

Clinical Characteristics of Bloodstream Infections in Pediatric Acute Leukemia: A Single-center Experience with 231 Patients

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Abstract

Background: Acute leukemia is the most common pediatric hematological malignancy. Bloodstream infections (BSIs) are severe complications in these patients during chemotherapy. This study aimed to explore the clinical presentation and etiology of BSI, as well as the common sites of infection, and to provide a basis for the rational regarding antibiotic use.

Methods: We performed a retrospective chart review of all pediatric patients who had acute leukemia accompanied by a BSI in our hospital from December 2011 to September 2015. All patients were selected based on clinical presentation and had to have at least one positive blood culture for inclusion. The basic clinical characteristics, blood culture results, and antimicrobial susceptibilities were analyzed.

Results: All 231 patients had a fever; of them, 12 patients continued to have a fever. Twenty-five patients had nonremitting (NR) leukemia, and 206 patients achieved complete remission (CR). Differences in the duration of fever between the NR and CR groups were significant (9.6 ± 7.9 vs. 5.1 ± 3.8 days, $P = 0.016$). One hundred and eighty patients had agranulocytosis. Differences in fever duration between the agranulocytosis and nonagranulocytosis groups were significant (6.2 ± 5.1 vs. 4.1 ± 2.6 days, $P = 0.001$). The other sites of infection in these 231 patients were the lung, mouth, digestive tract, and rectum. Blood culture comprised 2635 samples. There were 619 samples, which were positive. Of the 619 positive blood culture samples, 59.9% had Gram-negative bacteria, 39.3% had Gram-positive bacteria, and 0.8% had fungus. The primary pathogens were *Pseudomonas aeruginosa*, *Enterobactercloacae*, *Escherichia coli*, and *Klebsiella pneumoniae*. Of these 231 patients, 217 patients were cured. The effective treatment ratio was 94%.

Conclusions: Gram-negative bacteria were the main pathogenic bacteria in patients with acute leukemia in our center. NR primary illness, agranulocytosis, and drug-resistant pathogenic bacteria were all risk factors for poor prognosis.

Key words: Acute Leukemia; Agranulocytosis; Bloodstream Infection; Etiology; Pediatric

INTRODUCTION

Bloodstream infection (BSI) was defined as a positive isolate in a blood culture that was associated with clinical findings.^[1] BSI is usually a serious complication of a malignant hematologic disease and can be a cause of death. Blood cultures and drug sensitivity tests were used to establish a direct basis for blood infections. This study analyzed the clinical characteristics and etiology of BSIs in pediatric acute leukemia in our center to provide a basis for the rationale regarding antibiotic use.

METHODS

Ethical approval

Patients aged <18 years, diagnosed with acute leukemia at the Department of Hematology Oncology Center,

Beijing Children's Hospital (BCH), from December 2011 to September 2015 were enrolled in the study. The Ethics Committee of BCH approved this study.

Grouping criteria

1. Patients had a fever (axillary temperature $\geq 38.5^{\circ}\text{C}$) during hospitalization.
2. Patients had a positive blood culture.

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The incidence of concurrent BSI was 1.04% in our leukemia ward from December 2011 to September 2015. There were 231 patients in our center, including 132 male patients and 99 female patients. The age of onset ranged from 0.9 to 17.7 years; the median age was 5 years. There were 198 patients with acute lymphoblastic leukemia (ALL) and 33 patients with acute nonlymphocytic leukemia (ANLL). Of the 231 patients, 25 patients had nonremitting (NR) disease, and 206 patients achieved complete remission (CR). Chemotherapy regimens were as follows: patients with ALL were treated according to the CCLG-08 chemotherapy regimen, and patients with ANLL were treated according to the BFM-AML-05 chemotherapy regimen.

A retrospective review was conducted on 231 pediatric patients with acute leukemia accompanied by a BSI at BCH from December 2011 to September 2015. We analyzed the clinical presentation, etiology of BSI, etc.

Sample collection

1. For febrile patients with ALL ($T > 38.5^{\circ}\text{C}$), blood cultures were obtained from the double peripheral vein, and antimicrobial susceptibility was determined. If a peripherally inserted central catheter was placed, blood sampling was obtained from the venous catheter.
2. If the patients had multiple sites of infection, secretion samples were obtained and cultured from all sites of infection.
3. Blood cultures were again obtained one week later when the patients returned to normothermia.
4. Routine blood examinations including C-reactive protein (CRP) levels were assessed during the period of infection.

Diagnostic criteria and therapeutic evaluation criteria

Diagnosis of septicemia was carried out based on the "Hospital Infection Diagnosis Standard" published by the Ministry of Public Health of the People's Republic of China. Bacteremia was diagnosed according to the American Thoracic Society and Critical Care Medicine (ACCP/SCCN, 1991). Therapeutic effects criteria were referenced according to the "Anti-bacterial Drug Clinical Research Guiding Principles," published by the Ministry of Public Health of the People's Republic of China in 1993. Therapeutic evaluations were divided into effective and ineffective.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 statistical software (SPSS Inc., USA). In this study, the number of febrile days (temperature $> 37.5^{\circ}\text{C}$) is presented as mean \pm standard deviation (SD). First, a comparison between the two groups was conducted. For normal distributions, *t*-test was used. Otherwise, the Wilcoxon rank sum test was used. In this study, the number of febrile days was tested using the Kolmogorov-Smirnov test. The number of days was not normally distributed ($P = 0.00$), and hence the rank sum test was used; a value of $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics

The average length of hospital stay was 16.8 ± 10.8 days for the 231 patients. There were 184 patients who were treated with steroids during infection, within 3 months. A total of 2635 blood culture specimens were obtained from all 231 patients. The number of positive peripheral blood samples was 619; the positivity rate for the specimens was 23.5%. One hundred and eighty-one children had a single bacterial infection (78.4%) out of all 231 patients; 37 patients were infected with two kinds of bacteria (16%), and 13 patients (6%) simultaneously had at least three or more bacterial infections.

Clinical characteristics

General manifestations

Two hundred thirty-one patients had a fever, and of these patients, 12 patients had a persistent fever. The duration of fever ranged from 1 to 30 days, with an average of 5.6 ± 4.6 days. Twenty-five patients were NR with an average of 9.6 ± 7.9 febrile days, and 206 patients who achieved CR had with an average of 5.1 ± 3.8 febrile days. Differences in the duration of fever between the NR and CR groups were significant (9.6 ± 7.9 vs 5.1 ± 3.8 days, $P = 0.016$).

Other infections

Of the 231 patients with positive blood cultures, 50 had pneumonia; 34 had oral ulcers and mucositis; 24 had a digestive tract infection; 11 had a perianal infection; five had skin ulceration and local cellulitis; three had a urinary tract infection; two had a central nervous system infection; two had paronychia; two had a liver abscess; and one had a splenic abscess. Seven patients were infected with the same bacteria in both their blood and secretion cultures. Of the seven patients, a blood culture from one case indicated *Acinetobacter baumannii*, accompanied by a respiratory tract infection, according to a positive pharyngeal swab culture. One patient had a positive blood culture for *Stenotrophomonas maltophilia* and was infected by the same bacteria at other sites, including positive cultures obtained from the pharynx, the oral mucosa, and an oral ulcer. Another five patients had positive blood cultures for *Pseudomonas aeruginosa*, including one patient with pneumonia and a skin ulcer, one patient with vulvar cellulitis, one case with an umbilical infection, and two patients with a perianal infection. Five patients with ALL had positive cultures for *P. aeruginosa* from their infection sites.

Distribution and drug resistance of pathogenic bacteria

Among the 619 positive samples, the ratio of Gram-negative bacteria was 59.9%; the ratio of Gram-positive bacteria was about 39.3%; and the ratio of fungi was about 0.8%. The main pathogenic bacteria in the BSIs were Gram-negative bacteria at our center, as shown in Table 1. Gram-negative bacteria have a higher likelihood of drug resistance than Gram-positive bacteria; when children with a malignant hematologic disease experience septicemia

Table 1: Distribution of pathogenic bacteria in 231 children

Pathogen	n	Ratio (%)
Gram-positive bacteria	243	39.3
Human <i>Staphylococcus</i>	60	9.7
<i>S. epidermidis</i>	59	9.5
<i>S. haemolyticus</i>	8	1.3
Coagulase-negative Staphylococci	9	1.5
<i>E. faecium</i>	7	1.1
<i>E. faecalis</i>	16	2.6
<i>M. luteus</i>	10	1.6
<i>S. pneumoniae</i>	8	1.3
<i>S. oralis</i>	4	0.6
<i>S. mutans</i>	14	2.3
Other Streptococci	6	1.0
<i>C. jeikeium</i>	7	1.1
<i>Bacillus</i>	22	3.6
<i>Micrococcus</i>	3	0.5
Other Gram-positive bacilli	5	0.8
Other Gram-positive cocci	5	0.8
Gram-negative bacteria	371	59.9
<i>E. coli</i>	66	10.7
<i>K. pneumoniae</i>	64	10.3
<i>P. aeruginosa</i>	72	11.6
<i>E. cloacae</i>	69	11.2
<i>A. baumannii</i>	20	3.2
<i>S. maltophilia</i>	8	1.3
Other <i>Acinetobacter</i>	6	1.0
<i>K. pneumoniae</i>	12	1.9
<i>Salmonella</i>	2	0.3
Other unicellular bacteria	7	1.1
Holder bacteria	5	0.8
<i>A. faecalis</i>	2	0.3
Neisseria	8	1.3
Other <i>Enterobacteriaceae</i>	17	2.8
Other Gram-negative bacteria	13	2.1
Fungus	5	0.8
<i>C. albicans</i>	1	0.2
<i>T. asahii</i>	4	0.6

S. epidermidis: *Staphylococcus epidermidis*; *S. haemolyticus*: *Staphylococcus haemolyticus*; *E. faecium*: *Enterococcus faecium*; *E. faecalis*: *Enterococcus faecalis*; *M. luteus*: *Micrococcus luteus*; *S. pneumoniae*: *Streptococcus pneumoniae*; *S. oralis*: *Streptococcus oralis*; *S. mutans*: *Streptococcus mutans*; *C. jeikeium*: *Corynebacterium jeikeium*; *E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *E. cloacae*: *Enterobacter cloacae*; *A. baumannii*: *Acinetobacter baumannii*; *S. maltophilia*: *Stenotrophomonas maltophilia*; *A. faecalis*: *Alcaligenes faecalis*; *C. albicans*: *Candida albicans*; *T. asahii*: *Trichosporon asahii*.

during bone marrow suppression, de-escalation antibiotics are administered, so carbapenem antibiotics are widely used. Several common Gram-negative bacteria with carbapenem resistance are summarized in this article. *P. aeruginosa*, *Enterobacter cloacae*, *Escherichia coli*, and *Klebsiella pneumoniae* were the main pathogenic bacteria, and drug sensitivity test results showed that the rate of resistance to carbapenem was 65.3%, 26.1%, 12.1%, and 67.2%, respectively. However, amikacin is highly sensitive [Figure 1].

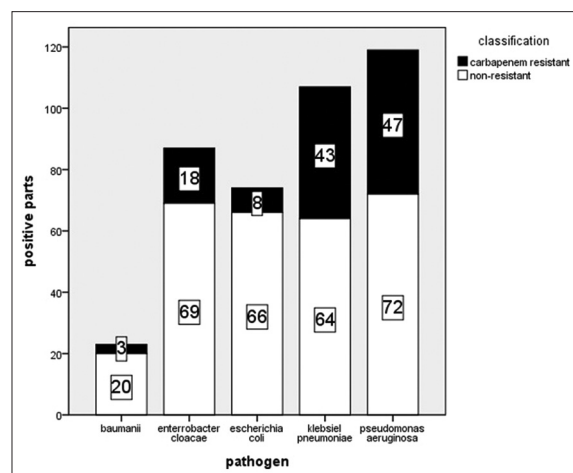


Figure 1: Distribution of carbapenem resistance in Gram-negative bacteria.

Relationship between the number of febrile days and the number of days of agranulocytosis

Of the 231 patients, 180 had agranulocytosis (absolute neutrophil count, $<0.5 \times 10^9/L$), in which 23 patients had serious agranulocytosis (absolute neutrophil count, $<0.1 \times 10^9/L$). The agranulocytosis time ranged from 1 to 79 days, with an average of 13.4 ± 10.1 days. Fifty-one patients did not have agranulocytosis. Of these patients, the agranulocytosis group had a fever duration ranging from 1 to 30 days, with an average of 6.2 ± 5.1 days, and the nonagranulocytosis group had a fever duration of 1–13 days, with an average of 4.1 ± 2.6 days; the difference was significant (6.2 ± 5.1 vs. 4.1 ± 2.6 days, $P = 0.001$). The agranulocytosis duration was more than 7 days; the duration of fever was 1–30 days, with an average of 5.7 ± 4.9 days; the duration of neutropenia was <7 days; and the duration of fever was 1–11 days, with an average of 4.9 ± 2.8 days, but without significance (5.7 ± 4.9 vs. 4.9 ± 2.8 days, $P = 0.25$). As for monitoring the CRP level, 180 children had varying degrees of increasing CRP levels; the maximum CRP level was 9–272 mg/L, with a median value of 57 mg/L.

Treatment outcome

Of the 231 patients, 217 patients were cured, demonstrating an effective treatment rate of 94%. Six patients died, and eight patients had ineffective infection control; thus, a total of 14 patients were administered ineffective anti-infection therapy. Nine of the 14 ineffectively treated patients had a carbapenem-resistant infection; four patients had infections with no drug sensitivities; and one patient had sensitive bacteria. The specific pathogens and drug sensitivity results for these 14 patients are shown in Table 2.

DISCUSSION

In pediatric patients with acute leukemia, BSIs are one of the most important infectious complications that could lead to a high mortality rate during treatment. Due to the disease

Table 2: Pathogenic bacteria and drug sensitivity in 14 children administered ineffective anti-infection therapy

Number	Gender	Age (years)	Primary disease	Combined with other infections	Pathogen	Strain (n)	Carbapenem resistant	Prognosis
1	Female	3.8	ALL	Pneumonia, cellulitis	<i>P. aeruginosa</i>	4	R	Discharged
2	Male	10.5	ALL	Pneumonia, cellulitis	<i>P. aeruginosa</i>	8	R	Discharged
3	Female	4.2	ANLL	Pneumonia	<i>B. cepacia</i>	4	S	Death
4	Female	1.2	ANLL	Pneumonia	<i>K. pneumoniae</i>	4	R	Death
5	Male	3.7	ALL	Pneumonia	<i>B. cereus</i>	8	No drug sensitivity	Death
6	Female	5.3	ANLL	Pneumonia	<i>P. aeruginosa</i>	2	R	Death
7	Female	3.3	ANLL	Intestinal infection	<i>Bacteroides</i>	2	No drug sensitivity	Death
8	Female	3.8	ALL	Pneumonia, encephalitis, urinary tract infection	<i>K. pneumoniae</i>	1	R	Discharged
9	Male	12.4	ALL	Pneumonia, digestive tract infection	<i>A. baumannii</i>	3	R	Death
10	Male	2.3	ALL	Pneumonia, intestinal infection	<i>K. pneumoniae</i>	4	R	Discharged
11	Female	5.7	ALL	Pneumonia	<i>Micrococcus</i>	1	No drug sensitivity	Discharged
12	Female	2.3	ALL	Pneumonia, liver abscess	<i>B. gladioli</i>	1	R	Discharged
13	Male	9.4	ANLL	Pneumonia	<i>T. asahii</i>	2	No drug sensitivity	Discharged
14	Female	4.3	ANLL	Gastrointestinal tract infection	<i>K. pneumoniae</i>	1	R	Discharged

ANLL: Acute nonlymphocytic leukemia; ALL: Acute lymphocytic leukemia; R: Carbapenem resistant; S: Carbapenem sensitive; *P. aeruginosa*: *Pseudomonas aeruginosa*; *B. cepacia*: *Burkholderia cepacia*; *K. pneumoniae*: *Klebsiella pneumoniae*; *B. cereus*: *Bacillus cereus*; *A. baumannii*: *Acinetobacter baumannii*; *B. gladioli*: *Burkholderia gladioli*; *T. asahii*: *Trichosporon asahii*.

characteristics and chemotherapy treatments, pediatric patients with ALL have the deficient immune function of varying degrees and are susceptible to infection. In patients with long-term neutropenia after chemotherapy, mucosal barrier damage, immunosuppressive agents, corticosteroids, and long-term broad-spectrum antimicrobial drug use result in an increased incidence of BSI.^[2] We summarized the clinical features of 231 pediatric patients with acute leukemia with a BSI in our center. We found that 371 strains of Gram-negative bacteria accounted for 59.9% of the 619-positive blood culture samples, consistent with previous reports,^[3,4] in which *P. aeruginosa*, *E. cloacae*, *E. coli*, and *K. pneumoniae* were the main pathogens;^[5,6] drug sensitivity tests showed that there were varying degrees of resistance to carbapenem antibiotics. The drug resistance rate was high.^[2,7-9] An analysis was conducted using specimens that were obtained from the same host, so the overall drug resistance rate increased. The Gram-positive bacteria included coagulase-positive *Staphylococcus epidermidis* and *Staphylococcus aureus*.^[10] Coagulase-negative *Staphylococcus* (central nervous system) was the most common pathogenic bacteria in the blood cultures but with the extensive use of broad-spectrum antibiotics and application of invasive diagnostic methods,^[11] the normal flora in the human central nervous system of had gradually become an important pathogenic bacteria. The results of this study showed that coagulase-positive *S. aureus* was the most common Gram-positive pathogen. In addition, because children with leukemia commonly have symptoms of anemia, collecting more than one blood sample can be difficult. Thus, strict disinfection and excellent puncture techniques to reduce blood culture contamination are both important. Five strains of fungi accounted for 0.8% in this study; thus, the detection rate for fungi was low. The

main reason was related to the prevention and treatment of fungal infection during myelosuppression.

This study involved 231 pediatric patients with a BSI, including 33 patients with ANLL and 198 patients with ALL.^[12] The primary disease, long-term repetitive chemotherapy, accompanied by infection in the lungs, digestive tract, oral cavity, anus, etc., which all led to decreased immune functions.^[13] A variety of invasive operations and the use of broad-spectrum antibacterial agents, which can destroy the mucosal barriers and normal flora in the respiratory system and gastrointestinal tract in patients with hematological diseases and other patients who are more prone to nosocomial infections. Thus, increased protective measures are necessitated for these patients, including their environment and mucosal function during chemotherapy.

Because patients with leukemia have abnormal white blood cells, the quality and quantity of neutrophil chemotaxis and phagocytosis are decreased after chemotherapy and bone marrow suppression. The duration and degree of neutropenia underscored the increased risk of life-threatening infections.^[14] Fever and neutropenia are common in patients with hematologic malignancies during chemotherapy, and approximately 10–30% of patients experience sepsis.^[15] Severe neutropenia is a risk factor for an infection that occurs in acute leukemia after chemotherapy and is an important factor that affects the prognosis of infection. In this study, 231 children had a BSI, including 180 patients with neutropenia. The statistical analysis showed that with the emergence of agranulocytosis, the longer the duration of agranulocytosis, the longer the fever lasted. There was a significant difference, often suggesting a poor prognosis. Thus, shortening the time of bone marrow suppression after chemotherapy and promoting leukocyte recovery

would be important to strengthen the immunoprotection of neutropenic patients.^[16] A meta-analysis by Clark *et al.*^[17] found that granulocyte-colony-stimulating factor (G-CSF) combined with neutrophils could shorten the time of antibiotic administration. Thus, early administration of G-CSF after chemotherapy could effectively shorten the duration of neutropenia and decrease the risk of severe infection. However, studies have also shown that G-CSF could aggravate the cytokine storm secreted by infection.^[18-20] This study was a retrospective study, without a randomized control, so additional study is necessitated. In addition, this study demonstrated a correlation between the primary disease and severity of the infection. Of the 231 patients, 25 patients had NR disease, and 206 patients were in remission. NR patients had more febrile days during their infection than patients who achieved remission, and there were significant differences between these two groups (9.6 ± 7.9 vs. 5.1 ± 3.8 days, $P = 0.016$). Due to the high rate of infection in children with leukemia who had agranulocytosis, empiric antibiotics should be administered quickly if these patients become febrile. In this study, all patients with an infection were administered varying degrees of empiric anti-infective therapy using ade-escalation method according to epidemiological findings and infection site and source.^[21-23] The effective rate was 94% in 231 patients administered anti-infection treatment.^[24]

This study had several limitations. First, the clinical presentations, physical examinations, and laboratory data were obtained from medical records, so some incomplete data were inevitable because of the retrospective design. Second, the number of cases was small, so some clinical characteristics and laboratory data reached limited statistical significance.

Effective control of infection is directly related to the survival of children with leukemia. In children with leukemia, bone marrow suppression can occur with chemotherapy resulting in fevers and chills, as well as other symptoms of infection; there is a high possibility of a BSI. Blood and secretion cultures and drug sensitivity tests should be collected timely for diagnosis, sampled in different parts and at different times, as well as repeatedly inspected to improve the diagnostic rate.^[25] In addition, empirical treatment is needed immediately to avoid serious complications. Based on the hospital epidemiological data and bacterial resistance data, because the diagnosis of the pathogen has not been reported.

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Conflicts of interest

There are no conflicts of interest.

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