Epidemiology, resistant pathogens and main causes of early death of bloodstream infection in patients with hematological malignancies from 2012 to 2019 in a Chinese tertiary hospital

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Research

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Abstract

Background: To investigate epidemiology, antibiotic-susceptibility of pathogens, and risk factors for mortality of bloodstream infection (BSI) in patients with hematological malignancies (HMs).

Methods: Single-centre retrospective analysis of BSI episodes in patients with HMs in a Chinese tertiary hospital from 2012 to 2019.

Results: Among 17,796 analyzed admissions, 508 BSI episodes (2.85%) were identified. Of the 522 isolates, 326 (62.45%) were Gram-negative bacteria, 173 (33.14%) were Gram-positive bacteria, and 23 (4.41%) were fungi. The incidence of BSI differed significantly among the patients with different HMs (P = 0.000): severe aplastic anemia (6.67%), acute leukemia (6.15%), myelodysplastic syndrome(3.22%), multiple myeloma (1.29%), and lymphoma (1.02%). *Escherichia coli* (30.65%, 160/522) was the most common pathogens, followed by Coagulase-negative staphylococci (CoNS) (19.35%, 101/522) and *Klebsiella pneumonia*（9.96%, 52/522).

The resistance rates of *E. coli*, *K. pneumonia*, *P. aeruginosa*, and *A. baumannii* to carbapenems were 6.42%, 15.00%, 27.78%, and 78.95%, respectively. All the Gram-positive pathogens were susceptible to linezolid, and 3 vancomycin-resistant *Enterococcus* were isolated. The overall 14-day mortality was 9.84%. The mortality of BSI caused by A. baumannii was 73.86%, while caused by other pathogens was 7.36% (p=0.000). A multivariate analysis showed that age >65 years, *A. baumannii* and non-remission of the malignancy were independent predictors of 14-day mortality.

Conclusion: Gram-negative bacteria continued to be the most common pathogens causing BSIs in HM patients. An extensive multi-drug resistant *baumanni* with high mortality rate in HM patients made empirical antimicrobial choice a highly challenging issue.

Background

Bloodstream infection (BSI) remains a severe complication in patients with hematological malignancies (HMs) entailing high morbidity and mortality. The incidence of BSI in patients with HMs ranges from 7.16–14.5%[1–3]. Over the past 3 decades, the pathogens of BSI have changed. During the 1980s–1990s, the pathogens of BSI in patients with HMs were mainly Gram-positive bacteria[4, 5]. However, the incidence of Gram-negative bacterial infections has risen in recent years[6]. Gram-negative pathogens have higher antimicrobial resistance profiles worldwide, especially in China (carbapenem-resistant *Klebsiella pneumoniae* [CRKP] 20.9% and carbapenem-resistant *Acinetobacter baumannii* [CRAB] 70.7% in 2017)[7]. The incidence and pathogens spectrum of BSI may differ by different HMs. Compared to lymphoma or multiple myeloma(MM), the incidence of BSI in patients with acute leukemia (AL) have a much more higher incidence of BSI[8]. Study showed that in Taiwan BSIs in patients with MM were mainly caused by Gram-negative bacteria[9],whereas in Italy[10] and Finland[11], the BSIs in AL patients were predominantly caused by Gram-positive bacteria. Yet, there have been limited data on BSI in Chinese patients with HMs.

In this study, we retrospectively analyzed the medical record on BSI in patients with different HMs in a Chinese tertiary hospital from 2012 to 2019. The epidemiology, antimicrobial susceptibility of pathogens and 14-day mortality of BSI were investigated.

Methods

1. Subject information

The hospital was a tertiary teaching hospital with 4,000 beds in Beijing in north China. There were 125 beds in the Hematology Department, including 20 beds in the hematopoietic stem cell transplantation (HSCT) ward. There were about 2000 patients admitted in Hematology ward every year. The patients admitted in our center between January 1, 2012 and December 31, 2019 were analyzed retrospectively, and predominantly included patients with AL, myelodysplastic syndrome (MDS), severe aplastic anemia (sAA), lymphoma, or multiple myeloma (MM). Patients with a hospital stay of ≤ 2 days were excluded.

2. Definitions

A BSI episode was considered present in patients with fever (axillary temperature > 38 °C for more than 1 h), with or without chill, and with one or more positive blood culturetests[12]. Nosocomial BSI was defined as the first positive blood culture obtained ≥ 48 h after hospital admission and with no evidence of infection at admission. A BSI caused by coagulase-negative staphylococcus (CoNS) or other potential skin contaminants was considered to be significant when the same species grew in at least two blood cultures within a 48-h period[13]. Neutropenia was defined as a peripheral blood neutrophil count of < 500 cells/mm^3[14].

3. Surveillance of BSI

Real-time automatic hospital-wide surveillance of nosocomial infections (NIs) and outbreaks has been established in our hospital since 2012[15]. In brief, this system automatically records and analyzes microbiological reports, antibiotic usage, imaging reports, fever histories, and other infectious information. The system develops NI prewarning alerts, including BSIs in HM patients. Infection control practitioners then work with the physician-in-charge to confirm the nosocomial BSI, as described in a previous study[15]. The information system automatically collects information, such as patient's age, sex, granulocyte count, BSI pathogens and their antimicrobial susceptibility, central venous catheterization, and previous HSCT.

4. Strain identification and antimicrobial susceptibility testing

The strains were isolated from the blood samples of patients with BSIs. Only the first detection of a specific pathogen in the same patient was recorded. Blood was cultured with the BacT/ALERT® 3D™ system (Becton-Dickinson, Sparks, MD, USA) in the microbiology laboratory. Species were identified and

then in vitro antibiotic susceptibility was determined with Vitek II (bioMeptibilitys, MD, USA), with the latest breakpoints defined by the Clinical and Laboratory Standards Institute[16].

5. Statistical analysis

The χ^2 test was used to compare the percentage differences in the univariate analysis. Values of $P < 0.05$ were considered statistically significant. Variables found to be significant ($P < 0.05$) in the univariate analysis were tested in a multivariate analysis, which was performed with a stepwise logistic regression model. All statistical analyses were performed with the SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Results

Characteristic of BSI in patients with HMs

There were 17,796 patients with HMs admitted in our center between January 2012 and December 2019. During this 8-year period, 519 BSI episodes were identified. The median age of patients with BSI was 42 years (range 11-94 years) and 335 patients (64.92%) were man. Table 1 shows baseline patient characteristics.

Incidence of BSI in patients with HMs

Over the study period, the overall incidence of BSI was 2.92% (519/17,796). The annual incidence of BSI ranged from 2.03% to 3.54%, which was significantly different ($\chi^2 = 16.126$, $P = 0.024$). The annual incidence of Gram-positive BSI increased significantly ($\chi^2 = 31.552$; $P = 0.000$). Gram-negative BSIs peaked in 2015 at 2.37%, but fell in 2019 to a frequency similar to that at the start of the study. The annual incidence of Gram-negative BSI and Fungus BSI did not change significantly during the study period ($\chi2 = 10.299$; $P = 0.172$ and $\chi2 = 8.523$; $P = 0.289$, respectively). (Figure 1)

The incidences of BSI according to the different types of HMs were (in descending order): sAA (6.67%, 15/225), AL (6.15%, 340/5530), MDS (3.22%, 23/715), MM (1.29%, 26/2018), lymphoma (1.02%, 92/9010), and other HMs (4.03%, 12/298). These incidences differed significantly ($\chi^2 = 346.709$, $P = 0.000$).

We divided the patients into two groups according to whether they had undergone HSCT or not. The incidence of BSIs was significantly higher in the HSCT group (10.15%) than in the non-HSCT group (2.45%; $\chi^2 = 161.367$; $P = 0.000$). The variations in BSIs in patients with different HMs are shown in Figure 2.

BSI pathogens and antibiotics susceptibility

From 2012 to 2019, there were 522 bacteria isolates in 508 patients with BSIs. Of these, Gram-negative bacteria accounted for 62.45% (326/522), Gram-positive bacteria for 33.14% (173/522), and fungi for 4.41% (23/522). The leading Gram-negative bacteria were *Escherichia coli* (160, 30.65%), *Klebsiella*

pneumonia (52, 9.96%), and *Pseudomonas aeruginosa* (41, 7.85%). *Staphylococcus epidermidis* (51, 9.77%), *S. hominis* (40, 7.66%) and *Enterococcus* (21, 4.02%) were the most commonly isolated Gram-positive bacteria. 97 CoNS were isolated, although 203 CoNS isolates were considered to be contaminants because only one positive blood culture. The pathogens associated with the different HMs are shown in Table 1.

Isolates of E. coli were highly susceptible to meropenem (90.91%), amikacin (93.58%) and imipenem(93.58%), but exhibited high resistant to ciprofloxacin (84.40%) in patients with HMs. The resistance rates of *K. pneumonia* and *P. aeruginosa* to carbapenems were 15.00% and 27.78%, respectively.The susceptibility rates for *K.* pneumoniae to meropenem and amikacin were above 80%. And the susceptibility rates for *P. aeruginosa*to to meropenem and amikacin were 69.44% and 100%, respectively. *A. baumannii* showed extensive resistance profile, with susceptibility rates to common antibiotics below 50%. Approximately 21.05% and 27.27% of *A. baumannii* isolates were susceptible to imipenem and meropenem, respectively (Table 2).

Methicillin-resistant strains accounted for 96.10% of all CoNS and 33.33% of *S. aureus*. All *Staphylococcus* were susceptible to linezolid. Three vancomycin-resistant *Enterococcus* isolates (15.79%) were detected (Table 3).

Outcomes and risk factors for 14-day mortality

Among the 508 patients with BSIs, 50 (9.84%) died within 14 days of BSI. The mortality of patients with *A. baumannii* bacteremia was significantly higher than that of patients infected with other pathogens (73.86% vs. 7.36%，χ^2 = 326.755, p=0.00). Among 19 episodes with *A. baumannii* bacteremia in our cohort, 15 patients with CRAB were identified and 14 of them died within 14 days of BSI. A univariate analysis revealed that age > 65 years, catheter-related infection, the type of pathogen, and the non-remission status of the malignancy correlated with the 14-day mortality, whereas sex, neutropenia, previous HSCT, and HMs subtype did not. The logistic regression analysis results are shown in Table 4. Independent predictors of 14-day mortality were age >65 years (odds ratio [OR]: 2.588; 95% confidence interval [CI]: 1.072–6.249; P = 0.034), *A. baumannii* infection (OR: 32.222; 95% CI: 8.232–126.126; P = 0.001), and non-remission status of the malignancy (OR: 0.051; 95% CI: 0.007–0.379; P = 0.000) (Table 4).

Discussion

The overall incidence of BSIs in patients with HMs was about 2.85% in 2012–2019 in our study, which is significantly lower than that reported in other surveys (about 7.16–14.5%)[1–3], but higher than the incidence of BSIs in HM patients reported in a retrospective study of a Chinese children's hospital in 2011–2015 (1.04%)[17]. The difference might be attributable to the variation of methods (prospective vs. retrospective) used to monitor BSIs and the different types of HMs or different disease states involved in studies. Another important factor may be the lower submitted blood culture rate in Chinese hospitals than

in hospitals in developed countries[18]. Since 2000, BSIs caused by Gram-negative bacteria have generally predominated in HM patients[6]. For example, Gram-negative bacteria predominated in studies in Taiwan[19] and in Italy multicenter survey in HM adult patients in 2009–2012[20], accounting for 57.0% and 52.8% of BSIs, respectively. In these two studies, *E. coli* was the most frequently detected Gram-negative bacterium. In our study, Gram-negative bacteria (62.45%) were the main pathogens of BSIs, and *E. coli* (30.65%) was the most frequently detected bacterium, which is consistent with the results of most studies in Tianwan[8, 19]and Italy[20]. We found that Gram-positive bacteria accounted for 33.14% of BSIs, but the incidence of it increased significantly from 0.67% in 2012 to 1.71% 2019 (P = 0.000). 97 strains of CoNS accounted for 18.58% of BSIs; it was consistent with previous reports in Taiwan (20.5%) [8] and in Italy (24.8%)[20], and in which CoNS were the main Gram-positive bacteria.

Our study found that the incidence of BSIs varied among patients with different types of HMs (P = 0.000). The incidence of BSIs was significantly higher in patients with sAA (6.67%) and AL (6.15%) than in those with MM (1.29%) or lymphoma (1.02%), consistent with the results reported in other studies. A study by Kara Ö [2] showed that the incidence of BSIs was 20.2% in the high-risk group, which contained patients with AL, whereas it was only 10.4% in the low-risk group,which included patients with non-Hodgkin's lymphoma, MM, or AA(P < 0.001). According to the report from Taiwan[8], the incidence of BSIs was highest in patients with AL (31.2%), whereas the rates in patients with myeloma, AA/MDS, and lymphoma were significantly lower (12.8%, 11.1%, and 11.9%, respectively).

In an Italian study of BSIs in patients with AL in 2012–2014[10], Gram-positive bacteria accounted for 44.8% and Gram-negative bacteria for 38.3% of the pathogens involved. More than half BSIs were observed in patients receiving Fluoroquinolone prophylaxis. This was probably the reason for the higher incidence of Gram-positive BSI in comparison with Gram-negative BSI. In another study of BSIs in 357 AML patients with 977 treatment episodes in 2003–2011 in Finland[11], Gram-positive bacteria were most frequently detected (65.7%). The leading Gram-positive bacteria were CoNS(24.7%). Contrarily, our results show that although Gram-positive bacteremia increased significantly during this period, the leading pathogens causing BSIs in 5530 admissions with AL were Gram-negative bacteria (64.76%), with more than half Gram-negative bacteria was *E. coli* (33.81%). Gram-negative bacteria have predominated in such patients in most reported studies from Taiwan[8, 19, 21]. These data suggested that the epidemic data for BSI in China was clearly different from that in Western countries.

In the present study, *E. coli* displayed the highest sensitivity rates to meropenem and amikacin. In contrast, the sensitive rate to ciprofloxacin was significantly lower than that previous reported in Taiwan[21] (15.6% vs. 50%). The total resistance rates of *K. pneumonia* and *A. baumannii* to imipenem were 15.00% and 78.95%, respectively. The first CRKP isolated in 2014 in Hematology Department, and it had a marked increase in the studied hospital in recent 5 years. And *A. baumannii* showed extensive antimicrobial resistance profile in the studied hospital. However, the trend of carbapenem-resistant bacteria in our study, was similar to that in the CHINET surveillance from 2005 to 2017 (*CRAB* ranging from 31%% to 70.7% vs. *CRKP* ranging from 4.0–20.9%)[7].

In this study, 9.84% of patients with BSIs died within 14 days of infection, which is basically consistent with the results reported in the literature (12%)[22]. A logistic multivariate regression analysis showed that age > 65 years, *A. baumannii* and the non-remission of the malignancy were independent risk factors for14-day mortality. Neutropenia was not associated with death from BSIs, which is consistent with results reported in Taiwan[8]. This finding is possibly related to the underlying disease and other factors clearly affecting mortality. It is worth noting that among 15 patients with CRAB bacteremia in our cohort, 14 patients died. The mortality of *A. baumannii* bacteremia was higher than that of other pathogens causing BSIs. In China, Tianshui Niu[23] reported that the 28-day mortality rate among 186 patients with *A. baumannii* BSIs was 45.2%, and the resistance rate of *A. baumannii* to imipenem was 82.6%. The high resistance of *A. baumanni* to carbapenems and its high mortality rate make empirical therapy very challenging.

This study has several limitations. It was a retrospective survey and the data were obtained from an information system. So some information collected might not be incomplete, which might affect the analysis of risk factors. Second, as a single-centre study, it could lead to an inevitable selection bias, and the multivariate logistic analysis might be affected by the sample size. Furthermore, the incidence of BSIs might be underestimated because of the low submission rate of blood culture in the hospital studied.

In conclusion, the incidence of BSIs varied among patients with different HMs. Although Gram-positive bacteremia increased significantly from 2012 to 2019, Gram-negative bacteria continued to be the most common cause of BSIs in each kinds of HM patients. Previous HSCT is a risk factor for BSIs, but did not correlate with 14-day mortality. Age > 65 years, *A. baumannii* infection, and non-remission status of the malignancy were independent predictors of 14-day mortality. The high resistance of *A. baumanni* to carbapenems and its high mortality rate should be more concerned.

Abbreviations

BSIs: bloodstream infections

HMs: hematological malignancies

AL: acute leukemia

sAA: severe aplastic anemia

MDS: myelodysplastic syndrome

HSCT: hematopoietic stem cell transplantation

NIs: nosocomial infections

CLSI: Clinical and Laboratory Standards Institute

MRSA: *Methicillin resistant Staphylococcus aureus*

Declarations

Ethics approval and consent to participate

This study was approved by the studied hospital institutional review board (S2019-142-02). For this type of study, formal consent is not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during the current study are not publicly available, to avoid disclosure of the individual privacy of the patients. However, they are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

M.L. and M.D. collected the data, interpreted the results and wrote the manuscript; H.L. collected and analyzed the data; Y.L. and D.L. designed the study and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Distribution of pathogens causing BSIs

Pathogens	Leukemia (n=349)	AA/MDS (n=39)	Lymphoma (n=94)	Myeloma (n=27)	Total (n=522)
G+	**105(30.09)**	**10(25.64)**	**42(44.68)**	**11(40.74)**	**173(33.14)**
Staphylococcus epidermidis	35(10.03)	3(7.69)	9(9.57)	1(3.70)	51(9.77)
Staphylococcus hominis	23(6.59)	3(7.69)	9(9.57)	4(14.81)	40(7.66)
Enterococcus	15(4.30)	2(5.13)	4(4.25)	0(0.00)	21(4.02)
Staphylococcus aureus	6(1.72)	1(2.56)	7(7.45)	3(11.11)	17(3.26)
Others	26(7.45)	1(2.56)	13(13.83)	4(14.81)	44(8.43)
G-	**226(64.76)**	**28(71.79)**	**51(54.26)**	**12(44.44)**	**326(62.45)**
Escherichia coli	118(33.81)	9(23.07)	25(26.60)	6(22.22)	160(30.65)
Klebsiella pneumoniae	34(9.74)	10(25.64)	5(5.32)	2(7.41)	52(9.96)
Pseudomonas aeruginosa	28(8.02)	5(12.82)	4(4.26)	2(7.41)	41(7.85)
Acinetobacter baumannii	10(2.87)	5(12.82)	5(5.32)	0(0.00)	19(3.64)
Stenotrophomonas maltophilia	9(2.58)	0(0.00)	0(0.00)	0(0.00)	13(2.49)
Others	27(7.74)	1(2.56)	12(12.77)	2(7.41)	41(7.85)
Fungus	**18(5.16)**	**1(2.56)**	**1(1.06)**	**3(11.11)**	**23(4.41)**

Table 2 Antimicrobial susceptibility profiles of Gram-negative bacteria

	Escherichia coli	Pseudomonas aeruginosa	Klebsiella pneumoniae	Acinetobacter baumannii
Cefepime	62.39（68/109）	77.78（28/36）	77.50（31/40）	21.05（4/19）
Ceftriaxone	35.29（36/102）	0.00（0/31）	61.76（21/34）	0.00（0/9）
Ceftazidime	65.74（71/108）	75.00（27/36）	70.00（28/40）	36.84（7/19）
Piperacillin tazobactam	87.01（67/77）	88.24（30/34）	83.33（25/30）	44.44（4/9）
Imipenem	93.58（102/109）	72.22（26/36）	85.00（34/40）	21.05（4/19）
Meropenem	90.91（30/33）	69.44（25/36）	88.88（16/18）	27.27（3/11）
Ciprofloxacin	15.60（17/109）	94.44（34/36）	70.00（28/40）	15.79（3/19）
Amikacin	93.58（102/109）	100.00（36/36）	92.50（37/40）	50.00（3/6）
Gentamycin	46.08（47/102）	96.97（32/33）	76.47（26/34）	44.44（4/9）
Nitrofurantoin	71.74（66/92）	0.00（0/31）	7.14（2/28）	0.00（0/8）
SMZ-TMP	34.83（31/89）	0.00（0/31）	51.61（16/31）	33.33（3/9）

Table 3 Antimicrobial susceptibility profiles of Gram-positive bacteria

	Staphylococcus epidermidis	Staphylococcus hominis	Staphylococcus aureus	Enterococcus
Oxacillin	2.50（1/40）	5.41（2/37）	66.67（8/12）	NA
Ofloxacin	22.50（9/40）	21.05（8/38）	72.73（8/11）	0.00（0/15）
Moxifloxacin	22.50（9/40）	21.05（8/38）	75.00（9/12）	0.00（0/19）
Ciprofloxacin	22.50（9/40）	21.05（8/38）	75.00（9/12）	0.00（0/15）
Gentamycin	64.29（27/42）	94.74（36/38）	64.29（9/14）	12.50（1/8）
Erythromycin	19.05（8/42）	7.89（3/38）	35.71（5/14）	13.33（2/15）
Tetracycline	77.50（31/40）	44.74（17/38）	91.67（11/12）	40.00（6/15）
Vancomycin	100.00（42/42）	100.00（38/38）	100.00（11/11）	84.21（16/19）
Linezolid	100（40/40）	100.00（38/38）	100.00（11/11）	100.00（15/15）
SMZ-TMP	17.50（7/40）	18.42（7/38）	54.55（6/11）	NA
Nitrofurantoin	100.00（26/26）	97.37（37/38）	100.00（11/11）	12.50（2/16）

Table 4 Univariate and multivariate analyses of 14-day death-related risk factors in patients with BSIs

Prognostic factor		*No. of patients*		*Univariate*	*analysis*	*Multivariate analysis*	
		Survival	*Death(%)*	*X^2*	*P Value*	OR (95%CI) (95%CI)	*P Value*
Age (years)				*X^2=11.247*	*P=0.001*	*2.588(1.072-6.249)*	*P=0.034*
>65		32	*11(25.58)*				
≤65		426	*39(8.39)*				
Gender				*X^2=0.026*	*P=0.871*		
	Female	161	17(9.55)				
	Male	297	33(10.00)				
Neutropenia				*X^2=0.004*	*P=0.950*		
Yes		359	39(9.80)				
No		99	11(10.00)				
Catheter-related infection				*X^2=5.106*	*P=0.024*	*3.627(0.746-17.636)*	*P=0.110*
Yes		73	2(2.67)				
No		385	48(11.09)				
HMs subtype				*X^2=8.060*	*P=0.153*		
	AL	312	28(8.24)				
	sAA	10	5(33.33)				
	MDS	20	3(13.04)				
	Lymphoma	83	9(9.78)				
	MM	23	3(11.54)				
	Others	*10*	*2(16.67)*				
Types of pathogens				*X^2=30.888*	*P=0.000*		*P=0.000*

	Gram-positive	*166*	*8(4.82)*			-	-
	Gram-negative (e.x. AB)	*281*	*25(8.62)*			1.450(0.642-3.274)	*P=0.315*
	AB	*5*	*14(70.59)*			35.483(9.441-133.352)	*P=0.000*
	Fungus	*20*	*3(9.52)*			2.494(0.667-9.325)	*P=0.630*
HSCT				X^2=4.684	P=0.096		
	Allogeneic HSCT	91	*16(14.95)*				
	Autologous HSCT	26	1(3.70)				
	No						
	No	341	33(8.82)				
Disease status				*X^2=22.811*	*P=0.000*	*0.051(0.007-0.379)*	*P=0.004*
	CR	*161*	*1(0.62)*				
	nCR	*297*	*49(14.16)*				

HM: hematological malignancy; AL: acute leukemia; MDS: myelodysplastic syndrome; sAA: severe aplastic anemia; MM: multiple myeloma; HSCT: hematopoietic stem cell transplantation; CR: complete remission; nCR: no complete remission; AB: *Acinetobacter baumannii*.

Figures

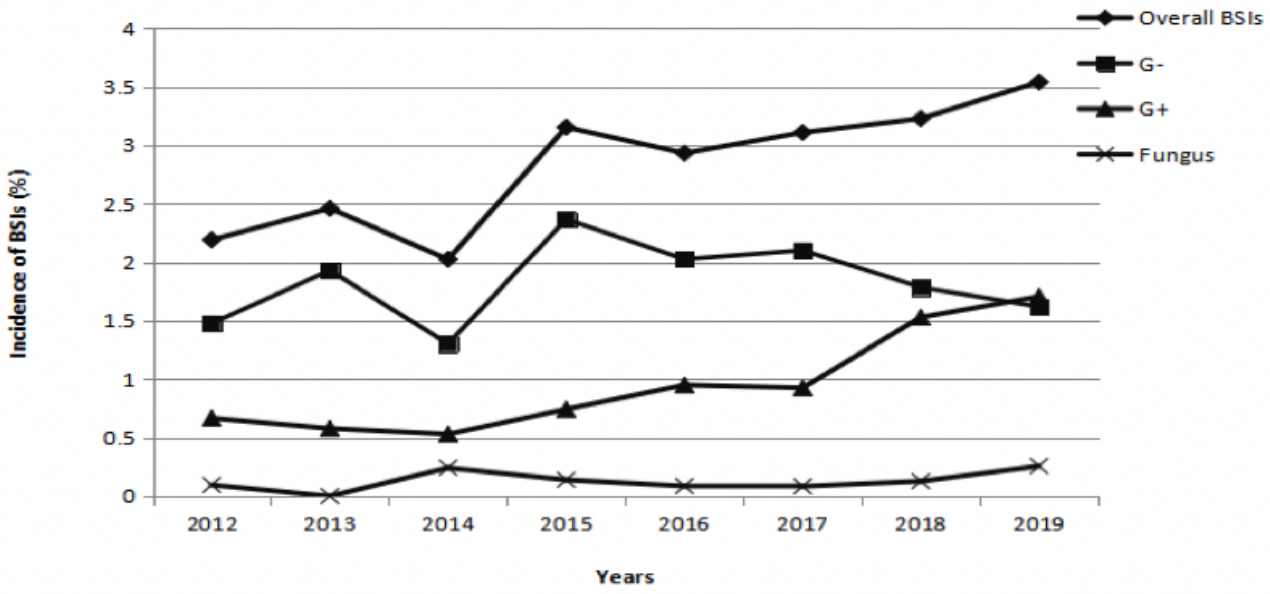

Figure 1

Trends in BSI pathogens among patients with hematologic malignancies in 2012–2019

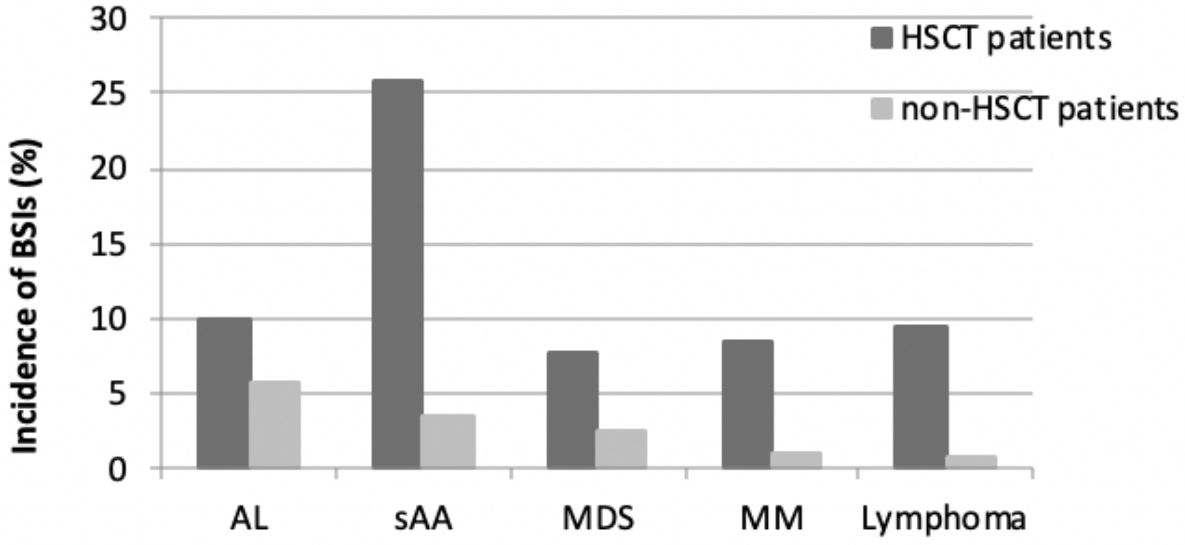

Figure 2

Incidence of BSIs in HSCT and non-HSCT patients with different HMs. AL: acute leukemia; sAA: severe aplastic anemia; MDS: myelodysplastic syndrome; MM: multiple myeloma. The incidence of BSIs was significantly higher in the HSCT group than in the non-HSCT group for all kinds of HM. AL: $\chi 2 = 11.046$, $P = 0.001$; sAA: $\chi 2 = 11.969$, $P = 0.001$; MDS: $\chi 2 = 4.712$, $P = 0.030$; MM: $\chi 2 = 17.140$, $P = 0.000$; lymphoma: $\chi 2 = 127.782$, $P = 0.000$.