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RESEARCH

Characteristics and antimicrobial therapy of bloodstream infections in tumour patients with special reference to antibiotic stewardship

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Abstract

Bloodstream infections (BSI) are among the most frequent infections in tumour patients. We analysed 123 tumour patients (105 retrospective, 18 prospective) with BSI. The most common underlying tumour diseases were acute leukaemia/myelodysplastic syndrome (40%), followed by lymphomas (25%) and multiple myeloma (20%). BSI were more frequently caused by Gram-negative than Gram-positive bacteria (53% vs. 40%), including *Escherichia coli* (33%), coagulase-negative *Staphylococcus* spp. (14%), and *Pseudomonas aeruginosa* (10%). The median time to fever resolution was 3 days (range 1–30 days). Neither pathogen type, initial antibiotic treatment, nor key patient characteristics significantly affected fever resolution time. Non-susceptibility of the pathogen to empirical antibiotic treatment was linked to prolonged fever resolution (HR 0.53, 95%-CI 0.28-1.0, $p=0.04$). The severity of neutropenia on admission had a significant impact on 60-day survival (HR 2.95, 95%-CI 1.10–7.93, $p=0.03$). In contrast, such an effect on survival was not observed by the non-susceptibility of the pathogen to primary empirical antibiotic treatment (HR 2.12, 95%-CI 0.71–6.30, $p=0.18$). Non-adherence or questionable adherence to antibiotic stewardship (ABS) recommendations ($n=42$, 34%) correlated with delayed fever resolution (median 3 days vs. 4 days; $p=0.04$) and was more frequent in retrospectively than in prospectively recorded patients (38% vs. 11%, $p=0.03$). Gram-negative bacteria still predominate as BSI agents in tumour patients. Prospective evaluation of anti-infective management may enhance adherence to ABS recommendations.

Keywords Bloodstream infection · Tumour · Neutropenia · Survival · Defervescence · Antibiotic stewardship

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Introduction

Infections are one of the most frequent complications in tumour patients and continue to contribute significantly to morbidity and mortality, while neutropenia is among the most important risk factors (Maschmeyer and Rolston 2014; Flowers et al. 2013). Hereby, the risk of febrile neutropenia (FN) varies depending on the underlying tumour type, while patients with acute leukaemia have an FN risk of ≥80% (Mandell and Douglas 2015). This risk is significantly lower in patients with solid neoplasms (usually<20%) (Flowers et al. 2013).

Bloodstream infections (BSI) in tumour patients frequently (around 40%) occur as central venous line-associated or -related BSI (CLABSI/CRBSI) (Raad and Chaftari 2014; Zakhour et al. 2016). In addition, BSI can, for example, occur as a consequence of pneumonia and urogenital, gastrointestinal, or soft tissue infections.

BSI account for 15–20% of documented bacterial infections in tumour patients (Maschmeyer and Rolston 2014). The incidence ranges from 9 to 190/1000 patient-years depending on the underlying tumour disease, antineoplastic treatment, response status of the tumour, and the definition used (Trecarichi et al. 2015). Epidemiological studies have found a nearly comparable incidence of Gram-negative and Gram-positive bacteria in tumour patients with BSI in recent years, although the pathogen spectrum may vary besides the regional incidences, due to treatment and remission status (Teh et al. 2017; Ghosh et al. 2021). Infections caused by multiple drug resistance (MDR) pathogens require special attention, as they are often associated with increased morbidity and mortality (Perdikouri et al. 2019).

Mortality of BSI ranges between 12% and 40%, depending on the underlying disease, the presence of comorbidities and the microorganism detected. Gram-negative bacterial BSI are generally associated with a higher mortality than Gram-positive BSI (Trecarichi et al. 2015; Klastersky et al. 2007). Furthermore, there are differences in mortality between different pathogens. BSI caused by coagulase-negative staphylococci (CoNS) are associated with a relatively good prognosis (mortality approximately 4%). In contrast, methicillin-resistant *Staphylococcus aureus* (MRSA) BSI may show a mortality of > 40% (Mahajan et al. 2012; Gustinetti and Mikulska 2016).

In recent decades, a contrary development has been observed between the increase in antimicrobial resistance and the number of approved new effective antibiotics. Compared to infections with susceptible pathogens, infections caused by MDR pathogens may result in increased treatment failure and medical costs, including direct therapy costs and prolonged therapy duration (Friedman et al. 2016). Therefore, further optimisation of antibiotic therapy is a challenge in terms of both BSI prognosis and antibiotic stewardship (ABS) principles in the era of increasing antibiotic resistance.

There is still limited data on the adherence of antimicrobial management to ABS principles in tumour patients (Barlam et al. 2016; Pillinger et al. 2020). To gain more insights into the characteristics of BSI in tumour patients, we analysed 123 patients with BSI across different tumour types, with a particular focus on adherence to ABS guidelines.

Materials and methods

Study design

We analysed a total of 123 patients with tumours and BSI - defined as a combination of distinct clinical symptoms (e.g., fever, chills) and the presence of microorganisms in

Table 1 Characteristics of tumour patients with BSI. Medians (ranges) and numbers of patients (%) are shown. The difference from the total number of patients ($n = 123$) in a given group represents non-evaluable patients who were not included in the analysis

Parameter	$n = 123$
Age, years	
Median	69
Range	24–95
Gender, n (%)	
Male	69 (56%)
Female	54 (44%)
Underlying malignancy, n (%)	
Acute myeloid leukaemia	35 (29%)
MDS	9 (7%)
Acute lymphoblastic leukaemia	5 (4%)
Diffuse large B cell lymphoma	18 (15%)
T cell non-Hodgkin lymphoma	4 (3%)
Hodgkin lymphoma	3 (2%)
Other lymphoma types	6 (5%)
Multiple myeloma	24 (20%)
Solid neoplasms	16 (13%)
Other[a]	3 (2%)
ECOG PS at admission, n (%)	
ECOG PS 0–1	53 (43%)
ECOG PS 2–3	21 (17%)
Not documented	49 (40%)
Antineoplastic therapy, n (%)[b]	
Classical chemotherapy +/- targeted therapy or immunotherapy	93 (76%)
Only targeted therapy/immunotherapy	5 (4%)
None	25 (20%)
Remission status, n (%)[c]	
First diagnosis	41 (33%)
Stable disease	1 (1%)
Partial remission	9 (8%)
Complete remission	1 (1%)
Progression	41 (33%)
Not assessable[d]	30 (24%)
Co-morbidities, n (%)	
None	15 (12%)
Arterial hypertension	83 (67%)
Cardial	41 (33%)
COPD	5 (4%)
Respiratory (without COPD)	18 (15%)
Gastroenterological	25 (20%)
Renal insufficiency	15 (12%)
Urological	22 (18%)
Onset of symptoms (related to BSI), n (%)	
Inpatient	38 (31%)
Outpatient	85 (69%)
Time from symptom onset to first BC positivity, n (%)	
<2 days vs.	78 (63%)
≥2 days	43 (35%)
Year of BSI episode, n (%)	

Table 1 (continued)

Parameter	$n = 123$
2017–2019	86 (70%)
2020–2021	37 (30%)

[a]Thymoma (two patients), systemic mastocytosis (one patient), [b]antineoplastic therapy in the last 4 weeks before the BSI diagnosis, [c]remission status of the underlying malignancy at the time of BSI diagnosis, [d]e.g., criteria for remission status not clearly defined, shortly after diagnosis with imaging not performed yet

BC – blood culture, BSI – bloodstream infection, COPD – chronic obstructive pulmonary disease, ECOG PS – Eastern Cooperative Oncology Group performance status, MDS – myelodysplastic syndrome, n – number of patients

the blood culture (BC) (Mandell and Douglas 2015) - who were treated at the clinic for haematology and oncology at the Carl-Thiem Clinic (since July 2024 Medical University Lausitz – Carl Thiem, MUL – CT) in Cottbus, Germany (Table 1). Hereby, 105 (85%) patients were analysed retrospectively, and 18 (15%) patients were included from an ongoing prospective study.

Retrospective data collection covered patients who developed a BSI (bacteraemia or fungaemia) from January 2017 to June 2020, with inclusion based on documented pathogen detection and the presence of infection. The prospective cohort included tumour patients who developed a BSI between July 2020 and September 2021 and provided written informed consent. In the prospective cohort, particular emphasis was placed on adherence to current, evidence-based guidelines for the management of BSI (Heinz et al. 2017; Böll et al. 2021; Averbuch et al. 2013). Additionally, clinical staff received targeted training to enhance awareness and vigilance regarding BSI, aiming to optimise diagnostic accuracy and therapeutic outcomes. Aside from these enhancements, clinical procedures and data collection processes were conducted in accordance with established standard practices.

The primary objectives of this study were to study microbiological characteristics (e.g., spectrum of infectious agents, antimicrobial resistance profiles), laboratory characteristics (e.g., neutropenia, C-reactive protein (CRP) serum concentrations at different time points), and the sequence of anti-infectious agents and to investigate the time to fever resolution.

Secondary objectives included the survival - within the BSI episode and until the last follow-up (maximum day 60 after BSI diagnosis) by the Kaplan-Meier method. Besides this, we studied the appropriateness of the therapeutic anti-infectious management according to ABS recommendations, as defined by guidelines by the Infectious Diseases Working Party (AGIHO) criteria of the German Society for Haematology and Medical Oncology (DGHO) or the European Conference on Infections in Leukaemia (ECIL) (Heinz et al. 2017; Böll et al. 2021; Averbuch et al. 2013).

A further secondary objective was to assess the association between BSI occurrence and prior colonisation by MDR pathogens.

This study was approved by the Ethics Committee of the Brandenburg State Medical Association on the 16th of July 2020 (ethics vote no.: S 29 (bB)/2020).

Different definitions used in this study are explained in detail in the Suppl. Material.

Patient selection

All tumour patients treated at the clinic of Haematology and Oncology at Carl-Thiem-Clinic/MUL – CT in Cottbus, Germany, with presence of a bacterium or a fungus in at least one BC between January 2017 and September 2021 were provided by the centre's Institute of Microbiology. As part of the retrospective analysis, we studied the electronic patient records of all patients in whom pathogen detection was documented in at least one BC during the above-mentioned period. Further requirements for inclusion in the study were a pre-existing tumour disease and the clinical presence of infection.

Data collection and study procedures

Important recorded basic patient characteristics included gender, age, admission date, Eastern Cooperative Oncology Group (ECOG) performance status at admission (Oken et al. 1982), type and remission status of the underlying tumour as well as concomitant diseases, current and previous anti-neoplastic therapy (in the last 4 weeks before BSI diagnosis). In addition, we documented major risk factors for BSI, such as a previous BSI or haematopoietic stem cell transplantation, neutropenia at the time of BSI diagnosis or presence of a central venous catheter (CVC).

Important microbiological characteristics of BSI were also recorded and included, for example, pathogen type, Gram stain result, profiles of antimicrobial resistance testing and date of first pathogen detection of the BSI episode. Laboratory peripheral blood values, such as total leukocytes, absolute neutrophil count (ANC), serum concentrations of CRP, procalcitonin (PCT), and creatinine, were evaluated at least at the time of patient admission, BSI diagnosis, termination of the antimicrobial therapy, and discharge. If the corresponding values were not available at the exact target time, the closest value in time was documented (max. ±3 days each). Furthermore, the time to fever resolution was documented. Besides this, mortality and causes of death were recorded. The survival analysis was performed from the time of BSI diagnosis until discharge (survival within BSI episode) and until the last follow-up (maximum 60 days after BSI diagnosis). In addition, the sequence of

antimicrobial (antibiotic and antifungal) therapy of BSI was documented in detail. This included, for example, anti-infective treatment regimens, the presence of antibiotic prophylaxis at the time of BSI diagnosis and at termination of targeted anti-infective treatment, the duration of antibiotic therapy for BSI, including anti-infectious agents and the reasons for anti-infective therapy changes.

Microbiological testing

The detection of colonisation with MDR pathogens was carried out within the framework of a MRSA and MDR Gram-negative bacteria (MRGN) screening. MRSA screening was carried out on all patients, while MRGN screening was only performed on selected patients in a risk-adapted manner (e.g., stay in countries with a high incidence of MRGN in the last 12 months or previous contact with patients with MRGN colonisation or infection). In this study, BC automation was performed using the BD™ BACTEC™ FX system (Becton Dickinson, Heidelberg, Germany). MDR pathogens were primarily detected using commercially available chromogenic screening media. For MRGN, the ChromID® CARBA SMART (BioMérieux, Nürtingen, Germany) was used, while ChromID® vancomycin-resistant enterococci (VRE) Agar (BioMérieux, Nürtingen, Germany) was applied for VRE screening, and ChromID® MRSA Agar (BioMérieux, Nürtingen, Germany) was used for MRSA detection. Confirmation of MRSA was performed according to international laboratory standards using the PASTOREX™ STAPH-PLUS agglutination test (Bio-Rad Laboratories, Redmond, USA) and the penicillin-binding protein 2a (PBP2a) culture colony test (Abbott, Chicago, Illinois, USA), as well as Polymerase Chain Reaction (PCR) methods to confirm the presence of the mecA gene. VRE confirmation involved sequencing the respective gene elements or using the GeneXpert® vanA/vanB assay (Cepheid GmbH, Krefeld, Germany). Carbapenemase-producing organisms were confirmed by direct colony immunochromatography (Bestbion, Hürth, Germany) or the direct Carbapenemase Inactivation Method (CIM) according to the current national standards outlined by the National Antibiotic Susceptibility Testing Committee in Germany.

ABS management

The management of infectious diseases in tumour patients is largely standardised in the clinic where the study was performed. For example, this includes the presence of different standardised operating procedures (SOPs), trainings besides a regular meeting with a clinical microbiologist where relevant patients and microbiological findings are discussed in detail. Both a clinical microbiologist and a physician specialised in haematology/oncology are available 24 h a day, 7 days a week. ABS adherence to recommendations was assessed based on specific criteria, including the timely initiation of empirical therapy aligned with AGIHO and ECIL guidelines, appropriate de-escalation based on microbiological findings, and the correct duration of antimicrobial therapy (Heinz et al. 2017; Böll et al. 2021; Averbuch et al. 2013). Each patient included in the prospective part of the study was reviewed by at least two independent clinicians to ensure consistency and reliability in adherence assessment. Discrepancies were resolved through discussion, and inter-rater reliability was considered during the evaluation process. The prospective part of this study was also accompanied by further trainings (including the management of sepsis) with the goal of enhancing vigilance, adherence to guidelines and, finally, outcome of our patients.

Statistics

For the statistical analyses, the patients were divided into four groups according to the Gram stain results of the detected blood pathogens: Gram-positive BSI, Gram-negative BSI, Gram-positive/Gram-negative polymicrobial BSI and fungal BSI. The groups were compared regarding basic patient characteristics, laboratory parameters, typical risk factors for BSI, microbiological characteristics and sequence of anti-infectious therapy. Differences between the groups were tested using Pearson's chi-square test (nominal variables). Mann-Whitney U or Kruskal-Wallis tests were used for metric variables. The association between selected variables and time to fever resolution or survival within the BSI episode and 60-day survival was investigated using COX regression and hazard ratios (HR). Differences in survival were plotted using the Kaplan-Meier curve and investigated using the log-rank test.

A significance level of $p < 0.05$ (two-tailed) was assumed. No adjustment for multiple testing was conducted due to the exploratory character of the study. Clinically relevant results with $p < 0.10$ were additionally examined with a multivariate analysis (multivariate binary logistic regression or multivariate COX regression). Due to the exploratory nature and the predominantly retrospective design of the study, no Bonferroni correction was applied. All statistical analyses were done by using SPSS (USA, Il, version 27).

Results

Patient and BSI characteristics

The main characteristics of the 123 patients with BSI are summarised in Table 1. Hereby, no statistically significant

differences were found between the 4 patient groups classified by Gram staining (data not shown).

Gram-positive BSI were found in 49 (40%), Gram-negative BSI in 65 (53%), Gram-positive/Gram-negative polymicrobial BSI in 7 (6%), and fungal BSI in 2 (2%) patients. The ratio of Gram-positive to Gram-negative bacteria (in total 0.75) showed no significant change in the 4 years analysed ($p=0.14$) (Figure S1). The most common pathogen causing BSI was *Escherichia coli* (41 patients, 33%). In 17 patients (14%), bacteria from the CoNS group were detected. Of these, *Staphylococcus epidermidis* was prevailing with 11 BSI episodes (9%). *Pseudomonas aeruginosa* was detected in 12 patients (10%). Causative agents of BSI also included *Staphylococcus aureus* (SA) and bacteria from the genus *Enterococcus*, each with 9 patients (7%). Only one patient had a BSI caused by an MDR pathogen (VRE, *Enterococcus faecium*).

MDR pathogen colonisation (VRE) was detected in only one patient (1%) within one year before the BSI diagnosis. Therefore, no detailed analyses on the association between BSI occurrence and prior colonisation by MDR pathogens were carried out.

Important laboratory parameters are shown in Table 2, and the presence of typical risk factors for the development of BSI (e.g., CVC at the time of BSI diagnosis, autologous haematopoietic stem cell transplantation in the last 3 months prior to BSI diagnosis) is presented in Table S1.

The serum concentrations of CRP did not differ significantly between Gram-negative and Gram-positive bacteria and between individual pathogens (Table 2 and Figure S2). However, Gram-negative BSI showed significantly higher serum concentrations of PCT ($p=0.02$) and creatinine ($p=0.03$) at maximum (±3 days from the BSI diagnosis) compared to Gram-positive BSI (Table 2).

Table 2 Selected laboratory parameters at admission or at the time of BSI diagnosis (minimal or maximal value±3 days) in tumour patients with BSI caused by different pathogen types. Number of patients (%) or medians (ranges) are shown. The difference from the total number of patients ($n=123$) in a given group represents non-evaluable patients who were not included in the analysis

Parameter	Gram-positive BSI ($n=49$; 40%)	Gram-negative BSI ($n=65$; 53%)	Gram-positive/Gram-negative polymicrobial BSI ($n=7$; 6%)	Fungal BSI ($n=2$; 2%)	*p*-value
ANC at admission (x10^9/l)					0.44
n	39	52	7	1	
Median (range)	2.91 (0.0-26.11)	2.53 (0.0-45.72)	0.92 (0.0-6.73)	4.79 (4.79–4.79)	
WBC_min[a](x10^9/l)					0.58
n	48	65	7	2	
Median (range)	0.78 (0.11–27.53)	0.72 (0.12–55.34)	0.12 (0.10–3.61)	3.38 (0.70–6.12)	
ANC_min[a](x10^9/l)					0.60
n	34	42	6	1	
Median (range)	0.82 (0.0-9.32)	0.37 (0.0-45.42)	0.0 (0.0-2.30)	3.0 (3.0–3.0)	
Severity of neutropenia at minimum[b], n (%)					0.24
ANC ≥ 1.0 × 10^9/l	16 (47%)	21 (50%)	1 (17%)	1 (100%)	
ANC < 1.0 × 10^9/l	18 (53%)	21 (50%)	5 (83%)	1 (0%)	
CRP_max[c](mg/l)					0.09
n	49	65	7	2	
Median (range)	188 (22–450)	257 (22–421)	303 (231–336)	141 (46–236)	
PCT_max[c](µg/l)					**0.02***
n	32	44	3	0	
Median (range)	0.59 (0.12–96.41)	2.42 (0.10–201.0)	12.0 (1.52–117.0)	-	
Creatinine_max[c](µmol/l)					**0.03***
n	49	65	7	2	
Median (range)	92 (36–394)	123 (41–744)	163 (61–273)	81 (68–93)	

[a]WBC_min and ANC_min were defined as minimum value±3 days from the BSI diagnosis, [b]severity of neutropenia at minimum was defined as minimum value±3 days from the BSI diagnosis, [c]CRP_max, PCT_max and creatinine_max were defined as maximum value±3 days from BSI diagnosis

When directly comparing the first two groups (Gram-positive vs. Gram-negative bacteria) after excluding the two groups with low patient numbers (Gram-positive/Gram-negative polymicrobial and fungal BSI), there was no other significant comparison ($p>0.05$). *Significant in the univariate analysis. No significance in the multivariate analysis

ANC – absolute neutrophil count, BSI – bloodstream infection, CRP – C-reactive protein, PCT – procalcitonin, n – number of patients, WBC – white blood cells

A CRBSI was present in a total of 26 patients (21%), and 18 patients (15%) met the criteria for definite CRBSI, while 6 patients (5%) were classified as probable and 2 (2%) as possible CRBSI, according to Böll et al. (Böll et al. 2021). Figure 1 shows the pathogen spectrum of CRBSI in comparison with other BSI. There was no significant difference in various patient characteristics (e.g., gender, age, underlying disease), different laboratory parameters (e.g., ANC, CRP or serum creatinine) compared to other BSI (data not shown).

Anti-infectious therapy

Primary empirical antibiotic therapy prior to identification of a causative infectious agent in the BC comprised piperacillin/tazobactam in 97 patients (79%). In 9 patients (7%), meropenem was used as primary empirical treatment. Other agents (e.g., fluoroquinolones, ampicillin/sulbactam, etc.) were used empirically as a single agent prior to the identification of a causative agent in 12 patients (10%). Primary targeted antimicrobial therapy was used in 5 patients (4%). Details regarding antimicrobial therapy are provided in Table 3. One patient (1%) with BSI caused by SA was treated primarily with vancomycin as a single agent (targeted) and two patients (2%) with BSI by *E. coli* were treated with fluoroquinolones (of which one was a targeted monotherapy and one was treated in combination with ceftazidime as primary empirical therapy). The remaining 3 documented primary targeted anti-infectious therapies comprised flucloxacillin as a single agent following diagnosis of SA BSI. An initial antibiotic combination was used in 9 patients (7%). These were, for example, a combination of piperacillin/tazobactam with metronidazole for suspected intra-abdominal infection, a combination of a carbapenem with a macrolide for severe infection and suspected pneumonia, and a combination of piperacillin/tazobactam and flucloxacillin for suspected SA infection. Fifteen patients (12%) underwent primary empirical antifungal therapy (caspofungin, liposomal amphotericin B, fluconazole in 6, 5 and 4 patients, respectively). Two patients (2%) were pre-emptively treated with antifungals (caspofungin and voriconazole) during the course of BSI, based on detection of serum galactomannan or suspicion for invasive fungal

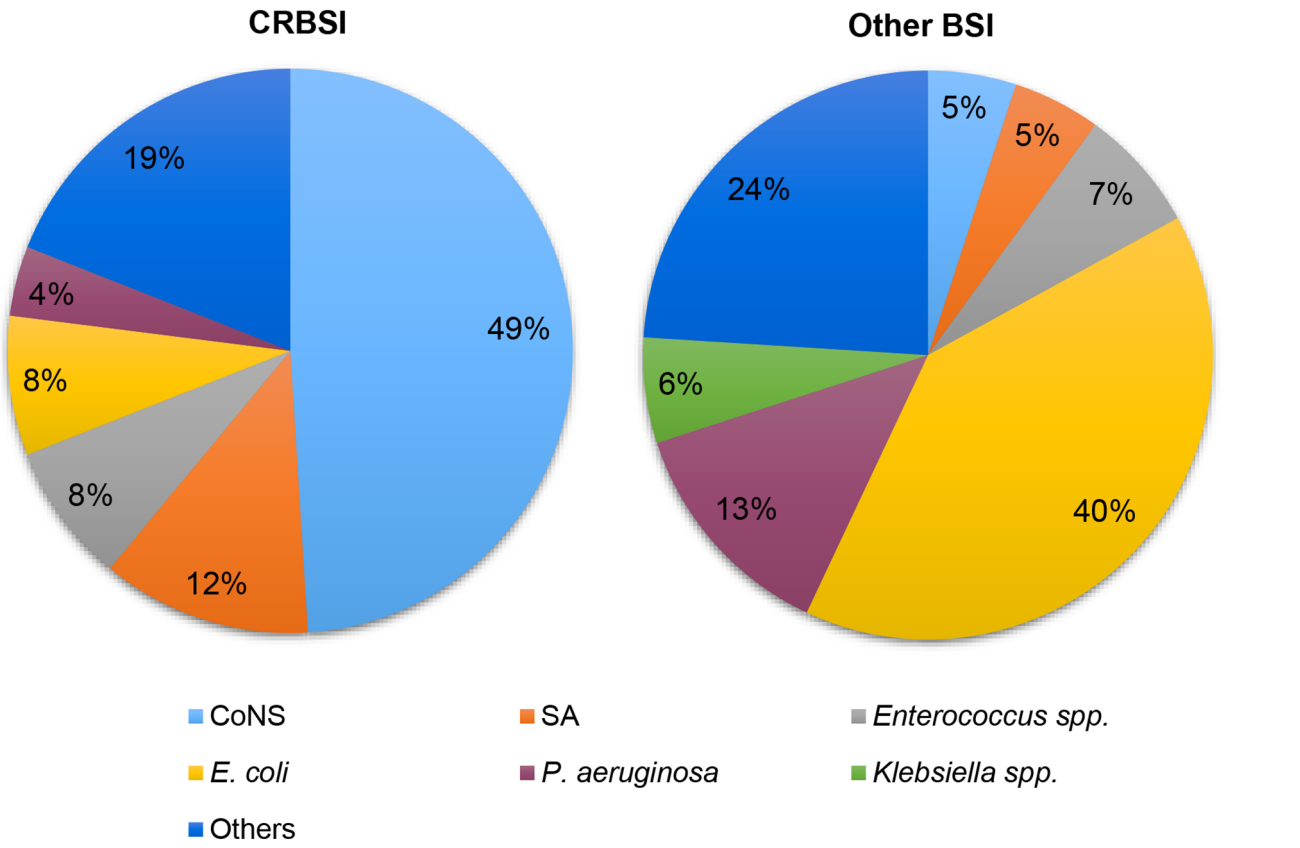

Fig. 1 Important pathogens of CRBSI ($n=26$) vs. other BSI ($n=97$) ($p<0.01$). BSI – bloodstream infection, CoNS – Coagulase-negative *Staphylococcus* spp., CRBSI – catheter-related bloodstream infection, E. – *Escherichia*, P. – *Pseudomonas*, SA – *Staphylococcus aureus*

Table 3 Antimicrobial therapy in tumour patients with BSI, categorised by the gram staining of the pathogen. The number of patients (%) or median values (ranges) are presented

Parameter	Gram-positive BSI (*n* = 49; 40%)	Gram-negative BSI (*n* = 65; 53%)	Gram-positive/Gram-negative polymicrobial BSI (*n* = 7; 6%)	Fungal BSI (*n* = 2; 2%)	*p*-value
Initial antibiotic therapy					0.05
Empirically	45 (92%)	64 (98%)	7 (100%)	2 (100%)	
Targeted	4 (8%)	1 (2%)	0	0	
Substances for primary antibiotic therapy[a]					**< 0.01***
Piperacillin/Tazobactam	37 (76%)	55 (84%)	4 (57%)	1 (50%)	
Carbapenem	2 (4%)	5 (8%)	2 (29%)	1 (50%)	
Fluoroquinolon	0	1 (2%)	1 (14%)	0	
Vancomycin	1 (2%)	0	0	0	
Others	9 (18%)	4 (6%)	0	0	
Addition of vancomycin during BSI episode					**< 0.01***
Yes	15 (31%)	6 (9%)	3 (43%)	2 (100%)	
No	34 (69%)	59 (91%)	4 (57%)	0	
Addition of fluoroquinolon during BSI episode					0.35
Yes	10 (20%)	6 (9%)	1 (14%)	0	
No	39 (80%)	59 (91%)	6 (86%)	2 (100%)	
Susceptibility of the BSI pathogen[b]					**< 0.01***
Yes	38 (78%)	61 (93%)	6 (86%)	0	
No	11 (22%)	3 (5%)	1 (14%)	2 (100%)	
Increased exposure susceptibility	0	1 (2%)	0	0	
Durations of anti-infectious therapy[c]					
Overall					0.19
Days	11	10	14	11	
Range	(4–50)	(6–50)	(2–18)	(7–15)	
After fever resolution					0.09
Days	7	5	8	13	
Range	(0–18)	(0–14)	(4–13)	(13–13)	

[a]Primary (empirical) antibiotic therapy upon the occurrence of signs of infection (usually fever) during the respective BSI episode, [b]Susceptibility of the pathogen to the primary antibiotic therapy, [c]Duration of antibiotic therapy (including empirical therapy before pathogen detection, but excluding antimicrobial prophylaxis)

When directly comparing the first two groups (Gram-positive vs. Gram-negative bacteria) after excluding the two groups with low patient numbers (Gram-positive/Gram-negative polymicrobial and fungal BSI), there was no other significant comparison ($p > 0.05$). *Significant in the univariate analysis. No significance in the multivariate analysis

BSI – bloodstream infection, n – number of patients

pneumonia in low-dose chest computed tomography scan. When fungal BSI were detected (2 patients, *Candida albicans and Pichia kudriavzevii*), primary empirical therapy was changed to targeted antifungal therapy (caspofungin and anidulafungin, respectively).

If vancomycin was added (primary one patient, during the BSI episode 26 patients), these were either patients with evidence of Gram-positive bacteria in BC or patients with clinical deterioration, including sepsis (Table 3). The addition of fluoroquinolones to the primary antibiotic therapy was recorded in 17 patients (14%), while there was no statistically significant difference between BSI caused by different pathogen types (Table 3).

The initial antibiotic therapy was changed in 72 patients (59%) during the course of anti-infectious therapy. The most frequent reason for a change in antibiotic therapy was an adjustment following the results of identification and resistance testing of pathogens in the BC (28 patients, 23%). In 19 patients (15%), the antibiotic therapy was changed due to a lack of fever resolution. In 9 patients (7%), the therapy was intensified due to ongoing sepsis. Seven patients (6%) developed a relevant clinical deterioration under the initial therapy. The antibiotic therapy was de-escalated in only 6 patients (5%). In 3 patients (2%), the reason for change of the antibiotic therapy could not be identified. There was no significant difference between the different types of pathogens regarding the change in anti-infectious therapy except the addition of vancomycin as stated above (data not shown).

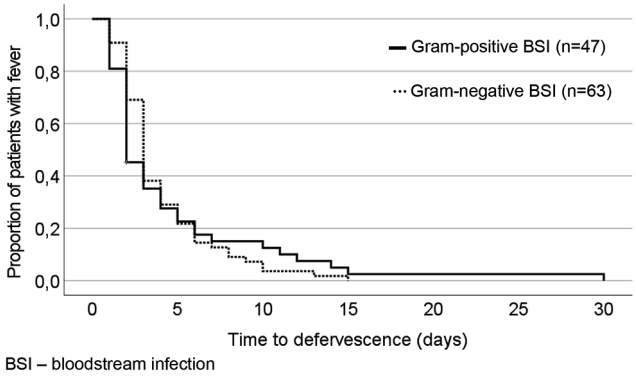

Fig. 2 Time to defervescence in patients with Gram-positive vs. Gram-negative BSI ($p=0.96$)

Time to fever resolution

Fever was the most common symptom of BSI (119 patients, 97%). The remaining patients showed urological, neurological or general symptoms without fever (4 patients, 3%). In patients with fever and BSI, fever disappeared after a median of 3 days (range, 1–30 days). The important variables, such as gender and the presence of a CVC (or its removal), showed no significant influence on the time to fever resolution (Tables S2 and S3).

There was also no significant difference in the median time to fever resolution between Gram-positive and Gram-negative bacteria (2 vs. 3 days, $p=0.96$) (Fig. 2). This was also the case when different Gram-positive (e.g., CoNS, SA) vs. Gram-negative bacteria (e.g., *E. coli*, *P. aeruginosa*) were considered individually (data not shown).

Furthermore, we analysed the influence of various laboratory parameters on the time to fever resolution, using COX regression and hazard ratios (HR), either as a Kaplan-Meier function (Table S2) or by comparing the time to fever resolution of <4 days vs. ≥4 days (Table S3). The neutropenia severity (ANC $\geq 1.0\times10^9$/l vs. ANC $<1.0\times10^9$/l) on admission and at the time of BSI diagnosis (ANC_min) were associated with prolonged time to fever resolution (HR 0.63, $p=0.06$). This was also true in the multivariate analysis (HR 0.27, $p=0.03$) (Table S2).

In addition, the choice of initial antibiotic therapy did not significantly affect the time to fever resolution, and there was no significant difference between patients who initially received antibiotic monotherapy and patients who received antibiotic combination therapy. There was also no significant difference between the individual substances of the initial antibiotic therapy. Finally, the addition of vancomycin showed no significant effect on the time to fever resolution (data not shown). Non-susceptibility to empirical antibiotic treatment was more frequent in Gram-positive than Gram-negative BSI (22% vs. 5%, $p<0.01$, Table 3) and was associated with delayed fever resolution (median 5 vs. 3 days; HR 0.53, $p=0.04$, Table S2).

Adherence to ABS (vs. non-adherence or questionable adherence) significantly shortened the time to fever resolution (median 3 days vs. 4 days; $p=0.04$).

Mortality and survival

We observed 12 deaths (10%) during BSI episodes. Hereby, BSI was the cause of death or contributed significantly to the patient's death in 10 patients (8%). Each one patient (1%) died due to progression of the underlying disease and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Only 2 patients (8%) with CRBSI died within the inpatient stay of the BSI episode (day 14 and 15 after BSI diagnosis), and in both patients the cause of death was CRBSI-associated sepsis. Up to 60 days from BSI diagnosis, 21 deaths (17%) were documented.

In the survival analysis, different pathogen types (defined on the basis of Gram stain results – Gram-positive vs. Gram-negative) had no influence on survival within the BSI episode (HR 0.60, 95%-CI 0.16–2.24, $p=0.45$) as well as on survival at day 60 (HR 0.70, 95%-CI 0.28–1.77, $p=0.46$). Individual pathogens of BSI neither had a significant impact on survival (data not shown). Likewise, other important variables such as gender and the presence of a CVC (or its removal) showed no significant influence on the survival (Table S4). Furthermore, the survival analysis (both univariate and multivariate) showed that the severity of neutropenia (ANC $\geq 1.0\times10^9$/l vs. ANC $<1.0\times10^9$/l) on admission had no impact on survival within the BSI episode (HR 2.73, 95%-CI 0.73–10.16, $p=0.14$) but showed a statistically significant impact on survival at day 60 (HR 2.95, 95%-CI 1.10–7.93, $p=0.03$) (Table S4). Patients treated initially with piperacillin/tazobactam showed in the survival analysis (both univariate and multivariate) a statistically significantly extended survival within the BSI episode as well as survival at day 60, compared to patients treated primarily with carbapenem (HR 4.83, 95%-CI 1.30-17.98, $p=0.02$; HR 6.18, 95%-CI 2.20-17.37, $p<0.01$, Figure S3). However, patients who received a carbapenem as primary antibiotic therapy (vs. patients treated with piperacillin/tazobactam) tended to be in poorer general health (ECOG PS ≥2, 33% in the meropenem group vs. 29% in the piperacillin/tazobactam group, $p=0.17$) and had significantly more frequent a prior history of BSI (70% vs. 22%; $p<0.01$). There was no significant difference in survival within BSI episode as well as in survival at day 60 between patients who were primarily treated empirically with a monotherapy and those who received an antibiotic combination therapy (HR 2.03, 95%-CI 0.44–9.25, $p=0.36$; HR 1.26, 95%-CI 0.29–5.43, $p=0.75$). Susceptibility to empirical antibiotic treatment

showed no significant influence on survival within the BSI episode or survival at day 60, compared to patients whose BSI pathogens were non-susceptible to empirical antibiotic treatment (HR 2.53, 95%-CI 0.68–9.34, $p=0.17$; HR 2.12, 95%-CI 0.71–6.30, $p=0.18$, Table S4). The presence of antibiotic prophylaxis at symptom onset also showed no significant effect on survival within the BSI episode (HR 1.41, 95%-CI 0.95.-2.09, $p=0.70$) or survival at day 60 (HR 3.33, 95%-CI 2.25–4.93, $p=0.26$) (Table S4).

Adherence to ABS recommendations

Anti-infectious therapy followed ABS guidelines in 81 patients (66%). Questionable adherence with these recommendations was found in 10 patients (8%). In 32 patients (26%), antibiotic therapy was assessed as non-ABS-adherent. This involved a lack of optimal antibiotic therapy duration in 14 patients (11% – in 9 patients too long vs. in 5 patients too short) (Böll et al. 2021). In 8 patients (7%), the choice of antibiotic therapy was the reason for a lack of adherence to ABS recommendations, while in 10 patients (8%), different ABS non-compliances were identified.

Primary empirical antibiotic therapy prior to identification of a causative infectious agent was ABS-adherent in all patients treated with piperacillin/tazobactam. Meropenem was used in 9 patients (7%), with ABS adherence in 7 patients (5%) and non-adherence in 2 patients (2%), where piperacillin/tazobactam could have been used according to the ECIL guideline (Averbuch et al. 2013).

Other agents, such as fluoroquinolones and ampicillin/sulbactam, were also used with full adherence to ABS. Primary targeted antimicrobial therapy was ABS-adherent in all cases.

Primary empirical antibiotic combination was documented in 9 patients (7%), which followed ABS recommendations only in 3 of these patients. In contrast, the primary empirical antibiotic combination therapy was evaluated in each of the 3 patients (2%) as non-ABS-adherent and questionably ABS-adherent. Various patient characteristics (e.g., gender, age, underlying disease), the causative BSI pathogen and different laboratory parameters did not show any significant association with ABS adherence (data not shown).

In retrospectively documented patients, anti-infectious therapy was considered ABS-adherent in 65/105 patients (62%) and not or questionably ABS-adherent in 40/105 patients (38%). In contrast, among the 18 prospectively recorded patients, therapy was ABS-adherent in 16 patients (89%) and not or questionably ABS-adherent in only 2 patients (11%, $p=0.03$).

Discussion

Gram-negative bacteria were more common (53%) than Gram-positive bacteria (40%) as causative agents of BSI, while *E. coli* (33%) was prevailing, followed by CoNS (14%) and *P. aeruginosa* (10%). SA was detected in only 7% of BSI. The proportion of Gram-positive/Gram-negative bacteria did not differ significantly in the analysed time period (2018–2021), varying between 0.63 and 0.95 ($p=0.14$) (Figure S1). Thus, our findings of a ratio of Gram-positive/Gram-negative bacteria of 0.75 confirm the trend of a shift of BSI in tumour patients from Gram-positive towards Gram-negative bacteria. A retrospective analysis of 317 BSI episodes in tumour patients from Denmark aligns well with our findings, reporting Gram-negative bacteria in 52% and Gram-positive bacteria in 46% of patients (Peri et al. 2023). Similarly, data from Queensland, Australia, analysing 7,749 BSI episodes in patients with haematological malignancies over a 20-year period, identified Gram-negative bacteria in 58% and Gram-positive bacteria in 42% of patients (Andersen et al. 2019). These consistent findings across different geographic regions underscore the current predominance of Gram-negative pathogens in BSI among tumour patients (Peri et al. 2023; Andersen et al. 2019).

The pathogen was resistant to primary empirical antibiotic treatment in 17 patients (Gram-positive – 11 patients vs. Gram-negative – 3 patients vs polymicrobial – 1 patient fungal – 2 patients, $p<0.01$). CoNS were resistant to piperacillin/tazobactam in 7 of 17 patients (41%). *Enterococcus* spp. showed piperacillin/tazobactam resistance in 4 of 9 patients (44%) with BSI. Others came to similar results in their analyses. Here, beta-lactam resistance was present in about 50% of each of the detected *Enterococcus* spp. as well as CoNS (Todeschini et al. 2006; Singh et al. 2016). Notably, only one BSI in our study was caused by a MDR pathogen (VRE), showing a low prevalence of these organisms in our centre.

Twenty-six patients (21%) with BSI met the definition of CRBSI (Böll et al. 2021). The ratio of Gram-positive to Gram-negative bacteria was significantly higher in CRBSI compared to other BSI (6.33 vs. 0.48, $p<0.01$). Schalk et al. detected 275 Gram-positive and 32 Gram-negative bacteria in their analysis of 335 CRBSI (ratio of Gram-positive to Gram-negative bacteria: 8.59) (Schalk et al. 2020). Thus, the pathogen spectrum in this work corresponds very well with that in this large register analysis.

There are only a few prospective data on the impact of various parameters on the time to fever resolution in tumour patients with BSI. Several possible predictors of prolonged time to fever resolution were identified, including age, underlying patient disease, ANC or CRP (McCarthy et al. 1980; Nakagawa et al. 2009). In our study, the presence of

ANC < 1.0×10^9/l (vs. patients with ANC ≥ 1.0×10^9/l) at the time of hospital admission and at the time of BSI diagnosis was associated with a longer time to defervescence (Table S2 and S3). We also found that non-susceptibility to empirical antibiotic treatment occurred more frequently in Gram-positive than Gram-negative BSI (22% vs. 5%, $p < 0.01$) and was also associated with a delayed time to fever resolution (HR 0.5, $p = 0.04$). However, since susceptibility to the primary antibiotic treatment did not significantly influence survival, we believe that piperacillin/tazobactam as the primary empirical treatment is still justified for the empirical management of febrile neutropenia, as also supported by other studies or recommendations (Trecarichi et al. 2015; Ghosh et al. 2021; Peri et al. 2023). The BSI episode and 60-day mortality rates of 10% and 17% in our study correspond to mortality rates from previously published studies (mortality < 10%) (Gustinetti and Mikulska 2016). In contrast to other published studies reporting higher mortality in Gram-negative than in Gram-positive BSI, we found no significant difference between BSI caused by Gram-positive vs. Gram-negative bacteria or between different pathogen species (Trecarichi et al. 2015; Klastersky et al. 2007; Mahajan et al. 2012; Gustinetti and Mikulska 2016).

The presence of neutropenia is a typical risk factor for the occurrence of infections in tumour patients (Gustinetti and Mikulska 2016; Schmidt-Hieber, Teschner et al. 2019). Our data show that it could also be a possible predictor of increased mortality in tumour patients with BSI.

Patients treated primarily empirically prior to detection of a causative agent with meropenem showed a significantly lower 60-day survival compared to patients treated primarily with piperacillin/tazobactam in our analysis. However, the former tended to be in worse general health (ECOG PS ≥ 2, 33% in the meropenem group vs. 29% in the piperacillin/tazobactam group, $p = 0.17$) and were significantly more likely to have a history of BSI (70% vs. 22%; $p < 0.01$). These factors are associated with increased mortality independent of BSI therapy (Huang et al. 2017). Therefore, we cannot exclude that decreased survival of patients primarily treated by a meropenem-based anti-infective regimen was due to these confounding factors.

Here, we focused in particular on 3 key crucial ABS points of anti-infectious therapy – selection of primary antibiotic therapy, switching (or lack of switching) of antibiotic therapy, and duration of antibiotic therapy. In our analysis, anti-infectious therapy complied with recommendations of the above-mentioned guidelines in 81 patients (66%), while 32 patients (26%) violated the therapy recommendation at least in one key point of the anti-infectious therapy (Heinz et al. 2017; Böll et al. 2021; Averbuch et al. 2013; Kochanek et al. 2019). In 10 patients (8%), adherence to the above-mentioned guideline recommendations could not be determined with certainty. These usually included highly complex anti-infectious therapies, so that an adequate comparison with guideline recommendations was not possible. Overall, therapy classified as ABS-non-adherent (or questionable adherent) was more likely to be over-therapy (23 patients, 21%) than under-therapy (9 patients, 7%).

Non-adherence or questionable adherence to ABS recommendations was significantly more common in retrospectively ($n = 105$) than in prospectively recorded patients ($n = 18$) (38% vs. 11%, $p = 0.03$). It is possible that in this observational study, staff awareness of ABS issues had a positive influence on their implementation. ABS compliance was associated with a significant reduction in time to fever resolution. However, it did not affect survival. Notably, patients who did not adhere to ABS or had questionable adherence more often presented with a complicated or severe disease course from the outset, which may have influenced the observed differences in fever resolution.

Limitations of our analysis are the predominantly retrospective setting, the comparably limited sample size ($n = 123$), and the low proportion of solid tumour cases. However, our study performed in a single centre highlights real-world patterns in ABS adherence and BSI management, contributing to the understanding of clinical practices and potential areas for improvement. Besides this, the retrospective/prospective design offered the possibility to elucidate the impact of a structured ABS programme, implemented in the prospective part of the study, on BSI outcome.

In summary, we found that Gram-negative bacteria still predominate over Gram-positive bacteria in BSI of tumour patients. Our data suggest that prospective evaluation of anti-infectious therapy might enhance vigilance and improve adherence to ABS recommendations.

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Author contributions MSH: designed the research, wrote the first version of the study manuscript with JR. JR: wrote the first version of the manuscript with MSH. AS: analysed data with JR. JR, MD, AS, PK, LG, AK, ML, JL, HPL, MSH: contributed patient data and/or were involved in interpretation of data/analyses. All authors approved the final version of the work.

Data availability Selected datasets might be available upon request.

Declarations

Research involving human participants and/or animals The study design adhered to the tenets of the Declaration of Helsinki and was was approved by the Ethics Committee of the Brandenburg State Medical Association on 16.07.2020 (ethics vote no.: S 29 (bB)/2020).

Informed consent Written informed consent was provided by all prospective registered patients.

Competing interests The authors declare no competing interests.

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