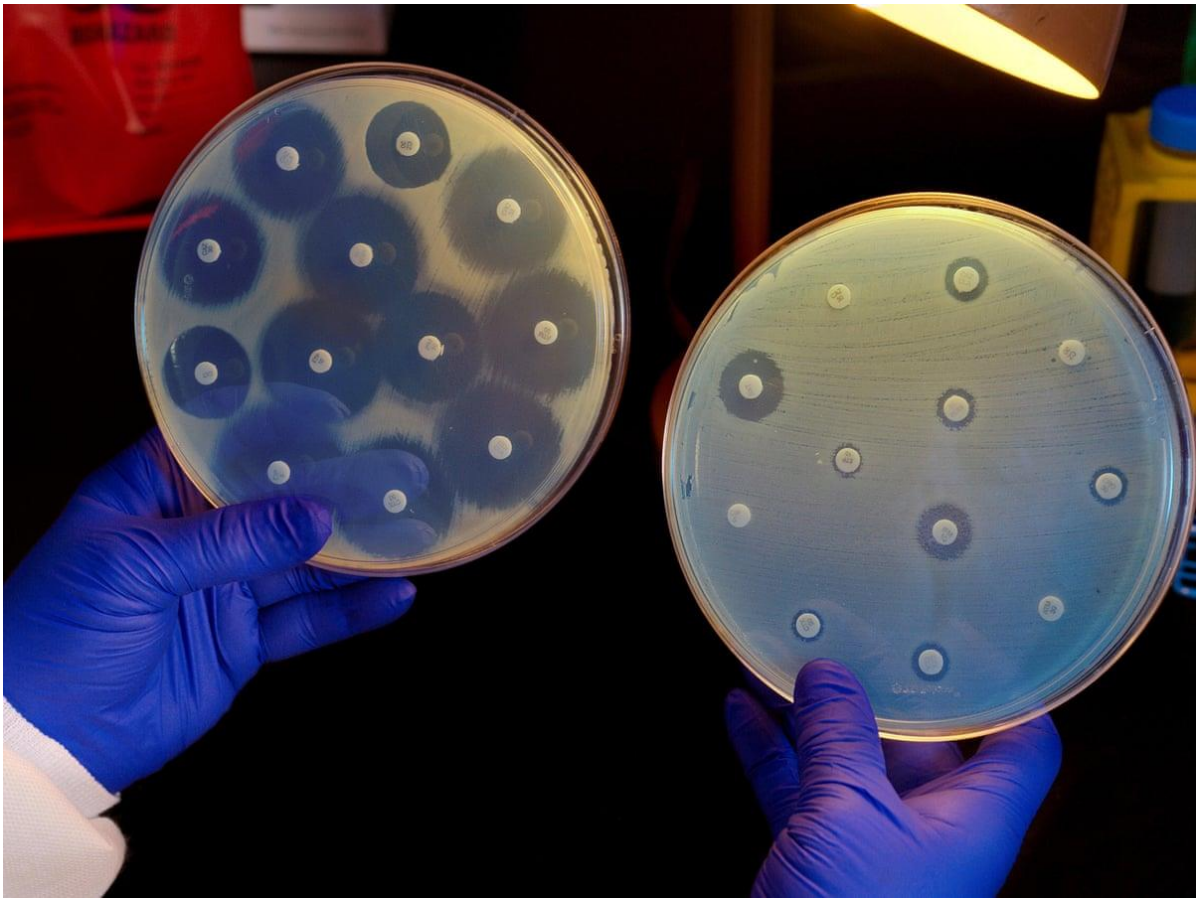
Evaluating the use of meropenem in hematologic patients with febrile neutropenia admitted to Meander Medical Centre

A retrospective observational single-cohort study



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Abstract

Objective

The Antibiotic Stewardship Team of Meander Medical Centre (MC) instigated a revaluation of its treatment protocol for hematologic patients admitted with febrile neutropenia. Current guidelines advise treating with meropenem for 72 hours, following therapy streamlining guided by microbiological cultures. In order to identify responsible adjustments to the current empiric meropenem regimen, this study aimed to determine the frequency of microorganisms resistant to alternative antibiotics, namely ceftazidime and piperacillin/tazobactam, in both prophylactic and diagnostic cultures.

Study design

This retrospective, observational, single-centre study used a single cohort design and included adult patients with a hematologic malignancy and febrile neutropenia admitted between October 2018 and June 2022. Collected metadata included patient characteristics such as age and BMI, microbiologic cultures, and antibiotic treatments.

Results

A total of 100 patients were recruited. One or more microorganisms resistant to ceftazidime or piperacillin/tazobactam were identified in blood and urine cultures in ten (10%) and four (4%) patients respectively. Empiric treatment with meropenem lasted longer than 72 hours as described in the protocol in 35 patients, and longer than 96 hours in 20 patients. In addition to identification of a microorganism indicating use of meropenem, persistent and reoccurring fever was noted as an argument for continued treatment.

Recommendations

Meander MC can reduce the use of meropenem by changing the empiric treatment protocol for patients with febrile neutropenia. As this study showed a lower resistance frequency to piperacillin/tazobactam, this antibiotic is the recommend alternative. Furthermore, increased awareness of when to discontinue empiric meropenem amongst the hospital's haematologists would lead to further reduction in their use of this broad-spectrum reserve antibiotic.

Keywords: *Antibiotic stewardship; antibiotic resistance; meropenem; carbapenems; febrile neutropenia*

Introduction

Patients with malignant hematologic diseases or those who have undergone haematopoietic stem cell transplantation (HSCT) have weakened immune systems as a result of their primary diagnosis and treatment[1]. Treatment can induce periods of neutropenia, during which absolute neutrophil count (ANC) decreases to <500 cells/µL[2,3]. Consequently, patients are at greater risk of infections, which often occur in this population[4]. In patients with chemo-induced neutropenia the prevalence of febrile neutropenia can rise to 80%[4]. It is a dangerous complication which can be lethal in up to 50% of patients depending on its severity and treatment with antibiotics is indicated[3,4].

Antibiotic use (AMU) or overuse, are one of the main factors constituting to antibiotic resistance (AMR), which is an increasingly concerning threat to global health[1,5,6]. Reducing antibiotic prescriptions can decrease the speed at which resistance develops[5]. The increase in the prevalence of extended-spectrum β-lactamase (ESBL)- and carbapenemase producing Enterobacteriaceae (CPE) is of specific concern[6,7]. Infections caused by these bacteria have limited alternative treatment options, which leads to an increased risk of mortality[1,6].

Meropenem is an ultra broad-spectrum antibiotic belonging to the β-lactam class, that is used to treat febrile neutropenia[8,9]. Empiric meropenem use reduces mortality risk in patients with infections caused by ESBL-producing microorganisms and other multidrug resistant (MDR) gram-negative bacteria[2]. However, meropenem use is associated with increased risk of clostridium infections and candidemia, as well as increased risk of acute graft-versus-host disease in patients undergoing allogeneic HSCT[10-15]. For these reasons, as well as for promoting antibiotic stewardship, the Dutch Working Party on Antibiotic Policy (SWAB) have labelled use of carbapenems, including meropenem, as a secondary treatment option[16].

Nationally recommended primary choice of antimicrobial therapy is dependent on a pre-emptive risk stratification based upon expected duration of neutropenia (≤7 days vs. >7 days)[16]. In high-risk neutropenic patients antipseudomonal β-lactams such as ceftazidime and piperacillin/tazobactam are the preferred choice of antibiotic therapy[16]. Low-risk neutropenic patients (expected short duration of neutropenia with low risk of complications) can be treated with oral antibiotics. Prior colonisation or infection with MDR pathogens (e.g., ESBL-producing Enterobacteriales) is the most important risk factor for recurrent infection with these pathogens[17,18]. In these cases, an alternative choice of therapy should be sought to avoid drug resistance.

Current guidelines in Meander MC advise treatment of febrile neutropenia with meropenem for at least 72 hours[9]. This practice, and lack of risk stratification, constitutes to high meropenem use compared to other Dutch hospitals[19]. Both ceftazidime and piperacillin/tazobactam are viable alternatives to meropenem[16]. However, as no data is available on local resistance patterns for either antibiotic in a Dutch setting, making unguided changes to the treatment protocol can be challenging in this vulnerable patient population.

This study aims to determine the frequency of bacteria resistant to either proposed first-choice treatment alternatives in prophylactic, blood and urine cultures in patients admitted with febrile neutropenia to Meander MC. By doing so, it can provide insight into the appropriateness of meropenem usage and possibilities for responsible adjustments to current febrile neutropenia treatment protocol.

Methods

Study design and population

A retrospective, observational, single-centre study was carried out at Meander MC - a teaching hospital in the Netherlands, using a single cohort design of adult patients admitted with febrile neutropenia between October 2018 and June 2021. Inclusion criteria were defined as: a) patients with a neutropenic episode, and b) primary diagnosis of a hematologic malignancy in the electronic patient file. Patients were excluded when they a) did not have a fever and neutropenia simultaneously; b) were below 18 years old at admission; c) had a documented meropenem allergy; d) had previously been included with a more recent admission; or e) the file concerned a test file.

Outcomes

Primary outcomes were ceftazidime and/or piperacillin/tazobactam resistant microorganisms in recent surveillance cultures and diagnostic blood and urine cultures taken on admission for febrile neutropenia. Surveillance cultures were only available for patients using selective digestive decontamination (SDD) as antibiotic prophylaxis.

Definitions

Primary diagnoses consisted of Acute Myeloid Leukemia (AML), Acute Lymphatic Leukemia (ALL) , Chronic Myeloid Leukemia (CML), Chronic Lymphatic Leukemia (CLL), Non-Hodgkin Lymphomas (NHL, all grades), Waldenström, Hairy Cell Leukemia (HCL), Multiple Myeloma (MM), myelofibrosis, Myelodysplastic Syndrome (MDS) or Refractory Anemia with Excess Blasts (RAEB). Fever was defined as a single temperature measurement of ≥38.5 C°[16]. In accordance with local treatment guidelines for neutropenic patients antibiotic prophylaxis consisted of one or more of the following groups: ciprofloxacin and/or fluconazole, cotrimoxazole and/or colistin, cefazolin or clindamycin[9]. Prophylactic antibiotics not belonging to these groups were specified as ''other''. Inventarisation cultures were taken from throat, rectum, or feces[9]. Only the most recent inventarisation culture taken before occurrence of fever and the first diagnostic blood and urine samples taken after occurrence of fever were included in the results. Two other relevant diagnostic cultures, namely a line tip and wound culture, were also included in data collection as their results were the base of treatment evaluation. Data on antibiotic resistance was collected for meropenem, ceftazidime, vancomycin, piperacillin/tazobactam, gentamicin, and other[16].

Data collection and ethics

Data was collected from electronic health records (EasyCare Healthcare, Deventer, The Netherlands), which was then coded and stored in Castor Electronic Data Capture (Ciwit BV, Amsterdam, the Netherlands). Duration of treatment was calculated based on information entered into the e-prescription system Zamicom (HI-System, Oosterhout, the Netherlands). Collection was carried out in accordance with the Dutch Medical Treatment Contracts Act (WGBO). The study was approved by the scientific research committee of the hospital.

Statistical analyses

Data was analyzed using SPSS (version 24). Categorical variables were reported as frequencies and percentages, for both overall patient population as well as specific subcategories, when applicable. Continuous variables were defined as mean and standard deviation when normally distributed, or as a median and interquartile range when they were not.

Although meropenem has an ultra-broad-spectrum coverage, it does not treat infections caused by some gram-positive cocci such as S. *epidermis* and E. *faecalis*[20]. With the exception of E. *faecalis*, which is sensitive to piperacillin/tazobactam, the aforementioned microorganisms show up as resistant to both meropenem as well as either of the alternatives[20]. When these gram-positive cocci are either suspected or found, they are treated with different antibiotics such as vancomycin[16]. To avoid reporting results biased as a higher resistance frequency, microorganisms are displayed separately based on their resistance status to meropenem.

Results

Population demographics

A total of 236 patients were admitted with febrile neutropenia between October 2018 and June 2021, of which 100 (58 male, 42 female) were included in this study (**Figure 1**) according to the inclusion criteria. The median age was 65.0 (54.0-73.8) years, median BMI was 24.95 (22.3-29.4) kg/m^2 and median duration of hospital admission was 21.5 (9.3-31.0) days. Additional population demographics are shown in **Table 1**.

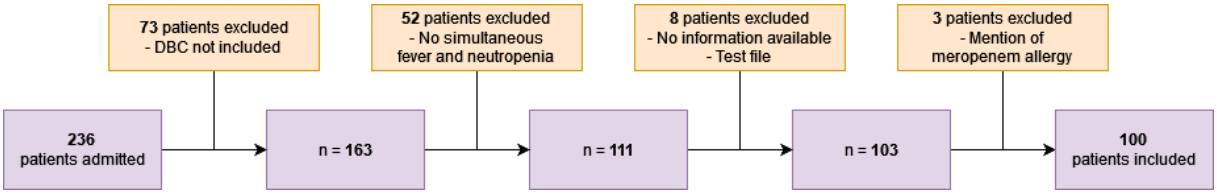

Figure 1 *– Patient enrolment.*

Microbiological cultures and resistance data

Prophylactic cultures

Out of 61 patients who had taken prophylactics, SDD cultures were available for 51, of which ten were positive for one or more bacteria (**Figure 2**). Resistance to ceftazidime was found in 4/61 (6.6%) patients. Since the hospital does not include piperacillin/tazobactam in their antibiograms when H. *parainfluenzae* is found, resistance to piperacillin/tazobactam could not be further specified beyond its occurrence in 3-5/61 (4.9-8.2%) patients.

Diagnostic cultures

Blood and urine cultures were taken in 100 and 62 patients respectively (**Figure 3**). Overall, resistance in either or both blood and urine cultures to ceftazidime was found in ten (10%) patients and to piperacillin/tazobactam in four (4%) patients.

Resistance to ceftazidime was found in blood cultures of eight (8%/8%) and urine cultures of two (2%/3.2%) patients. Resistance frequencies were lower for piperacillin/tazobactam, being confirmed in one (1%/1%) blood culture and three (3%/4.8%) urine cultures. The line tip and wound culture showed resistance to ceftazidime in one (1%) patient and none to piperacillin/tazobactam.

Overall, SSD cultures showing ceftazidime or piperacillin/tazobactam resistance were not predictive of diagnostic culture results. Of five patients carrying a microorganism of interest, one returned a positive diagnostic culture. However, the SDD and diagnostic cultures differed in the microorganisms present.

Table 1 *– Population demographics and characteristics (n = 100)*

Variable	**Frequency (%) / Relative frequency (%)**
Age (years)	
<60 years	35 (35)
≥60 years	65 (65)
Gender	
Male	58 (58)
Female	42 (42)
Primary diagnosis	
AML	38 (38)
NHL	31 (31)
MM	11 (11)
CLL/HCL	9 (9)
MDS	4 (4)
ALL	4 (4)
RAEB	1 (1)
CML	1 (1)
Myelofibrosis	1 (1)
BMI (kg/m^2)	
Unknown	2 (2)
<25	52 (52)
25-30	23 (23)
>30	23 (23)
Vital status	
Alive	86 (86)
Death ≤30 days after admission	10 (10)
Death during admission	4 (4)
Prophylactic antibiotics (n = 100 / n = 61)	
None	39 (39)
Ciprofloxacin and/or fluconazole	51 (51) / 51 (83.6)
Cotrimoxazole and/or colistin	12 (12) / 12 (19.6)
Cefazoline or clindamycin	28 (28) / 28 (45.9)
Other	12 (12) / 12 (19.6)
Lines (n = 100 / n = 45)	
None	55 (55)
Central	44 (44) / 44 (97.8)
Peripheral	1 (1) / 1 (2.2)
Duration of hospital admission	
<7 days	25 (25)
≥7 days	75 (75)
Readmission ≤ 3 months	
No	73 (73)
Yes	27 (27)

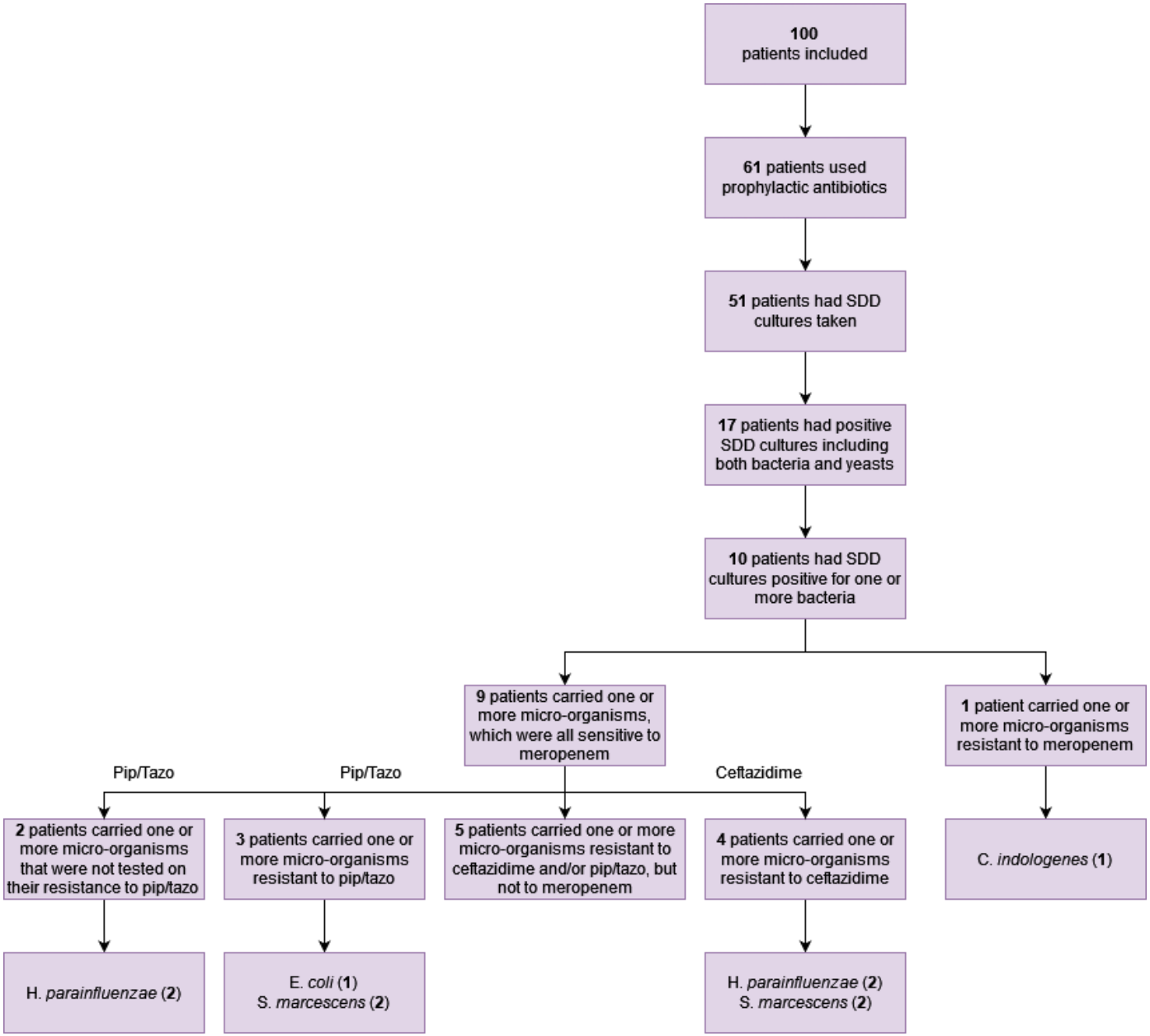

Figure 2 *– Microbiologic data on prophylactic (SDD) cultures (throat/rectum/faces). Only the most recent cultures available before diagnosis of febrile neutropenia are included.*

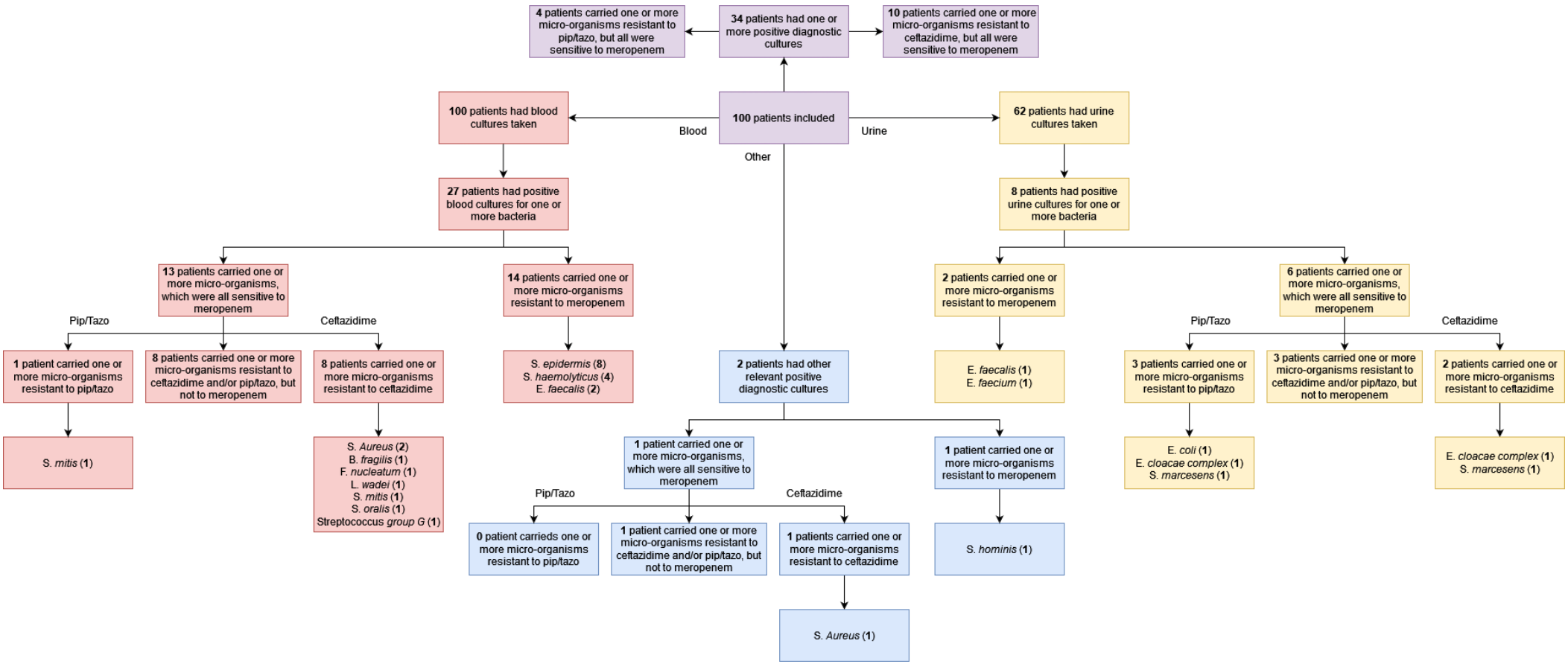

Figure 3 *– Microbiologic data on diagnostic cultures (blood/urine/other). Other; a line tip and wound culture. Only the first cultures taken after diagnosis of febrile neutropenia are included.*

Antibiotic treatment

Empiric meropenem was started for 91 patients developing febrile neutropenia, with 12 (13.2%) patients receiving additional antibiotics to broaden their coverage (**Table 2**). Of the remaining patients not receiving meropenem initially, four were switched to meropenem within ten hours of starting antibiotics following neutropenia diagnosis. Definitive therapy consisted of a wide array of antibiotics but is summarized in only a few categories in **Table 2** as this study focuses on empiric treatment. Median duration of empiric therapy was 65.5 (50.3-90.0) hours and total antibiotic treatment took an estimated 125 (67.2-202.3) hours.

Table 2 *– Antibiotic treatment data (n=100)*

Variable	**Frequency (%) / Relative frequency (%)**
Empiric treatment	
Meropenem	79 (79)
Meropenem and vancomycin	10 (10)
Meropenem and azithromycin	1 (1)
Meropenem and cotrimoxazole	1 (1)
Amoxicillin/clavulanate	2 (2)
Ceftriaxone	2 (2)
Flucloxacillin	2 (2)
Cefuroxime and gentamicin	1 (1)
Levofloxacin	1 (1)
Vancomycin and piperacillin/tazobactam	1 (1)
Empiric treatment duration	
<72 hours	62 (62)
72-96 hours	16 (16)
≥96 hours	22 (22)
Definitive therapy (n = 100 / n = 44)	
No antibiotics	54
Meropenem	2 (2) / 2 (4.3)
Meropenem and vancomycin	8 (8) / 8 (17.4)
Meropenem and other	7 (7) / 7 (15.2)
Other	29 (29) / 29 (63.0)
Total treatment duration	
<168 hours	64 (64)
≥168 hours	36 (36)

Analysis of the patient files showed that for 35 (38.5%) patients empiric meropenem treatment lasted longer than the recommended 72 hours. These patient files were re-analysed to determine the reasons for extended treatment beyond established protocols. For this analysis a cut-off of 96 rather than 72 hours was used to account for timestamp inaccuracies in patient files.

Meropenem was continued empirically for ≥96 hours in 20 (22.0%) patients. Valid arguments for extended treatment were identification of microorganisms indicating use of meropenem in diagnostic cultures, or when a medical microbiologist was consulted (**Table 3**). Invalid reasons included persistent or reoccurring fevers, awaiting cultures for ≥72 hours, when a patient had recovered from neutropenia, or when diagnostic cultures were not used to further streamline antibiotic therapy. **Table 3** displays all cases in which an invalid reason was mentioned as an argument, even when extending therapy was deemed valid overall.

Table 3 *– Treatment length of empiric meropenem (n = 100 / n = 20)*

Variable	Frequency (%) / Relative frequency (%)
Empiric meropenem treatment ≥96 hours	
For valid reasons	12 (12%) / 12 (60%)
For invalid reasons	8 (8%) / 8 (40%)
Invalid arguments used for continued treatment	
Persistent or reoccurring fever	9 (9%) / 9 (45%)
Awaiting blood cultures ≥72 hours	4 (4%) / 4 (20%)
Recovered neutropenia	3 (3%) / 3 (15%)
Not adjusting guided by cultures	3 (3%) / 3 (15%)

Discussion

Recommendations

The aim of this study was to determine the frequency of microorganisms resistant to either ceftazidime or piperacillin/tazobactam in hematologic patients admitted to Meander MC with febrile neutropenia. Retrospective analysis of blood and urine cultures showed a resistance frequency of 10% to ceftazidime and 4% to piperacillin/tazobactam, suggesting piperacillin/tazobactam is the preferred alternative to meropenem.

However, a risk/benefit evaluation on whether this alternative should be implemented is still needed. Benefits of advising meropenem as a secondary choice are decreased risk of development of meropenem resistance, as well as lower risk of clostridium and candidemia[5,10-14]. The main concern is a possible increased mortality risk in in patients who are infected with piperacillin/tazobactam resistant microorganisms[2]. Careful consideration regarding the implementation of this alternative treatment strategy is needed to minimise these risks.

An approach to reduce mortality risk due to undertreatment is to act on diagnostic culture results quickly. Microorganisms belonging to the ampC group, such as S. *marcescens*, C. *freundii* and E. *cloacae* complex, have been shown to develop resistance quickly to antibiotic therapies[25]. As blood cultures typically require ≤24 hours to return a positive result, switching from empiric therapy with meropenem to an alternative therapy could be done immediately, as resistance would be expected to develop[21-24]. This is already common practice in Meander MC and means that patients would only be exposed to this greater risk for 24 hours, rather than 72.

Results also showed empiric treatment with meropenem lasted longer than the 72 hours recommended by the treatment protocol in 35 patients, and was continued for ≥96 hours in 20 patients. Re-analysis revealed that empiric therapy was extended for a variety of reasons. As discussed below, this study sorts the stated reasons for extended treatment into “valid” and “invalid” categories using expert opinion supported by existing literature(**Table 3**).

Probability of bacteraemia is low when blood cultures remain negative for 24 hours, reinforcing that it is not necessary to await cultures for ≥72 hours[21,22]. Additionally, national guidelines advise discontinuation of empiric therapy after 48 hours when cultures are negative and fever is resolved[16].

If cultures remain negative but fever persists in a clinically stable patient discontinuation should be considered and treatment should be reverted to prophylaxis when applicable[16,26]. *Alegria et al.* found that short-term antibiotic treatment (≤7 days) did not lead to worse patient outcomes, even if patients remained febrile[27]. A questionnaire conducted by *Jara et al.* in 11 Dutch hospitals concerning their empiric treatment protocol for febrile neutropenia showed that treatment duration differed from 48 hours to 9 days, but was not dependent on a patient becoming afebrile[28]. We suggest that mainly persistent or reoccurring fevers alone are not valid reasons to continue empiric treatment.
Prompt adjustment of initial therapy when a causative microorganism is identified is also advised [1,16,29]. In patients with recovered ANC empiric treatment can be discontinued safely after absence of fever for two days[30]. Recovery of neutropenia also means these patients fall beyond the scope of the revaluated treatment protocol, and appropriate adjustments should be made individually. These results highlight the importance of following existing treatment guidelines, especially when continuing empiric meropenem treatment due to persistent or reoccurring fevers.

Strengths and limitations
This study provides data from a large sample readily applicable in the hospital's clinical practice. However, a prospective follow-up study comparing clinical outcomes before and after the suggested treatment adjustments can strengthen the recommendations made. These outcomes should involve both mortality risk as well as resistance patterns at a minimum to confirm the expected benefits, including antibiotic stewardship, without impairing clinical outcomes.
Patient characteristics available at admission, such as age, BMI, and recent hospital admissions, might hold predictive value and allow for more precise risk-stratification[1,2]. Inclusion of prospectively validated Multinational Association of Supportive Care in Cancer (MASCC)-scores or other alternatives would allow for more accurate assessments, thus further guiding clinicians to most appropriate antibiotic therapy[16,31].

A prospective study would also reduce inherent drawbacks of this retrospective study, such as data availability. It was not always possible to determine whether and which antibiotics had been administered due to conflicting or missing data. Furthermore, it could not always be ascertained if results of surveillance cultures were already available as treatment commenced. This limitation can be improved by gathering prospective data on when surveillance culture results are available and how they factor into treatment decisions. However, impact of this limitation on this study seems minimal since prophylactic cultures did not seem to hold any predictive value for diagnostic culture outcomes. Additionally, surveillance cultures and clinical outcomes might also not be correlated, further reducing influence of limited data availability[32].

Despite lack of external validation, it provides a practicable study design for other centres to evaluate their own broad-spectrum antibiotic use. Changes to treatment guidelines based on local resistance patterns can improve antibiotic stewardship while simultaneously ensuring patient safety. Both changing the empiric protocol for febrile neutropenia as well as being more critical of when to extend and discontinue empiric therapy with meropenem are ways for Meander MC to reduce their use of meropenem.

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