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Original Article

Clinical characteristics and risk factors for shock and death from *E. coli* bacteremia in pediatric hematological patients

Haichen Wang[1]*, Jianling Liu[2]*, Ziyan Huang[1], Xiaoyan Tao[1], Jun Li[1], Yongmei Hu[1], Qingya Dou[3], Mingxiang Zou[1], Qun Yan[1], Wen' en Liu[1]

[1] Department of Clinical Laboratory, Xiangya Hospital, Central South University, Kaifu District, Changsha, Hunan, China
[2] Department of Radiology, Xiangya Hospital, Central South University, Changsha, Hunan, China
[3] Department of Infection Control Center, Xiangya Hospital, Central South University, Changsha, Hunan, China

* These authors contributed to the work equally and should be regarded as co-first authors.

Abstract

Introduction: The aim of our study was to evaluate the epidemiology, clinical features and risk factors for shock and mortality from *Escherichia coli* bacteremia among children and adolescents with hematological disorders.

Methodology: A retrospective observational study of *E. coli* bacteremia in the hematology department at Xiangya Hospital from January 2013 to June 2018 was conducted. Clinical characteristics, laboratory results and antimicrobial susceptibility were analysed. Risk factors for shock and mortality were also investigated.

Results: Of the 45 strains of *E. coli*, 73.3% were multidrug-resistant (MDR). Septic shock was observed in 51.1% of patients, and the 30-day all-cause mortality was 22.2%. The risk factors associated with shock were an elevated red blood cell distribution (RDW) value when bloodstream infections (BSIs) occurred (> 15%, OR, 6.840; 95% CI, 1.571 – 29.788) and a lower WBC count (< 300/mm^3, OR, 6.761; 95% CI, 1.383 – 33.044). Multivariate analysis showed that only an elevated D-dimer level (> 0.5 mg/L, OR 12.250, 95% CI 1.268 – 118.361) was a risk factor for 30-day mortality. Furthermore, we observed decreases for RDW changes at two time points (neutropenia and BSIs occurred) in the non-shock group and survival group.

Conclusions: MDR infections from *E. coli* bacteremia were common in pediatric hematological patients. In our setting, the laboratory results may serve as a clue for physicians to distinguish patients at higher risk for shock and mortality. Furthermore, RDW could be used as a biomarker to elucidate potential disorders in hematological patients.

Key words: *Escherichia coli* bacteremia; hematological disorders; shock; mortality; risk factors.

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Introduction

Currently, with the development of chemotherapy and transplantation, the survival of patients with hematological diseases has improved dramatically. However, because of long hospitalizations, invasive medical procedures and immunosuppression, infections remain a great threat to the survival of hematological patients. Bloodstream infections (BSIs) is a leading type observed in neutropenic patients, accounting for approximately 11 - 38% of infections [1,2]. In recent years, a clear trend from Gram-positive towards Gram-negative bacterial BSIs infection has been observed [3,4]. Among the bacteria, *Escherichia coli* is the most common pathogen causing BSIs. More importantly, multi-drug resistant (MDR) *E. coli*, such as extended spectrum β-lactamase (ESBL) *E. coli*, is reported worldwide and has a negative impact on the outcome of hepatological patients [5,6]. However, limited information has been reported on the epidemiology, outcome and risk factors for *E. coli* bacteremia among children and adolescents with hematological disorders.

Therefore, we conducted a retrospective study of child and adolescent patients with hematological disorders who had *E. coli* bacteremia, regarding the clinical characteristics, laboratory results and outcomes as well as antimicrobial sensitivity, to assess the risk factors for shock and BSIs mortality among patients with *E. coli* bacteremia.

Methodology

Patients and study design

We conducted a retrospective observational study at Xiangya Hospital, Central South University, Changsha, China. From January 2013 to June 2018, patients aged

< 19 years who were admitted to the hematology department were enrolled if they had at least one episode of *E. coli* bacteremia. Xiangya Hospital, Central South University, is a university-affiliated tertiary teaching hospital with a separate department for children and adolescents with hematologic disorders. An average of 2000 patients are admitted annually. Clinical data were reviewed from medical records, and no additional medical procedures were performed.

The following data were collected: age, sex, underlying diseases, presence of septic shock, antimicrobial susceptibility profile, antimicrobial agents applied during the preceding 30 days, the presence of a peripherally inserted central catheter (PICC), and laboratory results. Clinical outcome (30 days after the infection episode) was classified as alive, dead, or lost to follow-up.

The study was approved by the Ethics Committee of Xiangya Hospital, Central South University. No informed consent was taken because this study did not cause additional medical procedure.

Microbiological tests

Blood samples were routinely collected when the patients had fever (> 38 °C) or systemic symptoms indicating bacteremia. Each 1 - 3 ml of blood sample was immediately inoculated into culture bottles (BD BACTECTM Peds Plus Culture Vial, Becton Dickinson, Sparks, MD, USA) and transferred to the laboratory. An automated system (BACTECTM FX 200, Becton Dickinson) was used for culturing. The bacterial identification was performed with a microflexTM LT/SH mass spectrometer (Bruker Daltonik, Bremen, Germany), and antibiotic susceptibility tests were conducted with a VITEK® system (bioMérieux, Hazelwood, MO, USA), except for cefoperazone-sulbactam, which is determined by Kirby-Bauer disk diffusion method.

Definitions

Neutropenia was defined as an absolute neutrophil count < 500/mm^3 or an expected absolute neutrophil count < 500/mm^3 within two or three days of the day on which fever developed [7]. Fever was defined as axillary or tympanic membrane temperatures above 37.5 °C or 38.0 °C, respectively. Shock was defined as a systolic blood pressure < 90 mmHg or received inotropic agents to maintain blood pressure.

E. coli bacteremia was diagnosed when at least one of the blood sample cultures was positive for *E. coli*. *E. coli* bacteremia episodes occurring within one month of a previous episode of *E. coli* bacteremia were considered relapses and were excluded from the study. Polymicrobial infection was defined as the identification of bacteria other than *E. coli* collected from blood samples on the same day as the *E. coli* was identified. Previous antimicrobial therapy was defined as exposure to any systemic antibiotics for more than 48 h within 30 days.

Hospital-associated *E.coli* bacteremia was defined as the samples were collected more than 48 h after the hospitalization; otherwise, the bacteremia were considered community-acquired.

Antibiotic susceptibility was determined according to the Clinical and Laboratory Standards Institute 2015 recommendations [8]. Intermediate and resistance were recognized as non-susceptible. MDR was defined as non-susceptible to at least one agent in ≥ 3 antimicrobial categories, according to Magiorakos *et al.* [9].

Statistical analysis

Numbers and percentages were reported for categorical variables. The means and standard deviations with variation or medians with interquartile range (IQR) were reported for continuous variables, depending on their distribution patterns. Categorical variables were compared using the Pearson chi-square test or Fisher`s exact test, when appropriate. Continuous variables were compared with the Mann-Whitney U test. P values < 0.05 were considered statistically significant. All variables that were associated with shock and death in the univariate analysis (P < 0.05) were entered into a multivariate logistic regression analysis. SPSS (version 22, IBM Corporation, Armonk, NY, USA) was used for all analyses.

Results

Characteristics of patients with E. coli bacteremia

A total of 45 episodes of *E. coli* bacteremia occurred in 43 pediatric patients within the study period. Among them, two patients suffered two episodes of *E. coli* bacteremia.

Demographic and clinical characteristics are shown in Table 1. The mean age of the patients was 9.4 ± 4.9 years, and 20 (44.4%) were female. Acute lymphoblastic leukemia (23, 51.5%) was the most common underlying disorder, followed by acute myeloid leukemia (14, 31.1%), severe aplastic anemia (4, 8.9%), lymphoma (3, 6.7%) and hemophagocytic syndrome (1, 2.2%). Considering the stage of hematological disorders, 11 (26.2%) were newly diagnosed, 30 (71.4%) were complete remission and only one (2.2%) patients suffered relapse. Only two

(4.4%) patients received hematopoietic stwm cell transplantation. Among the 45 episodes, all patiens suffered from neutropenie, with the average days of 18.6 ± 8.7 days, and a predominant ot patients (32, 71.1%) had a history of antibiotics within 30 days before the onset of bacteremia. In our study, no antibiotic prophylaxis was applied to any patients.

Most episodes of bacteremia (39, 86.7%) were considered as hospital associated. Polymicrobial infections were diagnosed in ten (22.2%) episodes: three of *klebsiella pneumoniae*, two each of *Acinetobacter baumani*, *Enterococcus faecium* and *Candida*, and one episode with *klebsiella pneumoniae* and *Pseudomonas aeruginosa*. In all 45 episodes, 23 (51.5%) patients suffered shock, and 30-day all-cause mortality was noted in ten cases (22.2%). The Kaplan-Meier survival curves of 30-day survival for patients with or without elevated D-dimmer (> 0.5mg/L) were shown in Figure 1.

Figure 1. Kaplan-Meier survival curves of 30-day survival for patients with or without elevated D-dimmer (>0.5mg/L).

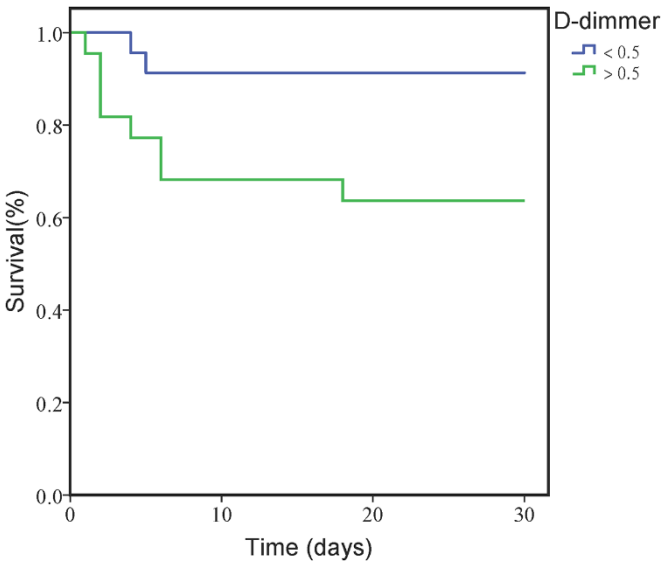

Table 1. Demographic and clinical characteristics of 45 episodes of *E. coli* bacteremia.

Characteristics	All patients	MDR	non-MDR	*P* value
Age, mean years ± SD	9.4 ± 4.9	8.9 ± 4.9	10.8 ± 4.4	0.180
Sex, number of females	20 (44.4)	14 (42.4)	6 (50.0)	0.741
Underlying disorders				0.958
Acute myeloid leukemia	14 (31.1)	11 (33.3)	3 (25.0)	
Acute lymphoblastic leukemia	23 (51.1)	16 (48.5)	7 (58.3)	
Severe aplastic anemia	4 (8.9)	3 (9.1)	1 (8.3)	
Lymphoma	3 (6.7)	2 (6.1)	1 (8.3)	
Hemophagocytic syndrome	1 (2.2)	1 (3.0)	0 (0.0)	
Stage of hematological disorders				1.000
Newly diagnosed	11 (26.2)	8 (25.8)	3 (27.3)	
Complete remission	30 (71.4)	22 (71.0)	8 (72.7)	
After relapse/refractory	1 (2.4)	1 (3.2)	0 (0.0)	
Hematopoietic stem cell transplantation	2 (4.4)	2 (6.1)	0 (0.0)	0.600
Infection on admission				0.668
Community acquired	6 (13.3)	5 (15.2)	1 (8.3)	
Hospital associated	39 (86.7)	28 (84.8)	11 (91.7)	
Empirical antibiotic therapy				0.130
Carbapenem alone or in combination	41 (91.1)	31 (93.9)	10 (83.3)	
Piperacillin-tazobactam	2 (4.2)	2 (6.1)	0 (0.0)	
Cefoperazone-sulbactam	2 (4.4)	0 (0.0)	2 (16.7)	
Length of days for neutropenia, mean ± SD	18.6 ± 8.7	19.2±8.0	17.0±9.7	0.226
Appropriateness of empirical therapy	43 (95.6)	31 (93.9)	12 (100.0)	1.000
PICC	27 (60.0)	20 (60.6)	7 (58.3)	1.000
Previous antimicrobial therapy, within 30 days	32 (71.1)	26 (78.8)	6 (50.0)	0.076
Shock	23 (51.1)	20 (60.6)	3 (25.0)	**0.047**
30-day mortality	10 (22.2)	9 (27.3)	1 (8.3)	0.246
Polymicrobial infection	10 (22.2)	5 (15.2)	5 (41.7)	0.101
Laboratory results				
WBC count < 300/mm^3	30 (66.7)	24 (72.7)	6 (50.0)	0.283
RDW level > 15 (neutropenia occurred)	30 (66.7)	22 (66.7)	8 (66.7)	1.000
RDW level > 15 (BSI occurred)	21 (46.7)	16 (48.5)	5 (41.7)	0.746
D-dimer level > 0.5 mg/L	21 (46.7)	17 (51.5)	4 (33.3)	0.329

PICC, peripherally inserted central catheter; RDW, red blood cell distribution; WBC, white blood cell.

Table 2. Antibiotic susceptibility rates of the *E. coli* strains (n, [%]).

Antibiotic	Susceptible	MDR	non-MDR	*P* value
Piperacillin-tazobactam	41 (91.1)	29 (87.9)	12 (100.0)	0.327
Cefazolin	10 (22.2)	0 (0.0)	10 (83.3)	**< 0.001**
Ceftriaxone	10 (22.2)	0 (0.0)	10 (83.3)	**< 0.001**
Ceftazidime	29 (64.4)	17 (51.5)	12 (100.0)	**0.003**
Cefepime	28 (62.2)	16 (48.5)	12 (100.0)	**0.001**
Aztreonam	22 (48.9)	10 (30;3)	12 (100.0)	**< 0.001**
Imipenem	43 (95.6)	31 (93.9)	12 (100.0)	0.600
Amikacin	41 (91.1)	29 (87.9)	12 (100.0)	0.561
Gentamycin	20 (44.4)	12 (36.4)	8 (66.7)	0.096
Ciprofloxacin	22 (48.9)	11 (33.3)	11 (91.7)	**0.001**
Trimethoprim-sulfamethoxazole	8 (17.8)	3 (9.1)	5 (41.7)	**0.022**
Cefoperazone-sulbactam	39 (86.7)	27 (81.8)	12 (100.0)	0.171

Among the 45 isolates of *E. coli*, 33 strains were detected in the presence of ESBLs, while two strains were classified as carbapenem-resistant Enterobacteriaceae (CRE). According to the susceptibility profiles, 33 strains were MDR, although tigecycline and fosfomycin were not involved in the panel of antibiotics we reported. The strains showed high susceptibility to imipenem, amikacin and piperacillin-tazobactam at susceptible rates of 95.6%, 91.1% and 91.1%, respectively. On the other hand, they were highly resistant to first- and second-generation cephalosporin and trimethoprim-sulfamethoxazole, with susceptible rates of 22.2%, 22.2% and 17.8%, respectively. The susceptible rates for other antibiotics tested were below 70%, as shown in Table 2. Compared to MDR *E. coli*, non-MDR *E. coli* showed higher susceptibility to cephalosporins, aztreonam and ciprofloxacin. Both MDR and non-MDR *E. coli* showed low susceptibility to trimethoprim-sulfamethoxazole. For the two CRE *E. coli* strains, one was only susceptible to amikacin, while the other was resistant to all tested antibiotics.

Table 3. Comparison of characteristics between the shock and non-shock groups.

Characteristics	shock group n = 23	non-shock group n = 22	*P* value
Age < 9 years, n (%)	12(52.2)	8(36.4)	0.373
Sex, number of females, n (%)	12 (52.2)	8 (36.4)	0.373
Underlying disorders, n (%)			0.297
Acute myeloid leukemia	8 (34.8)	6 (27.3)	
Acute lymphoblastic leukemia	13 (56.5)	10 (45.5)	
Other disorders	2 (8.7)	6 (27.3)	
Empirical antibiotic therapy, n (%)			0.269
Carbapenem	15 (65.2)	14 (63.6)	
Carbapenem with piperacillin-tazobactam	3 (13.0)	2 (9.1)	
Carbapenem with cefoperazone-sulbactam	3 (13.0)	0 (0.0)	
Carbapenem with AMB or TIG	2 (8.7)	2 (9.1)	
Piperacillin-tazobactam	0 (0.0)	2 (9.1)	
Cefoperazone-sulbactam	0 (0.0)	2 (9.1)	
Length of days for neutropenia, mean ± SD	18.5 ± 9.0	18.7 ± 8.5	0.794
Appropriateness of empirical therapy, n (%)	21 (91.3)	22 (100.0)	0.489
PICC, n (%)	17 (73.9)	10 (45.5)	0.071
Previous antimicrobial therapy, within 30 days, n (%)	18 (78.3)	14 (63.6)	0.337
30-day mortality, n (%)	7 (30.4)	3 (13.6)	0.284
Multidrug-resistant strain infections, n (%)	20 (87.0)	13 (59.1)	**0.047**
Polymicrobial infection, n (%)	4 (17.4)	6 (27.3)	0.491
Laboratory results, n (%)			
WBC count < 300/mm^3	19(82.6)	11(50.0)	**0.029**
RDW level > 15 (neutropenia occurred)	15(65.2)	15(68.2)	1.000
RDW level > 15 (BSI occurred)	15(65.2)	6(27.3)	**0.017**
D-dimer level > 0.5 mg/L	14(60.9)	7(31.8)	0.075

AMB, Amphotericin B; TIG, tigecycline; PICC, peripherally inserted central catheter; RDW, red blood cell distribution; WBC, white blood cell.

Clinical features of E. coli bacteremia

In the 45 episodes, MDR *E. coli* was predominant cause (33, 73.3%). The diffecrences of clinical features between MDR and non-MDR *E. coli* were analyzed in Table 1. In general, the baseline clinical characteristics and the laboratory results between the two groups showed no significant differents. Although more patients suffering MDR *E. coli* bacteremia reveived antimicrobial therapy within 30 days, the difference was also not statistically significant (78.8% vs 50.0%, $P = 0.076$). The MDR infections were only associated with higher incidences of shock (60.6% vs 58.3%, $P = 0.047$).

Initial antibiotic treatment

All patients received empirical antibiotic treatment immediately after the blood samples for microbiology culture were collected. Most of our patients received carbapenems alone (64.4%) or in combination (26.8%). For the remaining four patients, two received piperacillin-tazobactam and two received cefoperazone-sulbactam. Overall, 43 (95.6%) patients received appropriate initial antibiotics. Only two patients received inappropriate antibiotics because of CRE infection.

Clinical factors associated with shock

In general, 23 (51.1%) episodes of shock were noted in our study. As shown in Table 3, in the shock group, MDR *E. coli* infection was more frequent than that in the non-shock group (87.0% vs 59.1%, $P = 0.047$). The laboratory results showed that the shock group had lower WBC counts (< 300/mm^3, 82.6% vs 50.0%, $P = 0.029$) and higher RDW values when BSIs occurred (> 15%, 65.2% vs 27.3%, $P = 0.017$). After performing the multivariate logistic analysis, an elevated RDW value when BSIs occurred (> 15%, OR, 6.840; 95% CI, 1.571 – 29.788) and a lower WBC count (< 300/mm^3, OR, 6.761; 95% CI, 1.383 – 33.044) were risk factors associated with shock (Table 4).

In addition, we analysed the changes in RDW values between neutropenia and BSIs. In the non-shock group, the RDW values ranged from 12.0% to 20.80% (median, 16.30%, IQR, 14.05 – 17.65%) when neutropenia occurred. A dramatic decrease was observed for RDW when BSIs occurred (median, 13.70%, IQR, 12.70 – 15.13%, $P = 0.003$). However, in the shock group, the RDW values at the two time points were at the same level (median, 15.80%, IQR, 13.50 – 18.10%, vs median, 15.50%, IQR, 13.70 – 17.20%, $P = 0.792$).

Clinical factors associated with death

Table 5 shows the comparison of variables associated with mortality. The non-survival group patients were given more broad-spectrum antibiotics within 30 days (100.0% vs 62.9%, $P = 0.042$) and higher D-dimer values (> 0.5 mg/L, 80.0% vs 37.1%, $P = 0.029$). The survival group received more appropriate empirical treatment (100% vs 80%, $P = 0.045$). Multivariate analysis showed that only elevated D-dimer levels (> 0.5 mg/L, OR 12.250, 95% CI 1.268 – 118.361) were a risk factor for 30-day mortality (Table 6). However, no MDR infection or shock was associated with death ($P > 0.05$).

Similar results for RDW changes in survival group. A slight decrease was observed (median, 16.20%, IQR, 14.20 – 18.00% for neutropenia occurred, vs median, 14.60%, IQR, 12.90 – 15.80%, $P = 0.014$). Meanwhile, no significant changes in non-survival group was indicated (median, 15.45%, IQR, 13.25 – 18.35% for neutropenia occurred, vs median, 15.45%, IQR, 13.15 – 17.63%, $P = 0.853$).

Discussion

Hematological patients are more vulnerable to pathogens because of long-term hospitalization, chemotherapy-induced immune suppression and antibiotic exposure, leading to greater mortality. Currently, the rate is increasing for Gram-negative bacteremia in hematological patients, and *E. coli* is a predominant pathogen [3]. The prevalence rates are between 8% and 46% in different studies [10,11]. Therefore, we analysed 45 episodes of *E. coli* bacteremia among children and adolescents suffering from hematological conditions.

In recent years, the emergence and spread of MDR *E. coli* have been documented worldwide, which is a great threat to hematological patients. Our study focused on 45 strains of *E. coli* in the hematology department, and 73.3% were MDR strains, which is a rate similar to those found in other studies [12,13]. The patients we included all had hematological malignancies and required lengthy hospitalizations and broad-spectrum antibiotic treatment, which may contribute to MDR infections. However, the clinical characteristics and the laboratory results between MDR and non-MDR groups showed no significant differents. Although the patients suffering MDR infection received more previous antimicrobial therapy, which may contribute to the screening and colonization of the MDR strains, the difference was not statistically signifecant.

Table 4. Multivariate analysis of risk factors with the occurrence of shock.

Characteristics	*P* value	OR (95% CI)
RDW level > 15 (BSI occurred)	0.010	6.840 (1.571-29.788)
WBC count < 300/mm^3	0.018	6.761 (1.383-33.044)

RDW, red blood cell distribution; WBC, white blood cell.

Table 5. Comparison of characteristics between the survival and non-survival groups.

Characteristics	non-survival group n = 10	survival group n = 35	*P* value
Age < 9 years, n (%)	7(70.0)	13(37.1)	0.083
Sex, number of females, n (%)	5 (50.0)	15 (42.9)	0.731
Underlying disorders, n (%)			0.132
Acute myeloid leukemia	2 (20.0)	12 (34.3)	
Acute lymphoblastic leukemia	4 (40.0)	19 (54.3)	
Other disorders	4 (40.0)	4 (11.4)	
Empirical antibiotic therapy, n (%)			0.127
Carbapenem	6 (60.0)	23 (65.7)	
Carbapenem with piperacillin-tazobactam	0 (0.0)	5 (14.3)	
Carbapenem with cefoperazone-sulbactam	0 (0.0)	3 (8.6)	
Carbapenem with AMB or TIG	1 (10.0)	4 (11.4)	
Piperacillin-tazobactam	2 (20.0)	0 (0.0)	
Cefoperazone-sulbactam	1 (10.0)	2 (5.8)	
Length of days for neutropenia, mean ± SD	19.8 ± 11.8	18.3 ± 7.7	0.968
Appropriateness of empirical therapy, n (%)	8 (80.0)	35 (100.0)	**0.045**
PICC, n (%)	3 (30.0)	24 (68.6)	0.064
Previous antimicrobial therapy, within 30 days, n (%)	10 (100.0)	22 (62.9)	0.042
Shock, n (%)	7 (70.0)	16 (45.7)	0.284
Multidrug-resistant strain infections, n (%)	9 (90.0)	24 (68.6)	0.246
Polymicrobial infection, n (%)	4 (40.0)	6 (17.1)	0.194
Laboratory results, n (%)			
WBC count < 300/mm^3	5(50.0)	25(71.4)	0.263
RDW level > 15 (neutropenia occurred)	5(50.0)	25(71.4)	0.263
RDW level > 15 (BSI occurred)	6(60.0)	15(42.9)	0.476
D-dimer level > 0.5 mg/L	8(80.0)	13(37.1)	**0.029**

AMB, Amphotericin B; TIG, tigecycline; PICC, peripherally inserted central catheter; RDW, red blood cell distribution; WBC, white blood cell.

Table 6. Multivariate analysis of risk factors with the occurrence of death.

Characteristics	*P* value	OR (95% CI)
D-dimer level > 0.5 mg/L	0.030	12.250 (1.268-118.361)

The appropriateness of empirical antibiotic therapy is closely linked to mortality among hematological patients, which has been proven by previous works [14,15]. However, the clinicians' choice of antibiotics is still unclear. Although piperacillin-tazobactam showed excellent effects against the strains in vitro (a susceptible rate of 91.1%), empirical piperacillin-tazobactam therapy may be critical, as demonstrated by a study conducted by Tamma PD *et al*., in which a 1.92-fold increase in mortality was seen when piperacillin-tazobactam was employed instead of carbapenem, although the strains remained susceptible to piperacillin-tazobactam *in vitro* [16]. Similar results were obtained for cefepime, as MIC is a more important factor in predicting mortality and is superior to susceptibility [17]. Most of the strains were susceptible to carbapenem, which was consist with previous studies [12,18]. In our study, all patients were neutropenic when bacteremia occurred, so carbapenem alone or in combination was the first choice, and 95.6% of the episodes were considered appropriate. Different studies have also proven that inappropriate empirical therapy is a risk factor for death rather than MDR infection. The high rate of appropriate empirical therapy explained why shock and MDR infection were not associated with mortality in our study [19]. However, the susceptibility rate for amikacin was 91.1%. Han *et al*. discovered that a combination of cefepime or piperacillin-tazobactam and aminoglycoside showed effects comparable to those of empirical carbapenem therapy in febrile neutropenic children in ESBL *E. coli* and *K. pneumoniae* bacteremia [20]. Therefore, amikacin can be used as an alternative to reduce the use of carbapenem and retard the spread of CRE.

In our study, the rate of shock was 51.1%, which is much higher than the average rate of 5% - 30% in studies of patients of all ages [21]. The high rate of shock occurred because our patients were neutropenic children and adolescents, and their conditions deteriorated rapidly. Another study of *E. coli* bacteremia in pediatric patients with acute leukemia showed a higher shock/hypotension rate of 71% [22]. The multivariate analysis demonstrated that RDW level (> 15%) and WBC count (< 300/mm^3) were risk factors for shock. RDW is a routine test, as a part of the complete blood count, which reflects the heterogeneity of red blood cells (anisocytosis). However, recent studies have demonstrated the potential value of RDW in predicting mortality among patients with coronary artery disease, liver and kidney dysfunction, stroke, pulmonary embolism, and diabetes mellitus and among normal populations [23,24]. More recently, Kim *et al*. showed that changes in RDW values could also predict mortality among patients with severe sepsis or septic shock [25]. However, our study demonstrated the relationship between RDW values with the occurrence of shock, also decreases in RDW value both in non-shock group and survival group. Although RDW is influenced by chemotherapy and blood transfusion [26], multivariate analysis confirmed that the elevation of RDW (> 15%) when BSIs occurred was a risk factor for shock. Interestingly, an obvious decrease in the RDW value in the non-shock group and survival group between neutropenia and BSIs occurred, and the RDW value remained high in the shock group and non-survival group. Although the underlying mechanism for RDW remains unclear, several articles have provided clues. RDW is influenced by systemic inflammation, oxidative stress and malnutrition. Systemic inflammation impacts bone marrow function and iron metabolism, and excessive proinflammatory cytokines restrict the generation of erythropoietin, therefore inhibiting the maturation of erythrocytes and leading to an increase in the RDW value [27-29]. Systemic inflammation has been shown to predict progressive illness and death in intensive care unit patients. Oxidative stress is released by activated leukocytes when infections occur, and the imbalance in oxidative stress damages nucleic acids and lipids, influencing RDW [30,31]. Malnutrition is also common in patients receiving chemotherapy. Taken together, these results show that RDW may be a potential biomarker for analysing the level of human disorders.

Hematological patients suffered from severe bacteremia because of neutropenia, with poor clinical outcomes. In our study, we confirmed that elevated D-dimer (> 0.5 mg/L) was a risk factor for death. This result was consistent with those of previous work [32,33]. D-dimer is the degradation of cross-linked fibrin, which represents the activation of coagulation and the fibrinolysis system; it can be used as one of the indicators of thrombosis. D-dimer has mainly been used in the diagnosis of thrombotic diseases, such as pulmonary embolism. Extensive interactions have been observed between the coagulation system and the inflammatory pathways in infected patients [34]. Because of insufficient tissue perfusion, massive cytokine release and an imbalance of the anticoagulant system, patients with sepsis often suffer from coagulation abnormalities, resulting in microthrombosis, DIC or multiple organ dysfunction. Shorr AF *et al*. proved that the elevation of D-dimer was correlated with TNF-a and IL-6 in severe infections, which further illustrated the problem [35].

However, several limitations of this study should be mentioned. First, our analysis was a retrospective single-centre study design; thus, the results may not be generalizable to other settings. Second, our susceptibility tests were performed using the VITEK auto system. Third, our study of RDW values did not include vitamin B12, iron and erythropoietin due to a lack of clinical information. Fourth, our study focused on *E. coli* bacteremia in the hematology department; thus, our findings for RDW values only represented a portion of the bacteremia, and further analysis should be conducted to obtain more conclusive results.

Conclusion

In conclusion, *E. coli* bacteremia in pediatric patients with hematological diseases was prevalent, and ESBL and MDR strains were the predominant types. Imipenem, amikacin and piperacillin-tazobactam showed higher activity for the *E. coli* strains in our study. In our setting, the laboratory results, such as those of RDW and D-dimer, may serve as a clue for physicians in distinguishing patients at higher risk for shock and mortality. Furthermore, our findings demonstrated the important risk factors for shock and death in pediatric patients with hematological diseases, while RDW could be used as a biomarker to elucidate potential disorders.

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Corresponding author

Mingxiang Zou, PhD
Xiangya Hospital, Central South University, No.87, Xiangya Road; Kaifu district, Changsha; Hunan, China, 410008
Tel: +86 73184327440
Fax: +86 73184327440
E-mail: zoumingxiang@csu.edu.cn

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