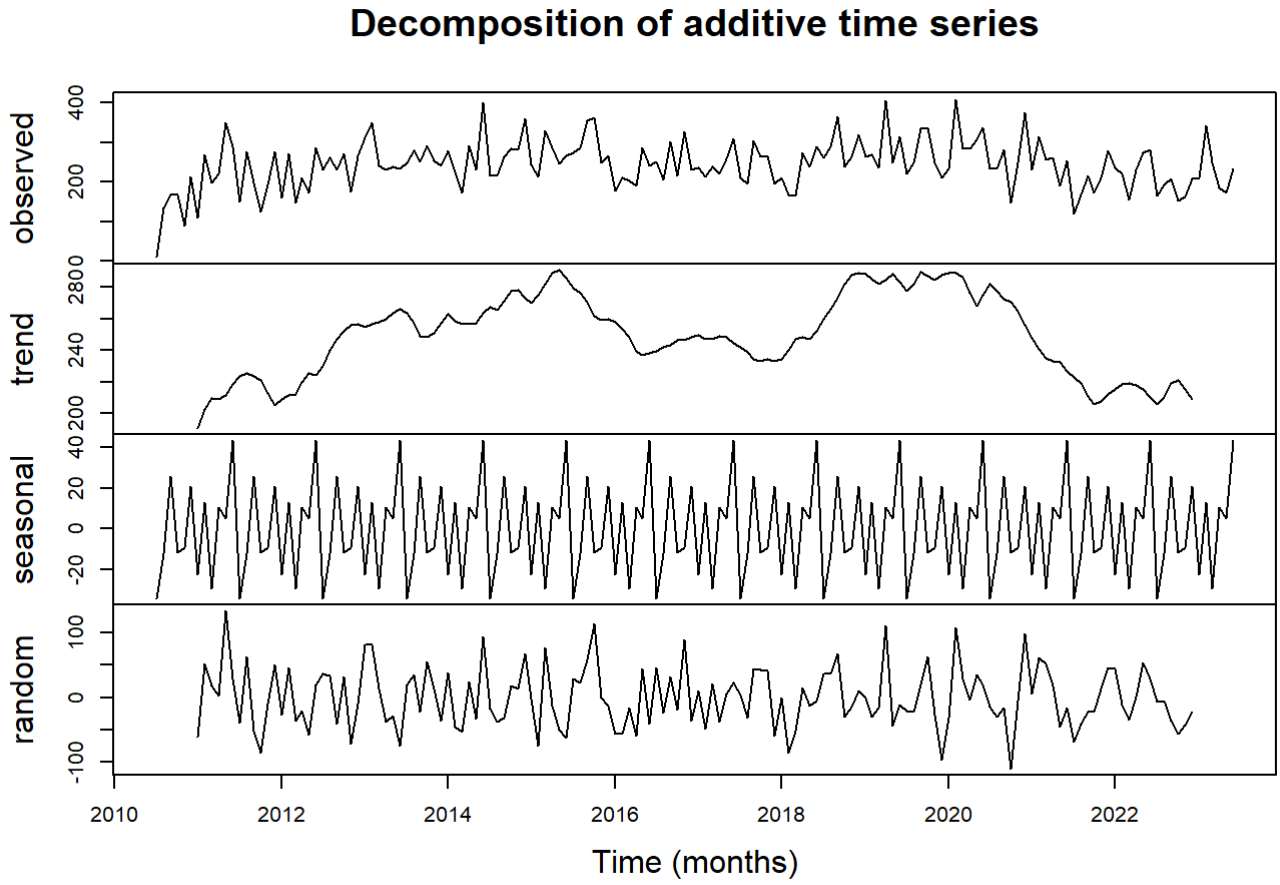
Change point analysis

```
## [1]   7  29  66  95 130
```



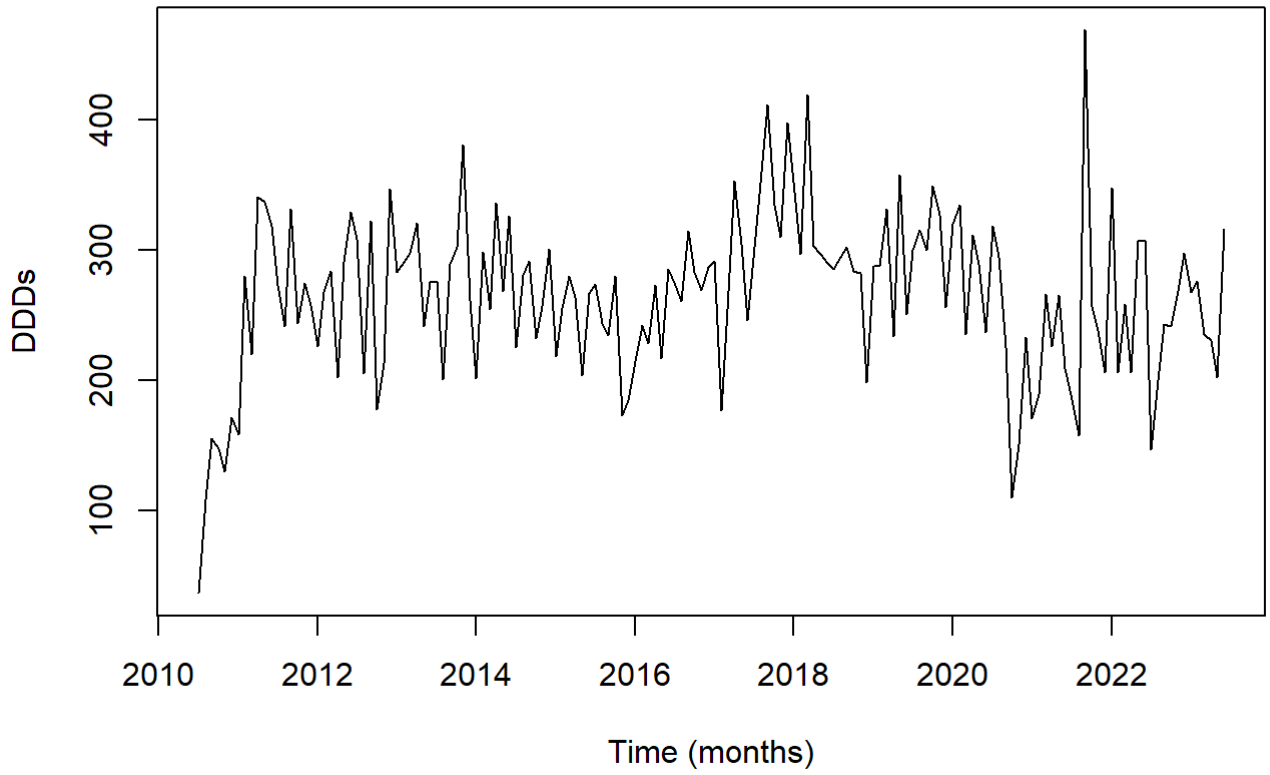

```
## $mean
## [1] 127.3714 225.6364 271.6973 235.1586 280.6714 211.1154
```

Decomposed into trend, seasonality, random component



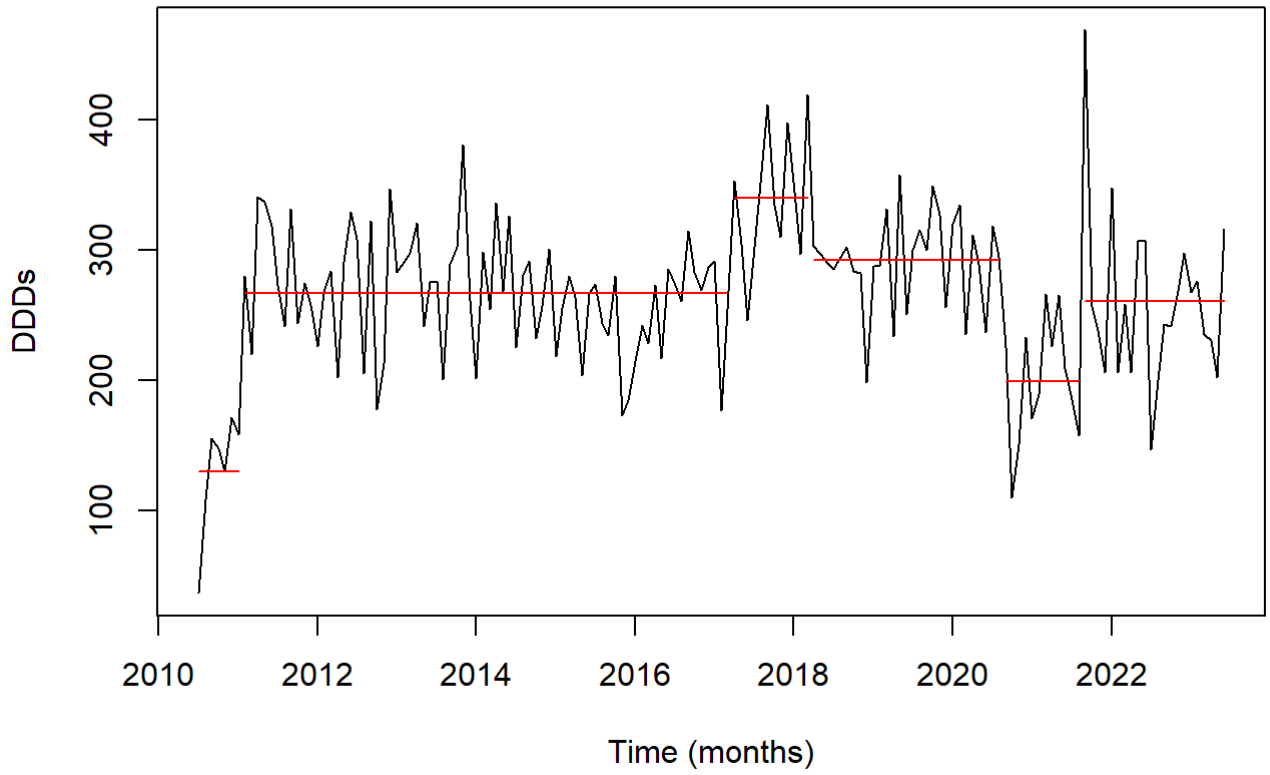
Overall total - Piperacillin with tazobactam

Prescribing Trends



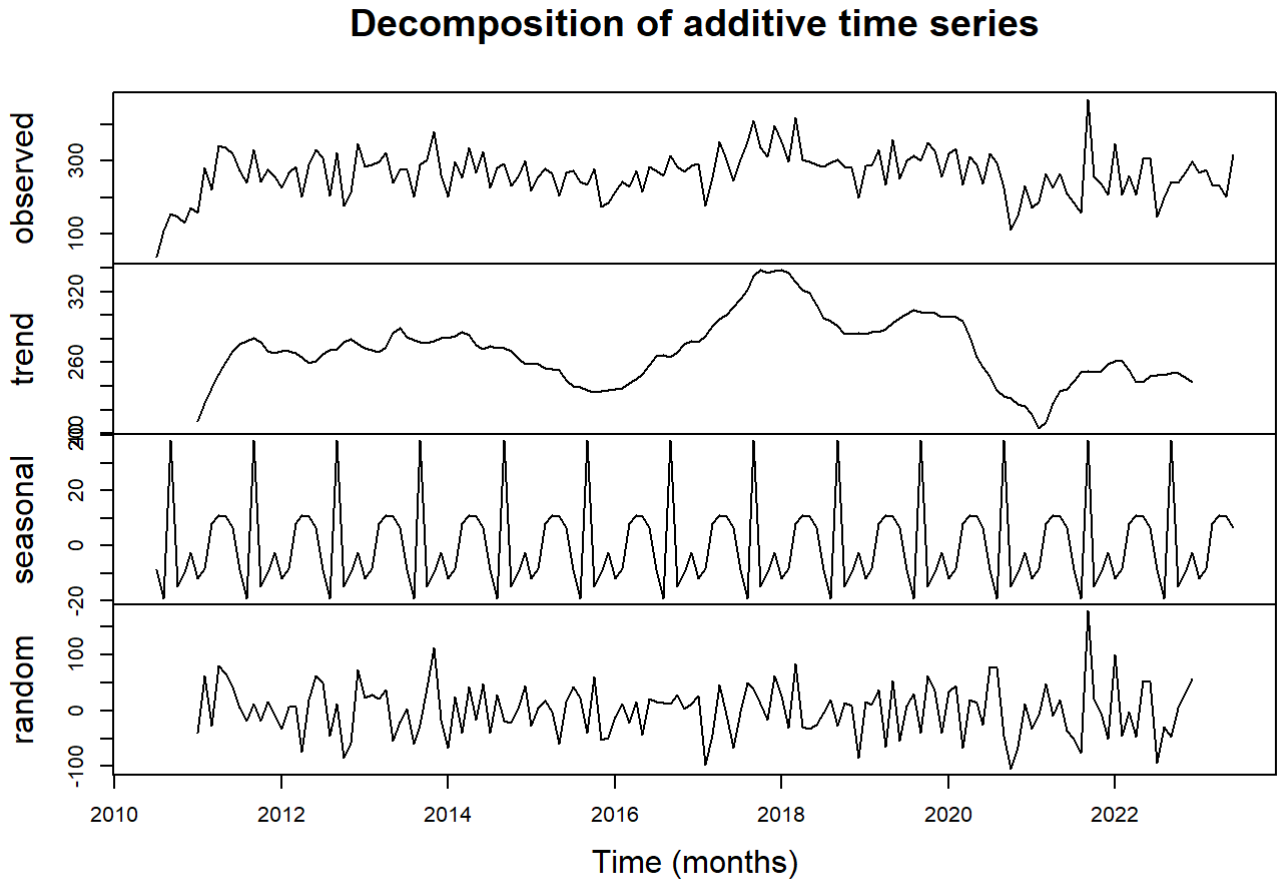
Change point analysis

```
## [1]   7  81  93 122 134
```




```
## $mean
## [1] 129.7571 266.7905 340.2500 292.3793 199.1417 260.5682
```

Decomposed into trend, seasonality, random component

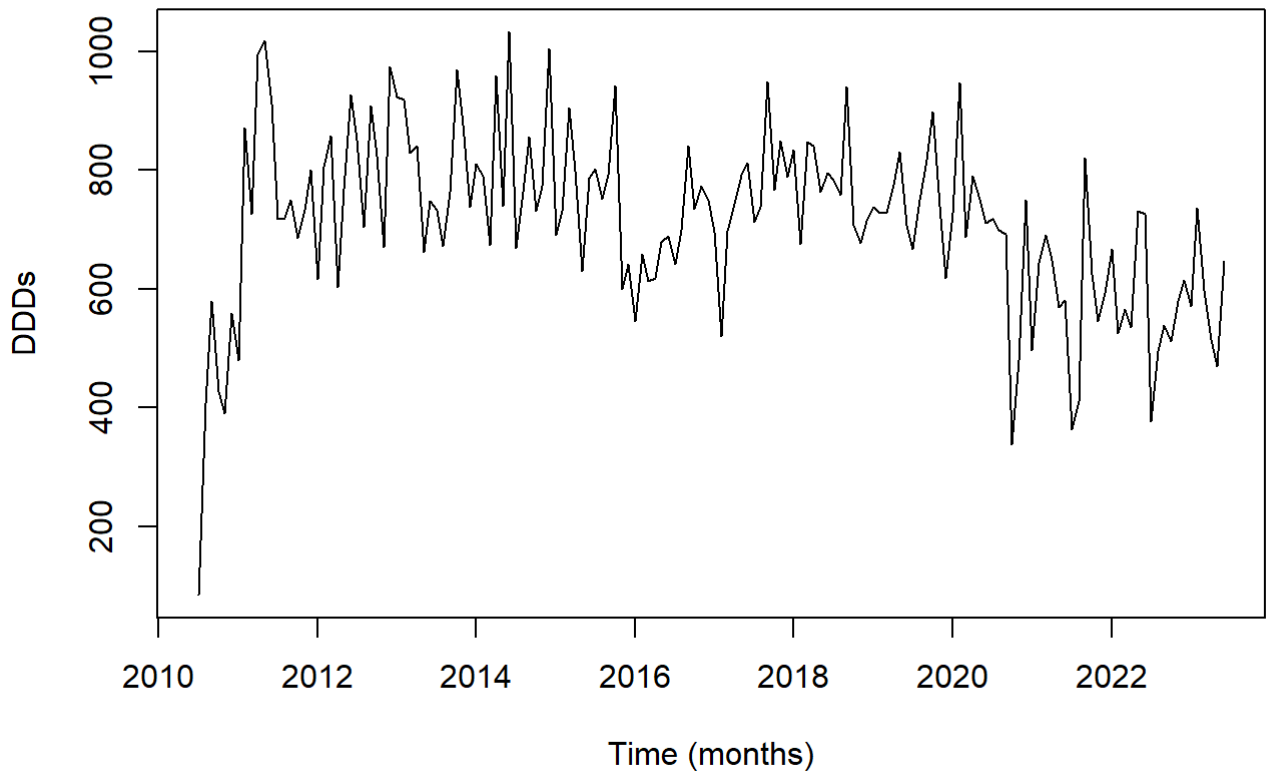


Summary - all ward groups combined

The mean monthly DDDs for aminoglycosides, carbapenems and piperacillin with tazobactam were similar in January 2014 prior to the opening of the QEUH. Use of aminoglycosides has declined over the timeframe of the analysis from a peak of mean monthly 305.7 DDDs to 113.3.

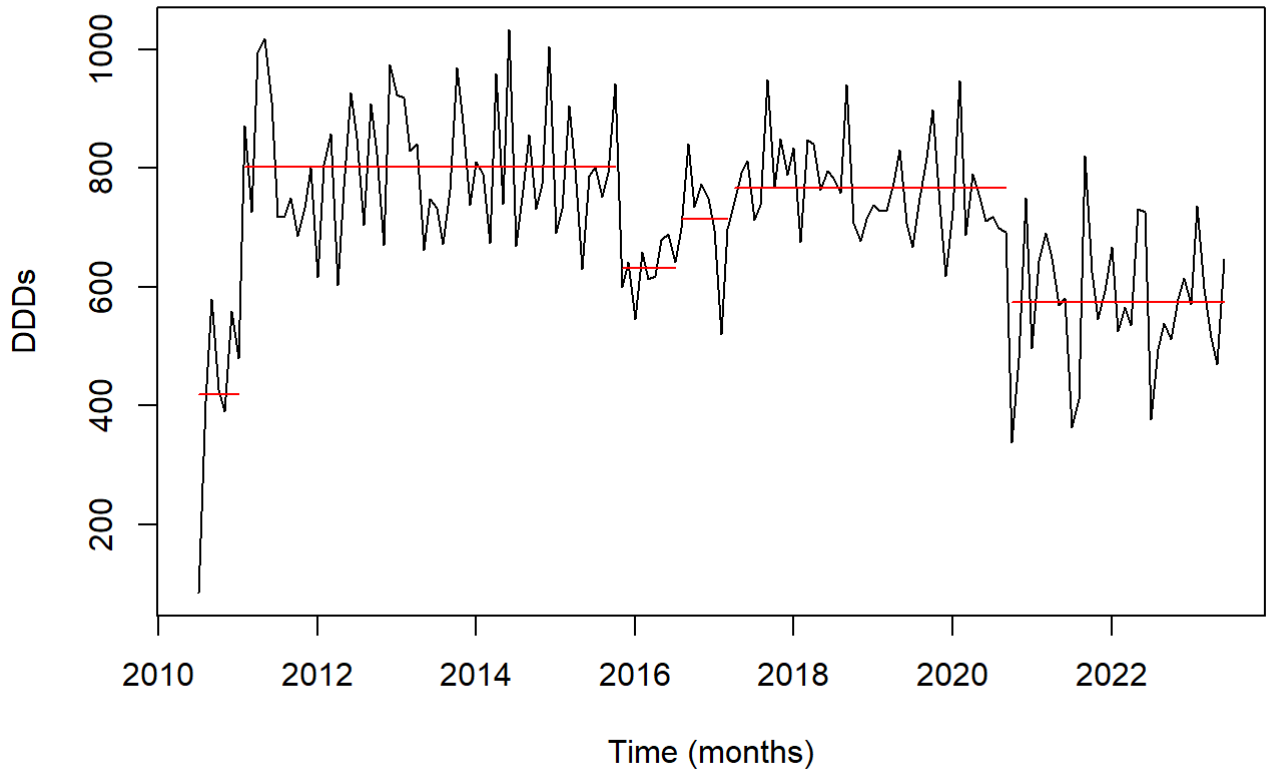
Carbapenems and piperacillin with tazobactam use has remained relatively constant through out the timeframe. There was an increase in piperacillin with tazobactam from March 2017 to February 2018 from 266.9 to 304.2 mean monthly DDDs.

Overall total - all groups combined



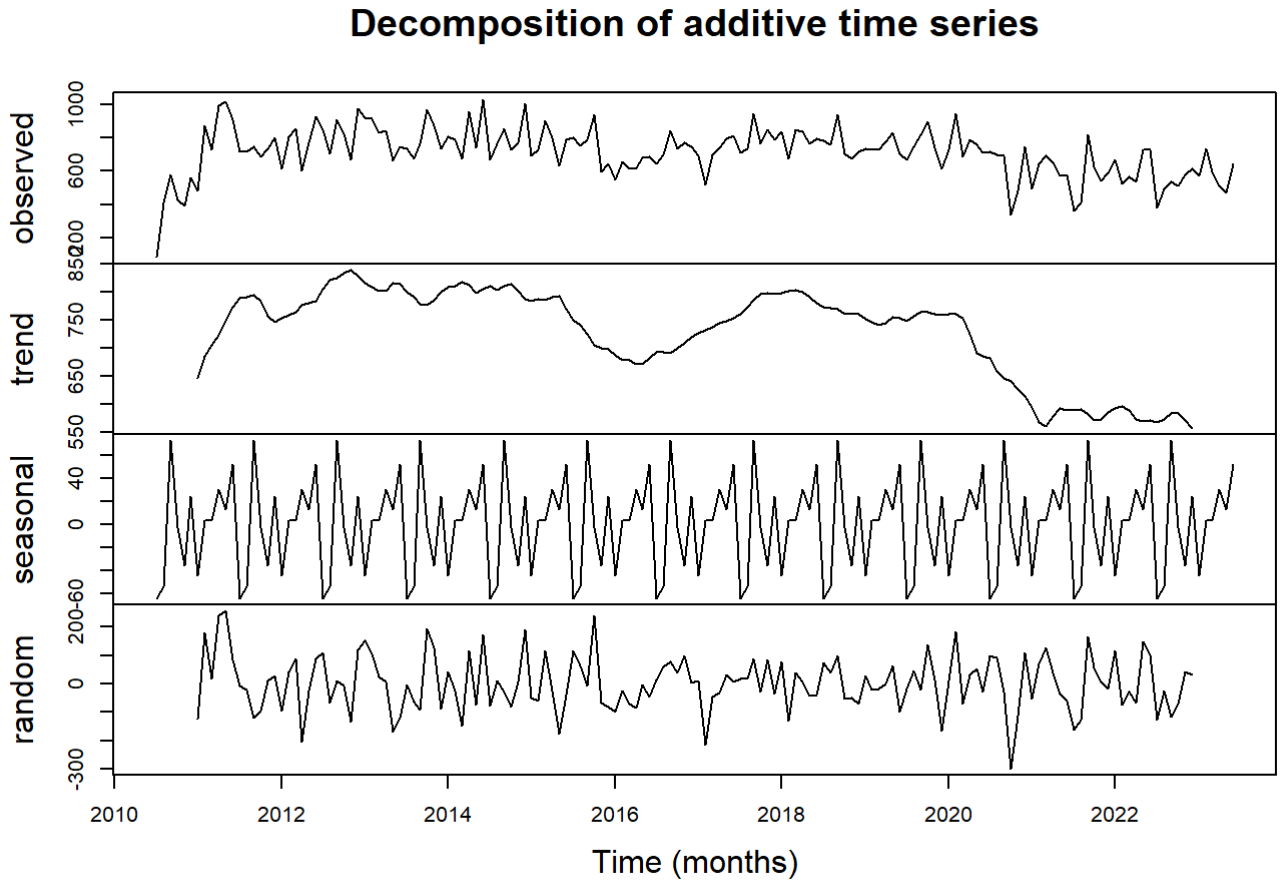
Change point analysis

```
## [1]   7  64  73  81 123
```



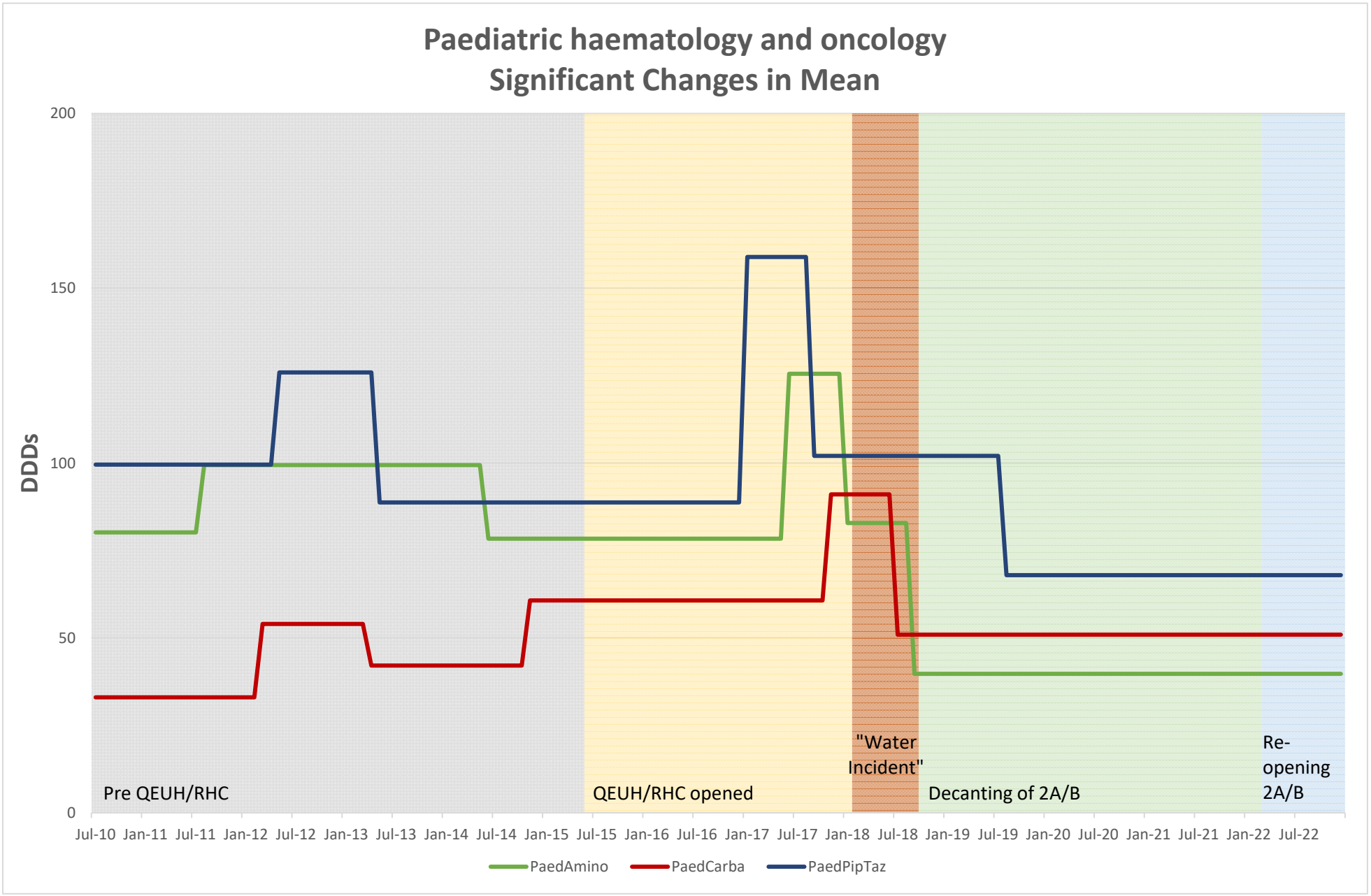

```
## $mean
## [1] 418.3257 802.4042 632.0667 713.6688 767.0095 574.6145
```

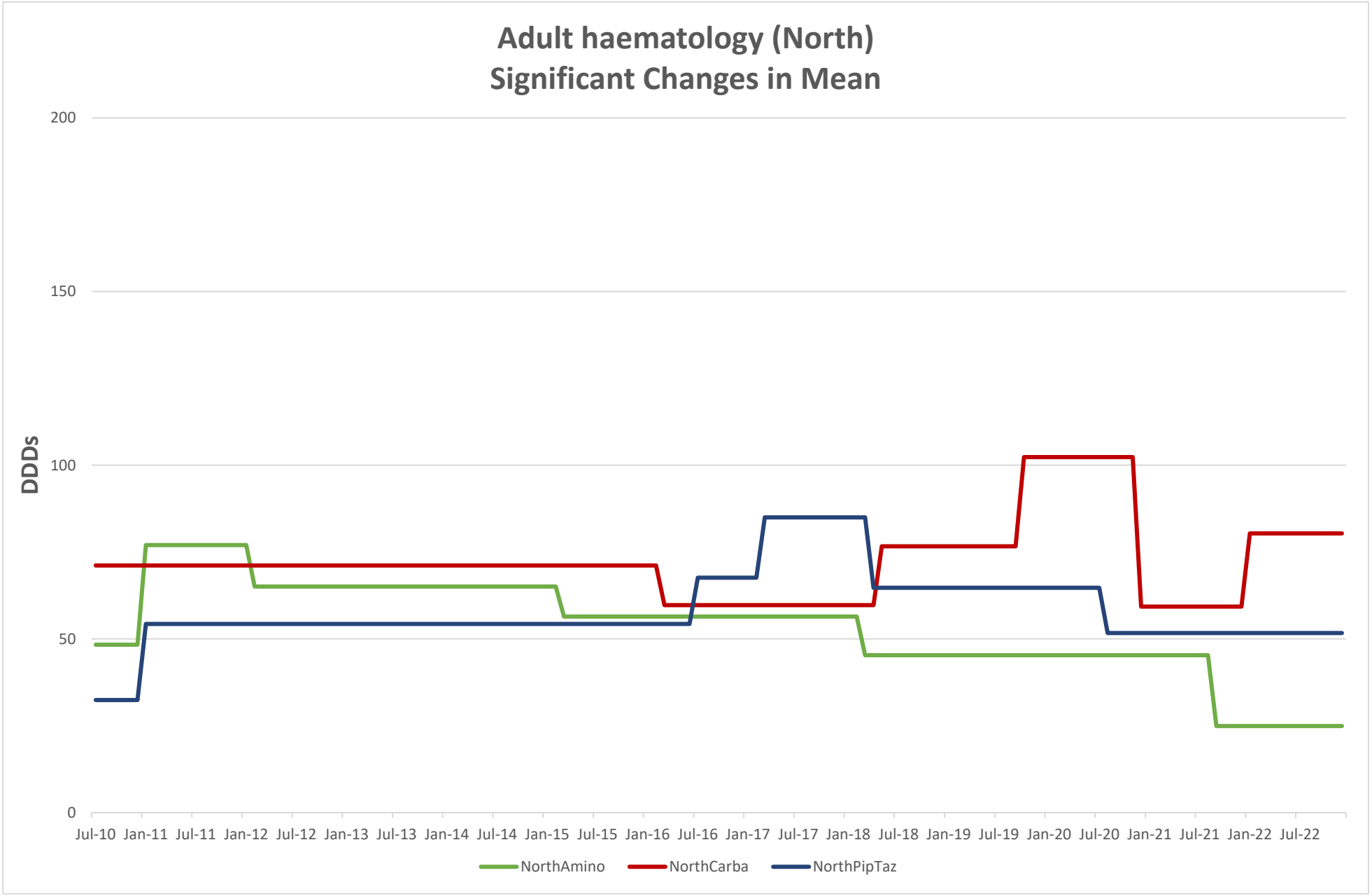
Decomposed into trend, seasonality, random component

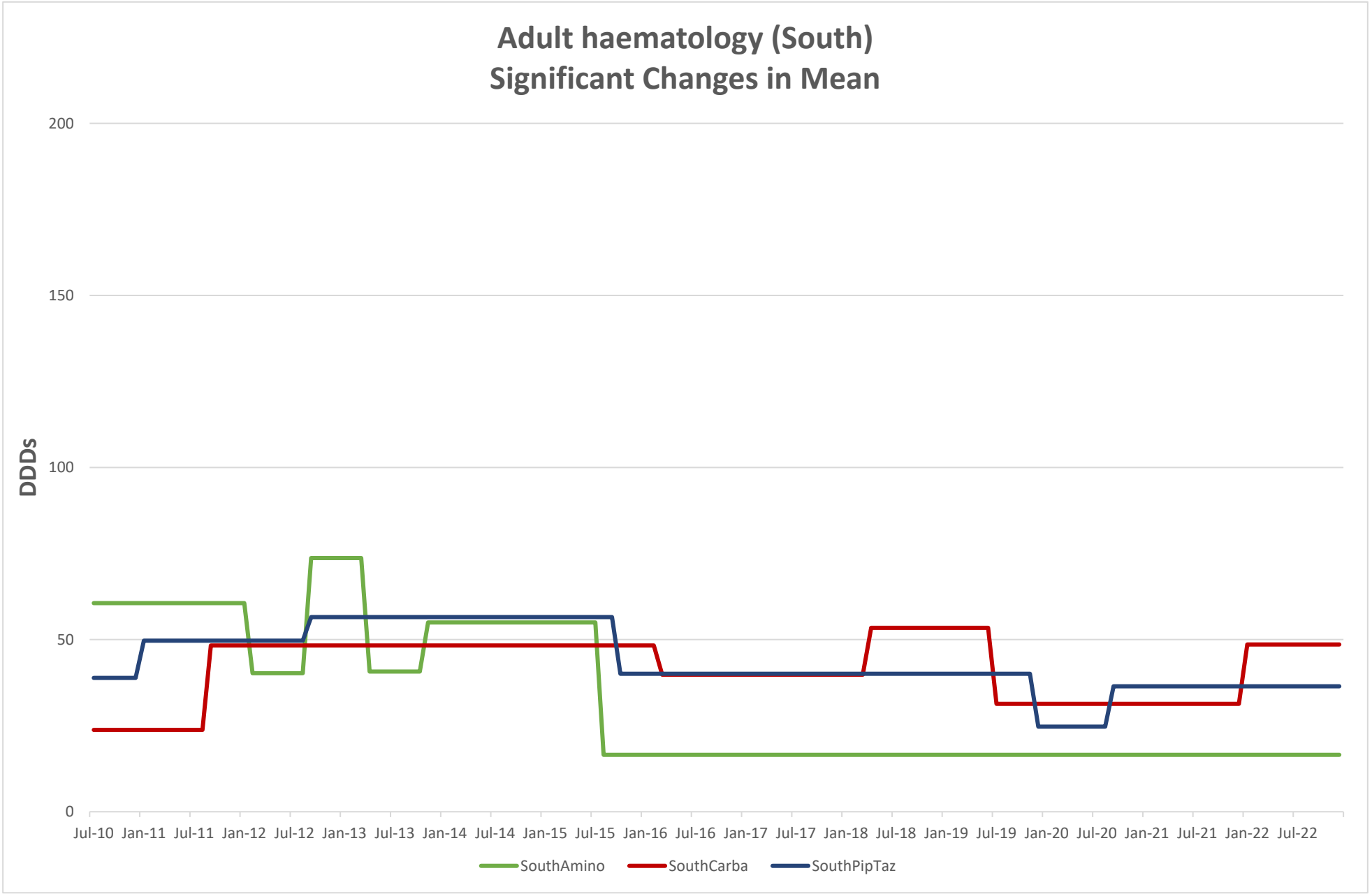


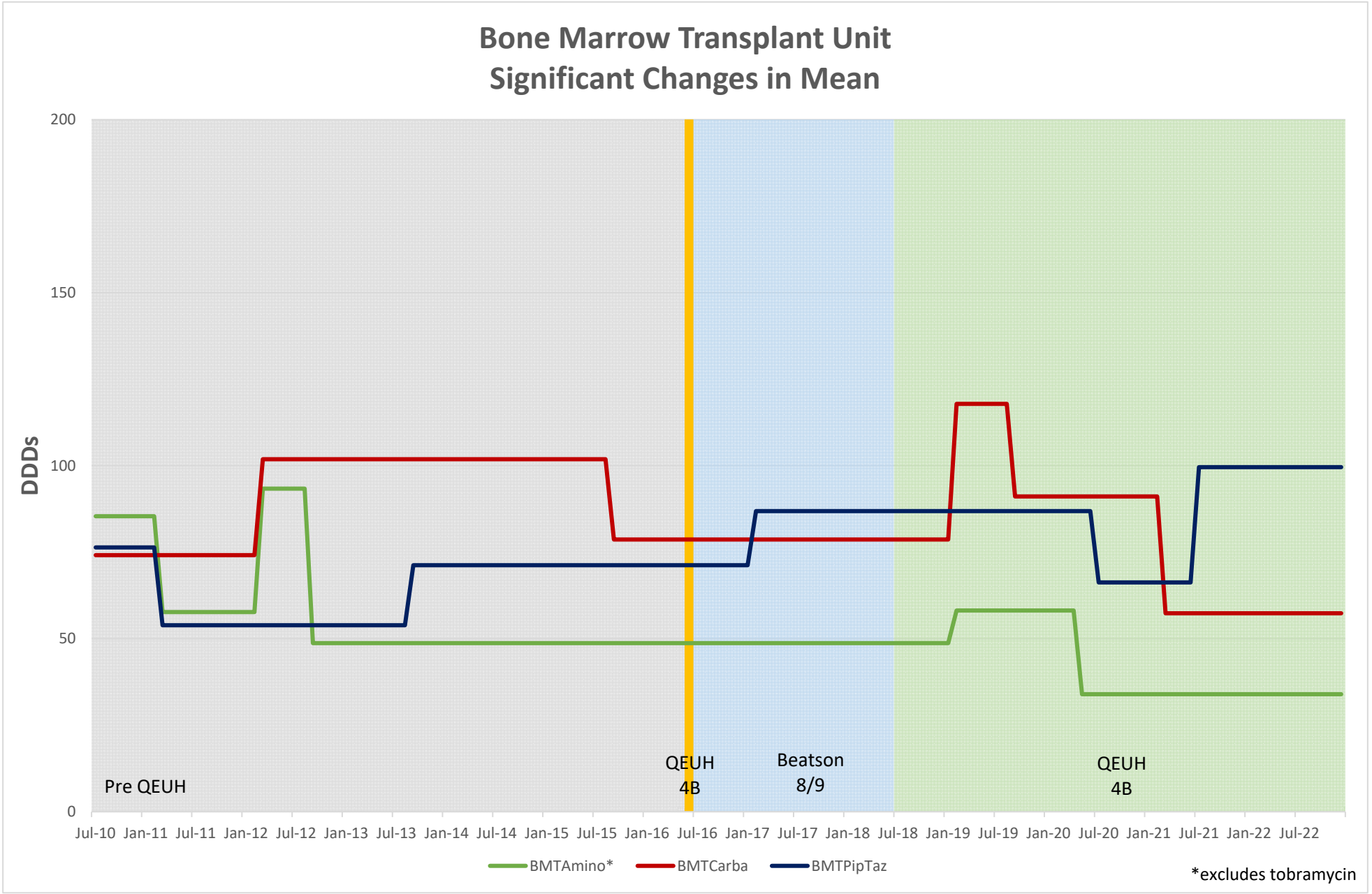
Summary - Overall total

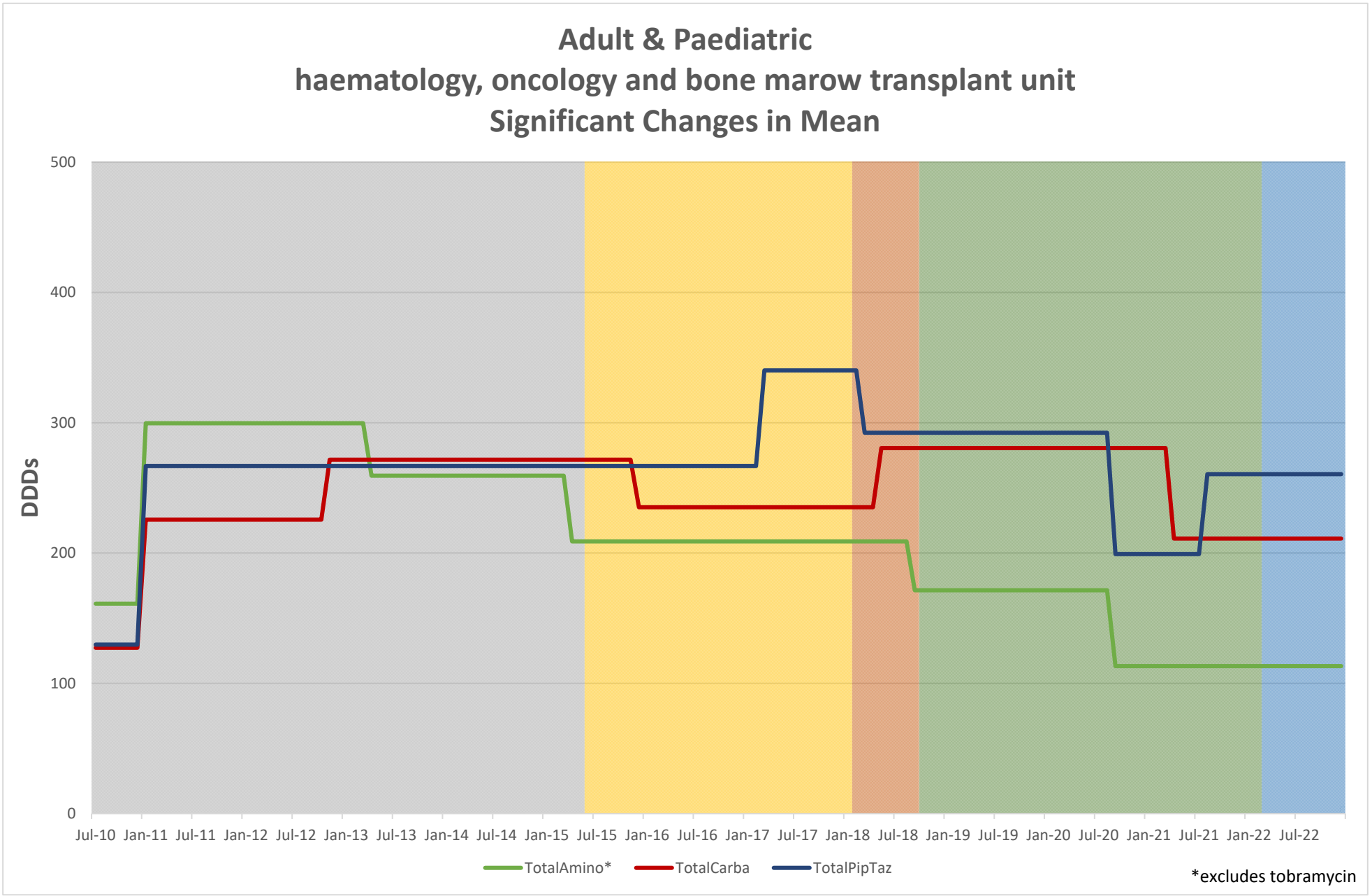
Overall use of the three classes of antibiotic for the selected wards was relatively constant between 2011 and 2016 with a decrease in 2016 and a return to similar levels of use in 2017. In 2020 there was a further decrease and this lower level of use has continued through into 2021 and 2022.

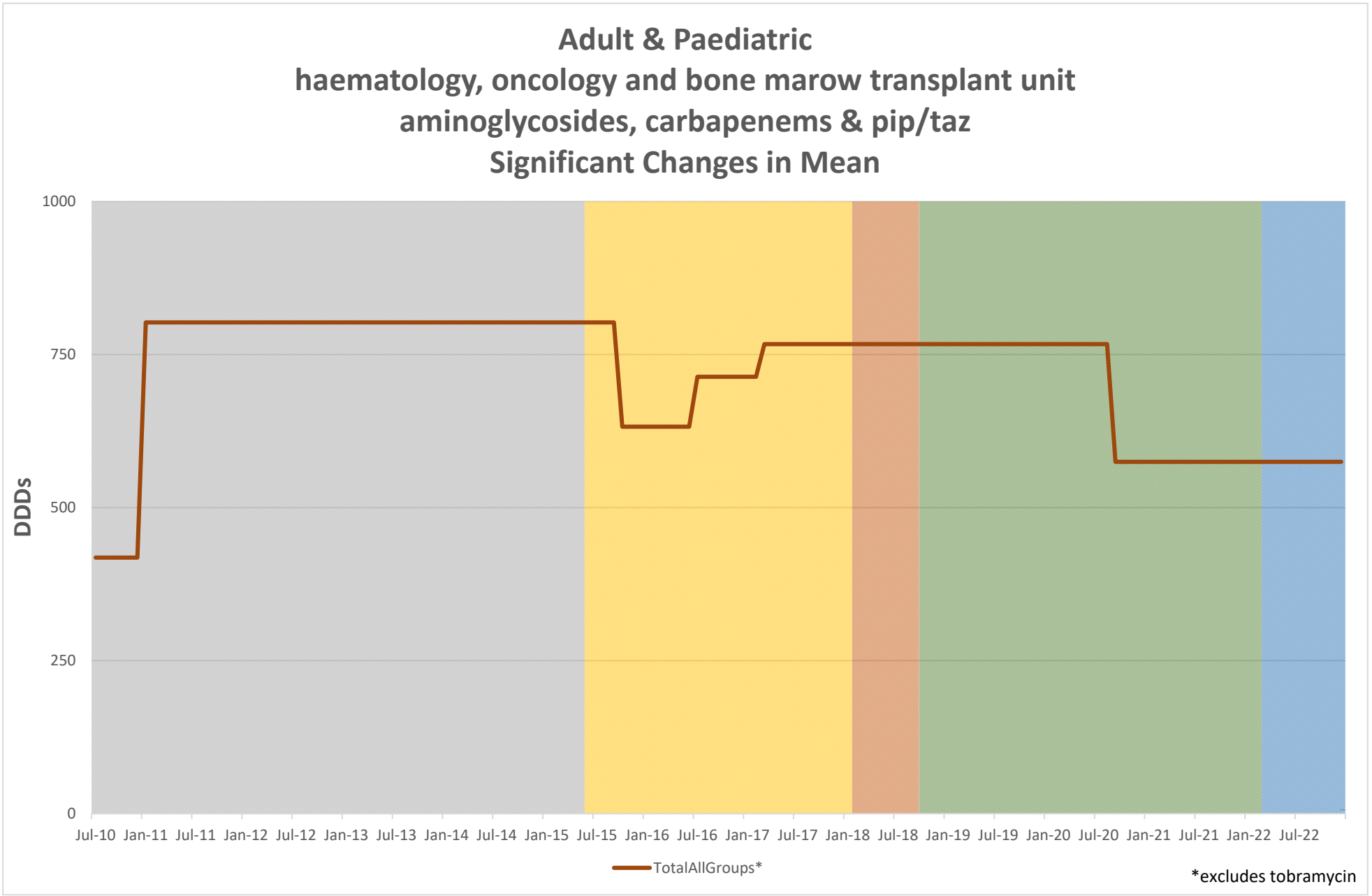

Paediatric haematology and oncology
Significant Changes in Mean
DDDs
200
150
100
50
0
Pre QEUH/RHC
QEUH/RHC opened
"Water Incident"
Decanting of 2A/B
Re-opening 2A/B
Jul-10 Jan-11 Jul-11 Jan-12 Jul-12 Jan-13 Jul-13 Jan-14 Jul-14 Jan-15 Jul-15 Jan-16 Jul-16 Jan-17 Jul-17 Jan-18 Jul-18 Jan-19 Jul-19 Jan-20 Jul-20 Jan-21 Jul-21 Jan-22 Jul-22
PaedAmino
PaedCarba
PaedPipTaz


Adult haematology (North)
Significant Changes in Mean
DDDs
200
150
100
50
0
Jul-10 Jan-11 Jul-11 Jan-12 Jul-12 Jan-13 Jul-13 Jan-14 Jul-14 Jan-15 Jul-15 Jan-16 Jul-16 Jan-17 Jul-17 Jan-18 Jul-18 Jan-19 Jul-19 Jan-20 Jul-20 Jan-21 Jul-21 Jan-22 Jul-22
NorthAmino
NorthCarba
NorthPipTaz


Adult haematology (South)
Significant Changes in Mean
DDDs
200
150
100
50
0
Jul-10
Jan-11
Jul-11
Jan-12
Jul-12
Jan-13
Jul-13
Jan-14
Jul-14
Jan-15
Jul-15
Jan-16
Jul-16
Jan-17
Jul-17
Jan-18
Jul-18
Jan-19
Jul-19
Jan-20
Jul-20
Jan-21
Jul-21
Jan-22
Jul-22
SouthAmino
SouthCarba
SouthPipTaz


Bone Marrow Transplant Unit
Significant Changes in Mean
DDDs
200
150
100
50
0
Pre QEUH
QEUH
4B
Beatson
8/9
QEUH
4B
Jul-10 Jan-11 Jul-11 Jan-12 Jul-12 Jan-13 Jul-13 Jan-14 Jul-14 Jan-15 Jul-15 Jan-16 Jul-16 Jan-17 Jul-17 Jan-18 Jul-18 Jan-19 Jul-19 Jan-20 Jul-20 Jan-21 Jul-21 Jan-22 Jul-22
BMTAmino*
BMTCarba
BMTPipTaz
*excludes tobramycin


Adult & Paediatric
haematology, oncology and bone marow transplant unit
Significant Changes in Mean
DDDs
500
400
300
200
100
0
Jul-10 Jan-11 Jul-11 Jan-12 Jul-12 Jan-13 Jul-13 Jan-14 Jul-14 Jan-15 Jul-15 Jan-16 Jul-16 Jan-17 Jul-17 Jan-18 Jul-18 Jan-19 Jul-19 Jan-20 Jul-20 Jan-21 Jul-21 Jan-22 Jul-22
TotalAmino*
TotalCarba
TotalPipTaz
*excludes tobramycin


Adult & Paediatric
haematology, oncology and bone marow transplant unit
aminoglycosides, carbapenems & pip/taz
Significant Changes in Mean
DDDs
1000
750
500
250
0
Jul-10 Jan-11 Jul-11 Jan-12 Jul-12 Jan-13 Jul-13 Jan-14 Jul-14 Jan-15 Jul-15 Jan-16 Jul-16 Jan-17 Jul-17 Jan-18 Jul-18 Jan-19 Jul-19 Jan-20 Jul-20 Jan-21 Jul-21 Jan-22 Jul-22
TotalAllGroups*
*excludes tobramycin

A52317814

Month	TimeSeries	Key Time	Pre-QEUH/RHC	QEUH/"Water Decant	Re-op BMT	P Move t	Move t	Move t	PaedAmino	PaedCarba	PaedPipTa	NorthAmino	NorthCarba	NorthPipTa	SouthAmino	SouthCarba	SouthPipTa	BMTAmino	BMTCarba	BMTPipTaz	TotalAmino	TotalCarba	TotalPipTaz	TotalAllGroups*
01/07/2010	1	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/08/2010	2	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/09/2010	3	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/10/2010	4	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/11/2010	5	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/12/2010	6	1	1000			1000			80.10714	33.00000	99.52795	48.33333	71.14493	32.40816	60.58500	23.77778	38.85714	85.38889	74.11905	76.34921	161.17140	127.37140	129.75710	418.32570
01/01/2011	7	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	85.38889	74.11905	76.34921	299.67280	225.63640	266.79050	802.40420
01/02/2011	8	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	85.38889	74.11905	76.34921	299.67280	225.63640	266.79050	802.40420
01/03/2011	9	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/04/2011	10	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/05/2011	11	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/06/2011	12	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/07/2011	13	1	1000			1000			80.10714	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/08/2011	14	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	23.77778	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/09/2011	15	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/10/2011	16	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/11/2011	17	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/12/2011	18	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/01/2012	19	1	1000			1000			99.43137	33.00000	99.52795	77.02564	71.14493	54.30303	60.58500	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/02/2012	20	1	1000			1000			99.43137	33.00000	99.52795	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	57.70000	74.11905	53.90476	299.67280	225.63640	266.79050	802.40420
01/03/2012	21	1	1000			1000			99.43137	53.97436	99.52795	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/04/2012	22	1	1000			1000			99.43137	53.97436	99.52795	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/05/2012	23	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/06/2012	24	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/07/2012	25	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/08/2012	26	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	40.22857	48.28395	49.67143	93.38333	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/09/2012	27	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/10/2012	28	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	225.63640	266.79050	802.40420
01/11/2012	29	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	271.69730	266.79050	802.40420
01/12/2012	30	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	271.69730	266.79050	802.40420
01/01/2013	31	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	271.69730	266.79050	802.40420
01/02/2013	32	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	271.69730	266.79050	802.40420
01/03/2013	33	1	1000			1000			99.43137	53.97436	125.86905	65.09009	71.14493	54.30303	73.70000	48.28395	56.57143	48.70000	101.85516	53.90476	299.67280	271.69730	266.79050	802.40420
01/04/2013	34	1	1000			1000			99.43137	42.03509	125.86905	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	53.90476	259.38890	271.69730	266.79050	802.40420
01/05/2013	35	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	53.90476	259.38890	271.69730	266.79050	802.40420
01/06/2013	36	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	53.90476	259.38890	271.69730	266.79050	802.40420
01/07/2013	37	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	53.90476	259.38890	271.69730	266.79050	802.40420
01/08/2013	38	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	53.90476	259.38890	271.69730	266.79050	802.40420
01/09/2013	39	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/10/2013	40	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	40.71429	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/11/2013	41	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/12/2013	42	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/01/2014	43	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/02/2014	44	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/03/2014	45	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/04/2014	46	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/05/2014	47	1	1000			1000			99.43137	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/06/2014	48	1	1000			1000			78.34722	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/07/2014	49	1	1000			1000			78.34722	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/08/2014	50	1	1000			1000			78.34722	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/09/2014	51	1	1000			1000			78.34722	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/10/2014	52	1	1000			1000			78.34722	42.03509	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/11/2014	53	1	1000			1000			78.34722	60.68519	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/12/2014	54	1	1000			1000			78.34722	60.68519	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/01/2015	55	1	1000			1000			78.34722	60.68519	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/02/2015	56	1	1000			1000			78.34722	60.68519	88.70130	65.09009	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/03/2015	57	1	1000			1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	259.38890	271.69730	266.79050	802.40420
01/04/2015	58	1	1000			1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	208.94310	271.69730	266.79050	802.40420
01/05/2015	59	1	1000			1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	208.94310	271.69730	266.79050	802.40420
01/06/2015	60	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	208.94310	271.69730	266.79050	802.40420
01/07/2015	61	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	54.96667	48.28395	56.57143	48.70000	101.85516	71.23345	208.94310	271.69730	266.79050	802.40420
01/08/2015	62	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	56.57143	48.70000	101.85516	71.23345	208.94310	271.69730	266.79050	802.40420
01/09/2015	63	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	56.57143	48.70000	78.66463	71.23345	208.94310	271.69730	266.79050	802.40420
01/10/2015	64	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	40.07286	48.70000	78.66463	71.23345	208.94310	271.69730	266.79050	632.06670
01/11/2015	65	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	40.07286	48.70000	78.66463	71.23345	208.94310	271.69730	266.79050	632.06670
01/12/2015	66	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/01/2016	67	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/02/2016	68	2		1000		1000			78.34722	60.68519	88.70130	56.43519	71.14493	54.30303	16.52234	48.28395	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/03/2016	69	2		1000		1000			78.34722	60.68519	88.70130	56.43519	59.71154	54.30303	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/04/2016	70	2		1000		1000			78.34722	60.68519	88.70130	56.43519	59.71154	54.30303	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/05/2016	71	2		1000		1000			78.34722	60.68519	88.70130	56.43519	59.71154	54.30303	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/06/2016	72	2		1000			1000		78.34722	60.68519	88.70130	56.43519	59.71154	54.30303	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	632.06670
01/07/2016	73	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/08/2016	74	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/09/2016	75	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/10/2016	76	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/11/2016	77	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/12/2016	78	2		1000				1000	78.34722	60.68519	88.70130	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/01/2017	79	2		1000				1000	78.34722	60.68519	158.94643	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	71.23345	208.94310	235.15860	266.79050	713.66880
01/02/2017	80	2		1000				1000	78.34722	60.68519	158.94643	56.43519	59.71154	67.63265	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	266.79050	713.66880
01/03/2017	81	2		1000				1000	78.34722	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/04/2017	82	2		1000				1000	78.34722	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/05/2017	83	2		1000				1000	78.34722	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/06/2017	84	2		1000				1000	125.54762	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/07/2017	85	2		1000				1000	125.54762	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/08/2017	86	2		1000				1000	125.54762	60.68519	158.94643	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/09/2017	87	2		1000				1000	125.54762	60.68519	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/10/2017	88	2		1000				1000	125.54762	60.68519	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/11/2017	89	2		1000				1000	125.54762	91.04167	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/12/2017	90	2		1000				1000	125.54762	91.04167	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/01/2018	91	2		1000				1000	82.81250	91.04167	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/02/2018	92	3			1000			1000	82.81250	91.04167	101.99379	56.43519	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	340.25000	767.00950
01/03/2018	93	3			1000			1000	82.81250	91.04167	101.99379	45.29365	59.71154	85.00000	16.52234	39.81333	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	292.37930	767.00950
01/04/2018	94	3			1000			1000	82.81250	91.04167	101.99379	45.29365	59.71154	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	208.94310	235.15860	292.37930	767.00950
01/05/2018	95	3			1000			1000	82.81250	91.04167	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	208.94310	280.67140	292.37930	767.00950
01/06/2018	96	3			1000			1000	82.81250	91.04167	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	208.94310	280.67140	292.37930	767.00950
01/07/2018	97	3			1000				82.81250	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	208.94310	280.67140	292.37930	767.00950
01/08/2018	98	3			1000			1000	82.81250	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	208.94310	280.67140	292.37930	767.00950
01/09/2018	99	3			1000			1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	171.45560	280.67140	292.37930	767.00950
01/10/2018	100	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	171.45560	280.67140	292.37930	767.00950
01/11/2018	101	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	171.45560	280.67140	292.37930	767.00950
01/12/2018	102	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	171.45560	280.67140	292.37930	767.00950
01/01/2019	103	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	48.70000	78.66463	86.85192	171.45560	280.67140	292.37930	767.00950
01/02/2019	104	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	58.14667	117.85714	86.85192	171.45560	280.67140	292.37930	767.00950
01/03/2019	105	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	58.14667	117.85714	86.85192	171.45560	280.67140	292.37930	767.00950
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01/06/2019	108	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667	64.71939	16.52234	53.44444	40.07286	58.14667	117.85714	86.85192	171.45560	280.67140	292.37930	767.00950
01/07/2019	109	4				1000		1000	39.70458	50.88050	101.99379	45.29365	76.66667

TITLE : ANTIBIOTIC PROPHYLAXIS POLICY for PATIENTS UNDERGOING CHEMOTHERAPY and/or RADIOTHERAPY

SOP No. BMT 100 005 02 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 19/03/2007
Authorised by:	Dr Anne Parker	Date: 30/04/2007
Authorised by: Quality Manager	Robert H Boyd	Date: 30/04/2007
Date of issue:	30/04/2007	
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Number of pages: (including this page)	6	

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1.0 INTRODUCTION

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~~It was agreed that these~~These recommendations ~~would~~will be reviewed annually in conjunction with data on the incidence of positive cultures and susceptibility for each of the sites.

2.0 PROPHYLAXIS of BACTERIAL INFECTION

2.1 ***CIPROFLOXACIN*** 500 mg bd orally

- If unable to tolerate oral drugs use: 200 mg bd iv~~)~~
- If allergic to ciprofloxacin use: ***cefixime 400mg od*** dependent on renal function

2.2 ***COLISTIN*** 1.5 MU tid orally ONLY

- N.B. It is NOT appropriate to use IV Colistin as prophylaxis

2.3 ***METRONIDAZOLE*** 400 mg TID orally

- If unable to tolerate po drugs 500 mg tid iv

2.4 To be used as follows:

~~8.~~ **Allograft Recipients**

CIPROFLOXACIN

~~METRONIDAZOLE~~

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

METRONIDAZOLE

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days

- **Autograft Recipients**

~~Gartnavel~~North ~~GRI, Stobhill~~South

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CIPROFLOXACIN CIPROFLOXACIN
~~COLISTIN~~

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **Acute Leukaemic Patients**

~~Gartnavel~~North	~~GRI, Stobhill~~South
CIPROFLOXACIN	CIPROFLOXACIN
COLISTIN	

Start - Once neutrophils< 1.0 x 10^9/l.

Stop - Neutrophils >0.5 x 10^9/l or on broad spectrum antibiotics.

~~9.~~ **Other Neutropenic Haematology ~~& Oncology~~ Patients**

CIPROFLOXACIN

Start - **ONLY** for the period when neutrophils < 0.5 x 10^9/l if likely to be more than 3-4 days.

Stop - Neutrophils >0.5 x 10^9/l.
Please see GCSF prophylaxis policy if associated with sepsis

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3.0 PROPHYLAXIS of PNEUMOCYSTIS (PCP):

PCP prophylaxis should be used in the following patient groups:

- ~~**HSCT auto and allografts**~~
- **Allografts**
  - Continue for minimum of 6 months post HSCT ~~or~~to continue until all immunosuppression discontinued~~, whichever is longer.~~ and CD4>0.4x10^9/l
  - Start first day of conditioning Septrin 960 mg daily and stop on day –1.
  - Restart after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.
- **Chronic GvHD on treatment**
- **HSCT autografts**
  - Continue for 6 months post HSCT
  - Start first day of conditioning Septrin 960 mg daily and stop on day –1.
  - Restart after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.

- **Acute Lymphoblastic Leukaemia** - As per UKALL ~~12~~XII and UKALL2003 trial protocol.
- **MabCampath treatment** – Until CD4 > 0.~~2~~4 x 10^9/l.
- **Purine analogue exposure, eg. Fludarabine, Cladribine** – Until CD4 > 0.~~2~~4 x 10^9/l.
- **High dose steroids (Methyl Pred)**
- **Consider if continuous prednisolone >20mg/ day and other risks**

It is NOT required routinely for the following groups unless they have had one of the agents mentioned above or it is part of a trial protocol, but maintain a high index of suspicion.

- **AML**
- **Lymphoma**

There are a number of different prophylactic agents available for PCP. The following are listed in order of efficacy and therefore preference. Some trials have different schedules please follow the trial protocol in these cases.

3.1 ***CO-TRIMOXAZOLE*** (Septrin) **960 mg od Mon, Wed, Fri**

NB – If also receiving ganciclovir, delay introducing Co-trimoxazole until completed ganciclovir course due to myelosuppression.

DAPSONE **100 mg od**

NB – Consider risk of G6PD deficiency. 40% cross over for intolerance with septrin. Can cause leucopenia.

PENTAMIDINE **300mg nebulised every 4 weeks**

NB – It is said not to penetrate the upper lobes and that there is a risk of 'lobar' PCP.

4.0 HYPOSPLENIC PROPHYLAXIS

4.1 ***Amoxil*** 500 mg od nocte

Clarithromycin 250mg bd (if penicillin allergic)

Start – In transplant recipients this should be on engraftment and on stopping ciprofloxacin

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4.1.1 **Allogeneic transplant recipients** – This should preferably be life long. They should be issued with the DoH leaflet and hyposplenic warning card.

4.1.2 **Autograft patients** – Should have ~~6~~12 months minimum and patients having TBI as part of their conditioning should have a minimum of 2 years, but this may be stopped earlier at the Consultants discretion.

4.1.3 For those patients unable to tolerate or unwilling to take prophylaxis, a 7 day supply of ***Amoxil 500mg tds*** should be provided.

5.0 PROPHYLAXIS for TOXOPLASMOSIS

This should be considered for all allogeneic transplants where patients and/or donors are Toxoplasma IgG positive (NB – This should be toxoplasma dye-test) and ONLY in CD34 selected autografts.

5.1 One of the following regimes should be used:

5.1.1	Cotrimoxazole	960 mg od
5.1.2	Dapsone	100 mg po od
5.1.3	Pyrimethamine	50 mg weekly
	Folinic acid	25 mg po weekly low risk

If receiving Cotrimoxazole/Dapsone as PCP prophylaxis, the above dose should be used. The critical period is 6 months post HSCT and the highest risk appears to be days 30-90.

6.0 LINE INSERTION

Prophylactic antibiotics can be used at the Consultants' discretion for Hickman line insertion, but should be used if recent proven coagulase negative staph infection.

6.1 ***Vancomycin*** ~~500 mg~~1g IV should be given immediately prior to insertion~~ and then a further 500 mg divided into 2 bags (one for each lumen) given 12 hours post~~.

6.2 ***Teicoplanin*** 400 mg IV should be given immediately prior to insertion.

Teicoplanin should ONLY be used in preference to Vancomycin in the following situations:

6.2.1 Out-patient use.

6.2.2 Fluid volume/infusion times an issue.

6.2.3 Patients with known renal failure i.e. creat cl <50 ml/min or doubling of creat since admission.

6.2.4 Patients already on 1 nephrotoxic drug (e.g. Cyclosporin A, Gentamicin, Amphotericin, etc).

7.0 AUDIT

Suggested topics include:

7.1 Adherence to protocol

7.2 Incidence of resistance to ciprofloxacin

7.3 Incidence of infection post line insertion

8.0 REFERENCES

8.1 Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients

8.2 Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : ANTIBIOTIC PROPHYLAXIS POLICY for PATIENTS UNDERGOING CHEMOTHERAPY and/or RADIOTHERAPY

SOP No. BMT 100 005 03 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 17/06/2010
Authorised by:	Dr Anne Parker	Date: 21/06/2010
Authorised by: Quality Manager	Robert H Boyd	Date: 21/06/2010
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1.0 INTRODUCTION

This protocol outlines the practice to be adopted for patients admitted to or attending ~~Wards 7a, 40, 41~~ Haemato-oncology patients within North and ~~42 and for neutropenic patients admitted elsewhere within North~~ South Glasgow Acute Services Division under the care of the haemato-oncology service. It is not intended as a substitute for appropriate discussion with microbiologists, pharmacists and senior colleagues.

~~It was agreed that these~~These recommendations ~~would~~will be reviewed annually in conjunction with data on the incidence of positive cultures and susceptibility for each of the sites.

2.0 PROPHYLAXIS of BACTERIAL INFECTION

2.1 ***CIPROFLOXACIN*** 500 mg bd orally

- If unable to tolerate oral drugs use: 200 mg bd iv~~)~~
- If allergic to ciprofloxacin use: ***cefixime 400mg od*** dependent on renal function

2.2 ***COLISTIN*** 1.5 MU tid orally ONLY

- N.B. It is NOT appropriate to use IV Colistin as prophylaxis

2.3 ***METRONIDAZOLE*** 400 mg TID orally

- If unable to tolerate po drugs 500 mg tid iv

2.4 To be used as follows:

~~8.~~ Allograft Recipients

CIPROFLOXACIN

~~METRONIDAZOLE~~

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

METRONIDAZOLE

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

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- **Autograft Recipients**

~~Gartnavel~~North	~~GRI, Stobhill~~South
CIPROFLOXACIN	CIPROFLOXACIN
~~COLISTIN~~	

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **Acute Leukaemic Patients**

~~Gartnavel~~North	~~GRI, Stobhill~~South
CIPROFLOXACIN	CIPROFLOXACIN
COLISTIN	

Start - Once neutrophils< 1.0 x 10^9/l.

Stop - Neutrophils >0.5 x 10^9/l or on broad spectrum antibiotics.

~~9.~~ **Other Neutropenic Haematology ~~& Oncology~~ Patients**

CIPROFLOXACIN

Start - **ONLY** for the period when neutrophils < 0.5 x 10^9/l if likely to be more than 3-4 days.

Stop - Neutrophils >0.5 x 10^9/l.
Please see GCSF prophylaxis policy if associated with sepsis

NB Ciprofloxacin is considered to promote a high risk of C.Diff – please consider risks when prescribing. If previous history of C Diff please consider using metronidazole for C Diff prophylaxis.

3.0 PROPHYLAXIS of PNEUMOCYSTIS (PCP):

PCP prophylaxis should be used in the following patient groups:

- ~~HSCT auto and allografts~~
- Allografts
  - Continue for minimum of 6 months post HSCT ~~or~~to continue until all immunosuppression discontinued~~, whichever is longer.~~ and CD4>0.4x10^9/l
  - Start first day of conditioning Septrin 960 mg bd and stop on day –1.

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- Restart after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.

- **Chronic GvHD on treatment**
- **HSCT autografts**
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  - Start after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.
- **Acute Lymphoblastic Leukaemia** - As per trial protocol or until maintenance completed.
- **Alemtuzumab treatment** – Until CD4 > 0.~~2~~4 x 10^9/l.
- **Purine analogue exposure, eg. Fludarabine, Cladribine** – Until CD4 > 0.~~2~~4 x 10^9/l.
- **High dose steroids (Methyl Pred)**
- **Consider if continuous prednisolone >20mg/ day and other risks**
- **Please see individual Chemotherapy management guidelines for requirement for PCP prophylaxis for Lymphoma and other diagnoses**

It is NOT required routinely for the following groups unless they have had one of the agents mentioned above or it is part of a trial protocol, but maintain a high index of suspicion.

There are a number of different prophylactic agents available for PCP. The following are listed in order of efficacy and therefore preference. Some trials have different schedules please follow the trial protocol in these cases.

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SOP Read and Understood By: (Print Name)	Staff Signature	Date

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A MINIMUM OF 2 YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

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SOP No. BMT 100 005 04 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 07/08/2012
Authorised by:	Dr Anne Parker	Date: 08/08/2012
Authorised by: Quality Manager	Robert H Boyd	Date: 08/08/2012
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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION

Line	Amendment	Date	Signature
2.4	Ciprofloxacin for neutropenia > 7 days	07/08/2012	ANP

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Comments:

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These recommendations will be reviewed annually in conjunction with data on the incidence of positive cultures and susceptibility for each of the sites.

2.0 PROPHYLAXIS of BACTERIAL INFECTION

2.1 ***CIPROFLOXACIN*** 500 mg bd orally

- If unable to tolerate oral drugs use: 200 mg bd iv
- If allergic to ciprofloxacin use: ***cefixime 400mg od*** dependent on renal function

2.2 ***COLISTIN*** 1.5 MU tid orally ONLY

- N.B. It is NOT appropriate to use IV Colistin as prophylaxis

2.3 ***METRONIDAZOLE*** 400 mg TID orally

- If unable to tolerate po drugs 500 mg tid iv

2.4 To be used as follows:

- **<u>Allograft Recipients</u>**

  CIPROFLOXACIN

  Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

  METRONIDAZOLE

  Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days

- **Autograft Recipients**

North	South
CIPROFLOXACIN	CIPROFLOXACIN

Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **Acute Leukaemic Patients**

North	South
CIPROFLOXACIN	CIPROFLOXACIN
COLISTIN	

Start - Once neutrophils< 1.0 x 10^9/l.

Stop - Neutrophils >0.5 x 10^9/l or on broad spectrum antibiotics.

- **Other Neutropenic Haematology Patients**

CIPROFLOXACIN

Start - **ONLY** for the period when neutrophils < 0.5 x 10^9/l if likely to be more than 7 days.

Stop - Neutrophils >0.5 x 10^9/l.
Please see GCSF prophylaxis policy if associated with sepsis

NB Ciprofloxacin is considered to promote a high risk of C.Diff – please consider risks when prescribing. If previous history of C Diff please consider using metronidazole for C Diff prophylaxis.

3.0 PROPHYLAXIS of PNEUMOCYSTIS (PCP):

PCP prophylaxis should be used in the following patient groups:

- **Allografts**
  - Continue for minimum of 6 months post HSCT, to continue until all immunosuppression discontinued and CD4>0.4x10^9/l
  - Start first day of conditioning Septrin 960 mg bd and stop on day –1.
  - Restart after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.

- **Chronic GvHD on treatment**
- **HSCT autografts**
  - Continue for 6 months post HSCT
  - Start after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.
- **Acute Lymphoblastic Leukaemia** - As per trial protocol or until maintenance completed.
- **Alemtuzumab treatment** – Until at least 6 months post therapy, ideally until CD4 > 0.4 x 10^9/l.
- **Purine analogue exposure, eg. Fludarabine, Cladribine** – Until at least 6 months post therapy, ideally until CD4 > 0.4 x 10^9/l.
- **High dose steroids (Methyl Pred) –** until end of therapy
- **Consider if continuous prednisolone >20mg/ day and other risks**
- **Please see individual Chemotherapy management guidelines for requirement for PCP prophylaxis for Lymphoma and other diagnoses**

It is NOT required routinely for the other groups unless they have had one of the agents mentioned above or it is part of a trial protocol, but maintain a high index of suspicion.

There are a number of different prophylactic agents available for PCP. The following are listed in order of efficacy and therefore preference. Some trials have different schedules please follow the trial protocol in these cases.

3.1 ***CO-TRIMOXAZOLE*** (Septrin) **960 mg od Mon, Wed, Fri**

NB – If also receiving ganciclovir, delay introducing Co-trimoxazole until completed ganciclovir course due to myelosuppression.

DAPSONE **100 mg od**

NB – Consider risk of G6PD deficiency. 40% cross over for intolerance with septrin. Can cause leucopenia.

PENTAMIDINE **300mg nebulised every 4 weeks**

NB – It is said not to penetrate the upper lobes and that there is a risk of 'lobar' PCP.

4.0 HYPOSPLENIC PROPHYLAXIS

4.1 ***Amoxicillin*** 500 mg od nocte

Clarithromycin 250mg bd (if penicillin allergic)

Start – In transplant recipients this should be on engraftment once ciprofloxacin stopped

4.1.1 **Allogeneic transplant recipients** – This should preferably be life long. They should be issued with the DoH leaflet and hyposplenic warning card.

4.1.2 **Autograft patients** – Should have 12 months minimum and patients having TBI as part of their conditioning should have a minimum of 2 years, but this may be stopped earlier at the Consultants discretion.

4.1.3 For those patients unable to tolerate or unwilling to take prophylaxis, a 7 day supply of ***Amoxicillin 500mg tds*** should be provided.

5.0 PROPHYLAXIS for TOXOPLASMOSIS

This should be considered for all allogeneic transplants where patients and/or donors are Toxoplasma IgG positive (NB – This should be toxoplasma dye-test) and ONLY in CD34 selected autografts.

5.1 One of the following regimes should be used:

5.1.1	Cotrimoxazole	960 mg od
5.1.2	Dapsone	100 mg po od
5.1.3	Pyrimethamine	50 mg weekly
	Folinic acid	25 mg po weekly low risk

If receiving Cotrimoxazole/Dapsone as PCP prophylaxis, the above dose should be used. The critical period is 6 months post HSCT and the highest risk appears to be days 30-90.

6.0 LINE INSERTION

Prophylactic antibiotics should not be used routinely, but can be used at the Consultants' discretion for Hickman line insertion, **<u>They should</u> be used if recent proven staphylococcal infection.**

6.1	***Vancomycin***	1g IV should be given immediately prior to insertion.
6.2	***Teicoplanin***	400 mg IV should be given immediately prior to insertion.

Teicoplanin should be used in preference to Vancomycin in the following situations:

6.2.1 Out-patient use.

6.2.2 Fluid volume/infusion times an issue.

6.2.3 Patients with known renal failure i.e. creat cl <50 ml/min or doubling of creat since admission.

6.2.4 Patients already on 1 nephrotoxic drug (e.g. Cyclosporin A, Gentamicin, Amphotericin, etc).

7.0 AUDIT

Suggested topics include:

7.1 Adherence to protocol

7.2 Incidence of resistance to ciprofloxacin

7.3 Incidence of infection post line insertion

8.0 REFERENCES

8.1 Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients

8.2 Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation, **http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm**

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT A MINIMUM OF 2 YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : ANTIBIOTIC PROPHYLAXIS POLICY for PATIENTS UNDERGOING CHEMOTHERAPY and/or RADIOTHERAPY

SOP No. BMT 100 005 05 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 15/12/2018
Authorised by:	Dr Anne Parker	Date: 27/12/2018
Authorised by: Quality Manager	Robert H Boyd	Date: 08/01/2019
Date of issue:	08/01/2019	
Effective date:	08/01/2019	
Review:	Every 2 Years	
Number of pages: (including this page)	5	

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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
2.1	delete cefixime prophyalxis	15/12/18	ANP
2.3	Delete colistin and metronidazole prophylaxis	15/12/18	ANP
3.0	Change CD4 level to 0.3	15/12/18	ANP
5.1	Add atovaquone	15/12/18	ANP

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Comments:

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2.1 ***CIPROFLOXACIN*** 500 mg bd orally

- If unable to tolerate oral drugs use: 200 mg bd iv

2.3 To be used as follows:

- **<u>Allograft Recipients</u>**

  CIPROFLOXACIN

  Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **<u>Autograft Recipients</u>**

  CIPROFLOXACIN

  Start - At the onset of conditioning chemo +/- radiotherapy to allow alteration of gut flora before neutropenia / mucosal damage.

  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **<u>Acute Leukaemic Patients</u>**

  Start - Once neutrophils< 1.0 x 10^9/l.

  Stop - Neutrophils >0.5 x 10^9/l or on broad spectrum antibiotics.

- **<u>Other Neutropenic Haematology Patients</u>**

  CIPROFLOXACIN

Start - **ONLY** for the period when neutrophils < 0.5 x 10^9/l if likely to be more than 7 days.

Stop - Neutrophils >0.5 x 10^9/l.
Please see GCSF prophylaxis policy if associated with sepsis

NB Ciprofloxacin is considered to promote a high risk of C.Diff – please consider risks when prescribing. If previous history of C Diff please consider using metronidazole for C Diff prophylaxis.

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PCP prophylaxis should be used in the following patient groups:

- **Allografts**
  - Continue for minimum of 6 months post HSCT, to continue until all immunosuppression discontinued and CD4>0.3x10^9/l
  - Start first day of conditioning Septrin 960 mg bd and stop on day –1.
  - Restart after day +28 at 960 mg od Mon, Wed, Fri once peripheral blood neutrophils >1.0 x 10^9/L and off platelet transfusions with platelet count >50 x 10^9/l.
- **Chronic GvHD on treatment**
- **HSCT autografts**
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DAPSONE **100 mg od**

NB – Consider risk of G6PD deficiency. 40% cross over for intolerance with septrin. Can cause leucopenia.

PENTAMIDINE **300mg nebulised every 4 weeks**
NB – It is said not to penetrate the upper lobes and that there is a risk of 'lobar' PCP.
ATOVAQUONE **750mg bd**
Should be taken with food, may not be absorbed if diarrhoea

4.0 HYPOSPLENIC PROPHYLAXIS

4.1 ***Amoxicillin*** 500 mg od nocte

Clarithromycin 250mg bd (if penicillin allergic)

Start – In transplant recipients this should be on engraftment once ciprofloxacin stopped

4.1.1 **Allogeneic transplant recipients** – This should preferably be life long. They should be issued with the DoH leaflet and hyposplenic warning card.

4.1.2 **Autograft patients** – Should have 12 months minimum and patients having TBI as part of their conditioning should have a minimum of 2 years, but this may be stopped earlier at the Consultants discretion.

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5.1.1	Cotrimoxazole	960 mg od
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5.1.3	Pyrimethamine Folinic acid	50 mg weekly 25 mg po weekly low risk
5.1.4	Atovaquone	750mg bd

If receiving Cotrimoxazole/Dapsone as PCP prophylaxis, the above dose should be used. The critical period is 6 months post HSCT and the highest risk appears to be days 30-90.

6.0 LINE INSERTION

Prophylactic antibiotics should not be used routinely, but can be used at the Consultants' discretion for Hickman line insertion, **They should be used if recent proven staphylococcal infection.**

6.1 ***Vancomycin*** 1g IV should be given immediately prior to insertion.

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Teicoplanin should be used in preference to Vancomycin in the following situations:

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AMENDMENTS FROM PREVIOUS VERSION
Implementation of 2 change requests against version 5 New SOP template

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  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **Autograft Recipients**

  CIPROFLOXACIN

  Start - On day 0 prior to stem cell re-infusion.

  Stop - Stable engraftment, i.e. neutrophils >0.5 x 10^9/l for 3 days or on broad spectrum antibiotics.

- **Acute Leukaemic Patients**

Start - Once neutrophils< 1.0 x 10^9/l.

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6.2.2 Fluid volume/infusion times an issue.

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Suggested topics include:

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7.2 Incidence of resistance to ciprofloxacin

7.3 Incidence of infection post line insertion

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TITLE : ANTIBIOTIC TREATMENT POLICY
SOP No. BMT 100 006 01 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 2713/0119/2007
Authorised by:	Dr Anne Parker	Date: 28/11/2007
Authorised by: Quality Manager	Robert H Boyd	Date: 28/11/2007
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Review:	Annually	
Number of pages: (including this page)	132	

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POLICY FOR ANTI-INFECTIVE USE IN IMMUNOCOMPROMISED PATIENTS

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically and frequently no causative organism can be found. The possibility of infection with opportunistic organisms such as PCP and reactivation of previous infections e.g. CMV, VZV should always be considered. Other infections such as a cold can cause pneumonitis and death in the post allograft setting All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.

This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to or attending Haemato-oncology services in Greater Glasgow. It is not intended as a substitute for appropriate discussion with microbiologists, pharmacists and senior colleagues.

Patients should be assessed in accordance with the 'Assessment of Infection in the Immunocompromised Patient'.

Antifungal therapy should be instituted as in 'Antifungal Prophylaxis and Therapy Guideline'

Antiviral therapy should be instituted as in 'Antiviral Use in Immunocompromised Patients'

The following should be used for patients who have:

- Neutrophils <1.0 x10^9/l
- Post Allograft
- Clinically Septic even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy

Patients who are low risk for overwhelming gram negative infection should be given the most appropriate antibiotic for their symptoms (e.g. Cefotaxime, Augmentin etc.), but consider switching to the following if slow to respond or clinically indicated.

2.0 TREATMENT of PYREXIA

2.1 FIRST LINE ANTIBIOTICS

If screening specimens have shown a resistant organism the following should be adoapted to provide adequate cover.

2.1.1 ***Tazocin*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose if creatinine clearance decreasing.

Penicillin allergy should be discussed with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.

For example:

- In cases of mild Penicillin allergy (e.g. possible rash), use Meropenem instead.
- In cases of proven Penicillin allergy use Ceftazidime.
- In cases of proven Penicillin, Carbopenem and Cephalosporin allergy, use Ciprofloxacin 400 mg bd IV and Amikacin.

2.1.2 ***Gentamicin***

The dose and frequency should be based on the creatinine clearance (see attached chart) and levels must be checked regularly.

If creatinine clearance <20 ml/min give single dose of 2.5 mg/kg. Check clearance by levels every 12 hours until below trough levels and then repeat dose.

The dose of drug and time given should be recorded on the chart (see attached sample) to ensure correct timing of samples for levels.

2.1.3 ***Vancomycin/Teicoplanin***

This should be added initially ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use (see gram positive section for dose & which drug).

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

NB – If Hickman line colonisation is suspected, this should be removed - after discussion with consultant in charge.

CONTINUE *Tazocin & Gentamicin (if clinically improving and/or temperature resolving [NB – This does not mean the patient has to be apyrexial])*

ONLY after a MINIMUM of 48 hours of therapy AND if no improvement clinically OR improvement in temperature pattern:

STOP *Tazocin* AND *Gentamicin*
START *MEROPENEM* 1g tds

If renal function deteriorates dose should be adjusted accordingly.

2.2 GRAM POSITIVE COVER

This should NOT be added automatically at 48 hours and MUST be discussed with the attending Consultant.

It can be considered if persistent pyrexia, but patient remains stable and if not already receiving gram positive cover add:

2.2.3 VANCOMYCIN (use calculated creatinine clearance and chart to determine dose)

If the patient has a dual lumen line divide into 2 and add each to 100mls of N/saline. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough and peak) and dose adjusted accordingly.

A52317814

2.2.4 TEICOPLANIN

400 mgs IV 12 hourly for 3 doses then daily thereafter.

NB – If Patient is >85 kg, use dose/kg

The full dose of teicoplanin is 6 mg/kg rounded off to nearest 200 mg, so in larger patients consider 600 or 800 mg/day if not responding. The dose should be split into 2 bags or 2 bolus injections.

NB – Teicoplanin is also nephrotoxic. Its dose should be adjusted according to the creatinine clearance (see attached sheet). Levels may be considered in this situation.

Teicoplanin should ONLY be used in preference to Vancomycin in the following situations:

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- Outpatient use.
- Fluid volume/infusion times an issue.
- Patients with known renal failure i.e. creatinine clearance <50 ml/min or doubling of creatinine since admission.
- Patients already on 1 nephrotoxic drug, (e.g. Cyclosporin A, Gentamicin, Amphotericin, etc).

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days. Because of the rise in organisms such as vancomycin-resistant enterococcus (VRE), many authorities now suggest that empiric vancomycin or teicoplanin should be avoided (i.e. not used unless there is some reason to suspect a line-associated or other Gram-positive bacterial infection), as coagulase-negative staphylococci are easy to detect by blood culture, and are rarely life threatening. However DO NOT FORGET that, though unusual, staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

2.3 STOP IV ANTIBIOTICS WHEN

1. Neut > 0.5 x 10^9/l patient is well and apyrexial for 3 days
2. Neut < 0.5 x 10^9/l patient is well and apyrexial for 5 days. Restart oral ciprofloxacin.

Gentamicin should ONLY ~~to~~ be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

2.4 IF TEMPERATURE REMAINS UNRESPONSIVE & NEUT <0.5 X 10^9/L

2.4.1 GROWTH FACTOR

G-CSF	1 vial/day s.c. (Lenograstim 263mcg/vial or Neupogen 300mcg/vial) ONLY if authorised by consultant in charge. NB 2 vials should be considered if patient >80 kg.

At any stage the following should be considered:

2.4.2 CLARITHROMYCIN IV

If suspicion of legionella or other atypical pneumonia.

2.4.3 ACICLOVIR IV

If suspicion of disseminated herpes simplex or zoster infection.

2.4.4 CO-TRIMOXAZOLE IV

If suspicion of pneumocystis.

2.4.5 METRONIDAZOLE IV

If persistent diarrhoea >24 hours while awaiting culture results.

2.4.6 GANCICLOVIR IV

If in at risk group for CMV reactivation.

2.5 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)
It should be remembered that hypothermia can denote severe infection.

If severe sepsis and ONLY after discussion with the attending Consultant the following can be substituted for gentamicin

Amikacin 7.5mg/kg bd (if renal function normal)

Please check amikacin peak and trough levels after third dose if renal function normal. Discuss with pharmacy re: interval between doses if renal function deteriorates. There is less resistance to Amikacin, partly due to less usage, and it should therefore only be used in this group of patients or on the advice of microbiology due to the presence of resistant organisms

3.0 PNEUMOCYSTIS CARINII PNEUMONIA (PCP)

Proven or suspected PCP

3.1 FIRST LINE THERAPY

START *CO-TRIMOXAZOLE (High Dose)*. 60 mg/kg iv ~~bd~~in 2-4 divided doses

Septrin contains sulphamethoxazole : trimethoprim 5:1

DURATION 2/52 minimum

Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 µg/ml.

The doses should be modified if renal impairment (see attached chart).

Consider giving folic acid supplements.

3.2 SECOND LINE THERAPY

IV PENTAMIDINE

4.0 TOXOPLASMOSIS

This must be discussed with consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

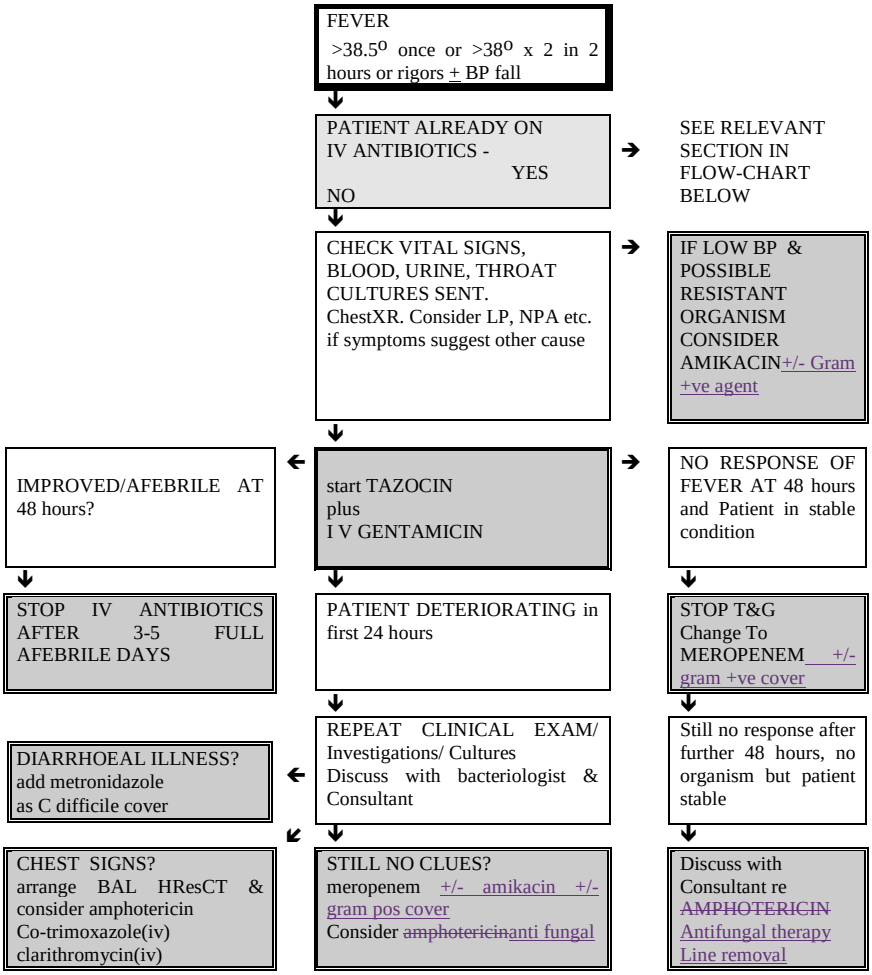
Then for the next 2-4 weeks minimum/until immunosuppression resolved

	PYRIMETHAMINE	0.5 mg/kg po bd
	SULPHADIAZINE	30 mg/kg po bd
	~~*FOLINIC ACID*~~*CALCIUM FOLINATE*	15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.

Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response.

5.0 ANTIBIOTICS IN THE MANAGEMENT OF FEVER



Gram positive cover with *Vancomycin/Teicoplanin* should be added at any time if positive cultures or other evidence of line related infection.

6.0 DRUG DOSE REDUCTION IN RENAL IMPAIRMENT

Renal disease may affect drug handling in several ways. Reduced glomerular filtration, altered tubular secretion or reabsorption and changes in renal and non-renal metabolism may have consequences for drug dosing. Individualisation of therapy based on pharmacokinetic principles will reduce the potential for toxic concentrations and optimise patient outcomes by providing efficacious yet safe plasma/serum drug concentrations.

6.1 ASSESSMENT OF RENAL FUNCTION

Glomerular filtration rate (GFR) is an assessment of the kidney's ability to excrete waste products of metabolism. Accurate estimation of GFR is essential for dose adjustments. In practice this is done by determining the creatinine clearance. Creatinine is almost exclusively excreted by the kidney. The Cockcroft-Gault equation (*Nephron 1976 15:31-41*) is commonly used to estimate creatinine clearance (CrCl) but has the following limitations.

- It assumes creatinine concentration is at a steady state and is not valid if the creatinine is changing
- It assumes normal creatinine production which is not seen in the malnourished, the elderly, hepatic disease and in patients with amputations or muscular disease.

~~The following dose reductions are from the 1998-1999 product data sheets. This list will be updated annually and as new data sheets are distributed. However, the prescriber must ensure that the most current information is used to make the decision on dosing schedules.~~. The following information is taken from the current SPCs (Summary of Product Characteristics (www.emc.medicines.org.uk) accessed October 2007. Where specialist advice is recommended a dose schedule is not included.

DRUG	DOSE SCHEDULE
Aciclovir	Oral prophylaxis - CrCl < 10ml/min give 200mg every 12 hours IV therapy - Cr Cl 25-50ml/min give dose every 12 hours Cr Cl 10-25 ml/min give dose every 24 hours
Amikacin	~~Discuss with Pharmacy~~Check current edition of GG&C Prescribing Guidance for Doctors
Ciprofloxacin	Oral & IV - CrCl < 20 ml/min or creatinine > 265 mol/l – give half the total daily dose
Clarithromycin	Creatinine clearance <30 ml/min 250 mg once or twice daily
Cotrimoxazole (Septrin)	Tablets - CrCl > 30 ml/min give normal dose CrCl 15 - 30 ml/min give half normal dose CrCl < 15 ml/min not recommended High Dose IV discuss with pharmacy
Gentamicin	See attached table
Meropenem	CrCl 26 - 50 ml/min give every 12 hours CrCl 10 - 25 ml/min give half normal dose every 12 hours CrCl < 10 ml/min give half normal dose every 24 hours
Metronidazole	No dose adjustment
Tazocin	Creatinine Cl > 80ml/min 4.5g qid Creatinine Cl 20 – 80 ml/min 4.5g tid Creatinine ~~e~~Cl <20 ml/min 4.5 g bd
Teicoplanin	Day 1-3 give usual dose From day 4 – CrCl 40 - 60 ml/min give dose every 48 hrs CrCl <40 ml/min give dose every 72 hrs
Vancomycin	See attached table

7.0 APPENDIX 1

VANCOMYCIN

1. Calculate creatinine clearance if it is not known. (Use ideal body weight if the patient is obese). If the creatinine concentration is <60 µmol/l, use 60 µmol/l.
2. Determine the starting dose from the table.
3. If creatinine clearance is less than 20 ml/min, give 1000 mg then take a sample after 24 hours.
4. Vancomycin should be administered by infusion at a concentration less than 5 mg/ml and at a rate NOT GREATER THAN 10 mg/min (i.e.1000 mg over 100-120 minutes.
5. Trough levels must be maintained at 5-12mg/L

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CrCl (ml/min)	<60 kg	>60 kg
20 – 29	1000 (48)	1000 (48)
30 – 49	750 (24)	750 (24)
50 – 59	1000 (24)	1000 (24)
60 – 69	500 (12)	1000 (24)
70 – 79	750 (12)	750 (12)
80 – 100	750 (12)	1000 (12)
>100	1250 (12)	1250 (12)

The dosage regimen is given as: dose mg (interval)

7.1 SAMPLING PROTOCOLS

Check peak (2h post infusion) and trough concentrations after 24-72 hours of therapy. Please ensure that the EXACT times of all doses and samples are recorded on the request form.

7.2 AUDIT

Suggested topics include

7.2.1 Adherence to protocol

7.2.2 Use of Vancomycin and Teicoplanin

7.2.3 Drug level monitoring for gentamicin and vancomycin

7.2.4 Incidence and sensitivity of identified organisms

8.0 APPENDIX 2

GENTAMICIN

1. Calculate creatinine clearance if it is not known. (Use ideal body weight if the patient is obese). If the creatinine concentration is <60 µmol/l, use 60 µmol/l.
2. Determine the starting dose from the table.
3. If creatinine clearance is less than 20 ml/min, give 2.5 mg/kg then take a sample after 24 hours.

Cr Cl (ml/min)	Weight (kg) 40-49	50-59	60-69	70-79	>79
20-29	100 (24)	100 (24)	100 (24)	160 (48)	180 (48)
30-39	120 (24)	120 (24)	140 (24)	140 (24)	160 (24)
40-49	120 (24)	140 (24)	140 (24)	160 (24)	180 (24)
50-59	100 (12)	140 (24)	160 (24)	180 (24)	180 (24)
60-69	120 (12)	140 (12)	140 (12)	180 (24)	180 (24)
70-79	140 (12)	140 (12)	160 (12)	180 (24)	200 (24)
80-89	140 (12)	160 (12)	160 (12)	160 (12)	180 (12)
90-99	160 (12)	160 (12)	180 (12)	180 (12)	180 (12)
>99	160 (12)	180 (12)	200 (12)	200 (12)	200 (12)

The dosage regimen is given as: dose (interval)

These are recommendations for initial doses and are designed to achieve peak concentrations of 7-10 mg/l and trough concentrations <2 mg/l.

8.1 BACTERIAL ENDOCARDITIS

Please consult Bacteriology for advice on the gentamicin dose and target concentrations.

8.2 SAMPLING PROTOCOLS

Check peak (1h post dose) and trough concentrations after ~~24-48~~48-72 hours of therapy.
For vancomycin, trough levels only are required
For gentamicin and amikacin at least one peak level is required even if IV access is difficult, in order to ensure patient is receiving an effective dose of antibiotic.
–Please ensure that the EXACT times of all doses and samples are recorded on the request form. (Samples not taken at the "ideal time" can be interpreted if the actual times are known).

For further information contact clinical pharmacist currently working in unit
or on-call pharmacist at evenings and weekends.

~~*For further information please contact: Clinical Pharmacist on:- Page 2013 (GRI)*~~
~~*Page 4190 (WIG)*~~

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~~*IDEAL*~~

9.0 APPENDIX 3

9.1 IDEAL BODY WEIGHT

Male 50 kg + (2.3 kg for every inch above 5ft)
Female 45.4 kg + (2.3 kg for every inch above 5ft)

9.2 CONVERSION CHARTS

HEIGHTS			
	4'	5'	6'
	121	152	182
1"	123	154	185
2"	127	157	187
3"	129	160	190
4"	132	162	193
5"	134	165	195
6"	137	167	198
7"	139	170	200
8"	142	172	202
9"	144	175	
10"	147	177	
11"	149	180	

WEIGHT			
STONES	KILOS	STONES	KILOS
4.0	25.40	10.0	63.50
4.5	28.57	10.5	66.67
5.0	31.75	11.0	69.85
5.5	34.92	11.5	73.02
6.0	38.10	12.0	76.20
6.5	41.27	12.5	79.37
7.0	44.45	13.0	82.55
7.5	47.62	13.5	85.72
8.0	50.80	14.0	88.90
8.5	53.97	14.5	92.07
9.0	57.15	15.0	95.24
9.5	60.32	15.5	98.42

Creatinine mg/100 ml x 88.4 = μmol/l.

9.3 ESTIMATION OF CREATININE CLEARANCE

$$\text{Creatinine CL (ml/min)} = \frac{(140 - \text{age (years)}) \times \text{weight (kg)}}{\text{Creatinine (}\mu\text{mol/l)}} \times \begin{cases} 1.23 & \text{(male)} \\ 1.04 & \text{(female)} \end{cases}$$

Cockcroft & Gault, Nephron 16: 31-41, 1976

10.0 APPENDIX 4

Patient Name.....

D.O.B.....

Unit No.....

ANTIBIOTIC RECORDING CHART (Aminoglycosides, Vancomycin)

DATE	DRUG	DOSE	TIME OF ADMINISTRATION (START OF INFUSION)	TIME INFUSION COMPLETE (IF APPROPRIATE)	SAMPLE TIME	GIVEN BY

For advice contact Sally McKendrick or Jonathan Allan in Pharmacy

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : ANTIBIOTIC TREATMENT POLICY
SOP No. BMT 100 006 021 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 22/10/2008~~13/09/2007~~
Authorised by:	Dr Anne Parker	Date: 06/11/2008
Authorised by: Quality Manager	Robert H Boyd	Date: 06/11/2008
Date of issue:	06/11/2008	
Effective date:	06/11/2008	
Review:	~~Annually~~Every 2 Years	
Number of pages: (including this page)	132	

To be used in conjunction with SOP(s):-
(current version)

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Haem OPD, SGH	1			
Day Med.Unit, Vict. Inf.	1			

SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
	Amnioglycoside and vancomycin dose use GG&C Therapeutics Handbook to calculate dose	22/10/2008	A Parker

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POLICY FOR ANTI-INFECTIVE USE IN IMMUNOCOMPROMISED PATIENTS

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically and frequently no causative organism can be found. The possibility of infection with opportunistic organisms such as PCP and reactivation of previous infections e.g. CMV, VZV should always be considered. Other infections such as a cold can cause pneumonitis and death in the post allograft setting. All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.

This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to or attending Haemato-oncology services in Greater Glasgow. It is not intended as a substitute for appropriate discussion with microbiologists, pharmacists and senior colleagues.

Patients should be assessed in accordance with the 'Assessment of Infection in the Immunocompromised Patient'.

Antifungal therapy should be instituted as in 'Antifungal Prophylaxis and Therapy Guideline'

Antiviral therapy should be instituted as in 'Antiviral Use in Immunocompromised Patients'

The following should be used for patients who have:

- Neutrophils <1.0 x10^9/l
- Post Allograft
- Clinically Septic even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy

Patients who are low risk for overwhelming gram negative infection should be given the most appropriate antibiotic for their symptoms (e.g. ~~Cefotaxime, Augmentin~~ Amoxil, clarithromycin etc. see GG&C Drugs Therapeutics handbook for recommended agent), but consider switching to the following if slow to respond or clinically indicated.

2.0 TREATMENT of PYREXIA

If screening specimens have shown a resistant organism the following should be adapted to provide adequate cover.

2.1 FIRST LINE ANTIBIOTICS

~~If screening specimens have shown a resistant organism the following should be adoapted to provide adequate cover.~~

2.1.1 ***Tazocin*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose if creatinine clearance decreasing.

Penicillin allergy should be discussed with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.

For example:

- In cases of mild Penicillin allergy (e.g. possible rash), use Meropenem instead.
- In cases of proven Penicillin allergy use Ceftazidime.
- In cases of proven Penicillin, Carbopenem and Cephalosporin allergy, use Ciprofloxacin 400 mg bd IV and Amikacin.

2.1.2 ***Gentamicin***

The dose, and frequency and monitoring should be based on the creatinine clearance (see attached chart) and levels must be checked regularly.

If creatinine clearance <20 ml/min give single dose of 2.5 mg/kg. Check clearance by levels every 12 hours until below trough levels and then repeat dose.obtained from the GG&C Therapeutics Handbook. This can be found on the Hospital intranet in the clinical guidelines section.

The dose of drug and time given should be recorded on the chart (see attached sample) to ensure correct timing of samples for levels.

Myeloma patients with impaired renal function willshould not be prescribed gentamicin as first line empirical therapy without discussion

2.1.3 ***Vancomycin/Teicoplanin***

This should be added initially ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use (see gram positive section for dose & which drug).

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

NB – If Hickman line colonisation is suspected, this should be removed - after discussion with consultant in charge.

CONTINUE	*Tazocin & Gentamicin (if clinically improving and/or temperature resolving [NB – This does not mean the patient has to be apyrexial])*

ONLY after a MINIMUM of 48 hours of therapy AND if no improvement clinically OR improvement in temperature pattern:

STOP	*Tazocin* AND *Gentamicin*
START	*MEROPENEM* 1g tds

If renal function deteriorates dose should be adjusted accordingly.

2.2 GRAM POSITIVE COVER

This should NOT be added automatically at 48 hours and MUST be discussed with the attending Consultant.

It can be considered if persistent pyrexia, but patient remains stable and if not already receiving gram positive cover add:

2.2.3 VANCOMYCIN (use ~~calculated creatinine clearance and chart to determine dose~~GG&C Therapeutics Handbook to calculate dose and monitor levels)

If the patient has a dual lumen line divide into 2 and add each to 100mls of N/saline. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough and peak) and dose adjusted accordingly.

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2.2.4 TEICOPLANIN

400 mgs IV 12 hourly for 3 doses then daily thereafter.

NB – If Patient is >85 kg, use dose/kg

The full dose of teicoplanin is 6 mg/kg rounded off to nearest 200 mg, so in larger patients consider 600 or 800 mg/day if not responding. The dose should be split into 2 bags or 2 bolus injections.

NB – Teicoplanin is also nephrotoxic. Its dose should be adjusted according to the creatinine clearance (see GG&C Therapeutics Handbook~~attached sheet~~). Levels may be considered in this situation.

Teicoplanin should ONLY be used in preference to Vancomycin in the following situations:

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- Outpatient use.
- Fluid volume/infusion times an issue.
- Patients with known renal failure i.e. creatinine clearance <50 ml/min or doubling of creatinine since admission.
- Patients already on 1 nephrotoxic drug, (e.g. Cyclosporin A, Gentamicin, Amphotericin, etc).

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days. Because of the rise in organisms such as vancomycin-resistant enterococcus (VRE), many authorities now suggest that empiric vancomycin or teicoplanin should be avoided (i.e. not used unless there is some reason to suspect a line-associated or other Gram-positive bacterial infection), as coagulase-negative staphylococci are easy to detect by blood culture, and are rarely life threatening. However DO NOT FORGET that, though unusual, staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

2.3 STOP IV ANTIBIOTICS WHEN

1. Neut > 0.5 x 10^9/l patient is well and apyrexial for 3 days
2. Neut < 0.5 x 10^9/l patient is well and apyrexial for 5 days. Restart oral ciprofloxacin.

Gentamicin should ONLY ~~to~~ be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

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2.4 IF TEMPERATURE REMAINS UNRESPONSIVE & NEUT <0.5 X 10^9/L

2.4.1 GROWTH FACTOR

G-CSF 1 vial/day s.c. (Lenograstim 263mcg/vial or Neupogen 300mcg/vial) ONLY if authorised by consultant in charge. NB 2 vials should be considered if patient >80 kg.

At any stage the following should be considered:

2.4.2 CLARITHROMYCIN IV

If suspicion of legionella or other atypical pneumonia.

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If suspicion of disseminated herpes simplex or zoster infection.

2.4.4 CO-TRIMOXAZOLE IV

If suspicion of pneumocystis.

2.4.5 METRONIDAZOLE IV

If persistent diarrhoea >24 hours while awaiting culture results.

2.4.6 GANCICLOVIR IV

If in at risk group for CMV reactivation.

2.5 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)
It should be remembered that hypothermia can denote severe infection.

If severe sepsis and ONLY after discussion with the attending Consultant the following can be substituted for gentamicin

Amikacin **use GG&C Therapeutics Handbook to calculate dose and monitor levels**~~7.5mg/kg bd (if renal function normal)~~

~~Please check amikacin peak and trough levels after third dose if renal function normal. Discuss with pharmacy re: interval between doses if renal function deteriorates.~~ There is less resistance to Amikacin, partly due to less usage, and it should therefore only be used in this group of patients or on the advice of microbiology due to the presence of resistant organisms

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DURATION 2/52 minimum

Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 µg/ml.

The doses should be modified if renal impairment (see attached chart).

Consider giving folic acid supplements.

3.2 SECOND LINE THERAPY

IV PENTAMIDINE

4.0 TOXOPLASMOSIS

This must be discussed with consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

Then for the next 2-4 weeks minimum/until immunosuppression resolved

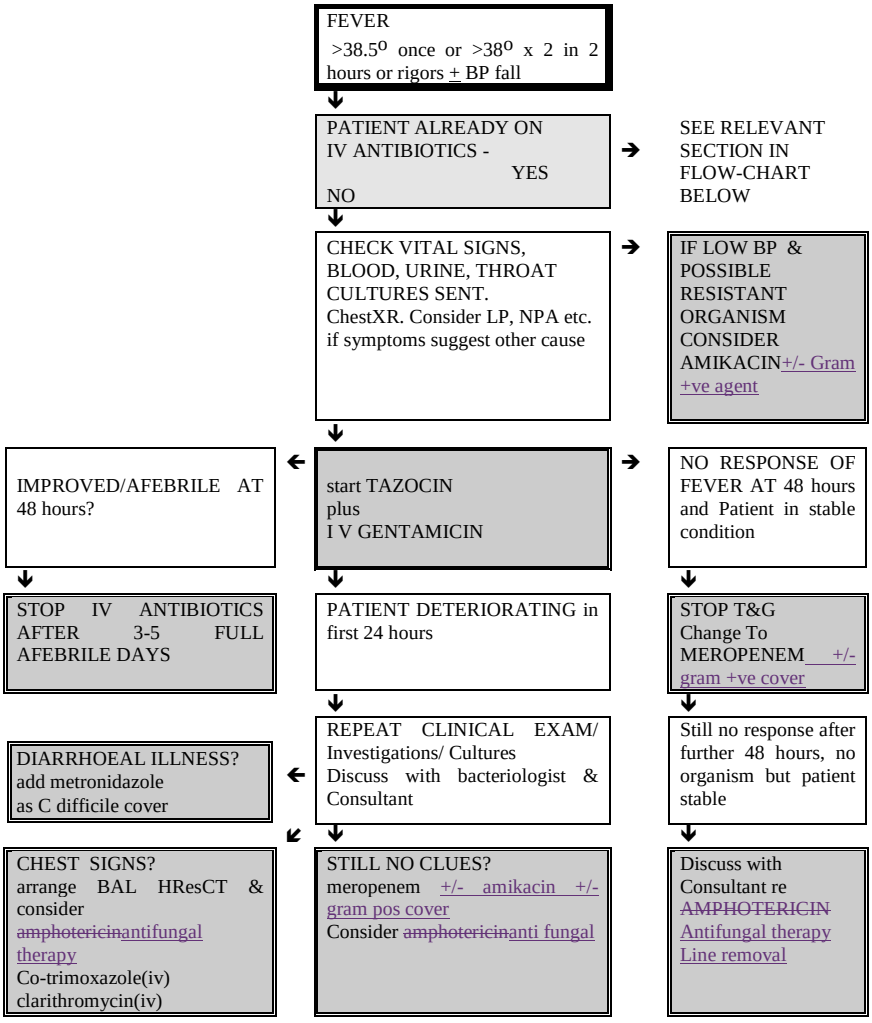
PYRIMETHAMINE	0.5 mg/kg po bd
SULPHADIAZINE	30 mg/kg po bd

~~*FOLINIC ACID*~~*CALCIUM FOLINATE* 15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.

Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response.

5.0 ANTIBIOTICS IN THE MANAGEMENT OF FEVER



Gram positive cover with *Vancomycin/Teicoplanin* should be added at any time if positive cultures or other evidence of line related infection.

6.0 DRUG DOSE REDUCTION IN RENAL IMPAIRMENT

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- It assumes creatinine concentration is at a steady state and is not valid if the creatinine is changing
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Aciclovir	Oral prophylaxis - CrCl < 10ml/min give 200mg every 12 hours IV therapy - Cr Cl 25-50ml/min give dose every 12 hours Cr Cl 10-25 ml/min give dose every 24 hours
Amikacin	use GG&C Therapeutics Handbook to calculate dose~~Discuss with Pharmacy~~~~Check current edition of GG&C Prescribing Guidance for Doctors~~
Ciprofloxacin	Oral & IV - CrCl < 20 ml/min or creatinine > 265 mol/l – give half the total daily dose
Clarithromycin	Creatinine clearance <30 ml/min 250 mg once or twice daily
Cotrimoxazole (Septrin)	Tablets - CrCl > 30 ml/min give normal dose CrCl 15 - 30 ml/min give half normal dose CrCl < 15 ml/min not recommended High Dose IV discuss with pharmacy
Gentamicin	use GG&C Therapeutic Handbook to calculate dose~~See attached table~~
Meropenem	CrCl 26 - 50 ml/min give every 12 hours CrCl 10 - 25 ml/min give half normal dose every 12 hours CrCl < 10 ml/min give half normal dose every 24 hours
Metronidazole	No dose adjustment
Tazocin	Creatinine Cl > 80ml/min 4.5g qid Creatinine Cl 20 – 80 ml/min 4.5g tid Creatinine ~~e~~Cl <20 ml/min 4.5 g bd
Teicoplanin	Use GG&C Therapeutics Handbook to calculate dose e~~Day 1-3 give usual dose~~ ~~From day 4 CrCl 40 - 60 ml/min give dose every 48 hrs~~ ~~CrCl <40 ml/min give dose every 72 hrs~~
Vancomycin	use GG&C Therapeutic Handbook to calculate dose~~See attached table~~

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~~7.0 APPENDIX 1~~

~~VANCOMYCIN~~

~~1. Calculate creatinine clearance if it is not known. (Use ideal body weight if the patient is obese). If the creatinine concentration is <60 µmol/l, use 60 µmol/l.~~
~~2. Determine the starting dose from the table.~~
~~3. If creatinine clearance is less than 20 ml/min, give 1000 mg then take a sample after 24 hours.~~
~~4. Vancomycin should be administered by infusion at a concentration less than 5 mg/ml and at a rate NOT GREATER THAN 10 mg/min (i.e.1000 mg over 100-120 minutes.~~
~~Trough levels must be maintained at 5-12mg/L~~

~~CrCl (ml/min)~~	~~<60 kg~~	~~>60 kg~~
~~20 – 29~~	~~1000 (48)~~	~~1000 (48)~~
~~30 – 49~~	~~750 (24)~~	~~750 (24)~~
~~50 – 59~~	~~1000 (24)~~	~~1000 (24)~~
~~60 – 69~~	~~500 (12)~~	~~1000 (24)~~
~~70 – 79~~	~~750 (12)~~	~~750 (12)~~
~~80 – 100~~	~~750 (12)~~	~~1000 (12)~~
~~>100~~	~~1250 (12)~~	~~1250 (12)~~

~~7.0 The dosage regimen is given as: dose mg (interval)~~

~~7.1 SAMPLING PROTOCOLS~~

~~Check peak (2h post infusion) and trough concentrations after 24-72 hours of therapy. Please ensure that the EXACT times of all doses and samples are recorded on the request form.~~

7.2 AUDIT

Suggested topics include

7.2.1 Adherence to protocol

7.2.2 Use of Vancomycin and Teicoplanin

7.2.3 Drug level monitoring for gentamicin and vancomycin

7.2.4 Incidence and sensitivity of identified organisms

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8.0 APPENDIX 1 2

~~GENTAMICIN~~

~~1. Calculate creatinine clearance if it is not known. (Use ideal body weight if the patient is obese). If the creatinine concentration is <60 µmol/l, use 60 µmol/l.~~
~~2. Determine the starting dose from the table.~~
~~3. If creatinine clearance is less than 20 ml/min, give 2.5 mg/kg then take a sample after 24 hours.~~

~~Cr Cl (ml/min)~~	~~Weight (kg) 40-49~~	~~50-59~~	~~60-69~~	~~70-79~~	~~>79~~
~~20-29~~	~~100 (24)~~	~~100 (24)~~	~~100 (24)~~	~~160 (48)~~	~~180 (48)~~
~~30-39~~	~~120 (24)~~	~~120 (24)~~	~~140 (24)~~	~~140 (24)~~	~~160 (24)~~
~~40-49~~	~~120 (24)~~	~~140 (24)~~	~~140 (24)~~	~~160 (24)~~	~~180 (24)~~
~~50-59~~	~~100 (12)~~	~~140 (24)~~	~~160 (24)~~	~~180 (24)~~	~~180 (24)~~
~~60-69~~	~~120 (12)~~	~~140 (12)~~	~~140 (12)~~	~~180 (24)~~	~~180 (24)~~
~~70-79~~	~~140 (12)~~	~~140 (12)~~	~~160 (12)~~	~~180 (24)~~	~~200 (24)~~
~~80-89~~	~~140 (12)~~	~~160 (12)~~	~~160 (12)~~	~~160 (12)~~	~~180 (12)~~
~~90-99~~	~~160 (12)~~	~~160 (12)~~	~~180 (12)~~	~~180 (12)~~	~~180 (12)~~
~~>99~~	~~160 (12)~~	~~180 (12)~~	~~200 (12)~~	~~200 (12)~~	~~200 (12)~~

~~The dosage regimen is given as: dose (interval)~~

~~These are recommendations for initial doses and are designed to achieve peak concentrations of 7-10 mg/l and trough concentrations <2 mg/l.~~

~~**8.1 BACTERIAL ENDOCARDITIS**~~

~~Please consult Bacteriology for advice on the gentamicin dose and target concentrations.~~

~~**8.2 SAMPLING PROTOCOLS**~~

~~Check peak (1h post dose) and trough concentrations after 24-48~~48-72 ~~hours of therapy.~~
~~For vancomycin, trough levels only are required~~
~~For gentamicin and amikacin at least one peak level is required even if IV access is difficult, in order to ensure patient is receiving an effective dose of antibiotic.~~
~~Please ensure that the EXACT times of all doses and samples are recorded on the request form. (Samples not taken at the "ideal time" can be interpreted if the~~ actual ~~times are known).~~

~~For further information contact clinical pharmacist currently working in unit or on-call pharmacist at evenings and weekends.~~

~~*For further information please contact: Clinical Pharmacist on:- Page 2013 (GRI) Page 4190 (WIG)*~~

~~*IDEAL*~~

~~*APPENDIX 1*~~

IDEAL BODY WEIGHT

MALES - IBW = 50.0kg + 2.3kg for every 2.5cm of height more than 152cm
FEMALES - IBM = 45.5kg + 2.3kg for every 2.5cm of height more than 152cm

MALES				FEMALES		
Height	**Height**	**IDEAL**		**Height**	**Height**	**IDEAL**

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Ft'inches"	cm	BODY WEIGHT		Ft'Inches"	cm	BODY WEIGHT
4'10"	147	50 kg		4'10"	147	45.5 kg
4'11"	150	50 kg		4'11"	150	45.5kg
5'	152	50 kg		5'	152	45.5 kg
5'1"	155	52.8 kg		5'1"	155	48.3 kg
5'2"	157	54.6 kg		5'2"	157	49.6 kg
5'3"	160	57.4 kg		5'3"	160	52.9 kg
5'4"	163	60.1 kg		5'4"	163	55.6 kg
5'5"	165	62 kg		5'5"	165	57.5 kg
5'6"	168	64.7 kg		5'6"	168	60.2 kg
5'7"	170	66.6 kg		5'7"	170	62.1 kg
5'8"	173	69.3 kg		5'8"	173	64.8 kg
5'9"	175	71.2 kg		5'9"	175	66.7 kg
5'10"	178	73.9 kg		5'10"	178	69.5 kg
5'11"	180	75.8 kg		5'11"	180	71.3 kg
6'	183	77.6 kg		6'	183	73.1 kg
6'1"	185	80.4 kg		6'1"	185	75.9 kg
6'2"	188	83.1 kg		6'2"	188	78.6 kg
6'3"	190	85 kg		6'3"	190	80.5 kg
6'4"	193	87.7 kg		6'4"	193	83.2 kg
6'5"	196	90.5 kg		6'5"	196	86 kg

S McKendrick 23.10.08

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9.0 APPENDIX 3

89.1 BODY WEIGHT

Male 50 kg + (2.3 kg for every inch above 5ft)
Female 45.4 kg + (2.3 kg for every inch above 5ft)

89.2 CONVERSION CHARTS

HEIGHTS			
	4'	5'	6'
	121	152	182
1"	123	154	185
2"	127	157	187
3"	129	160	190
4"	132	162	193
5"	134	165	195
6"	137	167	198
7"	139	170	200
8"	142	172	202
9"	144	175	
10"	147	177	
11"	149	180	

WEIGHT			
STONES	KILOS	STONES	KILOS
4.0	25.40	10.0	63.50
4.5	28.57	10.5	66.67
5.0	31.75	11.0	69.85
5.5	34.92	11.5	73.02
6.0	38.10	12.0	76.20
6.5	41.27	12.5	79.37
7.0	44.45	13.0	82.55
7.5	47.62	13.5	85.72
8.0	50.80	14.0	88.90
8.5	53.97	14.5	92.07
9.0	57.15	15.0	95.24
9.5	60.32	15.5	98.42

~~Creatinine mg/100 ml x 88.4 = µmol/l.~~

~~8~~9.3 ~~ESTIMATION OF CREATININE~~ ESTIMATION OF CREATININE CLEARANCE

Creatinine CL = (140 - age (years)) x weight (kg)
(ml/min) Creatinine (µmol/l)
x 1.23 (male)
x 1.04 (female)

Cockcroft & Gault, Nephron 16: 31-41, 1976

~~10.0 APPENDIX 24~~

Appendix 2 – Antibiotic Prescription, Administration and Monitoring Chart

ANTIBIOTIC PRESCRIPTION, ADMINISTRATION AND MONITORING CHART

Patient's name: Weight: Date of birth: Unit no:

Date	Drug	Dose (mg)	Time of dose	Prescribed by	Given By	Time infusion started	Time infusion stopped	Blood sample time	Concentration (mg/L)	Date of next dose	Time next dose is due	Signed

SAMPLE FORM

(For Useable Forms – Click Link Below)

http://staffnet/NR/rdonlyres/763BF92E-B2E0-4B89-A4ED-C5E05B9358A0/46618/ANTIBIOTICPRESCRIPTION.doc

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~~GENTAMICIN GUIDELINES~~	~~VANCOMYCIN GUIDELINES~~

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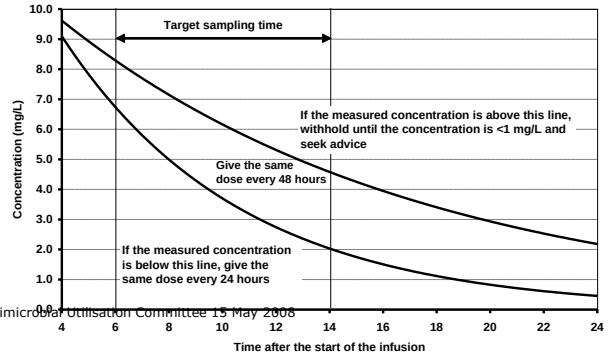
Creatinine CL = (140 – age (y)) x IBW (kg) / Creatinine (µmol/L)
× 1.23 (male) OR × 1.04 (female)
If creatinine is **<60 µmol/**L use 60 µmol/L
IBW = (Males 50 kg Females 45 kg) + 2.3 kg for every 2.5 cm >152 cm

Creat Cl (ml/min)	40 - 49 kg	50 - 59 kg	60 - 69 kg	70 - 80 kg	> 80 kg
< 21	2.5 mg/kg (max 180 mg) then take a sample after 24 hours				
21 - 30	180 mg 48 h	200 mg 48 h	240 mg 48 h	240 mg 48 h	260 mg 48 h
31 - 40	200 mg 48 h	240 mg 48 h	280 mg 48 h	300 mg 48 h	320 mg 48 h
41 - 50	240 mg 48 h	280 mg 48 h	320 mg 48 h	360 mg 48 h	400 mg 48 h
51 - 60	200 mg 24 h	240 mg 24 h	280 mg 24 h	300 mg 24 h	320 mg 24 h
> 60	240 mg 24 h	280 mg 24 h	320 mg 24 h	360 mg 24 h	400 mg 24 h

Synergistic use Lower doses are sometimes used for synergy e.g. in the treatment of endocarditis. Seek advice from microbiology.

MONITORING OF GENTAMICIN CONCENTRATIONS

- Take a sample 6 – 14 hours after the start of the first infusion
- Plot the concentration measurement on the graph
- The plot will indicate one of 3 options: (1) Continue the present dosage regimen, (2) adjust the dosage interval or (3) withhold and resample after 24 hours
- Seek advice if you are unsure how to interpret the result
- Monitor creatinine concentrations daily
- Take a further sample 6-14 hours post dose, once or twice a week as routine or earlier if the concentration is unexpectedly high, or if renal function alters.



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VANCOMYCIN PULSED INFUSION

1. Loading Dose

Creat Cl (ml/min)	< 60 kg	> 60 kg
< 75	1000 mg over 2 h	1000 mg over 2 h then 1000 mg over 2 h 12 hours later
>75	Loading dose not required – start maintenance dose	

2. Maintenance Dose

Creat Cl (ml/min)	Dose	Interval
< 20	500 mg over 1 h	48 hours
20 – 30	500 mg over 1 h	24 hours
31 – 40	750 mg over 1.5 h	24 hours
41 – 55	500 mg over 1 h	12 hours
56 – 75	750 mg over 1.5 h	12 hours
76 – 89	1000 mg over 2 h	12 hours
90 – 120	1250 mg over 2.5 h	12 hours
>120	1500 mg over 3 h	12 hours

MONITORING OF VANCOMYCIN CONCENTRATIONS

Target Trough: 10 – 15 mg/L *(15 – 20 mg/L may be required in some cases)*

VANCOMYCIN CONTINUOUS INFUSION

1. Loading Dose Weight <40 kg 500 mg over 1 hour
Weight 40-70 kg 1000 mg over 2 hours
Weight >70 kg 1500 mg over 3 hours

2. Maintenance Infusion *start immediately after the loading dose*

Creat Cl (ml/min)	Daily Dose	Dose for infusion in 250 ml saline over 12 hours
<20	500 mg	250 mg
20-34	750 mg	375 mg
35-59	1000 mg	500 mg
60-79	1500 mg	750 mg
80-99	2000 mg	1000 mg
>100	2500 mg	1250 mg

Target concentration range: 15 – 25 mg/L

Vancomycin conc	Suggested dosage change

<15 mg/L	Increase the daily dose by 500 mg
15 – 25 mg/L	No change
>25 mg/L	Decrease the daily dose by 500 mg
>30 mg/L	Stop until <25 mg/L then restart at a lower dose

GGC Antimicrobial Utilisation Committee 15 May 2008

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Patient Name.....

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D.O.B.....

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Unit No.....

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ANTIBIOTIC RECORDING CHART (Aminoglycosides, Vancomycin)

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DATE	DRUG	DOSE	TIME OF ADMINISTRATION (START OF INFUSION)	TIME INFUSION COMPLETE (IF APPROPRIATE)	SAMPLE TIME	GIVEN BY

For advice contact Sally McKendrick or Jonathan Allan in Pharmacy

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : ANTIBIOTIC TREATMENT POLICY
SOP No. BMT 100 006 03 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker/ Dr Brian Jones	Date: 14/09/2011
Authorised by:	Dr Anne Parker	Date: 21/09/2011
Authorised by: Quality Manager	Robert H Boyd	Date: 21/09/2011
Date of issue:	21/09/2011	
Effective date:	05/10/2011	
Review:	Every 2 Years	
Number of pages: (including this page)	13	

To be used in conjunction with SOP(s):- **BMT 100 002** **BMT 100 041**
(current version) **BMT 100 008**

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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
	Pi-Tazobactam (Pip-Tazo) substituted for Tazocin	29/08/2011	A Parker
	Corrected high dose cotrimoxazole to 120mg/kg/24 hrs	29/08/2011	A Parker
	Policy re-Formatted	21/09/2011	R Boyd

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POLICY FOR ANTI-INFECTIVE USE IN IMMUNOCOMPROMISED PATIENTS

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically and frequently no causative organism can be found. The possibility of infection with opportunistic organisms such as PCP and reactivation of previous infections e.g. CMV, VZV should always be considered. Other infections such as a cold can cause pneumonitis and death in the post allograft setting. All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.

This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to or attending Haemato-oncology services in Greater Glasgow. It is not intended as a substitute for appropriate discussion with microbiologists, pharmacists and senior colleagues.

Patients should be assessed in accordance with the 'Assessment of Infection in the Immunocompromised Patient' (BMT 100 041 – current version).

Antifungal therapy should be instituted as in 'Antifungal Prophylaxis and Therapy Guideline' (BMT 100 008 – current version).

Antiviral therapy should be instituted as in 'Antiviral Use in Immunocompromised Patients' (BMT 100 002 – current version).

The following should be used for patients who have:

- Neutrophils <1.0 $x10^9$/l
- Post Allograft
- Clinically Septic even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy

Patients who are low risk for overwhelming gram negative infection should be given the most appropriate antibiotic for their symptoms (e.g. Amoxil, clarithromycin etc. see GG&C Drugs Therapeutics handbook for recommended agent), but consider switching to the following if slow to respond or clinically indicated.

2.0 TREATMENT of PYREXIA

If screening specimens have shown a resistant organism the following should be adapted to provide adequate cover.

2.1 FIRST LINE ANTIBIOTICS

2.1.1 ***Pip- Tazobactam*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose if creatinine clearance decreasing.

Penicillin allergy should be discussed with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.

For example:

- In cases of mild Penicillin allergy (e.g. possible rash), use Meropenem instead.
- In cases of proven Penicillin allergy use Ceftazidime.
- In cases of proven Penicillin, Carbopenem and Cephalosporin allergy, use Ciprofloxacin 400 mg bd IV and Amikacin.

2.1.2 *Gentamicin*

The dose, frequency and monitoring should be obtained from the GG&C Therapeutics Handbook. This can be found on the Hospital intranet in the clinical guidelines section.

The dose of drug and time given should be recorded on the chart (see attached sample) to ensure correct timing of samples for levels.

Myeloma patients should not be prescribed gentamicin as first line empirical therapy without discussion with the attending Consultant

2.1.3 *Vancomycin/Teicoplanin*

This should be added initially ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use (see gram positive section for dose & which drug).

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

NB – If Hickman line colonisation is suspected, this should be removed - after discussion with consultant in charge.

CONTINUE	*Pip-Tazo & Gentamicin (if clinically improving and/or temperature resolving [NB – This does not mean the patient has to be apyrexial])*

ONLY after a MINIMUM of 48 hours of therapy AND if no improvement clinically OR improvement in temperature pattern:

STOP	*Pip-Tazo* AND *Gentamicin*	
START	*MEROPENEM*	1g tds

If renal function deteriorates dose should be adjusted accordingly.

2.2 GRAM POSITIVE COVER

This should NOT be added automatically at 48 hours and MUST be discussed with the attending Consultant.

It can be considered if persistent pyrexia, but patient remains stable and if not already receiving gram positive cover add:

2.2.3 VANCOMYCIN (use GG&C Therapeutics Handbook to calculate dose and monitor levels)

If the patient has a dual lumen line divide into 2 and add each to 100mls of N/saline. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough only, target 10-20mg/l) and dose adjusted accordingly.

2.2.4 TEICOPLANIN

400 mgs IV 12 hourly for 3 doses then daily thereafter.

NB – If Patient is >85 kg, use dose/kg

The full dose of teicoplanin is 6 mg/kg rounded off to nearest 200 mg, so in larger patients consider 600 or 800 mg/day if not responding. The dose should be split into 2 bags or 2 bolus injections.

NB – Teicoplanin is also nephrotoxic. Its dose should be adjusted according to the creatinine clearance (see GG&C Therapeutics Handbook). Levels may be considered in this situation.

Teicoplanin should ONLY be used in preference to Vancomycin in the following situations:

- Outpatient use.
- Fluid volume/infusion times an issue.
- Patients with known renal failure i.e. creatinine clearance <50 ml/min or doubling of creatinine since admission.
- Patients already on 1 nephrotoxic drug, (e.g. Cyclosporin A, Gentamicin, Amphotericin, etc).

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days. Because of the rise in organisms such as vancomycin-resistant enterococcus (VRE), many authorities now suggest that empiric vancomycin or teicoplanin should be avoided (i.e. not used unless there is some reason to suspect a line-associated or other Gram-positive bacterial infection), as coagulase-negative staphylococci are easy to detect by blood culture, and are rarely life threatening. However DO NOT FORGET that, though unusual, staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram

negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

2.3 STOP IV ANTIBIOTICS WHEN

1. Neut > 0.5 x 10^9/l patient is well and apyrexial for 3 days
2. Neut < 0.5 x 10^9/l patient is well and apyrexial for 5 days. Restart oral ciprofloxacin.

Gentamicin should ONLY be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

2.4 IF TEMPERATURE REMAINS UNRESPONSIVE & NEUT <0.5 X 10^9/L

2.4.1 GROWTH FACTOR

G-CSF 1 vial/day s.c. (Lenograstim 263mcg/vial or filgrastim 300mcg/vial) ONLY if authorised by consultant in charge. NB 2 vials should be considered if patient >80 kg.

At any stage the following should be considered:

2.4.2 CLARITHROMYCIN IV

If suspicion of legionella or other atypical pneumonia.

2.4.3 ACICLOVIR IV

If suspicion of disseminated herpes simplex or zoster infection.

2.4.4 CO-TRIMOXAZOLE IV

If suspicion of pneumocystis.

2.4.5 METRONIDAZOLE IV

If persistent diarrhoea >24 hours while awaiting culture results.

2.4.6 GANCICLOVIR IV

If in “at risk” group for CMV reactivation.

2.5 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)

It should be remembered that hypothermia can denote severe infection.

If severe sepsis and ONLY after discussion with the attending Consultant the following can be substituted for Pip-Tazo and gentamicin

MEROPENEM *1gm TID*

AMIKACIN **use GG&C Therapeutics Handbook to calculate dose and monitor levels.**

There is less resistance to Amikacin, partly due to less usage, and it should therefore only be used in this group of patients or on the advice of microbiology due to the presence of resistant organisms

3.0 PNEUMOCYSTIS CARINII PNEUMONIA (PCP)

Proven or suspected PCP

3.1 FIRST LINE THERAPY

START *CO-TRIMOXAZOLE (High Dose)*. 120 mg/kg iv in 2-4 divided doses.

Septrin contains sulphamethoxazole : trimethoprim 5:1

DURATION 2/52 minimum

Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 μg/ml.

The doses should be modified if renal impairment (see attached chart).

If patients are signficantly hypoxic consider prednisolone 60mg daily

Consider giving folic acid supplements and using antiemetics.

3.2 SECOND LINE THERAPY

IV PENTAMIDINE

4.0 TOXOPLASMOSIS

This must be discussed with consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

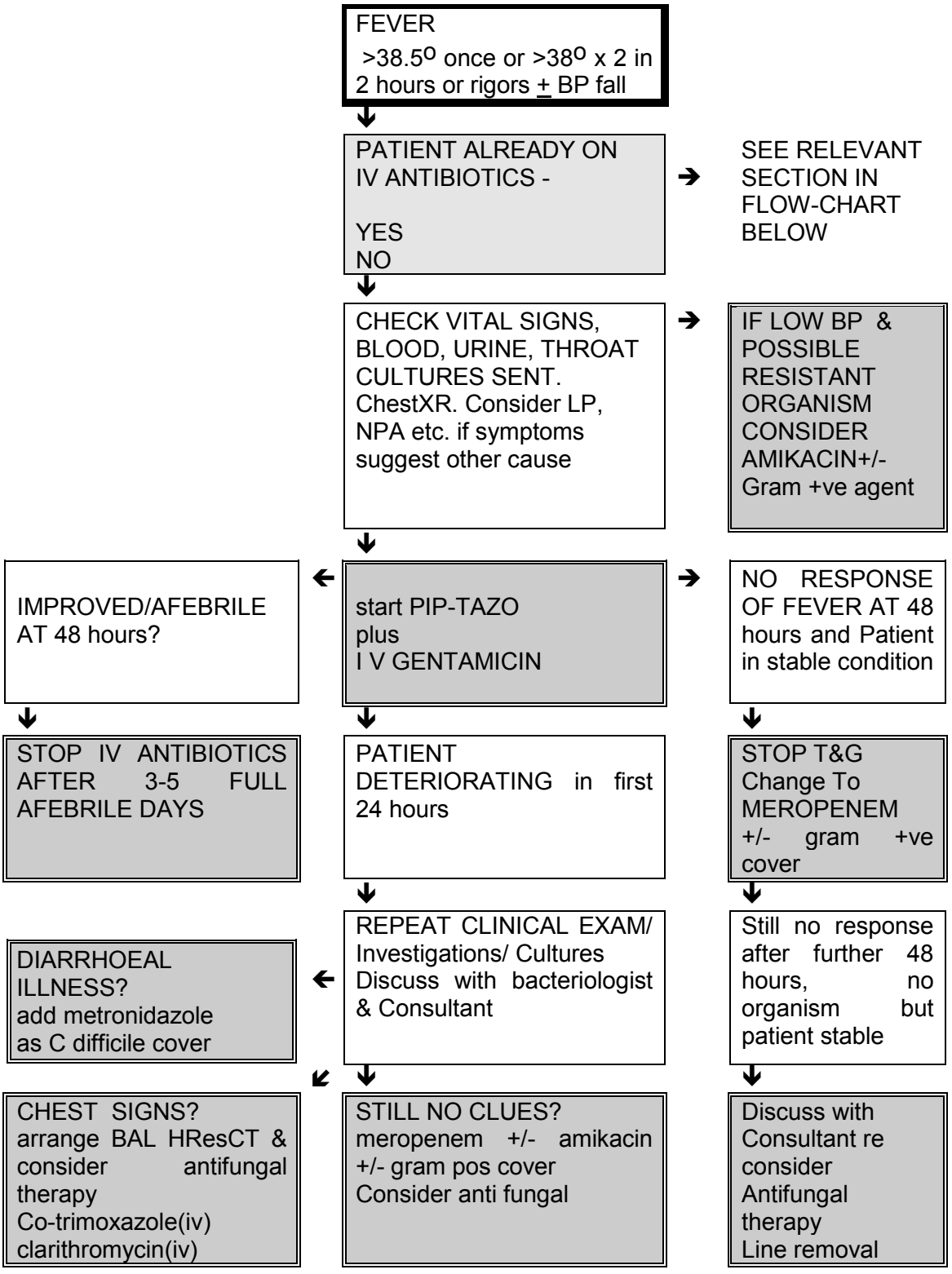
Then for the next 2-4 weeks minimum/until immunosuppression resolved

PYRIMETHAMINE	0.5 mg/kg po bd
SULPHADIAZINE	30 mg/kg po bd
CALCIUM FOLINATE	15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.

Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response.

5.0 ANTIBIOTICS IN THE MANAGEMENT OF FEVER



Gram positive cover with *Vancomycin/Teicoplanin* should be added at any time if positive cultures or other evidence of line related infection.

6.0 DRUG DOSE REDUCTION IN RENAL IMPAIRMENT

Renal disease may affect drug handling in several ways. Reduced glomerular filtration, altered tubular secretion or reabsorption and changes in renal and non-renal metabolism may have consequences for drug dosing. Individualisation of therapy based on pharmacokinetic principles will reduce the potential for toxic concentrations and optimise patient outcomes by providing efficacious yet safe plasma/serum drug concentrations.

6.1 ASSESSMENT OF RENAL FUNCTION

Glomerular filtration rate (GFR) is an assessment of the kidney's ability to excrete waste products of metabolism. Accurate estimation of GFR is essential for dose adjustments. In practice this is done by determining the creatinine clearance. Creatinine is almost exclusively excreted by the kidney. The Cockcroft-Gault equation (*Nephron 1976 15:31-41*) is commonly used to estimate creatinine clearance (CrCl) but has the following limitations.

- It assumes creatinine concentration is at a steady state and is not valid if the creatinine is changing
- It assumes normal creatinine production which is not seen in the malnourished, the elderly, hepatic disease and in patients with amputations or muscular disease.

The current GG&C Therapeutics Handbook or the most current Summary of Product Characteristics should be consulted for specific dosing advice (www.emc.medicines.org.uk).

7.0 AUDIT

Suggested topics include

7.2.1 Adherence to protocol

7.2.2 Use of Vancomycin and Teicoplanin

7.2.3 Drug level monitoring for gentamicin and vancomycin

7.2.4 Incidence and sensitivity of identified organisms

8.0 APPENDIX 1

IDEAL BODY WEIGHT

MALES - IBW = 50.0kg + 2.3kg for every 2.5cm of height more than 152cm
FEMALES - IBM = 45.5kg + 2.3kg for every 2.5cm of height more than 152cm

MALES				FEMALES		
Height Ft'inches"	Height cm	IDEAL BODY WEIGHT		Height Ft'Inches"	Height cm	IDEAL BODY WEIGHT
4'10"	147	50 kg		4'10"	147	45.5 kg
4'11"	150	50 kg		4'11"	150	45.5kg
5'	152	50 kg		5'	152	45.5 kg
5'1"	155	52.8 kg		5'1"	155	48.3 kg
5'2"	157	54.6 kg		5'2"	157	49.6 kg
5'3"	160	57.4 kg		5'3"	160	52.9 kg
5'4"	163	60.1 kg		5'4"	163	55.6 kg
5'5"	165	62 kg		5'5"	165	57.5 kg
5'6"	168	64.7 kg		5'6"	168	60.2 kg
5'7"	170	66.6 kg		5'7"	170	62.1 kg
5'8"	173	69.3 kg		5'8"	173	64.8 kg
5'9"	175	71.2 kg		5'9"	175	66.7 kg
5'10"	178	73.9 kg		5'10"	178	69.5 kg
5'11"	180	75.8 kg		5'11"	180	71.3 kg
6'	183	77.6 kg		6'	183	73.1 kg
6'1"	185	80.4 kg		6'1"	185	75.9 kg
6'2"	188	83.1 kg		6'2"	188	78.6 kg
6'3"	190	85 kg		6'3"	190	80.5 kg
6'4"	193	87.7 kg		6'4"	193	83.2 kg
6'5"	196	90.5 kg		6'5"	196	86 kg

S McKendrick 23.10.08

8.1

ESTIMATION OF CREATININE CLEARANCE

$$\text{Creatinine CL (ml/min)} = \frac{(140 - \text{age (years)}) \times \text{weight (kg)}}{\text{Creatinine } (\mu\text{mol/l})}$$

x 1.23 (male)
x 1.04 (female)

Cockcroft & Gault, Nephron 16: 31-41, 1976

Appendix 2 – Antibiotic Prescription, Administration and Monitoring Chart

ANTIBIOTIC PRESCRIPTION, ADMINISTRATION AND MONITORING CHART

Patient's name: **Weight:** **Date of birth:** **Unit no:**

Date	Drug	Dose (mg)	Time of dose	Prescribed by	Given By	Time infusion started	Time infusion stopped	Blood sample time	Concentration (mg/L)	Date of next dose	Time next dose is due	Signed

SAMPLE FORM

(For Useable Forms – Click Link Below)

http://staffnet/NR/rdonlyres/763BF92F-B2E0-4B89-A4ED-C5E05B9358A0/46618/ANTIBIOTICPRESCRIPTION.doc

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TITLE :	**ANTIBIOTIC TREATMENT GUIDELINE**	
SOP No.	**BMT 100 006 04**	**SUPERSEDES PREVIOUS VERSION**

Compiled by:	Dr Anne Parker/ Dr Brian Jones	Date: 04/04/2018
Authorised by:	Dr Anne Parker	Date: 20/04/2018
Authorised by: Quality Manager	Robert H Boyd	Date: 04/07/2018
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To be used in conjunction with SOP(s):- (current version) **BMT 100 002** **BMT 100 008** **BMT 100 041**

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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
44	Use sepsis 6 protocol where appropriate	04/04/2018	ANP
98	In myeloma patients and those with renal dysfunction use piperacillin-tazobactam as sole first line agent without gentamicin	04/04/2018	ANP
54	Drug level monitoring and Renal function to be checked on www.ggcmedicines.org	04/04/2018	ANP
174	Dose and monitoring for teicoplanin	04/04/2018	ANP
286	Grading of PCP to decide treatment	04/04/2018	ANP

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POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening, despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically, and frequently no causative organism can be found. The possibility of infection with opportunistic organisms, such as PCP and reactivation of previous infections e.g. CMV, VZV, should always be considered. Other infections, such as an upper respiratory tract infection can cause pneumonitis and death in the immunocompromised setting. All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.
This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to, or attending Haemato-oncology services in Greater Glasgow & Clyde. It is not intended as a substitute for appropriate discussion with microbiologists, infectious diseases, pharmacists and senior colleagues.

Patients should be assessed and managed in accordance with:

- Assessment of Infection in the Immunocompromised Patient (BMT 100 041 – current version).
- Sepsis 6 in immuno-compromised patients (BMT 100 070 – current version)
- Antifungal Prophylaxis and Therapy Guideline' (BMT 100 008 – current version)
- Antiviral Use in Immunocompromised Patients' (BMT 100 002 – current version).

Copies of these can be found on StaffNet or via Q-Pulse (available from B7 (WoSCC), 4B and 4C-Haem (QEUH) computers.
Information about drug monitoring, adaptation for renal function (creatinine clearance calculator) and other advice on the use of antimicrobials can be found at www.ggcmedicines.org. and in the Drugs and therapeutics handbook. This policy has been reviewed by the GG&C antibiotic utilisation policy group.

The following antibiotics should be used for patients who have:

- Neutrophils <1.0 $x10^9$/l
- Post Allograft
- Clinically septic i.e. fulfil immunocompromised sepsis 6 criteria even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy eg. Myeloma, CLL patients.

Patients, who are low risk for overwhelming gram negative infection, should be given the most appropriate antibiotic for their clinical infective syndrome (e.g. Amoxicillin, clarithromycin etc. see Drugs & Therapeutics handbook for recommended agent), but consider escalating to broad spectrum antibiotics as detailed overleaf if clinical deterioration with sepsis.

If screening specimens have shown a resistant organism the following should be adapted to provide adequate cover. If patients have grown a gram positive coagulase negative staphylococcus from routine cultures suggesting line colonisation, they do not always require treatment. However, if

they fulfil criteria for treatment (see below) they should receive appropriate treatment for this organism as well as gram negative cover if this is appropriate for the clinical situation.

2.0 TREATMENT of PYREXIA

Haemato-oncology patients who become pyrexial i.e. >38°C should be started on empirical antibiotics as set out below. Gram positive cover should be added if they have a known coagulase negative staphylococcus grown from blood cultures. All pyrexial patients or those with a NEWS>5 should be assessed as per Sepsis 6 in the immunocompromised patient.

2.1 FIRST LINE EMPIRICAL ANTIBIOTICS

PIPERACILLIN-TAZOBACTAM + GENTAMICIN

Providing patients do not meet Sepsis 6 in the immunocompromised patient criteria, it is acceptable to use pip-tazobactam as sole agent if renal function is a concern or other nephrotoxic agents are being used such as ambisome or cidofovir.

2.1.1 ***Piperacillin- Tazobactam*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose for creatinine clearance.

Penicillin allergy should be discussed with the patient at the time of admission and therapy should be clarified with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.

For example:

- In cases of proven Penicillin allergy use Meropenem
- In cases of proven Penicillin PLUS Carbapenem allergy, use Ciprofloxacin 400 mg bd IV and Gentamicin. Do not use ciprofloxacin prophylactically in this situation

Myeloma patients should be given piperacillin-tazobactam as sole agent for first line empirical therapy if concerns about renal function.

2.1.2 ***Gentamicin***

The dose, frequency and monitoring can be found on the Hospital intranet in the www.ggcmedicines.org section

The dose of drug and time given should be recorded on the GGC gentamicin chart to ensure correct timing of samples for levels.

Those patients with good renal function ie calc creat cl>80mls/min and no history of previous renal issues can be prescribed gentamicin as first line empirical therapy. In patients with a history of renal dysfunction or on ambisome, cidofovir or other nephrotoxic agents, the decision to use empirical gentamicin first line should be made with the attending Consultant, preferably before the patient becomes pyrexial.

Providing patients do not fulfil the immunocompromised sepsis 6 criteria or are rigoring, hypotensive and/ or significantly tachycardic it is acceptable to use piperacillin-tazobactam as sole agent in patients with renal dysfunction.
NB – If Hickman line infection/colonisation is suspected, consideration should be given to line removal - after discussion with consultant in charge as well as gram positive cover.

If patients are stable continue first line antibiotics unless culture results suggest alternative agents would be more appropriate. Persistent intermittent pyrexia does not mean a patient MUST switch antibiotics at 48 hours providing they are not respiratory compromised, cardiovascularly unstable or rigoring

2.2 Second Line Empirical Antibiotics

Antibiotics should be switched empirically ONLY on a consultant ward round after a MINIMUM of 48 - 96 hours of therapy AND if evidence of cardiovascular instability or clinical deterioration.

STOP *Piperacillin-Tazo* AND *Gentamicin*
START *MEROPENEM* 1g tds
Dose should be adjusted according to renal function.

GRAM POSITIVE COVER
This should be added as a first line agent

- ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use
- OR if previous gram positive organism grown on blood cultures recently suggesting colonisation
- OR evidence of skin/ soft tissue sepsis.
-

This should NOT be added automatically at 48 - 96 hours and MUST be discussed with the attending Consultant.

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

The decision as to which of the following agents to used will depend on
1) Sensitivity if any previous positive gram positive organisms identified
2) If concerns about fluid volumes, time taken to administer use teicoplanin
3) If concerns about renal function teicoplanin is preferable unless high doses are required

TEICOPLANIN

The dose, frequency and monitoring should be obtained from the GG&C Therapeutics Handbook. This can be found on the Hospital intranet in the clinical guidelines section.

VANCOMYCIN

If the patient has a dual lumen line split the dose evenly between each line. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough only, target 10-20mg/l) and dose adjusted accordingly.

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days.

DO NOT FORGET that staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

2.2.1 STOP IV ANTIBIOTICS WHEN

If no organism isolated

If Neut > 0.5 x 10^9/l and rising - patient is well and apyrexial for 2 days
If Neut < 0.5 x 10^9/l - patient is well and apyrexial for 3 days. Restart oral ciprofloxacin prophylaxis.

Gentamicin consider stopping after 3 days if no evidence of gentamicin only sensitive organism. It should **ONLY** be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

2.3 ADDITIONAL AGENTS to CONSIDER

At any stage the following should be considered:

2.3.1 GROWTH FACTOR if NEUT <0.5 X 10^9/L

G-CSF 1 vial/day s.c. (filgrastim 300mcg/vial) ONLY if authorised by consultant in charge. NB 480mcg should be considered if patient >80 kg.

2.3.2 CLARITHROMYCIN IV

If suspicion of community acquired pneumonia to cover legionella or other atypical pneumonia eg mycoplasma.
NB this can prolong the QTc, check what other agents may also do this and carry out ECG if concerns

2.3.3 ACICLOVIR IV
If suspicion of disseminated herpes simplex or zoster infection.

2.3.4 CO-TRIMOXAZOLE IV
If suspicion of pneumocystis.

2.3.6 GANCICLOVIR IV
If in "at risk" group for CMV reactivation.

2.4 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)
In patients with acidosis and profound hypotension eg systolic drop of >30mmHg and unresponsive to rapid fluids and initial antibiotics the following should be considered.
Institute prompt use of alternative vascular access , insert a femoral line if necessary, for drug and fluid infusion with removal of Hickman line, which may be colonised causing profound unresponsive hypotension if continues to be used. If unable to remove, clamp and remove ASAP.

MEROPENEM	*1gm TID (adjust dose if renal impairment)*
AMIKACIN	**use GG&C Therapeutics Handbook for dose & levels.**
***TEICOPLANIN* or VANCOMYCIN**	**use GG&C Therapeutics Handbook for dose & levels.**

The use of Amikacin should only be in this group of high risk profoundly unwell patients or on the advice of microbiology due to the presence of resistant organisms
It should be remembered that hypothermia can denote severe infection and that patients on high dose steroids may be apyrexial.
See SEPSIS 6 SOP

3.0 PNEUMOCYSTIS CARINII PNEUMONIA (PCP)
Discuss with consultant; ensure appropriate specimens sent to ensure correct diagnosis
Proven or suspected PCP - level of severity can be assessed by degree of hypoxia
Moderate to severe - room air pO_2 <70 mm Hg or Alveolar-arterial O_2 gradient ≥35 mm Hg

3.1 MODERATE to SEVERE

3.1.1 FIRST LINE THERAPY
START
CO-TRIMOXAZOLE (High Dose). 120 mg/kg iv in 3-4 divided doses.
NB consider checking G6PD levels

If moderate to severe PCP start PREDNISOLONE
Days 1-5 40mg po bid

Days 6-10 40 mg daily
Days 11-21 20 mg od
IV M pred can be used at 75% dose if unable to take oral

Give regular iv ondansetron as antiemetic and switch to oral on discharge
Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 μg/ml.
DURATION 14-21 days

3.1.2 *SECOND LINE THERAPY*
For patients allergic to Septrin discuss with infectious diseases or microbiology teams

3.2 MILD TO MODERATE

3.2.1 *First line*

3.2.2 Cotrimoxazole:

- 90-120mg/kg daily
- *960mg x2 three times daily*

3.2.3 *Second Line*

- Discuss with infectious diseases or microbiology if alternative agents are needed because of allergy or toxicity

4.0 TOXOPLASMOSIS

This should be discussed with infectious diseases team and attending consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

Then for the next 2-4 weeks minimum/until immunosuppression resolved

	PYRIMETHAMINE	0.5 mg/kg po bd
	SULPHADIAZINE	30 mg/kg po bd
	CALCIUM FOLINATE	15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.
Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response or cannot tolerate sulphadiazine.
See IDSA guidelines on treating toxoplasmosis in HIV

5.0 DRUG DOSE REDUCTION IN RENAL & HEPATIC IMPAIRMENT

Please use a calculated creatintine clearance rather than eGFR when assessing renal function

The current GG&C Therapeutics Handbook or the most current Summary of Product Characteristics should be consulted for specific dosing advice (www.emc.medicines.org.uk).

6.0 AUDIT

Suggested topics include:

- Adherence to protocol eg length of time on iv antibiotics
- Use of Vancomycin and Teicoplanin
- Drug level monitoring for gentamicin and vancomycin
- Incidence and sensitivity of identified organisms

Recording of penicillin allergy and clarification

Haemopoietic Stem Cell Transplantation Services

Title: ANTIBIOTIC TREATMENT GUIDELINE
SOP No: BMT 100 006 05

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

AMENDMENTS FROM PREVIOUS VERSION
Addition of Daptomycin

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening, despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically, and frequently no causative organism can be found. The possibility of infection with opportunistic organisms, such as PCP and reactivation of previous infections e.g. CMV, VZV, should always be considered. Other infections, such as an upper respiratory tract infection can cause pneumonitis and death in the immunocompromised setting. All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.
This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to, or attending Haemato-oncology services in Greater Glasgow & Clyde. It is not intended as a substitute for appropriate discussion with microbiologists, infectious diseases, pharmacists and senior colleagues.

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Information about drug monitoring, adaptation for renal function (creatinine clearance calculator) and other advice on the use of antimicrobials can be found at www.ggcmedicines.org. and in the Drugs and therapeutics handbook. This policy has been reviewed by the GG&C antibiotic utilisation policy group.

The following antibiotics should be used for patients who have:

- Neutrophils <1.0 $x10^9$/l
- Post Allograft
- Clinically septic i.e. fulfil immunocompromised sepsis 6 criteria even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy eg. Myeloma, CLL patients.

Patients, who are low risk for overwhelming gram negative infection, should be given the most appropriate antibiotic for their clinical infective syndrome (e.g. Amoxicillin, clarithromycin etc. see

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

Drugs & Therapeutics handbook for recommended agent), but consider escalating to broad spectrum antibiotics as detailed overleaf if clinical deterioration with sepsis.

If screening specimens have shown a resistant organism the following should be adapted to provide adequate cover. If patients have grown a gram positive coagulase negative staphylococcus from routine cultures suggesting line colonisation, they do not always require treatment. However, if they fulfil criteria for treatment (see below) they should receive appropriate treatment for this organism as well as gram negative cover if this is appropriate for the clinical situation.

2.0 TREATMENT of PYREXIA

Haemato-oncology patients who become pyrexial i.e. >38°C should be started on empirical antibiotics as set out below. Gram positive cover should be added if they have a known coagulase negative staphylococcus grown from blood cultures. All pyrexial patients or those with a NEWS>5 should be assessed as per Sepsis 6 in the immunocompromised patient.

2.1 FIRST LINE EMPIRICAL ANTIBIOTICS

PIPERACILLIN-TAZOBACTAM + GENTAMICIN

Providing patients do not meet Sepsis 6 in the immunocompromised patient criteria, it is acceptable to use pip-tazobactam as sole agent if renal function is a concern or other nephrotoxic agents are being used such as ambisome or cidofovir.

2.1.1 ***Piperacillin- Tazobactam*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose for creatinine clearance.

Penicillin allergy should be discussed with the patient at the time of admission and therapy should be clarified with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.
For example:

- In cases of proven Penicillin allergy use Meropenem
- In cases of proven Penicillin PLUS Carbapenem allergy, use Ciprofloxacin 400 mg bd IV and Gentamicin. Do not use ciprofloxacin prophylactically in this situation

Myeloma patients should be given piperacillin-tazobactam as sole agent for first line empirical therapy if concerns about renal function.

2.1.2 ***Gentamicin***

The dose, frequency and monitoring can be found on the Hospital intranet in the www.ggcmedicines.org section

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

The dose of drug and time given should be recorded on the GGC gentamicin chart to ensure correct timing of samples for levels.
Those patients with good renal function ie calc creat cl>80mls/min and no history of previous renal issues can be prescribed gentamicin as first line empirical therapy. In patients with a history of renal dysfunction or on ambisome, cidofovir or other nephrotoxic agents, the decision to use empirical gentamicin first line should be made with the attending Consultant, preferably before the patient becomes pyrexial. Providing patients do not fulfil the immunocompromised sepsis 6 criteria or are rigoring, hypotensive and/ or significantly tachycardic it is acceptable to use piperacillin-tazobactam as sole agent in patients with renal dysfunction.
NB – If Hickman line infection/colonisation is suspected, consideration should be given to line removal - after discussion with consultant in charge as well as gram positive cover.

If patients are stable continue first line antibiotics unless culture results suggest alternative agents would be more appropriate. Persistent intermittent pyrexia does not mean a patient MUST switch antibiotics at 48 hours providing they are not respiratory compromised, cardiovascularly unstable or rigoring

2.2 Second Line Empirical Antibiotics

Antibiotics should be switched empirically ONLY on a consultant ward round after a MINIMUM of 48 - 96 hours of therapy AND if evidence of cardiovascular instability or clinical deterioration.

STOP	*Piperacillin-Tazo* AND *Gentamicin*	
START	*MEROPENEM*	1g tds

Dose should be adjusted according to renal function.

GRAM POSITIVE COVER

This should be added as a first line agent

- ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use
- OR if previous gram positive organism grown on blood cultures recently suggesting colonisation
- OR evidence of skin/ soft tissue sepsis.
- OR if concerns about enterococci

This should **NOT** be added automatically at 48 - 96 hours and MUST be discussed with the attending Consultant.

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

The decision as to which of the following agents to used will depend on

1) Sensitivity if any previous positive gram positive organisms identified
2) If concerns about fluid volumes, time taken to administer use teicoplanin
3) If concerns about renal function teicoplanin is preferable unless high doses are required
4) If patient very unwell or previous VRE identified for daptomycin or linezolid INSTEAD of vancomycin or teicoplanin

TEICOPLANIN

The dose, frequency and monitoring should be obtained from the GG&C Therapeutics Handbook. This can be found on the Hospital intranet in the clinical guidelines section.

VANCOMYCIN

If the patient has a dual lumen line split the dose evenly between each line. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough only, target 10-20mg/l) and dose adjusted accordingly.

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days.

DO NOT FORGET that staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

DAPTOMYCIN

Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly, and more frequently in those with renal impairment) during treatment.

The dose is calculated using actual body weight unless the patient is obese with a BMI ≥ 30 kg/m2. If BMI ≥ 30 kg/m2 an adjusted body weight (AdjBW) should be used to calculate the daptomycin mg/kg dose. Round the dose up to the nearest whole vial (350mg and 500mg vial strengths are available).Unless, the calculated dose is ≤ 10 % above the available whole vial, in which case, round the dose down.

If CrCl <30ml/min, the dosage frequency should be reduced to 48 hourly and more frequent monitoring is required.

Daptomycin may cause myopathy and rhabdomyolysis. Where possible, the drug's manufacturers recommend avoiding concomitant administration with other drugs which may also be associated with myopathies.

Daptomycin is classes as a "protected agent". To obtain a supply, send a complete Protected Antimicrobial ordering form and indent to pharmacy.
The form should be completed by prescribers, stating the indication. Clinical pharmacists can complete the form in conjunction with prescribers.

2.2.1 STOP IV ANTIBIOTICS WHEN

If no organism isolated

If Neut > 0.5 x 10^9/l and rising - patient is well and apyrexial for 2 days
If Neut < 0.5 x 10^9/l - patient is well and apyrexial for 3 days. Restart oral ciprofloxacin prophylaxis.

Gentamicin consider stopping after 3 days if no evidence of gentamicin only sensitive organism. It should **ONLY** be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

2.3 ADDITIONAL AGENTS to CONSIDER

At any stage the following should be considered:

2.3.1 GROWTH FACTOR if NEUT <0.5 X 10^9/L

G-CSF 1 vial/day s.c. (filgrastim 300mcg/vial) ONLY if authorised by consultant in charge. NB 480mcg should be considered if patient >80 kg.

2.3.2 CLARITHROMYCIN IV

If suspicion of community acquired pneumonia to cover legionella or other atypical pneumonia eg mycoplasma.
NB this can prolong the QTc, check what other agents may also do this and carry out ECG if concerns

2.3.3 ACICLOVIR IV

If suspicion of disseminated herpes simplex or zoster infection.

2.3.4 CO-TRIMOXAZOLE IV

If suspicion of pneumocystis.

2.3.6 GANCICLOVIR IV

If in "at risk" group for CMV reactivation.

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

2.4 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)

In patients with acidosis and profound hypotension eg systolic drop of >30mmHg and unresponsive to rapid fluids and initial antibiotics the following should be considered. Institute prompt use of alternative vascular access , insert a femoral line if necessary, for drug and fluid infusion with removal of Hickman line, which may be colonised causing profound unresponsive hypotension if continues to be used. If unable to remove, clamp and remove ASAP.

MEROPENEM	*1gm TID (adjust dose if renal impairment)*
AMIKACIN	**use GG&C Therapeutics Handbook for dose & levels.**
***TEICOPLANIN* or VANCOMYCIN**	**use GG&C Therapeutics Handbook for dose & levels.**

The use of Amikacin should only be in this group of high risk profoundly unwell patients or on the advice of microbiology due to the presence of resistant organisms
It should be remembered that hypothermia can denote severe infection and that patients on high dose steroids may be apyrexial.
See SEPSIS 6 SOP

3.0 PNEUMOCYSTIS CARINII PNEUMONIA (PCP)

Discuss with consultant; ensure appropriate specimens sent to ensure correct diagnosis
Proven or suspected PCP - level of severity can be assessed by degree of hypoxia
Moderate to severe - room air pO_2 <70 mm Hg or Alveolar-arterial O_2 gradient ≥35 mm Hg

3.1 MODERATE to SEVERE

3.1.1 FIRST LINE THERAPY

START
CO-TRIMOXAZOLE (High Dose). 120 mg/kg iv in 3-4 divided doses.
NB consider checking G6PD levels

If moderate to severe PCP start PREDNISOLONE
Days 1-5 40mg po bid
Days 6-10 40 mg daily
Days 11-21 20 mg od
IV M pred can be used at 75% dose if unable to take oral

Give regular iv ondansetron as antiemetic and switch to oral on discharge
Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 μg/ml.
DURATION 14-21 days

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

3.1.2 *SECOND LINE THERAPY*
For patients allergic to Septrin discuss with infectious diseases or microbiology teams

3.2 MILD TO MODERATE

3.2.1 *First line*

3.2.2 Cotrimoxazole:

- 90-120mg/kg daily
- *960mg x2 three times daily*

3.2.3 *Second Line*

- Discuss with infectious diseases or microbiology if alternative agents are needed because of allergy or toxicity

4.0 TOXOPLASMOSIS

This should be discussed with infectious diseases team and attending consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

Then for the next 2-4 weeks minimum/until immunosuppression resolved

	PYRIMETHAMINE	0.5 mg/kg po bd
	SULPHADIAZINE	30 mg/kg po bd
	CALCIUM FOLINATE	15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.
Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response or cannot tolerate sulphadiazine.
See IDSA guidelines on treating toxoplasmosis in HIV

5.0 DRUG DOSE REDUCTION IN RENAL & HEPATIC IMPAIRMENT

Please use a calculated creatintine clearance rather than eGFR when assessing renal function
The current GG&C Therapeutics Handbook or the most current Summary of Product Characteristics should be consulted for specific dosing advice (www.emc.medicines.org.uk).

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

6.0 AUDIT

Suggested topics include:

- Adherence to protocol eg length of time on iv antibiotics
- Use of Vancomycin and Teicoplanin
- Drug level monitoring for gentamicin and vancomycin
- Incidence and sensitivity of identified organisms

Recording of penicillin allergy and clarification

POLICY FOR ANTI-INFECTIVE USE IN HAEMATO-ONCOLOGY PATIENTS

AMENDMENTS FROM PREVIOUS VERSION
Daptomycin dosing information

1.0 INTRODUCTION

Infection in the immunocompromised patient can be life threatening, despite the use of prophylaxis. Patients thought to be infected should be assessed rapidly and treatment initiated promptly. It must be remembered that immunocompromised patients can present atypically without pyrexia and without any localising features as to the source of the infection. In the majority of cases treatment is therefore started empirically, and frequently no causative organism can be found. The possibility of infection with opportunistic organisms, such as PCP and reactivation of previous infections e.g. CMV, VZV, should always be considered. Other infections, such as an upper respiratory tract infection can cause pneumonitis and death in the immunocompromised setting. All of these factors should be taken into consideration when initiating and considering changing anti-infective agents.
This protocol outlines the antibiotic usage to be adopted for neutropenic/ immunocompromised patients admitted to, or attending Haemato-oncology services in Greater Glasgow & Clyde. It is not intended as a substitute for appropriate discussion with microbiologists, infectious diseases, pharmacists and senior colleagues.

Patients should be assessed and managed in accordance with:

- Assessment of Infection in the Immunocompromised Patient (BMT 100 041 – current version).
- Sepsis 6 in immuno-compromised patients (BMT 100 070 – current version)
- Antifungal Prophylaxis and Therapy Guideline' (BMT 100 008 – current version)
- Antiviral Use in Immunocompromised Patients' (BMT 100 002 – current version).

Copies of these can be found on StaffNet or via Q-Pulse (available from B7 (WoSCC), 4B and 4C-Haem (QEUH) computers.
Information about drug monitoring, adaptation for renal function (creatinine clearance calculator) and other advice on the use of antimicrobials can be found at www.ggcmedicines.org. and in the Drugs and therapeutics handbook. This policy has been reviewed by the GG&C antibiotic utilisation policy group.

The following antibiotics should be used for patients who have:

- Neutrophils <1.0 $x10^9$/l
- Post Allograft
- Clinically septic i.e. fulfil immunocompromised sepsis 6 criteria even if normal neutrophil count, but known to be immunosuppressed due to underlying disease or recent therapy eg. Myeloma, CLL patients.

Patients, who are low risk for overwhelming gram negative infection, should be given the most appropriate antibiotic for their clinical infective syndrome (e.g. Amoxicillin, clarithromycin etc. see Drugs & Therapeutics handbook for recommended agent), but consider escalating to broad spectrum antibiotics as detailed overleaf if clinical deterioration with sepsis.

If screening specimens have shown a resistant organism the following should be adapted to provide adequate cover. If patients have grown a gram positive coagulase negative staphylococcus from routine cultures suggesting line colonisation, they do not always require treatment. However, if they fulfil criteria for treatment (see below) they should receive appropriate treatment for this organism as well as gram negative cover if this is appropriate for the clinical situation.

2.0 TREATMENT of PYREXIA

Haemato-oncology patients who become pyrexial i.e. >38°C should be started on empirical antibiotics as set out below. Gram positive cover should be added if they have a known coagulase negative staphylococcus grown from blood cultures. All pyrexial patients or those with a NEWS>5 should be assessed as per Sepsis 6 in the immunocompromised patient.

2.1 FIRST LINE EMPIRICAL ANTIBIOTICS

PIPERACILLIN-TAZOBACTAM + GENTAMICIN
Providing patients do not meet Sepsis 6 in the immunocompromised patient criteria, it is acceptable to use pip-tazobactam as sole agent if renal function is a concern or other nephrotoxic agents are being used such as ambisome or cidofovir Patients undergoing a cytokine storm (i.e. Car-T and haplo) should also receive pip-tazobactam as a sole agent.

2.1.1 ***Piperacillin- Tazobactam*** 4.5 g IV qds starting dose if Cr Cl >80ml/min

Adjust dose for creatinine clearance.

Penicillin allergy should be discussed with the patient at the time of admission and therapy should be clarified with the consultant in charge and microbiology before the patient becomes septic so that an individual strategy can be developed.
For example:

- In cases of proven Penicillin allergy use Meropenem
- In cases of proven Penicillin PLUS Carbapenem allergy, use Ciprofloxacin 400 mg bd IV and Gentamicin. Do not use ciprofloxacin prophylactically in this situation

Myeloma patients should be given piperacillin-tazobactam as sole agent for first line empirical therapy if concerns about renal function.

2.1.2 ***Gentamicin***
The dose, frequency and monitoring can be found on the Hospital intranet in the www.ggcmedicines.org section

The dose of drug and time given should be recorded on the GGC gentamicin chart to ensure correct timing of samples for levels.
Those patients with good renal function ie calc creat cl>80mls/min and no history of previous renal issues can be prescribed gentamicin as first line empirical therapy. In patients with a history of renal dysfunction or on ambisome, cidofovir or other nephrotoxic agents, the decision to use empirical gentamicin first line should be made with the attending Consultant, preferably before the patient becomes pyrexial. Providing patients do not fulfil the immunocompromised sepsis 6 criteria or are rigoring, hypotensive and/ or significantly tachycardic it is acceptable to use piperacillin-tazobactam as sole agent in patients with renal dysfunction.
NB – If Hickman line infection/colonisation is suspected, consideration should be given to line removal - after discussion with consultant in charge as well as gram positive cover.

If patients are stable continue first line antibiotics unless culture results suggest alternative agents would be more appropriate. Persistent intermittent pyrexia does not mean a patient MUST switch antibiotics at 48 hours providing they are not respiratory compromised, cardiovascularly unstable or rigoring

2.2 Second Line Empirical Antibiotics

Antibiotics should be switched empirically ONLY on a consultant ward round after a MINIMUM of 48 - 96 hours of therapy AND if evidence of cardiovascular instability or clinical deterioration.

STOP	*Piperacillin-Tazo* AND *Gentamicin*	
START	*MEROPENEM*	1g tds

Dose should be adjusted according to renal function.

GRAM POSITIVE COVER

This should be added as a first line agent

- ONLY if a line infection is suspected, e.g. rigors/pyrexia with line use
- OR if previous gram positive organism grown on blood cultures recently suggesting colonisation
- OR evidence of skin/ soft tissue sepsis.
- OR if concerns about enterococci

This should **NOT** be added automatically at 48 - 96 hours and MUST be discussed with the attending Consultant.

NB – If a line infection is thought to be the most likely cause of fever in a patient who is otherwise well with neutrophil count > 0.5 x 10^9/l and no other obvious focus of

infection, it is permissible to use vancomycin/teicoplanin as the ONLY first line IV antibiotic therapy (for dosage see appendix).

The decision as to which of the following agents to used will depend on

1) Sensitivity if any previous positive gram positive organisms identified
2) If concerns about fluid volumes, time taken to administer use teicoplanin
3) If concerns about renal function teicoplanin is preferable unless high doses are required
4) If patient very unwell or previous VRE identified for daptomycin or linezolid INSTEAD of vancomycin or teicoplanin
5) Suspected or confirmed enterococcal infections for daptomycin INSTEAD of vancomycin or teicoplanin.

TEICOPLANIN

The dose, frequency and monitoring should be obtained from the GG&C Therapeutics Handbook. This can be found on the Hospital intranet in the clinical guidelines section.

VANCOMYCIN

If the patient has a dual lumen line split the dose evenly between each line. The two infusions should run concurrently through both lumina of the line over 2 hours. Levels should be checked after 2 doses (trough only, target 10-20mg/l) and dose adjusted accordingly.

If there is no proven line infection, the vancomycin/teicoplanin should be stopped after 5 days.

DO NOT FORGET that staph aureus septicaemia can occur and is then life-threatening. In a patient with septic shock, which is either related to use of the Hickman line, or is not responding to broad spectrum (anti-gram negative) antibiotics, vancomycin or teicoplanin MUST be added. Line removal should also be considered as soon as possible in this situation.

DAPTOMYCIN

Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly, and more frequently in those with renal impairment) during treatment.

An unlicensed dose of 10mg/kg is used to treat infections caused by or expected to be caused by enterococcus as per the GGC Daptomycin Dosing in Adults 18 years or more guidance NHSGGC Clinical Guideline Platform. The dose is calculated using actual body weight unless the patient is obese with a BMI ≥ 30 kg/m2. If BMI ≥ 30 kg/m2 an adjusted body weight (AdjBW) should be used to calculate the daptomycin mg/kg dose. Round the dose up to the nearest whole vial (350mg and 500mg vial strengths are available).Unless, the calculated dose is ≤ 10 % above the available whole vial, in which case, round the dose down.

If CrCl <30ml/min, the dosage frequency should be reduced to 48 hourly and more frequent monitoring is required.

Daptomycin may cause myopathy and rhabdomyolysis. Where possible, the drug's manufacturers recommend avoiding concomitant administration with other drugs which may also be associated with myopathies.

Daptomycin is classes as a "protected agent". To obtain a supply, send a complete Protected Antimicrobial ordering form and indent to pharmacy.
The form should be completed by prescribers, stating the indication. Clinical pharmacists can complete the form in conjunction with prescribers.

2.2.1 STOP IV ANTIBIOTICS WHEN

If no organism isolated

If Neut > 0.5 x 10^9/l and rising - patient is well and apyrexial for 2 days
If Neut < 0.5 x 10^9/l - patient is well and apyrexial for 3 days. Restart oral ciprofloxacin prophylaxis.

Gentamicin consider stopping after 3 days if no evidence of gentamicin only sensitive organism. It should **ONLY** be continued beyond a maximum of 5 days if there is a proven infection with a gentamicin only - sensitive organism.

2.3 ADDITIONAL AGENTS to CONSIDER

At any stage the following should be considered:

2.3.1 GROWTH FACTOR if NEUT <0.5 X 10^9/L

G-CSF — 1 vial/day s.c. (filgrastim 300mcg/vial) ONLY if authorised by consultant in charge. NB 480mcg should be considered if patient >80 kg.

2.3.2 CLARITHROMYCIN IV

If suspicion of community acquired pneumonia to cover legionella or other atypical pneumonia eg mycoplasma.
NB this can prolong the QTc, check what other agents may also do this and carry out ECG if concerns

2.3.3 ACICLOVIR IV

If suspicion of disseminated herpes simplex or zoster infection.

2.3.4 CO-TRIMOXAZOLE IV

If suspicion of pneumocystis.

2.3.6 GANCICLOVIR IV

If in "at risk" group for CMV reactivation.

2.4 SEPTIC SHOCK (i.e. severe hypotension +/- hypothermia)

In patients with acidosis and profound hypotension eg systolic drop of >30mmHg and unresponsive to rapid fluids and initial antibiotics the following should be considered. Institute prompt use of alternative vascular access , insert a femoral line if necessary, for drug and fluid infusion with removal of Hickman line, which may be colonised causing profound unresponsive hypotension if continues to be used. If unable to remove, clamp and remove ASAP.

MEROPENEM	*1gm TID (adjust dose if renal impairment)*
AMIKACIN	**use GG&C Therapeutics Handbook for dose & levels.**
***TEICOPLANIN* or VANCOMYCIN**	**use GG&C Therapeutics Handbook for dose & levels.**

The use of Amikacin should only be in this group of high risk profoundly unwell patients or on the advice of microbiology due to the presence of resistant organisms
It should be remembered that hypothermia can denote severe infection and that patients on high dose steroids may be apyrexial.
See SEPSIS 6 SOP

3.0 PNEUMOCYSTIS CARINII PNEUMONIA (PCP)

Discuss with consultant; ensure appropriate specimens sent to ensure correct diagnosis
Proven or suspected PCP - level of severity can be assessed by degree of hypoxia
Moderate to severe - room air pO_2 <70 mm Hg or Alveolar-arterial O_2 gradient ≥35 mm Hg

3.1 MODERATE to SEVERE

3.1.1 FIRST LINE THERAPY

START
CO-TRIMOXAZOLE (High Dose). 120 mg/kg iv in 3-4 divided doses.
NB consider checking G6PD levels

If moderate to severe PCP start PREDNISOLONE
Days 1-5 40mg po bid
Days 6-10 40 mg daily
Days 11-21 20 mg od
IV M pred can be used at 75% dose if unable to take oral

Give regular iv ondansetron as antiemetic and switch to oral on discharge

Levels should be measured if concern over failure to respond aiming for trimethoprim level >5 μg/ml.
DURATION 14-21 days

3.1.2 *SECOND LINE THERAPY*
For patients allergic to Septrin discuss with infectious diseases or microbiology teams

3.2 MILD TO MODERATE

3.2.1 *First line*

3.2.2 Cotrimoxazole:

- 90-120mg/kg daily
- *960mg x2 three times daily*

3.2.3 *Second Line*

- Discuss with infectious diseases or microbiology if alternative agents are needed because of allergy or toxicity

4.0 TOXOPLASMOSIS

This should be discussed with infectious diseases team and attending consultant before commencement and blood and CSF samples sent to Raigmore for confirmation of diagnosis & ongoing monitoring by PCR.

START	*PYRIMETHAMINE*	100mg po daily for 1-2 days
	SULPHADIAZINE	1g po 6 hourly for 1-2 days

Then for the next 2-4 weeks minimum/until immunosuppression resolved

	PYRIMETHAMINE	0.5 mg/kg po bd
	SULPHADIAZINE	30 mg/kg po bd
	CALCIUM FOLINATE	15 mg po every 3 days should be given while on treatment

Monitor anti-toxo PCR with weekly samples to Raigmore.
Consider adding *CLINDAMYCIN* 10 mg/kg or *AZITHROMYCIN* if no response or cannot tolerate sulphadiazine.
See IDSA guidelines on treating toxoplasmosis in HIV

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Suggested topics include:

- Adherence to protocol eg length of time on iv antibiotics
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Recording of penicillin allergy and clarification

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HAEMATO-ONCOLOGY ANTIFUNGAL POLICY

Author:
Dr A Parker

Review Group:
Dr M Leach, Dr B Jones, Mr I Butcher, Mr I MacDonald, Ms S McKendrick, Ms Y Mc Kenna, Ms G Caldwell and Ms M Campbell.

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Contents

1. Context
2. Introduction
3. Risk factors for development of invasive fungal infections
   3.1 Low risk patients
   3.2 High risk patients
4. Diagnosis of invasive fungal infections
5. Monitoring of renal function
6. Primary prophylaxis
   6.1 Low risk patients
   6.2 High risk patients
7. Secondary prophylaxis
8. Empirical/possible IFI therapy
   8.1 Low risk patients
   8.2 High risk patients
9. Proven/probable IFI therapy

Appendices

Appendix 1: Flow chart for antifungal prescribing in haemato-oncology patients
Appendix 2: Additional prescribing information.
Appendix 3: Cost summary.
Appendix 4: Definitions of fungal infections.

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1. Context

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential ~~cytotoxic~~ nephrotoxic chemotherapy regimens.

In addition, antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across ~~North Glasgow University Hospitals NHS Trust (NGUHT)~~Greater Glasgow Hospitals.

2. Introduction

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- U~~u~~nderlying disease being treated
- C~~c~~hemo +/- ~~-~~radiotherapy damaging the integrity of the gut mucosa
- P~~p~~artial ablation/ disruption of the immune system (duration depending on treatment)
- ~~graft-~~Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI~~infection~~ may be reduced ~~through~~by:

- ~~environmental~~Environmental controls e.g. reduction in airborne dust, water filtration etc.
- U~~u~~se of prophylactic antifungals
- S~~s~~urveillance for potential infectious signs and symptoms
- ~~the p~~Prompt treatment of probable/ proven infection.

3. Risk factors for development of invasive fungal infections

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

3.1 Low risk patients:

- Oral chemotherapy
- Lymphoma
- Auto peripheral blood stem cell transplant (PBSCT) (non total body irradiation)

- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

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3.2 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- High dose cytarabine
- Neutrophils less than $0.5x10^9$/L for more than two weeks
- Steroids plus neutrophils less than $1.0\ x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils $<1.0\ x10^9$/L)
- Acute leukaemia
- Total body irradiation autograft
- Campath recipient

4. Diagnosis of invasive fungal infections

It is imperative that patients are regularly assessed for clinical features of IFI i.e.

- Daily physical examination
- Early CT imaging following persistent pyrexia for more than 96 hours i.e. within 48-72 hours of commencing antifungal therapy.

EORTC (European Organisation for Research and Treatment of Cancer) criteria are helpful in determining the likelihood of proven/probable IFI (Appendix 4)

5. Monitoring of renal function

Many antifungal medicines are potentially nephrotoxic, therefore it is important that a baseline creatinine clearance is measured and renal function is monitored daily during treatment.

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10. On commencing antifungal therapy arrange a measured creatinine clearance or EDTA clearance.
11. If this is not available, estimate creatinine clearance using Cockcroft-Gault equation. It MUST be borne in mind that many haemato-oncology patients have a poor appetite and the estimated creatinine clearance using Cockcroft-Gault may be falsely low. If there is a recent creatinine clearance available (e.g. pre-transplant) this can be used as a baseline if lower than estimated.
12. Monitor serum creatinine daily during treatment.
13. If the creatinine rise is more than 1.5 times baseline, arrange EDTA clearance.

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Please refer to Appendix 2 for additional prescribing information for all antifungal medicines recommended in this policy.

6. Primary prophylaxis

Prophylactic treatment should commence on admission.

All patients should receive topical therapy ~~*amphotericin suspension 2mls four times daily*~~ to reduce gastrointestinal tract colonisation. ~~This should be rinsed round the mouth and swallowed.~~

- **Amphotericin lozenges 5mg four times daily**
- **Nystatin suspension 1ml four times daily** to be rinsed round mouth and swallowed

6.1 Low risk patients (see 3.1)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as it does not reduce the risk of aspergillus.

- **Fluconazole capsules, 100mg once daily**

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

6.2 High risk patients (see 3.2)

Itraconazole has been shown to reduce the risk of IFI but only if adequate plasma concentrations are achieved. Itraconazole levels should be measured once a week and the dose adjusted to maintain trough concentrations above 0.5mg/ml.

NOTE: Itraconazole and voriconazole should not be used for 5 days pre and post vinca alkaloid therapy i.e. vincristine, vinblastine or vinorelbine.
Itraconazole/ Voriconazole should not be given until ~~after the completion of TBI in cyclophosphamide/TBI transplant patients~~day 0 for any transplant regime containing cyclophosphamide

First line:

- **Itraconazole oral liquid 2.5mg/kg twice daily**

If immediate cover is required prescribe two doses of itraconazole intravenous injection 200mg, 12 hours apart then continue with oral liquid – this should be used for patients being conditioned with Cyclophosphamide ~~TBI~~ containing regimes with loading starting on Day 0 post transplant .
For aphagic patients prescribe itraconazole intravenous injection (see 2nd line for dose).
Capsules can be used in the non-neutropenic setting and may be possible in some neutropenic patients intolerant of liquid, but high doses are required to maintain levels.

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Second line:

High risk patients who are intolerant of the oral formulations of itraconazole or fail to achieve adequate therapeutic concentrations should be prescribed:

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Third line:

This should be used ONLY if patients are intolerant of all forms of itraconazole

Patients will receive prophylaxis according to the following categories:

Category I

ONLY in the following patient groups:

- relapsed Acute Myeloid Leukaemia (AML)
- AML on intensive chemotherapy with preceding documented MDS
- FLA or FLAG as current therapy
- Acute GvHD on steroids
- ALL on phase II induction
-

Prescribe *Voriconazole tablets*

- Loading *400mg twice daily for two doses*

- Maintenance *200mg twice daily (for patients >40kg)* (If <40kg see BNF)

N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.

Category II

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ONLY in Allograft patients intolerant of itraconazole not on steroids

Prescribe *Fluconazole capsules 400mg once daily.*

Category III

All other high risk patients who do not fall into categories I or II

Prescribe *Fluconazole 100mg daily*

7. Secondary prophylaxis

This is ONLY for patients with previous Proven/ Probable IFI

Patients who have had proven/probable IFI (see EORTC criteria) may not have cleared the infection at the start of their next course of chemotherapy and therefore are at high risk of infection reactivation. These patients should be prescribed:

- *Voriconazole tablets*

  - Loading *400mg twice daily for two doses*

  - Maintenance *200mg twice daily (for patients >40kg)*

  (If <40kg see BNF)

If patient is unable to tolerate oral therapy:

- *Voriconazole intravenous*

  - Loading *6mg/kg twice daily for two doses*

  - Maintenance *4mg/kg twice daily*

The need for voriconazole prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.

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8. Empirical/possible IFI therapy

Patients eligible for **empirical therapy** should either:

- Be in a high risk group with a pyrexia unresponsive to broad spectrum antibiotics for more than 96 hours

or

- fulfil the **EORTC Criteria for Possible IFI** (see appendix 4**)**

POSSIBLE INVASIVE INFECTION
At least 1 host criterion
AND
EITHER 1 microbiological criterion
OR 1 major OR 2 minor clinical criteria

All patients fulfilling the above criteria should have liver and chest +/- brain CT/MRI scans as soon as possible. This is to ensure patients with proven / probable IFI are receiving optimal therapy.

The choice of antifungal should be based on patient risk factors for developing invasive fungal infection, current prophylaxis (if any) and the potential complications of antifungal therapy and whether these complications will compromise future patient management.

8.1 Low risk patients

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Change to oral liquid capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5mg/ml until patient is no longer immunocompromised at the end of therapy.

8.2 High Rrisk patients

Categorise patient into category I, II or III
Patients in categories II & III must be discussed with the Consultant in charge for authorisation of non-conventional amphotericin use.

Category I
If the patient fulfils all the following criteria:

- Creatinine clearance > 70ml/min
- Central venous access
- NO concomitant nephrotoxic drugs
- NOT allograft recipients

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- NOT had a previous proven/probable IFI

Prescribe: ***Conventional Amphotericin B 0.5-1.0 mg/kg/day over 12 hours***

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Category II

If the patient has any of the following:

- experiences a severe reaction e.g. rigors to conventional amphotericin despite adequate pre-medication
- has no central venous access
- an allograft
- had a previous IFI
- requires outpatient amphotericin administration
- Unable to maintain serum potassium greater than 3.3mmol/L despite amiloride 10mg daily and 120mmol intravenous potassium replacement per day
- Pre-existing renal impairment defined as a creatinine clearance <70 ml/min
- A doubling of creatinine on amphotericin from baseline at diagnosis
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant

Prescribe: ***Ambisome 3mg/kg/day over 1 hour***

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Category III
Consider if the following apply

- Ppre-existing renal impairment defined as creatinine clearance less than 50ml/min
- Aa doubling of creatinine on ~~conventional amphotericin or~~ Ambisome from baseline i.e. at diagnosis
- Aa reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- Aat least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant.

Can be considered if the patient has any of the following:

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

Prescribe: ***Caspofungin***

Ablecet 5mg/kg can be considered in patients who are intolerant of ambisome, but for whom liposomal amphotericin is indicated as in category II. It is not included as part of the policy due to the high incidence of side effects.

9. Proven/probable IFI therapy
See Appendix 4 for definition.

PROBABLE INVASIVE INFECTION
At least 1 host criterion
AND 1 microbiological criterion
AND 1 major OR 2 minor clinical criteria

N.B. For individuals with evidence of intracerebral infection intravenous *voriconazole* is the drug of choice due to excellent penetration of the blood brain barrier.

First Line Therapy

- *Ambisome 3mg/kg/day administered over 1 hour*

Second Line Therapy:

- *Caspofungin*
  - Loading dose — *70 mg over one hour on day 1*
  - Maintenance — *50 mg once daily (if < 80 kg)*
    70 mg once daily (if > 80kg).

There is thought to be a synergistic activity between caspofungin and amphotericin therefore combination therapy may be considered, however caspofungin may have poor CNS penetration.
Dual therapy should be continued for a minimum of three days and then, if the patient is responding clinically, change to single therapy with caspofungin.

Mucormycosis
This is rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, *et al* 2005). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to Fluconazole, Voriconazole and the echinocandins e.g. Caspofungin. In individuals who are suspected of mucormycosis the following regime should be considered;

- *Posaconazole 400mg bd with food (200mg qid if not tolerated)*

N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.

- *Ambisome 3mg/kg daily*

On discharge
The duration of intravenous antifungal therapy will depend on the patient's individual response and underlying condition.

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The following may be used as oral therapy as an outpatient unless mucormycosis was suspected and should be continued during subsequent periods of chemotherapy and associated immunosuppression

- *Voriconazole tablets 200mg twice daily*

N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.

Additional Agents

The addition of the following agents to antifungal therapy can be considered depending on the patients' clinical condition **ONLY** if authorised by consultant in charge:

- *G-CSF one vial/day by subcutaneous injection*
  - Lenograstim 263µg /vial
  - Filgrastim 300µg /vial (filgrastim 480µg /vial if patient > 80kg).

ONLY for Candida infections

- *Flucytosine 50mg/kg three times daily over 20–40 minutes*

Reference

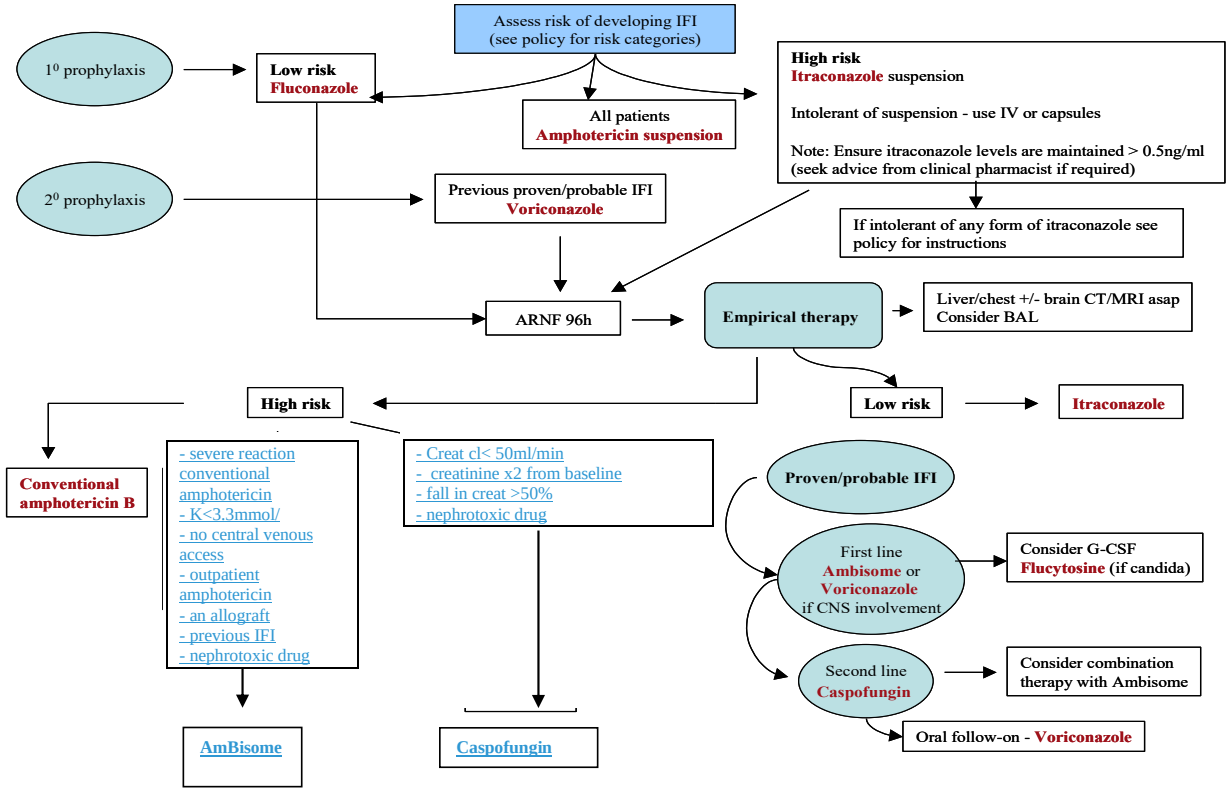
Spellberg, B., Edwards, J., Jr. & Ibrahim, A. (2005) Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management. *Clin. Microbiol. Rev.*, **18,** 556-569.

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Appendix 1

FLOW CHART FOR ANTIFUNGAL USE (see written policy & appendices for detail on doses etc)



Appendix 2
Additional prescribing information for antifungal medicines

Amphotericin Prescribing Information

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	Conventional Amphotericin	Abelcet	Ambisome
Test dose	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis
Pre-med	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.
Dose	**0.5 –1.0mg/kg/day**	**5mg/kg/day**	**3mg/kg/day**
Infusion time	**12 hours**	**2 hours**	**1 hour**

- Sodium loading by administering 1000ml sodium chloride 0.9% may protect against nephrotoxicity. All patients should receive a minimum of 1.5 litre/m^2 per day while receiving conventional amphotericin.
- Monitor urea and electrolytes DAILY, especially potassium, magnesium and creatinine.
- Hypokalaemia is common with amphotericin B. Amiloride 5-10mg orally daily should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations.
- Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours.

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Licensed Indications

- Ambisome - *By intravenous infusion*, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.
- Abelcet - *By intravenous infusion*, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where

toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients

Caspofungin Prescribing Information

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULT over 18 years, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg)

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~~**Caspofungin Prescribing Information**~~

- Dosage adjustment is necessary in patients with hepatic insufficiency as follows:
  - Mild hepatic impairment (Child-Pugh score 5 to 6) No dosage adjustment
  - Moderate hepatic impairment (Child-Pugh score 7 to 9) 70mg loading dose then
  - 35mg daily
  - Severe hepatic impairment (Child-Pugh score >9) No clinical experience

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Flucytosine Prescribing Information

- Plasma concentration must be measured after 3-4 days.
- Blood samples should be taken 2 hours after completing infusion.
- Plasma concentration for optimum response 50-80 mcg/ml. In renal impairment this should be lower 40-60 mcg/ml to allow for rapid deterioration in function.
- Concentration should not be allowed to exceed 100mcg/ml

Dosage in renal impairment

- Creatinine clearance 20-40 ml/min: 25-50 mg/kg every 12 hours.
- Creatinine clearance 10-20ml/min:25- 50 mg/kg every 24 hours.
- Creatinine clearance <10 ml/min: an initial single dose of 25 mg/kg; monitor level after 12hours. Subsequent doses should be calculated according to the results of regular monitoring of the serum concentration which should not be allowed to exceed 80 micrograms/ml

Fluconazole Prescribing Information

Licensed Indication

Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion*, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs.
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

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Itraconazole Prescribing Information

Licensed Indications

- Oropharyngeal candidiasis
- Prophylaxis in patients with haematological malignancy or undergoing bone-marrow transplant
- Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective

Dose

- *Liquid* 5 mg/kg daily in 2 divided doses
- *Caspules* 200mg twice daily
- *Intravenous Infusion* 200 mg every 12 hours for 2 days, then 200 mg once daily

~~•Itraconazole has been shown to reduce the risk of IFI but only if adequate plasma concentrations are achieved.~~

~~•Itraconazole levels should be measured once a week and the dose adjusted to maintain trough concentrations above 0.50mg/ml.~~

~~•Itraconazole oral liquid 2.5mg/kg twice daily should be used first line in high risk patients for primary prophylaxis.~~

~~•Higher doses may be required to achieve therapeutic concentrations.~~

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.

•In patients receiving cyclophosphamide as part of conditioning itraconazole should not be started until D0~~+1~~

•

•~~Itraconazole oral~~ L~~l~~iquid may cause nausea and vomiting. If nausea and vomiting persists with ~~itraconazole~~ oral liquid, and the patient has adequate therapeutic concentrations then ~~itraconazole~~ capsules 200mg twice daily may be used. Concentrations should be measured to ensure adequate levels are maintained following the switch to capsules. The dose may need to be increased.

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- Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). Itraconazole should **not be used within 5 days of vinca alkaloid** therapy. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.
- Patients who are neutropenic and those prescribed concomitant H2-antagonists e.g. ranitidine or proton pump inhibitors e.g. omeprazole will not achieve therapeutic concentrations unless the oral liquid is prescribed.
- ~~Patients with renal impairment defined as~~ A creatinine clearance ~~below~~ < 30ml/min should not be treated with ~~intravenous~~ iv itraconazole, but oral may be used.
- To administer ~~intravenously~~ iv add 25ml of itraconazole ~~intravenous~~ to the 50ml sodium chloride infusion bag provided. Administer 60ml of this solution over one hour i.e. 200mg. N.B. As soon as the infusion is completed a complete flush procedure must be started to avoid blocking the patient's line/cannula.
- Following rare reports of heart failure the CSM has advised caution when prescribing itraconazole to patients at high risk of heart failure.

~~Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular itraconazole should not be used within 5 days of vinca alkaloid therapy. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.~~

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Voriconazole Prescribing Information

Licensed Indications

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Dose

By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours;

By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months;

- Voriconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- Patients should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients with moderate to severe renal impairment defined as creatinine clearance < 30ml/min should not be treated with intravenous Voriconazole, but oral maybe used.
- In patients receiving cyclophosphamide as part of conditioning Voriconazole should not be started until D0 ~~+1~~
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- Liver function tests must be monitored before and during treatment

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Flucytosine Prescribing Information

- Plasma concentration must be measured after 3-4 days.
- Blood samples should be taken 2 hours after completing infusion.
- Plasma concentration for optimum response 50-80 mcg/ml. In renal impairment this should be lower 40-60 mcg/ml to allow for rapid deterioration in function.
- Concentration should not be allowed to exceed 100mcg/ml

Dosage in renal impairment

- Creatinine clearance 20-40 ml/min: 25-50 mg/kg every 12 hours.
- Creatinine clearance 10-20ml/min:25- 50 mg/kg every 24 hours.
- Creatinine clearance <10 ml/min: an initial single dose of 25 mg/kg; monitor level after 12hours. Subsequent doses should be calculated according to the results of regular monitoring of the serum concentration which should not be allowed to exceed 80 micrograms/ml

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Appendix 3

Cost Summary

The following information has been included as a guide to the relative costs of the drugs discussed in this policy and to show why it is important that the drugs are used as much as possible within an evidence based framework to ensure best use of health care resources.

All prices are taken from the BNF March 2003 – Hospital prices are lower than this.
Costs are based on a 70kg person for 1 week

Capsules

Fluconazole £33.22
Itraconazole £29.34
Voriconazole £520.77 (week 1), £455.68(subsequent weeks)

Liquid

Fluconazole £66.42
Itraconazole £85.39

Intravenous

Amphotericin B £18.13 to £36.26
Fluconazole £102.48
Itraconazole £514.8 (week 1), £400.40 (subsequent weeks)
Voriconazole £1621.20 (week 1), £1513.12 (subsequent weeks)
Ablecet £2012.19
Caspofungin £2382.8 (week 1), £2293.69 (subsequent weeks)
Ambisome £4017

Appendix ~~3~~4

Definitions of Fungal Infections
EORTC-IFICG and MSG criteria

PROVEN INVASIVE FUNGAL INFECTION

DEEP TISSUE INFECTIONS	
Moulds	*Yeasts*
Histo/ cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging)	Histo/ cytopathology showing yeast cells and/or pseudohyphae with evidence of associated tissue damage (either microscopically or unequivocally by imaging) from a needle aspiration or biopsy excluding mucous membranes
OR	OR
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (india ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF
FUNGAEMIA	
Positive blood culture of fungi excluding aspergillus spp. And penicillium spp other than P. marneffei, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism	Positive blood culture of candida and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism

PROBABLE INVASIVE INFECTION	POSSIBLE INVASIVE INFECTION
At least 1 host criterion	At least 1 host criterion
AND 1 microbiological criterion	AND
AND 1 major OR 2 minor clinical criteria	EITHER 1 microbiological criterion
	OR 1 major OR 2 minor clinical criteria

probable candidaemia - Clinical criteria are not required (no definition for possible)
Chronic disseminated Candida – microbial criteria not required for probable

Microbiological Criteria

- Positive culture of a mould (including aspergillus spp., Fusarium pp., zygomycetes, scedosporium pp), C Neoformans from sputum or BAL
- Positive culture or cytology/ direct microscopy for moulds from sinus aspirate
- Positive cytology/ direct microscopy for a mould or cryptococcus from sputum, BAL
- Positive aspergillus antigen in BAL, CSF or >2 blood samples
- Positive cryptococcal antigen in blood
- Positive cytology/ direct microscopy for fungal elements (eg cryptococcus in CSF) in sterile body fluids
- Two positive urine cultures of yeasts in the absence of urinary catheter
- Candida casts in the urine in the absence of urinary catheter
- Positive blood culture of candida spp.

Host Factors

- Neutropenia: PMN <500 $x10^9$/l for >10 days
- Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment
- Body temperature either >38^{0}C or <36^{0}C AND any of the following
    - Prolonged neutropenia (>10 days) in the previous 60 days
    - Recent or current use of significant immunosuppressive agents in the previous 30 days
    - Proven or probable invasive fungal infection in a previous episode
    - Coexistence of AIDS
- Signs & symptoms of GVHD, particularly severe (>grade 2) or chronic extensive disease
- Prolonged use of corticosteroids in previous 60 days (>3 weeks)

Clinical Criteria

Should be related to the site of microbiological criteria and temporarily related to current episode

MAJOR	MINOR
Lower Respiratory Tract Infection	
Any of the following new infiltrates on CT imaging; • halo sign, • air-crescent sign • cavity within an area of consolidation	• Symptoms of LRTI (cough, chest pain, haemoptysis) • Physical finding of pleural rub • Any new infiltrate not fulfilling major criterion • Pleural effusion
Sino Nasal Infection	
• Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighbouring structures, extensive base of skull destruction)	• URTI symptoms (nasal discharge etc.) • Nose ulceration or eschar of nasal mucosa or epistaxis • Periorbital swelling • Maxillary tenderness • Black necrotic lesions or perforation of the hard palate
CNS Infection	
• Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes, intracerebral abscesses or infarcts)	• CSF culture negative for other pathogens & malignant cells by microscopy and culture • Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) • Mental changes • Meningeal irritation findings • Abnormalities in CSF biochemistry and cell count
Disseminated Fungal Infection	
• Papular or nodular skin lesions without any other explanation • Intraocular findings suggestive of haematogenous fungal chorioretinitis or endophthalmitis	•
Chronic Disseminated Candidiasis (Probable)	
One host factor **AND** small peripheral target like abscesses (Bull's eye) in liver and or spleen demonstrated by CT, MRI or USS	

SOP Read and Understood By: (Print Name)	Staff Signature	Date	Supervisor's Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

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TITLE : ANTIFUNGAL POLICY
SOP No. 03 BMT 100 008 01 SUPERSEDES PREVIOUS VERSION

Compiled by	Dr Anne Parker	Date: 12/04/2005
Authorised by Dept. Head		Date:
Authorised by Quality Manager		Date:
Date of issue	21/06/2005	
Review	Annually	
Status	Valid until June 2006	
Number of pages (including this page)	22	

To be used in conjunction with SOP(s):

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	Posaconazole substituted for voriconazole as 2nd prophylaxis and if intolerant of itraconazole as primary prophylaxis	09/05/2008~~18/12/2006~~	Dr A Parker

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HAEMATO-ONCOLOGY ANTIFUNGAL POLICY

Author:
Dr A Parker

Review Group:
Dr M Leach, Dr B Jones, Mr I Butcher, Mr I MacDonald, Ms S McKendrick, Ms Y Mc Kenna, Ms G Caldwell and Ms M CampbellMs J Laskey, Mr J Allan, Ms K Baillie, Ms L Meehan.

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Contents

1. Context
2. Introduction
3. Risk factors for development of invasive fungal infections
   3.1 Low risk patients
   3.2 High risk patients
4. Diagnosis of invasive fungal infections
5. Monitoring of renal function
6. Primary prophylaxis
   6.1 Low risk patients
   6.2 High risk patients
7. Secondary prophylaxis
8. Empirical/possible IFI therapy
   8.1 Low risk patients
   8.2 High risk patients
9. Proven/probable IFI therapy

Appendices

Appendix 1: Flow chart for antifungal prescribing in haemato-oncology patients
Appendix 2: Additional prescribing information.
Appendix 3: Cost summary.
Appendix 4: Definitions of fungal infections.

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1. Context

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential cytotoxic nephrotoxic chemotherapy regimens.

In addition, antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across North Glasgow University Hospitals NHS Trust (NGUHT)Greater Glasgow Hospitals.

2. Introduction

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Uunderlying disease being treated
- Cchemo +/- -radiotherapy damaging the integrity of the gut mucosa
- Ppartial ablation/ disruption of the immune system (duration depending on treatment)
- graft-Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFIinfection may be reduced throughby:

- environmentalEnvironmental controls e.g. reduction in airborne dust, water filtration etc.
- Uuse of prophylactic antifungals
- Ssurveillance for potential infectious signs and symptoms
- the pPrompt treatment of probable/ proven infection.

3. Risk factors for development of invasive fungal infections

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

3.1 Low risk patients:

- Oral chemotherapy
- Lymphoma
- Auto peripheral blood stem cell transplant (PBSCT) (non total body irradiation)

- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

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3.2 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- High dose cytarabine
- Neutrophils less than $0.5x10^9$/L for more than two weeks
- Steroids plus neutrophils less than $1.0\ x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils $<1.0\ x10^9$/L)
- Acute leukaemia
- Total body irradiation autograft
- Campath recipient

4. Diagnosis of invasive fungal infections

It is imperative that patients are regularly assessed for clinical features of IFI i.e.

- Daily physical examination
- Early CT imaging following persistent pyrexia for more than 96 hours i.e. within 48-72 hours of commencing antifungal therapy.

EORTC (European Organisation for Research and Treatment of Cancer) criteria are helpful in determining the likelihood of proven/probable IFI (Appendix 4)

5. Monitoring of renal function

Many antifungal medicines are potentially nephrotoxic, therefore it is important that a baseline creatinine clearance is measured and renal function is monitored daily during treatment.

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10. On commencing antifungal therapy arrange a measured creatinine clearance or EDTA clearance.
11. If this is not available, estimate creatinine clearance using Cockcroft-Gault equation. It MUST be borne in mind that many haemato-oncology patients have a poor appetite and the estimated creatinine clearance using Cockcroft-Gault may be falsely low. If there is a recent creatinine clearance available (e.g. pre-transplant) this can be used as a baseline if lower than estimated.
12. Monitor serum creatinine daily during treatment.
13. If the creatinine rise is more than 1.5 times baseline, arrange EDTA clearance.

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Please refer to Appendix 2 for additional prescribing information for all antifungal medicines recommended in this policy.

6. Primary prophylaxis

Prophylactic treatment should commence on admission.

All patients should receive topical therapy ~~*amphotericin suspension 2mls four times daily*~~ to reduce gastrointestinal tract colonisation. ~~This should be rinsed round the mouth and swallowed.~~

- **Amphotericin lozenges 5mg four times daily**
- **Nystatin suspension 1ml four times daily** to be rinsed round mouth and swallowed

6.1 Low risk patients (see 3.1)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as it does not reduce the risk of aspergillus.

- **Fluconazole capsules, 100mg once daily**

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

6.2 High risk patients (see 3.2)

Itraconazole has been shown to reduce the risk of IFI but only if adequate plasma concentrations are achieved. Itraconazole levels should be measured once a week and the dose adjusted to maintain trough concentrations above 0.~~5mg~~5microg/ml.

NOTE: Itraconazole, Posaconazole, ~~and~~ voriconazole should not be used for 5 days pre and post vinca alkaloid therapy i.e. vincristine, vinblastine or vinorelbine.
~~Itraconazole/ Voriconazole~~These should not be given until ~~after the completion of TBI in cyclophosphamide/TBI transplant patients~~day 0 for any transplant regime containing cyclophosphamide

First line:

- **Itraconazole oral liquid 2.5mg/kg twice daily**

If immediate cover is required prescribe two doses of itraconazole intravenous injection 200mg, 12 hours apart then continue with oral liquid – this should be used for patients being conditioned with Cyclophosphamide ~~TBI~~ containing regimes with loading starting on Day 0 post transplant .
For aphagic patients prescribe itraconazole intravenous injection (see 2nd line for dose).
Capsules can be used in the non-neutropenic setting and may be possible in some neutropenic patients intolerant of liquid, but high doses are required to maintain levels.

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Second line:

High risk patients who are intolerant of the oral formulations of itraconazole or fail to achieve adequate therapeutic concentrations should be prescribed:

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Third line:

This should be used ONLY if patients are intolerant of all forms of itraconazole

Patients will receive prophylaxis according to the following categories:

Category I

ONLY in the following patient groups:

- relapsed Acute Myeloid Leukaemia (AML)
- AML on intensive chemotherapy with preceding documented MDS
- FLA or FLAG as current therapy
- Acute GvHD on steroids
- ALL on phase II induction i.e. NOT receving vincristine

Prescribe ~~*Voriconazole*~~ *Posaconazole tablets*

~~- Loading~~ *2~~4~~00mg ~~twice~~ three times daily ~~for two doses~~*

~~- Maintenance 200mg twice daily (for patients >40kg) (If <40kg see BNF)~~

~~**N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.**~~

Category II

ONLY in Allograft patients intolerant of itraconazole not on steroids

Prescribe *Fluconazole capsules 400mg once daily.*

Category III

All other high risk patients who do not fall into categories I or II

Prescribe *Fluconazole 100mg daily*

7. Secondary prophylaxis

This is ONLY for patients with previous Proven/ Probable IFI

Patients who have had proven/probable IFI (see EORTC criteria) may not have cleared the infection at the start of their next course of chemotherapy and therefore are at high risk of infection reactivation. These patients should be prescribed:

Prescribe *Posaconazole tablets*

200mg three times daily

~~•*Voriconazole tablets*~~

~~- Loading *400mg twice daily for two doses*~~

~~- Maintenance *200mg twice daily (for patients >40kg)*~~

~~(If <40kg see BNF)~~

If patient is unable to tolerate oral therapy:

- *Voriconazole intravenous*

  - Loading *6mg/kg twice daily for two doses*

  - Maintenance *4mg/kg twice daily*

N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.

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The need for Posaconzole/ voriconazole prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

~~N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.~~

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8. Empirical/possible IFI therapy

Patients eligible for **empirical therapy** should either:

- Be in a high risk group with a pyrexia unresponsive to broad spectrum antibiotics for more than 96 hours

or

- fulfil the **EORTC Criteria for Possible IFI** (see appendix 4**)**

POSSIBLE INVASIVE INFECTION
At least 1 host criterion
AND
EITHER 1 microbiological criterion
OR 1 major OR 2 minor clinical criteria

All patients fulfilling the above criteria should have liver and chest +/- brain CT/MRI scans as soon as possible. This is to ensure patients with proven / probable IFI are receiving optimal therapy.

The choice of antifungal should be based on patient risk factors for developing invasive fungal infection, current prophylaxis (if any) and the potential complications of antifungal therapy and whether these complications will compromise future patient management.

8.1 Low risk patients

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Change to oral liquid capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5microg/ml until patient is no longer immunocompromised at the end of therapy.

8.2 High Risk patients

Categorise patient into category I, II or III
Patients in categories II & III must be discussed with the Consultant in charge for authorisation of non-conventional amphotericin use.

Category I
If the patient fulfils all the following criteria:

- Creatinine clearance > 70ml/min
- Central venous access
- NO concomitant nephrotoxic drugs
- NOT allograft recipients

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- NOT had a previous proven/probable IFI

Prescribe: ***Conventional Amphotericin B 0.5-1.0 mg/kg/day over 12 hours***

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Category II

If the patient has any of the following:

- experiences a severe reaction e.g. rigors to conventional amphotericin despite adequate pre-medication
- has no central venous access
- an allograft
- had a previous IFI
- requires outpatient amphotericin administration
- Unable to maintain serum potassium greater than 3.3mmol/L despite amiloride 10mg daily and 120mmol intravenous potassium replacement per day
- Pre-existing renal impairment defined as a creatinine clearance <70 ml/min
- A doubling of creatinine on amphotericin from baseline at diagnosis
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant

Prescribe: ***Ambisome 3mg/kg/day over 1 hour***

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Category III
Consider if the following apply

- Pre-existing renal impairment defined as creatinine clearance less than 50ml/min
- A doubling of creatinine on ~~conventional amphotericin or~~ Ambisome from baseline i.e. at diagnosis
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant.

Can be considered if the patient has any of the following:

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

Prescribe: ***Caspofungin***

Ablecet 5mg/kg can be considered in patients who are intolerant of ambisome, but for whom liposomal amphotericin is indicated as in category II. It is not included as part of the policy due to the high incidence of side effects.

9. Proven/probable IFI therapy
See Appendix 4 for definition.

PROBABLE INVASIVE INFECTION
At least 1 host criterion
AND 1 microbiological criterion
AND 1 major OR 2 minor clinical criteria

N.B. For individuals with evidence of intracerebral infection intravenous *voriconazole* is the drug of choice due to excellent penetration of the blood brain barrier.

First Line Therapy

- *Ambisome 3mg/kg/day administered over 1 hour*

Second Line Therapy:

- *Caspofungin*
  - Loading dose — *70 mg over one hour on day 1*
  - Maintenance — *50 mg once daily (if < 80 kg)*
    70 mg once daily (if > 80kg).

There is thought to be a synergistic activity between caspofungin and amphotericin therefore combination therapy may be considered, however caspofungin may have poor CNS penetration.
Dual therapy should be continued for a minimum of three days and then, if the patient is responding clinically, change to single therapy with caspofungin.

Mucormycosis
This is rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, *et al* 2005). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to Fluconazole, Voriconazole and the echinocandins e.g. Caspofungin. In individuals who are suspected of mucormycosis the following regime should be considered;

- *Posaconazole 400mg bd with food (200mg qid if not tolerated)*

~~**N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.**~~

- *Ambisome 3mg/kg daily*

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On discharge

The duration of intravenous antifungal therapy will depend on the patient's individual response and underlying condition.

The following may be used as oral therapy as an outpatient unless mucormycosis was suspected and should be continued during subsequent periods of chemotherapy and associated immunosuppression

Prescribe *Posaconazole tablets* *200mg three times daily*

- ~~*Voriconazole tablets 200mg twice daily*~~

~~**N.B. This is an unlicensed indication and should be discussed with the patient and documented in the notes.**~~

Additional Agents

The addition of the following agents to antifungal therapy can be considered depending on the patients' clinical condition **ONLY** if authorised by consultant in charge:

- *G-CSF one vial/day by subcutaneous injection*
  - Lenograstim 263µg /vial
  - Filgrastim 300µg /vial (filgrastim 480µg /vial if patient > 80kg).

ONLY for Candida infections

- *Flucytosine 50mg/kg three times daily over 20–40 minutes*

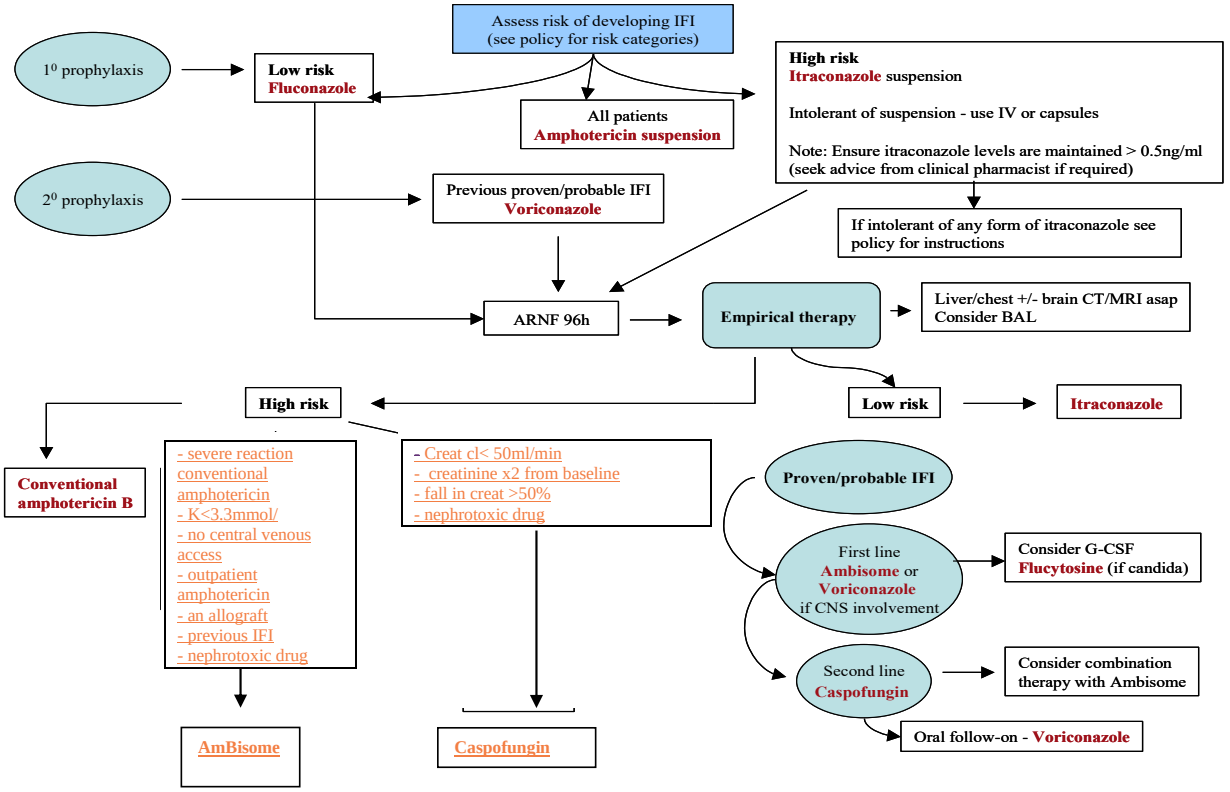
Reference

Spellberg, B., Edwards, J., Jr. & Ibrahim, A. (2005) Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management. *Clin. Microbiol. Rev.*, **18,** 556-569.

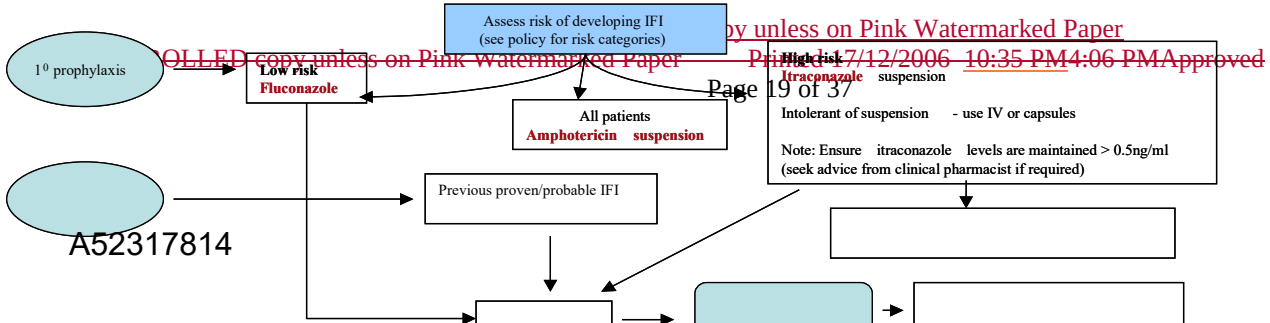
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Appendix 1

FLOW CHART FOR ANTIFUNGAL USE (see written policy & appendices for detail on doses etc)



FLOW CHART FOR ANTIFUNGAL USE (see written policy & appendices for detail on doses etc)



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Appendix 2
Additional prescribing information for antifungal medicines

Amphotericin Prescribing Information

	Conventional Amphotericin	Abelcet	Ambisome
Test dose	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis
Pre-med	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.
Dose	**0.5 –1.0mg/kg/day**	**5mg/kg/day**	**3mg/kg/day**
Infusion time	**12 hours**	**2 hours**	**1 hour**

- Sodium loading by administering 1000ml sodium chloride 0.9% may protect against nephrotoxicity. All patients should receive a minimum of 1.5 litre/m^2 per day while receiving conventional amphotericin.
- Monitor urea and electrolytes DAILY, especially potassium, magnesium and creatinine.
- Hypokalaemia is common with amphotericin B. Amiloride 5-10mg orally daily should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations.
- Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours.

Licensed Indications

- Ambisome - *By intravenous infusion*, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.
- Abelcet - *By intravenous infusion*, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where

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toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients

Caspofungin Prescribing Information

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULT over 18 years, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg)

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~~**Caspofungin Prescribing Information**~~

- Dosage adjustment is necessary in patients with hepatic insufficiency as follows:
  - Mild hepatic impairment (Child-Pugh score 5 to 6) No dosage adjustment
  - Moderate hepatic impairment (Child-Pugh score 7 to 9) 70mg loading dose then
  - 35mg daily
  - Severe hepatic impairment (Child-Pugh score >9) No clinical experience

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

~~**Flucytosine Prescribing Information**~~

- ~~Plasma concentration must be measured after 3-4 days.~~
- ~~Blood samples should be taken 2 hours after completing infusion.~~
- ~~Plasma concentration for optimum response 50-80 mcg/ml. In renal impairment this should be lower 40-60 mcg/ml to allow for rapid deterioration in function.~~
- ~~Concentration should not be allowed to exceed 100mcg/ml~~

~~Dosage in renal impairment~~
- ~~Creatinine clearance 20-40 ml/min: 25-50 mg/kg every 12 hours.~~
- ~~Creatinine clearance 10-20ml/min:25- 50 mg/kg every 24 hours.~~
- ~~Creatinine clearance <10 ml/min: an initial single dose of 25 mg/kg; monitor level after 12hours. Subsequent doses should be calculated according to the results of regular monitoring of the serum concentration which should not be allowed to exceed 80 micrograms/ml~~

Fluconazole Prescribing Information

Licensed Indication

Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion*, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

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- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

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Itraconazole Prescribing Information

Licensed Indications

- Oropharyngeal candidiasis
- Prophylaxis in patients with haematological malignancy or undergoing bone-marrow transplant
- Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective

Dose

- *Liquid* 5 mg/kg daily in 2 divided doses
- *Caspules* 200mg twice daily
- *Intravenous Infusion* 200 mg every 12 hours for 2 days, then 200 mg once daily

~~•Itraconazole has been shown to reduce the risk of IFI but only if adequate plasma concentrations are achieved.~~

~~•Itraconazole levels should be measured once a week and the dose adjusted to maintain trough concentrations above 0.50mg/ml.~~

~~•Itraconazole oral liquid 2.5mg/kg twice daily should be used first line in high risk patients for primary prophylaxis.~~

~~•Higher doses may be required to achieve therapeutic concentrations.~~

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.

•In patients receiving cyclophosphamide as part of conditioning itraconazole should not be started until D0~~+1~~

•

•~~Itraconazole oral~~ Liquid may cause nausea and vomiting. If nausea and vomiting persists with ~~itraconazole~~ oral liquid, and the patient has adequate therapeutic concentrations then ~~itraconazole~~ capsules 200mg twice daily may be used. Concentrations should be measured to ensure adequate levels are maintained following the switch to capsules. The dose may need to be increased.

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- Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). Itraconazole should **not be used within 5 days of vinca alkaloid** therapy. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.
- Patients who are neutropenic and those prescribed concomitant H2-antagonists e.g. ranitidine or proton pump inhibitors e.g. omeprazole will not achieve therapeutic concentrations unless the oral liquid is prescribed.
- ~~Patients with renal impairment defined as~~ A creatinine clearance ~~below~~ < 30ml/min should not be treated with ~~intravenous~~ iv itraconazole, but oral may be used.
- To administer ~~intravenously~~ iv add 25ml of itraconazole ~~intravenous~~ to the 50ml sodium chloride infusion bag provided. Administer 60ml of this solution over one hour i.e. 200mg. N.B. As soon as the infusion is completed a complete flush procedure must be started to avoid blocking the patient's line/cannula.
- Following rare reports of heart failure the CSM has advised caution when prescribing itraconazole to patients at high risk of heart failure.

~~Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular itraconazole should not be used within 5 days of vinca alkaloid therapy. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.~~

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Posaconazole Prescribing Information

Licensed Indications

Treatment of invasive aspergillosis either unresponsive to, or in patients intolerant of, amphotericin or itraconazole; fusariosis either unresponsive to, or in patients intolerant of, amphotericin; chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole; coccidioidomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole

Dose 400mg twice daily with food *or* if food not tolerated, 200 mg 4 times daily

Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole and itraconazole,

Dose 200mg 3 times daily with food,
starting before transplantation or before chemotherapy and continued until neutrophil count recovers

- Posaconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients receiving cyclophosphamide as part of conditioning Posaconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

Side-effects

gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, and flatulence); dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia; blood disorders (including anaemia, neutropenia, and thrombocytopenia), electrolyte disturbances; dry mouth; rash; *less commonly* pancreatitis, hepatic disorders, arrhythmias, palpitation, changes in blood pressure, oedema, convulsions, neuropathy, tremor, hyperglycaemia, menstrual disorders, renal failure, musculoskeletal pain, visual disturbances, mouth ulcers, and alopecia; *rarely* ileus, cardiac failure, myocardial infarction, stroke, thrombosis, syncope, pneumonitis, psychosis, depression, encephalopathy, adrenal insufficiency, breast pain, hearing impairment, and Stevens-Johnson syndrome

~~**Voriconazole Prescribing Information**~~

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Voriconazole Prescribing Information

Licensed Indications

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Dose

By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours;

By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months;

- Voriconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- Patients should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients with moderate to severe renal impairment defined as creatinine clearance < 30ml/min should not be treated with intravenous Voriconazole, but oral maybe used.
- In patients receiving cyclophosphamide as part of conditioning Voriconazole should not be started until D0+1
-
- Liver function tests must be monitored before and during treatment

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Voriconazole Prescribing Information

Licensed Indications

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*).

Dose

By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours;

By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months;

- Voriconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- Patients should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients with moderate to severe renal impairment defined as creatinine clearance < 30ml/min should not be treated with intravenous Voriconazole, but oral maybe used.
- In patients receiving cyclophosphamide as part of conditioning Voriconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea), jaundice; oedema, hypotension, chest pain; respiratory distress syndrome, sinusitis; headache, dizziness, asthenia, anxiety, depression, confusion, agitation, hallucinations, paraesthesia, tremor; influenza-like symptoms; hypoglycaemia; haematuria; blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia; visual disturbances including altered perception, blurred vision, and photophobia; rash, pruritus, photosensitivity, alopecia, cheilitis; injection-site reactions; *less commonly* cholecystitis, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, and Stevens-Johnson syndrome; *rarely* pseudomembranous colitis, convulsions, sleep disturbances, tinnitus, hearing disturbances, extrapyramidal effects, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, retinal haemorrhage, optic atrophy, and taste disturbances

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Flucytosine Prescribing Information

- Plasma concentration must be measured after 3-4 days.
- Blood samples should be taken 2 hours after completing infusion.
- Plasma concentration for optimum response 50-80 mcg/ml. In renal impairment this should be lower 40-60 mcg/ml to allow for rapid deterioration in function.
- Concentration should not be allowed to exceed 100mcg/ml

Dosage in renal impairment

- Creatinine clearance 20-40 ml/min: 25-50 mg/kg every 12 hours.
- Creatinine clearance 10-20ml/min:25- 50 mg/kg every 24 hours.
- Creatinine clearance <10 ml/min: an initial single dose of 25 mg/kg; monitor level after 12hours. Subsequent doses should be calculated according to the results of regular monitoring of the serum concentration which should not be allowed to exceed 80 micrograms/ml

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Appendix 3

Cost Summary

The following information has been included as a guide to the relative costs of the drugs discussed in this policy and to show why it is important that the drugs are used as much as possible within an evidence based framework to ensure best use of health care resources.

All prices are taken from the BNF March 2003 – Hospital prices are lower than this.
Costs are based on a 70kg person for 1 week

Capsules

Fluconazole	£33.22
Itraconazole	£29.34
Voriconazole	£520.77 (week 1), £455.68(subsequent weeks)

Liquid

Fluconazole	£66.42
Itraconazole	£85.39

Intravenous

Amphotericin B	£18.13 to £36.26
Fluconazole	£102.48
Itraconazole	£514.8 (week 1), £400.40 (subsequent weeks)
Voriconazole	£1621.20 (week 1), £1513.12 (subsequent weeks)
Ablecet	£2012.19
Caspofungin	£2382.8 (week 1), £2293.69 (subsequent weeks)
Ambisome	£4017

Appendix ~~3~~4

Definitions of Fungal Infections
EORTC-IFICG and MSG criteria

PROVEN INVASIVE FUNGAL INFECTION

DEEP TISSUE INFECTIONS	
Moulds	*Yeasts*
Histo/ cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging)	Histo/ cytopathology showing yeast cells and/or pseudohyphae with evidence of associated tissue damage (either microscopically or unequivocally by imaging) from a needle aspiration or biopsy excluding mucous membranes
OR	OR
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (india ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF
FUNGAEMIA	
Positive blood culture of fungi excluding aspergillus spp. And penicillium spp other than P. marneffei, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism	Positive blood culture of candida and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism

PROBABLE INVASIVE INFECTION	POSSIBLE INVASIVE INFECTION
At least 1 host criterion	At least 1 host criterion
AND 1 microbiological criterion	AND
AND 1 major OR 2 minor clinical criteria	EITHER 1 microbiological criterion
	OR 1 major OR 2 minor clinical criteria

probable candidaemia - Clinical criteria are not required (no definition for possible)
Chronic disseminated Candida – microbial criteria not required for probable

Microbiological Criteria

- Positive culture of a mould (including aspergillus spp., Fusarium pp., zygomycetes, scedosporium pp), C Neoformans from sputum or BAL
- Positive culture or cytology/ direct microscopy for moulds from sinus aspirate
- Positive cytology/ direct microscopy for a mould or cryptococcus from sputum, BAL
- Positive aspergillus antigen in BAL, CSF or >2 blood samples
- Positive cryptococcal antigen in blood
- Positive cytology/ direct microscopy for fungal elements (eg cryptococcus in CSF) in sterile body fluids
- Two positive urine cultures of yeasts in the absence of urinary catheter
- Candida casts in the urine in the absence of urinary catheter
- Positive blood culture of candida spp.

Host Factors

- Neutropenia: PMN <500 $x10^9$/l for >10 days
- Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment
- Body temperature either >38^{0}C or <36^{0}C AND any of the following
    - Prolonged neutropenia (>10 days) in the previous 60 days
    - Recent or current use of significant immunosuppressive agents in the previous 30 days
    - Proven or probable invasive fungal infection in a previous episode
    - Coexistence of AIDS
- Signs & symptoms of GVHD, particularly severe (>grade 2) or chronic extensive disease
- Prolonged use of corticosteroids in previous 60 days (>3 weeks)

Clinical Criteria

Should be related to the site of microbiological criteria and temporarily related to current episode

MAJOR	MINOR
Lower Respiratory Tract Infection	
Any of the following new infiltrates on CT imaging; • halo sign, • air-crescent sign • cavity within an area of consolidation	• Symptoms of LRTI (cough, chest pain, haemoptysis) • Physical finding of pleural rub • Any new infiltrate not fulfilling major criterion • Pleural effusion
Sino Nasal Infection	
• Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighbouring structures, extensive base of skull destruction)	• URTI symptoms (nasal discharge etc.) • Nose ulceration or eschar of nasal mucosa or epistaxis • Periorbital swelling • Maxillary tenderness • Black necrotic lesions or perforation of the hard palate
CNS Infection	
• Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes, intracerebral abscesses or infarcts)	• CSF culture negative for other pathogens & malignant cells by microscopy and culture • Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) • Mental changes • Meningeal irritation findings • Abnormalities in CSF biochemistry and cell count
Disseminated Fungal Infection	
• Papular or nodular skin lesions without any other explanation • Intraocular findings suggestive of haematogenous fungal chorioretinitis or endophthalmitis	•
Chronic Disseminated Candidiasis (Probable)	
One host factor **AND** small peripheral target like abscesses (Bull's eye) in liver and or spleen demonstrated by CT, MRI or USS	

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TITLE : Antifungal Policy
SOP No. BMT 100 008 0~~43~~ SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: ~~09/05/2008~~31/03/2009
Authorised by:	Dr Anne Parker	Date: ~~19/05/2008~~31/03/2009
Authorised by: Quality Manager	Robert H Boyd	Date: ~~19/05/2008~~31/03/2009
Date of issue:	~~19/05/2008~~31/03/2009	
Effective date:	~~19/05/2008~~31/03/2009	
Review:	~~Annually~~Every 2 Years	
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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
	Posaconazole as first line prophylaxis in selected group of patients	31/03/2009	Dr A Parker
	Removal of conventional amphotericin from policy		
	Removal of flucytosine from policy		

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HAEMATO-ONCOLOGY ANTIFUNGAL POLICY

Author:
Dr A Parker

Review Group:
Dr M Leach, Dr B Jones, Mr I Butcher, Mr I MacDonald, Ms S McKendrick, Ms J Laskey, Mr J Allan, Ms K Baillie, Ms L Meehan.

Contents

1. Context
2. Introduction
3. Risk factors for development of invasive fungal infections
   3.1 Low risk patients
   3.2 High risk patients
4. Diagnosis of invasive fungal infections
5. Monitoring of renal function
6. Primary prophylaxis
   6.1 Low risk patients
   6.2 High risk patients
7. Secondary prophylaxis
8. Empirical/possible IFI therapy
   8.1 Low risk patients
   8.2 High risk patients
9. Proven/probable IFI therapy

Appendices

Appendix 1: Flow chart for antifungal prescribing in haemato-oncology patients
Appendix 2: Additional prescribing information.
~~Appendix 3: Cost summary.~~
Appendix 34: Definitions of fungal infections.

1. Context

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow Hospitals.

2. Introduction

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

3. Risk factors for development of invasive fungal infections

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

3.1 Low risk patients:

- Oral chemotherapy
- Lymphoma
- Auto peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

3.2 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- High dose cytarabine
- Neutrophils less than $0.5x10^9$/L for more than two weeks
- Steroids plus neutrophils less than $1.0\ x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils $<1.0\ x10^9$/L)
- Acute leukaemia
- Total body irradiation autograft
- Campath recipient

4. Diagnosis of invasive fungal infections

It is imperative that patients are regularly assessed for clinical features of IFI i.e.

- Daily physical examination
- Early CT imaging following persistent pyrexia for more than 72- 96 hours i.e. preferably before, but definitely within 48-72 hours of commencing antifungal therapy.

EORTC (European Organisation for Research and Treatment of Cancer) criteria are helpful in determining the likelihood of proven/probable IFI (Appendix 4)

5. Monitoring of renal function

Many antifungal medicines are potentially nephrotoxic, therefore it is important that a baseline creatinine clearance is measured and renal function is monitored daily during treatment.

- On commencing antifungal therapy arrange a measured creatinine clearance or EDTA clearance.
- If this is not available, estimate creatinine clearance using Cockcroft-Gault equation. It MUST be borne in mind that many haemato-oncology patients have a poor appetite and the estimated creatinine clearance using Cockcroft-Gault may be falsely low. If there is a recent creatinine clearance available (e.g. pre-transplant) this can be used as a baseline if lower than estimated.
- Monitor serum creatinine daily during treatment.
- If the creatinine rise is more than 1.5 times baseline, arrange EDTA clearance.

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Antifungal Policy

Please refer to Appendix 2 for additional prescribing information for all antifungal medicines recommended in this policy.

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6. Primary prophylaxis

Prophylactic treatment should commence on admission.

All patients should receive topical therapy to reduce gastrointestinal tract colonisation.

- **Amphotericin lozenges 10mg four times daily**
- **Nystatin suspension 1ml four times daily** to be rinsed round mouth and swallowed

6.1 Low risk patients (see 3.1)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as it does not reduce the risk of aspergillus.

- **Fluconazole capsules, 100mg once daily**

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

6.2 High risk patients (see 3.2)

NOTE: Itraconazole, Posaconazole, voriconazole should NOT be used for 5 days PRE and POST vinca alkaloid therapy i.e. vincristine, vinblastine or vinorelbine. These should not be given until day 0 for any transplant regime containing cyclophosphamide

- **Posaconazole**
  - **Oral Liquid 200mg three times daily**

For the following indications

- Acute Myeloid Leukaemia (AML) on intensive therapy
- Acute GvHD on steroids
- Cord transplant recipients
- ALL on phase II induction i.e. NOT receving vincristine

- This should ONLY be used in patients who have a reasonable diet due to poor adsorption unless the diet has a reasonable fat content. There is no iv formulation available currently. **Itraconazole**
  - **oral** **liquid 2.5mg/kg twice daily for neutropenic patients**
    Capsules 200mg twice daily for non-neutropenic
  - **Intravenous.** **Loading dose *200mg twice daily for two days***
    Maintenance *200mg daily*

If immediate cover is required prescribe four doses of itraconazole intravenous injection 200mg, 12 hours apart then continue with oral liquid – this should be used for patients being conditioned with Cyclophosphamide containing regimes with loading starting on Day 0 post transplant . For aphagic patients prescribe itraconazole intravenous injection (see 2nd line for dose).

Capsules can be used in the non-neutropenic setting and may be possible in some neutropenic patients intolerant of liquid, but higher doses are required to maintain levels.

Itraconazole has been shown to reduce the risk of IFI but only if adequate plasma concentrations are achieved. Itraconazole levels should be measured once a week and the dose adjusted to maintain trough concentrations above 0.5microg/ml.5mg/L

In patients who are intolerant of other azoles due to liver dysfunction

- Fluconazole
  - Allografts 400mg once daily
  - All other patients 100mg daily

7. Secondary prophylaxis

This is ONLY for patients with previous Proven/ Probable IFI

Patients who have had proven/probable IFI (see EORTC criteria) may not have cleared the infection at the start of their next course of chemotherapy and therefore are at high risk of infection reactivation.
Patients previously received Itraconazole prophylaxis

- **Posaconazole** *liquid 200mg three times daily*

N.B. The following are unlicensed indications/ doses and should be discussed with the patient and documented in the notes.

If patient had posaconazole prophylaxis or is unable to tolerate oral therapy or has poor diet

- **Voriconazole**
  - *oral 400mg twelve hourly forfor2 (2 doses) 4 doses then 200mg twice daily*
  - *IV 6mg/kg twelve hourly for 4 days 2 doses then 4mg/kg daily*

In patients who have had proven/ probable IFI and are due further intensive therapy but have poor liver function or are intolerant of azoles consider

- **Ambisome iv 3-5mg/kg two - five times weekly**

Or

- **Caspofungin treatment dose**

The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

8. Empirical/possible IFI therapy

Patients eligible for **empirical therapy** should either:

- Be in a high risk group with a pyrexia unresponsive to broad spectrum antibiotics for more than 96 hours

or

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- fulfil the **EORTC Criteria for Possible IFI** (see appendix 34**)**

POSSIBLE INVASIVE INFECTION
At least 1 host criterion
AND
EITHER 1 microbiological criterion
OR 1 major OR 2 minor clinical criteria

All patients fulfilling the above criteria should have liver and chest +/- brain CT/MRI scans as soon as possible. This is to ensure patients with proven / probable IFI are receiving optimal therapy.

The choice of antifungal should be based on patient risk factors for developing invasive fungal infection, current prophylaxis (if any) and the potential complications of antifungal therapy and whether these complications will compromise future patient management.

8.1 Low risk patients

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Change to oral liquid / capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5mg/l until patient is no longer immunocompromised at the end of therapy.

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8.2 High Risk patients

Patients must be discussed with the Consultant in charge for authorisation.

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First Line Therapy

Ambisome 3mg/kg/day over 1 hour

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance less than 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant

Second Line Therapy

Caspofungin
- Loading dose *70 mg over one hour on day 1*
- Maintenance *50 mg once daily (if < 80 kg)*
70 mg once daily (if > 80kg).

NB **It should be remembered that this has a much narrower spectrum of activity compared with amphotericin**

Ablecet 5mg/kg can be considered in patients who are intolerant of ambisome, but require an amphotericin containing product. It is not included as part of the policy due to the high incidence of side effects.

9. Proven/probable IFI therapy
See Appendix 4 for definition.

PROBABLE INVASIVE INFECTION
At least 1 host criterion
AND 1 microbiological criterion
AND 1 major OR 2 minor clinical criteria

N.B. For individuals with evidence of intracerebral infection intravenous *voriconazole* is the drug of choice due to excellent penetration of the blood brain barrier.

First Line Therapy

- *Ambisome 3mg/kg/day administered over 1 hour*

Second Line Therapy:

- *Caspofungin*
  - Loading dose *70 mg over one hour on day 1*
  - Maintenance *50 mg once daily (if < 80 kg)*
  70 mg once daily (if > 80kg).

Combination therapy can be used if patient deteriorating despite treatment with ambisome or caspofungin for 5-7 days(Prentice, *et al* 2007). Choice will depend on suspected organism and clinical condition of patient particularly in terms of renal function. This should be discussed with the microbiology team before initiating
options include
- caspofungin with voriconazole,
- ambisome with caspofungin,
- ambisome with posaconazole

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Mucormycosis
This is rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, *et al* 2005). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to Fluconazole, Voriconazole and the echinocandins e.g. Caspofungin. In individuals who are suspected of mucormycosis the following regime should be considered;

- *Posaconazole 400mg bd with food or nutritional supplement – approximately 12-14 grams of fat (200mg qid if inadequate food intake)*
- *Ambisome 3mg/kg daily*

On discharge
The duration of intravenous antifungal therapy will depend on the patient's individual response and underlying condition.
The following may be used as oral therapy as an outpatient and should be continued during subsequent periods of chemotherapy and associated immunosuppression

Prescribe *Posaconazole liquid* *200mg three times daily*

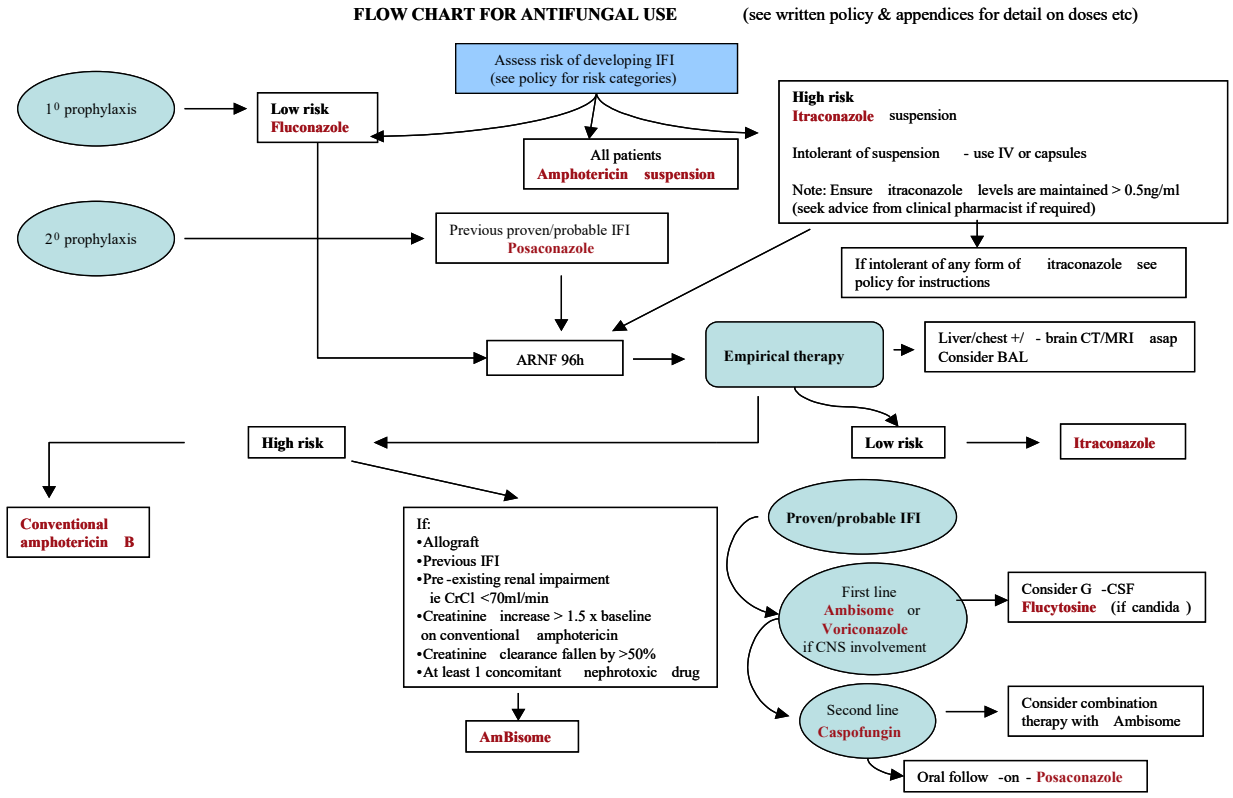
Additional Agents
The addition of the following agents to antifungal therapy can be considered depending on the patients' clinical condition **ONLY** if authorised by consultant in charge:

- *G-CSF one vial/day by subcutaneous injection*
  - Lenograstim 263µg /vial
  - Filgrastim 300µg /vial (filgrastim 480µg /vial if patient > 80kg).

Reference
Prentice, A., Glasmacher, A., Hobson, R., Schey, S.A., Barnes, R., Donnelly, J. & Jackson, G. (2007) *Guidelines on the management of invasive fungal infection during therapy for haematological malignancy (BCSH).*
Spellberg, B., Edwards, J., Jr. & Ibrahim, A. (2005) Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management. *Clin. Microbiol. Rev.*, **18,** 556-569.

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Appendix 1


FLOW CHART FOR ANTIFUNGAL USE
(see written policy & appendices for detail on doses etc)
Assess risk of developing IFI
(see policy for risk categories)
1⁰ prophylaxis
Low risk
Fluconazole
All patients
Amphotericin suspension
High risk
Itraconazole suspension
Intolerant of suspension - use IV or capsules
Note: Ensure itraconazole levels are maintained > 0.5ng/ml
(seek advice from clinical pharmacist if required)
2⁰ prophylaxis
Previous proven/probable IFI
Posaconazole
If intolerant of any form of itraconazole see policy for instructions
ARNF 96h
Empirical therapy
Liver/chest +/ - brain CT/MRI asap
Consider BAL
High risk
Low risk
Itraconazole
Conventional amphotericin B
If:
•Allograft
•Previous IFI
•Pre -existing renal impairment
ie CrCl <70ml/min
•Creatinine increase > 1.5 x baseline
on conventional amphotericin
•Creatinine clearance fallen by >50%
•At least 1 concomitant nephrotoxic drug
AmBisome
Proven/probable IFI
First line
Ambisome or
Voriconazole
if CNS involvement
Consider G -CSF
Flucytosine (if candida)
Second line
Caspofungin
Consider combination
therapy with Ambisome
Oral follow -on - Posaconazole

Appendix 2
Additional prescribing information for antifungal medicines

Amphotericin Prescribing Information

AMPHOTERICIN MUST BE PRESCRIBED AS THE PROPRIETARY PRODUCT – AMBISOME OR ABELCET

Prescribing as *amphotericin* has led to serious medication errors (National Patient Safety Agency Rapid Response Report 2 Septmber 2007)

GUIDANCE ON PRESCRIPTION, PREPARATION AND ADMINISTRATION OF INJECTABLE AMPHOTERICIN PRODUCTS

- **Use the proprietary name – Ambisome, Abelcet**
- **Conventional amphotericin is no longer included in this policy. However if it is to be prescribed for any reason, it must be prescribed using both terms *non-lipid amphotericin and Fungizone***
- **Verify the dose and preparation before prescribing, preparing or administering the product**
- **Record on the kardex and patient's weight and dose calculation used**

		Abelcet	Ambisome
Test dose		5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphalaxis
Pre-med		Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.
Dose		**5mg/kg/day**	**3mg/kg/day**
Infusion time		**2 hours**	**1 hour**

- Monitor urea and electrolytes DAILY, especially potassium, magnesium and creatinine.
- Hypokalaemia is common with Ambisome and Abelcet. Amiloride 5-10mg orally daily should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations.

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- Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours.

Licensed Indications

- Ambisome - *By intravenous infusion*, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.
- Abelcet - *By intravenous infusion*, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients

Caspofungin Prescribing Information

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

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Dose

By intravenous infusion, ADULT over 18 years, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg)

Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

- Mild hepatic impairment (Child-Pugh score 5 to 6) No dosage adjustment
- Moderate hepatic impairment (Child-Pugh score 7 to 9) 70mg loading dose then35mg daily
- Severe hepatic impairment (Child-Pugh score >9) No clinical experience

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised Bilirubin.

Fluconazole Prescribing Information

Licensed Indication
Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion*, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

Itraconazole Prescribing Information

Licensed Indications

- Oropharyngeal candidiasis
- Prophylaxis in patients with haematological malignancy or undergoing bone-marrow transplant
- Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective

Dose

- *Liquid* 5 mg/kg daily in 2 divided doses
- *Caspules* 200mg twice daily
- *Intravenous Infusion* 200 mg every 12 hours for 2 days, then 200 mg once daily

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients receiving cyclophosphamide as part of conditioning itraconazole should not be started until D0
- Liquid may cause nausea and vomiting. If nausea and vomiting persists with oral liquid, and the patient has adequate therapeutic concentrations then capsules 200mg twice daily may be used. Concentrations should be measured to ensure adequate levels are maintained following the switch to capsules. The dose may need to be increased.
- Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). Itraconazole should **not be used within 5 days of vinca alkaloid** therapy. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.
- Patients who are neutropenic and those prescribed concomitant H2-antagonists e.g. ranitidine or proton pump inhibitors e.g. omeprazole will not achieve therapeutic concentrations unless the oral liquid is prescribed.
- A creatinine clearance < 30ml/min should not be treated with iv itraconazole, but oral may be used.
- To administer iv add 25ml of itraconazole to the 50ml sodium chloride infusion bag provided. Administer 60ml of this solution over one hour i.e. 200mg. N.B. As soon as the infusion is completed a complete flush procedure must be started to avoid blocking the patient's line/cannula.

- Following rare reports of heart failure the CSM has advised caution when prescribing itraconazole to patients at high risk of heart failure.

Posaconazole Prescribing Information

Licensed Indications

Treatment of invasive aspergillosis either unresponsive to, or in patients intolerant of, amphotericin or itraconazole; fusariosis either unresponsive to, or in patients intolerant of, amphotericin; chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole; coccidioidomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole

Dose 400 mg twice daily with food *or* if food not tolerated, 200 mg 4 times daily

Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole and itraconazole,

Dose 200 mg 3 times daily with food,
starting before transplantation or before chemotherapy and continued until neutrophil count recovers

- Posaconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients receiving cyclophosphamide as part of conditioning Posaconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

Side-effects

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gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, and flatulence); dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia; blood disorders (including anaemia, neutropenia, and thrombocytopenia), electrolyte disturbances; dry mouth; rash; *less commonly* pancreatitis, hepatic disorders, arrhythmias, palpitation, changes in blood pressure, oedema, convulsions, neuropathy, tremor, hyperglycaemia, menstrual disorders, renal failure, musculoskeletal pain, visual disturbances, mouth ulcers, and alopecia; *rarely* ileus,

cardiac failure, myocardial infarction, stroke, thrombosis, syncope, pneumonitis, psychosis, depression, encephalopathy, adrenal insufficiency, breast pain, hearing impairment, and Stevens-Johnson syndrome

Voriconazole Prescribing Information

Licensed Indications

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Dose

By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours;

By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months;

- Voriconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- Patients should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients with moderate to severe renal impairment defined as creatinine clearance < 30ml/min should not be treated with intravenous Voriconazole, but oral maybe used.
- In patients receiving cyclophosphamide as part of conditioning Voriconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

Side-effects

gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea), jaundice; oedema, hypotension, chest pain; respiratory distress syndrome, sinusitis; headache, dizziness, asthenia, anxiety, depression, confusion, agitation, hallucinations, paraesthesia, tremor; influenza-like symptoms; hypoglycaemia; haematuria; blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia; visual disturbances including altered perception, blurred vision, and photophobia; rash, pruritus, photosensitivity, alopecia, cheilitis; injection-site reactions; *less commonly* cholecystitis, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia,

nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, and Stevens-Johnson syndrome; *rarely* pseudomembranous colitis, convulsions, sleep disturbances, tinnitus, hearing disturbances, extrapyramidal effects, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, retinal haemorrhage, optic atrophy, and taste disturbances.

Appendix 3

Definitions of Fungal Infections
EORTC-IFICG and MSG criteria

PROVEN INVASIVE FUNGAL INFECTION

DEEP TISSUE INFECTIONS	
Moulds	*Yeasts*
Histo/ cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging)	Histo/ cytopathology showing yeast cells and/or pseudohyphae with evidence of associated tissue damage (either microscopically or unequivocally by imaging) from a needle aspiration or biopsy excluding mucous membranes
OR	OR
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (india ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF
FUNGAEMIA	
Positive blood culture of fungi excluding aspergillus spp. And penicillium spp other than P. marneffei, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism	Positive blood culture of candida and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism

PROBABLE INVASIVE INFECTION	POSSIBLE INVASIVE INFECTION
At least 1 host criterion	At least 1 host criterion
AND 1 microbiological criterion	AND
AND 1 major OR 2 minor clinical criteria	EITHER 1 microbiological criterion
	OR 1 major OR 2 minor clinical criteria

probable candidaemia - Clinical criteria are not required (no definition for possible)
Chronic disseminated Candida – microbial criteria not required for probable

Microbiological Criteria

- Positive culture of a mould (including aspergillus spp., Fusarium pp., zygomycetes, scedosporium pp), C Neoformans from sputum or BAL
- Positive culture or cytology/ direct microscopy for moulds from sinus aspirate
- Positive cytology/ direct microscopy for a mould or cryptococcus from sputum, BAL
- Positive aspergillus antigen in BAL, CSF or >2 blood samples
- Positive cryptococcal antigen in blood
- Positive cytology/ direct microscopy for fungal elements (eg cryptococcus in CSF) in sterile body fluids
- Two positive urine cultures of yeasts in the absence of urinary catheter
- Candida casts in the urine in the absence of urinary catheter
- Positive blood culture of candida spp.

Host Factors

- Neutropenia: PMN <500 x10^9/l for >10 days
- Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment
- Body temperature either >38^{0}C or <36^{0}C AND any of the following
    - Prolonged neutropenia (>10 days) in the previous 60 days
    - Recent or current use of significant immunosuppressive agents in the previous 30 days
    - Proven or probable invasive fungal infection in a previous episode
    - Coexistence of AIDS
- Signs & symptoms of GVHD, particularly severe (>grade 2) or chronic extensive disease
- Prolonged use of corticosteroids in previous 60 days (>3 weeks)

Clinical Criteria

Should be related to the site of microbiological criteria and temporarily related to current episode

MAJOR	**MINOR**
Lower Respiratory Tract Infection	
Any of the following new infiltrates on CT imaging; • halo sign, • air-crescent sign • cavity within an area of consolidation	• Symptoms of LRTI (cough, chest pain, haemoptysis) • Physical finding of pleural rub • Any new infiltrate not fulfilling major criterion • Pleural effusion
Sino Nasal Infection	
• Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighbouring structures, extensive base of skull destruction)	• URTI symptoms (nasal discharge etc.) • Nose ulceration or eschar of nasal mucosa or epistaxis • Periorbital swelling • Maxillary tenderness • Black necrotic lesions or perforation of the hard palate
CNS Infection	
• Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes, intracerebral abscesses or infarcts)	• CSF culture negative for other pathogens & malignant cells by microscopy and culture • Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) • Mental changes • Meningeal irritation findings • Abnormalities in CSF biochemistry and cell count
Disseminated Fungal Infection	
• Papular or nodular skin lesions without any other explanation • Intraocular findings suggestive of haematogenous fungal chorioretinitis or endophthalmitis	•
Chronic Disseminated Candidiasis (Probable)	
One host factor **AND** small peripheral target like abscesses (Bull's eye) in liver and or spleen demonstrated by CT, MRI or USS	

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : Antifungal Policy
SOP No. BMT 100 008 05 **SUPERSEDES PREVIOUS VERSION**

Compiled by:	Dr Anne Parker	Date: 01/07/2010
Authorised by:	Dr Anne Parker	Date: 04/08/2011
Authorised by: Quality Manager	Robert H Boyd	Date: 04/08/2011
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Review:	Every 2 Years	
Number of pages: (including this page)	17	

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Antifungal Policy

Contents

1. Context
2. Introduction
3. Risk factors for development of invasive fungal infections
   3.1 Low risk patients
   3.2 Intermediate risk patients
   3.3 High risk patients
4. Diagnosis of invasive fungal infections
5. Monitoring of renal function
6. Prophylaxis
7. Secondary prophylaxis
8. Decision to Treat
9. Therapy

Appendices

Appendix 1: Flow chart for management of haemato-oncology patients
Appendix 2: Additional prescribing information.
Appendix 3: Definitions of fungal infections.

1. Context

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients, due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow & Clyde Hospitals.

2. Introduction

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

3. Risk factors for development of invasive fungal infections

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

3.1 Low risk patients

~~4.~~ Oral chemotherapy
~~5.~~ Lymphoma
~~6.~~ Auto peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
~~7.~~ Acute lymphoblastic leukaemia on maintenance
~~8.~~ Other groups not considered as high risk

3.2 Moderate Risk patients

~~9.~~ Steroids plus neutrophils less than 1.0 x10^9/L for more than one week
~~10.~~ Fluconazole resistant colonisation
~~11.~~ Colonisation of more than one site plus neutropenia (neutrophils <1.0 x10^9/L)
~~12.~~ Alemtuzumab recipient

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3.3 High risk patients:

- ~~13.~~ GvHD
- ~~14.~~ Allogeneic Marrow & PBSCT
- ~~15.~~ High dose cytarabine
- ~~16.~~ Neutrophils less than $0.5x10^9$/L for more than two weeks eg. aplastic anaemia, hairy cell leukaemia
- ~~17.~~ Acute leukaemia on intensive therapy

~~18.~~4. Diagnosis of invasive fungal infections

It is imperative that patients are regularly assessed for clinical features of IFI

- Daily physical examination
- History of pleuritic pain, sinus discomfort etc.
- **Early CT** imaging of chest & sinuses, following persistent pyrexia unresponsive to broad spectrum antibiotics for more than 72- 96 hours
  - Consideration of abdo and pelvis CT if symptoms suggestive of infection
- BAL/ Sinus washout with Galactomannan

~~19.~~5. Monitoring of renal function

Many antifungal medicines are potentially nephrotoxic, therefore it is important that a baseline creatinine clearance is measured and renal function is monitored daily during treatment.

- Monitor serum creatinine and eGFR daily during treatment.
- If the creatinine rise is more than 1.5 times baseline, arrange EDTA clearance.

Please refer to Appendix 2 for additional prescribing information for all antifungal medicines recommended in this policy.

6. Primary prophylaxis

Prophylactic treatment should commence on admission or Day 0 for autografts.

6.1 Low & moderate risk patients (see 3.1 & 3.2)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as fluconazole does not reduce the risk of aspergillus.

- **Fluconazole capsules, 100mg once daily**

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

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6.2 High risk patients (see 3.2)

NOTE: Itraconazole, Posaconazole, voriconazole should NOT be used for 5 days PRE and POST vinca alkaloid therapy i.e. vincristine, vinblastine or vinorelbine or Gemtuzumab ozogamicin.
These should not be given until day 0 for any transplant regime containing cyclophosphamide

Posaconazole

- **Oral** **Liquid 200mg three times daily**

For the following indications

- Acute Myeloid Leukaemia (AML) on intensive chemotherapy
  - with preceding MDS
  - relapse
- Acute GvHD on steroids
- Cord transplant recipients
- ALL on phase II induction i.e. NOT receiving vincristine

- This should ONLY be used in patients who have a reasonable diet due to poor absorption unless the diet has a reasonable fat content (12-14 g fat with each dose eg 2 portions butter, 1 portion ice-cream, 1 full fat yogurt, half a CalShake if not able to eat normal meal). There is no iv formulation available currently.

For all other high risk patients

Itraconazole

- **oral** **liquid** **2.5mg/kg bd for neutropenic patients**
  Capsules **200mg bd for non-neutropenic**
- **Intravenous.** **Loading dose *200mg bd for two days***
  Maintenance *200mg daily*

If immediate cover is required prescribe four doses of itraconazole intravenous injection 200mg, 12 hours apart then continue with oral liquid – this should be used for patients being conditioned with Cyclophosphamide containing regimens with loading starting on Day 0 post transplant.
For aphagic patients prescribe itraconazole intravenous injection.
Capsules can be used in the non-neutropenic setting and may be possible in some neutropenic patients intolerant of liquid, but higher doses are required to maintain levels. Itraconazole has been shown to reduce the risk of IFI, but only if adequate plasma concentrations are achieved. Itraconazole levels should be measured once a week and the dose adjusted to **maintain trough concentrations above 0.5microgam/ml.**

In high risk patients who are intolerant of other azoles due to liver dysfunction

- Fluconazole
  - Allografts 400mg once daily
  - All other patients 100mg daily

ALL patients during induction receiving weekly vincristine/ vinblastine ONLY

- Ambisome 3mg/kg twice weekly

NB this is an unlicensed indication and must be discussed with the patient & documented in the notes

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7. Secondary prophylaxis

This is ONLY for patients previously treated for probable/ proven IFI

Patients who have had therapy for previous IFI may not have cleared the infection at the start of their next course of chemotherapy and therefore are at high risk of reactivation of infection during subsequent periods of neutropenia.
Patients previously received Itraconazole prophylaxis

- **Posaconazole** *liquid 200mg three times daily*

If patient had posaconazole prophylaxis previously or is unable to tolerate oral therapy or has poor diet

- **Voriconazole**
  - *oral 400mg twelve hourly for 2 doses then 200mg twice daily*
  - *IV 6mg/kg twelve hourly for 2 doses then 4mg/kg twice daily*

N.B. The above is an unlicensed indication and should be discussed with the patient and documented in the notes.

In patients who have had proven/ probable IFI and are due to receive further intensive therapy but have poor liver function or are intolerant of azoles consider

- **Ambisome** **iv 1 mg/kg daily**
  iv 3-5mg/kg two - three times weekly

Or

- **Caspofungin** **daily as per treatment dose**

The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

- Acute leukaemia – once neutrophils > 1 x 10^9/l
- Allograft – at consultants discretion

8. Decision to Treat

The decision to start therapy should be based on a combination of the following (Barnes, White et al. 2009)

- **Clinical features**
  - Pyrexia unresponsive to broad spectrum antibiotics for 96 hrs with no positive cultures
  - Haemoptysis, sinus discomfort, pleuritic pain, visual disturbance etc.
  - Pleural rub, facial swelling, retinal infiltrates etc.
- **Radiological features**
  - CXR infiltrates
  - CT scan changes suggestive of IFI
- **Galactomannan result positive**
  - Blood
  - BAL/ sinus washings etc.

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Patients who have clinical features suggestive of IFI should have the following

- Daily Blood for galactomannan
- Urgent CT scan of chest + any additional area of significant symptoms/ signs
- Urgent BAL/ sinus washout if indicated
- Ophthalmology/ ENT/ respiratory review if indicated

The decision to treat should be based on the treatment algorithm (appendix 1)

NB. The presence of sequential positive blood galactomannan MUST not be the sole means of deciding to initiate therapy, but as an adjunct to aid in the decision as to whether IFI is the most likely cause of the patients symptoms, as false positives can occur due to diet and antibiotic therapy. However, a positive result from BAL or sinus washings is a strong indicator(Leeflang, Debets-Ossenkopp et al. 2009).

9. Therapy

The choice of antifungal should be based on the following

- Patient risk factors for developing invasive fungal infection,
- Current prophylaxis (if any)
- Potential complications of antifungal therapy and whether these complications will compromise future patient management.
- Culture results (if any)
- Clinical & radiological features

9.1 Low risk patients

- *Itraconazole intravenous,*
  - Loading dose *200mg twice daily for two days*
  - Maintenance *200mg daily*

Change to oral liquid / capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5microgram/ml until patient is no longer immunocompromised at the end of therapy.

9.2 Moderate & High Risk patients

Patients must be discussed with the Consultant in charge for authorisation.

First Line Therapy

Ambisome 3mg/kg/day over 1 hour

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance < 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant
- In patients with CNS fungal infection iv voriconazole should be added as it has good CNS penetration.

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Second Line Therapy

Caspofungin

- Loading dose *70 mg over one hour on day 1*
- Maintenance *50 mg once daily (if < 80 kg)*
  70 mg once daily (if > 80kg).

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

- May be as first line therapy in cord transplants/ acute leukaemia where renal function is a concern
- May be used as first line therapy in invasive candidiasis

Ablecet 5mg/kg can be considered in patients who are intolerant of ambisome, but require an amphotericin containing product. It is not included as part of the policy due to the high incidence of side effects.

9.3 Duration

The duration of antifungal therapy will depend on

- Probability of IFI
- Patient's individual response to therapy
- Underlying condition & degree of immunosuppression

Antifungal therapy should be discontinued when there is resolution of clinical features. Consideration should be given to the requirement for secondary prophylaxis once the current episode has resolved.
The use of surgery to remove isolated persisting lesions may be appropriate

9.4 Combination therapy

This can be used if patient has IFI and is deteriorating despite treatment with ambisome or caspofungin for 5-7 days(Prentice, Glasmacher et al. 2007). Choice will depend on suspected organism and clinical condition of patient particularly in terms of renal function. This should be discussed with the microbiology team before initiating
Options include

- caspofungin with voriconazole,
- ambisome with caspofungin,
- ambisome with posaconazole

9.5 Mucormycosis

This is a rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, Edwards et al. 2005). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to Fluconazole, Voriconazole and the echinocandins e.g. Caspofungin. In individuals who are suspected of mucormycosis the following regimen should be considered;

- *Posaconazole* *400mg bd with food or nutritional supplement – approximately 12-14 grams of fat (200mg qid if inadequate food intake)*

PLUS

- *Ambisome* *3mg/kg daily*

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9.6 Additional Agents

The addition of the following agents to antifungal therapy can be considered for neutropenic patients depending on the patients' clinical condition **ONLY** if authorised by consultant in charge:

~~10.~~ *G-CSF one vial/day by subcutaneous injection*
- Lenograstim 263µg /vial
- Filgrastim 300µg /vial (filgrastim 480µg /vial if patient > 80kg).

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Reference

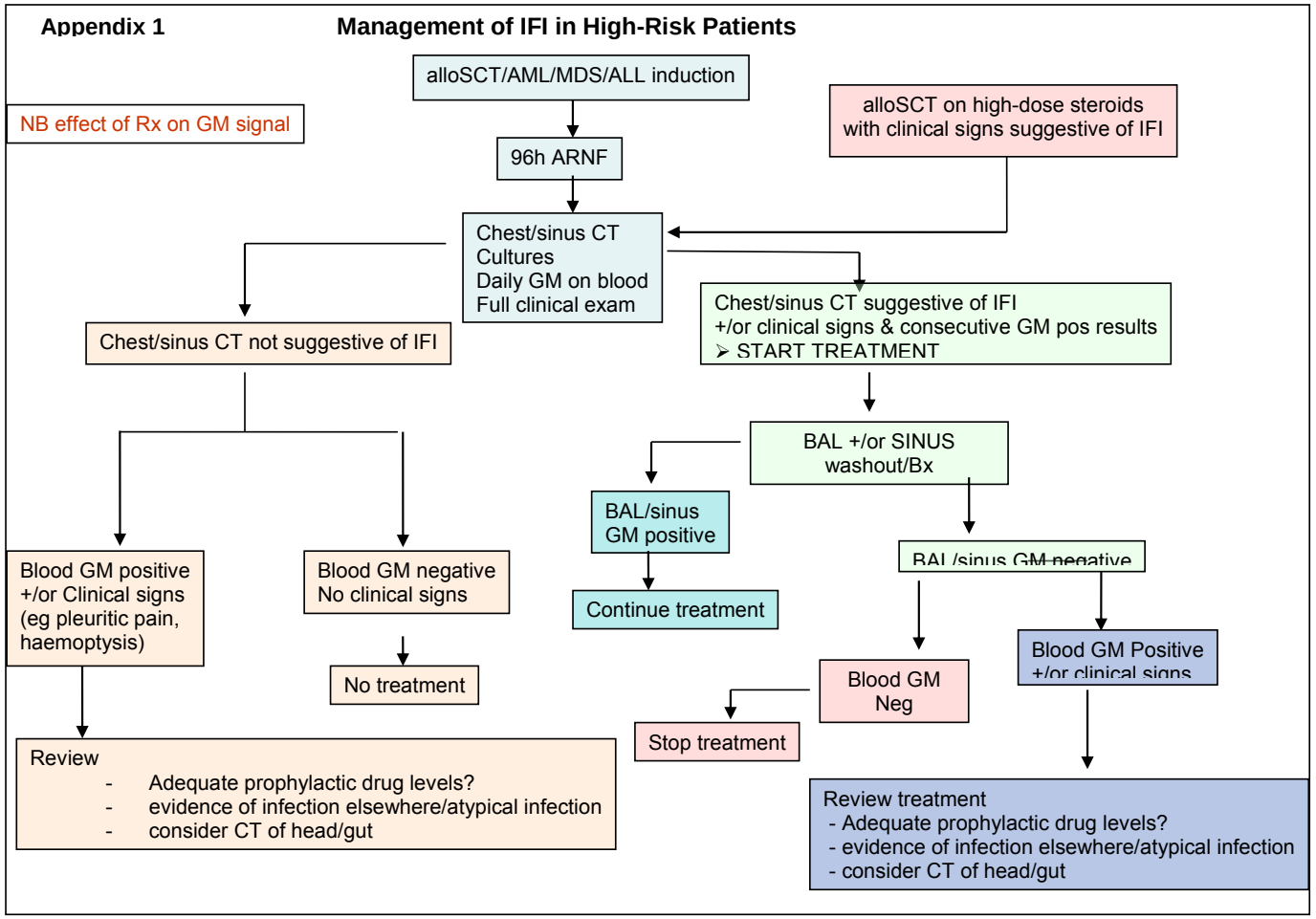
Barnes, R. A., P. L. White, et al. (2009). "Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients." Journal of Clinical Pathology **62**(1): 64-69.

Leeflang, M. M., Y. J. Debets-Ossenkopp, et al. (2009). "Galactomannan detection for invasive aspergillosis in immunocompromized patients." Cochrane Reviews **3**.

Prentice, A., A. Glasmacher, et al. (2007) "Guidelines on the management of invasive fungal infection during therapy for haematological malignancy (BCSH)."

Spellberg, B., J. Edwards, Jr., et al. (2005). "Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management." Clin. Microbiol. Rev. **18**(3): 556-569.

Appendix 1 **Management of IFI in High-Risk Patients**



Appendix 2
Additional prescribing information for antifungal medicines

Amphotericin Prescribing Information

AMPHOTERICIN MUST BE PRESCRIBED AS THE PROPRIETARY PRODUCT – AMBISOME OR ABELCET
Prescribing as *amphotericin* has led to serious medication errors (National Patient Safety Agency Rapid Response Report 2 Septmber 2007)

- **Use the proprietary name – Ambisome, Abelcet**
- **Conventional amphotericin is no longer included in this policy. However if it is to be prescribed for any reason, it must be prescribed using both terms *non-lipid amphotericin and Fungizone***
- **Verify the dose and preparation before prescribing, preparing or administering the product**
- **Record on the kardex and patient's weight and dose calculation used**

	Abelcet	Ambisome
Test dose	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphylaxis	5-10ml over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphylaxis
Pre-med	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.	Paracetamol 1g orally and chlorpheniramine 10mg intravenously 20 minutes before start of the infusion. Pethidine 25mg intravenously can be used for rigors.
Dose	**5mg/kg/day**	**3mg/kg/day**
Infusion time	**2 hours**	**1 hour**

- Monitor urea and electrolytes DAILY, especially potassium, magnesium and creatinine.
- Hypokalaemia is common with Ambisome and Abelcet. Amiloride 5-10mg orally daily should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations.
- Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours.

Licensed Indications

- Ambisome - *By intravenous infusion*, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.
- Abelcet - *By intravenous infusion*, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients

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- **Caspofungin Prescribing Information**

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULT over 18 years, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg)

Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

- Mild hepatic impairment (Child-Pugh score 5 to 6) No dosage adjustment
- Moderate hepatic impairment (Child-Pugh score 7 to 9) 70mg loading dose then35mg daily
- Severe hepatic impairment (Child-Pugh score >9) No clinical experience

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised Bilirubin.

Fluconazole Prescribing Information

Licensed Indication
Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion,* 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

Itraconazole Prescribing Information

Licensed Indications

- Oropharyngeal candidiasis
- Prophylaxis in patients with haematological malignancy or undergoing bone-marrow transplant
- Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective

Dose

- *Liquid* 5 mg/kg daily in 2 divided doses
- *Caspules* 200mg twice daily
- *Intravenous Infusion* 200 mg every 12 hours for 2 days, then 200 mg once daily

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients receiving cyclophosphamide as part of conditioning itraconazole should not be started until D0
- Liquid may cause nausea and vomiting. If nausea and vomiting persists with oral liquid, and the patient has adequate therapeutic concentrations then capsules 200mg twice daily may be used. Concentrations should be measured to ensure adequate levels are maintained following the switch to capsules. The dose may need to be increased.
- Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). Itraconazole should **not be used within 5 days of vinca alkaloid** therapy or **Gemtuzumab oxogamicin**. Alterations in itraconazole dose will change ciclosporin and tacrolimus levels.
- Patients who are neutropenic and those prescribed concomitant H2-antagonists e.g. ranitidine or proton pump inhibitors e.g. omeprazole will not achieve therapeutic concentrations unless the oral liquid is prescribed.
- A creatinine clearance < 30ml/min should not be treated with iv itraconazole, but oral may be used.
- To administer iv add 25ml of itraconazole to the 50ml sodium chloride infusion bag provided. Administer 60ml of this solution over one hour i.e. 200mg. N.B. As soon as the infusion is completed a complete flush procedure must be started to avoid blocking the patient's line/cannula.
- Following rare reports of heart failure the CSM has advised caution when prescribing itraconazole to patients at high risk of heart failure.

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Posaconazole Prescribing Information

Licensed Indications

Treatment of invasive aspergillosis either unresponsive to, or in patients intolerant of, amphotericin or itraconazole; fusariosis either unresponsive to, or in patients intolerant of, amphotericin; chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole; coccidioidomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole

Dose 400 mg twice daily with food *or* if food not tolerated, 200 mg 4 times daily

Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole and itraconazole,

Dose 200 mg 3 times daily with food,
starting before transplantation or before chemotherapy and continued until neutrophil count recovers

- Posaconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumab ozogamicin**. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients receiving cyclophosphamide as part of conditioning Posaconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

Side-effects

gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, and flatulence); dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia; blood disorders (including anaemia, neutropenia, and thrombocytopenia), electrolyte disturbances; dry mouth; rash; *less commonly* pancreatitis, hepatic disorders, arrhythmias, palpitation, changes in blood pressure, oedema, convulsions, neuropathy, tremor, hyperglycaemia, menstrual disorders, renal failure, musculoskeletal pain, visual disturbances, mouth ulcers, and alopecia; *rarely* ileus, cardiac failure, myocardial infarction, stroke, thrombosis, syncope, pneumonitis, psychosis, depression, encephalopathy, adrenal insufficiency, breast pain, hearing impairment, and Stevens-Johnson syndrome.

Voriconazole Prescribing Information
Licensed Indications

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Dose

By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours;

By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months;

- Voriconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumab ozogamicin**. Alterations in voriconazole dose will change ciclosporin and tacrolimus levels.
- Patients should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- In patients with moderate to severe renal impairment defined as creatinine clearance < 30ml/min should not be treated with intravenous Voriconazole, but oral maybe used.
- In patients receiving cyclophosphamide as part of conditioning Voriconazole should not be started until D0
- Liver function tests must be monitored before and during treatment

Side-effects
gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea), jaundice; oedema, hypotension, chest pain; respiratory distress syndrome, sinusitis; headache, dizziness, asthenia, anxiety, depression, confusion, agitation, hallucinations, paraesthesia, tremor; influenza-like symptoms; hypoglycaemia; haematuria; blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia; visual disturbances including altered perception, blurred vision, and photophobia; rash, pruritus, photosensitivity, alopecia, cheilitis; injection-site reactions; *less commonly* cholecystitis, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, and Stevens-Johnson syndrome; *rarely* pseudomembranous colitis, convulsions, sleep disturbances, tinnitus, hearing disturbances, extrapyramidal effects, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, retinal haemorrhage, optic atrophy, and taste disturbances.

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THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT A MINIMUM OF 2 YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

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SOP No. BMT 100 008 06 SUPERSEDES PREVIOUS VERSION

Compiled by:	Dr Anne Parker	Date: 26/04/2015
Authorised by:	Dr Anne Parker	Date: 27/04/2015
Authorised by: Quality Manager	Robert H Boyd	Date: 27/04/2015
Date of issue:	27/04/2015	
Effective date:	27/04/2015	
Review:	Every 2 Years	
Number of pages: (including this page)	14	

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SIGNIFICANT AMENDMENTS FROM PREVIOUS VERSION			
Line	Amendment	Date	Signature
4.0	galactomannan changed to Aspergillus antigen	26/04/2015	ANP
5.0	Delete monitoring of renal function	26/04/2015	ANP
5.2	To start day after completed chemotherapy	26/04/2015	ANP
	Pozaconazole Therapeutic Monitoring – amendments to Prophylaxis and Treatment	26/04/2015	ANP

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CONTEXT
Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular, those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients, due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, the majority of antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow &ClydeHospitals.

1. INTRODUCTION

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

2. RISK FACTORS FOR DEVELOPMENT OF INVASIVE FUNGAL INFECTIONS

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

3.1 Low risk patients

- Oral chemotherapy
- Lymphoma
- Autologous peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

3.2 Moderate Risk patients

- Steroids plus neutrophils less than 1.0 $x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils <1.0 $x10^9$/L)

3.3 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- Neutrophils less than $0.5x10^9$/L for more than two weeks eg. aplastic anaemia, hairy cell leukaemia
- Acute leukaemia on intensive therapy
- Alemtuzumab recipient

4. DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

It is imperative that patients are regularly assessed for clinical features of IFI

- Daily physical examination
- History of pleuritic pain, sinus discomfort etc.
- **Early CT** imaging of chest& sinuses, following persistent pyrexia unresponsive to broad spectrum antibiotics for more than 72- 96 hours
  - Consideration of abdo and pelvis CT if symptoms suggestive of infection
- BAL/ Sinus washout with aspergillus antigen (Galactomannan) testing

5. PRIMARY PROPHYLAXIS

Prophylactic treatment should commence on admission or Day 0 for autografts.
The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

- Acute leukaemia – once neutrophils > 1 x 10^9/l and restarted with the next course
- Allograft – at consultants discretion

5.1 Low & moderate risk patients (see 3.1& 3.2)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as fluconazole does not reduce the risk of aspergillus.

FLUCONAZOLE

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

5.2 High risk patients (see 3.2)

To start the day after completed chemotherapy, if no evidence of pre-existing IFI, due to concerns about interactions with anthracyclines

First Choice ITRACONAZOLE

In high risk patients who are intolerant of other azoles due to liver dysfunction use

FLUCONAZOLE

- Allografts 400mg once daily
- All other patients 100mg daily

ONLY in ALL patients during induction receiving weekly vincristine/ vinblastine

AMBISOME 3mg/kg twice weekly

NB this is an unlicensed indication and must be discussed with the patient & documented in the notes

Alternative to Itraconazole POSACONAZOLE

ONLY to be used forthe following indications

- Relapsed Acute Myeloid Leukaemia (AML) on intensive chemotherapy
-
- GvHD on steroids
- Cord or haploidentical donor transplant recipients
- ALL on phase II induction i.e. NOT receiving vincristine

6. SECONDARY PROPHYLAXIS

Patients who have had therapy for previous IFI may not have cleared the infection at the start of their next course of chemotherapy and are at higher risk of reactivation of infection during subsequent periods of neutropenia.

The following is ONLY for patients previously treated forprobable/ proven IFI

6.1 Posaconazole for patients who have previously received Itraconazole/ posaconazole prophylaxis

6.3 Ambisomeor Caspofunginfor patients who have had proven/ probable IFI and are due to receive further intensive therapy but have poor liver function or are intolerant of azoles.

7. DECISION TO TREAT

The decision to start therapy should be based on a combination of the following(Barnes, White et al. 2009)

- **Clinical features**
  - Pyrexia unresponsive to broad spectrum antibiotics for 96 hrs with no positive cultures
  - Haemoptysis, sinus discomfort, pleuritic pain, visual disturbance etc.
  - Pleural rub, facial swelling, retinal infiltrates etc.
- **Radiological features**
  - CXR infiltrates
  - CT scan changes suggestive of IFI
- **Aspergillus Antigen (Galactomannan) result positive**
  - Blood
  - BAL/ sinus washings etc.

Patients who have clinical features suggestive of IFI should have the following

- Daily blood for aspergillus antigen (galactomannan)
- Urgent CT scan of chest + any additional area of significant symptoms/ signs
- Urgent BAL/ sinus washout if indicated
- Ophthalmology/ ENT/ respiratory review if indicated

NB. The presence of sequential positive blood aspergillus antigen (galactomannan) MUST not be the sole means of deciding to initiate therapy, but as an adjunct to aid in the decision as to whether IFI is the most likely cause of the patients symptoms, as false positives can

rarely occur due to diet and antibiotic therapy. However, a positive result from BAL or sinus washings is a strong indicator(Leeflang, Debets-Ossenkopp et al. 2009).

8. THERAPY

The choice of antifungal should be based on the following

- Patient risk factors for developing invasive fungal infection,
- Current prophylaxis (if any)
- Potential complications of antifungal therapy and whether these complications will compromise future patient management.
- Culture results (if any)
- Clinical & radiological features
- Concurrent chemotherapy e.g. vinca alkaloid, Mylotarg

8.1 Low risk patients *IV ITRACONAZOLE*

Change to oral liquid / capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5microgram/ml until patient is no longerimmunocompromised at the end of therapy.

8.2 Moderate &High Risk patients

Patients must be discussed with the Consultant in charge for authorisation.

First Line Therapy ***AMBISOME***

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance < 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant
- In patients with CNS fungal infection IV voriconazole should be added as it has good CNS penetration.

Second Line Therapy ***CASPOFUNGIN***

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

- May be as first line therapy in cord transplants/ acute leukaemia where renal function is a concern
- May be used as first line therapy in invasive candidiasis

8.3 Duration

The duration of antifungal therapy will depend on

- Probability of IFI
- Patient's individual response to therapy
- Underlying condition & degree of immunosuppression

Antifungal therapy should be discontinued when there is resolution of clinicalfeatures. Consideration should be given to the requirement for secondary prophylaxis once the current episode has resolved.

The use of surgery to remove isolated persisting lesions may be appropriate

8.4 Combination therapy

There is little data to support this action in terms of improved outcome apart from specific circumstances detailed below. This MUSTbe discussed with **the microbiology team** before initiating

8.5 Mucormycosis

This is a rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, Edwards et al. 2005, Cornely et al 2014). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to fluconazole, voriconazole and the echinocandins e.g. caspofungin. In individuals who are suspected of mucormycosis the following regimen should be considered;

POSACONAZOLE + AMBISOME

Reference

Barnes, R. A., P. L. White, et al. (2009). "Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients." Journal of Clinical Pathology**62**(1): 64-69.

Cornely, O et al (2014)"ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013."Clin Microbiol Infect; **20** (Suppl. 3): 5–26

Leeflang, M. M., Y. J. Debets-Ossenkopp, et al. (2009). "Galactomannan detection for invasive aspergillosis in immunocompromized patients." Cochrane Reviews**3**.

Spellberg, B., J. Edwards, Jr., et al. (2005). "Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management." Clin. Microbiol. Rev.**18**(3): 556-569.

Additional prescribing information for antifungal medicines

AMBISOME® Prescribing Information

Licensed Indications

By intravenous infusion, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.

TREATMENT **intravenous 3mg/kg daily**

PROPHYLAXIS **intravenous 3mg/kg twice a week (unlicensed)**

- Use the proprietary name – Ambisome®
- Verify the dose and preparation before prescribing, preparing or administering the product

1. **Test Dose** given as 5-10ml (approx. 1mg)of prescribed dose over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphylaxis
2. **Pre- medication**20 minutes before start of the infusion
    - Paracetamol 1g orally
    - chlorpheniramine 10mg intravenously.
    - Pethidine 25mg intravenously can be used for rigors.
3. **Monitoring**
    - DAILY urea and electrolytes, especially potassium, magnesium and creatinine
    - Hypokalaemia is common. **Amiloride 5-10mg orally daily** should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations
    - Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours as per clinical handbook

AMPHOTERICIN MUST BE PRESCRIBED AS THE PROPRIETARY PRODUCT – AMBISOME®

Prescribing as *amphotericin* has led to serious medication errors (National Patient Safety Agency Rapid Response Report 2 September 2007)

Conventional amphotericin is no longer included in this policy. However if it is to be prescribed for any reason, it must be prescribed using both terms *non-lipid amphotericin and Fungizone*®

CASPOFUNGIN

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULTover 18 years,

Weight < 80Kg	70 mg on first day then 50 mg once daily
Weight 80kg or more	70 mg once daily

There is no change in dose if using for prophylaxis
Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

Mild hepatic impairment	No dosage adjustment	Child-Pugh score 5 to 6
Moderate hepatic impairment	70mg loading dose then35mg daily	Child-Pugh score 7 to 9
Severe hepatic impairment	No clinical experience	Child-Pugh score >9

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised bilirubin.

Co-administration with inducers of metabolic enzymes

Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered in adult patients (see Summary of Product Characteristics for more information).

FLUCONAZOLE

Licensed Indication
Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50 to 400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion,* 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs - monitor
- Reduce by 50% if CrCl≤50mlmin
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

ITRACONAZOLE

Dose

oral	**liquid**	**2.5mg/kg bdtwice daily for neutropenic patients**
	Capsules	**200mg bdtwice daily for non-neutropenic**
Intravenous.	**Loading dose**	**200mg twice daily for two days**
	Maintenance	**200mg daily**

Therapeutic Monitoring of oral doses

- Trough levels should be measured weekly to ensure absorption aiming of a level > 0.5microg/ ml.
- The dose can be increased if subtherapeutic levels are found

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**itraconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in itraconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on itraconazole the dose should be carefully monitored
- Avoid antacids and PPIs if possible with itraconazole capsules

Transplant Protocols

- It should not be started until D0for patients receiving cyclophosphamide as part of conditioning

Heart Failure

- The MHRA has advised caution when prescribing itraconazole to patients at high risk of heart failure

POSACONAZOLE Prescribing Information

Dose

Oral tablets **Loading dose300mg BDtwice daily for one day then**
Maintenance dose300mgdaily

Oral suspension **200mg (5ml) three times daily for prophylaxis WITH food**
400mg (10ml) twice daily for treatment WITH food

The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Intravenous **Loading dose** **300mg twice daily for one day**
Maintenance dose **300mg daily**

This should be by central line access ONLY

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption.The dose can be increased if subtherapeutic levels are foundaiming for a level of
  - **Prophylaxis** > 0.5/ ml.
  - **Treatment >0.**7 / ml
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in posaconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on posaconazole the dose should be carefully monitored
- Avoid PPIs, if possible, with oral posaconazole

VORICONAZOLE

Dose

	Intravenous	Oral (Tablets and Suspension)	
		*Patients 40 kg and above**	*Patients less than 40 kg**
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg (10 ml) every 12 hours	200 mg (5 ml) every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg (5 ml) twice daily	100 mg (2.5 ml) twice daily

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.
If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.
If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption aiming of afor level > 0.5/ ml. The dose can be increased if subtherapeutic levels are found
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

DURATION

- Treatment duration **should be as short as possible** depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Switch to oral if possible.

Liver Dysfunction

- Regular monitoring of LFTs is required
- It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.
- Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

- For example, voriconazole is contraindicated in combination with somepotent enzyme inducers or if the combination is strictly required the dosage of voriconazole is required to be increased. Please refer to SPC for more details.
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**voriconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin**. **(Mylotarg)**.
- Alterations in voriconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started the dose should be carefully monitored
- Exposure might be increased by concomitant omeprazole

Side Effects

- Patient should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF)
- Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis, discontinuation should be considered after multidisciplinary advice
- **SQUAMOUS CELL CARCINOMA OF THE SKIN (SCC**) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT A MINIMUM OF 2 YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE :	**ANTIFUNGAL POLICY**	
SOP No.	**BMT 100 008 07**	**SUPERSEDES PREVIOUS VERSION**

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CONTEXT

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular, those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients, due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, the majority of antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow & ClydeHospitals.

1. INTRODUCTION

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

2. RISK FACTORS FOR DEVELOPMENT OF INVASIVE FUNGAL INFECTIONS

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

2.1 Low risk patients

- Oral chemotherapy
- Lymphoma
- Autologous peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

2.2 Moderate Risk patients

- Steroids plus neutrophils less than 1.0 x10^9/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils <1.0 x10^9/L)

2.3 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- Neutrophils less than $0.5x10^9$/L for more than two weeks eg. aplastic anaemia, hairy cell leukaemia
- Acute leukaemia on intensive therapy
- Alemtuzumab recipient

3. DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

It is imperative that patients are regularly assessed for clinical features of IFI

- Daily physical examination
- History of pleuritic pain, sinus discomfort etc.
- **Early CT** imaging of chest& sinuses, following persistent pyrexia unresponsive to broad spectrum antibiotics for more than 72- 96 hoursConsideration of abdo and pelvis CT if symptoms suggestive of infection
- BAL/ Sinus washout with aspergillus antigen (Galactomannan) and PCR testing

Prophylactic treatment should commence on admission or Day 0 for autografts.
The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

- Acute leukaemia – once neutrophils > 1 x 10^9/l and restarted with the next course
- Allograft – D100 or later at consultants discretion

3.1 Low & moderate risk patients (see 3.1& 3.2)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as fluconazole does not reduce the risk of aspergillus.

FLUCONAZOLE

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

3.2 High risk patients (see 3.2)

To start the day after completed chemotherapy, if no evidence of pre-existing IFI, due to concerns about interactions with anthracyclines

First Choice POSACONAZOLE capsules

300mg bd loading dose and then 300mg daily po
NB If posaconazole liquid is used dose is 200mg tid to be taken with food

ONLY in ALL patients during induction receiving weekly vincristine/ vinblastine
AMBISOME 3mg/kg twice weekly
NB this is an unlicensed indication and must be discussed with the patient & documented in the notes

ISAVUCONAZOLE 200mg tid for 48 hours loading dose then 200mg od
To be used in patients with

- **Liver Dysfunction**
- **Long QTc**
- **Poor cardiac function**
- **Patients on sirolimus**

4. SECONDARY PROPHYLAXIS

Patients who have had therapy for previous IFI may not have cleared the infection at the start of their next course of chemotherapy and are at higher risk of reactivation of infection during subsequent periods of neutropenia.

The following is ONLY for patients previously treated for probable/ proven IFI

4.1 **Voriconazole** for patients who have previously received posaconazole prophylaxis. NB patients should be warned about risk of visual disturbance, photosensitivity and given warning leaflets about risk of skin cancer. It should stopped as soon as possible

4.2 **Ambisome or Caspofungin** for patients who have had proven/ probable IFI and are due to receive further intensive therapy but have poor liver function or are intolerant of azoles.

5. DECISION TO TREAT

The decision to start therapy should be based on a combination of the following(Barnes, White et al. 2009). Please discuss with consultant and microbiology

- **Clinical features**
  - Pyrexia unresponsive to broad spectrum antibiotics for 72-96 hrs with no positive cultures
  - Haemoptysis, sinus discomfort, pleuritic pain, visual disturbance etc.
  - Pleural rub, facial swelling, retinal infiltrates etc.
- **Radiological features**
  - CXR infiltrates
  - CT scan changes suggestive of IFI
- **Aspergillus Antigen (Galactomannan) and PCR**
  - Blood
  - BAL/ sinus washings etc.

Patients who have clinical features suggestive of IFI should have the following

- Daily blood for aspergillus antigen (galactomannan)
- Urgent CT scan of chest + any additional area of significant symptoms/ signs
- Urgent BAL/ sinus washout if indicated
- Ophthalmology/ ENT/ respiratory review if indicated

NB. The presence of sequential positive blood aspergillus antigen (galactomannan) MUST not be the sole means of deciding to initiate therapy, but as an adjunct to aid in the decision as to whether IFI is the most likely cause of the patients symptoms, as false positives can rarely occur due to diet and antibiotic therapy. However, a positive result from BAL or sinus washings is a strong indicator(Leeflang, Debets-Ossenkopp et al. 2009).

6. THERAPY

The choice of antifungal should be based on the following

- Patient risk factors for developing invasive fungal infection,
- Current prophylaxis (if any)
- Potential complications of antifungal therapy and whether these complications will compromise future patient management.
- Culture results (if any)
- Clinical & radiological features
- Concurrent chemotherapy e.g. vinca alkaloid, Mylotarg

6.1 Low risk patients *IV ITRACONAZOLE*

Change to oral liquid / capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5microgram/ml until patient is no longer immunocompromised at the end of therapy.

6.2 Moderate & High Risk patients

Patients must be discussed with the Consultant in charge for authorisation.

First Line Therapy ***AMBISOME***

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance < 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant
- In patients with CNS fungal infection IV voriconazole should be added as it has good CNS penetration.

Second Line Therapy ***CASPOFUNGIN***

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

- May be as first line therapy in cord transplants/ acute leukaemia where renal function is a concern
- May be used as first line therapy in invasive candidiasis

6.3 Duration

The duration of antifungal therapy will depend on

- Probability of IFI
- Patient's individual response to therapy
- Underlying condition & degree of immunosuppression

Antifungal therapy should be discontinued when there is resolution of clinicalfeatures. Consideration should be given to the requirement for secondary prophylaxis once the current episode has resolved.

The use of surgery to remove isolated persisting lesions may be appropriate

6.4 Combination therapy

There is little data to support this action in terms of improved outcome apart from specific circumstances detailed below. This MUSTbe discussed with **the microbiology team** before initiating

6.5 Mucormycosis

This is a rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, Edwards et al. 2005, Cornely et al 2014). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to fluconazole, voriconazole and the echinocandins e.g. caspofungin. In individuals who are suspected of mucormycosis the following regimen should be considered;

POSACONAZOLE + AMBISOME

Reference

Barnes, R. A., P. L. White, et al. (2009). "Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients." Journal of Clinical Pathology**62**(1): 64-69.

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Additional prescribing information for antifungal medicines

AMBISOME® Prescribing Information

Licensed Indications

By intravenous infusion, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.

TREATMENT **intravenous 3mg/kg daily**

PROPHYLAXIS **intravenous 3mg/kg twice a week (unlicensed)**

- Use the proprietary name – Ambisome®
- Verify the dose and preparation before prescribing, preparing or administering the product

1. **Test Dose** given as 5-10ml (approx. 1mg)of prescribed dose over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphylaxis
2. **Pre- medication**20 minutes before start of the infusion
    - Paracetamol 1g orally
    - chlorpheniramine 10mg intravenously.
    - Pethidine 25mg intravenously can be used for rigors.
3. **Monitoring**
    - DAILY urea and electrolytes, especially potassium, magnesium and creatinine
    - Hypokalaemia is common. **Amiloride 5-10mg orally daily** should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations
    - Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours as per clinical handbook

AMPHOTERICIN MUST BE PRESCRIBED AS THE PROPRIETARY PRODUCT – AMBISOME®

Prescribing as *amphotericin* has led to serious medication errors (National Patient Safety Agency Rapid Response Report 2 September 2007)

Conventional amphotericin is no longer included in this policy. However if it is to be prescribed for any reason, it must be prescribed using both terms *non-lipid amphotericin and Fungizone*®

CASPOFUNGIN

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULTover 18 years,

Weight < 80Kg	70 mg on first day then 50 mg once daily
Weight 80kg or more	70 mg once daily

There is no change in dose if using for prophylaxis
Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

Mild hepatic impairment	No dosage adjustment	Child-Pugh score 5 to 6
Moderate hepatic impairment	70mg loading dose then35mg daily	Child-Pugh score 7 to 9
Severe hepatic impairment	No clinical experience	Child-Pugh score >9

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised bilirubin.

Co-administration with inducers of metabolic enzymes

Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg

loading dose, should be considered in adult patients (see Summary of Product Characteristics for more information).

FLUCONAZOLE

Licensed Indication
Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50 to 400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion,* 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs - monitor
- Reduce by 50% if CrCl≤50mlmin
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

ITRACONAZOLE

Dose

oral	**liquid**	**2.5mg/kg bdtwice daily for neutropenic patients**
	Capsules	**200mg bdtwice daily for non-neutropenic**
Intravenous.	**Loading dose**	**200mg twice daily for two days**
	Maintenance	**200mg daily**

Therapeutic Monitoring of oral doses

- Trough levels should be measured weekly to ensure absorption aiming of a level > 0.5microg/ ml.
- The dose can be increased if subtherapeutic levels are found

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**itraconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in itraconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on itraconazole the dose should be carefully monitored
- Avoid antacids and PPIs if possible with itraconazole capsules

Transplant Protocols

- It should not be started until D0for patients receiving cyclophosphamide as part of conditioning

Heart Failure

- The MHRA has advised caution when prescribing itraconazole to patients at high risk of heart failure

POSACONAZOLE Prescribing Information

Dose

Oral tablets **Loading dose300mg BDtwice daily for one day then**
Maintenance dose300mgdaily

Oral suspension **200mg (5ml) three times daily for prophylaxis WITH food**
400mg (10ml) twice daily for treatment WITH food

The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Intravenous **Loading dose** **300mg twice daily for one day**
Maintenance dose **300mg daily**

This should be by central line access ONLY

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption.The dose can be increased if subtherapeutic levels are foundaiming for a level of
  - **Prophylaxis** > 0.5/ ml.
  - **Treatment >0.**7 / ml
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in posaconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on posaconazole the dose should be carefully monitored
- Avoid PPIs, if possible, with oral posaconazole

VORICONAZOLE

Dose

	Intravenous	Oral (Tablets and Suspension)	
		*Patients 40 kg and above**	*Patients less than 40 kg**
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg (10 ml) every 12 hours	200 mg (5 ml) every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg (5 ml) twice daily	100 mg (2.5 ml) twice daily

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.
If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.
If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption aiming of afor level > 0.5/ ml. The dose can be increased if subtherapeutic levels are found
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

DURATION

- Treatment duration **should be as short as possible** depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Switch to oral if possible.

Liver Dysfunction

- Regular monitoring of LFTs is required
- It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.
- Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

- For example, voriconazole is contraindicated in combination with somepotent enzyme inducers or if the combination is strictly required the dosage of voriconazole is required to be increased. Please refer to SPC for more details.
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**voriconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin**. **(Mylotarg)**.
- Alterations in voriconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started the dose should be carefully monitored
- Exposure might be increased by concomitant omeprazole

Side Effects

- Patient should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF)
- Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis, discontinuation should be considered after multidisciplinary advice
- **SQUAMOUS CELL CARCINOMA OF THE SKIN (SCC**) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

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Antifungal Policy

CONTEXT

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular, those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients, due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, the majority of antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow & ClydeHospitals.

1. INTRODUCTION

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

2. RISK FACTORS FOR DEVELOPMENT OF INVASIVE FUNGAL INFECTIONS

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

2.1 Low risk patients

- Oral chemotherapy
- Lymphoma
- Autologous peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

2.2 Moderate Risk patients

- Steroids plus neutrophils less than 1.0 $x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils <1.0 $x10^9$/L)

2.3 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- Neutrophils less than $0.5x10^9$/L for more than two weeks eg. aplastic anaemia, hairy cell leukaemia
- Acute leukaemia on intensive therapy
- Alemtuzumab recipient

3. DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

It is imperative that patients are regularly assessed for clinical features of IFI

- Daily physical examination
- History of pleuritic pain, sinus discomfort etc.
- **Early CT** imaging of chest& sinuses, following persistent pyrexia unresponsive to broad spectrum antibiotics for more than 72- 96 hoursConsideration of abdo and pelvis CT if symptoms suggestive of infection
- BAL/ Sinus washout with aspergillus antigen (Galactomannan) and PCR testing

Prophylactic treatment should commence on admission or Day 0 for autografts.
The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

- Acute leukaemia – once neutrophils > 1 x 10^9/l and restarted with the next course
- Allograft – D100 or later at consultants discretion

3.1 Low & moderate risk patients (see 3.1& 3.2)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as fluconazole does not reduce the risk of aspergillus.

FLUCONAZOLE

For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

3.2 High risk patients (see 3.2)

To start the day after completed chemotherapy, if no evidence of pre-existing IFI, due to concerns about interactions with anthracyclines

First Choice POSACONAZOLE capsules

300mg bd loading dose and then 300mg daily po
NB If posaconazole liquid is used dose is 200mg tid to be taken with food

Posaconazole Levels prophylaxis >0.7ng/ml

These should be checked weekly for patients on liquid
For tablets they should be checked 7 days and 28 days after posaconazole commences
-

ONLY in ALL patients during induction receiving weekly vincristine/ vinblastine

AMBISOME 3mg/kg twice weekly

NB this is an unlicensed indication and must be discussed with the patient & documented in the notes

ISAVUCONAZOLE 200mg tid for 48 hours loading dose then 200mg od
To be used in patients with

- **Liver Dysfunction**
- **Long QTc**
- **Poor cardiac function**
- **Patients on sirolimus**

4. SECONDARY PROPHYLAXIS

Patients who have had therapy for previous IFI may not have cleared the infection at the start of their next course of chemotherapy and are at higher risk of reactivation of infection during subsequent periods of neutropenia.

The following is ONLY for patients previously treated for probable/ proven IFI

4.1 **Voriconazole** for patients who have previously received posaconazole prophylaxis. NB patients should be warned about risk of visual disturbance, photosensitivity and given warning leaflets about risk of skin cancer. It should stopped as soon as possible

4.2 **Ambisome or Caspofungin** for patients who have had proven/ probable IFI and are due to receive further intensive therapy but have poor liver function or are intolerant of azoles.

5. DECISION TO TREAT

The decision to start therapy should be based on a combination of the following(Barnes, White et al. 2009). Please discuss with consultant and microbiology

- **Clinical features**
  - Pyrexia unresponsive to broad spectrum antibiotics for 72-96 hrs with no positive cultures
  - Haemoptysis, sinus discomfort, pleuritic pain, visual disturbance etc.
  - Pleural rub, facial swelling, retinal infiltrates etc.
- **Radiological features**
  - CXR infiltrates
  - CT scan changes suggestive of IFI
- **Aspergillus Antigen (Galactomannan) and PCR**
  - Blood
  - BAL/ sinus washings etc.

Patients who have clinical features suggestive of IFI should have the following

- Daily blood for aspergillus antigen (galactomannan)
- Urgent CT scan of chest + any additional area of significant symptoms/ signs
- Urgent BAL/ sinus washout if indicated
- Ophthalmology/ ENT/ respiratory review if indicated

NB. The presence of sequential positive blood aspergillus antigen (galactomannan) MUST not be the sole means of deciding to initiate therapy, but as an adjunct to aid in the decision as to whether IFI is the most likely cause of the patients symptoms, as false positives can

rarely occur due to diet and antibiotic therapy. However, a positive result from BAL or sinus washings is a strong indicator(Leeflang, Debets-Ossenkopp et al. 2009).

6. THERAPY

The choice of antifungal should be based on the following

- Patient risk factors for developing invasive fungal infection,
- Current prophylaxis (if any)
- Potential complications of antifungal therapy and whether these complications will compromise future patient management.
- Culture results (if any)
- Clinical & radiological features
- Concurrent chemotherapy e.g. vinca alkaloid, Mylotarg

6.1 Low risk patients *IV ITRACONAZOLE*

Change to oral liquid / capsules once significant response to therapy with monitoring of levels weekly to maintain >0.5microgram/ml until patient is no longer immunocompromised at the end of therapy.

6.2 Moderate & High Risk patients

Patients must be discussed with the Consultant in charge for authorisation.

First Line Therapy ***AMBISOME***

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance < 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
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Second Line Therapy ***CASPOFUNGIN***

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

- May be as first line therapy in cord transplants/ acute leukaemia where renal function is a concern
- May be used as first line therapy in invasive candidiasis

6.3 Duration

The duration of antifungal therapy will depend on

- Probability of IFI
- Patient's individual response to therapy
- Underlying condition & degree of immunosuppression

Antifungal therapy should be discontinued when there is resolution of clinicalfeatures. Consideration should be given to the requirement for secondary prophylaxis once the current episode has resolved.

The use of surgery to remove isolated persisting lesions may be appropriate

6.4 Combination therapy

There is little data to support this action in terms of improved outcome apart from specific circumstances detailed below. This MUSTbe discussed with **the microbiology team** before initiating

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POSACONAZOLE + AMBISOME

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PROPHYLAXIS **intravenous 3mg/kg twice a week (unlicensed)**

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- Verify the dose and preparation before prescribing, preparing or administering the product

1. **Test Dose** given as 5-10ml (approx. 1mg)of prescribed dose over 15-20 minutes with no cover, then observe for 30minutes for bronchospasm or anaphylaxis
2. **Pre- medication**20 minutes before start of the infusion
    - Paracetamol 1g orally
    - chlorpheniramine 10mg intravenously.
    - Pethidine 25mg intravenously can be used for rigors.
3. **Monitoring**
    - DAILY urea and electrolytes, especially potassium, magnesium and creatinine
    - Hypokalaemia is common. **Amiloride 5-10mg orally daily** should be prescribed. Intravenous potassium supplements may be required in addition to maintain potassium concentrations
    - Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours as per clinical handbook

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Weight < 80Kg	70 mg on first day then 50 mg once daily
Weight 80kg or more	70 mg once daily

There is no change in dose if using for prophylaxis
Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

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Severe hepatic impairment	No clinical experience	Child-Pugh score >9

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	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points

Grade B 7-9 points

Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

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ABC of diseases of liver, pancreas and biliary system
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BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised bilirubin.

Co-administration with inducers of metabolic enzymes

Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg

loading dose, should be considered in adult patients (see Summary of Product Characteristics for more information).

FLUCONAZOLE

Licensed Indication
Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50 to 400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion,* 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation

- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.

- Can cause deranged LFTs - monitor
- Reduce by 50% if CrCl≤50mlmin

- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

ITRACONAZOLE

Dose

oral	**liquid**	**2.5mg/kg bdtwice daily for neutropenic patients**
	Capsules	**200mg bdtwice daily for non-neutropenic**
Intravenous.	**Loading dose**	**200mg twice daily for two days**
	Maintenance	**200mg daily**

Therapeutic Monitoring of oral doses

- Trough levels should be measured weekly to ensure absorption aiming of a level > 0.5microg/ ml.
- The dose can be increased if subtherapeutic levels are found

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**itraconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in itraconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on itraconazole the dose should be carefully monitored
- Avoid antacids and PPIs if possible with itraconazole capsules

Transplant Protocols

- It should not be started until D0for patients receiving cyclophosphamide as part of conditioning

Heart Failure

- The MHRA has advised caution when prescribing itraconazole to patients at high risk of heart failure

POSACONAZOLE Prescribing Information

Dose

Oral tablets **Loading dose300mg BDtwice daily for one day then**
Maintenance dose300mgdaily

Oral suspension **200mg (5ml) three times daily for prophylaxis WITH food**
400mg (10ml) twice daily for treatment WITH food

The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Intravenous **Loading dose** **300mg twice daily for one day**
Maintenance dose **300mg daily**

This should be by central line access ONLY

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption.The dose can be increased if subtherapeutic levels are foundaiming for a level of
  - **Prophylaxis** > 0.5/ ml.
  - **Treatment >0.**7 / ml
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Consider switch to oral.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in posaconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on posaconazole the dose should be carefully monitored
- Avoid PPIs, if possible, with oral posaconazole

VORICONAZOLE

Dose

	Intravenous	Oral (Tablets and Suspension)	
		*Patients 40 kg and above**	*Patients less than 40 kg**
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg (10 ml) every 12 hours	200 mg (5 ml) every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg (5 ml) twice daily	100 mg (2.5 ml) twice daily

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.
If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.
If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption aiming of afor level > 0.5/ ml. The dose can be increased if subtherapeutic levels are found
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

DURATION

- Treatment duration **should be as short as possible** depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance

Renal Dysfunction

- Intravenous preparation should not be used if creatinine clearance <30ml/min and used with caution if <50ml/min. Switch to oral if possible.

Liver Dysfunction

- Regular monitoring of LFTs is required
- It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.
- Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoAreductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

- For example, voriconazole is contraindicated in combination with somepotent enzyme inducers or if the combination is strictly required the dosage of voriconazole is required to be increased. Please refer to SPC for more details.
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular**voriconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin**. **(Mylotarg)**.
- Alterations in voriconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started the dose should be carefully monitored
- Exposure might be increased by concomitant omeprazole

Side Effects

- Patient should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF)
- Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis, discontinuation should be considered after multidisciplinary advice
- **SQUAMOUS CELL CARCINOMA OF THE SKIN (SCC**) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

Haemopoietic Stem Cell Transplantation Services

Title: ANTIFUNGAL POLICY
SOP No: BMT 100 008 09

AMENDMENTS FROM PREVIOUS VERSION
comment re pre-meds for ambisome on monograph to make it absolutely clear for nurses, Updated units on the target levels for posaconazole as per what clinical portal says for these. Added a note about benefit vs risk of using IV posa and vori if CrCl <50ml/min as per the SPC (due to risk of accumulation of the vehicle)

CONTEXT

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in patients with haematological malignancies, in particular, those with prolonged and severe neutropenia. Treatment of invasive fungal infection with antifungal medicines is complicated in haemato-oncology patients, due to the need for other potentially nephrotoxic medicines e.g. aminoglycosides, ciclosporin, tacrolimus and concomitant or potential nephrotoxic chemotherapy regimens.

In addition, the majority of antifungal medicines are expensive and result in a significant cost pressure in the management of this patient group.

This policy has been developed to ensure the safe, clinical and cost effective use of antifungal medicines in haemato-oncology patients across Greater Glasgow & Clyde Hospitals.

1. INTRODUCTION

Patients undergoing chemotherapy, but particularly allogeneic bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo +/- radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (duration depending on treatment)
- Graft-versus-host disease (GvHD) in allografts leading to additional immunosuppression.

The risk of morbidity and mortality due to IFI may be reduced by:

- Environmental controls e.g. reduction in airborne dust, water filtration etc.
- Use of prophylactic antifungals
- Surveillance for potential infectious signs and symptoms
- Prompt treatment of probable/ proven infection.

2. RISK FACTORS FOR DEVELOPMENT OF INVASIVE FUNGAL INFECTIONS

By identifying patients at high risk of IFI appropriate prophylaxis can be prescribed and treatment of suspected fungal infection instituted early.

2.1 Low risk patients

- Oral chemotherapy
- Lymphoma
- Autologous peripheral blood stem cell transplant (PBSCT) (non total body irradiation)
- Acute lymphoblastic leukaemia on maintenance
- Other groups not considered as high risk

2.2 Moderate Risk patients

- Steroids plus neutrophils less than 1.0 $x10^9$/L for more than one week
- Fluconazole resistant colonisation
- Colonisation of more than one site plus neutropenia (neutrophils <1.0 $x10^9$/L)

2.3 High risk patients:

- GvHD
- Allogeneic Marrow & PBSCT
- Neutrophils less than 0.5$x10^9$/L for more than two weeks eg. aplastic anaemia, hairy cell leukaemia
- Acute leukaemia on intensive therapy
- Alemtuzumab recipient
- CAR-T and other cellular therapy patients receiving lympho-depleting treatment

3. DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

It is imperative that patients are regularly assessed for clinical features of IFI

- Daily physical examination
- History of pleuritic pain, sinus discomfort etc.
- **Early CT** imaging of chest& sinuses, following persistent pyrexia unresponsive to broad spectrum antibiotics for more than 72- 96 hours. Consideration of abdo and pelvis CT if symptoms suggestive of infection
- BAL/ Sinus washout with aspergillus antigen (Galactomannan) and PCR testing

Prophylactic treatment should commence on admission or Day 0 for autografts.
The need for prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

- Acute leukaemia – once neutrophils > 1 x 10^9/l and restarted with the next course
- Allograft – D100 or later at consultants discretion

3.1 Low & moderate risk patients (see 3.1& 3.2)

Antifungal prophylaxis can be considered in this group of patients, but is NOT obligatory. It is primarily used to reduce the risk of oral thrush as fluconazole does not reduce the risk of aspergillus.

FLUCONAZOLE
For dysphagic patients prescribe fluconazole liquid 100mg once daily and for aphagic patients prescribe fluconazole intravenous 200mg daily.

3.2 High risk patients (see 3.2)
To start the day after completed chemotherapy, if no evidence of pre-existing IFI, due to concerns about interactions with anthracyclines

First Choice **POSACONAZOLE capsules**

300mg bd loading dose and then 300mg daily po
NB If posaconazole liquid is used dose is 200mg tid to be taken with food

Posaconazole Levels prophylaxis >0.7mg/L
These should be checked weekly for patients on liquid

For tablets they should be checked 7 days and 28 days after posaconazole commences

ONLY in ALL patients <u>during induction receiving weekly vincristine/ vinblastine</u>
AMBISOME 3mg/kg twice weekly
NB this is an unlicensed indication and must be discussed with the patient & documented in the notes

Second Choice **CASPOFUNGIN for in patients**
ISAVUCONAZOLE for out patients

ISAVUCONAZOLE 200mg tid for 48 hours loading dose then 200mg od
To be used in patients with
- **Liver Dysfunction -**
- **Long QTc**
- **Poor cardiac function**
- **Patients on sirolimus**

4. SECONDARY PROPHYLAXIS

Patients who have had therapy for previous IFI may not have cleared the infection at the start of their next course of chemotherapy and are at higher risk of reactivation of infection during subsequent periods of neutropenia.

The following is ONLY for patients previously treated for probable/ proven IFI

4.1 **Voriconazole** for patients who have previously received posaconazole prophylaxis. NB patients should be warned about risk of visual disturbance, photosensitivity and given warning leaflets about risk of skin cancer. It should stopped as soon as possible

4.2 **Ambisome or Caspofungin** for patients who have had proven/ probable IFI and are due to receive further intensive therapy but have poor liver function or are intolerant of azoles.

5. DECISION TO TREAT

The decision to start therapy should be based on a combination of the following (Barnes, White et al. 2009). Please discuss with consultant and microbiology

- **Clinical features**
  - Pyrexia unresponsive to broad spectrum antibiotics for 72-96 hrs with no positive cultures
  - Haemoptysis, sinus discomfort, pleuritic pain, visual disturbance etc.
  - Pleural rub, facial swelling, retinal infiltrates etc.

- **Radiological features**
  - CXR infiltrates
  - CT scan changes suggestive of IFI
- **Aspergillus Antigen (Galactomannan) and PCR**
  - Blood
  - BAL/ sinus washings etc.

Patients who have clinical features suggestive of IFI should have the following

- Daily blood for aspergillus antigen (galactomannan)
- Urgent CT scan of chest + any additional area of significant symptoms/ signs
- Urgent BAL/ sinus washout if indicated
- Ophthalmology/ ENT/ respiratory review if indicated

NB. *The presence of sequential positive blood aspergillus antigen (galactomannan) MUST not be the sole means of deciding to initiate therapy, but as an adjunct to aid in the decision as to whether IFI is the most likely cause of the patients symptoms, as false positives can rarely occur due to diet and antibiotic therapy. However, a positive result from BAL or sinus washings is a strong indicator(Leeflang, Debets-Ossenkopp et al. 2009)*.

6. THERAPY

The choice of antifungal should be based on the following

- Patient risk factors for developing invasive fungal infection,
- Current prophylaxis (if any)
- Potential complications of antifungal therapy and whether these complications will compromise future patient management.
- Culture results (if any)
- Clinical & radiological features
- Concurrent chemotherapy e.g. vinca alkaloid, Mylotarg

6.1 **Low risk patients** ***Posaconazole oral or iv***

6.2 **Moderate & High Risk patients**

Patients must be discussed with the Consultant in charge for authorisation.

First Line Therapy ***AMBISOME***

If the following apply consider using/ switching to 2nd line therapy

- Pre-existing renal impairment defined as creatinine clearance < 50ml/min
- A reduction in creatinine clearance by more than 50% from baseline i.e. at diagnosis
- At least one other essential nephrotoxic drug prescribed concurrently e.g. aminoglycosides, ciclosporin, vancomycin. Patients receiving vancomycin should be changed to teicoplanin unless the organism is resistant
- In patients with CNS fungal infection IV voriconazole should be added as it has good CNS penetration.

Second Line Therapy ***CASPOFUNGIN***

NB It should be remembered that this has a much narrower spectrum of activity compared with amphotericin

- May be as first line therapy in cord transplants/ acute leukaemia where renal function is a concern
- May be used as first line therapy in invasive candidiasis

6.3 Duration

The duration of antifungal therapy will depend on

- Probability of IFI
- Patient's individual response to therapy
- Underlying condition & degree of immunosuppression

Antifungal therapy should be discontinued when there is resolution of clinical features. Consideration should be given to the requirement for secondary prophylaxis once the current episode has resolved.

The use of surgery to remove isolated persisting lesions may be appropriate

6.4 Combination therapy

There is little data to support this action in terms of improved outcome apart from specific circumstances detailed below. This MUST be discussed with **the microbiology team** before initiating

6.5 Mucormycosis

This is a rare mould which can cause severe sinus infection with direct and haematogenous spread to other organs as well as pulmonary infection (Spellberg, Edwards et al. 2005, Cornely et al 2014). It has a very high mortality and should be considered as a possible cause of sinus infection in any significantly immunocompromised patient. It has a poor response to many antifungal agents with minimal response to fluconazole, voriconazole and the echinocandins e.g. caspofungin. In individuals who are suspected of mucormycosis the following regimen should be considered;

POSACONAZOLE + AMBISOME

Additional prescribing information for antifungal medicines

AMBISOME® Prescribing Information

Licensed Indications

By intravenous infusion, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin. Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials.

TREATMENT **intravenous 3mg/kg daily**

PROPHYLAXIS **intravenous 3mg/kg twice a week (unlicensed)**

- Use the proprietary name – Ambisome®
- Verify the dose and preparation before prescribing, preparing or administering the product

1. **Test Dose** given as 5-10ml (approx. 1mg)of prescribed dose over 15-20 minutes, then observe for 30minutes for bronchospasm or anaphylaxis
   NOTE: Cover with chlorphenamine or paracetamol not required, however if the patient reacts to test dose cover can then be given to improve tolerability of infusion.

2. **Monitoring**
   - DAILY urea and electrolytes, especially potassium, magnesium and creatinine
   - Hypokalaemia is common. Consider prescribing **Amiloride 5-10mg orally daily**. Intravenous potassium supplements may be required in addition to oral to maintain potassium concentrations
   - Hypomagnesaemia can also occur and supplements may be required. Prescribe either magnesium glycerophosphate orally, 1-2 tablets three times daily or intravenous magnesium sulphate, 10-20mmol in 500ml of sodium chloride 0.9% or glucose 5% infused over a minimum of 6 hours as per clinical handbook

AMPHOTERICIN MUST BE PRESCRIBED S THE PROPRIETARY PRODUCT – AMBISOME®

Prescribing as *amphotericin* has led to serious medication errors (National Patient Safety Agency Rapid Response Report 2 September 2007)

Conventional amphotericin is no longer included in this policy. However if it is to be prescribed for any reason, it must be prescribed using both terms *non-lipid amphotericin and Fungizone*®

CASPOFUNGIN

Licensed Indications

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Dose

By intravenous infusion, ADULTover 18 years,

Weight < 80Kg	70 mg on first day then 50 mg once daily
Weight 80kg or more	70 mg once daily

There is no change in dose if using for prophylaxis
Dosage adjustment is necessary in patients with hepatic insufficiency as follows:

Mild hepatic impairment	No dosage adjustment	Child-Pugh score 5 to 6
Moderate hepatic impairment	70mg loading dose then35mg daily	Child-Pugh score 7 to 9
Severe hepatic impairment	No clinical experience	Child-Pugh score >9

Child Pugh Scoring

	1	2	3
Bilirubin micromols/ml	<34	34-51	>51
Albumin g/l	>35	28-35	<28
Prolongation PT (sec)	1-4	4-6	>6
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight	Moderate to severe

Grade A 5-6 points, Grade B 7-9 points, Grade C 10-15 points

Taken from Oxford Textbook of Medicine 3rd Edn.1996

References

ABC of diseases of liver, pancreas and biliary system
J E J Krige, I J Beckingham
BMJ Vol.322 10 February 2001 p348

Note that assessment of liver function using Child Pugh scoring is valid in patients with cirrhosis but should be applied with care in other groups – haematology patients may have other causes of low albumin and raised bilirubin.

Co-administration with inducers of metabolic enzymes

Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered in adult patients (see Summary of Product Characteristics for more information).

FLUCONAZOLE

Licensed Indication

Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50 to 400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

Dose

- Mucosal candidiasis (except genital), *by mouth*, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections);
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), *by mouth or intravenous infusion*, 400 mg daily (400 mg initially then 200 mg daily in invasive candidal infections, increased if necessary to 400 mg daily); treatment continued according to response (at least 8 weeks for cryptococcal meningitis);
- Prevention of fungal infections in immunocompromised patients, *by mouth or by intravenous infusion,* 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range;

- It should NOT be used in patients with a history of QT interval prolongation
- It should be used with caution in patients where concomitant use with other drugs that prolong QT interval is felt to be essential.
- Can cause deranged LFTs - monitor
- Reduce by 50% if CrCl≤50mlmin
- It has NO activity against Moulds i.e. Aspergillus, Mucormycosis

POSACONAZOLE Prescribing Information

Dose

Oral tablets	**Loading dose300mg BD twice daily for one day then**	
	Maintenance dose300mgdaily	
Oral suspension	**200mg (5ml) three times daily for prophylaxis WITH food**	
	400mg (10ml) twice daily for treatment WITH food	

The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Intravenous	**Loading dose**	**300mg twice daily for one day**
	Maintenance dose	**300mg daily**

This should be by central line access ONLY

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption.The dose can be increased if subtherapeutic levels are foundaiming for a level of
  - **Prophylaxis** > 0.7mg/L
  - **Treatment** >1.3mg/L
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

Renal Dysfunction

- In patients with moderate or severe renal impairment (CRCL<50 mL/min), accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Avoid IV formulation unless benefit outweighs the risk.

Liver Dysfunction

- Regular monitoring of LFTs is required

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoA reductase inhibitors** such as atorvastatin as can cause rhabdomyolysis
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **posaconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin (Mylotarg)**. Alterations in posaconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started in a patient on posaconazole the dose should be carefully monitored
- Avoid PPIs, if possible, with oral posaconazole

VORICONAZOLE

Dose

	Intravenous	Oral (Tablets and Suspension)	
		*Patients 40 kg and above**	*Patients less than 40 kg**
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg (10 ml) every 12 hours	200 mg (5 ml) every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg (5 ml) twice daily	100 mg (2.5 ml) twice daily

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.
If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.
If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

Therapeutic Monitoring

- **Suspension -** Trough levels should be measured weekly to ensure absorption aiming for level > 2-4mg/L. The dose can be increased if subtherapeutic levels are found
- **Tablets/ Intravenous –** measure a level after 1 week of therapy to ensure that appropriate levels have been achieved particularly if <60kg or>120kg.
- **Drug interactions -**Also measure a level if drugs such as rifampicin etc. are given

DURATION

- Treatment duration **should be as short as possible** depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance

Renal Dysfunction

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous voriconazole.

Liver Dysfunction

- Regular monitoring of LFTs is required
- It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.
- Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Drug Interactions

- Use with caution in combination with other drugs that prolong QTc
- Do NOT use if history of prolonged QTc
- **STOP all HMGCoA reductase inhibitors** such as atorvastatin as can cause rhabdomyolysis

- Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.
- For example, voriconazole is contraindicated in combination with somepotent enzyme inducers or if the combination is strictly required the dosage of voriconazole is required to be increased. Please refer to SPC for more details.
- It can inhibit the metabolism of drugs metabolised by the cytochrome 3A family (see BNF for full list). In particular **voriconazole should not be used within 5 days of vinca alkaloid** therapy or **gemtuzumabozogamicin**. **(Mylotarg)**.
- Alterations in voriconazole dose will change ciclosporin, sirolimus and tacrolimus levels.If these drugs are started the dose should be carefully monitored
- Exposure might be increased by concomitant omeprazole

Side Effects

- Patient should be warned about visual disturbances including altered perception, blurred vision, and photophobia. These usually resolve after 1-2 weeks
- It has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF)
- Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis, discontinuation should be considered after multidisciplinary advice

- **SQUAMOUS CELL CARCINOMA OF THE SKIN (SCC)** has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

Reference

Barnes, R. A., P. L. White, et al. (2009). "Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients." Journal of Clinical Pathology**62**(1): 64-69.

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Spellberg, B., J. Edwards, Jr., et al. (2005). "Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management." Clin. Microbiol. Rev.**18**(3): 556-569.

TITLE : ASSESSMENT OF INFECTION IN THE IMMUNOCOMPROMISED PATIENT
SOP No. BMT 100 041 01 SUPERSEDES PREVIOUS VERSION

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Comments:

1.0 INTRODUCTION

Patients undergoing chemotherapy, but particularly bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo-radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (length of time depends on treatment)
- Graft-versus-host disease in allografts leads to additional immunosuppression

Infection problems may be managed in various ways and this is summarised as follows:

- Separating the patient from infections (physical isolation)
- Prophylactic antimicrobials
- Surveillance of the patient
- Prompt treatment of infection

The following details are applicable to all patients undergoing haemopoietic stem cell transplantation or therapy for leukaemia and related disorders particularly patients who are neutropenic (i.e. Neut $<0.5 \times 10^9$/l). However, all patients who have had a bone marrow transplant remain at risk of infection for sometime, but particularly in the first 100 days following transplant and the approach can essentially be applied to all such patients regardless of their neutrophil count. A few exceptions may occur in patients who have sibling transplants or autografts, stable engraftment, are well and out of hospital and come back in with an inflamed Hickman line as their only apparent source of infection. Such patients may quite reasonably be commenced on treatment against coagulase negative staphylococcus only as first line. An additional group of patients who are susceptible to infections are those who have received Campath-1H and a high index of suspicion with regard to atypical infections such as fungal infection, CMV and PCP should be maintained in this group.

The main role of first line antibiotics in neutropenic patients following their transplant/ chemotherapy is to keep them well long enough to determine what the responsible organism is or until their blood counts recover. Accordingly, it is important that first line antibiotics are effective against a broad spectrum of life threatening organisms, which in the first episode of neutropenic fever is most likely to be a gram-negative rod, including E. Coli and in particular Pseudomonas. This determines the choice of a combination of a broad spectrum Ureidopenicillin and an aminoglycoside as initial treatment. See Protocol for Anti-Infective Use in Immunocompromised Patients.

2.0 INITIAL ASSESSMENT

Fever is defined as

- Temperature of greater than 38.5 ^oC, ***or***
- Two temperatures within two hours of 38 ^oC or greater

When a patient develops such a fever the nursing staff will alert the Medical Officer. They will take a history of the past few hours particularly with regard to Hickman line use and onset of fever/rigors. The recent transfusion of any blood products should also be considered and the possibility of a transfusion reaction or infected blood products also taken into consideration. The medical officer will examine the patient looking for a source of infection. Areas for particular attention are:

- Mouth
- Chest
- Perianal area (do not do digital rectal examination in neutropenics unless essential)
- Hickman exit site/tunnel

In the presence of localising signs of infection the patient still needs empirical broad spectrum antibiotics as in other cases of neutropenic fever, but additional agents may be appropriate e.g. vancomycin or teicoplanin for inflammation of Hickman, and metronidazole for perianal inflammation.

NB – It should be remembered that occasionally septic patients do not mount a fever or may even develop hypothermia. Infection should be considered in any neutropenic patient who is unexpectedly unwell, shocked, lost consciousness etc. and the same approach should be followed

3.0 INVESTIGATIONS

The following investigations will be carried out for a new occurrence of a fever:

- *Blood cultures* (at least two sets, preferably one peripheral; volume is important and at least 20mls should be taken). Unlike other sampling from a Hickman catheter, the first few mls are not discarded but are used for the cultures.

- *Chest x-ray* (Focal infiltrates raise suspicion of aspergillosis which may require amphotericin, diffuse infiltrates may suggest pneumocystis or CMV pneumonitis in susceptible patients eg ALL or post allograft patients). Unless the patient has signs or symptoms relevant to the chest or it is going to alter therapy, CXR can be done in the morning for patients febrile during the night.

- Urine microscopy and culture.

- Other bacteriology specimens including those for viruses such as naso-pharyngeal aspirate, as relevant to the clinical situation (e.g. diarrhoea will require a stool sample etc).

4.0 ON-GOING ASSESSMENT

4.1 The medical officer must assess patients who are febrile on antibiotics at least twice per day. If patients remain pyrexial further blood cultures should be carried out at least daily. Use of other investigations such as repeat CXR, CT scan, BAL, LP etc. should be considered depending on the patient's symptoms.

4.2 Alteration/cessation of antibiotics will be as per the anti-infective protocols. Stopping antibiotics in a profoundly neutropenic patient is a Consultant or SpR decision.

4.3 Some unusual gram-negative rods, e.g. Stenotrophomonas (formerly known as Xanthomonas), are line-associated and may be almost impossible to eradicate without removing the line.

4.4 All neutropenic patients and any individual who has received T cell immunosuppression (e.g. Campath, fludarabine) are at risk of developing invasive fungal infections. Assessment for the likelihood of an underlying invasive fungal infection should be carried out daily whilst the patient is pyrexial using the EORTC criteria. Early use of CT imaging should be considered in patients at high risk for fungal infection to aid in making a rapid diagnosis of probable/possible infections and instigating the appropriate treatment.

5.0 APPENDIX 1

Definitions of Fungal Infections

EORTC-IFICG and MSG criteria

PROVEN INVASIVE FUNGAL INFECTION

DEEP TISSUE INFECTIONS	
Moulds	***Yeasts***
Histo/cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging).	Histo/cytopathology showing yeast cells and/or pseudohyphae from a needle aspiration or biopsy excluding mucous membranes.
OR	**OR**
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection.	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (india ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF.
FUNGAEMIA	
Positive blood culture of fungi excluding aspergillus spp. and penicillium spp. other than P. marneffei, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism.	Positive blood culture of candida and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism.

PROBABLE INVASIVE INFECTION	**POSSIBLE INVASIVE INFECTION**
At least 1 host criterion	At least 1 host criterion
AND 1 microbiological criterion	AND
AND 1 major OR 2 minor clinical criteria	EITHER 1 microbiological criterion
	OR 1 major OR 2 minor clinical criteria

Microbiological Criteria

1) Positive culture of a mould (including aspergillus spp., Fusarium pp., zygomycetes, scedosporium pp), C Neoformans from sputum or BAL.
2) Positive culture or cytology/direct microscopy for moulds from sinus aspirate.
3) Positive cytology/direct microscopy for a mould or cryptococcus from sputum, BAL.
4) Positive aspergillus antigen in BAL, CSF or >2 blood samples.
5) Positive cryptococcal antigen in blood.
6) Positive cytology/direct microscopy for fungal elements other than cryptococcus in sterile body fluids.
7) Two positive urine cultures of yeasts in the absence of urinary catheter.
8) Candida casts in the urine in the absence of urinary catheter.
9) Positive blood culture of candida spp.
10) Pulmonary abnormality and negative bacterial cultures of any possible bacteria from any specimen related to the lower respiratory tract infection including blood, sputum and BAL, etc.

6.0 APPENDIX 2

Clinical Criteria

Should be related to the site of microbiological criteria and temporarily related to current episode.

MAJOR	MINOR
Lower Respiratory Tract Infection	
Any of the following new infiltrates on CT imaging; halo sign, air-crescent sign or cavity within an area of consolidation.	1) Symptoms of LRTI (cough, chest pain, haemoptysis) 2) Physical finding of pleural rub 3) Any new infiltrate not fulfilling major criterion
Sino Nasal Infection	
Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighbouring structures, extensive base of skull destruction).	1) URTI symptoms (nasal discharge, etc). 2) Nose ulceration or eschar of nasal mucosa or epistaxis 3) Periorbital swelling 4) Maxillary tenderness 5) Black necrotic lesions or perforation of the hard palate
CNS Infection	
Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes, intracerebral abscesses or infarcts).	(CSF culture negative for other pathogens & malignant cells by microscopy and culture) 1) Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) 2) Mental changes 3) Meningeal irritation findings 4) Abnormalities in CSF biochemistry and cell count
Disseminated Fungal Infection	
	1) Papular or nodular skin lesions without any other explanation 2) Intraocular findings suggestive of haematogenous fungal chorioretinitis or endophthalmitis
Chronic Disseminated Candidiasis (Probable)	
One host factor **AND** small peripheral target like abscesses (Bull's eye) in liver and or spleen demonstrated by CT, MRI or USS.	

Host Factors

1) Neutropenia: PMN $<0.5 \times 10^9$/l for >10 days
2) Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment
3) Body temperature either $>38^0$C or $<36^0$C AND any of the following
   a) Prolonged neutropenia (>10 days) in the previous 60 days)
   b) Recent or current use of significant immunosuppressive agents in the previous 30 days
   c) Invasive fungal infection in a previous episode
4) Coexistence of AIDS

SOP Read and Understood By: (Print Name)	Staff Signature	Date

THIS DOCUMENT MUST BE HELD BY HEAD OF DEPARTMENT AND REVIEWED AT A MINIMUM OF 2 YEARLY INTERVALS TO ENSURE INFORMATION IS ACCURATE.

TITLE : ASSESSMENT OF INFECTION IN THE IMMUNOCOMPROMISED PATIENT
SOP No. BMT 100 041 02 SUPERSEDES PREVIOUS VERSION

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1.0 INTRODUCTION

Patients undergoing chemotherapy, but particularly bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo-radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (length of time depends on treatment)
- Graft-versus-host disease in allografts leads to additional immunosuppression

Infection problems may be managed in various ways and this is summarised as follows:

- Separating the patient from infections (physical isolation)
- Prophylactic antimicrobials
- Surveillance of the patient
- Prompt treatment of infection

The following details are applicable to all patients undergoing haemopoietic stem cell transplantation or therapy for leukaemia and related disorders particularly patients who are neutropenic (i.e. Neut $<0.5 \times 10^9$/l). However, all patients who have had a bone marrow transplant remain at risk of infection for sometime, but particularly in the first 100 days following transplant and the approach can essentially be applied to all such patients regardless of their neutrophil count. A few exceptions may occur in patients who have sibling transplants or autografts, stable engraftment, are well and out of hospital and come back in with an inflamed Hickman line as their only apparent source of infection. Such patients may quite reasonably be commenced on treatment against coagulase negative staphylococcus only as first line. An additional group of patients who are susceptible to infections are those who have received Alemtuzumab and a high index of suspicion with regard to atypical infections such as fungal infection, CMV and PCP should be maintained in this group.

The main role of first line antibiotics in neutropenic patients following their transplant/ chemotherapy is to keep them well long enough to determine what the responsible organism is or until their blood counts recover. Accordingly, it is important that first line antibiotics are effective against a broad spectrum of life threatening organisms, which in the first episode of neutropenic fever is most likely to be a gram-negative rod, including E. Coli and in particular Pseudomonas. This determines the choice of a combination of a broad spectrum Ureidopenicillin and an aminoglycoside as initial treatment. See Protocol for Anti-Infective Use in Immunocompromised Patients.

2.0 INITIAL ASSESSMENT

Fever is defined as

- Temperature of greater than 38.5 ^oC, ***or***
- Two temperatures within two hours of 38 ^oC or greater

When a patient develops such a fever the nursing staff will alert the Medical Officer. They will take a history of the past few hours particularly with regard to Hickman line use and onset of fever/rigors. The recent transfusion of any blood products should also be considered and the possibility of a transfusion reaction or infected blood products also taken into consideration. The medical officer will examine the patient looking for a source of infection. Areas for particular attention are:

- Mouth
- Chest
- Perianal area (do not do digital rectal examination in neutropenics unless essential)
- Hickman exit site/tunnel

In the presence of localising signs of infection the patient still needs empirical broad spectrum antibiotics as in other cases of neutropenic fever, but additional agents may be appropriate e.g. vancomycin or teicoplanin for inflammation of Hickman, and metronidazole for perianal inflammation.

NB – It should be remembered that occasionally septic patients do not mount a fever or may even develop hypothermia. Infection should be considered in any neutropenic patient who is unexpectedly unwell, shocked, lost consciousness etc. and the same approach should be followed.

3.0 INVESTIGATIONS

The following investigations will be carried out for a new occurrence of a fever:

- *Blood cultures* (at least two sets, preferably one peripheral; volume is important and at least 20mls should be taken). Unlike other sampling from a Hickman catheter, the first few mls are not discarded but are used for the cultures.

- *Chest x-ray* (Focal infiltrates raise suspicion of aspergillosis which may require amphotericin, diffuse infiltrates may suggest pneumocystis or CMV pneumonitis in susceptible patients eg ALL or post allograft patients). Unless the patient has signs or symptoms relevant to the chest or it is going to alter therapy, CXR can be done in the morning for patients febrile during the night.

- Urine microscopy and culture.

- Other bacteriology specimens including those for viruses such as naso-pharyngeal aspirate, as relevant to the clinical situation (e.g. diarrhoea will require a stool sample to both microbiology and virology).

4.0 ON-GOING ASSESSMENT

4.1 The medical officer must assess patients who are febrile on antibiotics at least twice per day. If patients remain pyrexial further blood cultures should be carried out at least daily preferably both peripheral and central line cultures.

4.2 Alteration/cessation of antibiotics will be as per the anti-infective protocols. Stopping antibiotics in a profoundly neutropenic patient is a Consultant or SpR decision.

4.3 Some unusual gram-negative rods, e.g. Stenotrophomonas (formerly known as Xanthomonas), are line-associated and may be almost impossible to eradicate without removing the line.

4.4 Additional investigations such as Broncho-alveolar lavage, echocardiogram, lumbar puncture should be requested where appropriate.

4.5 All neutropenic patients and any individual who has received T cell immunosuppression (e.g. Alemtuzumab, Fludarabine) are at risk of developing invasive fungal infections. Early use of CT imaging should be considered in patients at high risk for fungal infection to aid in making a rapid diagnosis of probable/possible infections and instigating the appropriate treatment. Galactomannan my be useful – see antifungal protocol for further details

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TITLE : ASSESSMENT OF INFECTION IN THE IMMUNOCOMPROMISED PATIENT
SOP No. BMT 100 041 03 SUPERSEDES PREVIOUS VERSION

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Patients undergoing chemotherapy, but particularly bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo-radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (length of time depends on treatment)
- Graft-versus-host disease in allografts leads to additional immunosuppression

Infection problems may be managed in various ways and this is summarised as follows:

- Separating the patient from infections (physical isolation)
- Prophylactic antimicrobials
- Surveillance of the patient
- Prompt treatment of infection

The following details are applicable to all patients undergoing haemopoietic stem cell transplantation or therapy for leukaemia and related disorders particularly patients who are neutropenic (i.e. Neut $<0.5 \times 10^9$/l). However, all patients who have had a bone marrow transplant remain at risk of infection for sometime, but particularly in the first 100 days following transplant and the approach can essentially be applied to all such patients regardless of their neutrophil count. A few exceptions may occur in patients who have sibling transplants or autografts, stable engraftment, are well and out of hospital and come back in with an inflamed Hickman line as their only apparent source of infection. Such patients may quite reasonably be commenced on treatment against coagulase negative staphylococcus only as first line. An additional group of patients who are susceptible to infections are those who have received Alemtuzumab and a high index of suspicion with regard to atypical infections such as fungal infection, CMV and PCP should be maintained in this group.

The main role of first line antibiotics in neutropenic patients following their transplant/ chemotherapy is to keep them well long enough to determine what the responsible organism is or until their blood counts recover. Accordingly, it is important that first line antibiotics are effective against a broad spectrum of life threatening organisms, which in the first episode of neutropenic fever is most likely to be a gram-negative rod, including E. Coli and in particular Pseudomonas. This determines the choice of a combination of a broad spectrum Ureidopenicillin and an aminoglycoside as initial treatment. See Protocol for Anti-Infective Use in Immunocompromised Patients.

2.0 INITIAL ASSESSMENT

Fever is defined as

- Temperature of 38 ^oC or greater

When a patient develops such a fever the nursing staff will alert the Medical Officer. They will take a history of the past few hours particularly with regard to Hickman line use and

onset of fever/rigors. The recent transfusion of any blood products should also be considered and the possibility of a transfusion reaction or infected blood products also taken into consideration. The medical officer will examine the patient looking for a source of infection. Areas for particular attention are:

- Mouth
- Chest
- Perianal area (do not do digital rectal examination in neutropenics unless essential)
- Hickman exit site/tunnel

In the presence of localising signs of infection the patient still needs empirical broad spectrum antibiotics as in other cases of neutropenic fever, but additional agents may be appropriate e.g. vancomycin or teicoplanin for inflammation of Hickman site, and metronidazole for perianal inflammation.

NB – It should be remembered that occasionally septic patients do not mount a fever or may even develop hypothermia. Infection should be considered in any neutropenic patient who is unexpectedly unwell, shocked, lost consciousness etc. and the same approach should be followed.

3.0 INVESTIGATIONS

The following investigations will be carried out for a new occurrence of a fever:

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- Urine microscopy and culture.

- Other bacteriology specimens including those for viruses such as naso-pharyngeal aspirate, as relevant to the clinical situation (e.g. diarrhoea will require a stool sample to both microbiology and virology).

4.0 ON-GOING ASSESSMENT

4.1 The medical officer must assess patients who are febrile on antibiotics at least twice per day. If patients remain pyrexial further blood cultures should be carried out at least daily preferably both peripheral and central line cultures.

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4.4 Additional investigations such as Broncho-alveolar lavage, echocardiogram, lumbar puncture should be requested where appropriate.

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4.6 Lumbar puncture may be indicated in some circumstances. In allogeneic or other heavily immunosuppressed patients samples should be sent for bacteriology, glucose, protein, lactate, cytospin,and virology requesting JC virus, HSV, VZV, CMV, HHV6

TITLE : ASSESSMENT OF INFECTION IN THE IMMUNOCOMPROMISED PATIENT
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- Surveillance of the patient
- Prompt treatment of infection

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2.0 INITIAL ASSESSMENT

Fever is defined as:

- Temperature of 38 ^oC or greater on single occasion
- *NB* – It should be remembered that occasionally septic patients do not mount a fever or may even develop hypothermia. Infection should be considered in any neutropenic

patient who is unexpectedly unwell, shocked, lost consciousness etc. and the same approach should be followed.

When a patient develops such a fever or other features the nursing staff will alert the Medical Officer. They will take a history of the past few hours particularly with regard to Hickman line use and onset of fever/rigors. The recent transfusion of any blood products should also be considered and the possibility of a transfusion reaction or infected blood products also taken into consideration. The medical officer will examine the patient looking for a source of infection. Areas for particular attention are:

- Mouth
- Chest
- Perianal area (do not do digital rectal examination in neutropenics unless essential)
- Hickman exit site/tunnel

In the presence of localising signs of infection the patient still needs empirical broad spectrum antibiotics as in other cases of neutropenic fever, but additional agents may be appropriate e.g. vancomycin or teicoplanin for inflammation of Hickman site, and metronidazole for perianal inflammation.

If this fever could be due to a viral respiratory infection or other contagious organism initiate infection control procedures as per BMT-100-029 Isolation and Infection Control

3.0 INVESTIGATIONS

The following investigations will be carried out for a new occurrence of a fever:

- *Blood cultures* (at least two sets, preferably one peripheral; volume is important and at least 20mls should be taken). Unlike other sampling from a Hickman catheter, the first few mls are not discarded but are used for the cultures. Cultures should be taken from all lumens of lines.

- *Chest x-ray* (Focal infiltrates raise suspicion of aspergillosis which may require amphotericin, diffuse infiltrates may suggest pneumocystis or CMV pneumonitis in susceptible patients eg ALL or post allograft patients). Unless the patient has signs or symptoms relevant to the chest or it is going to alter therapy, CXR can be done in the morning for patients febrile during the night.

- Urine microscopy and culture.

- Other bacteriology specimens including those for viruses such as viral gargle or swab (see virology advice for current requirements), as relevant to the clinical situation (e.g. diarrhoea will require a stool sample to both microbiology and virology).

4.0 ON-GOING ASSESSMENT

4.1 The medical officer must assess patients who are febrile on antibiotics at least twice per day. If patients remain pyrexial further blood cultures should be carried out at least daily preferably both peripheral and central line cultures.

4.2 Alteration/cessation of antibiotics will be as per the anti-infective protocols. Stopping antibiotics in a profoundly neutropenic patient is a Consultant or specialist Trainee decision.

4.3 Some unusual gram-negative rods, e.g. Stenotrophomonas (formerly known as Xanthomonas), are line-associated and may be almost impossible to eradicate without removing the line.

4.4 Additional investigations such as Broncho-alveolar lavage, echocardiogram, lumbar puncture should be requested where appropriate.

4.5 All neutropenic patients and any individual who has received T cell immunosuppression (e.g. Alemtuzumab, Fludarabine) are at risk of developing invasive fungal infections. Early use of CT imaging should be considered in patients at high risk for fungal infection to aid in making a rapid diagnosis of probable/possible infections and instigating the appropriate treatment. Galactomannan my be useful – see antifungal protocol for further details

4.6 Lumbar puncture may be indicated in some circumstances. In allogeneic or other heavily immunosuppressed patients samples should be sent for bacteriology, glucose, protein, lactate, cytospin,and virology requesting JC virus, HSV, VZV, CMV, HHV6

AMENDMENTS FROM PREVIOUS VERSION
General update and move to new template

1.0 INTRODUCTION

Patients undergoing chemotherapy, but particularly bone marrow transplantation, have virtually no resistance to infection because of the following factors:

- Underlying disease being treated
- Chemo-radiotherapy damaging the integrity of the gut mucosa
- Partial ablation/ disruption of the immune system (length of time depends on treatment)
- Graft-versus-host disease in allografts leads to additional immunosuppression

Infection problems may be managed in various ways and this is summarised as follows:

- Separating the patient from infections (physical isolation)
- Prophylactic antimicrobials
- Surveillance of the patient
- Prompt treatment of infection

The following details are applicable to all patients undergoing haemopoietic stem cell transplantation or therapy for leukaemia and related disorders particularly patients who are neutropenic (i.e. Neut $<0.5 \times 10^9$/l). However, all patients who have had a bone marrow transplant remain at risk of infection for sometime, but particularly in the first 100 days following transplant and the approach can essentially be applied to all such patients regardless of their neutrophil count.

A few exceptions may occur in patients who have sibling transplants or autografts, stable engraftment, are well and out of hospital and come back in with an inflamed Hickman line as their only apparent source of infection. Such patients may quite reasonably be commenced on treatment against coagulase negative staphylococcus only as first line.
An additional group of patients who are susceptible to infections are those who have received Alemtuzumab and a high index of suspicion with regard to atypical infections such as fungal infection, CMV and PCP should be maintained in this group.

The main role of first line antibiotics in neutropenic patients following their transplant/ chemotherapy is to keep them well long enough to determine what the responsible organism is or until their blood counts recover.

Accordingly, it is important that first line antibiotics are effective against a broad spectrum of life threatening organisms, which in the first episode of neutropenic fever is most likely to be a gram-negative rod, including E.coli and in particular Pseudomonas. This determines the choice of a combination of a broad spectrum Ureidopenicillin and an aminoglycoside as initial treatment.
See Protocol for Anti-Infective Use in Immunocompromised Patients.

2.0 INITIAL ASSESSMENT

Fever is defined as:

- Temperature of 38 °C or greater on single occasion
  NB – It should be remembered that occasionally septic patients do not mount a fever or may even develop hypothermia. Infection should be considered in any neutropenic patient who is unexpectedly unwell, shocked, lost consciousness etc. and the same approach should be followed.

When a patient develops such a fever or other features the nursing staff will alert the Medical Officer. They will take a history of the past few hours particularly with regard to Hickman line use and onset of fever/rigors. The recent transfusion of any blood products should also be considered and the possibility of a transfusion reaction or infected blood products also taken into consideration. The medical officer will examine the patient looking for a source of infection.

Areas for particular attention are:

- Mouth
- Chest
- Perianal area (do not do digital rectal examination in neutropenics unless essential)
- Hickman exit site/tunnel

In the presence of localising signs of infection the patient still needs empirical broad spectrum antibiotics as in other cases of neutropenic fever, but additional agents may be appropriate e.g. vancomycin or teicoplanin for inflammation of Hickman site, and metronidazole for perianal inflammation.

If this fever could be due to a viral respiratory infection or other contagious organism initiate infection control procedures as per BMT-100-029 Isolation and Infection Control

3.0 INVESTIGATIONS

The following investigations will be carried out for a new occurrence of a fever:

- ***Blood cultures*** (at least two sets, preferably one peripheral; volume is important and at least 20mls should be taken). Unlike other sampling from a Hickman catheter, the first few mls are not discarded but are used for the cultures. Cultures should be taken from all lumens of lines.

- ***Chest x-ray*** (Focal infiltrates raise suspicion of aspergillosis which may require amphotericin, diffuse infiltrates may suggest pneumocystis or CMV pneumonitis in susceptible patients eg ALL or post allograft patients). Unless the patient has signs or symptoms relevant to the chest or it is going to alter therapy, CXR can be done in the morning for patients febrile during the night.

- **Urine** microscopy and culture.

- **Other** bacteriology specimens including those for viruses such as viral gargle or swab (see virology advice for current requirements), as relevant to the clinical situation (e.g. diarrhoea will require a stool sample to both microbiology and virology).

4.0 ON-GOING ASSESSMENT

4.1 The medical officer must assess patients who are febrile on antibiotics at least twice per day. If patients remain pyrexial further blood cultures should be carried out at least daily preferably both peripheral and central line cultures.

4.2 Alteration/cessation of antibiotics will be as per the anti-infective protocols. Stopping antibiotics in a profoundly neutropenic patient is a Consultant or Specialist Trainee decision.

4.3 Some unusual gram-negative rods, e.g. Stenotrophomonas (formerly known as Xanthomonas), are line-associated and may be almost impossible to eradicate without removing the line.

4.4 Additional investigations such as Broncho-alveolar lavage, echocardiogram, lumbar puncture should be requested where appropriate.

4.5 All neutropenic patients and any individual who has received T cell immunosuppression (e.g. Alemtuzumab, Fludarabine) are at risk of developing invasive fungal infections. Early use of CT imaging should be considered in patients at high risk for fungal infection to aid in making a rapid diagnosis of probable/possible infections and instigating the appropriate treatment.
Galactomannan and aspergillus PCR may be useful and should always be requested if BAL is carried out – see antifungal protocol for further details

4.6 Lumbar puncture may be indicated in some circumstances.
In allogeneic or other heavily immunosuppressed patients samples should be sent for bacteriology, glucose, protein, lactate, cytospin, TB, toxoplasma PCR and virology requesting JC virus, HSV, VZV, CMV, HHV6, adenovirus, EBV etc.

MANAGEMENT OF NEUTROPENIA AND FEVER

ANTIBIOTIC POLICY

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Haemato-Oncology (Schiehallion) Unit
Royal Hospital for Sick Children
Yorkhill Division

August 2010

Contents	Page Number(s)
1. Introduction	3
2. Febrile Neutropenia	3
2.1 Criteria for Treatment	3 – 4
2.2 History and Examination	4
2.3 Investigations	4
2.4 Treatment	4
2.5 Microbiological Cultures	4 – 5
3. Antibiotic Protocol for Neutropenic Patients	5
3.1 First Line Therapy	5 – 6
3.2 Second Line Therapy	6
3.3 Penicillin Allergy	6
3.4 Duration of Antibiotic Treatment	6
4. Non-Neutropenic Fever	6
5. Antibiotic Doses	6
5.1 Tazocin	6 - 7
5.2 Gentamicin	7
5.3 Ciprofloxacin	8
5.4 Vancomycin	8
5.5 Teicoplanin	8
5.6 Ambisome	8
5.7 Meropenem	8
6. Opportunistic Chest Infections	9
6.1 General	9
6.2 Mycoplasma Pneumoniae	9
6.3 Pneumocystis Carinii	9
7. Supportive Care / Miscellaneous	10
7.1 Central Lines	10
7.2 Antipyrexial Treatment	10
7.3 Chemotherapy	10
7.4 Examination	10
7.5 Constipation	10
7.6 Maintenance Co-trimoxazole	10
7.7 Mouth Ulcers	10
7.8 Diarrhoea	11
Appendix 1 – Criteria for Treatment	12

1. Introduction

Neutropenia is defined as a neutrophil count of <1 x 10^9/L and patients who are neutropenic are vulnerable to **overwhelming infection**. The frequency and severity of infective episodes correlates inversely with the degree and duration of neutropenia and is particularly marked in children whose neutrophil count is below 0.5 x 10^9/l.

2. Febrile Neutropenia

2.1 Criteria for Treatment (see Appendix 1)

2.1.1 Any child with a single temperature of 38.5^{0}C or above should receive intravenous antibiotics.

2.1.2 Any child with a temperature above 38°C but below 38.5^{0}C should have his/her temperature repeated 30 minutes later and if it is still above 38°C he/she should receive intravenous antibiotics. Paracetamol should not be given until the decision to treat has been taken because it may mask a fever. Particular care should be exercised with SCT patients who are neutropenic and they should receive intravenous antibiotics for an isolated temperature above 38^{0}C

2.1.3 Any child who deteriorates and looks sick or rigors regardless of his/her temperature and neutrophil count should receive intravenous antibiotics.

2.1.4 A well child who is not neutropenic with an obvious focus of infection can receive treatment appropriate for that infection e.g. otitis media. Err on the side of caution and if in doubt **admit the child and give IV antibiotics. Be particularly careful with possible/probable line-related infections because, although these are most often colonised with coagulase negative staphylococci, they can be colonised with gram-negative organisms, and can result in gram-negative septicaemia and septic shock.**

2.1.5 A febrile neutropenic child must be admitted and carefully monitored. Paracetamol should not be given until the decision to give antibiotic treatment has been made, because it may mask fever. If the temperature is >38.5^{o}C on any occasion (including at home) or above 38°C on 2 successive occasions 30 minutes apart, intravenous antibiotics are indicated, even if the patient appears otherwise completely well. It is always better to over rather than under treat these patients. **These children can deteriorate rapidly.**

IN A NEUTROPENIC PATIENT, THE OCCURRENCE OF FEVER MUST BE REGARDED AS AN EMERGENCY

!!!! You have 15 minutes to <u>see</u> the patient

!!!! You have 30 minutes to <u>treat</u> the patient

2.1.6 An **'ill'** child must be assessed immediately by the admitting experienced middle grade staff member even in the absence of a fever. **A DELAY IN ADMINISTERING THE FIRST DOSE OF ANTIBIOTICS MAY PROVE FATAL** – and must not be delayed for any reason (including shift changes, ward rounds, radiological examination, problems with venous access). **Blood cultures should be taken before giving the first dose of antibiotics.**

!!!! The first dose of antibiotics can precipitate septic shock

!!!!! Be prepared to resuscitate the patient

2.1.7 Patients who are unwell or hypotensive should immediately receive resuscitation fluids and IV antibiotics, even if they are not pyrexial. Remember steroids can mask an inflammatory response.

2.1.8 If a patient deteriorates after using/flushing his/her central line consideration should be given to siting a peripheral cannula and stopping using the line.

2.1.9 All haematology/oncology patients admitted overnight must be seen by the most experienced middle grade doctor on for hospital cover who should discuss any patient causing concern with the consultant haematologist/oncologist on-call.

2.2 History and Examination

2.2.1 **Keep the history brief**. The following will help predict the likely degree and duration of neutropenia and identify a potential focus that might guide antibiotic therapy. Note:

- The diagnosis
- The date and type of the last chemotherapy given
- Any recent blood counts
- The duration of fever
- The presence of a central line (NB line associated sepsis)
- The presence of bleeding
- Any muscle, joint or abdominal pain
- The presence of mucositis
- Any local cause for fever

2.2.2 **Examination: Ask yourself:**

- Does the child require resuscitation?
- Is the child septicaemic or shocked?
- What is the temperature, HR, RR, BP, oxygen saturation and Capillary Refill Time (CRT)
- Is there an obvious focus for infection?

2.3 Investigations

- Blood cultures (take a large volume)
- FBC and differential
- CRP
- U&Es
- LFTs and Coagulation screen: PT, APTT, Fibrinogen +/- d-dimers if unwell – every child does not require a coagulation screen.
- Swabs of any lesions
- TS/Sputum/Stool / Urine culture
- Consider a CXR (this must not delay therapy)
- If respiratory symptoms, consider NPA

2.4 Treatment

2.4.1 Resuscitate the child
2.4.2 Give antibiotics
2.4.3 Give blood products as indicated.

2.5 Microbiological Cultures

2.5.1 Blood Cultures

2.5.1.1 Blood cultures should be taken from the central line, or where there is no central line from a peripheral stab.

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2.5.1.2 The volume required is **5 - 10 mls** or a **minimum of 3-5 mls** from an infant. In the case of a double lumen long line, or two separate central lines, blood cultures should be taken **from each lumen**.

2.5.1.3 Blood cultures should be repeated in the event of:

- Clinical deterioration
- Rigors
- Persistent pyrexia after 48 hours and thereafter 48-72 hourly if the patient remains pyrexial
- Prior to any antibiotic change
- Recurrence of fever after an apyrexial period

2.5.1.4 If blood cultures are initially positive, repeat cultures should be taken after 48 hrs to confirm the organism has been eradicated (in vitro sensitivities do not always correlate with in vivo sensitivity).

2.5.1.5 In the case of a central line infection, which is often due to bacterial growth in a biofilm, it is advisable to repeat line cultures after stopping antibiotics to check that the organism has been eradicated.

2.5.2 Additional investigations should be performed:

2.5.2.1 Swab of central line exit site(s)

2.5.2.2 Consider

- Viral serology or culture if symptoms are suggestive of viral infection
- Nose swab
- Throat swab
- Sputum culture
- Urine culture
- Stool culture

2.5.2.3 A chest X-ray may be indicated. Remember that in pneumocystits carinii pneumonia the chest may be clinically clear when there is marked radiological change.

3. Antibiotic Protocol for Neutropenic Patients

3.1 First Line Therapy

3.1.1 First line therapy is with Tazocin and Gentamicin in neutropenic patients in the absence of positive blood cultures which would indicate alternative antibiotics. Tazocin is a penicillin based antibiotic and penicillin allergy should be excluded. Patients known to be colonised with ESBL producing organisms should receive Meropenem instead of Tazocin (dosing schedule given under second line therapy).

Dosing regimen: **Tazocin (90mg/kg/dose 4 times a day) plus Gentamicin (7mg/kg/once daily)**

3.1.2 Please prescribe Tazocin according to pharmacy dose banding chart. **A copy of the Tazocin chart is kept in the IV Kardex folder and is in on back of order form.**

3.1.3 Gentamicin requires caution in patients at risk of renal impairment. However, it is extremely unlikely that one single dose of gentamicin will do harm and a single dose should be given and levels measured before any subsequent doses.

3.1.4 **Antibiotic cover for line-related therapy:** Vancomycin or Teicoplanin should be added to the initial therapy only if there is proven or very high suspicion of line infection. Teicoplanin is preferable for patients on other nephrotoxic drugs. The criteria for risk of line infections include:

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- Local Sepsis: Erythema at exit site or skin tunnel; pain over tunnel or on moving that arm/shoulder.
- Previously documented catheter related sepsis with an organism sensitive to Vancomycin or Teicoplanin with the current central venous catheter.
- Rigor or fever after flushing line (within 4 hours).
- Relevant positive blood culture

3.2 Second Line Therapy

3.2.1 Patients who remain pyrexial after 72 hours of empirical therapy should change to second line therapy. Second line therapy is with Meropenem and Gentamicin.

Dosing regimen: **Meropenem (20mg/kg/dose three times a day) plus Gentamicin (7mg/kg/once daily)**

3.2.2 Patients who remain pyrexial at 5 days and who are or have been persistently neutropenic with no evidence of line related infection should have **AmBisome** added. This should be discussed with the responsible consultant.

3.3 Penicillin Allergy

3.3.1 Serious allergy is one that causes an anaphylactic or urticarial reaction. 10% of patients with reactions to penicillin-based antibiotics will also have a reaction with cephalosporins.

3.3.2 Patients who have had an allergic reaction classified as non-serious should receive **Ceftazidime & Gentamicin**.

3.3.3 Patients who have had an allergic reaction classified as serious should receive **ciprofloxacin & vancomycin.** If ciprofloxacin has been given as prophylaxis, please discuss treatment with Consultant Microbiologist on call.

3.4 Duration of Antibiotic Treatment

This depends on the degree and duration of neutropenia and the organism cultured, but as a general rule:

- Patients who are blood culture negative; stop antibiotics after 48 hours of apyrexia if the patient is well.
- Patients who are culture positive: this depends on the organism and the degree and duration of neutropenia. The child should be well and apyrexial and have a minimum of 7 days treatment including 48 hours of apyrexia. Preferably repeat blood cultures should be documented to be negative.
- Gentamicin should not be given for more than 10 days.

4. Non-Neutropenic Fever

Dosage: Tazocin (90mg/kg/dose 4 times a day)

5. Antibiotic Doses

For children aged 1-18 years:

5.1 Tazocin

- **90 mg/kg** (max 4.5g) four times a day
- Vial size 2.25g, 4.5g
- Give by IV bolus over 3-5 mins
- Dose reductions:

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* Creatinine clearance 20-50 ml/min: tazocin 90 mg/kg three times a day
* Creatinine clearance < 20 ml/min: tazocin 90 mg/kg twice a day

5.2 Gentamicin

5.2.1 Gentamicin dosing in patients with normal renal function:

- **Gentamicin 7mg/kg/once daily** (max 500mg/dose)
- Give by IV infusion in 50 – 100ml Sodium Chloride 0.9% over 60 minutes
- **Prescribe** dose for all patients at **12noon** each day
- **Measure level after 1st dose**

Trough: **Plasma samples at 18-24 hrs post-dose (i.e. with morning bloods)**
Expected level <1mg/L

NB in many patients the reported level will be <0.1mg/L, which is acceptable

- If trough level is >1mg/L, the dosing interval is normally increased by 12 hours. Please discuss further dosing with pharmacy/microbiology
- If trough level >2mg/L, patient is unsuitable for pulsed dosing regimen, and subsequent doses should be guided by levels.
- If there is no change in dosage regimen or renal function, repeat trough levels only every 4 days

5.2.2 Gentamicin dosing in patients with renal impairment (Estimated creatinine clearance ≤50 ml/min):

- Initial dose - Gentamicin 5mg/kg
- Trough levels as above
- Prescribe as a single dose and consult pharmacy/microbiology for further dosage advice

5.2.3 Managing **patients admitted out of hours:**

5.2.3.1: Patients admitted in the afternoon until 12 midnight
- Give 7mg/kg dose on admission
- Trough samples with morning bloods
- Prescribe at 12 noon the following day

5.2.3.2: Patients admitted between 12 midnight and 6am
- Give 7mg/kg dose on admission
- Arrange with microbiology for emergency levels to be done at 12 noon that day.
- If trough level is reported at <2.5mg/L, give second dose as close as possible to midday.
- If trough level is >2.5mg/L, consult pharmacy/microbiology for further dosage advice.

5.2.3.2 Patients admitted between 6am and 12noon
- Give 7mg/kg dose on admission
- Trough levels the following day with morning bloods.
- Prescribe dose on following and subsequent days 2 hours later, until dosing time of 12 noon is achieved.

NB: Do not forget to indicate on the microbiology request form the actual time the sample was taken – levels taken outwith the recommended times can still be interpreted, if an accurate sampling time is recorded.

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5.3 Ciprofloxacin

5.3.1 Ciprofloxacin may be used in children where the benefit is considered to outweigh any potential risk:

5.3.2 Dosing regimen for prophylaxis against gram negative organisms in patients undergoing SCT is 7.5mg/kg po/IV (see below for maximum dosing).

5.3.3 Dosing regimen for treatment

Intravenous:	1month – 18 years 10mg/kg three times a day (maximum dose of 400mg)
Occasionally give orally:	20mg/kg bd (maximum dose of 750mg)

5.3.4 Available preparations 100mg, 250mg, 500mg, 750mg tablets, 250/5ml oral suspension. 100mg/50ml and 200mg/100ml IV infusion.

5.3.5 Oral absorption is good but do not use with oral Mg, Ca, or Fe supplements as these affect absorption.

5.3.6 Infuse undiluted IV over 30-60 minutes - flush with Sodium Chloride 0.9%.

5.3.7 Creatinine clearance <20 ml/minute: reduce dose by 50%.

5.4 Vancomycin

5.4.1 Dosing regimen: 15mg/kg three times daily. (NB To achieve optimal plasma profile it is vital to ensure doses are administered as close to an eight hour interval as possible)

5.4.2 Infuse over 1-2 hours in Sodium Chloride 0.9%.

5.4.3 Measure trough level before the 3rd dose is given.

5.4.4 Target trough 10mg/L minimum

5.5 Teicoplanin

5.5.1 10mg/kg (max 400mg) every 12 hours for 3 doses then 10mg/kg (max 400mg) daily

5.5.2 Administration: Slow IV bolus or Infusion over 30 mins diluted in Sodium Chloride

5.5.3 Dose in renal impairment: CrCl 20-50: 50% of normal dose; <20: 30% of normal dose

5.5.4 No monitoring required

5.6 Ambisome

5.5.1 Dosing regimen: dependent on clinical situation

- **3 mg/kg/day** with proven or highly suspicious fungal infection (doses of up to 10 mg/kg/day have been used for proven infections)
- 2mg/kg alternate days for anti-fungal prophylaxis in stem cell transplant patients and 1mg/kg alternate days in other patients.

5.5.2 Infuse in Glucose 5% ONLY at a concentration of 0.2-2.0 mg/ml. If dose ≥5mg/kg infuse over 2 hours otherwise 1 hour.

5.7 Meropenem

5.6.1 Dosing regimen: 20 mg/kg three times a day (max 1g/dose).Can increase to 40 mg/kg in severe infections (max 2g/dose).

5.6.2 Give as IV bolus over 5 minutes or infuse over 15-30 minutes (dilute 1g in at least 50 ml Sodium Chloride 0.9% or Glucose 5%).

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6. Opportunistic Chest Infections

6.1 General

6.1.1 There are a variety of opportunistic lung infections that can occur in long-term immunosuppressed children that must be considered in a child with respiratory symptoms.

6.1.2 Note the respiratory rate, any signs of respiratory distress and check pulse oximetry.

6.1.3 Give supplemental oxygen therapy if required and arrange blood gases.

6.1.4 Ask for ITU consult if the patient's condition, respiratory rate or oxygen requirements suggest that artificial ventilation may be necessary.

6.1.5 Discuss these patients with the consultant on call for haematology/oncology.

6.2 Mycoplasma Pneumoniae

6.2.1 This may present with a multitude of symptoms.

6.2.2 The disease tends to have a prodrome (fevers, chills, headaches) and the cough may persist for several weeks.

6.2.3 The chest x-ray may show diffuse patchy consolidation and the MCV may be raised due to cold agglutinins.

6.2.4 Treatment is with IV **Clarithromycin** 7.5mg/kg per dose twice a day (max 500mg/dose).

Consider using **Azithromycin** if patient is able to tolerate **oral** medications at following doses:

Dose: over 6 months 10mg/kg once daily for 3 days

Or	15-25kg	200mg once daily for 3 days
	26-35kg	300mg once daily for 3 days
	36-45kg	400mg once daily for 3 days
	>45kg	500mg once daily for 3 days

6.3 Pneumocystits Carinii

6.3.1 Signs of infection include tachypnoea, dry cough, dyspnoea on exertion and cyanosis. The chest is often clear on auscultation.

6.3.2 Check pulse oximetry and blood gases as oxygen desaturation often precedes x-ray changes. CXR may show bilateral infiltrates, but can be similar to viral infection or fluid overload.

6.3.3 Although pneumocystis is less common with the use of prophylactic Co-Trimoxazole, it still occurs. Exercise a high level of suspicion in children using alternatives to Co-Trimoxazole as PCP prophylaxis

6.3.4 Treatment is with **high dose intravenous Co-Trimoxozole 60mg/kg per dose twice a day.**

- Give by IV infusion over 20-60 minutes. Dilute each 480mg ampoule in 75mls 5% Glucose.
- In severe fluid restriction Co-Trimoxozole may be given undiluted via a central line only and over at least 60 minutes.
- Consider the need for concomitant steroids, discuss with on call consultant.

NOTE: Adenovirus, Paraflu and RSV can be fatal in stem cell transplant patients. Any transplant patient who develops respiratory symptoms or distress should be discussed with the BMT consultant

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7. Supportive Care / Miscellaneous

7.1 Central Lines:

7.1.1 Central lines can be a source of infections with gram-negative and gram-positive organisms in neutropenic and non-neutropenic patients.

7.1.2 If a patient becomes pyrexial or deteriorates after flushing or sampling a Hickman line **add Teicoplanin.** Consider stopping using the line and inserting a cannula for antibiotics.

7.2 Antipyrexial Treatment:

7.2.1 Once cultures have been taken and antibiotics started it is acceptable to treat the fever with Paracetamol.

7.2.2 **Do not** give **non-steroidal anti-inflammatories such as ibuprofen**. Non-steroidals are contraindicated because of their effect on platelet function.

7.3 Chemotherapy

Refer to **Schiehallion Unit "Cytotoxic Agents Guidance"** to establish if Chemotherapy should be stopped temporarily in the neutropenic patient. **Note:** In certain protocols, chemotherapy is continued even in neutropenic fever. Discuss with consultant.

7.4 Examination

The child should be examined daily for signs of infection including sites such as the mouth, axillae, ears, perineum and central catheter site.

7.5 Constipation

7.5.1 Must be avoided if possible. As well as causing distress, it may precipitate septicaemia through mucosal damage.

7.5.2 Enemas, suppositories, rectal temperatures and rectal examinations should be avoided in neutropenic patients for the same reason. Ask about bowel function daily and consider laxatives as necessary.

7.6 Maintenance Co-trimoxazole

Continue maintenance co-trimoxazole whilst other antibiotics are being given unless the patient is receiving high dose co-trimoxazole intravenously or consultant thinks that co-trimoxazole should be temporarily discontinued to allow count recovery. Prophylaxis need not be given intravenously but can be temporarily withheld in patients who are nil by mouth.

7.7 Mouth Ulcers

7.7.1 All patients are advised on mouthcare.

7.7.2 Swab for virology (herpes simplex) and bacteriology.

7.7.3 Consider Aciclovir.

Aciclovir dosing:

Oral: Over 2 years: 200mg x 5/day for 5 days
Under 2 years: 100mg x 5/day for 5 days

The dose may be doubled in immunocompromised patients.

IV: 250-500mg/m^2 three times daily.

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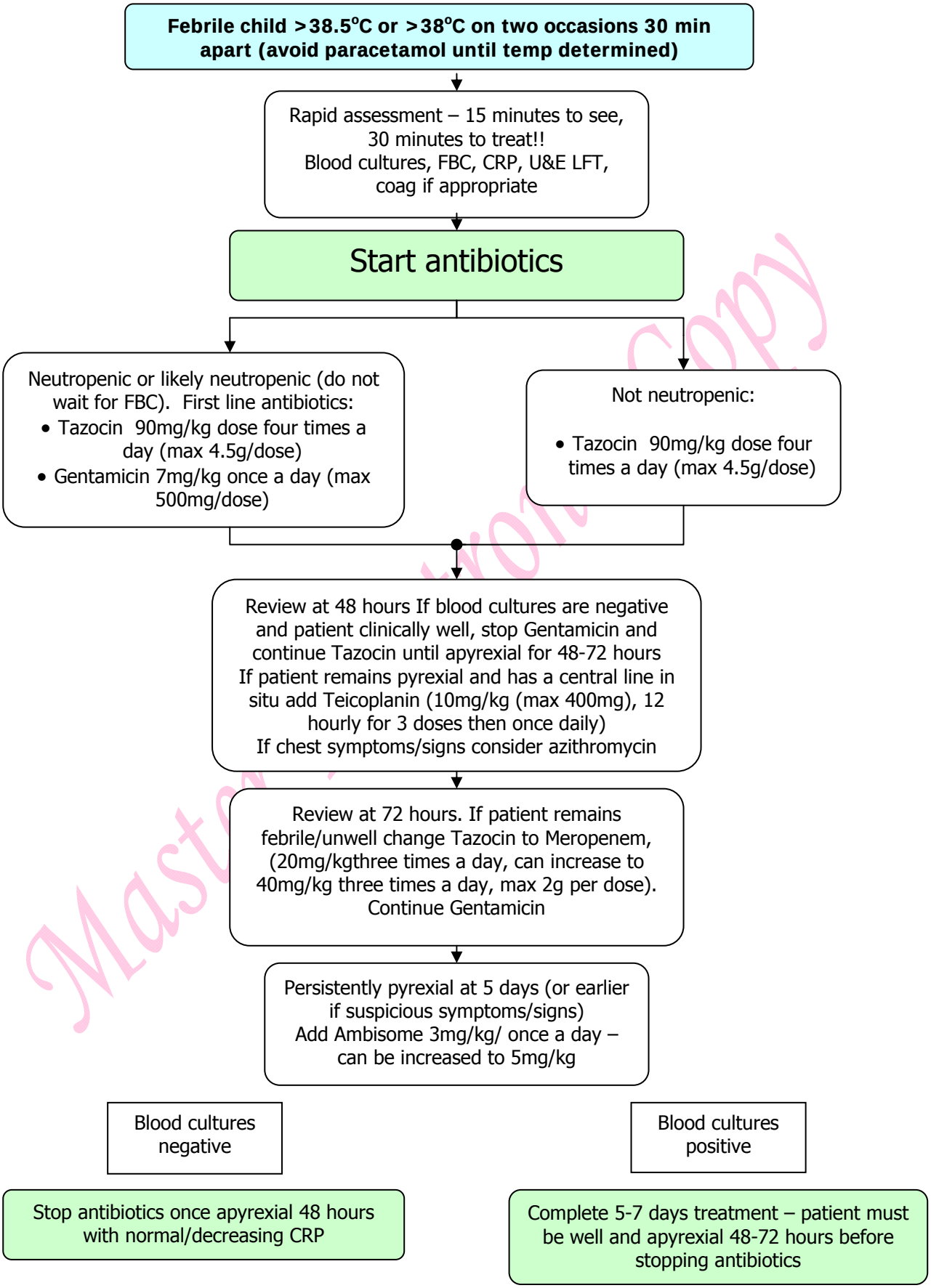
7.8 Diarrhoea:

7.8.1 Send stools for viruses, parasites, cryptosporidium and Clostridium difficile toxin.

7.8.2 Metronidazole should be considered for mucositis or perianal infections

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Appendix 1: Criteria for Treatment



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Management of Neutropenia & Fever - Antibiotic Policy

1. INTRODUCTION

Neutropenia is defined as a neutrophil count of <1 x 10^9/L and patients who are neutropenic are vulnerable to overwhelming infection. The frequency and severity of infective episodes correlates inversely with the degree and duration of neutropenia and is particularly marked in children whose neutrophil count is below 0.5 x 10^9/l.

2. RELATED DOCUMENTATION

This policy should be read in conjunction with the Assessment, Diagnosis and Management of Neutropenic Sepsis, Best Practice Statement, publication date: September 2011. This is a policy for use in adults and this current policy has been modified for paediatric use.

3. AUTHORISED PERSONNEL/SPECIFIC STAFF COMPETENCIES

3.1 The diagnosis and management of febrile neutropenia and fever will be directed by the Consultant/Associate Specialist or a senior member of the medical team.

3.2 The Medical/Nursing team will be responsible for monitoring & investigating.

4. EQUIPMENT/MATERIALS

None.

5. PROCEDURE

5.1 FEBRILE NEUTROPENIA

CRITERIA FOR TREATMENT

- Any child with a single temperature of 38.5°C or above should receive intravenous antibiotics.
- Any child with a temperature above 38°C but below 38.5°C should have his/her temperature repeated 30 minutes later and if it is still above 38°C he/she should receive intravenous antibiotics. Paracetamol should not be given until the decision to treat has been taken because it may mask a fever. Particular care should be exercised with HSCT patients who are neutropenic and they should receive intravenous antibiotics for an isolated temperature above 38°C.
- Any child who deteriorates and looks sick or rigors regardless of his/her temperature and neutrophil count should receive intravenous antibiotics. Fever may be suppressed by steroids, particularly Dexamethasone, and these children may become septic and deteriorate rapidly without exhibiting fever.

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- A well child who is not neutropenic with an obvious focus of infection can receive treatment appropriate for that infection e.g. otitis media. Err on the side of caution and if in doubt **admit the child and give IV antibiotics.** Be particularly careful with possible/probable line-related infections because, although these are most often colonised with coagulase negative staphylococci, they can be colonised with gram-negative organisms, and can result in gram-negative septicaemia and septic shock.
- A febrile neutropenic child must be admitted and carefully monitored. Paracetamol may mask fever - see above. If the temperature is >38.5°C on any occasion (including at home) or above 38°C on 2 successive occasions 30 minutes apart, intravenous antibiotics are indicated, even if the patient appears otherwise completely well. It is always better to over rather than under treat these patients. **These children can deteriorate rapidly.**

IN A NEUTROPENIC PATIENT, THE OCCURRENCE OF FEVER MUST BE REGARDED AS AN EMERGENCY

!!!! You have 15 minutes to see the patient

!!!! You have 30 minutes to treat the patient

- An **'ill'** child must be assessed immediately by the admitting experienced middle grade doctor/ANP even in the absence of a fever. **A DELAY IN ADMINISTERING THE FIRST DOSE OF ANTIBIOTICS MAY PROVE FATAL** – and must not be delayed for any reason (including shift changes, ward rounds, radiological examination, problems with venous access). **Blood cultures should be taken before giving the first dose of antibiotics.**

!!!! The first dose of antibiotics can precipitate septic shock

!!!!! Be prepared to resuscitate the patient

- Patients who are unwell or hypotensive should immediately receive resuscitation fluids and IV antibiotics, even if they are not pyrexial. Remember steroids can mask an inflammatory response.
- If a patient deteriorates after using/flushing his/her central line consideration should be given to siting a peripheral cannula and stopping using the line.
- All haematology/oncology patients admitted overnight must be seen by the most experienced middle grade doctor on for hospital cover who should discuss any patient causing concern with the consultant haematologist/oncologist on-call.

HISTORY AND EXAMINATION

- **Keep the history brief**. The following will help predict the likely degree and duration of neutropenia and identify a potential focus that might guide antibiotic therapy. Note:
  - The underlying diagnosis
  - The date and type of the last chemotherapy given

  - Any recent blood counts
  - The duration of fever
  - The presence of a central line (NB line associated sepsis)
  - The presence of bleeding
  - Any muscle, joint or abdominal pain
  - The presence of mucositis
  - Any local cause for fever

- **Examination: Ask yourself:**
  - Does the child require resuscitation?
  - Is the child septicaemic or shocked?
  - What is the temperature, HR, RR, BP, oxygen saturation and Capillary Refill Time (CRT)
  - Is there an obvious focus for infection?

INVESTIGATIONS

- Blood cultures (take a large volume)
- FBC and differential
- CRP
- U&Es & LFTs
- Coagulation screen: PT, APTT, Fibrinogen +/- d-dimers if unwell – every child does not require a coagulation screen.
- Swabs of any lesions
- TS/Sputum/Stool / Urine culture
- Consider a CXR (this must not delay therapy)
- If respiratory symptoms, consider NPA

TREATMENT

- Resuscitate the child
- Give antibiotics
- Give blood products as indicated

MICROBIOLOGICAL CULTURES

Blood Cultures:

- Blood cultures should be taken from the central line, or in the absence of a central line from a peripheral stab.
- The blood volume required is **5 - 10 mls** or a **minimum of 3-5 mls** from an infant. In patients with a double lumen central line, or two separate central lines, blood cultures should be taken **from each lumen**.
- Blood cultures should be repeated in the event of:
  - Clinical deterioration
  - Rigors
  - Persistent pyrexia after 48 hours and thereafter 48-72 hourly if the patient remains pyrexial
  - Prior to any antibiotic change
  - Recurrence of fever after an apyrexial period

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- If blood cultures are initially positive, repeat cultures should be taken after 48 hrs to confirm the organism has been eradicated (in vitro sensitivities do not always correlate with in vivo sensitivity).
- Central line infections are often associated with bacterial growth in a biofilm, and it is advisable to repeat line cultures after stopping antibiotics to check that the organism has been eradicated.

Additional investigations should be performed:

- Swab of central line exit site(s)
- Consider:
  - Viral serology or culture if symptoms are suggestive of viral infection
  - Nose swab
  - Throat swab
  - Sputum culture
  - Urine culture
  - Stool culture
- A chest X-ray may be indicated. Remember that in pneumocystits carinii pneumonia the chest may be clinically clear in the presence of marked radiological change.

5.2 Antibiotic Protocol for Neutropenic Patients

First Line Therapy

- First line therapy is with Tazocin and Gentamicin in neutropenic patients in the absence of positive blood cultures indicating alternative antibiotics. Tazocin is a penicillin based antibiotic and penicillin allergy should be excluded. Patients known to be colonised with ESBL producing organisms should receive Meropenem instead of Tazocin (dosing schedule given under second line therapy).

Dosing regimen: Tazocin (90mg/kg/dose 4 times a day) plus Gentamicin (7mg/kg/once daily)

- Gentamicin requires caution in patients at risk of renal impairment. However, it is extremely unlikely that one single dose of gentamicin will do harm and a single dose should be given and levels measured before any subsequent doses.
- Caution should also be exercised in patients at risk of ototoxicity. In particular children with Down Syndrome should receive Meropenem rather than Tazocin and Gentamicin because of their potential for underlying hearing difficulties. Caution should also be exercised in children receiving a cisplatinum based regimen.
- Please prescribe Tazocin according to pharmacy dose banding chart. **A copy of the Tazocin chart is kept in the IV Kardex folder and is in on back of order form.**

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- **Antibiotic cover for line-related therapy:** Vancomycin or Teicoplanin should be added to the initial therapy only if there is proven or very high suspicion of line related infection. Teicoplanin is preferable for patients receiving other nephrotoxic drugs and most oncology patients are in this category. The criteria for risk of line infections include:
  - Local Sepsis: Erythema at exit site or skin tunnel; pain over tunnel or on moving that arm/shoulder
  - Previously documented catheter related sepsis with an organism sensitive to Vancomycin or Teicoplanin with the current central venous catheter
  - Rigor or fever after flushing line (within 4 hours)
  - Relevant positive blood culture

SECOND LINE THERAPY

- Patients who remain pyrexial after 72 hours of empirical therapy should change to second line therapy. Second line therapy is with Meropenem and with or with out Gentamicin.

  Dosing regimen: Meropenem (20mg/kg/dose three times a day) plus Gentamicin (7mg/kg/once daily)

- Patients who remain pyrexial at 5 days and who are or have been persistently neutropenic with no evidence of line related infection should have **AmBisome** added. This should be discussed with the responsible consultant.

PENICILLIN ALLERGY

- Serious allergy is one that causes an anaphylactic or urticarial reaction. 10% of patients with reactions to penicillin-based antibiotics will also have a reaction with cephalosporins.
- Patients who have had an allergic reaction classified as non-serious should receive **Ceftazidime & Gentamicin**.
- Patients who have had an allergic reaction classified as serious should receive **Ciprofloxacin & Vancomycin.** If ciprofloxacin has been given as prophylaxis, please discuss treatment with Consultant Microbiologist on call.

DURATION OF ANTIBIOTIC TREATMENT

This depends on the degree and duration of neutropenia and the organism cultured, but as a general rule:

- Patients who are blood culture negative; stop antibiotics after 48 hours of apyrexia if the patient is well.
- Patients who are culture positive: this depends on the organism and the degree and duration of neutropenia. The child should be well and apyrexial and have a minimum of 7 days treatment including 48 hours of apyrexia. Preferably repeat blood cultures should be documented to be negative.
- Gentamicin should not be given for more than 10 days.

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5.3. NON-NEUTROPENIC FEVER

First line therapy is single agent Tazocin for patients who are known to be not neutropenic or expected not to be neutropenic and considered as low risk for developing severe sepsis.

Dosaging regimen: Tazocin (90mg/kg/dose 4 times a day)

5.4. ANTIBIOTIC DOSES

For children aged 1-18 years:

TAZOCIN

- **90 mg/kg** (max 4.5g) four times a day
- Vial size 2.25g, 4.5g
- Give by IV bolus over 3-5 mins
- Dose reductions:
  - Creatinine clearance 20-50 ml/min: tazocin 90 mg/kg three times a day
  - Creatinine clearance < 20 ml/min: tazocin 90 mg/kg twice a day

GENTAMICIN

- Gentamicin dosing in patients with normal renal function:
  - **Gentamicin 7mg/kg/once daily** (max 500mg/dose)
  - Give by IV infusion in 50 – 100ml Sodium Chloride 0.9% over 60 minutes
  - **Prescribe** dose for all patients at **12noon** each day
  - Measure **level after 1st dose**

    Trough: Plasma samples at 18-24 hrs post-dose (i.e. with morning bloods)
    Expected level <1mg/L

    NB in many patients the reported level will be <0.1mg/L, which is acceptable
  - If trough level is >1mg/L, the dosing interval is normally increased by 12 hours. Please discuss further dosing with pharmacy/microbiology
  - If trough level >2mg/L, patient is unsuitable for pulsed dosing regimen, and subsequent doses should be guided by levels.
  - If there is no change in dosage regimen or renal function, repeat trough levels every 4 days only
- Gentamicin dosing in patients with renal impairment (estimated creatinine clearance ≤50 ml/min):
  - Initial dose - Gentamicin 5mg/kg
  - Trough levels as above
  - Prescribe as a single dose and consult pharmacy/microbiology for further dosage advice
- Managing **patients admitted out of hours:**
  - Patients admitted in the afternoon until 12 midnight

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- Give 7mg/kg dose on admission
- Trough samples with morning bloods
- Prescribe at 12 noon the following day

- Patients admitted between 12 midnight and 6am
  - Give 7mg/kg dose on admission
  - Arrange with microbiology for emergency levels to be done at 12 noon that day.
  - If trough level is reported at <2.5mg/L, give second dose as close as possible to midday.
  - If trough level is >2.5mg/L, consult pharmacy/microbiology for further dosage advice.

- Patients admitted between 6am and 12noon
  - Give 7mg/kg dose on admission
  - Trough levels the following day with morning bloods.
  - Prescribe dose on following and subsequent days 2 hours later, until dosing time of 12 noon is achieved.

NB: Do not forget to indicate on the microbiology request form the actual time the sample was taken – levels taken outwith the recommended times can still be interpreted, if an accurate sampling time is recorded.

CIPROFLOXACIN

- Ciprofloxacin may be used in children where the benefit is considered to outweigh any potential risk:
- Dosing regimen for prophylaxis against gram negative organisms in patients undergoing HSCT is 7.5mg/kg po/IV (see below for maximum dosing).
- Dosing regimen for treatment
  - Intravenous: 1month – 18 years
10mg/kg three times a day
(maximum dose of 400mg)
  - Occasionally give orally: 20mg/kg bd (maximum dose of 750mg)
- Available preparations 100mg, 250mg, 500mg, 750mg tablets, 250/5ml oral suspension. 100mg/50ml and 200mg/100ml IV infusion.
- Oral absorption is good but do not use with oral Mg, Ca, or Fe supplements as these affect absorption.
- Infuse undiluted IV over 30-60 minutes - flush with Sodium Chloride 0.9%.
- Creatinine clearance <20 ml/minute: reduce dose by 50%.

VANCOMYCIN

- Dosing regimen: 15mg/kg three times daily. (NB To achieve optimal plasma profile it is vital to ensure doses are administered as close to an eight hour interval as possible)
- Infuse over 1-2 hours in Sodium Chloride 0.9%.

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- Measure trough level before the 3rd dose is given.
- Target trough 10mg/L minimum

TEICOPLANIN

- 10mg/kg (max 400mg) every 12 hours for 3 doses then 10mg/kg (max 400mg) daily
- Administration: Slow IV bolus or Infusion over 30 mins diluted in Sodium Chloride
- Dose in renal impairment: CrCl 20-50ml/minute : 50% of normal dose; <20ml/minute : 30% of normal dose
- No monitoring required

AMBISOME

- Dosing regimen: dependent on clinical situation
- **3 mg/kg/day** with proven or highly suspicious fungal infection (doses of up to 10 mg/kg/day have been used for proven infections)
- 2mg/kg alternate days for anti-fungal prophylaxis in HSCT patients and 1mg/kg alternate days in other patients.
- Infuse in Glucose 5% ONLY at a concentration of 0.2-2.0 mg/ml. If dose ≥5mg/kg infuse over 2 hours otherwise 1 hour.

MEROPENEM

- Dosing regimen: 20 mg/kg three times a day (max 1g/dose).Can increase to 40 mg/kg in severe infections (max 2g/dose).
- Give as IV bolus over 5 minutes or infuse over 15-30 minutes (dilute 1g in at least 50 ml Sodium Chloride 0.9% or Glucose 5%).

5.5. OPPORTUNISTIC CHEST INFECTIONS

GENERAL

- There are a variety of opportunistic lung infections that can occur in long-term immunosuppressed children that must be considered in a child with respiratory symptoms.
- Note the respiratory rate, any signs of respiratory distress and check pulse oximetry.
- Give supplemental oxygen therapy if required and arrange blood gases.
- Ask for ITU consult if the patient's condition, respiratory rate or oxygen requirements suggest that ventilatory support may be necessary.
- Discuss these patients with the consultant on call for haematology/oncology.

MYCOPLASMA PNEUMONIAE

- This may present with a multitude of symptoms.

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- The disease tends to have a prodrome (fevers, chills, headaches) and the cough may persist for several weeks.
- The chest x-ray may show diffuse patchy consolidation and the MCV may be raised due to cold agglutinins.
- Treatment is with IV **Clarithromycin** 7.5mg/kg per dose twice a day (max 500mg/dose). Consider using **Azithromycin** if patient is able to tolerate **oral** medications at following doses:

  Dose: over 6 months 10mg/kg once daily for 3 days

Or	15-25kg	200mg once daily for 3 days
	26-35kg	300mg once daily for 3 days
	36-45kg	400mg once daily for 3 days
	>45kg	500mg once daily for 3 days

PNEUMOCYSTITS CARINII

- Signs of infection include tachypnoea, dry cough, dyspnoea on exertion and cyanosis. The chest is often clear on auscultation.
- Check pulse oximetry and blood gases as oxygen desaturation often precedes x-ray changes. CXR may show bilateral infiltrates, but can be similar to viral infection or fluid overload.
- Although pneumocystis is less common with the use of prophylactic Co-Trimoxazole, it still occurs. Exercise a high level of suspicion in children using alternatives to Co-Trimoxazole as PCP prophylaxis or in those with suspected poor compliance.
- Treatment is with **high dose intravenous Co-Trimoxozole 60mg/kg per dose twice a day.**
  - Give by IV infusion over 20-60 minutes. Dilute each 480mg ampoule in 75mls 5% Glucose.
  - In severe fluid restriction Co-Trimoxozole may be given undiluted via a central line only and over at least 60 minutes.
  - Consider the need for concomitant steroids, discuss with on call consultant.

NOTE: Adenovirus, Paraflu and RSV can be fatal in stem cell transplant patients. Any transplant patient who develops respiratory symptoms or distress should be discussed with the HSCT consultant

5.6. SUPPORTIVE CARE/MISCELLANEOUS

CENTRAL LINES

- Central lines can be a source of infections with gram-negative and gram-positive organisms in neutropenic and non-neutropenic patients.
- If a patient becomes pyrexial or deteriorates after flushing or sampling a central line **add Teicoplanin**. Consider stopping using the central line and insert a cannula for antibiotics.

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ANTIPYREXIAL TREATMENT

- Once cultures have been taken and antibiotics started it is acceptable to treat the fever with Paracetamol.
- **Do not** give **non-steroidal anti-inflammatories such as ibuprofen**. Non-steroidals are contraindicated because of their effect on platelet function.

CHEMOTHERAPY

Chemotherapy is often temporarily halted in the presence of febrile neutropenia. However, this recommendation varies by protocol and phase of treatment. The patient's protocol should be referred to and the need to stop or continue chemotherapy discussed with the responsible consultant

EXAMINATION

The child should be examined daily for signs of infection including sites such as the mouth, axillae, ears, perineum and central catheter site.

CONSTIPATION

- Must be avoided if possible. As well as causing distress, it may precipitate septicaemia through mucosal damage.
- Enemas, suppositories, rectal temperatures and rectal examinations should be avoided in neutropenic patients for the same reason. Ask about bowel function daily and consider laxatives as necessary.

MAINTENANCE CO-TRIMOXAZOLE

Continue maintenance co-trimoxazole whilst other antibiotics are being given unless the patient is receiving high dose co-trimoxazole intravenously or consultant thinks that co-trimoxazole should be temporarily discontinued to allow count recovery. Prophylaxis need not be given intravenously but can be temporarily withheld in patients who are nil by mouth.

MOUTH ULCERS

- All patients are advised on mouthcare.
- Swab for virology (herpes simplex) and bacteriology.
- Consider Aciclovir.

Aciclovir dosing:

Oral: Over 2 years: 200mg x 5/day for 5 days
Under 2 years: 100mg x 5/day for 5 days

The dose may be doubled in immunocompromised patients.

IV: 250-500mg/m^2 three times daily.

DIARRHOEA

- Send stools for viruses, parasites, cryptosporidium and Clostridium difficile toxin.

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- Metronidazole should be considered in patients with mucositis or perianal infections

6. REFERENCES

Assessment, Diagnosis and Management of Neutropenic Sepsis - Best Practice Statement (publication date: September 2011) - www.gov.scot (put "neutropenic sepsis" into the search engine)- see section 2.

7. AUDIT AND REVIEW PROCESS

This SOP will be reviewed in 6 months time with particular reference to MSN CYPC febrile neutropenia guidelines.

8. FURTHER INFORMATION/EXCEPTIONS

None.

9. APPENDICES

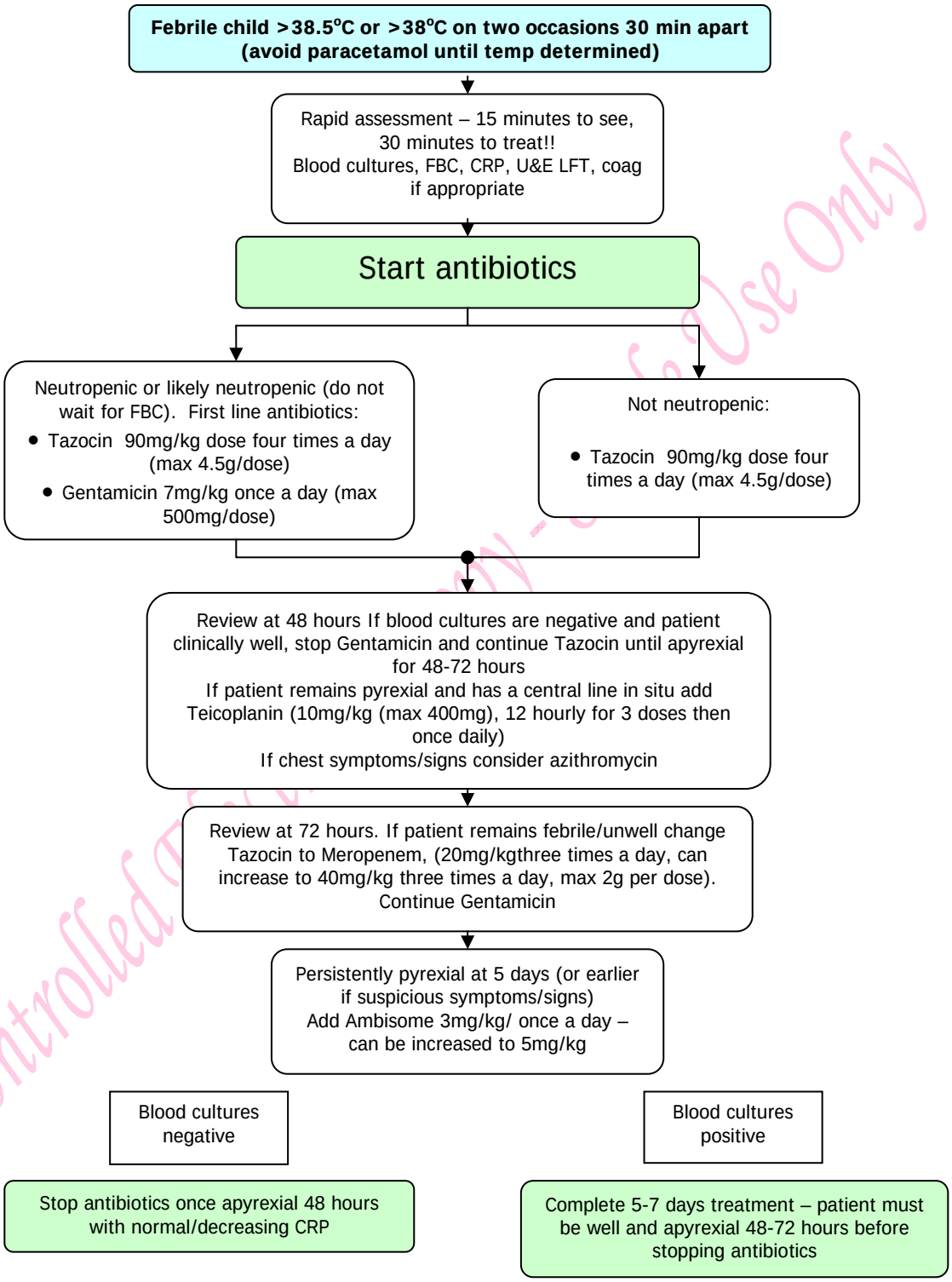
Appendix 1: Criteria for Treatment

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Haematology and Oncology Unit
Royal Hospital for Children, Glasgow

NHS Greater Glasgow and Clyde

Appendix 1: Criteria for Treatment



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Management of Neutropenia & Fever - Antibiotic Policy

1. INTRODUCTION

Neutropenia is defined as a neutrophil count of <1 x 10^9/L and patients who are neutropenic are vulnerable to overwhelming infection. The frequency and severity of infective episodes correlates with the degree and duration of neutropenia and is particularly marked in children whose neutrophil count is below 0.5 x 10^9/l.

2. RELATED DOCUMENTATION

This policy should be read in conjunction with the assessment, diagnosis and management of Neutropenic Sepsis, Best Practice Statement, publication date: September 2011 (see Point 6 – References).

3. AUTHORISED PERSONNEL/SPECIFIC STAFF COMPETENCIES

3.1 The diagnosis and management of febrile neutropenia will be directed by the Consultant/Associate Specialist or a senior member of the medical team.

3.2 The Medical/Nursing team will be responsible for admitting, assessing, investigating and administrating treatment, and monitoring response.

4. EQUIPMENT/MATERIALS

None.

5. PROCEDURE

5.1 FEBRILE NEUTROPENIA

CRITERIA FOR TREATMENT

- Any child with a single temperature of 38°C or above should receive intravenous antibiotics (in line with the national policy).
- Paracetamol should not be given until the decision to treat has been taken because it may mask a fever. Particular care should be exercised with HSCT patients who are neutropenic.
- Any child who deteriorates, looks unwell or rigors regardless of his/her temperature and neutrophil count should receive intravenous antibiotics. Fever may be suppressed by steroids, particularly Dexamethasone, and these children may become septic and deteriorate rapidly without exhibiting fever.

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- A well child who is not neutropenic with an obvious focus of infection can receive treatment appropriate for that infection e.g. otitis media. Err on the side of caution and if in doubt **admit the child and give IV antibiotics.** Be particularly careful with possible/probable line-related infections because, although lines are most often colonised with coagulase negative staphylococci, they can be colonised with gram-negative organisms, and can result in gram-negative septicaemia and septic shock.
- It is always better to over rather than under treat these patients. **These children can deteriorate rapidly.**

IN A NEUTROPENIC PATIENT, THE OCCURRENCE OF FEVER MUST BE REGARDED AS AN EMERGENCY

- **The initial nursing assessment of the patient must happen within 15 minutes of the patient's arrival. Medical assessment and administration of antibiotics must happen within 60 minutes from the patient's arrival.**
- An **'ill'** child must be assessed immediately even in the absence of a fever. **A DELAY IN ADMINISTERING THE FIRST DOSE OF ANTIBIOTICS MAY PROVE FATAL** – and antibiotic administration must not be delayed for any reason (including shift changes, ward rounds, radiological examination, problems with venous access). **Blood cultures should be taken before giving the first dose of antibiotics.**

!!!! The first dose of antibiotics can precipitate septic shock

!!!!! Be prepared to resuscitate the patient

- Patients who are unwell or hypotensive should immediately receive resuscitation fluids and IV antibiotics, even if they are not pyrexial. Remember steroids can mask an inflammatory response.
- If a patient deteriorates after using/flushing his/her central line consideration should be given to siting a peripheral cannula and stopping using the line.
- All haematology/oncology patients admitted overnight who are ill, must be seen by the most experienced middle grade doctor on for hospital cover who should discuss the patient causing concern with the consultant haematologist/oncologist on-call.

HISTORY AND EXAMINATION

- **Keep the history brief**. The following will help predict the likely degree and duration of neutropenia and identify a potential focus that might guide antibiotic therapy. Note:
  - The diagnosis
  - The date and type of the last chemotherapy given
  - Any recent blood counts
  - The duration of fever
  - The presence of a central line (NB line associated sepsis)

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- The presence of bleeding
- Any muscle, joint or abdominal pain
- The presence of mucositis
- Any local cause for fever

- **Examination: Ask yourself:**
  - Does the child require resuscitation?
  - Is the child septicaemic or shocked?
  - What is the temperature, HR, RR, BP, oxygen saturation and Capillary Refill Time (CRT)
  - Is there an obvious focus for infection?

INVESTIGATIONS

- Blood cultures (take a large volume)
- FBC and differential
- CRP
- U&Es
- LFTs and Coagulation screen: PT, APTT, Fibrinogen +/- d-dimers if unwell – every child does not require a coagulation screen
- Consider a CXR if respiratory signs or symptoms (this must not delay therapy)
- If upper respiratory symptoms are present, consider NPA

TREATMENT

- Resuscitate the child
- Give antibiotics
- Give blood products as indicated

MICROBIOLOGICAL CULTURES

Blood Cultures:

- Blood cultures should be taken from the central line, or where there is no central line, from a peripheral stab.
- The volume required is **5 - 10 mls** or a **minimum of 3-5 mls** from an infant. In the case of a double lumen long line, or two separate central lines, blood cultures should be taken **from each lumen**.
- Blood cultures should be repeated in the event of:
  - Clinical deterioration
  - Rigors
  - Persistent pyrexia after 24 and 48 hours and thereafter 48-72 hourly if the patient remains pyrexial
  - Prior to any antibiotic change
  - Recurrence of fever after period of apyrexia
- If blood cultures are initially positive, repeat cultures should be taken after 48 hrs to confirm the organism has been eradicated (in vitro sensitivities do not always correlate with in vivo sensitivity).

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- In the case of a central line infection, which is often due to bacterial growth in a biofilm, it is advisable to repeat line cultures after stopping antibiotics to check that the organism has been eradicated.

Additional investigations should be performed:

- Swab of central line exit site(s)
- Consider:
  - Viral serology or culture if symptoms are suggestive of viral infection
  - Nose swab
  - Throat swab
  - Sputum culture
  - Urine culture
  - Stool culture
  - Swabs of any lesion or potential focus
- A chest X-ray may be indicated. Remember that in pneumocystits carinii pneumonia the chest may be clear to auscultation when there is hypoxia and marked radiological change.

5.2 Antibiotic Protocol for Neutropenic Patients

First Line Therapy

- First line therapy in neutropenic patients is with Tazocin and Gentamicin in the absence of positive blood cultures which would indicate alternative antibiotics. Tazocin is a penicillin based antibiotic and penicillin allergy should be excluded. Patients known to be colonised with ESBL producing organisms should receive Meropenem instead of Tazocin (dosing schedule given under second line therapy).

Dosing regimen: Tazocin (90mg/kg/dose 4 times a day) plus Gentamicin (7mg/kg/once daily)

- Prescribe Tazocin according to pharmacy dose banding chart.
- Gentamicin requires caution in patients at risk of renal impairment. However, it is extremely unlikely that one single dose of gentamicin will do harm and a single dose should be given and levels measured before any subsequent doses.
- Please prescribe Tazocin according to pharmacy dose banding chart, which is available on ward 2a, 2b, A&E and CDU.
- Tazocin, as a single agent, is first line therapy for patients who are known not to be neutropenic or who are expected not to be neutropenic and considered at low risk for developing severe sepsis.
- Patients initially started on both Tazocin and Gentamicin can stop gentamicin if subsequently shown not to be neutropenic, if neither septic or shocked.

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- **Antibiotic cover for line-related infection:** Teicoplanin should be added to the initial therapy only if there is a proven or a very high suspicion of central line infection. Teicoplanin is preferable to vancomycin for patients receiving other nephrotoxic drugs and most haemato/oncology patients are on other nephrotoxic drugs. Factors suggesting line infection include:
  - Local Sepsis: Erythema at exit site or skin tunnel; pain over tunnel or on moving that arm/shoulder
  - Previously documented catheter related sepsis involving the current central venous line
  - Rigor or fever after flushing line (within 4 hours)
  - Blood culture positive for an organism associated with the related infection

  Vancomycin, rather than Teicoplanin should only be used in patients suspected to have a line related infection and who are scepticaemic.

SECOND LINE THERAPY

- Patients who remain pyrexial after 72 hours of empirical therapy should change to second line therapy. Second line therapy is with Meropenem and with or without Gentamicin.

  Dosing regimen: Meropenem (20mg/kg/dose three times a day) plus /minus Gentamicin (7mg/kg/once daily)

- Patients who remain pyrexial at 5 days and who are or have been persistently neutropenic with no evidence of line related infection should have **Ambisome** added. This should be discussed with the consultant responsible for the care of the patient.

PENICILLIN ALLERGY

- Serious allergy is one that causes an anaphylactic or urticarial reaction. 10% of patients with reactions to penicillin-based antibiotics will also have a reaction with cephalosporins.
- Patients who have had an allergic reaction classified as serious should receive **Ciprofloxacin & Vancomycin.**
- If ciprofloxacin has been given as prophylaxis, please discuss treatment with Consultant Microbiologist on call.

DURATION OF ANTIBIOTIC TREATMENT

This depends on the degree and duration of neutropenia and the organism cultured, but as a general rule:

- Patients who are blood culture negative; stop antibiotics after 48 hours of apyrexia if the patient is well and if the blood cultures are negative.
- Patients who are culture positive: this depends on the organism and the degree and duration of neutropenia. The child should be well and apyrexial and have a minimum of 7 days treatment including 48 hours of apyrexia. Preferably repeat blood cultures should be documented to have no growth.

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- Gentamicin should not be given for more than 7 days. If the child needs additional gram negative non-aminoglycoside antimicrobial cover, discuss with the microbiologist.

5.3. Non-Neutropenic Fever

- First line therapy for patients who are known not to be neutropenic or expected not to be neutropenic, and considered low risk for developing severe sepsis, should be single agent at Tazocin.
- Patients started on both Tazocin and Gentamicin should stop gentamicin if subsequently found not to be neutropenic, if neither septic nor shocked.

5.4. Antibiotic Doses

For children aged 1-18 years:

Tazocin

- 90 mg/kg (max 4.5g) four times a day
- Vial size 2.25g, 4.5g
- Give by IV bolus over 3-5 mins
- Renal Impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

Gentamicin

- Gentamicin dosing in patients with normal renal function:
  - Gentamicin 7mg/kg/once daily (max 500mg/dose)
  - Give by IV infusion in 50 – 100ml Sodium Chloride 0.9% over 60 minutes
  - Prescribe dose for all patients at 12noon each day
  - Measure level after 1st dose

    Trough: Plasma samples at 18-24 hrs post-dose (i.e. with morning bloods)
    Expected level <1mg/L

    NB in many patients the reported level will be <0.1mg/L, which is acceptable
  - If trough level is >1mg/L, the dosing interval is normally increased by 12 hours. Please discuss further dosing with pharmacy/microbiology
  - If trough level >2mg/L, patient is unsuitable for pulsed dosing regimen, and subsequent doses should be guided by levels
  - If there is no change in dosage regimen or renal function, repeat trough levels every 4 days only
- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 70ml/min or less

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- Initial dose - Gentamicin 5mg/kg
- Trough levels as above
- Prescribe as a single dose and consult pharmacy/microbiology for further dosage advice

- Managing patients admitted out of hours:
  - Patients admitted in the afternoon until 12 midnight:
    - Give 7mg/kg dose on admission
    - Trough samples with morning bloods
    - Prescribe at 12 noon the following day
  - Patients admitted between 12 midnight and 6am:
    - Give 7mg/kg dose on admission
    - Arrange with microbiology for emergency levels to be done at 12 noon that day
    - If trough level is reported at <2.5mg/L, give second dose as close as possible to midday
    - If trough level is >2.5mg/L, consult pharmacy/microbiology for further dosage advice
  - Patients admitted between 6am and 12noon:
    - Give 7mg/kg dose on admission
    - Trough levels the following day with morning bloods
    - Prescribe dose on following and subsequent days 2 hours later, until dosing time of 12 noon is achieved

NB: Do not forget to indicate on the microbiology request form the actual time the sample was taken – levels taken outwith the recommended times can still be interpreted, if an accurate sampling time is recorded.

CIPROFLOXACIN

- Ciprofloxacin may be used in children where the benefit is considered to outweigh any potential risk.
- **NB: Committee on Safety of Medicines (CSM) warning: Quinolone antibiotics may lower seizure threshold & may induce convulsions in patients with or without previous history.**
- Tendon damage is a rare side effect of quinolone antibiotics: if tendinitis is suspected, discontinue immediately.
- Dosing regimen for prophylaxis against gram negative organisms in patients undergoing HSCT is 10mg/kg bd (max 750mg/dose) (see below for maximum dosing). Children with Downs syndrome and ALL, and infants with ALL, also receive ciprofloxacin prophylaxis.
- Dosing regimen for treatment:
  - Intravenous: 1month – 18 years
10mg/kg three times a day
(maximum dose of 400mg)
  - Oral: 20mg/kg bd (max 750mg/dose)

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- Available preparations:
  - Tablets: 100mg, 250mg, 500mg, 750mg tablets;
  - Oral Suspension: 250mg/5ml
  - Premixed solution for IV infusion: 2mg/ml (50ml & 100ml bags available)
- Oral absorption is good but do not use with oral Mg, Ca, or Fe supplements as these affect absorption.
- Infuse undiluted IV over 30-60 minutes - flush with Sodium Chloride 0.9%.
- Renal Impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

VANCOMYCIN

- Dosing regimen: 15mg/kg three times daily. **(NB: To achieve optimal plasma profile it is vital to ensure doses are administered as close to an eight hour interval as possible).**
- Infuse over 1-2 hours in Sodium Chloride 0.9%.
- Measure trough level before the 3rd dose is given.
- Target trough: 15-20mg/L.
- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 50ml/min or less

TEICOPLANIN

- 10mg/kg (max 400mg) every 12 hours for 3 doses then 10mg/kg (max 400mg) daily.
- Administration: Slow IV bolus or infusion over 30 mins diluted in Sodium Chloride.
- Renal impairment:
  - Dose adjustments required for GFR 80ml/min or less. Refer to Renal Drug Database
  - No monitoring required

AMBISOME

- Dosing regimen: dependent on clinical situation.
- 3 mg/kg/day with proven or highly suspicious fungal infection (doses of up to 5 mg/kg/day have been used for proven infections).
- 2mg/kg (M/W/F) anti-fungal prophylaxis in stem cell transplant patients and 1mg/kg (M/W/F) in other high-risk patients.
- Infuse in Glucose 5% ONLY at a concentration of 0.2-2.0 mg/ml. If dose ≥5mg/kg infuse over 2 hours otherwise 1 hour.

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- Renal impairment:
  - No dose adjustments regardless of degree of renal impairment. Due to the size of AmBisome liposomes, there is no renal elimination

MEROPENEM

- Dosing regimen: 20 mg/kg three times a day (max 1g/dose).Can increase to 40 mg/kg in severe infections (max 2g/dose).
- Give as IV bolus over 5 minutes or infuse over 15-30 minutes (dilute 1g in at least 50 ml Sodium Chloride 0.9% or Glucose 5%).
- Renal impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

5.5. OPPORTUNISTIC CHEST INFECTIONS

GENERAL

- There are a variety of opportunistic lung infections that can occur in long-term immunosuppressed children that must be considered in a child with respiratory symptoms.
- Note the respiratory rate, any signs of respiratory distress and check pulse oximetry.
- Give supplemental oxygen therapy if required and arrange blood gases.
- Ask for ITU consult if the patient's condition, respiratory rate or oxygen requirements suggest that artificial ventilation may be necessary.
- Discuss these patients with the consultant on call for haematology/oncology.

MYCOPLASMA PNEUMONIAE

- This may present with a multitude of symptoms.
- The disease tends to have a prodrome (fevers, chills, headaches) and the cough may persist for several weeks.
- The chest x-ray may show diffuse patchy consolidation and the MCV may be raised due to cold agglutinins.
- Treatment is with IV **Clarithromycin** 7.5mg/kg per dose twice a day (max 500mg/dose). Consider using **Azithromycin** if patient is able to tolerate **oral** medications at following doses:

Dose: over 6 months 10mg/kg once daily (max 500mg) for 3 days

Or	15-25kg	200mg once daily for 3 days
	26-35kg	300mg once daily for 3 days
	36-45kg	400mg once daily for 3 days
	>45kg	500mg once daily for 3 days

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PNEUMOCYSTITS CARINII

- Signs of infection include tachypnoea, dry cough, dyspnoea on exertion and cyanosis. The chest is often clear on auscultation.
- Check pulse oximetry and blood gases as oxygen desaturation often precedes x-ray changes. CXR may show bilateral infiltrates, but can be similar to viral infection or fluid overload.
- Although pneumocystis is less common with the use of prophylactic Co-Trimoxazole, it still occurs. Exercise a high level of suspicion in children using alternatives to Co-Trimoxazole as PCP prophylaxis or in those with suspected poor compliance.
- Treatment is with **high dose intravenous Co-Trimoxazole 60mg/kg per dose twice a day.**
  - Give by IV infusion over 20-60 minutes. Dilute each 480mg ampoule in 75mls 5% Glucose.
  - In severe fluid restriction, Co-trimoxazole may be given undiluted via a central line only and over at least 60 minutes.
  - Consider the need for concomitant steroids, discuss with on call consultant.

  NOTE: Adenovirus, Paraflu and RSV can be fatal in stem cell transplant patients. Any transplant patient who develops respiratory symptoms or distress should be discussed with the HSCT consultant.

- Renal impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

5.6. SUPPORTIVE CARE/MISCELLANEOUS

CENTRAL LINES

- Central lines can be a source of infections with gram-negative and gram-positive organisms in neutropenic and non-neutropenic patients.
- If a patient becomes pyrexial or deteriorates after flushing or sampling a central line **add Teicoplanin**. Consider stopping using the line and inserting a cannula for antibiotics.

ANTIPYREXIAL TREATMENT

- Once cultures have been taken and antibiotics started it is acceptable to treat the fever with Paracetamol.
- **Do not** give **non-steroidal anti-inflammatories such as ibuprofen**. Non-steroidals are contraindicated because of their effect on platelet function.

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CHEMOTHERAPY

Withhold oral chemotherapy for Acute Leukaemia patients. Refer to individual treatment protocol /guidelines for other haemato/oncology patients to establish if chemotherapy should be stopped temporarily in the neutropenic patient. **Note:** In certain protocols, chemotherapy is continued even in the presence of neutropenic fever. Discuss with consultant.

EXAMINATION

The child should be examined daily for signs of infection including sites such as the mouth, axillae, ears, perineum and central catheter site.

CONSTIPATION

- Must be avoided if possible. As well as causing distress, it may precipitate septicaemia through mucosal damage.
- Enemas, suppositories, rectal temperatures and rectal examinations should be avoided in neutropenic patients for the same reason. Ask about bowel function daily and consider laxatives as necessary.

CO-TRIMOXAZOLE AS PCP PROPHYLAXIS

Continue prophylaxis co-trimoxazole whilst other antibiotics are being given unless the patient is receiving high dose co-trimoxazole intravenously or consultant thinks that co-trimoxazole should be temporarily discontinued to allow count recovery. Prophylaxis need not be given intravenously but can be temporarily withheld in patients who are nil by mouth.

MOUTH ULCERS

- All patients are advised on mouthcare.
- Swab for virology (herpes simplex) and bacteriology.
- Consider Aciclovir.

Aciclovir dosing:

Herpes Simplex:	Oral:	1-23months:	100-200mg x 5/day for 5 days
		2-17 years:	200-400mg x 5/day for 5 days (Use the higher dose in immunocompromised patients)
Varicella/Herpes zoster:	Oral:	1-23 months:	200mg x4/day for 5 days
		2-5yrs:	400mg x4/day for 5 days
		6-11yrs:	800mg x4/day for 5 days
		12-17yrs:	800mg x5/day for 5 days
	IV:	3mo – 12 years:	250-500mg/m^2 three times daily.
		12-18 years:	5-10mg/kg three times daily

- **NB: IV fluids at 2500ml/m2/day MUST be prescribed during IV Aciclovir treatment**

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- Renal impairment:
  - IV - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database
  - Oral-Dose adjustments required for GFR 25
  - ml/min or less. Refer to Renal Drug Database

DIARRHOEA

- Send stools for viruses, parasites, cryptosporidium and Clostridium difficile toxin.
- Metronidazole should be considered for mucositis or perianal infections

6. REFERENCES

6.1 Assessment, Diagnosis and Management of Neutropenic Sepsis - Best Practice Statement (publication date: September 2011) - www.gov.scot (put "neutropenic sepsis" into the search engine).

6.2 BNF – access via www.medicinescomplete.com

6.3 BNF for Children – access via www.medicinescomplete.com

6.4 www.renaldrugdatabase.com

7. AUDIT AND REVIEW PROCESS

This SOP will be reviewed in 24 months time.

8. FURTHER INFORMATION/EXCEPTIONS

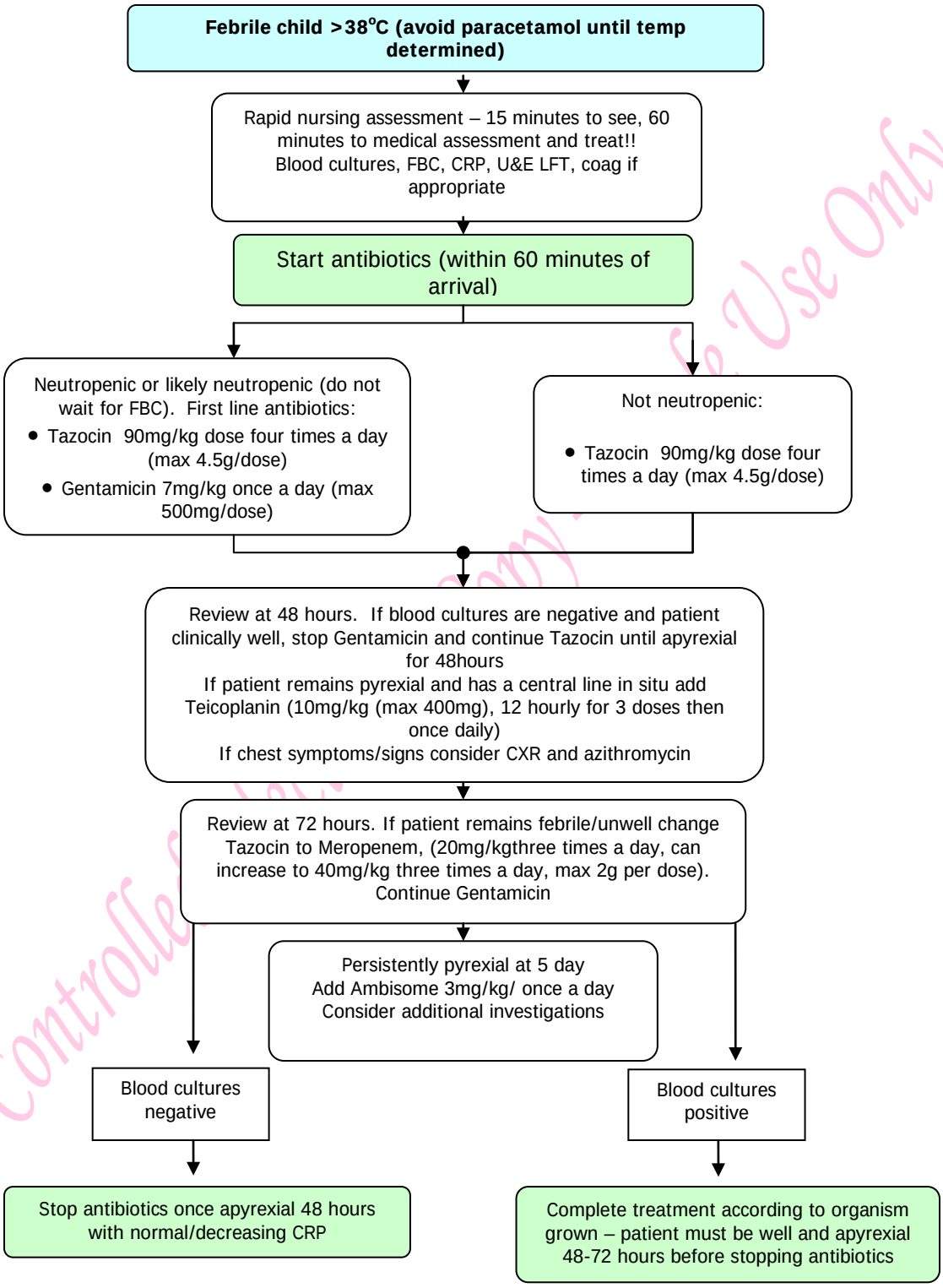
None.

9. APPENDICES

Appendix 1: Criteria for Treatment

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Appendix 1: Criteria for Treatment



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Management of Neutropenia & Fever - Antibiotic Policy

1. INTRODUCTION

Neutropenia is defined as a neutrophil count of <1 x 10^9/L and patients who are neutropenic are vulnerable to overwhelming infection. The frequency and severity of infective episodes correlates with the degree and duration of neutropenia and is particularly marked in children whose neutrophil count is below 0.5 x 10^9/l.

2. RELATED DOCUMENTATION

This policy should be read in conjunction with the assessment, diagnosis and management of Neutropenic Sepsis, Best Practice Statement, publication date: September 2011 (see Point 6 – References).

3. AUTHORISED PERSONNEL/SPECIFIC STAFF COMPETENCIES

3.1 The diagnosis and management of febrile neutropenia will be directed by the Consultant/Associate Specialist or a senior member of the medical team.

3.2 The Medical/Nursing team will be responsible for admitting, assessing, investigating and administrating treatment, and monitoring response.

4. EQUIPMENT/MATERIALS

None.

5. PROCEDURE

5.1 FEBRILE NEUTROPENIA

CRITERIA FOR TREATMENT

- Any child with a single temperature of 38°C or above should receive intravenous antibiotics (in line with the national policy).
- Paracetamol should not be given until the decision to treat has been taken because it may mask a fever. Particular care should be exercised with HSCT patients who are neutropenic.
- Any child who deteriorates, looks unwell or rigors regardless of his/her temperature and neutrophil count should receive intravenous antibiotics. Fever may be suppressed by steroids, particularly Dexamethasone, and these children may become septic and deteriorate rapidly without exhibiting fever.

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- A well child who is not neutropenic with an obvious focus of infection can receive treatment appropriate for that infection e.g. otitis media. Err on the side of caution and if in doubt **admit the child and give IV antibiotics.** Be particularly careful with possible/probable line-related infections because, although lines are most often colonised with coagulase negative staphylococci, they can be colonised with gram-negative organisms, and can result in gram-negative septicaemia and septic shock.
- It is always better to over rather than under treat these patients. **These children can deteriorate rapidly.**

IN A NEUTROPENIC PATIENT, THE OCCURRENCE OF FEVER MUST BE REGARDED AS AN EMERGENCY

- **The initial nursing assessment of the patient must happen within 15 minutes of the patient's arrival. Medical assessment and administration of antibiotics must happen within 60 minutes from the patient's arrival.**
- An **'ill'** child must be assessed immediately even in the absence of a fever. **A DELAY IN ADMINISTERING THE FIRST DOSE OF ANTIBIOTICS MAY PROVE FATAL** – and antibiotic administration must not be delayed for any reason (including shift changes, ward rounds, radiological examination, problems with venous access). **Blood cultures should be taken before giving the first dose of antibiotics.**

!!!! The first dose of antibiotics can precipitate septic shock

!!!!! Be prepared to resuscitate the patient

- Patients who are unwell or hypotensive should immediately receive resuscitation fluids and IV antibiotics, even if they are not pyrexial. Remember steroids can mask an inflammatory response.
- If a patient deteriorates after using/flushing his/her central line consideration should be given to siting a peripheral cannula and stopping using the line.
- All haematology/oncology patients admitted overnight who are ill, must be seen by the most experienced middle grade doctor on for hospital cover who should discuss the patient causing concern with the consultant haematologist/oncologist on-call.

HISTORY AND EXAMINATION

- **Keep the history brief**. The following will help predict the likely degree and duration of neutropenia and identify a potential focus that might guide antibiotic therapy. Note:
  - The diagnosis
  - The date and type of the last chemotherapy given
  - Any recent blood counts
  - The duration of fever
  - The presence of a central line (NB line associated sepsis)

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  - The presence of bleeding
  - Any muscle, joint or abdominal pain
  - The presence of mucositis
  - Any local cause for fever
- **Examination: Ask yourself:**
  - Does the child require resuscitation?
  - Is the child septicaemic or shocked?
  - What is the temperature, HR, RR, BP, oxygen saturation and Capillary Refill Time (CRT)
  - Is there an obvious focus for infection?

INVESTIGATIONS

- Blood cultures (take a large volume)
- FBC and differential
- CRP
- U&Es
- LFTs and Coagulation screen: PT, APTT, Fibrinogen +/- d-dimers if unwell – every child does not require a coagulation screen
- Consider a CXR if respiratory signs or symptoms (this must not delay therapy)
- If upper respiratory symptoms are present, consider NPA

TREATMENT

- Resuscitate the child
- Give antibiotics
- Give blood products as indicated

MICROBIOLOGICAL CULTURES

Blood Cultures:

- Blood cultures should be taken from the central line, or where there is no central line, from a peripheral stab.
- The volume required is **5 - 10 mls** or a **minimum of 3-5 mls** from an infant. In the case of a double lumen long line, or two separate central lines, blood cultures should be taken **from each lumen**.
- Blood cultures should be repeated in the event of:
  - Clinical deterioration
  - Rigors
  - Persistent pyrexia after 24 and 48 hours and thereafter 48-72 hourly if the patient remains pyrexial
  - Prior to any antibiotic change
  - Recurrence of fever after period of apyrexia
- If blood cultures are initially positive, repeat cultures should be taken after 48 hrs to confirm the organism has been eradicated (in vitro sensitivities do not always correlate with in vivo sensitivity).

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- In the case of a central line infection, which is often due to bacterial growth in a biofilm, it is advisable to repeat line cultures after stopping antibiotics to check that the organism has been eradicated.

Additional investigations should be performed:

- Swab of central line exit site(s)
- Consider:
  - Viral serology or culture / PCR if symptoms are suggestive of viral infection
  - Nose swab
  - Throat swab
  - Sputum culture
  - Urine culture
  - Stool culture
  - Swabs of any lesion or potential focus
- A chest X-ray may be indicated. Remember that in pneumocystits carinii pneumonia the chest may be clear to auscultation when there is hypoxia and marked radiological change.

5.2 Antibiotic Protocol for Neutropenic Patients

First Line Therapy

- First line therapy in neutropenic patients is with Tazocin and Gentamicin in the absence of positive blood cultures which would indicate alternative antibiotics. Tazocin is a penicillin based antibiotic and penicillin allergy should be excluded. Patients known to be colonised with ESBL producing organisms should receive Meropenem instead of Tazocin (dosing schedule given under second line therapy).

Dosing regimen: Tazocin (90mg/kg/dose 4 times a day) plus Gentamicin (7mg/kg/once daily)

- Prescribe Tazocin according to pharmacy dose banding chart.
- Gentamicin requires caution in patients at risk of renal impairment. However, it is extremely unlikely that one single dose of gentamicin will do harm and a single dose should be given and levels measured before any subsequent doses.
- Please prescribe Tazocin according to pharmacy dose banding chart, which is available on ward 2a, 2b, A&E and CDU.
- Tazocin, as a single agent, is first line therapy for patients who are known not to be neutropenic or who are expected not to be neutropenic and considered at low risk for developing severe sepsis.
- Patients initially started on both Tazocin and Gentamicin can stop gentamicin if subsequently shown not to be neutropenic, if neither septic or shocked.

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- **Antibiotic cover for line-related infection:** Teicoplanin should be added to the initial therapy only if there is a proven or a very high suspicion of central line infection. Teicoplanin is preferable to vancomycin for patients receiving other nephrotoxic drugs and most haemato/oncology patients are on other nephrotoxic drugs. Factors suggesting line infection include:
  - Local Sepsis: Erythema at exit site or skin tunnel; pain over tunnel or on moving that arm/shoulder
  - Previously documented catheter related sepsis involving the current central venous line
  - Rigor or fever after flushing line (within 4 hours)
  - Blood culture positive for an organism associated with the related infection

  Vancomycin, rather than Teicoplanin should only be used in patients suspected to have a line related infection and who are scepticaemic.

SECOND LINE THERAPY

- Patients who remain pyrexial after 72 hours of empirical therapy should change to second line therapy. Second line therapy is with Meropenem and with or without Gentamicin.

  Dosing regimen: Meropenem (20mg/kg/dose three times a day) plus /minus Gentamicin (7mg/kg/once daily)

- Patients who remain pyrexial at 5 days and who are or have been persistently neutropenic with no evidence of line related infection should have **Ambisome** added. This should be discussed with the consultant responsible for the care of the patient.

PENICILLIN ALLERGY

- Serious allergy is one that causes an anaphylactic or urticarial reaction. 10% of patients with reactions to penicillin-based antibiotics will also have a reaction with cephalosporins.
- Patients who have had an allergic reaction classified as serious should receive **Ciprofloxacin & Vancomycin.**
- If ciprofloxacin has been given as prophylaxis, please discuss treatment with Consultant Microbiologist on call.

DURATION OF ANTIBIOTIC TREATMENT

This depends on the degree and duration of neutropenia and the organism cultured, but as a general rule:

- Patients who are blood culture negative; stop antibiotics after 48 hours of apyrexia if the patient is well and if the blood cultures are negative.
- Patients who are culture positive: this depends on the organism and the degree and duration of neutropenia. The child should be well and apyrexial and have a minimum of 7 days treatment including 48 hours of apyrexia. Preferably repeat blood cultures should be documented to have no growth. Discuss the duration of antibiotics with the microbiology consultant.

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- Gentamicin should not be given for more than 7 days. If the child needs additional gram negative non-aminoglycoside antimicrobial cover, discuss with the microbiologist.

5.3. Non-Neutropenic Fever

- First line therapy for patients who are known not to be neutropenic or expected not to be neutropenic, and considered low risk for developing severe sepsis, should be single agent at Tazocin.
- Patients started on both Tazocin and Gentamicin should stop gentamicin if subsequently found not to be neutropenic, if neither septic nor shocked.

5.4. Antibiotic Doses

For children aged 1-18 years:

Tazocin

- 90 mg/kg (max 4.5g) four times a day
- Vial size 2.25g, 4.5g
- Give by IV bolus over 3-5 mins
- Renal Impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

Gentamicin

- Gentamicin dosing in patients with normal renal function:
  - Gentamicin 7mg/kg/once daily (max 500mg/dose)
  - Give by IV infusion in 50 – 100ml Sodium Chloride 0.9% over 60 minutes
  - Prescribe dose for all patients at 12noon each day
  - Measure level after 1st dose

    Trough: Plasma samples at 18-24 hrs post-dose (i.e. with morning bloods)
    Expected level <1mg/L

    NB in many patients the reported level will be <0.1mg/L, which is acceptable
  - If trough level is >1mg/L, the dosing interval is normally increased by 12 hours. Please discuss further dosing with pharmacy/microbiology
  - If trough level >2mg/L, patient is unsuitable for pulsed dosing regimen, and subsequent doses should be guided by levels
  - If there is no change in dosage regimen or renal function, repeat trough levels every 4 days only
- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 70ml/min or less

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- Initial dose - Gentamicin 5mg/kg
- Trough levels as above
- Prescribe as a single dose and consult pharmacy/microbiology for further dosage advice

- Managing patients admitted out of hours:
  - Patients admitted in the afternoon until 12 midnight:
    - Give 7mg/kg dose on admission
    - Trough samples with morning bloods
    - Prescribe at 12 noon the following day
  - Patients admitted between 12 midnight and 6am:
    - Give 7mg/kg dose on admission
    - Arrange with microbiology for emergency levels to be done at 12 noon that day
    - If trough level is reported at <2.5mg/L, give second dose as close as possible to midday
    - If trough level is >2.5mg/L, consult pharmacy/microbiology for further dosage advice
  - Patients admitted between 6am and 12noon:
    - Give 7mg/kg dose on admission
    - Trough levels the following day with morning bloods
    - Prescribe dose on following and subsequent days 2 hours later, until dosing time of 12 noon is achieved

NB: Do not forget to indicate on the microbiology request form the actual time the sample was taken – levels taken outwith the recommended times can still be interpreted, if an accurate sampling time is recorded.

CIPROFLOXACIN

- Ciprofloxacin may be used in children where the benefit is considered to outweigh any potential risk.
- **NB: Committee on Safety of Medicines (CSM) warning: Quinolone antibiotics may lower seizure threshold & may induce convulsions in patients with or without previous history.**
- Tendon damage is a rare side effect of quinolone antibiotics: if tendinitis is suspected, discontinue immediately.
- Dosing regimen for prophylaxis against gram negative organisms in patients undergoing HSCT is 10mg/kg bd (max 750mg/dose) (see below for maximum dosing). Children with Downs syndrome and ALL, and infants with ALL, also receive ciprofloxacin prophylaxis.
- Dosing regimen for treatment:
  - Intravenous: 1month – 18 years
10mg/kg three times a day
(maximum dose of 400mg)
  - Oral: 20mg/kg bd (max 750mg/dose)

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- Available preparations:
  - Tablets: 100mg, 250mg, 500mg, 750mg tablets;
  - Oral Suspension: 250mg/5ml
  - Premixed solution for IV infusion: 2mg/ml (50ml & 100ml bags available)
- Oral absorption is good but do not use with oral Mg, Ca, or Fe supplements as these affect absorption.
- Infuse undiluted IV over 30-60 minutes - flush with Sodium Chloride 0.9%.
- Renal Impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

VANCOMYCIN

- Dosing regimen: 15mg/kg three times daily. **(NB: To achieve optimal plasma profile it is vital to ensure doses are administered as close to an eight hour interval as possible).**
- Infuse over 1-2 hours in Sodium Chloride 0.9%.
- Measure trough level before the 3rd dose is given.
- Target trough: 15-20mg/L.
- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 50ml/min or less

TEICOPLANIN

- 10mg/kg (max 400mg) every 12 hours for 3 doses then 10mg/kg (max 400mg) daily.
- Administration: Slow IV bolus or infusion over 30 mins diluted in Sodium Chloride.
- Renal impairment:
  - Dose adjustments required for GFR 80ml/min or less. Refer to Renal Drug Database
  - No monitoring required

AMBISOME

- Dosing regimen: dependent on clinical situation.
- 3 mg/kg/day with proven or highly suspicious fungal infection (doses of up to 5 mg/kg/day have been used for proven infections).
- 2mg/kg (M/W/F) anti-fungal prophylaxis in stem cell transplant patients and 1mg/kg (M/W/F) in other high-risk patients.
- Infuse in Glucose 5% ONLY at a concentration of 0.2-2.0 mg/ml. If dose ≥5mg/kg infuse over 2 hours otherwise 1 hour.

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- Renal impairment:
  - No dose adjustments regardless of degree of renal impairment. Due to the size of AmBisome liposomes, there is no renal elimination

MEROPENEM

- Dosing regimen: 20 mg/kg three times a day (max 1g/dose).Can increase to 40 mg/kg in severe infections (max 2g/dose).
- Give as IV bolus over 5 minutes or infuse over 15-30 minutes (dilute 1g in at least 50 ml Sodium Chloride 0.9% or Glucose 5%).
- Renal impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

5.5. OPPORTUNISTIC CHEST INFECTIONS

GENERAL

- There are a variety of opportunistic lung infections that can occur in long-term immunosuppressed children that must be considered in a child with respiratory symptoms.
- Note the respiratory rate, any signs of respiratory distress and check pulse oximetry.
- Give supplemental oxygen therapy if required and arrange blood gases.
- Ask for ITU consult if the patient's condition, respiratory rate or oxygen requirements suggest that artificial ventilation may be necessary.
- Discuss these patients with the consultant on call for haematology/oncology.

MYCOPLASMA PNEUMONIAE

- This may present with a multitude of symptoms.
- The disease tends to have a prodrome (fevers, chills, headaches) and the cough may persist for several weeks.
- The chest x-ray may show diffuse patchy consolidation and the MCV may be raised due to cold agglutinins.
- Treatment is with IV **Clarithromycin** 7.5mg/kg per dose twice a day (max 500mg/dose). Consider using **Azithromycin** if patient is able to tolerate **oral** medications at following doses:

  Dose: over 6 months 10mg/kg once daily (max 500mg) for 3 days

Or	15-25kg	200mg once daily for 3 days
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PNEUMOCYSTITS CARINII

- Signs of infection include tachypnoea, dry cough, dyspnoea on exertion and cyanosis. The chest is often clear on auscultation.
- Check pulse oximetry and blood gases as oxygen desaturation often precedes x-ray changes. CXR may show bilateral infiltrates, but can be similar to viral infection or fluid overload.
- Although pneumocystis is less common with the use of prophylactic Co-Trimoxazole, it still occurs. Exercise a high level of suspicion in children using alternatives to Co-Trimoxazole as PCP prophylaxis or in those with suspected poor compliance.
- Treatment is with **high dose intravenous Co-Trimoxazole 60mg/kg per dose twice a day.**
  - Give by IV infusion over 20-60 minutes. Dilute each 480mg ampoule in 75mls 5% Glucose.
  - In severe fluid restriction, Co-trimoxazole may be given undiluted via a central line only and over at least 60 minutes.
  - Consider the need for concomitant steroids, discuss with on call consultant.

  NOTE: Adenovirus, Paraflu and RSV can be fatal in stem cell transplant patients. Any transplant patient who develops respiratory symptoms or distress should be discussed with the HSCT consultant.

- Renal impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

5.6. SUPPORTIVE CARE/MISCELLANEOUS

CENTRAL LINES

- Central lines can be a source of infections with gram-negative and gram-positive organisms in neutropenic and non-neutropenic patients.
- If a patient becomes pyrexial or deteriorates after flushing or sampling a central line **add Teicoplanin**. Consider stopping using the line and inserting a cannula for antibiotics.

ANTIPYREXIAL TREATMENT

- Once cultures have been taken and antibiotics started it is acceptable to treat the fever with Paracetamol.
- **Do not** give **non-steroidal anti-inflammatories such as ibuprofen**. Non-steroidals are contraindicated because of their effect on platelet function.

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CHEMOTHERAPY

Withhold oral chemotherapy for Acute Leukaemia patients. Refer to individual treatment protocol /guidelines for other haemato/oncology patients to establish if chemotherapy should be stopped temporarily in the neutropenic patient. **Note:** In certain protocols, chemotherapy is continued even in the presence of neutropenic fever. Discuss with consultant.

EXAMINATION

The child should be examined daily for signs of infection including sites such as the mouth, axillae, ears, perineum and central catheter site.

CONSTIPATION

- Must be avoided if possible. As well as causing distress, it may precipitate septicaemia through mucosal damage.
- Enemas, suppositories, rectal temperatures and rectal examinations should be avoided in neutropenic patients for the same reason. Ask about bowel function daily and consider laxatives as necessary.

CO-TRIMOXAZOLE AS PCP PROPHYLAXIS

Continue prophylaxis co-trimoxazole whilst other antibiotics are being given unless the patient is receiving high dose co-trimoxazole intravenously or consultant thinks that co-trimoxazole should be temporarily discontinued to allow count recovery. Prophylaxis need not be given intravenously but can be temporarily withheld in patients who are nil by mouth.

MOUTH ULCERS

- All patients are advised on mouthcare.
- Swab for virology (herpes simplex) and bacteriology.
- Consider Aciclovir.

Aciclovir dosing:

Herpes Simplex:	Oral:	1-23months:	100-200mg x 5/day for 5 days
		2-17 years:	200-400mg x 5/day for 5 days (Use the higher dose in immunocompromised patients)
Varicella/Herpes zoster:	Oral:	1-23 months:	200mg x4/day for 5 days
		2-5yrs:	400mg x4/day for 5 days
		6-11yrs:	800mg x4/day for 5 days
		12-17yrs:	800mg x5/day for 5 days
	IV:	3mo – 12 years:	250-500mg/m^2 three times daily.
		12-18 years:	5-10mg/kg three times daily

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- **NB: Adequate hydration (normal maintenance, as per age and weight of the child) MUST be maintained during IV Aciclovir treatment. Monitor renal functions and fluid balance daily**

- Renal impairment:
  - IV - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database
  - Oral-Dose adjustments required for GFR 25
  - ml/min or less. Refer to Renal Drug Database

DIARRHOEA

- Send stools for viruses, parasites, cryptosporidium and Clostridium difficile toxin.
- Metronidazole should be considered for mucositis or perianal infections

6. REFERENCES

6.1 Assessment, Diagnosis and Management of Neutropenic Sepsis - Best Practice Statement (publication date: September 2011) - www.gov.scot (put "neutropenic sepsis" into the search engine).

6.2 BNF – access via www.medicinescomplete.com

6.3 BNF for Children – access via www.medicinescomplete.com

6.4 www.renaldrugdatabase.com

7. AUDIT AND REVIEW PROCESS

This SOP will be reviewed in 24 months time.

8. FURTHER INFORMATION/EXCEPTIONS

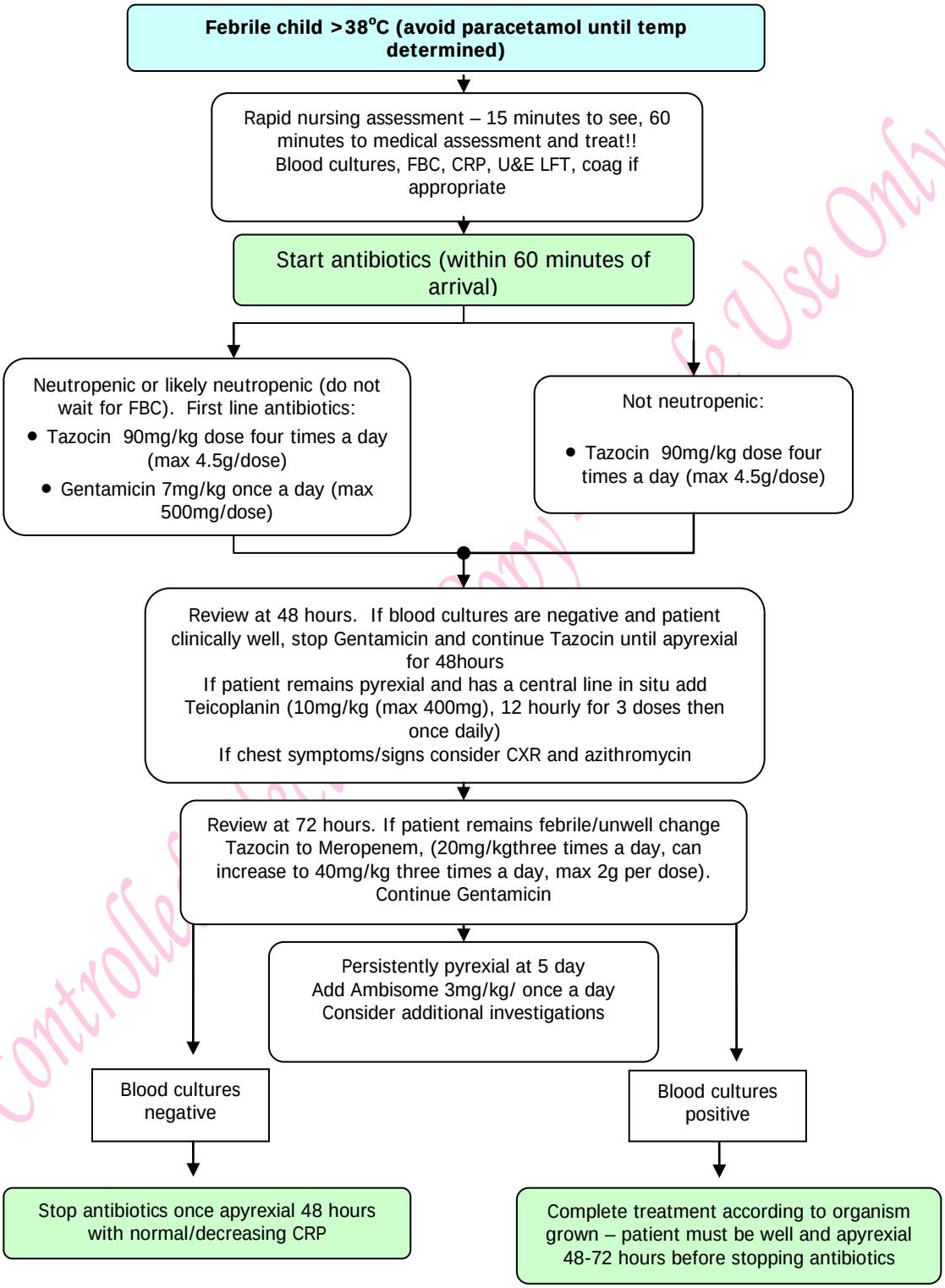
None.

9. APPENDICES

Appendix 1: Criteria for Treatment

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Appendix 1: Criteria for Treatment



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Haematology and Oncology Unit
Royal Hospital for Children, Glasgow

Management of Neutropenia & Fever - Antibiotic Policy

1. INTRODUCTION

Neutropenia is defined as a neutrophil count of <1 x 10^9/L and patients who are neutropenic are vulnerable to overwhelming infection. The frequency and severity of infective episodes correlates with the degree and duration of neutropenia and is particularly marked in children whose neutrophil count is below 0.5 x 10^9/l.

2. RELATED DOCUMENTATION

This policy should be read in conjunction with:

- The assessment, diagnosis and management of Neutropenic Sepsis, Best Practice Statement, publication date: September 2011 (see Point 6 – References).
- Guidelines for the management of paediatric line-related sepsis available via the Clinical Guidelines site - https://www.clinicalguidelines.scot.nhs.uk/nhsggc-paediatric-clinical-guidelines/nhsggc-guidelines/infectious-disease/guidelines-for-the-management-of-paediatric-line-related-sepsis/

3. AUTHORISED PERSONNEL / SPECIFIC STAFF COMPETENCIES

3.1 The diagnosis and management of febrile neutropenia will be directed by the Consultant/Associate Specialist or a senior member of the medical team.

3.2 The Medical/Nursing team will be responsible for admitting, assessing, investigating and administrating treatment, and monitoring response.

4. EQUIPMENT / MATERIALS

None.

5. PROCEDURE

5.1 FEBRILE NEUTROPENIA

CRITERIA FOR TREATMENT

- Any child with a single temperature of 38°C or above should receive intravenous antibiotics (in line with the national policy).
- Paracetamol should not be given until the decision to treat has been taken because it may mask a fever. Particular care should be exercised with HSCT patients who are neutropenic.

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- Any child who deteriorates, looks unwell or rigors regardless of his/her temperature and neutrophil count should receive intravenous antibiotics. Fever may be suppressed by steroids, particularly Dexamethasone, and these children may become septic and deteriorate rapidly without exhibiting fever.
- A well child who is not neutropenic with an obvious focus of infection can receive treatment appropriate for that infection e.g. otitis media. Err on the side of caution and if in doubt **admit the child and give IV antibiotics.** Be particularly careful with possible/probable line-related infections because, although lines are most often colonised with coagulase negative staphylococci, they can be colonised with gram-negative organisms, and can result in gram-negative septicaemia and septic shock.
- It is always better to over rather than under treat these patients. **These children can deteriorate rapidly.**

IN A NEUTROPENIC PATIENT, THE OCCURRENCE OF FEVER MUST BE REGARDED AS AN EMERGENCY

- **The initial nursing assessment of the patient must happen within 15 minutes of the patient's arrival. Medical assessment and administration of antibiotics must happen within 60 minutes from the patient's arrival.**
- An **'ill'** child must be assessed immediately even in the absence of a fever. **A DELAY IN ADMINISTERING THE FIRST DOSE OF ANTIBIOTICS MAY PROVE FATAL** – and antibiotic administration must not be delayed for any reason (including shift changes, ward rounds, radiological examination, problems with venous access). **Blood cultures should be taken before giving the first dose of antibiotics.**

!!!! The first dose of antibiotics can precipitate septic shock

!!!!! Be prepared to resuscitate the patient

- Patients who are unwell or hypotensive should immediately receive resuscitation fluids and IV antibiotics, even if they are not pyrexial. Remember steroids can mask an inflammatory response.
- If a patient deteriorates after using/flushing his/her central line consideration should be given to siting a peripheral cannula and stopping using the line.
- All haematology/oncology patients admitted overnight who are ill, must be seen by the most experienced middle grade doctor on for hospital cover who should discuss the patient causing concern with the consultant haematologist/oncologist on-call.

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HISTORY AND EXAMINATION

- **Keep the history brief**. The following will help predict the likely degree and duration of neutropenia and identify a potential focus that might guide antibiotic therapy. Note:
  - The diagnosis
  - The date and type of the last chemotherapy given
  - Any recent blood counts
  - The duration of fever
  - The presence of a central line (NB line associated sepsis)
  - The presence of bleeding
  - Any muscle, joint or abdominal pain
  - The presence of mucositis
  - Any local cause for fever
- **Examination: Ask yourself:**
  - Does the child require resuscitation?
  - Is the child septicaemic or shocked?
  - What is the temperature, HR, RR, BP, oxygen saturation and Capillary Refill Time (CRT)
  - Is there an obvious focus for infection?

INVESTIGATIONS

- Blood cultures (take a large volume)
- FBC and differential
- CRP
- U&Es
- LFTs and Coagulation screen: PT, APTT, Fibrinogen +/- d-dimers if unwell – every child does not require a coagulation screen
- Consider a CXR if respiratory signs or symptoms (this must not delay therapy)
- If upper respiratory symptoms are present, consider NPA

TREATMENT

- Resuscitate the child
- Give antibiotics
- Give blood products as indicated

MICROBIOLOGICAL CULTURES

Blood Cultures:

- Blood cultures should be taken from the central line, or where there is no central line, from a peripheral stab.
- The volume required is **5 - 10 mls** or a **minimum of 3-5 mls** from an infant. In the case of a double lumen long line, or two separate central lines, blood cultures should be taken **from each lumen**.

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- Blood cultures should be repeated in the event of:
  - Clinical deterioration
  - Rigors
  - Persistent pyrexia after 24 and 48 hours and thereafter 48-72 hourly if the patient remains pyrexial
  - Prior to any antibiotic change
  - Recurrence of fever after period of apyrexia
- If blood cultures are initially positive, repeat cultures should be taken after 48 hrs to confirm the organism has been eradicated (in vitro sensitivities do not always correlate with in vivo sensitivity).
- In the case of a central line infection, which is often due to bacterial growth in a biofilm, it is advisable to repeat line cultures after stopping antibiotics to check that the organism has been eradicated.

Additional investigations should be performed:

- Swab of central line exit site(s)
- Consider:
  - Viral serology or culture / PCR if symptoms are suggestive of viral infection
  - Nose swab
  - Throat swab
  - Sputum culture
  - Urine culture
  - Stool culture
  - Swabs of any lesion or potential focus
- A chest X-ray may be indicated. Remember that in pneumocystits carinii pneumonia the chest may be clear to auscultation when there is hypoxia and marked radiological change.

5.2 Antibiotic Protocol for Neutropenic Patients

Antibiotic doses in this SOP are appropriate for empirical treatment or sensitive organisms only. For any organism categorised as 'I' (Susceptible – increased exposure), seek further advice on appropriate dose selection'.

First Line Therapy

- First line therapy in neutropenic patients is with Tazocin and Gentamicin in the absence of positive blood cultures which would indicate alternative antibiotics. Tazocin is a penicillin based antibiotic and penicillin allergy should be excluded. Patients known to be colonised with ESBL producing organisms should receive Meropenem instead of Tazocin (dosing schedule given under second line therapy).

Dosing regimen: **Tazocin (90mg/kg/dose 4 times a day) plus Gentamicin (7mg/kg/once daily)**

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- Prescribe Tazocin according to pharmacy dose banding chart.
- Gentamicin requires caution in patients at risk of renal impairment. However, it is extremely unlikely that one single dose of gentamicin will do harm and a single dose should be given and levels measured before any subsequent doses.
- Please prescribe Tazocin according to pharmacy dose banding chart, which is available on ward 2a, 2b, A&E and CDU.
- Tazocin, as a single agent, is first line therapy for patients who are known not to be neutropenic or who are expected not to be neutropenic and considered at low risk for developing severe sepsis.
- Patients initially started on both Tazocin and Gentamicin can stop gentamicin if subsequently shown not to be neutropenic, if neither septic or shocked.

NB: Piperacillin increases the risk of toxicity when given with Methotrexate. For any patient imminently due IV Methotrexate or who is post Methotrexate and has not cleared to acceptable levels, prescribe Meropenem as first line empirical therapy.

- **Antibiotic cover for line-related infection:** Teicoplanin should be added to the initial therapy only if there is a proven or a very high suspicion of central line infection. Teicoplanin is preferable to vancomycin for patients receiving other nephrotoxic drugs and most haemato/oncology patients are on other nephrotoxic drugs. Factors suggesting line infection include:
  - Local Sepsis: Erythema at exit site or skin tunnel; pain over tunnel or on moving that arm/shoulder
  - Previously documented catheter related sepsis involving the current central venous line
  - Rigor or fever after flushing line (within 4 hours)
  - Blood culture positive for an organism associated with the related infection

  Vancomycin, rather than Teicoplanin should only be used in patients suspected to have a line related infection and who are scepticaemic.

SECOND LINE THERAPY

- Patients who remain pyrexial after 72 hours of empirical therapy should change to second line therapy. Second line therapy is with Meropenem and with or without Gentamicin.

  Dosing regimen: Meropenem (20mg/kg/dose three times a day) plus /minus Gentamicin (7mg/kg/once daily)

- Patients who remain pyrexial at 5 days and who are or have been persistently neutropenic with no evidence of line related infection should have **Ambisome** added. This should be discussed with the consultant responsible for the care of the patient.

PENICILLIN ALLERGY

- Serious allergy is one that causes an anaphylactic or urticarial reaction. 10% of patients with reactions to penicillin-based antibiotics will also have a reaction with cephalosporins.

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- Patients who have had an allergic reaction classified as serious should receive **Ciprofloxacin & Vancomycin.**
- If ciprofloxacin has been given as prophylaxis, please discuss treatment with Consultant Microbiologist on call.

DURATION OF ANTIBIOTIC TREATMENT

This depends on the degree and duration of neutropenia and the organism cultured, but as a general rule:

- Patients who are blood culture negative; stop antibiotics after 48 hours of apyrexia if the patient is well and if the blood cultures are negative.
- Patients who are culture positive: this depends on the organism and the degree and duration of neutropenia. The child should be well and apyrexial and have a minimum of 7 days treatment including 48 hours of apyrexia. Preferably repeat blood cultures should be documented to have no growth. Discuss the duration of antibiotics with the microbiology consultant.
- Gentamicin should not be given for more than 7 days. If the child needs additional gram negative non-aminoglycoside antimicrobial cover, discuss with the microbiologist.

5.3. NON-NEUTROPENIC FEVER

- First line therapy for patients who are known not to be neutropenic or expected not to be neutropenic, and considered low risk for developing severe sepsis, should be single agent at Tazocin.
- Patients started on both Tazocin and Gentamicin should stop gentamicin if subsequently found not to be neutropenic, if neither septic nor shocked.

5.4. ANTIBIOTIC DOSES

For children aged 1-18 years:

TAZOCIN

- 90 mg/kg (max 4.5g) four times a day
- Vial size 2.25g, 4.5g
- Give by IV bolus over 3-5 mins
- Renal Impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

GENTAMICIN

- Gentamicin dosing in patients with normal renal function:
  - Gentamicin 7mg/kg/once daily (max 500mg/dose)
  - Give by IV infusion in 50 – 100ml Sodium Chloride 0.9% over 60 minutes
  - Prescribe dose for all patients at 12noon each day

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- Measure level after 1st dose

  Trough: Plasma samples at 18-24 hrs post-dose (i.e. with morning bloods)
  Expected level <1mg/L

  NB in many patients the reported level will be <0.1mg/L, which is acceptable
- If trough level is >1mg/L, the dosing interval is normally increased by 12 hours. Please discuss further dosing with pharmacy/microbiology
- If trough level >2mg/L, patient is unsuitable for pulsed dosing regimen, and subsequent doses should be guided by levels
- If there is no change in dosage regimen or renal function, repeat trough levels every 4 days only

- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 70ml/min or less
  - Initial dose - Gentamicin 5mg/kg
  - Trough levels as above
  - Prescribe as a single dose and consult pharmacy/microbiology for further dosage advice
- Managing patients admitted out of hours:
  - Patients admitted in the afternoon until 12 midnight:
    - Give 7mg/kg dose on admission
    - Trough samples with morning bloods
    - Prescribe at 12 noon the following day
  - Patients admitted between 12 midnight and 6am:
    - Give 7mg/kg dose on admission
    - Arrange with microbiology for emergency levels to be done at 12 noon that day
    - If trough level is reported at <2.5mg/L, give second dose as close as possible to midday
    - If trough level is >2.5mg/L, consult pharmacy/microbiology for further dosage advice
  - Patients admitted between 6am and 12noon:
    - Give 7mg/kg dose on admission
    - Trough levels the following day with morning bloods
    - Prescribe dose on following and subsequent days 2 hours later, until dosing time of 12 noon is achieved

NB: Do not forget to indicate on the microbiology request form the actual time the sample was taken – levels taken outwith the recommended times can still be interpreted, if an accurate sampling time is recorded.

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CIPROFLOXACIN

- Ciprofloxacin may be used in children where the benefit is considered to outweigh any potential risk.
- **NB: Committee on Safety of Medicines (CSM) warning: Quinolone antibiotics may lower seizure threshold & may induce convulsions in patients with or without previous history.**
- Tendon damage is a rare side effect of quinolone antibiotics: if tendinitis is suspected, discontinue immediately.
- Dosing regimen for prophylaxis against gram negative organisms in patients undergoing HSCT is 10mg/kg bd (max 750mg/dose) (see below for maximum dosing). Children with Downs syndrome and ALL, and infants with ALL, also receive ciprofloxacin prophylaxis.
- Dosing regimen for treatment:
  - Intravenous: 1month – 18 years 10mg/kg three times a day (maximum dose of 400mg)
  - Oral: 20mg/kg bd (max 750mg/dose)
- Available preparations:
  - Tablets: 100mg, 250mg, 500mg, 750mg tablets;
  - Oral Suspension: 250mg/5ml
  - Premixed solution for IV infusion: 2mg/ml (50ml & 100ml bags available)
- Oral absorption is good but do not use with oral Mg, Ca, or Fe supplements as these affect absorption.
- Infuse undiluted IV over 30-60 minutes - flush with Sodium Chloride 0.9%.
- Renal Impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

VANCOMYCIN

- Dosing regimen: 15mg/kg three times daily. **(NB: To achieve optimal plasma profile it is vital to ensure doses are administered as close to an eight hour interval as possible).**
- Infuse over 1-2 hours in Sodium Chloride 0.9%.
- Measure trough level before the 3rd dose is given.
- Target trough: 15-20mg/L.
- Renal Impairment:
  - Use with caution. Dose reduction required for GFR 50ml/min or less

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TEICOPLANIN

- 10mg/kg (max 400mg) every 12 hours for 3 doses then 10mg/kg (max 400mg) daily.
- Administration: Slow IV bolus or infusion over 30 mins diluted in Sodium Chloride.
- Renal impairment:
  - Dose adjustments required for GFR 80ml/min or less. Refer to Renal Drug Database
  - No monitoring required

AMBISOME

- Dosing regimen: dependent on clinical situation.
- 3 mg/kg/day with proven or highly suspicious fungal infection (doses of up to 5 mg/kg/day have been used for proven infections).
- 2mg/kg (M/W/F) anti-fungal prophylaxis in stem cell transplant patients and 1mg/kg (M/W/F) in other high-risk patients.
- Infuse in Glucose 5% ONLY at a concentration of 0.2-2.0 mg/ml. If dose ≥5mg/kg infuse over 2 hours otherwise 1 hour.
- Renal impairment:
  - No dose adjustments regardless of degree of renal impairment. Due to the size of AmBisome liposomes, there is no renal elimination

MEROPENEM

- Dosing regimen: 20 mg/kg three times a day (max 1g/dose).Can increase to 40 mg/kg in severe infections (max 2g/dose).
- Give as IV bolus over 5 minutes or infuse over 15-30 minutes (dilute 1g in at least 50 ml Sodium Chloride 0.9% or Glucose 5%).
- Renal impairment:
  - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database

5.5. OPPORTUNISTIC CHEST INFECTIONS

GENERAL

- There are a variety of opportunistic lung infections that can occur in long-term immunosuppressed children that must be considered in a child with respiratory symptoms.
- Note the respiratory rate, any signs of respiratory distress and check pulse oximetry.
- Give supplemental oxygen therapy if required and arrange blood gases.

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- Ask for ITU consult if the patient's condition, respiratory rate or oxygen requirements suggest that artificial ventilation may be necessary.
- Discuss these patients with the consultant on call for haematology/oncology.

MYCOPLASMA PNEUMONIAE

- This may present with a multitude of symptoms.
- The disease tends to have a prodrome (fevers, chills, headaches) and the cough may persist for several weeks.
- The chest x-ray may show diffuse patchy consolidation and the MCV may be raised due to cold agglutinins.
- Treatment is with IV **Clarithromycin** 7.5mg/kg per dose twice a day (max 500mg/dose). Consider using **Azithromycin** if patient is able to tolerate **oral** medications at following doses:

  Dose: over 6 months 10mg/kg once daily (max 500mg) for 3 days

Or	15-25kg	200mg once daily for 3 days
	26-35kg	300mg once daily for 3 days
	36-45kg	400mg once daily for 3 days
	>45kg	500mg once daily for 3 days

PNEUMOCYSTITS CARINII

- Signs of infection include tachypnoea, dry cough, dyspnoea on exertion and cyanosis. The chest is often clear on auscultation.
- Check pulse oximetry and blood gases as oxygen desaturation often precedes x-ray changes. CXR may show bilateral infiltrates, but can be similar to viral infection or fluid overload.
- Although pneumocystis is less common with the use of prophylactic Co-Trimoxazole, it still occurs. Exercise a high level of suspicion in children using alternatives to Co-Trimoxazole as PCP prophylaxis or in those with suspected poor compliance.
- Treatment is with **high dose intravenous Co-Trimoxazole 60mg/kg per dose twice a day.**
  - Give by IV infusion over 20-60 minutes. Dilute each 480mg ampoule in 75mls 5% Glucose.
  - In severe fluid restriction, Co-trimoxazole may be given undiluted via a central line only and over at least 60 minutes.
  - Consider the need for concomitant steroids, discuss with on call consultant.

NOTE: Adenovirus, Paraflu and RSV can be fatal in stem cell transplant patients. Any transplant patient who develops respiratory symptoms or distress should be discussed with the HSCT consultant.

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- Renal impairment:
  - Dose adjustments required for GFR 30ml/min or less. Refer to Renal Drug Database

5.6. Supportive Care/Miscellaneous

Central Lines

- Central lines can be a source of infections with gram-negative and gram-positive organisms in neutropenic and non-neutropenic patients.
- If a patient becomes pyrexial or deteriorates after flushing or sampling a central line **add Teicoplanin**. Consider stopping using the line and inserting a cannula for antibiotics.

Antipyrexial Treatment

- Once cultures have been taken and antibiotics started it is acceptable to treat the fever with Paracetamol.
- **Do not** give **non-steroidal anti-inflammatories such as ibuprofen**. Non-steroidals are contraindicated because of their effect on platelet function.

Chemotherapy

Withhold oral chemotherapy for Acute Leukaemia patients. Refer to individual treatment protocol /guidelines for other haemato/oncology patients to establish if chemotherapy should be stopped temporarily in the neutropenic patient. **Note:** In certain protocols, chemotherapy is continued even in the presence of neutropenic fever. Discuss with consultant.

Examination

The child should be examined daily for signs of infection including sites such as the mouth, axillae, ears, perineum and central catheter site.

Constipation

- Must be avoided if possible. As well as causing distress, it may precipitate septicaemia through mucosal damage.
- Enemas, suppositories, rectal temperatures and rectal examinations should be avoided in neutropenic patients for the same reason. Ask about bowel function daily and consider laxatives as necessary.

Co-trimoxazole as PCP Prophylaxis

Continue prophylaxis co-trimoxazole whilst other antibiotics are being given unless the patient is receiving high dose co-trimoxazole intravenously or consultant thinks that co-trimoxazole should be temporarily discontinued to allow count recovery. Prophylaxis need not be given intravenously but can be temporarily withheld in patients who are nil by mouth.

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MOUTH ULCERS

- All patients are advised on mouthcare.
- Swab for virology (herpes simplex) and bacteriology.
- Consider Aciclovir.

Aciclovir dosing:

Herpes Simplex:	Oral:	1-23months: 100-200mg x 5/day for 5 days
		2-17 years: 200-400mg x 5/day for 5 days (Use the higher dose in immunocompromised patients)
Varicella/Herpes zoster:	Oral:	1-23 months: 200mg x4/day for 5 days
		2-5yrs: 400mg x4/day for 5 days
		6-11yrs: 800mg x4/day for 5 days
		12-17yrs: 800mg x5/day for 5 days
	IV:	3mo – 12 years: 250-500mg/m^2 three times daily.
		12-18 years: 5-10mg/kg three times daily

  - **NB: Adequate hydration (normal maintenance, as per age and weight of the child) MUST be maintained during IV Aciclovir treatment. Monitor renal functions and fluid balance daily**

- Renal impairment:
  - IV - Dose adjustments required for GFR 50ml/min or less. Refer to Renal Drug Database
  - Oral-Dose adjustments required for GFR 25
  - ml/min or less. Refer to Renal Drug Database

DIARRHOEA

- Send stools for viruses, parasites, cryptosporidium and Clostridium difficile toxin.
- Metronidazole should be considered for mucositis or perianal infections

6. REFERENCES

6.1 Assessment, Diagnosis and Management of Neutropenic Sepsis - Best Practice Statement (publication date: September 2011) - www.gov.scot (put "neutropenic sepsis" into the search engine).

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6.3 BNF for Children – access via www.medicinescomplete.com

6.4 www.renaldrugdatabase.com

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7. AUDIT AND REVIEW PROCESS

This SOP will be reviewed in 24 months time.

8. FURTHER INFORMATION/EXCEPTIONS

None.

9. APPENDICES

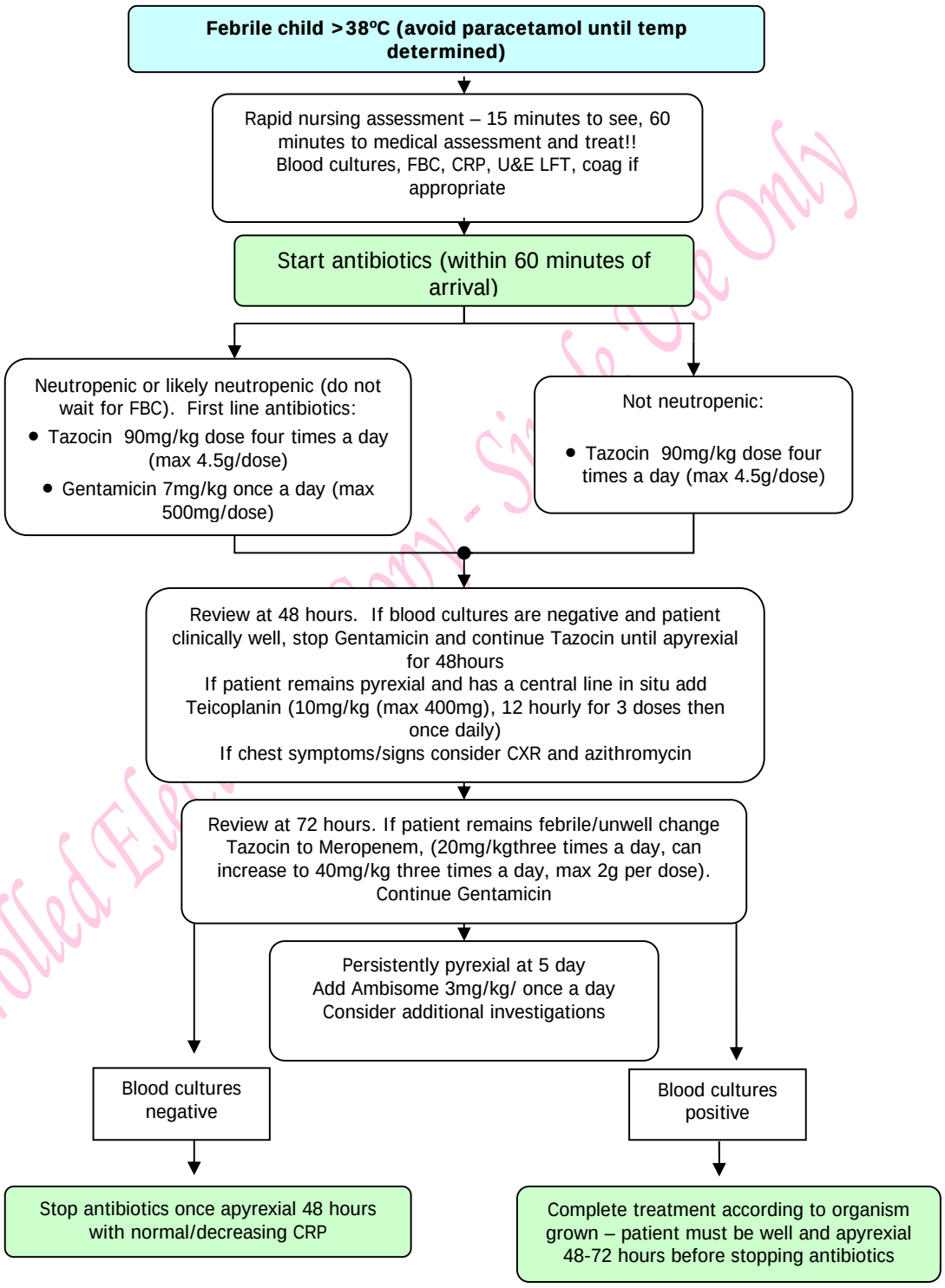
Appendix 1: Criteria for Treatment

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Haematology and Oncology Unit
Royal Hospital for Children, Glasgow

NHS Greater Glasgow and Clyde

Appendix 1: Criteria for Treatment



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Summary Report: Review of NHSGG&C paediatric haemato-oncology data (October 2019)

A Management Information publication for Scotland

Publication date: November 2019

About this release

This is a summary report of the review of NHSGG&C paediatric haemato-oncology data undertaken by Health Protection Scotland.

Introduction

In October 2019, NHS Greater Glasgow and Clyde (NHSGG&C) requested that Health Protection Scotland (HPS) provide independent expert support to review the data being used to inform their risk assessment and decision making in relation to wards 6A and 4B at Queen Elizabeth University Hospital (QEUH) and Royal Hospital for Children (RHC). The purpose of this report is to provide a summary of the work undertaken, the findings and the recommendations.

Background

Yorkhill Hospital (YH) relocated into the newly built RHC in June 2015. To allow refurbishment works to be carried out in RHC wards 2A/2B, patients were transferred to wards 6A and 4B at QEUH in September 2018. Admissions to ward 6A have been restricted since 1st August 2019 because of a suspected increase in bloodstream infections. NHSGG&C set up an Incident Management Team (IMT) to investigate the situation. As part of these investigations, HPS were asked to undertake an independent, expert, epidemiological review of NHSGG&C datasets to make an assessment as to whether numbers of positive blood samples were higher than expected.

The objectives of this review were agreed as:

1. To describe the differences in the datasets being used by GG&C to investigate cases of bacteraemia in patients cared for the in paediatric haemato-oncology wards in NHSGG&C.
2. To review the environmental Gram-negative blood cultures in the paediatric haemato-oncology population.
3. To identify whether there is a change in the type of reported environmental Gram-negative blood cultures in the paediatric haemato-oncology population.

Methods

Case identification

Blood samples were included in the investigation if the patients had been cared for in the paediatric haematology oncology (child cancer) specialty in NHSGG&C. Cancer and certain treatments increase the risk of developing infections, meaning some infections cannot be avoided

in this high-risk population. Data prior to the move from Yorkhill until September 2019 were reviewed to make an assessment as to whether numbers of positive blood samples were higher than expected since the move to 6A/4B.

Dataset selection

Four datasets were considered by the review. Three were provided by NHSGG&C and one by HPS.

- NHSGG&C Central Line Associated Bloodstream Infection (CLABSI) surveillance data
- NHSGG&C Enhanced Communication of Surveillance in Scotland (ECOSS) local extract
- NHSGG&C microbiology laboratory information management system (LIMS) surveillance data
- HPS ECOSS national extract

Grouping of positive blood samples

The positive blood samples reported were from a wide range of different bacteria and with some samples reported having more than one type of bacteria. To take account of samples with more than one type of bacteria the samples were considered in four broad groups. As these groups can overlap some types of bacteria may be included in more than one group. The four groups were as follows:

- Gram-positive bacteria
- Gram-negative bacteria
- Environmental bacteria
- Environmental bacteria including enteric bacteria (bacteria that may be found in the gut)

Patients who had multiple positive blood samples with the same group of bacteria and within the same 14-day period were counted only once (in line with national case definitions), since the positive tests were assumed to be related to the same episode.

Incidence rates and charts

Examining trends in the rates of positive blood samples is an appropriate method of identifying periods of time where rates are higher or lower than the range expected simply by random variation. However, they depend on having a stable period to establish an expected baseline level. The analysis took into account the number of patients in a unit by calculating rates in relation to total occupied bed-days (TOBDs). Statistical analyses were performed to examine any unexpected level of positive blood samples. A benchmarking comparison was undertaken with two other paediatric hospitals in Scotland.

Verification of analysis

The data were independently analysed by HPS and then peer reviewed by a Professor of Public Health Epidemiology in order to verify the results.

Results

1. Dataset differences

CLABSI data were of good quality, however, due to only including central line associated samples the data were considered to be too restrictive for complete monitoring. When comparing the other two NHSGG&C data sets, they were found to be broadly consistent with the data held nationally.

2. Types of positive blood samples

HPS (ECOSS) data were used to count positive blood samples among paediatric haemato-oncology patients under 18 years of age between July 2013 and September 2019. Based on the four broad groups described above, there were 176 samples in the Gram-negative bacteria group, 390 in the Gram-positive bacteria group, 70 in the environmental bacteria group and 132 in the group made up of environmental including enteric bacteria.

Rates of positive blood samples due to Gram-positive bacteria did not significantly increase following the move to RHC. However, there were significant increases in rates in some months, including January 2016, January 2017, April 2017 and June 2017, and levels above the trigger point (requiring further investigation) in some other months. There have been no data points above the trigger point since December 2017.

For the Gram-negative group there was an upward shift in rates between March and December 2017, identified by a run of 10 months with rates above the average (mean). This occurred after the opening of RHC but before the move to wards 6A/4B at QEUH. There have been three months above the trigger point since the move to RHC, most recently in September 2019. For the environmental group of bacteria, the trigger point was crossed for one month in June 2018.

For the environmental including enteric group of bacteria, the trigger point was crossed in two months; March 2018 and March 2019.

When comparing the overall RHC rate with the combined rate of the two largest paediatric hospitals, the rate (June 2015 to September 2019) was higher in RHC for environmental including enteric group but lower for Gram-positive group. There was no difference in Gram-negative group or environmental group.

The same comparison was also made using data following the move to ward 6A/4B QEUH, October 2018 to September 2019 and there was no difference in Gram-negative group, environmental including enteric group or environmental group however the rate was lower for the Gram positive group. The numbers were small and interpretation of this data should be made with caution.

3. Change in organism type

Analysis also showed some changes in the types of bacteria found within positive blood samples over time, however the number in each group are small. Therefore, the significance of this is not fully understood and should be part of the ongoing monitoring.

Limitations of analysis

The HPS (ECOSS) results may include interim results, contaminants or positive results which may not be true blood samples. Information about the location of samples may be incorrect and therefore some cases may have been missed. Data on Gram-negative bacteria may be incomplete for September 2019. Some of the bacteria included in this analysis are normally present in some humans, making it difficult to conclude that they were definitely the cause of an infection.

Conclusions

1. The review compared different sources of data on positive blood samples among children being treated for cancer in NHSGG&C. The results suggest that the datasets provided by NHSGG&C are broadly consistent with the data held nationally by HPS and therefore are suitable for ongoing monitoring.
2. The statistical analysis highlighted months in which rates of positive blood samples were higher than would be expected. The purpose of these analyses is to prompt further investigation and to ensure that any appropriate action is taken.
3. Analysis of different types of bacteria showed some changes, however the number in each group are small. Therefore, the significance of this is not fully understood and should be part of the ongoing monitoring.

In conclusion, the analyses presented in this report do not provide evidence of a single point of exposure causing bloodstream infections. They also suggest that measures to restrict clinical services for newly diagnosed patients should now be reconsidered. However, they also underline the need to continually monitor risk in this patient population.

Recommendations

The following recommendations should be considered:

- NHS GG&C should systematically collect clinical data on cases to describe risk in this patient population and ensure ongoing monitoring is in place.
- NHS GG&C should further characterise cases in terms of “person” and “place” to support identification of when there are more cases than normally expected.
- NHS GG&C should consider the epidemiological characterisation of cases in the context of environmental risks and incidents e.g. water testing results, ventilation testing results.
- NHS GG&C should consider the data provided in the context of the findings from the action plan
- NHS GG&C should consider current control measures around restriction on services for newly diagnosed patients as there is no evidence from the HPS review of the data to support the continued restriction of services.
- HPS will review the categorisation of environmental organisms following the literature reviews for Chapter 4 of the National Infection Prevention and Control Manual.
- HPS will further support the development of an appropriate trigger for ongoing monitoring.
- HPS should consider these findings when developing methods to support other boards in monitoring infection risk associated with environmental organisms.

Contact

Health Protection Scotland
NSS.HPSHAIIC@nhs.net

Further Information

For more information please see the full report. For related topics, please see the HPS pages.

Methodology of obtaining admissions data

Paediatric haematology and oncology:

The data for the Royal Hospital for Children was extracted from Trak Care using the speciality codes of Haematology and Oncology.

The data pre-2013 (going back to 2008) was migrated onto Trak Care from the previous Patient Admin System, called Meditech, as part of the Trak implementation process in 2013. Prior to the data being recorded on Trak Care, all the paediatric haematology and oncology data was recorded under the specialty code of Haematology, only after implementation of Trak Care was the speciality code Oncology also used.

The dataset consists of all inpatients and day case admissions with a length of stay greater than 0.

Adult haematology:

A list of consultants was provided for the specialty in NHS GGC from 2015 by HR. The adult haematology service lead nurse advised that the service was subdivided into 4 sectors (North, South, Clyde and Bone Marrow Transplant Unit) and that there were no other consultants from 2013 onwards. The Lead Nurse identified which consultants corresponded to which sector. The Clyde sector consultants were removed as Clyde is predominantly day units with less inpatient beds. The data for the North, South and Bone Marrow Transplant Unit consultants was extracted from Trak Care for all adult hospitals for the period of January 2013 to June 2023 in order to provide data for each of these sectors.

The dataset consists of all inpatients and day case admissions with a length of stay greater than 0.

Glasgow Hospitals Case Note Review requested by Scottish Government: notes and commentary on environmental bacteria.

Draft 3 October 5th 2023

Professor Peter M Hawkey BSc PhD DSc MB BS MD FRCPath FFPath FRCPI

Professor Emeritus of Clinical & Public Health Bacteriology, University of Birmingham & Consultant Clinical Microbiologist, Grampian Health Board

1. How bacteria are named

Living organisms are classified according to the binomial system established Carl Linnaeus in the 18th century. He came up with the concept of a species which represented animals and plants that had a very high degree of similarity (e.g. flower structure) and bred between themselves. Those species that were similar to each other he grouped together into a genus. The first name of a living organism is that of the genus and the second the species. These names are derived from Latin and Greek roots and often refer to characteristics of the organisms or the person that first named them. Hence modern man is *Homo sapiens:* genus *Homo* (meaning man), species *sapiens* (meaning wise). The two other human species now extinct were *Homo erectus* and *Homo neanderthalensis (*Neanderthal man) who were the other members of the genus *Homo*. The species name is always set in italics. The first mention of a species in text has the full name spelt out e.g., *Escherichia coli* and thereafter the genus is usually shortened to a single letter *E. coli*. Bacteria (singular bacterium) were not properly visualised by microscopy and staining until the latter part of the 19th century because of their small size (1-5 micrometres (μm) - 1 μm is a thousandth of a millimetre). It was then noted that bacteria had different shapes: round balls-cocci and

rods-bacilli being the most common. They were also divided by the Gram stain into positive: staining purple and negative: staining red. Whilst the microscopic appearance of bacteria was useful in trying to classify them it was limited in its ability to differentiate bacteria, so species and genus assignment was not easy. Subsequently once bacteria could be cultured on artificial media (nutrient containing agar in Petri dishes) a particular bacterium's ability to ferment different sugars, produce different enzymes and other biochemical properties enabled a much more accurate classification which broadly forms the current taxonomy (the science of naming organisms). The big advance was the use of genotypic data which is based on DNA sequence which initially in the 1980s measured the relatedness of the different bacterial genomes. Bacteria do not have chromosomes just one small double stranded piece of DNA. Relatedness was initially determined by allowing different single stranded pieces of genomic DNA to hybridise between each other and the amount of hybridization of identical sequences being determined by a radiochemical method. More recently the actual sequence of different DNA bases can be compared giving much more information.

Bacteria are single celled organisms which have much simpler cell structures than higher organisms (e.g., plants, mammals etc.). Bacteria are divided up into major groups called phyla (singular phylum), these are further subdivided into classes. The Gram stain reflects fundamental chemical differences in the bacterial cell wall and does broadly divide bacteria. There is one large phylum of Gram positive bacteria called the Firmicutes (now sometimes referred to as the Bacillota). This phylum includes the medically important Gram positive bacteria such as *Staphylococcus aureus*, *Clostridium* spp. (abbreviation referring to all the species in this genus), *Lactobacillus* spp. and *Bacillus anthracis* (cause of anthrax). This phylum contains

mainly Gram-positive bacteria which can be both bacilli and cocci in shape. There are a number of other clades in the Firmicutes of which both Gram positive and negative bacteria exist in the environment and have no medical significance. Another phylum consisting mainly of Gram-negative bacteria of considerable medical importance is the Pseudomonata. Two classes within this Phylum are important in medical bacteriology. These are the Betaproteobacteria and Gammaproteobacteria. The Betaproteobacteria includes the genus *Neisseria* which causes gonorrhoea and meningitis and plant pathogens such as *Ralstonia* spp. and *Burkholderia* spp. and *Xylophilus* spp. that are common and widely distributed in the natural environment to which we are exposed all of the time. These bacteria very rarely, and only in immune-compromised patients, can cause infection often associated with intravascular lines (tubes inserted into veins to provide fluids). Bacteria cannot easily be classified as pathogens or non-pathogens as a continuum exists from rare highly pathogenic bacteria which almost invariably cause disease e.g. (*Yersina pestis* - causes plague) to bacteria that are part of our normal flora living in harmony with us, often referred to as commensal bacteria, but in certain situations can cause overt disease (e.g. Escherichia coli - causing urinary tract infections). In individuals with greatly impaired immune systems the environmental bacteria which frequent live on and in plants and the soil can rarely cause infection (e.g. *Delftia* spp. in bone marrow transplant patients). The other class of Gammaproteobacteria are Gram-negative bacteria with a range of morphologies the bacilli, coccus, spirals and filaments. The Gammaproteobacteria class contains over 250 genera of bacteria making it the most genus rich taxonomic group of the prokaryotes. These bacteria live in both marine and terrestrial environments including extreme ones such as hydrothermal vents. As might be expected they have a range of metabolisms both aerobic (requiring oxygen) and anaerobic. Although the

Gammaproteobacteria are mainly environmental (e.g., *Methylococcus* that feed on methane) they include many important human adapted pathogens as well as free living bacteria which do not require a mammalian host. A number of these bacteria can cause disease in humans particularly those with immuno-compromise. The order Pseudomonales (next grouping below class) contains the genera *Pseudomonas* and *Acinetobacter* both important hospital acquired pathogens, but many members also are pure environmental bacteria and/or plant pathogens. Another order of the class Gammaproteobacteria, Xanthomonales contains the genus *Stenotrophomonas* most species of which our soil plant associated, however one species *S.maltophilia*, in addition to being a plant associated bacterium can cause hospital acquired infections. Arguably the most important from a medical perspective order in the class Gammaproteobacteria is the order Enterobacterales. This comprises genera which are plant pathogens such as *Erwinia* but also the key family of Enterobacteriaceae. This family has the genera: *Salmonella. Shigella, Klebsiella, Enterobacter, Citrobacter* and *Escherichia* which are predominately predominantly human pathogens. The genus *Escherichia* contains the world's most well characterised bacterium *E. coli*. Many of the Enterobacterales bacteria are described as opportunistic pathogens. They surround us, colonise our gut and are in our food outside of the hospital environment. Some strains (a subdivision of a specific species (e.g. *E. coli* 0157) have special disease causing properties that make them more likely than the "ordinary" strains to cause disease in normal people.

2. What is meant by an outbreak

The term outbreak is both emotive and superficially well understood, but on detailed consideration is somewhat nebulous. A strict definition is the occurrence of two or more cases of infection caused by genetically indistinguishable micro-organisms. Practically, precise genetic subtyping of microorganisms rarely identifies the outbreak as it is a relatively slow and complicated process and therefore typically carried out retrospectively. More often it is an increase beyond the normally expected numbers of a specific infection. Usually the causative bacterium is known to species level and therefore draws attention rather than a general increase in different species and or genera of bacteria. This is described as an exceedance beyond the normally expected number of cases of infection and this is what often draws attention to the possibility of outbreak occurring. Frequently such exceedances occur in patients that are related in time and space providing further circumstantial evidence for cross infection and therefore potentially an outbreak. Further when defining a putative outbreak it is necessary to identify 3 features: the source of the infecting organisms, the route of transmission and the portal of entry into the patient. When considering bloodstream infections in haematology oncology patients the source is variable. Although there are many reports of outbreaks of bloodstream infections (BSI), the majority of episodes are single episodes. One reason for this not being obvious is that when the scientific literature is examined it is dominated by reports of outbreaks this causes publication bias. This is a situation where peer review journals generally are more interested in publishing reports that identify controllable sources with a clear understanding of the routes of transmission and portals of entry rather than accepting reports with lots of single sporadic unrelated cases of infections. The widely recognised source for BSI in neutropenic patients, particularly for Gram-negative bacteria is the gut (Rolston et al. 2014). The frequent administration of antibiotics to neutropenic patients also induces

a gut microbiome dysbiosis with colonisation by multi resistant Gram-negative bacteria. This has been supported by a recent study in a cohort of 63 patients with acute myeloid leukaemia (AML) and BSI, using whole genome sequencing based strain typing on the BSI isolates and digital drop PCR combined with 16S rRNA sequencing to identify matching species in oral and gut microbiome. They found a highly significant correlation between BSI and oral/faecal carriage of the same bacterial strain compared to other BSI cases where there was no colonisation. The effect was particularly marked for *E. coli*, *Pseudomonas aeruginosa* and viridans streptococci (McMahon et al. 2023). In another study using powerful metagenomic tools further explored the relationship between prior gut colonisation with BSI pathogens in bone marrow transplant (BMT) recipients (Tamburini et al. 2018), the authors compared the role of translocation of gut bacteria versus non enteric commensal and environmental bacteria accessing the bloodstream through intravenous lines or breaks in the skin. They prospectively studied 30 BMT patients with 32 episodes of BSI in 18 months in a major USA cancer hospital. As might be expected pathogens regarded as gut derived such as *E. coli , Klebsiella pneumoniae, Enterococcus faecium* and *Streptococcus mitis* were identified at strain level in both gut flora and blood. In opposition to current dogma which states that environmental bacteria such a *Pseudomonas aeruginosa* are not generally found in the gut was the finding that both *P.aeruginosa* and *Staphylococcus epidermidis* were found as indistinguishable strains in the patient's gut metagenome and BSI (Tamburini et al. 2018). The importance of patient infection with *Klebsiella pneumoniae* developing from their own strain carried in the gut was recently reaffirmed by a study of ICU patients in which 45% of admission rectal swab culture positive patients had a subsequent infection caused by the same often unique strain as determined by whole genome

sequencing. This was in contrast to only 12% percent of episodes being attributable to spread amongst hospital patients (Gorrie et al. 2017). Whilst quite correctly there is a focus on identifying environmental sources of nosocomial infection in haematology oncology units, the “environmental” bacteria as will be seen from the detailed descriptions below, occur widely in the general environment. An example would be a recent study of Glasgow municipal tap water which demonstrated bacteria such as *Cupriavidus* spp., and *Burkholderia* spp. etc can be found at low levels in the drinking water (Khan et al. 2016). The Case Note Review Overview Report (CNR) regards many of these bacteria as being acquired from a ward environmental source and to cause BSI in 70% of cases. Patients spend long periods at home when there is ample opportunity for colonisation by these environmental bacteria as has been demonstrated in cystic fibrosis patients for *Stenotrophomonas maltophilia* (Denton et al.1998) and also for *Burkholderia* spp. (Tavares et al. 2020) It is therefore reasonable, particularly in the light of the metagenomic studies above, to assume that a smaller percentage of the BSI in the CNR are derived from an environmental source than 70%. It is a matter of opinion but I would regard probably a figure that is significantly lower (e.g. closer to 20% as being reasonable). Broad spectrum antibiotics, of which haematology oncology patients receive a large number also select for gut carriage of multi resistant Gram-negative bacteria which are often of the “environmental” type because these bacteria possess high levels of intrinsic resistance to broad spectrum antibiotics. The patients are frequently exposed to them and as the bacteria are resistant they become dominant in the gut flora because the more sensitive bacteria are killed. This is eloquently illustrated by the study of both colonisation and infection by *Stenotrophomonas maltophilia* in haematology oncology patients in the USA (Aitken et al. 2021). These authors showed that in following a cohort of 90 patients

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receiving remission induction chemotherapy for acute myeloid leukaemia (AML) there was a statistically significant association of both oral colonisation and subsequent systemic infection (BSI) from *Stenotrophomonas maltophilia* with the prior administration of carbapenem antibiotics (e.g. meropenem) to which the bacterium is intrinsically resistant.

3. Clinical significance and epidemiology of the 6 most common groups of presumed environmental bacteria selected for inclusion by the expert panel

Order Enterobacterales

This order comprises genera which are plant pathogens such as *Erwinia* but also the key family of Enterobacteriaceae. This family has the genera: *Salmonella. Shigella, Klebsiella, Enterobacter, Serratia, Citrobacter* and *Escherichia* which are predominately gut commensals which can be human pathogens. The genus *Escherichia* contains the world's most well characterised bacterium *E. coli*.

Three genera referred to sometimes as the KES (*Klebsiella, Enterobacter, Serratia*) bacteria are most commonly associated with nosocomial (hospital acquired) infections and generally are multiply drug resistant (MDR). *Klebsiella* together with the closely related genus Enterobacter are arguably the most common causes of nosocomial infection within the family Enterobacteriaceae. *Serratia* which has some special antibiotic resistance characteristics are also included in the KES group.

The numbers of positive blood cultures featured in the CNR are shown in brackets.

3.1 *Klebsiella* spp.(30)

This genus of bacteria belong to the order Enterobacteriales which is a member of the class Gammaproteobacteria which contain most of the Gram-negative bacilli that cause human infections. The natural habitat of *Klebsiella* spp. is the mammalian gut. In common with *E. coli* and other members the Enterobacteriales there are many individuals in the community with asymptomatic gut carriage of *Klebsiella* spp.. A European study showed that between 5-35% of healthy individuals carry *Klebsiella* in their gut flora (Calderon-Gonzalez et al. 2021). Rarely in certain situations infection in these individuals will develop. Carriage rates in hospitalised patients are often higher and not confined to the gut but also include the naso-pharynx and skin which then acts as a source for spread to other patients often by transfer on staff hands. There are two species: *K pneumoniae* which is the most frequently encountered and *K. oxytoca* which has become more common in recent times and has a similar epidemiology and pathogenicity to *K .pneumoniae* (Neong et al 2021). I will concentrate on *K. pneumoniae* which has a more extensive literature. The usual source for nosocomial infection is the patient with faecal colonisation. As described above community carriage can be a source and was detected at a rate of 6% in ICU admissions from the community (19% for those with previous healthcare contact) (Gorrie et al.2017). Those patients found to be colonised on admission had a statistically higher rate of subsequent infection (16% V 3% OR 6.9) with 80% of infections having a genetically matched between colonising and infecting strains (Gorrie et al. 2017). This colonisation in ward patients is most frequently acquired from another patient usually due to transfer on staff hands or contact with contaminated surfaces in the ward, food/drink and from additional wet sources in which the *Klebsiella* can survive and multiply. This route of transmission was identified nearly 50 years ago together with an

effective control of transmission by using hand wash containing Chlorhexidine (Casewell et al.1977). At the time resistance to the newly developed and very important antibiotic gentamicin drove a major problem with serious infections in hospitals which was easily identifiable because of the antibiotic resistance marker of gentamicin resistance. Faecally colonised patients also had significant numbers of *K.pneumoniae* on their skin and in their nasopharynx. This resulted in spread on nurses and doctors hands to colonise other patients in the ward. Control was achieved by using Chlorhexidine hand washing gel with rigorous attention to hand washing together with screening for identification of those patients with faecal colonisation (Casewell et al.1977). These careful early studies of the epidemiology of *Klebsiella* are often forgotten and the importance of the colonised patient is underestimated. Careful investigation of outbreaks of infection nowadays can reveal lapses in hand hygiene which probably represents the most common route of transmission in hospital wards. In some cases there have been reports of sink traps and drains, bowls, cloths and other stagnant wet materials which have been implicated as a source of infection when molecular typing to trace infecting bacteria to individual patient infections has been undertaken (Kizny-Gordon et al. 2017). These authors review focused on carbapenem resistant organisms (CRO) but the basic bacterial epidemiology is unaffected by the antibiotic resistance genes carried. Sink traps (U bends or P traps) which always contain water and therefore large bacterial populations, usually in a biofilm, are sometimes seen as the most important source of Gram-negative infections in wards with vulnerable patients (e.g. haematology/oncology, intensive care units, burns units etc.). It is important to maintain a balanced view, as just because bacteria of the same species can be found in those sites they are not necessarily the source of infection. *Klebsiella* spp. together with *Pseudomonas* spp., Acinetobacter spp. and

Enterobacter spp. are the bacteria most often suggested to cause infections related to sink traps (Kizny-Gordon et al. 2017). A recent review reported that *Pseudomonas aeruginosa* was the most frequently reported bacterium in such studies (41%) (Kizny-Gordon et al. 2017). The authors drew attention to the various limitations of their work: failure in 60% of studies to undertake admission screening to detect existing colonisation, publication bias (focus on discrete outbreaks) and the use of poorly discriminatory strain typing techniques. A recent study looked intensively at an intensive care unit over a long time using highly discriminative WGS typing to assess the role of sink traps in *Pseudomonas aeruginosa* infections (Couchoud et al. 2023). They concluded "that genome based typing revealed the contamination of patients by *P. aeruginosa* originating from sink traps to be infrequent (1.5%) and that only 7.75% of patients acquired *P. aeruginosa* from another patient" suggesting that endogenously acquired infections are much more significant. In summary although sink traps have a diverse bacterial population which is enriched repeatedly by human derived materials being poured into the sink they are not necessarily the dominant source of BSI when compared to gut/oral microbiomes of patients.

Commented [AR2]: Note Q from Inquiry to AL, whether WGS can be used to exclude a link or can it only confirm a link. Would be useful to have PH's view on this.

A recent review reported that there are relatively few reports of environmental sources for multi-resistant *Klebsiella pneumoniae* as the majority involved *Pseudomonas aeruginosa* (41% of studies) (Kizny-Gordon et al. 2017). The authors concluded that *Pseudomonas* spp. and *Acinetobacter* spp. are environmental colonisers surviving in low nutrient conditions whereas the Enterobacteriales are predominantly of human origin and their concentration in drains may represent a different ecosystem and inoculation from human waste. A detailed study using whole genome sequencing (WGS) of a collection of 250 *K. pneumoniae* strains from UK and Ireland were compared to 10 WGS databases of globally distributed strains. WGS data correlated

very closely with multilocus sequence type (MLST) that defines highly related clones of *Klebsiella* by a sequence type (ST) (Moradigaravand et al.2017). The UK hospital isolates had representatives from all of the major global ST's, the most common being ST15. The authors were able to conclude that the UK *Klebsiella pneumoniae* population was highly diverse and that some clones have emerged and spread across the country with potential links to European hospitals. They also stated that as a commensal opportunistic pathogen *K. pneumoniae* has the potential to rapidly spread between hospitals via carriage in patients transferring between countries (Moradigaravand et al. 2017). To summarise Klebsiella are important nosocomial pathogens, the most common sources are the community colonised patients admitted to hospital and a colonised hospital patient with transfer to colonise other patients via contact with contaminated surfaces, hands of medical/nursing staff and sometimes food. On occasions wet sources such as sink traps, drains, medical equipment and cleaning cloths can act as primary sources for infection having been contaminated by material from colonised patients.

3.2 *Enterobacter* spp.(27)

After *Klebsiella pneumoniae*, *Enterobacter* cloacae was the next most frequently isolated pathogen from blood in the CNR. *E. cloacae* has a complex taxonomy but most human infections are caused by *E. cloacae* or very closely related bacterial species referred to as the *Enterobacter cloacae* complex. The next most common species encountered in hospitals is *E. hormaechie* which used to be classified as *E.cloacae* and is still often misidentified as *E.cloacae* by conventional biochemical identification techniques (Davin-Regli et al. 2019). The epidemiology is very similar to

Klebsiella pneumoniae with the colonised patient as the most common source which can then rarely lead to contamination of the environment particularly drains (Denissen et al.2022). Most infections are endogenous and outbreaks from a single environmental source would typically be with genetically indistinguishable strains. When outbreaks of *Enterobacter cloaceae* involving environmental sources occur molecular typing using WGS usually demonstrates a clear cluster of a specific strain type. A good example is the outbreak described by Nurjadi et al. 2021, in a 58 bed haematology unit between 2018 and 2020 involving *E cloacae* producing OXA-48 carbapenemase, a distinctive antibiotic resistance marker. They used WGS, assigning isolates to different sequence types (ST) which is a highly discriminative subtyping method. A total of 41 patients over the time period were colonised in the gut and nine patients developed BSI. There was no clear epidemiological link between the patients. Sequence typing of all *E. cloaceae* isolates across the hospital revealed many ST types (ST 66, ST 231, ST27,ST90, ST 96) with a notable excess of ST66 isolates in the haematology wards. The wastewater traps in 20 of 38 patients rooms were positive for OXA-48 *E cloacae* most of which were ST66. Disinfection of traps with acetic acid and the use of an autoclavable shower insert to reduce splash from the waste outlet terminated the outbreak completely. This study shows that when sink traps are a significant source then WGS typing readily identifies a number of indistinguishable isolates which are found in both patients and the environment. As with *K. pneumoniae* certain clones of *E. cloacae* are highly adapted and successful in the hospital setting. They usually carry important antibiotic resistance genes such as those for the carbapenemases e.g. KPC (Kneckt et al. 2022). The use of antibiotics in hospital wards therefore has a strong influence on the occurrence of these nosocomial bacteria, particularly third generation cephalosporins (Eichel et al. 2020). In some

cases *E. cloacae* outbreaks when investigated over an extended time show a diversity of strains are causing infection which suggests there is no constant single environmental source but rather introduction by individual faecally colonised patients. Such a study over 6 years in a major neonatal unit using WGS strain typing which is very sensitive and reliable showed waves of different diverse clones occurred, suggesting introduction from different sources (Ferry et al. 2020). The authors commented that the infant gut was the most likely source with spread via hands and contaminated objects.

3.3 *Serratia marcescens* (7)

Serratia marcescens is by far the most common species of the genus *Serratia* causing human infections, particularly in neonatal and immunocompromised patients. That said, it is a rare cause of human infection, most cases being sporadic. Publication bias has led to hospital outbreaks being reported more commonly. It is a member of the Enterobacterales and is common in the neonatal microbiome whereas in adults it is rare (Lewis et al 1983). In a study of pre term neonates the presence of *Serratia* in the faecal microbiome was strongly associated with a high degree of immaturity as well as antibiotic therapy and mechanical ventilation (Moles et al 2020). Whilst environmental sources for nosocomial outbreaks are described those sources tend to be equipment such as bronchoscopes, scalp vein needles or disinfectants (Knowles et al 2000). Numerically the most important source for both sporadic cases and outbreaks is the colonised patient (predominantly faecal) which then leads to general environmental contamination and transfer on staff hands from that environment and/or the patient (Lewis et al 1983; Knowles et al 200;, Montanaro et al 1984). Because *S.*

marcescens has intrinsic resistance to a range of antibiotics, antibiotic usage in the ward is reported to be associated with outbreaks (Knowles at al 2000; Lewis et al 1983). *S. marcescens* is the only species of *Serratia* which can carries the *aac* 6'-Ic gene conferring resistance to aminoglycosides, all strains carry the gene thus explaining perhaps its dominance in causing human infections under antibiotic selection (Snelling et al 1993). The *aac6'-Ic* gene is normally not expressed, so isolates are sensitive to a aminoglycoside antibiotics. However if a patient is treated with an aminoglycoside (e.g. gentamicin, netilmicin or amikacin) the gene is derepressed. This process results in the full expression of resistance. That strain will often retain expression of resistance even after no longer being exposed to the aminoglycoside antibiotic and therefore pass as a resistant strain from patient to patient (Snelling et al. 1993).

S. marcescens should not be viewed as an environmental bacterium in the way non-fermenters such as *Stenotrophomonas*, *Cupriavidus*, *Rhizobium* etc. are, as the colonised patient is the common source of outbreaks. *S.marcescens* should however be seen as a commensal of the paediatric gut which under antibiotic selection leads to heavy faecal colonisation in the patient which in turn acts as a source for nosocomial transmission.

3.4 *Citrobacter* spp.(5)

This bacterium is another member of the order Enterobacterales and in the CNR only represented 3.2% of isolates, so not in the top 6 number of isolates. It is much less frequently encountered in nosocomial infection compared to *Klebsiella* and

Enterobacter but has a similar epidemiology to *E. coli* that was excluded from consideration by the CNR.

Order Pseudomonales

3.5 *Pseudomonas* spp.(17) - *P. aeruginosa* (9), *P. putida* (7) and *P. stutzeri* (1)

These bacteria belong to a different order to the Enterobacteriales to which the above bacteria belong, the order is Pseudomonales. This means that although they are Gram-negative bacilli they have different properties to the Enterobacteriales. The main difference is that they are not normally animal gut commensals, but live in association with plants and soil. The most common human pathogen is *Pseudomonas aeruginosa* which belongs to the family Pseudomonadaceae. This is a very large family of bacteria of mainly environmental and plant associated bacteria some of which are capable or fixing atmospheric nitrogen to the benefit of the plant host. The genus *Pseudomonas* has 313 species most of which are plant pathogens.

P. aeruginosa is probably the most common environmental derived pathogen seen almost exclusively in immunocompromised, burns, ICU and cystic fibrosis patients. Faecal colonisation can occur even in healthy individuals in the community one study reporting a carriage rate of 8.2% (Estepa et al. 2014). Higher rates of colonisation are seen in hospital patients. Colonisation may lead to the development of infection by invasion from the bowel in immunocompromised patients subsequently making it difficult to define exactly the original source for infection This accords with the relative infrequency of infection derived directly from the environment as reported in the study of *P. aeruginosa* environmental epidemiology in four very large critical care units using WGS typing In only 5.1% of colonised patients was the *P. aeruginosa* definitely

acquired from a water outlet in the unit. This is in the background where in the largest unit 25-28% of the 231 outlets sampled on three separate occasions were positive for *P. aeruginosa* carriage (Halstead et al. 2021). *P. aeruginosa* is capable of successful colonisation of biofilms in most wet environments particularly if there is plastic or rubber present as the bacteria can use these as a nutritional source. It is the most important bacterium when considering colonisation of hospital water systems which then can lead to infection in susceptible patients (Kinzy- Gordon et al. 2017). Thermostatic mixer valves contaminated when tested following manufacture have been particularly implicated as sources and certain clones of the *P. aeruginosa* have been identified as causing both colonisation and infection in augmented care units (ICU/burns) (Halstead et al. 2021). *P. aeruginosa* is the main bacterium colonising water supplies as opposed to waste traps when other bacteria such as *Klebsiella* and *Enterobacter* tend to colonise hand washing sink traps potentially from the disposal of patient materials (urine, washing water with traces of faeces etc.) (Hayward et al. 2022).

Pseudomonas putida is a plant associated bacterium whose ecological niche is to act as a growth stimulant for plants in the rhizosphere (the microbial community surrounding plant roots) (Costa-Gutierrez et al.2022). Because of its very widespread distribution outside of hospitals it can colonise compromised patients at home as well as in the hospital environment. Although rarer than *P. aeruginosa* in causing infections it's frequency appears to be increasing and it is now regarded as the next most common species of pseudomonas after *P. aeruginosa* causing outbreaks in hospital associated with patient colonisation and wet sources in high dependency areas (Baykal et al.2022).

3.6 *Acinetobacter* spp. (11).

Bacteria of the genus *Acinetobacter* are important soil organisms frequenting the rhizosphere. They belong to the order Pseudomonales like pseudomonas but are in the family Moraxellaceae being very different in their metabolism and epidemiology. There are a very large number of species found in the general environment but only a very small number associated with hospital infections, the most common being *Acinetobacter baumannii* and more rarely *A. ursingii* and *A. pittii (*Kiyasu et al.2020). The reason for their success is thought to be their high levels of antibiotic/disinfectant resistance, metabolic flexibility and desiccation resistance allowing survival for long periods on surfaces contaminated by colonised patients (Jawad et al. 1998). The epidemiology of *Acinetobacter* is therefore rather different to *Pseudomonas* and *Klebsiella* in that although there are reports of contamination of wet medical equipment together with isolates from sink traps as outbreak sources, surface contamination and resistance to drying is the most important source (Cruz- Lopez 2022). This difference in epidemiology was illustrated by the successful control of a long term outbreak in a neurosurgical unit by increased environmental and surface cleaning rather than controlling any wet sources (Denton et al 2004).

3.7 *Stenotrophomonas maltophilia* (23).

The natural habitat of *Stenotrophomonas maltophilia* is the rhizosphere (microbial community surrounding plant roots) (Mukherjee and Roy 2016). It belongs to the order Xanthomonales and is therefore not closely related to either Enterobacterales or Pseudomonales. Although an aerobic bacterium it has the ability to use nitrate as a terminal electron acceptor in the absence of oxygen so can grow in an anaerobic

environment. It can utilise a wide range of organic molecules as an energy source including toxic solvents (trichloroethylene, chloroform etc) and plastics (Mukherjee and Roy 2016). The ability to survive in a low nutrient, wet and anaerobic environments combined with high levels of intrinsic antimicrobial resistance means that it can cause a range of nosocomial infections. Despite low pathogenicity, infections in ventilated ICU, immunocompromised and patients with cystic fibrosis are moderately common (Brooke 2021). A wide range of wet environmental sources of infection in hospital have been reported such as sink traps, plastic medical equipment, taps etc. (Brooke 2013). Acquisition of *S. maltophilia* from environments other than the hospital such as the home have been reported, an example being that of cystic fibrosis patients (Denton et al 1998). Every isolate of *S. maltophilia* carries a chromosomal beta-lactamase (L1) which confers resistance to carbapenem antibiotics. The use of carbapenems has been demonstrated to be significantly associated with patient colonisation in a cohort and subsequent development of infection caused by *S. maltophilia* in vulnerable patients (Aitken et al 2021). Patients with hematologic malignancy who develop infection usually have prior colonisation and dominance in their faecal microbiome by the infecting bacterium. In the case of Enterobacterales the infection is generally primary bacteraemia following gastrointestinal translocation which was preceded by colonisation often driven by antibiotic administration (Velden et al 2014). In contrast Aitken and colleagues found that colonisation with *S. maltophilia* was mainly oral rather than faecal as seen with other Enterobacterales which could fit with the predominance of respiratory and catheter related blood stream infections in this population. The acquisition of multi drug resistant Gram-negative bacilli may be from environmental sources but can also be from sources outwith the hospital or from the patients indigenous microbiome.

4. Other more rarely reported bacteria in the CNR selected by the panel.

Very small numbers of a wide range of different species of gram-negative bacteria were reported from cases of bacteraemia over the extended time period. Most of these bacteria are associated with plant/soil and can therefore be acquired by immunocompromised patients in a non-hospital setting as well as in hospital. Some such as *Elizabethkingia* spp. have been reported as colonising wet hospital environments and causing single environmental source outbreaks as determined on molecular typing. Many of the other species are very common in the general environment and can very rarely cause infection in immune-compromised patient. These short descriptions provide background on the most common habitats and their association with human disease.

4.1 *Pantoea* spp. (3)

This genus was comparatively recently established and involved the transfer of *Enterobacter agglomerans* (a bacterium well recognised as a human pathogen) into the genus with about 20 other species which are most commonly associated with plants (Walterson & Stavrinides 2015). As a member of the order Enterobacteriales, *Pantoea* forms a mono-phyletic group (highly related) with the genera *Tatumella* and *Erwinia* which mainly consist of plant pathogens (Walterson & Stavrinides 2015).

A number of species have been found in clinical samples, WGS studies suggest that environmental and clinical isolates do not form distinct clusters. This implies

colonisation, mainly from general environmental sources plants soil etc, occurs and then very rarely infection develops in both immunocompetent and immune-compromised patients (Walterson & Stavrinides 2015). Recent genomic studies have demonstrated that this genus has two major clades (groups which are highly genetically related). One of them contains *Enterobacter agglomerans*, renamed *Pantoea agglomerans* which is well recognised as a rare pathogen in humans. The genus has been considerably expanded and now has 21 species. While some other species such as *P. septica*, *P. calida* and *P. dispersa* have been isolated from both human immune-compromised and immunocompetent patients, the majority of species are associated either with plant disease or act as endosymbionts (symbiotic bacteria that grow within a plant). They do not have any particular association with aquatic environments. The closely related genus of *Erwinia* is a well-recognised plant pathogen consisting of very many species as are the other genera in the Enterobacteriales which are plant pathogens (*Tatumella*, *Dickeya*, *Brenneria*, *Pectobacterium* and *Sodalis*).

4.2 *Raoultella* spp. (2)

Raoultella is another member of the Enterobacteriales which is rarely encountered causing human disease and is most commonly isolated from plants (Sekowska 2017). It was formerly classified in the genus *Klebsiella* and similarly has the ability to colonise the human gut (Sekowska 2017). The epidemiology of infections is very similar to *Klebsiella*, with infections occurring in intensive care, haematology-oncology units in patients with comorbidities but also in non-immunocompromised patients usually

following broad spectrum antibiotic treatment and/or implanted devices (Appel et al 2021).

4.3 *Elizabethkingia* spp. (6)

Although these appear to be a newly recognised species of bacteria, however it is the result of the reclassification of *Flavobacterium meningosepticum*. This bacterium was recognised by Miss Elizabeth O King in the USA in the late 1950s as causing clusters of neonatal meningitis (Jean et al 2014). A new genus was created and named in her honour which has eight species including *E. meningosepticum* (which is phylogenetically distinct from the others) and of which *E. anopheles*, *E. ursingii* are the most frequently encountered other species in clinical settings (Zajmi etal. 2022). The genus belongs to the very large order Flavobacteriales which are environmental bacteria of which only *Elizabethkingia* and *Capnocytophaga* are associated with human disease. From their first description these bacteria have been frequently reported causing nosocomial outbreaks of bacteraemia, meningitis, soft tissue and line infections (Lin al 2019; Jean et al 2014). There are a number of reports which have wet sources such as sink traps, taps, humidification systems and contaminated aqueous solutions (e.g. saline or Chlorhexidine disinfectant) act as sources (Jean et al 2014; Moore et al 2016). *Elizabethkingia* spp. are ubiquitous in general aquatic environments and can colonise both domestic and healthcare water systems. They carry multiple resistance genes often conferring resistance to broad spectrum antimicrobials such as carbapenems and 3rd generation cephalosporins (Hem et al 2022; Moore et al 2016). Identification by conventional phenotypic biochemical methods does not allow reliable species differentiation and even MALDI-TOF does not

reliably differentiate some species e.g. *E. meningosepticum* and *E. anopheles* (Lin et al. 2019). Highly discriminatory strain typing has to be applied to link patient isolates with any environmental isolates as it is a common bacterium in aquatic systems.

Most frequently infected patients are those receiving intensive care, paediatric/ neonatal and immunocompromised often because of the proximity to sources and the multiple portals of entry for the bacteria (Moore et al 2016; Lim et al 2019). Infected and colonised patients become prolific sources of the bacteria which can then contaminate surfaces such as keyboards, locker tops and medical equipment leading to further cases (Moore et al 2016; Jean et al 2014).

4.4 *Chryseobacterium* spp. (5)

This is a very widely distributed bacterium in the general environment with over 100 species recognised. Originally known as *Flavobacterium* (on account of the production of yellow orange pigmented colonies on agar) the most important human pathogen *C. meningosepticum* was reclassified to another genus *Elizabethkingia*. The vast majority of *Chryseobacterium* together with *Flavobacterium* spp. are the most abundant bacteria in the plant rhizosphere (Nishioka et al 2016). *Chryseobacterium* have plant growth promoting properties, protect plants from infection by producing antifungal/antibacterial compounds and releasing nutrients by secreting biodegrading enzymes such as chitinase as well as degrading aromatic hydrocarbon pollutants (e.g. 2-4 dinitro toluene) (Nishioka et al 2016). Therefore only two species are rare causes of human infection namely *Chryseobacterium indologenes* and *Chryseobacterium gleum*, which were recognised when an expanded MALDI-TOF databases was used (Lin at al 2018). They have a propensity to be associated with intra-venous lines, intra-

cerebral and plastic shunt infections as well as bacteraemia in immune-compromised patients (Lin et al 2018; Ozcan et al 2013). Environmental nosocomial sources such as sink traps have rarely been reported as sources so acquisition from contact with soil and plants or other infected patients with subsequent gut colonisation and invasion across the gut wall seems to be the most common source of infections (Hsueh et al 1996; Mukerji et al 2016).

4.5 Order Burkholderiales

This large order of bacteria is dominated by families of bacteria found in soil and water with a very few that can cause human disease even in immunocompromised patients. I have grouped them together because they have similar properties, particularly in that they cannot ferment sugars to provide energy unlike the order Enterobacteriales. The following genera belong to the order Burkholderiales and are represented in CNR bacteraemia series.

4.5.1 *Burkholderia* spp. (2)

The species of the genus *Burkholderia* (part of the Burkholderaceae family) most frequently encountered in human infections is *B. cepacia* formerly known as *Pseudomonas cepacia* which causes colonisation and pneumonia in patients with cystic fibrosis (CF). There are now 24 other species of which are those encountered in human infections are dominantly in CF patients, being *B. cenocepacia* and *B. multivorans* (Tavares et al 2020). Unlike Enterobacteriales and some other Gram-negative bacteria, commensal gut carriage is not common and infections are acquired in hospital settings or directly from the environment (soil and water). In the case of *B. cenocepacia* (formerly *B. cepacia genomovar III*) in CF patients, the strains of the

species found in soil and water and in patients homes are indistinguishable from the infecting bacteria (Tavares et al 2020). Spread amongst patients in hospitals is associated with intravenous and urinary catheters, endotracheal tubes, human dialysis and long periods of hospitalisation. Spread is thought to occur by aerosols and direct or indirect contact (via surfaces) with infected patients (Tavares et al 2020). Another quite commonly reported source for nosocomial infection caused by *Burkholderia* is contaminated water based pharmaceutical and cleaning products, where it is recognised as the most commonly identified causative bacterium (Tavares et al 2020).

4.5.2 *Delftia* spp. (3)

This bacterium used to be called *Pseudomonas acidovorans* and has been recognised since the late 1960s has an extremely rare cause of infection in patients with comorbidities or immunocompromise (Bhat et al 2022). Its normal habitat is a wide range of environmental sites as it is part of the rhizosphere (microbial community surrounding plant roots) microbiome. It is capable of fixing nitrogen and also acts as a plant growth promoting bacterium when it is described as an endophytosphere bacterium growing within plant cells inside the plant. It is also capable of removing heavy metals so is found in a wide range of aquatic environments and is used in bioremediation of metal contaminated soils (Bhat et al 2022). Infections have been reported from both immune-competent and immunocompromised patients but low numbers of cases appear in the literature (Bilgin et al 2022). Colonisation of wet sites such as sink traps is possible as the bacterium has been reported to have the ability to coaggregate with other bacteria and provide nutritional support for those bacteria to form biofilms (Afonso et al 2023).

4.5.3 *Cupriavidus* spp. (2)

These bacteria belong to the family Burkholderaceae (as do *Ralstonia*) which are very widely distributed in soil and water with 17 species currently recognised. *C. pauculus* has been identified as a rare cause of bacteraemia in immunocompromised patients (Inkster et al 2021). Three cases were identified over a five-year period, molecular typing was undertaken and all isolates were distinguishable suggesting a common source was unlikely, there was no mention of correlation with environmental isolates in the report. *C. pauculus* has been identified as being present in water collected from 5/10 hospitals in the UK, although *Acidovorax*, *Blastomonas*, *Brevundimonas*, *Pseudomonas aeruginosa* and *Sphingomonas* were identified at a greater number of hospital sites (Inkster et al 2022). Patients are likely to come into contact with *Cupriavidus* outside of hospital because of its widespread distribution in water, soil and plants. A recent study has shown that together with *Ralstonia* and *Pseudomonas* they were the most commonly isolated bacteria from final rinse water used to prepare lettuce and spinach (Gu et al 2020). The authors postulated that resistance to the sanitizer (chlorine) added to the rinse water increased counts of these bacteria. As these foods are eaten without cooking this represents a significant risk for colonisation in the compromised patient.

4.5.4 *Achromobacter* spp. (1)

Another genus in the Burkholderaceae which contains *Achromobacter xylosoxidans* which has been reported as a rare cause of human infection. It most is most frequently encountered in patients with cystic fibrosis, probably selected by repeated courses of broad spectrum antibiotics (Isler et al 2020). It is rarely encountered as a nosocomial pathogen, although older outbreaks have been associated with contamination of disinfectant solutions such as aqueous Chlorhexidine to which it is resistant.

4.5.6 *Herbaspirillum* spp. (1)

Like other members of the Burkholderaceae this genus are endophytes, many being able to fix nitrogen and are very common in soil and vegetation. Reports of human infections are mainly confined to single case reports in patients with immune-compromise or cystic fibrosis (Dhital et al 2020). There is a report of a hospital based cluster of eight cases, seven with bacteraemia, of *Herbaspirllum* infections at the M D Anderson Cancer Center, Texas (Chemaly et al 2015). Five cases were hospitalised between 19- 28 July 2011 so were tightly clustered in time and four of those isolates had indistinguishable PFGE typing patterns, however all the patients were on different wards and floors of the hospital. Despite extensive investigation of the environment including water sink traps etc. no environmental source was found. It was concluded that it could have been spread on hands of staff resulting in colonisation of central venous lines or ingestion of a common uncooked plant based food (Chemaly et al 2015)

4.6 *Aeromonas* spp. (2)

These bacteria have a natural habitat of surface waters and are well recognised as causing local soft tissue infections and gastroenteritis which can evolve into septicaemia particularly in elderly patients (Pinto-Cora et al 2023). Hospital outbreaks are unusual and when reported usually relate to the consumption of unchlorinated tap water by compromised patients (Fernandez-Bravo & Figueras 2020; Picard & Goullet 1987). Most compromised patients probably acquire the bacterium from water or food in the general environment (Pinto-Cora et al 2023).

4.7 *Sphingomonas* spp. (1)

These are plant associated bacteria that can be acquired from environmental sources such as water and food. Most reports are of sporadic hospital acquired outbreaks often in immunocompromised patients (Askin et al 2022). However, these reports are subject to reporting bias and a very large population-based survey in Australia over a 20 year time frame showed 134 of 282 episodes of bloodstream infection caused by Sphingomonas were community associated and the overall mortality was only 6% (Laupland et al 2022).

4.8 Roseomonas spp (1)

This is a group of bacteria of which many species have been found in water and soil. Therefore when there are rare reports of infections they are often related to intravascular catheters and compromised patients, an environmental source such as water is often hypothesised as the cause (Shao et al 2019). This assumption has been challenged as a genomic study demonstrated that the skin microbiome is the source of *Roseomonas mucosa*, the most commonly encountered species in humans (Romano-Bertrand et al 2016).

4.9 Rhizobium spp (1)

These bacteria are one of the most important nitrogen fixing bacteria for plants and are therefore obligate plant endosymbionts. Human infections are rare usually community acquired and associated with indwelling plastic devices (Tiwari & Beriha 2015).

4.10 *Brevundimonas* spp. (1)

This is a large genus consisting of 34 species of plant growth promoting and plant pathogenic bacteria. They are rare pathogens of compromised patients with a total of 49 cases found in the world literature up until 2018, the majority being *B. vesicularis* (Ryan & Pembroke 2018). The bacterium has been identified as an important component of biofilm communities and provides nutrients to enable *Legionella pneumophila* to grow (Koide et al 2014). Although capable of colonising low nutrient wet environments in healthcare facilities it is very widely distributed in the general environment as evidenced by its frequent occurrence in plant debris on beaches in numbers sufficient to raise concerns for human safety (Suzuki et al 2021).

5. Preliminary comments on the Case Note Review report

It is not clear to me exactly how many cases of BSI occurred in the time period studied and what the causative bacteria were in terms of species type. The March 2021 final report document suggests that (paragraph 3.2) the cases for review were selected on the basis of a protocol referenced as #27. This reference document is not available, so it is not clear that all or only some cases of BSI caused by bacterial species regarded as having an environmental origin were included or not. It seems that all *E. coli* were excluded but were all cases of the other bacteria included. This is important as there is a description at 3.6.6 that a variety of patient clinical and epidemiological (location & clustering) data for each case was used to assign a relative likelihood that the infection was acquired from an environmental source in the hospital. The term cluster is a very loose one, as most people see it as being a number of isolates of the

same bacterial species (sometimes further defined by preliminary strain typing) occurring in a setting where they may be arising as the result of cross infection. I do not think it is appropriate to group different species of bacteria as a cluster despite the panel suggesting that the putative environmental sources had multiple types of many different species and therefore there is a high probability these are the sources of the BSI. Their method of “defining” outbreaks/clusters in my experience is an unusual and rather limited method of investigation. Considering that they did not wish to consider the WGS strain typing data (section 8.3.1) from patient isolates and appropriate environmental isolates which were made at the time of the infection in the patient in which the reported BSI occurred it is probably the only possible approach.

The generally accepted epidemiological definition for acquisition is that indistinguishable bacterial types are found in the source and the patient (defined by the group as definite). The panel accepted this definition but had to report that none of the BSI episodes satisfied this criterion (p.68 & Table 5.3). The next category of degree of association with a putative environmental source was “probable” to which 28% of cases are allocated just three 3% being assigned to “strong probable” The criteria used for “probable” and a larger weaker category “possible and strong possible” (50% of all BSI cases) was based on an opinion that “the environment was likely to be the source (on the grounds of probability), using a standard infection prevention and control assessment of the available data/information” (p.44). It seems to me that there is likely to be too much reliance placed on the occurrence of episodes of BSI caused by the same bacterial species in a certain time and place frame which can easily arise by chance. Without molecular typing and characterisation of the repeated occurrence of the same strain and it being actively identified in the environment this methodology seems highly speculative. It is it is notable and

commented on by the panel that the two most frequently encountered genera of bacteria causing BSI are *Stenotrophomonas* and *Klebsiella*. *Stenotrophomonas* is particularly highlighted by the panel to be over represented in a particular timeframe and there is speculation that this has come from the environment. However the *Stenotrophomonas* cluster could equally be derived by the use of carbapenem antibiotics in the same manner as reported by Aitken and colleagues (see section 3.7 this report and below). If the categorisation was made purely on the basis of the occurrence of a particular species of bacterium in a certain time frame then endogenous infections rather than environmentally acquired is more likely as typically this can occur in cases of infection with *Klebsiella* and some other species of Enterobacteriales. As described at 3.1 above *Klebsiella* can be spread from an environmental source-but the colonised patient is most often the source in ward transmission events. The panel is dismissive of the WGS typing data as a tool for refuting the clusters of *Stenotrophomonas maltophilia* BSIs (8.3.1 p.96) on the grounds of poor strain representation. However, isolates from 15/23 total infections were typed together with 59 environmental isolates & 10 other clinical isolates none of which were indistinguishable and therefore not related. In my opinion this is a reasonable sample and should be compared to the findings of a cluster investigation of BSIs caused by *Stenotrophomonas maltophilia* in a large German haematology unit (Kampmeier et al. 2017). They identified 4 cases of BSI between February & July 2016, a clear exceedance from their 0.5 cases/year. WGS showed no relationship between the isolates, typing of environmental isolates only identified one of the four BSI isolates to be indistinguishable from a shower head isolate. Using the CNR panel's criteria this would be classified as an outbreak of 4 cases, not as shown by WGS not to be an outbreak but a single acquisition from an environmental source. *E. coli* BSI is

completely excluded from consideration by the panel with no explanation. Whilst most infections are likely to arise following community colonisation careful molecular typing studies have occasionally shown that it is capable of ward based transmission, this being particularly apparent when strains are multi resistant (Woodford et al 2007). I think this reflects a lack of detailed understanding of the epidemiology of Gram-negative bacteria.

Although fleetingly mentioned (bottom p.68) that environmental pathogens in immunocompromised patients can be acquired outside of hospital no allowance for this appears to be made in the analysis. My review of the literature around all of the selected bacterial species (see above) shows that this is not an uncommon occurrence and I think this is a significant shortcoming in the report. Despite this the panel classify 76 (70%) episodes of BSI as possible and 33 (30%) as probable from being acquired from a hospital environmental source.

The panel draw attention to two clusters of *Stenotrophomonas maltophilia* BSI in January-September 2018 and April-September 2019 (p.56). They tested with Chi squared for statistical significance of these temporal clusters being in the “most likely” category for the source of infection and found the result to be statistically significant (p.70). It is my understanding that none of these isolates were indistinguishable by strain typing which if a single source was considered to be likely then I would expect that at least some of the isolates would be indistinguishable. The report draws attention to the cluster of *Stenotrophomonas maltophilia* cases in 2018 as being significant. The inclusion of these strains as having an environmental source greatly boosts the number presumed to have come from the environment as they have ignored the WGS typing data which by analogy with the Kampmeier study would mean that there was no environmental source outbreak There is also good evidence that the

use of carbapenem antibiotics results in colonisation with *Stenotrophomonas maltophilia* as it is always resistant to carbapenems [Aitken et al 2021]. It is also not necessarily true that colonisation with *Stenotrophomonas* always comes from the hospital, as there are as many home environmental sources which have been shown in CF patients to be the source of colonisation (Denton et al 1998). In 2017-18 there was a worldwide shortage of piperacillin/tazobactam which resulted in many units switching to carbapenem antibiotics. Was this true in NHSGGC? If so, this may explain the cluster of *Stenotrophomonas*.

There is no comparison of the overall rates of infection with other similar institutions which is very important. Comments about there being an excess of specific species associated with the environment would then be set in context as well as understanding whether there was actually an increase in infections during the period relative to other establishments. The report appears to be written from a preconceived view that environmental sources in the hospital resulted in most if not all of cases of BSI caused by Gram-negative bacteria which by virtue of their identification are presumed almost automatically to come from the environment. I think this is a dangerous assumption.

Initial bullet point thoughts on executive summary for report to Scottish hospitals inquiry by Prof Peter Hawkey.

1 All haematology oncology patients have an increased incidence of infection. The occurrence of infections is variable both in chronology and infecting organism.

2 Because of the reduced immunity of these patients in addition to conventional pathogens [e.g. E.coli, Staphylococcus aureus, etc.] bacteria with low pathogenic potential that frequently occur in the environment can cause serious infections.

3 Although these bacteria can come from the hospital environment home and other environmental sites can also frequently result an infection caused by these bacteria

4 The large number of bacterial species classified together as having an environmental source by the CNR all themselves are very diverse, particularly in their epidemiology and pathogenic potential.

5Prior colonisation of patients, often in the gut but also as in the case of Stenotrophomonas in the upper respiratory tract often driven by broad spectrum antibiotics, is a common precursor to the occurrence of bloodstream infection (BSI).

6 Environmental sources in hospitals typically result in clusters of infections caused by one or two species rather than a very large range of species over a long period of time. This proliferation in the environmental source only becomes a threat to patients providing a route of transmission and a portal of entry into the patient occurs, then BSI clusters are seen. When the implicated strains cause infection the usual finding is that one or two specific strains of those species cause the majority of the infections and in careful environmental investigations show those same strains can be identified in the environment.

7 The finding of large numbers of potential pathogens which are environmentally located in hospital wards is not unusual and their occurrence does not necessarily mean that there will be increased rates of infection as routes of transmission and portals of entry are essential for infection to occur.

NOTE BY COUNSEL TO THE INQUIRY

PROVISIONAL POSITION PAPER 5: THE HISTORY OF INFECTION CONCERN (HOIC)

1. The Chair has directed that the present version of the HOIC should be published on the Inquiry's website along with the responses received from Core Participants (CPs). That being so, it is important that the nature and role of the HOIC and the responses are understood. This is explained at the outset of the HOIC, but it is worth reiterating the key points.

2. First, the subject matter of the document must be emphasised. It is only concerned with events that have been said by some to indicate concerns (i) about the incidence of infection in the QEUH/RHC; (ii) about the safety of key building systems (notably water, drainage and ventilation systems); and (iii) about the suggestion of links between (i) and (ii).

3. A number of the responses from CPs cover matters outwith this scope. These responses are helpful and will be investigated, but discussion of that will not be addressed by the Inquiry within the HOIC.

4. Second, the underlining in paragraph 2 is a reminder that no one should read the HOIC as setting out a narrative of proved facts. The HOIC does no more than set out what people have said as regards their concerns. The job of the Inquiry is to go on and investigate those concerns. The HOIC will frame that investigation.

5. Third, the HOIC should not be seen as claiming to set out every story that bears on the three questions identified at paragraph 2 above. It is obvious that a document that

attempted to set out the entire history of all individual events bearing on these questions would be enormous (assuming it was even possible to prepare such a document). The Inquiry has already heard a number of the stories within that history in the evidence provided by patients and families. The HOIC adds to this by setting out some of the notable events from publicly available and other prominent source material. The ingathering and analysis of source material continues.

6. Fourth, the HOIC is not intended to provide the detail of any of the events it narrates. It provides no more than a spine. The process of seeking responses is to identify aspects of that spine that are incomplete and aspects that require detailed investigation. The process also ensures that this all happens in public. The responses are helpful as regards achieving that purpose.

7. Fifth, as has been identified by CPs, the HOIC is a work in progress; it is just the start of a process. I will reflect on how that process might be taken forward in the most efficient way.

8. Finally, I would simply note that a number of the responses identified clear drafting errors within the HOIC. I have corrected these, and they are shown as tracked in the published version.

Alastair Duncan KC

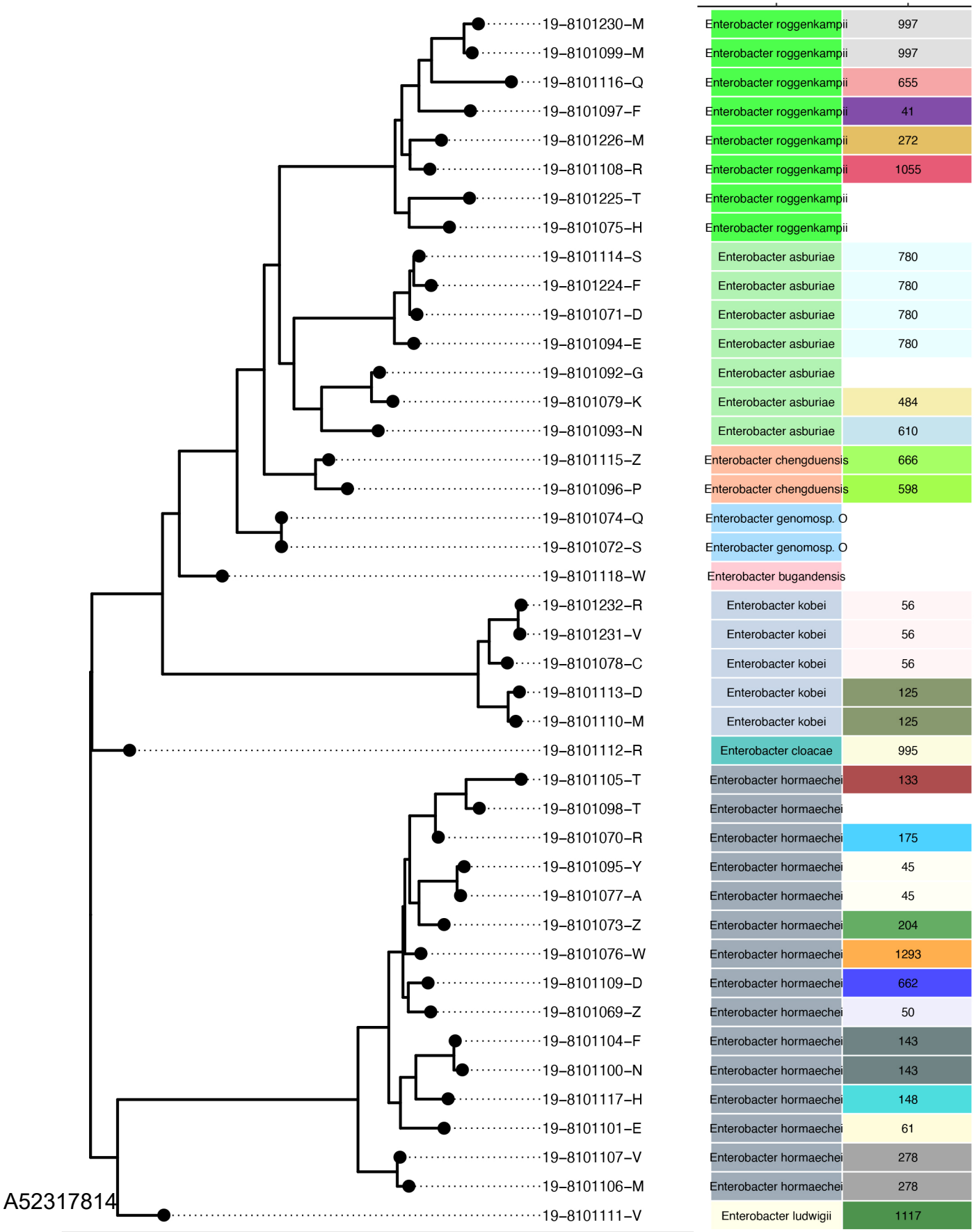
28 April 2023

Lan Number	Date	Organism	Organism		Isolate Y or N	Failed to grow	Sent for WGS				
18.1840657.X	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0012	Main Building	2nd Floor Sch 063	Ward 2A Treatment Room Pre
18.1840658.L	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0013	Main Building	2nd Floor Sch 063	Ward 2A Treatment Room Post
18.1840659.G	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0014	Main Building	2nd Floor Sch 030	Prep Room SSS Pre
18.1840661.X	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0016	Main Building	2nd Floor Sch 058	Room 15 WHB Pre
18.1840662.L	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0017	Main Building	2nd Floor Sch 058	Room 15 WHB Post
18.1840664.N	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0019	Main Building	2nd Floor Sch 059	Room 15 Shower Post
18.1840665.E	19.02.2018	Cupriavidus species	Pseudomonas aeruginosa		Y		Y	RHC/0020	Main Building	2nd Floor TCT 003	Room 3 WHB Pre
18.1840671.P	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0026	Main Building	2nd Floor TCT 009	Room 6 Bathroom Pre
18.1840673.T	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0028	Main Building	2nd Floor Sch 027	Room 26 WHB Pre
18.1840674.M	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0029	Main Building	2nd Floor Sch 027	Room 26 WHB Post
18.1840675.V	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0030	Main Building	2nd Floor Sch 022	Room 26 Bathroom Pre
18.1840676.R	19.02.2018	Cupriavidus species		0	Y		Y	RHC/0031	Main Building	2nd Floor Sch 022	Room 26 Bathroom Post
18.1840722.R	21.02.2018	Cupriavidus species		0	Y		Y	RHC/0033	Children's Hospital	2nd Floor Sch 057	Ward 2A Schiehallion/TCT Room 14 WHB Post
18.1840723.D	21.02.2018	Cupriavidus species		0	Y		Y	RHC/0034	Children's Hospital	2nd Floor Sch 055	Ward 2A Schiehallion/TCT Room 14 Bathroom Pre
18.1840725.Z	21.02.2018	Cupriavidus species		0	Y		Y	RHC/0036	Children's Hospital	2nd Floor Sch 033	Ward 2A Schiehallion/TCT Room 2 WHB Pre
18.1840726.Q	21.02.2018	Cupriavidus species		0	Y		Y	RHC/0037	Children's Hospital	2nd Floor Sch 033	Ward 2A Schiehallion/TCT Room 2 WHB Post
18.1840727.H	21.02.2018	Cupriavidus species		0	Y		Y	RHC/0038	Children's Hospital	2nd Floor Sch 032	Ward 2A Schiehallion/TCT Room 2 WHB Pre
18.1840834.F	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0040	Children's Hospital	Ward 2A 2nd Floor	Sch 027 Room 26 WHB
18.1840835.T	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0041	Children's Hospital	Ward 2A 2nd Floor	Sch 027 Room 26 WHB
18.1840836.M	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0042	Children's Hospital	Ward 2A 2nd Floor	Sch 027 Room 26 Pre
18.1840838.R	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0044	Children's Hospital	Ward 2A 2nd Floor	Sch 058 Room 15 WHB
18.1840839.D	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0045	Children's Hospital	Ward 2A 2nd Floor	Sch 058 Room 15 WHB
18.1840840.M	02.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0046	Children's Hospital	Ward 2A 2nd Floor	Sch 058 Room 15 Pre
18.1840852.W	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0048	Children's Hospital	Ward 2A 2nd Floor	Room 3 Tct 003 WHB Pre
18.1840853.A	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0049	Children's Hospital	Ward 2A 2nd Floor	Room 3 Tct 003 WHB Post
18.1840857.B	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0053	Children's Hospital	Ward 2A 2nd Floor	Room 6 Tct 009 Post
18.1840858.X	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0054	Children's Hospital	Ward 2A 2nd Floor	Room 15 Sch 058 WHB Pre
18.1840862.X	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0058	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 027 WHB Pre
18.1840864.G	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0060	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 022 Pre
18.1840866.E	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0062	Children's Hospital	Ward 2A 2nd Floor	Treatment Room Sch 063 Pre
18.1840867.Y	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0063	Children's Hospital	Ward 2A 2nd Floor	Treatment Room Sch 063 Post
18.1840869.F	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0065	Children's Hospital	Ward 2A 2nd Floor	Prep Room SSS Sch 030 Post
18.1840870.E	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0066	Children's Hospital	Ward 2A 2nd Floor	Room 21 Sch 084 WHB Pre
18.1840871.Y	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0067	Children's Hospital	Ward 2A 2nd Floor	Room 21 Sch 084 WHB Post
18.1840872.P	05.03.2018	Cupriavidus pauculus	Delftia acidovorans		Y		Y	RHC/0068	Children's Hospital	Ward 2A 2nd Floor	Room 21 Sch 085 Pre
18.1840874.T	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0070	Children's Hospital	Ward 2A 2nd Floor	Room 2 Sch 033 WHB Pre
18.1840878.D	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0074	Children's Hospital	Ward 2A 2nd Floor	Room 14 Sch 057 Pre
18.1840879.S	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0075	Children's Hospital	Ward 2A 2nd Floor	Room 14 Sch 057 Post
18.1840881.R	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0077	Children's Hospital	Ward 2A 2nd Floor	Room 14 Sch 055 Post
18.1840884.Z	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0080	Children's Hospital	Ward 2A 2nd Floor	Room 1 Sch 031 Pre
18.1840885.Q	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0081	Children's Hospital	Ward 2A 2nd Floor	Room 1 Sch 031 Post
18.1840890.H	05.03.2018	Cupriavidus species		0	Y		Y	RHC/0086	Children's Hospital	Ward 2A 2nd Floor	Room 11 Sch 050 WHB Pre
18.1840907.N1	06.03.2018	Cupriavidus pauculus		0	Y		Y (2 Isolates)	RHC/0094	Children's Hospital	Daycare Unit 2nd Floor	Room 1 DCU-024 Pre
18.1840907.N2	06.03.2018	Cupriavidus gilardii		0	Y		Y (2 Isolates)	RHC/0094	Children's Hospital	Daycare Unit 2nd Floor	Room 1 DCU-024 Pre
18.1840908.E	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0095	Children's Hospital	Daycare Unit 2nd Floor	Room 1 DCU-024 Post
18.1840909.Y	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0096	Children's Hospital	Daycare Unit 2nd Floor	Room 3 DCU-021 Pre
18.1840910.G	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0097	Children's Hospital	Daycare Unit 2nd Floor	Room 3 DCU-021 Post
18.1840911.N	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0098	Children's Hospital	Daycare Unit 2nd Floor	Room 5 DCU-019 Pre
18.1840912.E	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0099	Children's Hospital	Daycare Unit 2nd Floor	Room 5 DCU-019 Post
18.1840914.P	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0101	Children's Hospital	Daycare Unit 2nd Floor	Dirty Utility SSS DCU-018 Post
18.1840915.F	06.03.2018	Cupriavidus species		0	Y		Y	RHC/0102	Children's Hospital	Daycare Unit 2nd Floor	Dirty Utility WHB DCU-018 Pre
18.1841009.Z1	13.03.2018	Cupriavidus pauculus			Y		Y (2 Isolates)	RHC/0104	Children's Hospital	2nd Floor Ward 2B	Room 1 DCU-024 Pre
18.1841009.Z2	13.03.2018	Cupriavidus gilardii			Y		Y (2 Isolates)	RHC/0104	Children's Hospital	2nd Floor Ward 2B	Room 1 DCU-024 Pre
18.1841010.R	13.03.2018	Cupriavidus gilardii	Saprophytic fungi		Y		Y	RHC/0105	Children's Hospital	2nd Floor Ward 2B	Room 1 DCU-024 Post
18.1841011.D	13.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0106	Children's Hospital	2nd Floor Ward 2B	Room 3 DCU-021 Pre
18.1841012.S	13.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0107	Children's Hospital	2nd Floor Ward 2B	Room 3 DCU-021 Post
18.1841013.Z	13.03.2018	Cupriavidus pauculus	Brevundimonas species		Y		Y	RHC/0108	Children's Hospital	2nd Floor Ward 2B	Room 5 DCU-019 Pre
18.1841014.Q	13.03.2018	Cupriavidus pauculus	Brevundimonas species		Y		Y	RHC/0109	Children's Hospital	2nd Floor Ward 2B	Room 5 DCU-019 Post
18.1841017.A	13.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0112	Children's Hospital	2nd Floor Ward 2B	Dirty Utility S/S DCU 018 Pre
18.1841018.C	13.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0113	Children's Hospital	2nd Floor Ward 2B	Dirty Utility S/S DCU 018 Post
18.1841026.X	13.03.2018	Cupriavidus pauculus	Environmental GNB		Y		Y	RHC/0121	Children's Hospital	3rd Floor 3C	Room 5 GW1-038 Post
18.1841029.N	13.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0124	Children's Hospital	3rd Floor 3C	Room 8 GW1-045 Pre
18.1841030.X	13.03.2018	Cupriavidus pauculus	Comamonas testosteroni		Y		Y	RHC/0125	Children's Hospital	3rd Floor 3C	Room 8 GW1-045 Post
18.1841035.Y	13.03.2018	Cupriavidus pauculus	Brevundimonas species		Y		Y	RHC/0128	Children's Hospital	3rd Floor 3C	Room 9 GW1-053 Pre
18.1841036.P	13.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0129	Children's Hospital	3rd Floor 3C	Room 9 GW1-053 Post
18.1841039.M	13.03.2018	Cupriavidus pauculus	Achromobacter species		Y		Y	RHC/0132	Children's Hospital	3rd Floor 3C	Room 21 GW1-007 Pre
18.1841049.Q	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0149	Children's Hospital	Ward 2A 2nd Floor	Room 21 Sch 084
18.1841051.S	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0151	Children's Hospital	Ward 2A 2nd Floor	Room 21 Sch 084 Post
18.1841054.H	14.03.2018	Cupriavidus gilardii	Saprophytic fungi		Y		Y	RHC/0154	Children's Hospital	Ward 2A 2nd Floor	Prep Room Utility Sch 030 Pre
18.1841058.K	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0138	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 027
18.1841059.J	14.03.2018	Cupriavidus pauculus	Pseudomonas putida		Y		Y	RHC/0139	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 027
18.1841060.A	14.03.2018	Cupriavidus pauculus	Pseudomonas putida		Y		Y	RHC/0140	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 027 Pre
18.1841061.C	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0141	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 027 Post
18.1841075.P	14.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0165	Children's Hospital	Ward 2A 2nd Floor	Room 12 Bathroom Sch 052 Post
18.1841153.N	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0194	Children's Hospital	Ward 2A 2nd Floor	Room 5 TCT 008 Pre
18.1841154.E	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0195	Children's Hospital	Ward 2A 2nd Floor	Room 5 TCT 008 Post
18.1841157.F	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0198	Children's Hospital	Ward 2A 2nd Floor	Room 3 TCT 004 Pre
18.1841159.M	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0200	Children's Hospital	Ward 2A 2nd Floor	Room 9 Sch 048 Pre
18.1841161.F	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0202	Children's Hospital	Ward 2A 2nd Floor	Room 10 Sch 047 Pre
18.1841162.T	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0203	Children's Hospital	Ward 2A 2nd Floor	Room 10 Sch 047 Post
18.1841165.R	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0206	Children's Hospital	Ward 2A 2nd Floor	Room 13 Sch 056 Pre
18.1841166.D	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0207	Children's Hospital	Ward 2A 2nd Floor	Room 13 Sch 056 Post
18.1841167.S	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0208	Children's Hospital	Ward 2A 2nd Floor	Room 14 Sch 055 Pre
18.1841173.Q	14.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0214	Children's Hospital	Ward 2A 2nd Floor	Room 1 Sch 031 Pre
18.1841250.R	16.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0248	Children's Hospital	Ward 2A 2nd Floor	Room 2 Sch 033 Pre
18.1841251.D	16.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0249	Children's Hospital	Ward 2A 2nd Floor	Room 2 Sch 033 Post
18.1841260.W	16.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0258	Children's Hospital	Ward 2A 2nd Floor	Room 26 Sch 022 Pre
18.1841278.T	16.03.2018	Cupriavidus pauculus	Environmental GNB		Y		Y	RHC/0276	Adult	4th Floor 4B	Bed 75 How 195 Pre
18.1841285.R	17.03.2018	Cupriavidus pauculus	Chryseomonas indologenes		Y		Y	RHC/0327	Children's Hospital	Ward 2A	Room 2 Sch 032 Post
18.1841340.H	18.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0334	Children's Hospital	Level 2	C2 Sch-038 Riser Feeding 2A/Anaesthetics Pre
18.1841341.W	18.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0335	Children's Hospital	Level 2	C2 Sch-038 Riser Feeding 2A/Anaesthetics Post
18.1841365.V	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0359	Children's Hospital	4th Floor	Expansion Vessel at Cal 78343 Post
18.1841366.R	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0360	Children's Hospital	4th Floor	Cal 78344 (Mid) Pre
18.1841368.S	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0362	Children's Hospital	4th Floor	Expansion vessel at Cal 78344 Pre
18.1841369.Z	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0363	Children's Hospital	4th Floor	Expansion vessel at Cal 78344 Post
18.1841371.D	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0365	Children's Hospital	4th Floor	Cal 78345 Post
18.1841372.S	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0366	Children's Hospital	4th Floor	Expansion Vessel at Cal 78345 Pre
18.1841373.Z	18.03.2018	Cupriavidus gilardii		0	Y		Y	RHC/0367	Children's Hospital	4th Floor	Expansion Vessel at Cal 78345 Post
18.1841387.L	18.03.2018	Cupriavidus pauculus	Aspergillus versicolor		Y		Y	RHC/0383	Adult	Basement	Bulk CWST 2B Drain
18.1841455.Q	21.03.2018	Cupriavidus pauculus	Rhizobium radiobacter		Y		Y	RHC/0418	Ward 1D	PICU	Female Change CCW-025 Post
18.1841462.A	21.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0425	Ward 1D	PICU	Bed 5 CCW-084
18.1841463.C	21.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0426	Ward 1D	PICU	Bed 5 CCW-084
18.1841674.G	23.03.2018	Cupriavidus pauculus	Comamonas testosteroni		Y	X	N	RHC/0592	Adults Hospital	Ward 6A	Bed 2A GEW1-006 Pre
18.1841690.V	26.03.2018	Cupriavidus pauculus		0	Y		Y	RHC/0608	Adults Hospital	Ward 4A	RENW-281 DSR Pre
18.1841692.D	26.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0610	Adults Hospital	Ward 4A	RENW-281 DSR Pre
18.1841693.S	26.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0611	Adults Hospital	Ward 4A	RENW-281 DSR Post
18.1841704.W	26.03.2018	Cupriavidus pauculus	Achromobacter xylosoxidans		Y		Y	RHC/0622	Adults Hospital	Ward 7B	Bed 111 A7 GENW8-004 Pre
18.1841708.J	26.03.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/0626	Adults Hospital	Ward 7B	Bed 93 A7 GENW8-045 Pre
18.1842217.V	10.04.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/964	Children's Hospital	Ward 2A	Treatment Room WHB
18.1842375.M	17.04.2018	Cupriavidus pauculus		0	Y		Y	RHC/1009	Children's Hospital	Basement	CWST 1A Bulk
18.1842382.D	17.04.2018	Cupriavidus pauculus	Pseudoxanthomonas mexicana		Y		Y	RHC/1017	Children's Hospital	Basement	Raw CWST 2A
18.1842422.V	18.04.2018	Cupriavidus gilardii		0	Y		Y	RHC/1046	Children's Hosptial	4th Floor	4th Floor Riser Pre
18.1842424.D	18.04.2018	Cupriavidus gilardii		0	Y		Y	RHC/1048	Children's Hosptial	4th Floor	4th Floor Riser Pre
18.1842551.Q	18.04.2018	Cupriavidus gilardii		0	Y		Y	RHC/1150	Children's Hosptial	1st Floor	1st Floor Riser Pre
18.1842552.H	18.04.2018	Cupriavidus gilardii		0	Y		Y	RHC/1151	Children's Hosptial	1st Floor	1st Floor Riser Post
18.1843111.M	27.04.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/1589	Adult's	3rd Floor	Plant Room 32
18.1843114.D	27.04.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/1592	Adult's		Ward 6A
18.1843115.S	27.04.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/1593	Adult's		Ward 6A
18.1843197.W	27.04.2018	Cupriavidus gilardii		0	Y		Y	RHC/1675	Children's	4th Floor	Plant Room 41
18.1843212.J	01.05.2018	Cupriavidus pauculus		0	Y		Y	RHC/1684	Adult's	2nd Floor	Plant Room 21
18.1843213.B	01.05.2018	Cupriavidus pauculus	Saprophytic fungi		Y		Y	RHC/1685	Adult's	2nd Floor	Plant Room 21
18.1847226.N	17.12.2018	Cupriavidus pauculus		0	Y		Y	KID/2575	Childrens	2nd Floor	Play Room
18.1847232.Y	17.12.2018	Cupriavidus pauculus		0	Y		Y	KID/2581	Childrens	2nd Floor	TCT Room 3
18.1847239.D	17.12.2018	Cupriavidus pauculus		0	Y		Y	KID/2588	Childrens	2nd Floor	Room 6
19.1840904.S	25/02/2019	Cupriavidus pauculus		0	Y		Y	KID/2840	Childrens	2nd Floor Ward 2A	QEUH W2A TCT ROOM 3 COLD TCT 003
19.1840917.B	25/02/2019	Cupriavidus pauculus		0	Y		Y	KID/2853	Childrens	2nd Floor Ward 2A	QEUB W2A TCT RM6 SHOWER MIX TCT010
19.1841716.Q	08/04/2019	Cupriavidus pauculus		0	Y		Y	KID/3086	Childrens	2nd Floor Ward 2A	KID 3086
19.1844303.V	02/08/2019	Cupriavidus pauculus		0	Y		Y	KID 4340	Childrens	2nd Floor Ward 2A	W2A TCT ROOM 3 COLD TCT003
19.1844455.F	09/08/2019	Cupriavidus pauculus		0	Y		Y	KID 4379	Childrens	2nd Floor Ward 2A	W2A TCT ROOM 6 SHOWER (MIX) TCT010

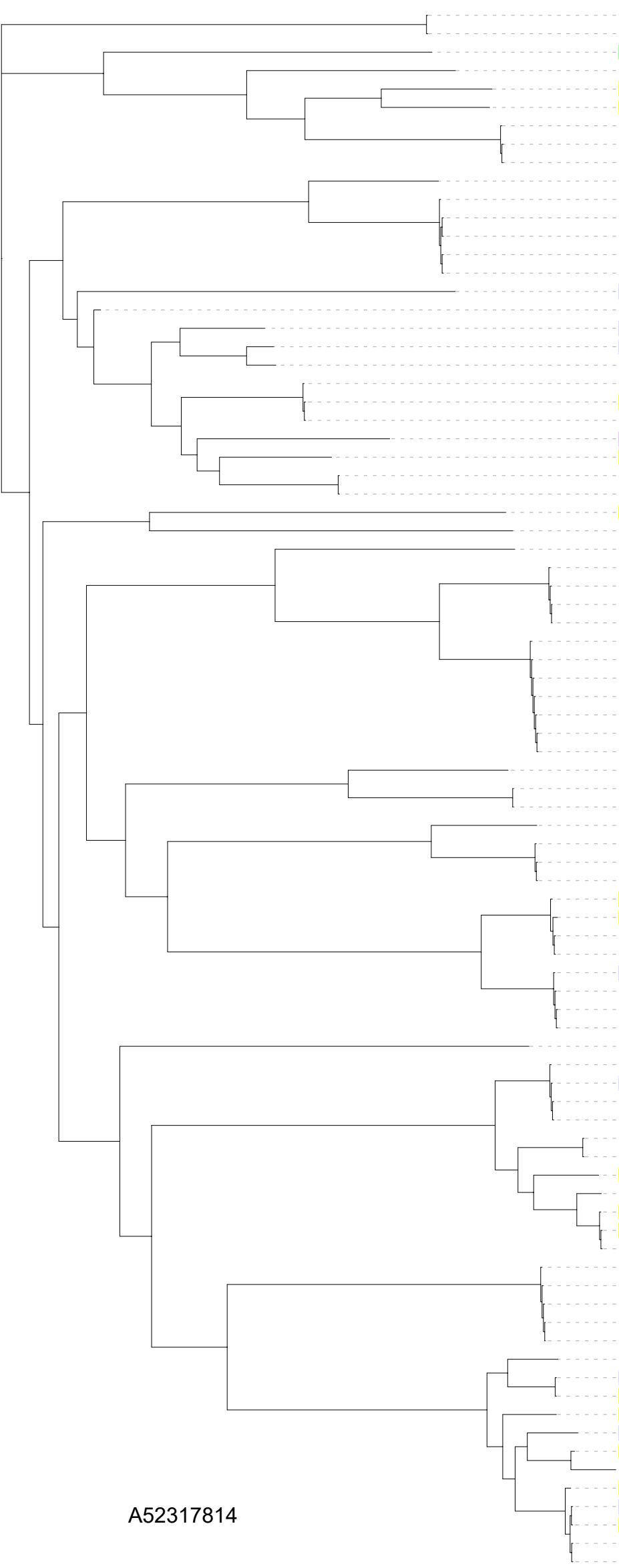
Cupriavidus pauculus	71
Cupriavidus gilardii	16
Cupriavidus species	42

A52317814

Enterobacter species tree



Tree scale: 0.1



SMG-20-1724 M19.5371617.H - Wd 6A, Rm9, drain - QEUH - 2019-12-04
SMG-20-1715 M19.5371553.G - Wd 6A, Rm9, CHWB drain - QEUH - 2019-11-18
SMG-20-1953 M19.5505741.T - Human - [redacted] - General OP Clinics, RAH - 2019-03-05
SMG-20-1669 W20.1843867.S - Basement Tank A&C, Filter Unit 1, SP7 (6730) - QEUH, KID - 2020-06-04
SMG-20-1947 M18.5511421.B - Human - [redacted] - Wd 2A, RHC, QEUH - 2018-05-18
SMG-20-1945 M19.5509335.N - Human - [redacted] - Wd 6A, RHC, QEUH - 2019-04-14
SMG-20-1674 M19.5371763.F1 - Wd 1D, water from leaking ceiling at reception - QEUH, RHC - 2019-12-10
SMG-20-1734 M19.5371763.F2 - Wd 1D, water from leaking ceiling at reception - QEUH, RHC - 2019-12-10
SMG-20-1718 M19.5371763.F3 - Wd 1D, water from leaking ceiling at reception - QEUH, RHC - 2019-12-10
SMG-20-1737 M19.5371763.F4 - Wd 1D, water from leaking ceiling at reception - QEUH, RHC - 2019-12-10
SMG-20-1663 W20.1843636.A - Basement Tank A&C, Filter Unit 3, SP5 (6670) - QEUH, KID - 2020-06-17
SMG-20-1661 W19.1846923.Y - Basement Tank A&C, Filter Unit 3, SP5 (5044) - QEUH, KID - 2019-12-11
SMG-20-1657 W19.1845968.A - Basement Tank A&C, Bulk Filtrate CWST 2A Drain (4789)- QEUH, KID - 2019-10-31
SMG-20-1665 W20.1842307.J - Basement Tank A&C, Filter Unit 3, SP5 (5937) - QEUH, KID - 2020-04-28
SMG-20-1649 W20.1843378.R - Basement Tank A&C, Filter Unit 3, SP5 (6516)- QEUH, KID - 2020-06-10
SMG-20-1915 M15.5510460.S - Human - [redacted] - Wd 4B2, QEUH - 2015-06-14
Reference Genome K279a : AM743169.1
SMG-20-1955 M19.5505332.Y - Human - [redacted] - ARU5 General Surgery, QEUH - 2019-02-28
SMG-20-1941 M19.5514729.M - Human - [redacted] - Wd 56, QEUH - 2019-06-14
SMG-20-1639 W18.1842494.T - Lvl 2 Anaesthetics, Hosp at Night, Pre, Tap, Hot (1120) - QEUH, RCH - 2018-04-17
SMG-20-1731 M20.5370084.D - Wd 6A, Rm2, ensuite shower drain inner - QEUH - 2020-01-14
SMG-20-1919 M17.5521105.D - Human - [redacted] - RHC Wd 2A - 2017-09-24
SMG-20-1727 M19.5371654.Z - Wd 6A, Rm6, ensuite shower - QEUH - 2019-12-04
SMG-20-1931 M20.5500487.V - Human - [redacted] Clinic P, ACH VIC - 2020-01-06
SMG-20-1951 M18.5520998.H - Human - [redacted] - Wd 2B Day Surgery, RHC, QEUH, 2018-09-14
SMG-20-1697 M20.5370254.H - Wd 1D, ante-room drain outer - QEUH, RCH - 2020-02-11
SMG-20-1692 M19.5371656.H - Wd 1D, Rm5, ante-room drain - QEUH, RCH - 2019-12-09
SMG-20-1907 M18.5506583.Q - Human - [redacted] - WD 2A, RHC, QEUH - 2018-03-16
SMG-20-1691 W20.1844373.B - DMA Water Treatment - Potable Water - RAH - 2020-07-08
SMG-20-1647 W19.1840446.F - Doctors' kitchen (water cooler) pre-flush - RAH - 2019-01-31
SMG-20-1708 W18.1845073.B - Basement Tank Childrens, Filter 1, Cintropur Point 2 (2197) - QEUH, RHC - 2018-08-09
SMG-20-1667 W18.1844913.X - Basement Tank Childrens, Filter 2, Post-Cintropur Point 3 (2157) - QEUH, RHC - 2018-07-26
SMG-20-1655 contigs/1-272782
SMG-20-1643 W18.1845071.K - Basement Tank Childrens, Filter 1, Unit 1 FL01 Point 1 (2195) - QEUH, RHC - 2018-08-09
SMG-20-1671 W18.1844914.L - Basement Tank Childrens, Filter 2, Post-Cintropur Point 3 (2158) - QEUH, RHC - 2018-07-26
SMG-20-1672 W18.1845089.R - Basement Tank Childrens, Filter 2, PL01 Filter Point 1, Pre, Drain, Cold (2213) - QEUH, RHC - 2018-08-09
SMG-20-1617 W18.1843683.H - Basement Tank A&C, Filter 2, FL01 Filter, Post, Drain, Cold (1951) - QEUH, RHC - 2018-05-16
SMG-20-1662 W18.1845090.T - Basement Tank Childrens, Filter 2, PL01 Filter Point 1, Post, Drain, Cold (2214) - QEUH, RHC - 2018-08-09
SMG-20-1635 W18.1844909.X - Basement Tank Childrens, Filter 2, PL01 Filter Point 1, Pre, Drain, Cold (2153) - QEUH, RHC - 2018-07-26
SMG-20-1656 W18.1844910.K - Basement Tank Childrens, Filter 2, PL01 Filter Point 1, Post, Drain, Cold (2154) - QEUH, RHC - 2018-07-26
SMG-20-1636 W18.1843682.Q - Basement Tank A&C, Filter 2, FL01 Filter, Pre, Drain, Cold (1950) - QEUH, RHC - 2018-05-16
SMG-20-1732 M20.5370106.X - Wd 6A, Rm7, ensuite shower drain inner - QEUH - 2020-01-14
SMG-20-1624 W18.1844894.Q - Basement Tank Childrens, Filter 1, Cintropur Point 2, Post, Filter Drain, Cold (2138) - QEUH, RHC - 2018-07-26
SMG-20-1611 W18.1844893.Z - Basement Tank Childrens, Filter 1, Cintropur Point 2, Pre, Filter Drain, Cold (2137) - QEUH, RHC - 2018-07-26
SMG-20-1726 M20.5370073.Y - Wd 6A, Rm1, ensuite shower drain inner - QEUH - 2020-01-14
SMG-20-1712 M20.5370114.E - Wd 6A, Rm 21, ensuite drain inner - QEUH - 2020-01-14
SMG-20-1722 M19.5371771.R - Wd 6A, Rm21, pt Bathroom, CHWB drain - QEUH - 2019-12-16
SMG-20-1721 M20.5370113.N - Wd 6A, Rm21, ensuite drain outer - QEUH - 2020-01-14
SMG-20-1933 M19.5523757.F - Human - [redacted] - Wd 4BCH, Kids Bone Marrow Transplant, RHC, QEUH - 2019-09-28
SMG-20-1918 M18.5512619.H - Human - [redacted] - Wd 2A, RHC, QEUH - 2018-06-02
SMG-20-1735 M19.5371805.F - Wd 6A, Rm9, B/Room CHWB Dr18 - QEUH - 2019-12-16
SMG-20-1716 M19.5371621.H - Wd 1D, Rm5, pendant - RHC, QEUH - 2019-11-27
SMG-20-1960 M20.5502748.P - Human - [redacted] - CritCare Un2, HDU 1120, QEUH - 2020-01-30
SMG-20-1666 W19.1844583.R - Wd 2A/B Childrens Anaesthetics Kitchen (4387) - QEUH, KID - 2019-08-16
SMG-20-1673 W19.1843164.M - Childrens 2nd Floor Anaesthetics Kitchen (3739) cold - QEUH, KID - 2019-06-19
SMG-20-1654 W19.1844832.S - Childrens 2nd Floor Anaesthetics Kitchen (4503) cold - QEUH, KID - 2019-08-28
SMG-20-1676 M18.5384331.B - Wd 2A, TR room, trough sink - QEUH RHC - 2018-09-05
SMG-20-1634 W18.1841947.K - Adults Hosp. Wd 5B, Bed 85 GENWD-065 Post, Horne Optitherm, Mixed (804) - QEUH RCH - 2018-03-28
SMG-20-1929 M19.5526947.G - Human - [redacted] - Wd 11D, QEUH - 2019-11-05
SMG-20-1641 W18.1840896.B - Childrens Hosp. Wd 2A 2nd Floor, Room 12 Sch 052 Pre, Shower, Mixed (0092) - QEUH, RCH - 2018-03-05
SMG-20-1615 W18.1840897.X - Childrens Hosp. Wd 2A 2nd Floor, Room 12 Sch 052 Post, Shower, Mixed (0093) - QEUH, RCH - 2018-03-05
SMG-20-1618 W18.1841772.R - Adults Hosp. CCU, Bed 67 CCU-054 Pre, Shower, Mixed (684) - QEUH, RCH - 2018-03-26
SMG-20-1614 W18.1841773.D - Adults Hosp. CCU, Bed 67 CCU-054 Post, Shower, Mixed (685) - QEUH, RCH - 2018-03-26
SMG-20-1943 M18.5520357.W - Human - [redacted] - Wd 1A Theatres, RHC, QEUH - 2018-09-06
SMG-20-1679 M19.5371810.T - Wd 1D, Bed 8, CHWB drain - QEUH, RHC - 2019-12-17
SMG-20-1924 M17.5515572.X - Human - [redacted] - Wd 2B Day Surgery, RHC, QEUH - 2017-07-13
SMG-20-1923 M17.5510811.T - Human - [redacted] - Wd 2A, RHC, QEUH - 2017-05-14
SMG-20-1628 W18.1844884.M - Basement Tank Childrens, Bulk CWST 1A, CWST Drain, Cold (2128) - QEUH, RHC - 2018-07-26
SMG-20-1631 W18.1842259.S - Childrens Hosp. Wd 3B, Staff Kitchen Water Line, Post, Pipework, Cold (973) - QEUH, RHC - 2018-04-11
SMG-20-1623 W18.1842496.V - Lvl 2 Anaesthetics, Hosp at Night, Pre, Tap, Cold (1122) - QEUH, RCH - 2018-04-17
SMG-20-1625 W18.1842258.D - Childrens Hosp. Wd 3B, Staff Kitchen Water Line, Pre, Pipework, Cold (972) - QEUH, RHC - 2018-04-11
SMG-20-1629 W18.1842257.R - Childrens Hosp. Wd 3B, GW2-003, Staff Kitchen Drinks Fountain, Pre, Fountain, Cold (971) - QEUH, RHC - 2018-04-11
SMG-20-1620 W18.1842260.V - Childrens Hosp. Wd 3B, Staff Kitchen Drinks Fountain, Post, Fountain , Cold (974) - QEUH, RHC - 2018-04-11
SMG-20-1646 W19.1842553.F - Basement Tank Childrens, Bulk CWST 2A (3325) - QEUH, KID - 2019-05-21
SMG-20-1939 M20.5512677.V - Human - [redacted] - Bone Marrow Transplant, QEUH - 2020-06-18
SMG-20-1910 M17.5509066.M - Human - [redacted] - RHC Wd 2A - 2017-04-22
SMG-20-1932 M19.5518875.A - Human - [redacted] - Wd 6A, RHC, QEUH - 2019-08-03
SMG-20-1936 M19.5504964.P - Human - [redacted] - Wd 8C, QEUH - 2019-02-24
SMG-20-1935 M19.5512526.J - Human - [redacted] - Wd 6A Day Unit, RHC, QEUH - 2019-05-20
SMG-20-1688 W20.1844383.Y - DMA Water Treatment - Potable Water - RAH - 2020-07-08
SMG-20-1908 M18.5507975.G - Human - [redacted] - RHC Wd 2B - 2018-04-03
SMG-20-1957 M19.5508310.H - Human - [redacted] - Bone Marrow Transplant, QEUH - 2019-04-03
SMG-20-1927 M17.5516311.N - Human - [redacted] - RHC Wd 2A - 2017-07-24
SMG-20-1637 W18.1841939.H - Adults Hosp. Wd 5C, Bed 71 GENWC-034 Pre, Shower, Mixed (796) - QEUH, RCH - 2018-03-28
SMG-20-1613 W18.1841940.S - Adults Hosp. Wd 5C, Bed 71 GENW-034 Post, Shower, Mixed (797) - QEUH, RCH - 2018-03-28

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Ward moves

Adult haematology (South):

- Moved from Ward 24 SGH to Ward 4C QEUH between 1-3 May 2015

Adult BMT:

- Moved from Beatson B8/9 to Ward 4B QEUH on 6 June 2015
- Moved from Ward 4B QEUH to Beatson B8/9 on 8 July 2015
- Moved from Beatson B8/9 to QEUH 4B on 30 June 2018

Paediatric haematology and oncology

- Moved from Yorkhill Schiehallion/DCU to RHC Wards 2A & 2B on 10 June 2015
- Moved from RHC Wards 2A (inpatients) & 2B (day care) to QEUH Wards 4B (paediatric BMT patients) and 6A (inpatients and day care) on 26 September 2018
- Moved from QEUH 6A to RHC CDU on 22 Jan 2019 (the move to CDU was for the 6A inpatients – day care attendance for 6A patients took place in RHC 1A during this decant period)
- Moved from RHC CDU to QEUH 6A on 11 Feb 2019
- Moved from QEUH 6A and 4B to RHC 2A & 2B on 9 March 2022

MALDI

It was May 2012 when the labs moved to using MALDI for identification of organisms on blood cultures.

SCOTTISH HOSPITALS INQUIRY

Bundle of documents for Oral hearings commencing from 19 August 2025 in relation to the Queen Elizabeth University Hospital and the Royal Hospital for Children, Glasgow

Bundle 44 – Documents in respect of NHS GGC - Expert Report by Prof Peter Hawkey, Dr Samir Agrawal and Dr Lydia Drumright - The evidence of risk of infection from water and ventilation systems at QEUH and RHC - 24 July 2024 ("HAD Report")

Volume 1

A52317814