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ORIGINAL RESEARCH

Which Type of Empiric Antibiotic Therapy is Appropriate? A 20-Year Retrospective Study of Bloodstream Infections in Childhood Cancer

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ABSTRACT

Introduction: Sufficient empirical antimicrobial therapy in febrile patients with cancer is challenging, owing to the limited arsenal of available antibiotics in an era of growing resistance. Because of the emergence of gram-negative bacteria resistant to ceftazidime and piperacillin, a combination antibiotic therapy was employed that uses meropenem combined with gentamicin and/or vancomycin if the patient further deteriorates.

Methods: A retrospective cohort analysis was performed including all patients with catheter-associated bloodstream infections (BSIs) and treated for childhood cancer in a tertiary single centre between 1 January 2000 and 31 June 2018. We calculated the prevalence and the risk for BSIs and compared the in vitro susceptibility to various antimicrobial agents.

Results: Of 653 patients with childhood cancer, 113 patients (17.3%) were identified with a total of 139 BSIs, most of them occurring in patients with leukaemia ($n = 90$, 64.7%) and were associated with gram-positive bacteria (60.5%). In our cohort, all BSIs with gram-negative bacteria exhibited in vitro susceptibility against meropenem alone without any signs of resistance development. The antibiotic coverage of our meropenem-based combination therapy was also highly effective for gram-positive and non-fermenting bacteria. Thus, BSI-related mortality in all 139 BSI episodes was 1.4%. *Clostridium difficile* infections (CDIs), as main adverse event of carbapenem usage, occurred in only 16 (2.5%) patients.

Conclusion: Our meropenem-based combination therapy showed sufficient empirical antibiotic coverage in the majority of BSIs (96.4%) and did not result in an increased rate of unwanted side effects or development of antibiotic resistance.

Keywords: Antibiotics; Bloodstream infections; Childhood cancer; Susceptibility

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Key Summary Points

Why carry out this study?

Bacterial bloodstream infections (BSIs) represent the most frequent and life-threatening adverse events, accounting for more than 60% of treatment-related mortalities in patients with leukaemia.

Whether or not initial empiric therapy should be given across a very broad spectrum is highly controversial.

What was learned from the study?

Empiric meropenem-based combination therapy in febrile patients with childhood cancer was safe and showed sufficient antibiotic coverage.

Twenty-year long-term usage of meropenem in our single-centre study is not associated with resistance development and unwanted side effects.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14113382.

INTRODUCTION

Intensified cytotoxic chemotherapy combined with improved supportive care has largely been successful in the treatment of childhood cancer during the last decades [1, 2]. Whereas the vast majority of patients can be cured, some patients suffer from severe and potentially preventable complications. Among these, bacterial bloodstream infections (BSIs) represent the most frequent and life-threatening adverse events, accounting for more than 60% of treatment-related mortalities (TRM), as documented in several contemporary acute lymphoblastic leukaemia (ALL)/acute myeloid leukaemia (AML) trials [3–5]. While several risk factors, including diagnosis, coexisting Down syndrome, type of indwelling catheter and neutropenia, have clearly been identified [3, 6, 7], there is an ongoing conceptual debate on how to empirically treat the presumptive pathogen. The increasing rate of antibiotic resistance, the prevalence of *Clostridium difficile* infections (CDIs) and the potential antibiotic-related toxicities provide the rationale for a monotherapy, whereas the combination of antibiotics increases the likelihood of adequate coverage until the results of in vitro susceptibility testing for the isolated bacteria are available [8–11]. The selection of an initial empirical antibiotic therapy is definitely essential, as delayed onset is strongly associated with increased mortality [12–16]. This is also highlighted by several recently published cohort studies indicating that monotherapy for BSIs is associated with insufficient empirical antibiotic coverage and decreased survival [13, 17, 18].

As a result of the characteristics of the local epidemiology at our centre, the emergence of extended-spectrum beta-lactamase-producing (ESBL) Enterobacteriaceae [19] led us to initiate in 2000 a standardized approach using a meropenem-based broad-spectrum combination therapy that has remained unchanged until today. The objective of this study was to descriptively report our long-term experience with empiric meropenem-based combination therapy in febrile patients with childhood cancer regarding antibiotic coverage, tolerance and particularly development of antimicrobial resistance.

METHODS

Compliance with Ethics Guidelines

The Ethics Committee of the Medical University of Innsbruck approved retrospective evaluation (EC No. 1301/2020) and also waived the need for patient consent because of its retrospective nature. All data were obtained from medical records. This study was performed in accordance with the declaration of Helsinki.

Patients and Data Collection

All oncologic paediatric and adolescent patients below age 18 years, who were treated at our centre between January 2000 and June 2018 and who needed a long-term central venous access device (CVAD), were retrospectively analysed in the study. The date of the last follow-up was 31 December 2019. The medical records of 856 patients were screened; 58 patients were lost to follow-up and further 252 oncology patients were treated without CVAD insertion. The remaining 546 patients were included and in 107 of these patients a relapse of the underlying malignancy was diagnosed. Thus, 653 treatment episodes were analysed (Fig. S1 in the supplementary material). For the major group of patients with ALL and AML, further details of the chemotherapy regimens were previously described [2]. Data in electronic records were analysed and included baseline demographic information, baseline pathology, type and duration of CVAD use, microbiological diagnostic and therapeutic treatment as well as complications and side effects. Catheter-related BSIs were defined as clinical manifestations of infection with signs of sepsis and that the same organism grows from at least two quantitative blood cultures obtained through two different catheter lumens [20].

Microbiology

Species identification and susceptibility testing were performed at the Institute for Hygiene and Medical Microbiology of Innsbruck Medical University. Antimicrobial susceptibility testing was performed according to NCCLS/CLSI guidelines until 2011 [21]. In 2011, Austrian microbiological laboratories switched their methodology to EUCAST (Breakpoint tables for interpretation of MICs and zone diameters—2011–2019, Versions 1.3 to 9.0). Strains were classified as susceptible or resistant according to the breakpoints applied in the year of their isolation. Thus, 139 BSIs were identified with a total of 162 pathogens (in 20 cases polymicrobial infections occurred). For antibiotic coverage analysis antibiograms of 152 pathogens were included. The in vitro susceptibility to meropenem and the other recommended monotherapy options (piperacillin/tazobactam, ceftazidime or cefepime) were compared to evaluate antibiotic coverage and resistance development against meropenem.

Supportive Care and Pre-emptive Strategy

Supportive care guidance was detailed in institutional standardized protocols and universally included the use of *Pneumocystis jirovecii* pneumonia prophylaxis for all patients treated with chemotherapy. Since 2010, antifungal prophylaxis was restricted to high-risk patients in aplasia and mainly consisted of intravenously administered 3–5 mg/kg/dose liposomal amphotericin B three times a week. Further details on antifungal prophylaxis are described in a recent publication [2]. All patients with neutropenia (defined as an absolute neutrophilic count of less than 500/μL) and fever (defined as an increase in body temperature above 38.5 °C or a permanent increase for more than 15 min above 38.0 °C) were treated empirically with meropenem (20 mg/kg IV every 8 h) and gentamicin (5 mg/kg IV every 24 h). If signs of sepsis were present (defined as either the presence of tachycardia with heart rate above the 95th percentile and tachypnoea with respiratory rate above the 95th percentile or additionally the presence of hypotension with a systolic blood pressure of less than 80 mmHg and reduced capillary refill time of less than 3 s) and/or clinical deterioration, vancomycin (20 mg/kg IV every 12 h) was added within 24 h (37 cases; 26.6%). If fever persisted over 72 h, daily antifungal treatment was included. Further modification and/or discontinuation after 24 h was based on the patient's clinical course and adapted according to the results of susceptibility testing. Irrespective of the neutrophil count, de-escalation to sufficient antibiotics with narrowed spectrum was considered at availability of antibiograms and continued until full haematopoietic recovery.

Statistical Analysis

Descriptive statistics were performed for all variables of interest, giving medians and

interquartile ranges for quantitative variables, and absolute and relative frequencies for qualitative variables. The chi-squared test was used to test for associations between cancer type and frequency of BSI. To compare the antibiotic coverage between meropenem and the three other monotherapeutic options, the Mann–Whitney test was used. Data visualization analysis was performed using GraphPad Prism, version 8.4.

RESULTS

Patient Demographics and CVAD-Related Factors

The study cohort consisted of 546 patients with 653 treatment episodes, and 298 (45.6%) of the patients were female. Median age at inclusion was 7.14 years (IQ1 = 3.25 IQ3 = 13.30). In 107 (16.4%) patients a relapse of the underlying malignancy was diagnosed and 91 (13.9%) patients underwent haematopoietic stem cell transplantation (HSCT) (49 autologous, 41 allogenic, one both). The majority suffered from leukaemia (n = 269, 41.2%), soft tissue sarcoma (STS) (n = 129, 19.8%), lymphoma (n = 83, 12.7%) and central nervous system (CNS) tumours (n = 74, 11.3%). In total, 200,486 catheter days (CDs) were recorded with a median of 266 CDs per patient (range 6–2648). Overall, 145,753 (72.7%) CDs were documented in tunnelled CVADs, while 54,733 (27.3%) CDs were observed in totally implanted CVADs. In 113 (17.3%) patients, a total number of 139 BSIs were observed, most of them in patients with leukaemia (n = 90, 64.7%). Clinical characteristics and CVAD-related factors are listed in Table 1.

Antibiotic Coverage and Resistance Development

Patients with haematologic malignancies, in particular AML, exhibited more BSIs than patients with solid tumour (1.0–2.4/1000 CDs versus 0.1–0.7/1000 CDs; Table 1, p = 0.002). The most commonly isolated entity was coagulase-negative staphylococci (CoNS) (24.7%), followed by *Escherichia coli* (16.7%), *Streptococcus* spp. (16.7%), other Enterobacteriaceae (9.9%) and *Pseudomonas aeruginosa* (9.9%) (Table 2). To evaluate development of antimicrobial resistance, we compared each antibiotic from our meropenem-based combination therapy with the other three recommended monotherapy options either (i) piperacillin/tazobactam, (ii) ceftazidime or (iii) cefepime and summarized the pathogens as gram-negative, gram-positive or non-fermenting bacteria allocated to four time periods.

In cases of BSI with gram-positive bacteria meropenem showed similar antibiotic coverage as piperacillin/tazobactam and cefepime, whereas ceftazidime had poor gram-positive activity, as is already known (Fig. 1; $p < 0.05$). Despite our meropenem usage within the last 20 years, the frequency of meropenem-resistant BSI did not significantly change.

The majority of the isolated gram-negative bacteria would have been susceptible to piperacillin/tazobactam or ceftazidime (n = 38, 86.4%) or cefepime (n = 41, 93.2%); however, all BSIs with gram-negative bacteria exhibited in vitro susceptibility against meropenem alone (Fig. 1). Again, we did not observe resistance development to meropenem.

Non-fermenting bacteria, in particular *P. aeruginosa*, which are generally associated with high hospital mortality, were isolated in 11.8% of the BSI episodes (Table 2). Meropenem alone showed insufficient coverage in only four cases (21.1%; Fig. 1). Our approach of meropenem + gentamicin extended coverage to one additional BSI with non-fermenting bacteria. Resistance to one of the suggested agents for monotherapy occurred in two (piperacillin/tazobactam; 10.5%), four (ceftazidime; 21.1%) or three (cefepime; 15.8%) cases.

Outcome of Bacterial BSIs

In our cohort, two BSIs were causally related to a fatal outcome and both patients were infected with *P. aeruginosa*. Thus, BSI-related mortality in all 139 BSI episodes was 1.4%. Despite timely

Table 1 Clinical characteristics of patients with childhood cancer and CVAD-related factors

Malignancy	Number of patients	Relapse (%)	Median age, years	Tunnelled CVAD (%)[b]	Catheter days	Number of BSIs	Number of patients with at least one BSI	BSI per 1000 catheter days[c]
Leukaemia								
ALL	219	10.5	5.7	83.1	61,476	59	50	0.96
AML	48	27.1	9.5	97.9	13,221	31	19	2.34
CML + JMML	2	0	1.7	50	2279	0	0	0.00
Lymphoma								
Burkitt + NHL	44	4.5	9.8	61.4	8610	7	7	0.81
MB Hodgkin	39	25.6	14.7	25.6	7837	0	0	0.00
CNS tumour								
Astrocytoma	18	11.1	2.3	77.8	7917	0	0	0.00
Ependymoma	15	40	6.1	46.7	5444	3	3	0.55
Medulloblastoma	22	18.2	7.4	50	8043	2	2	0.25
Other CNS tumour	19	10.5	4.5	68.4	6746	0	0	0.00
STS								
Ewing sarcoma	39	23.1	13.6	71.8	15,736	11	8	0.70
Osteosarcoma	31	25.8	14.5	38.7	10,168	1	1	0.10
Rhabdomyosarcoma	27	18.5	6.3	81.5	7309	5	4	0.68
Other STS	32	15.6	9.7	53.1	12,958	5	5	0.39
Neuroblastoma	41	17.1	2.6	97.6	13,416	7	7	0.52
Wilms tumour	24	8.3	2.9	83.3	7344	1	1	0.14
Other tumours	33	27.3	4.2	72.7	11,982	7	6	0.58
Total	653	16.4	7.1[a]	72.7	200,486	139	113	0.69

ALL acute lymphoblastic leukaemia, *AML* acute myeloblastic leukaemia, *CML* chronic myeloblastic leukaemia, *JMML* juvenile myelomonocytic leukaemia, *NHL* non-Hodgkin's lymphoma, *CNS* central nervous system, *STS* soft tissue sarcoma, *CVAD* central venous access devices, *BSI* bloodstream infection

[a] IQ1 = 3.3, IQ3 = 13.3

[b] Tunnelled CVADs (Broviac and Hickman), the remaining patients received totally implanted CVADs (Port-a-Cath)

[c] Patients with haematologic malignancies (leukaemia and lymphoma) exhibited more BSIs than patients with solid tumour (Pearson's chi-squared test, $p = 0.002$)

admission to the paediatric intensive care unit and in vitro susceptibility to first-line treatment with meropenem and gentamicin (resistant to vancomycin), one patient with AML died 5 days later from multiple organ failure and cerebral haemorrhage. The second fatal outcome occurred in a patient diagnosed with an atypical rhabdoid tumour, who underwent autologous HSCT 5 days before the BSI. A multidrug-resistant *P. aeruginosa* strain with combined

Table 2 Bacteria isolated in 139 episodes of CVAD-associated BSIs

Pathogens	Number*	%	Part of Polymicrobial bacteraemia
Gram-negative bacteria[a]			
Escherichia coli	27	16.7	3
Other Enterobacteriaceae	16	9.9	7
Other gram-negative bacteria	1	0.6	1
Gram-positive bacteria			
Coagulase-negative Staphylococci[b]	40	24.7	9
Streptococcus spp.[c]	27	16.7	9
Other gram-positive bacteria	13	8.0	7
Staphylococcus aureus[d]	12	7.4	3
Enterococcus spp.	6	3.7	4
Non-fermenting bacteria[e]			
Pseudomonas spp.	16	9.9	2
Other non-fermenting bacteria	3	1.9	1
Other			
Anaerobes	1	0.6	
Total	162	100	

*In 22 cases, polymicrobial bacteraemia occurred
[a] Include four ESBL-producing
[b] Include 29 methicillin-resistant
[c] Include four penicillin resistant
[d] Include one MRSA, e include three carbapenem resistant

resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides and additional resistance to carbapenems was isolated (Table S1 in the supplementary material, BSI isolate 14). This strain was not susceptible to our combination therapy or any of the monotherapy agents. Overall, neither gram-negative nor gram-positive bacteria have caused a fatal outcome in our cohort since 2000.

Prevalence of *C. difficile* Infections (CDIs)

In our cohort 16 (2.5%) patients had a mild episode of CDI within 30 days following antibiotic administration; the majority underwent treatment for leukaemia (56.3%; Table 3). Median time from diagnosis to onset of CDI was 57.5 days (IQ1 = 30 IQ3 = 137.5), so that 62.5% (10/16) of the CDIs occurred during the induction chemotherapy phase within the first 90 days after diagnosis (Table 3).

DISCUSSION

Our study, which was based on a retrospective analysis of standardized treatment of febrile patients with childhood cancer in a single tertiary centre, is the largest study with the longest observation period to have been conducted to date on in vitro susceptibility of bloodstream infections. Our findings show that broad-spectrum antimicrobial therapy with meropenem

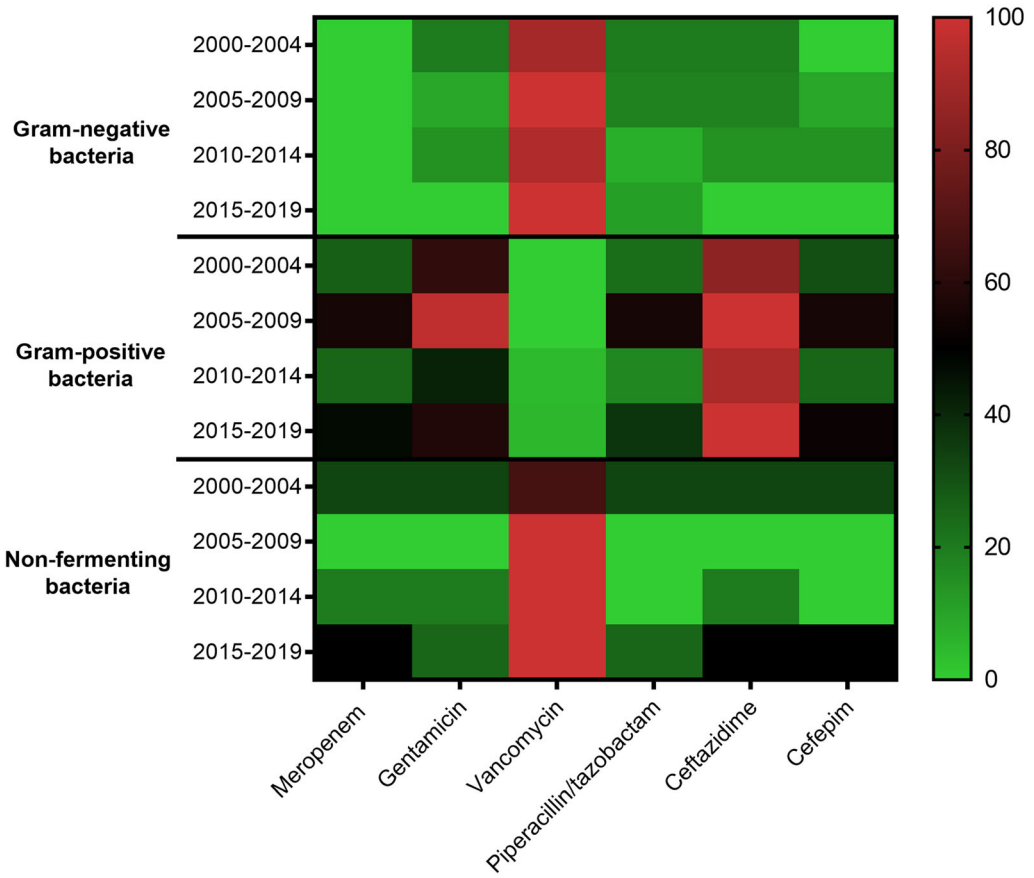

Fig. 1 In vitro susceptibility of bacteria isolated from BSIs. For 129 BSI episodes with a total of 152 pathogens the frequency of in vitro susceptibility of isolated bacteria is shown. Pathogens were summarized as gram-negative, gram-positive or non-fermenting bacteria and allocated to the four time periods. The frequency was calculated for each group of bacteria and time period separately by the proportion of resistance to susceptibly pathogens. Dark green indicates high frequency of susceptibility, whereas dark red shows high in vitro resistance

and in combination with gentamicin and vancomycin is sufficient as empirical pre-emptive therapy and is associated with low mortality and rare episodes of CDIs.

Whether or not initial empiric antibiotic therapy should be given across a very broad spectrum is highly controversial [10, 22, 23]. The biggest concern surrounding the escalation strategy, defined as the use of a monotherapy that covers most gram-negative bacteria and is mostly recommended by international societies [22, 23], is limited coverage for gram-positive bacteria (e.g. CoNS, streptococci), which are much more frequently identified in BSIs in patients with neutropenia [24, 25]. To be even more specific, only in the case of clinical deterioration or when a resistant pathogen is isolated is therapy escalated to a different antibiotic or combination with a broader spectrum, e.g. carbapenem plus an aminoglycoside. In contrast, a de-escalation therapy is defined as administration of a very broad initial empirical regimen to cover highly resistant pathogens such as ESBL-producing Enterobacteriaceae and/or multidrug-resistant *P. aeruginosa*. In this case the use of carbapenems (e.g. imipenem or meropenem) alone or in combination with aminoglycosides (e.g. gentamicin) is initiated. If a gram-positive infection is suspected or the patient deteriorates, a further agent against gram-positive cocci is added. Once microbiology results are available, the therapy is de-

Table 3 CDI in patients treated with antibiotics in the previous 30 days

Malignancy	Number of patients	Number of patients with CDI	CDI (% of patients)	CDI (% of all CDIs)	Diagnosis to onset of CDI (median days)
Leukaemia					
ALL	219	4	1.8	25.0	33
AML	48	5	10.4	31.3	140
CML + JMML	2	0	–	–	–
Lymphoma					
Burkitt + NHL	44	1	2.3	6.3	157
MB Hodgkin	39	0	–	–	–
CNS tumour					
Astrocytoma	18	0	–	–	–
Ependymoma	15	0	–	–	–
Medulloblastoma	22	0	–	–	–
Other CNS tumour	19	0	–	–	–
STS					
Ewing sarcoma	39	1	2.6	6.3	53
Osteosarcoma	31	0	–	–	–
Rhabdomyosarcoma	27	0	–	–	–
Other STS	32	1	3.1	6.3	40
Neuroblastoma	41	3	7.3	18.8	14
Wilms tumour	24	0	–	–	–
Other tumours	33	1	3.0	6.3	83
Total	653	16	2.5	100	57.5[a]

ALL acute lymphoblastic leukaemia, *AML* acute myeloblastic leukaemia, *CML* chronic myeloblastic leukaemia, *JMML* juvenile myelomonocytic leukaemia, *NHL* non-Hodgkin's lymphoma, *CNS* central nervous system, *STS* soft tissue sarcoma, *CDI Clostridium difficile* infections

[a] IQ1 = 30, IQ3 = 137.5, range (12–157)

escalated and continued until full neutrophil recovery. Although these approaches are well established in adult patients with cancer, particularly in those treated for severe sepsis in intensive care units [22, 26, 27], there are very few data on escalation strategy in paediatric patients with cancer and no data on de-escalation strategies can be identified.

Analysis of our local epidemiology before the year 2000 [19] indicated the emergence of certain gram-negative strains resistant to cefamandole, piperacillin or ceftazidime. Thus, after the year 2000 meropenem was used in combination with gentamicin and/or vancomycin if the patient further deteriorates. Antibiotic resistance in Enterobacteriaceae, in particular due to the production of

carbapenemases, is challenging on a worldwide scale as it is associated with increased mortality rates. However, combination therapy is linked to a protective effect on survival [13, 28]. Our 20-year experience with a meropenem-based combination therapy approach provides comprehensive data on antibiotic management in a paediatric haematology setting. In our cohort, no patient died from a BSI with Enterobacteriaceae, and moreover, we did not observe any carbapenem-resistant Enterobacteriaceae throughout our 20 years of experience (Table S1 in the supplementary material).

The most recently published cohort analysis of 21,608 US patients with BSI indicated that approximately one out of five patients received a discordant empirical antibiotic therapy (in our cohort only 3.6%), which is associated with increased mortality [17]. The highest percentages of discordant empirical antibiotic therapy were noted in patients with bloodstream infections caused by *Enterococcus* spp. (OR 4.73) and *P. aeruginosa* (OR 3.08) [17]. For enterococci, our meropenem alone would not be sufficient; however, most of them would be covered with the expansion to vancomycin (Table S1 in the supplementary material). Therapy with meropenem had a similar efficacy in BSIs caused by *P. aeruginosa* as the other monotherapeutic options (Table S1 in the supplementary material). However, a lethal outcome associated with insufficient antibiotic coverage might have occurred in only one patient in our study cohort, who was infected with a multidrug-resistant strain of *P. aeruginosa*. In total, two BSIs were causally related to a fatal outcome, leading to a BSI-related mortality of only 1.4% in our cohort since 2000.

One last point applies to the carbapenems, as they are associated with the emergence of CDIs (including the rare event of a pseudomembranous colitis), for which the thoughtless use of carbapenems is viewed critically. Children with cancer have an increased risk for CDIs that is associated with age, the underlying malignancy, exposure to chemotherapy as well as supportive medications, for instance gastric acid blockers [29, 30]. However, the antibiotic treatment in the previous 30 days is the most important risk factor [29, 31]. Several meta-analyses and systematic reviews with mainly adult patients demonstrate this association [32, 33]. However, cohort studies conducted in exclusively patients with childhood cancer did not show the same association [29, 31]. Indeed, in our cohort study only 16 (2.5%) patients developed a CDI, most of them patients with leukaemia during the induction phase, whereby other factors such as chemotherapy and supportive medicine at least partially contributed to CDI.

This study has some limitations. The medical record of clinical signs of BSIs was recorded in a standardized manner but the hypothesis of the study and analysis of data were performed retrospectively. The main issue is that the comparison of antibiotic coverage between the recommended monotherapeutic options is only based on the in vitro susceptibility analysis of antibiograms and not a real-life response. An efficacy analysis of antibiotic coverage would need direct comparison of the different antibiotics and would be effected by many other patient-related factors. Moreover, our results reflect the situation in a tertiary single centre and the local epidemiology, and cannot be a general recommendation for empirical antibacterial therapy in other clinics.

CONCLUSIONS

With 200,468 catheter days (550 years) our cohort study is the largest single-centre study administering a standardized and unchanged treatment over 20 years. We demonstrate that careful use of meropenem alone and in combination is safe and not associated with further selection of resistance or unwanted side effects.

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Authorship Contributions. RC, GK and CLF designed the study. BH and CB collected the data. AM, MK and RC analysed the data. AM and RC wrote the manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

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Compliance with Ethics Guidelines. The Ethics Committee of the Medical University of Innsbruck approved the retrospective evaluation (EC No. 1301/2020). All data were obtained from medical records. This study was performed in accordance with the declaration of Helsinki. The IRB/ethics committee waived the need for patient consent because of its retrospective nature.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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