Risk Management and Healthcare Policy

Open Access Full Text Article

ORIGINAL RESEARCH

Risk Factors and Clinical Management Strategies for Bloodstream Infections in Pediatric Hematological Malignancies

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Purpose: Chemotherapy remains the primary treatment for haematological malignancies (HMs). While recent therapeutic advances have improved patient survival, treatment-induced immunosuppression and prolonged neutropenia significantly elevate the risks of bloodstream infection (BSI), contributing to higher mortality. This study identifies risk factors for BSI in pediatric HM patients, aiming to establish evidence-based protocols for infection prevention and risk stratification, thereby informing targeted healthcare policies to reduce complications and improve treatment outcomes.

Patients and Methods: We retrospectively analyzed 682 pediatric HM patients presenting with fever at our institution, including 98 BSI-confirmed cases.Results were statistically compared across multiple aspects.

Results: Pediatric HM patients with bloodstream infection showed significantly higher AML prevalence (47.96% vs 33.22%, P = 0.005) and Gram-negative bacteria predominance (66.33%), notably *Escherichia coli* (*E. coli*) (27.55%). *Stenotrophomonas maltophilia* infection rates were significantly higher in lymphoma patients than in other hematological malignancies (P < 0.05). Multivariable analysis identified four modifiable risk factors: peak body temperature (OR = 5.468, 95% CI 3.407–8.775, P < 0.001), duration of neutropenia (OR = 1.181, 95% CI 1.120–1.245, P < 0.001), febrile neutropenia (OR = 8.193, 95% CI 3.574–18.780, P < 0.001), and invasive procedures (OR = 4.265, 95% CI 1.920–9.474, P < 0.001).

Conclusion: To reduce BSI complications in pediatric HM patients, we recommend implementing risk-stratified temperature protocols and strict neutropenia control (≤7 days), emphasizing rigorous clinical criteria for invasive procedures (PICC). These findings provide an evidence base for healthcare policies aimed at reducing infection-related mortality through optimized treatment protocols and enhanced clinical care standards.

Keywords: haematological malignancies, bloodstream infection, duration of neutropenia, invasive procedures, febrile neutropenia

Introduction

Haematological malignancies(HMs) are the most prevalent tumors in children, accounting for 30–40% of malignant neoplasms in children under under 15 years of age. Among these, childhood leukemia and lymphoma rank first and third respectively among pediatric malignancies.[1–5] Despite growing attention towards targeted therapy and immunotherapy in recent years, chemotherapy remains the primary modality for cancer treatment.[6,7] However, a significant drawback of chemotherapy is its potential to induce bone marrow suppression, leading to decreased neutrophil count, compromised immunity in children, and an increased susceptibility to infections.[8] The risk escalates as neutrophil counts progressively decline during treatment cycles.[9] Numerous domestic and international studies have underscored the significance of early prevention measures.[5,10–13] This retrospective analysis identified the factors contributing to bloodstream infection in

Received: 21 May 2025
Accepted: 27 September 2025
Published: 13 October 2025

pediatric patients with HMs, enabling timely implementation of individualized preventive measures to reduce infection-related mortality.

Material and Methods

Study Population

A retrospective review was performed on data from individuals diagnosed with HMs who developed fever during treatment at the Second Hospital of Hebei Medical University from January 2018 to February 2022. Inclusion criteria: (1) Age ≤18 years; (2) Confirmed HM diagnosis; (3) Fever during chemotherapy. Exclusion criteria: Non-hematologic malignancies or false-positive blood cultures. A total of 682 individuals were included. This study was approved by the Research Ethics Committee of the Second Hospital of Hebei Medical University (2021-R379) and was granted exemption from patient informed consent requirements due to anonymized data processing. All data handling complied with the Declaration of Helsinki, ensuring patient privacy.

Definitions

Haematological malignancies(HMs) were diagnosed in our hospital based on bone marrow morphology, immunology, cytogenetics, and molecular genetics examinations.[5] Granulocytopenia is defined as an absolute neutrophil count (ANC) of less than 1.5×10^9/L; Agranulocytosis is defined as an ANC of less than 0.5×10^9/L.[14] Fever is characterized by a single measurement of oral temperature ≥38.3 °C or ≥38.0 °C lasting for at least one hour, excluding non-infectious factors such as the tumor itself, drugs, blood transfusion products, or graft versus host disease.[15] Febrile neutropenia (FN) is defined as a single temperature measurement ≥38.5 °C or ≥38.0 °C for at least one hour with an ANC <500/mm^3 or expected to decrease to <500/mm^3 within 48 hours. Maximum body temperature: the highest recorded body temperature measured prior to and during diagnosis. Duration of chemotherapy: from the first day of the last chemotherapy session until fever onset.[16] Duration of granulocytopenia: the period from when the ANC falls below the normal reference range until fever onset. Duration of fever: the time elapsed between fever onset and blood culture collection. Bloodstream infection (BSI) is defined as positive blood cultures in a patient exhibiting systemic signs of infection, which may be either secondary to a known source or primary without an identified origin.[17] Invasive operations generally refer to various therapeutic operations involving trauma during clinical diagnosis and treatment activities, such as peripherally inserted central catheter (PICC), drainage tube, catheter etc.

Data Collection

Medical records of enrolled children presenting with fever were collected, encompassing general characteristics (such as gender, age, hematological malignancy type, leukocyte parameters, and blood culture results), clinical features (fever and infection), treatment details (antibiotic usage: nearly all patients received empirical therapy with biapenem and norvancomycin)., and outcomes. Episodes where a single skin contaminant was cultured were deemed clinically insignificant and exclude. Only cases with two or more positive blood cultures within 48 hours in patients exhibiting one or more signs or symptoms (fever, chills, rigors, hypotension) were included. Based on blood culture results, patients were categorized into BSI and non-BSI groups.

Statistical analysis

Results are presented as mean ± standard deviation (SD) and were analyzed using GraphPad Prism software. A multivariable logistic regression model was used to examine key factors potentially causing bloodstream infections. By Hosmer and Lemeshow tests, p-value>0.05. Odds ratios and corresponding 95% confidence intervals were reported. A p-value < 0.05 was considered statistically significant. Data analysis used SPSS version 25.

Results

The study included 682 patients: 584 without bloodstream infections and 98 with bloodstream infection. The mean age was 7.9±4.3 years, and the male-to-female ratio was 1.7:1 (63.49%/36.51%). Further clinical characteristics are presented

Table 1 Clinical Characteristics of the Study Population (n = 682)

	Total (n=682)	Non-BSI (n=584)	BSI (n=98)	*P* Value
Characteristics				
Age (years)(mean±SD)	7.9±4.3	7.8±4.3	8.9±4.2	0.019
Sex (%) male	433 (63.49%)	368 (63.0%)	65 (66.3%)	0.528
Female	249 (36.51%)	216 (37.0%)	33 (33.7%)	
Primary diagnosis				
Acute lymphoblastic leukemia (ALL)	346 (50.73%)	308 (52.74%)	38 (38.78%)	0.011
Acute myeloid leukemia (AML)	241 (35.34%)	194 (33.22%)	47 (47.96%)	0.005
Burkitt's Lymphoma (BL)	24 (3.52%)	20 (3.43%)	4 (4.08%)	0.744
T lymphoblastic lymphoma (TLBL)	21 (3.08%)	19 (3.25%)	2 (2.04%)	0.520
Anaplastic large cell lymphoma(ALCL)	11 (1.61%)	10 (1.71%)	1 (1.02%)	0.615
Non-Hodgkin lymphoma (NHL)	25 (3.67%)	24 (4.11%)	1 (1.02%)	0.132
Follicular lymphoma	3 (0.44%)	3 (0.51%)	0 (0.00%)	0.477
Hodgkin lymphoma (HL)	5 (0.73%)	4 (0.69%)	1 (1.02%)	0.719
Blastic plasmacytoid dendritic cell neoplasm	2 (0.29%)	2 (0.34%)	0 (0.00%)	0.562
Mixed cell leukemia	4 (0.59%)	0 (0.00%)	4 (4.08%)	<0.001

in Table 1. We observed that compared to those without bloodstream infections, patients with BSI were older (p=0.019) and exhibited a higher proportion of acute myeloid leukemia (AML)(p=0.005), while had a lower proportion of acute lymphoblastic leukemia (ALL)(p=0.011).

In our study, Gram-negative bacteria (66.33%) were the predominant pathogens responsible for bloodstream infections, followed by Gram-positive bacteria (27.55%) and fungi (6.12%) (Table 2). Of which the most prevalent pathogen was *Escherichia coli*(27.55%), followed by *Klebsiella pneumoniae subsp* (18.37%), *Pseudomonas aeruginosa* (7.14%),

Table 2 List of All Organisms Causing Bloodstream Infection

Microbial	Number	Percentage	Microbial	Number	Percentage
Gram-negative bacteria	**65**	**66.33%**	**Gram-positive bacteria**	**27**	**27.55%**
Escherichia coli	27	27.55%	*Staphylococcus hominis subsp*	5	5.10%
Klebsiella pneumoniae subsp	18	18.37%	*Streptococcus mitis*	5	5.10%
Pseudomonas aeruginosa	7	7.14%	*Staphylococcus aureus*	3	3.06%
Stenotrophomonas maltophilia	3	3.06%	*Micrococcus luteus*	3	3.06%
Acinetobacter baumannii	3	3.06%	*Streptococcus viridans group*	1	1.02%
Enterobacter cloacae	3	3.06%	*Streptococcus agalactiae*	1	1.02%
Klebsiella oxytoca	2	2.04%	*Corynebacterium spp*	1	1.02%
Proteus mirabilis	1	1.02%	*Kocuria kristinae*	1	1.02%
Proteus penneri	1	1.02%	*Staphylococcus cohnii subsp*	1	1.02%
Fungi	**6**	**6.12%**	*Leuconostoc pseudomesenteroides*	1	1.02%
Candida tropicalis	6	6.12%	*Staphylococcus epidermidis*	1	1.02%
			Staphylococcus capitis	1	1.02%
			Staphylococcus caprae	1	1.02%
			Staphylococcus haemolyticus	1	1.02%
			Bacillus subtilis	1	1.02%
			TOTAL	**98**	**100%**

Table 3 Bloodstream Infection Microbiota Profiles Across Distinct Hematologic Malignancies

Microbial	Total	AML	ALL	Mixed Cell Leukemia	Lymphoma
Gram-negative bacteria	**65**	**33 (70.21%)**	**24 (63.16%)**	**2 (50.00%)**	**6 (66.67%)**
Escherichia coli	27	13 (27.66%)	12 (31.58%)	2 (50.00%)	0 (0.00%)
Klebsiella pneumoniae subsp	18	11 (23.40%)	4 (10.53%)	0 (0.00%)	3 (33.33%)
Pseudomonas aeruginosa	7	4 (8.51%)	2 (5.26%)	0 (0.00%)	1 (11.11%)
Stenotrophomonas maltophilia	3	0 (0.00%)	1 (2.63%)	0 (0.00%)	2 (22.22%)
Acinetobacter baumannii	3	1 (2.13%)	2 (5.26%)	0 (0.00%)	0 (0.00%)
Enterobacter cloacae	3	2 (4.26%)	1 (2.63%)	0 (0.00%)	0 (0.00%)
Klebsiella oxytoca	2	1 (2.13%)	1 (2.63%)	0 (0.00%)	0 (0.00%)
Proteus mirabilis	1	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)
Proteus penneri	1	1 (2.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gram-positive bacteria	**27**	**12 (25.53%)**	**12 (31.58%)**	**0 (0.00%)**	**3 (33.33%)**
Fungi (*Candida tropicalis*)	**6**	**2 (4.26%)**	**2 (5.26%)**	**2 (50.00%)**	**0 (0.00%)**

Abbreviations: AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia.

Candida tropicalis (6.12%), *Streptococcus miti*s (5.1%), *Staphylococcus aureus* (3.06%), *Stenotrophomonas maltophilia* (3.06%), *Acinetobacter baumannii* (3.06%), *Enterobacter cloacae* (3.06%) and *Klebsiella oxytoca* (2.04%) respectively.

As shown in Table 3, *Escherichia coli* was the predominant pathogen in children with acute myeloid leukemia (AML), comprising 27.66%, with *Klebsiella pneumoniae* (23.4%), *Pseudomonas aeruginosa* (8.51%), *Candida tropicalis* (4.26%), and *Enterobacter cloacae* (4.26%). The predominant pathogens in acute lymphocytic leukemia(ALL) included *Escherichia coli* (31.58%), *Klebsiella pneumoniae* (10.53%), *Pseudomonas aeruginosa* (5.26%), *Candida tropicalis* (5.26%), *Acinetobacter baumannii*(5.26%), and *Enterobacter cloacae*(2.63%). In mixed leukemia, *Escherichia coli* and *Candida tropicalis* contribute equally (50% each). Among lymphoma patients, *Klebsiella pneumoniae subspecies pneumonia* was predominant (33.33%), followed by *Stenotrophomonas maltophilia* (22.22%) and *Pseudomonas aeruginosa* (11.11%).

By conducting statistical analysis on the distribution of the same pathogen across various hematologic malignancies, it can be observed that *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, Gram-positive bacteria, and Fungi exhibit no significant differences among patients with ALL (Figure 1A), AML (Figure 1B), and Lymphoma (Figure 1C). However, a notable difference was observed in the distribution of *Stenotrophomonas maltophilia* between lymphoma patients and those with other hematologic malignancies (Figure 1C).

Logistic regression analysis of factors relevant to BSI in pediatric HM patients (Tables 4 and 5) identified maximum body temperature, duration of granulocytopenia, FN, and invasive procedures (such as PICC, drainage tube, catheter etc) as independent risk factors for BSI. Other conditions showed no significant associations.

Discussion

In our study, the proportion of AML was the highest among the children with BSI. This suggests children with AML exhibited higher susceptibility to infection compared to those with ALL, aligning with the findings reported by Wu, H et al.[9] The underlying cause may be abnormal morphology and impaired function of granulocytes in these patients, resulting in ineffective pathogen eradication and compromised phagocytosis. This supports risk-adapted surveillance protocols for AML patients during chemotherapy-induced neutropenia. Both Peri, A.M. et al[18] and Wu, H. et al[9] reported Gram-negative bacteria constitute the predominant causative pathogens of bloodstream infections in adult patients with HMs. In our investigation, consistent findings were observed in pediatric HM patients, which aligns with previous reports by Raad, C. et al[19] in this Pediatric population. In the 1970s and early 1980s, Gram-negative bacteria constituted the primary isolates; however, there was a shift towards increased prevalence of Gram-positive bacteria during the late 1980s and early 1990s.[20] Despite this trend, no large-scale clinical study has investigated the impact of Gram-positive and Gram-negative bacteria on final outcomes. Our analysis also demonstrated that Gram-positive bacteria accounted for

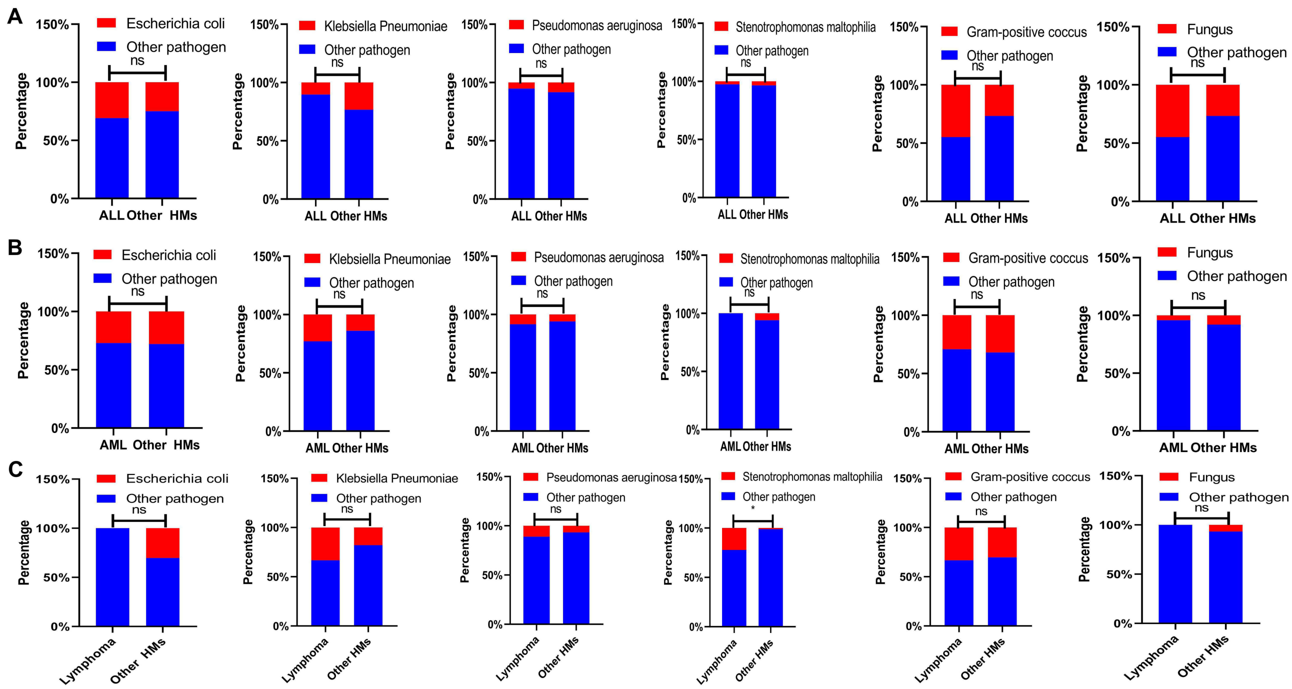

Figure 1 Statistical analysis of main pathogens in common pediatric haematological malignancies. (**A**) Acute lymphoblastic leukemia, ALL; (**B**) Acute myeloid leukemia, AMLl; (**C**) Lymphoma. (*, *P*< 0.05; ns, no statistical significance).

27.55% of BSI, with fungi at 6.12%. Henceforth, Vigilance towards Gram-negative bacterial infections is crucial, but attention should also be given to Gram-positive and fungal infections for early detection and improved efficacy.

Males represented a significantly higher proportion, which aligns with Elseady et al.[21] Although this study found no correlation between gender and BSI, there was a notable disparity in the number of male and female patients. Increasing evidence suggests that males are more susceptible to infections compared to females.[22,23] This susceptibility may be attributed to poor hygiene practices among males, leading to pathogenic bacterial infections. Additionally, estrogen secretion in females can inhibit the expression of certain microbial virulence factors.[24] Our study observed the average

Table 4 Univariate Logistic Regression Analysis of Factors Associated with Bloodstream Infection in Children with Haematological Malignancies

	Non-BSI (n=584, 85.6%)	BSI (n=98, 14.4%)	OR (95% CI)	*P* Value
Characteristics				
Age(years)(mean±SD)	7.8±4.3	8.9±4.2	1.050 (0.998–1.106)	0.060
Sex (%) male	368(63.0%)	65(66.3%)	1.399 (0.870–2.251)	0.166
Female	216(37.0%)	33(33.7%)		
T_{max}	38.34±0.63	39.11±0.79	5.035 (3.417–7.420)	<0.001
Duration of fever (hour)	26.08±23.00	29.02±23.93	1.005 (0.996–1.015)	0.265
WBC (10^9/L)	2.33±3.82	1.46±1.96	0.888 (0.795–0.992)	0.036
Neutrophil count (10^9/L)	1.28±2.45	0.83±1.51	0.847 (0.718–0.999)	0.049
Duration of granulocytopenia (day)	4.75±4.70	12.20±12.18	1.138 (1.098–1.180)	<0.001
Duration of chemotherapy (day)	10.64±6.55	14.18±13.55	1.049 (1.018–1.080)	0.002
Duration of GSF(day)	5.77±5.59	7.07±4.60	1.043(0.989–1.100)	0.121
FN	353(60.47%)	73 (74.49%)	1.980(1.195–3.279)	0.008
Invasive operation	123(21.06%)	35(35.71%)	2.588 (1.615–4.148)	<0.001

Abbreviations: BSI, Bloodstream infection; T_{max}, Maximum body temperature; GSF, Granulocyte stimulating factor; FN, Febrile neutropenia.

Table 5 Multivariable Logistic Regression Analysis of Factors Associated with Bloodstream Infection in Children with Haematological Malignancies

	OR (95% CI)	*P* Value
Characteristics		
T_{max}	5.468 (3.407–8.775)	<0.001
WBC (10^9/L)	0.954 (0.763–1.192)	0.677
Neutrophil count (10^9/L)	0.906 (0.660–1.245)	0.543
Duration of granulocytopenia(day)	1.181 (1.120–1.245)	<0.001
Duration of chemotherapy(day)	1.009 (0.979–1.040)	0.561
FN	8.193(3.574–18.780)	<0.001
Invasive operation	4.265 (1.920–9.474)	<0.001

Abbreviations: T_{max}, Maximum body temperature; FN, Febrile neutropenia.

age range of 7–8 years differed from previous domestic and international studies, possibly reflecting sample size constraints.[16,21] While previous reports indicated a negative correlation between age and infection incidence,[25] our study yielded contrasting results. This may be attributable to our institution's stringent protective isolation protocols for children under 5 years, featuring mandatory single-room isolation, dedicated medical equipment, reduced invasive procedures and high-frequency vital sign monitoring.

Furthermore, we found that patients with BSI presented significantly higher body temperatures (mean:39.11°C) than non-BSI patients (mean:38.34°C), indicating a strong association with BSI—consistent with previous research.[16] While existing literature indicates that initial fever peaks exceeding 39.5°C predict severe infections,[5] our study observed a lower median peak temperature in BSI patients. This downward shift may be associated with widespread empirical antibiotic use in our institution during febrile episodes, potentially reducing fever peaks. Previous reports have demonstrated an inverse relationship between absolute neutrophil count and infection incidence rate,[14] further supporting this notion. Notably, we observed a significant increase in BSI when neutrophils<0.4×109/L(P=0.0191), with even higher incidence for granulocyte deficiency exceeding 7 days (P<0.0001). These findings emphasize the importance of monitoring ANC duration in children with hematological malignancies following chemotherapy treatment. Although most patients received recombinant granulocyte stimulating factor(GSF) during chemotherapy as part of their current treatment regimen, no correlation was found between GSF usage and neutrophil count (P=0.562) or BSI prevention (P=0.121).

Our study revealed that invasive procedures were performed in 35.71% of BSI patients, with PICC being most prevalent (80%). Fisher M et al revealed central venous catheters as a significant risk factor for severe infection.[26] Similarly, Ruiz-Ruigómez M et al highlighted a significantly higher frequency of positive blood culture in patients with central venous catheters.[27] Therefore, invasive procedures contribute to the risk of BSI. It is imperative to enhance the care provided to patients undergoing such procedures.

This study has several limitations. Firstly, it is a retrospective single-center analysis. Secondly, traditional blood culture detection rates might be low, resulting in relatively few bloodstream infection patients. Future research will include more pediatric HM patients with confirmed BSI.

Conclusion

This study comprehensively analyzes the disease spectrum, pathogen profiles, and risk factors associated with BSI in pediatric HM patients. Key clinical recommendations include strict control of neutropenia duration (≤7 days) during chemotherapy and optimized invasive procedure management, such as enhanced sterile maintenance for PICC lines. These measures are essential for reducing infection incidence and improving quality of life in this vulnerable population.

Acknowledgments

Yaping Zhang and Jiao Li contributed equally to this work and were co-first authors.

Funding

The study was funded by Key Project of Medical Science Research in Hebei Province (20221151).

Disclosure

The authors report no conflicts of interest in this work.

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