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Clinical Features of Bloodstream Infection in Children with Haematological Malignancies

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Abstract ***Purpose:*** Sepsis and bacteraemia are both referred to as bloodstream infection (BSI). It contributed majorly to the mortality of the children with blood cancer. In order to reveal the clinical features of BSI and improve its outcome, we performed the investigation among the inpatients in haematology/oncology department. ***Methods:*** Neutropenia was defined as an absolute neutrophil count (ANC) in peripheral blood of $<0.5\times10^9$/L. Microbiologically documented infection (MDI) was defined when causative pathogen was isolated from blood. Drug susceptibility test was performed using the VITEK-60 Auto Microbic System and Kirby-Baue disk diffusion method. Relative cytokines in the sera were detected through flow cytometry (FCM). All of the data were analysed with STATA software (version 9.0). ***Results:*** The incidence of BSI was 10.73% (161/1500), the rate of MDI for BSI was 43.48% (70/161). There was no statistical significance between non-MDI and MDI groups on the clinical characteristics. Total 79 strains were detected from 70 blood samples. Gram-positive bacteria, gram-negative bacteria and fungi accounted for 55.70% (44/79), 43.04% (34/79) and 1.27% (1/79), respectively. The most common pathogens were *Staphylococcus epidermidis* (20.25%), *Escherichia coli* (15.19%) and *Klebsiella pneumoniae* (15.19%). Staphylococcus showed no/low resistance to linezolid, vancomycin and furantoin. Gram-negative bacteria showed no/low resistance to cefoxitin, imipenem, piperacillin/tazobactam and amikacin. The mortality of BSI was 3.1% (5/161). ***Conclusions:*** BSI had no specific signs and symptoms clinically, and gram-positive bacteria were the dominant pathogens. Antibiotics selection according to the susceptibility test was superior to the empirical treatment. Improved prevention, early detection, and advanced therapeutic strategies might decrease the incidence of the BSI and improve its treatment outcome.

Key words Bloodstream infection (BSI); Cancer; Children; Treatment

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Introduction

Sepsis is a blood infection caused by different pathogenic microorganisms and their toxin in blood flow. If there is only transient and a few numbers of blood bacteria without obvious toxemia, it is called bacteremia. Now sepsis and bacteraemia are both referred to as bloodstream infection (BSI).[1] Children with the blood cancers often suffer from neutropenia, immune suppression and damage of the skin, oral cavity, mucous membrane of digestive tract, due to their own disease characteristics, high doses of chemotherapy and the application of immunosuppressant, which lead to bacteria in other parts of the body invading to bloodstream through the mucous membrane barrier easily.[2] In order to elucidate the clinical features of BSI of the children with blood cancers in our hospital, we carried out investigation on the BSI among the inpatients in haematological department of Children's Hospital of Zhejiang University's Medical School from January 2010 to December 2010.

Patients and Methods

Methods

Neutropenia was defined as an absolute neutrophil count (ANC) in peripheral blood of $<0.5\times10^9$/L.[3,4] Granulocyte colony-stimulating factor (G-CSF) and venous injection immunoglobulin were administered on the chemotherapeutic children with neutropenia at the same time of antimicrobial therapy, but the G-CSF was considered only when bone marrow reached to completed remission (CR) stage for the myeloid leukaemia. Regarding prophylaxis of fungal infection, 3 days' oral fluconazole was administered while ANC $<1.0\times10^9$/L. Febrile patients were defined as one ear temperature measurement ≥38.5 centigrade or two measurements of 38-38.4 centigrade made within a 4h interval.[4] When a causative pathogen was isolated from blood, microbiologically documented infection (MDI) was defined.[5,6] BSI was diagnosed according to the hospital infection diagnostic standard published by the Medical Administration Department of the Chinese Health Ministry in 2001.[7] Clinical diagnosis was defined with temperature above 38 centigrade or below 36 centigrade, and come up to one of the following conditions: (1) invasion or migration lesions; (2) systemic toxic symptoms without apparent focal infection; (3) with skin rash or petechia, hepatosplenomegaly, increased neutrophil with nuclear shift to left, and there are no other explanations; (4) systolic blood pressure below 12 kPa (90 mmHg), or the blood pressure drop more than 5.3 kPa (40 mmHg) compared to the original systolic pressure. Aetiologic diagnosis was based on the clinical diagnosis, and confirmed by one of the two points: (1) pathogenic microorganism was cultured from the blood; (2) pathogen antigen was detected in the blood.

Patients

From January 2010 to December 2010 in the Children's Hospital Affiliated to the Medical School of Zhejiang University, total 1500 patients were newly admitted and treated in haematology/oncology department, and total 161 cases (93 boys and 68 girls, with a median age of 7 years (range, 1 month to 17 years) developed BSI. The basic disease included acute lymphocytic leukaemia (112 cases), acute myeloid leukaemia (34 cases), lymphoma (10 cases), haemophagocytic syndrome (4 cases) and langerhans cell histiocytosis (1 case). The clinically diagnosed patients with negative blood culture was categorised as non-MDI group, the aetiologically diagnosed patients with positive blood culture was defined as MDI group. There were no recurrent MDI during the study period of 2010. All of the 161 BSI diagnosed patients were catheterised via femoral or external jugular vein.

Instruments and Reagents

Bacteria were identified through a VITEK-60 Auto Microbic System which was bought from Marcel Mérieux Company. Susceptibility paper and susceptibility medium (MH medium) were purchased from the UK Oxiod and Marcel Mérieux, respectively. Human Th1/Th2 Cytokine kit II was from BD Biosciences (San Jose, CA, USA).

Antibiotic Susceptibility Test

Total 161 blood samples were cultured, and routine drug susceptibility test was performed using the VITEK-60 Auto Microbic System and Kirby-Baue disk diffusion method. The extended-spectrum β-lactamase (ESBL) strains were detected by double disk test. Quality control strains included *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* ATCC 90028, and *Escherichia coli* ATCC 35218. The criteria of drug resistance followed the Clinical Laboratory Standards Institute (CLSI) guidelines set in

2008.[8] If more than two consecutive results were the same in one patient, we recorded the results of blood culture one time; if the results were different, we recorded the each result of blood culture.

Cytokine Assay

The serum cytokines of all patients were examined during fever. The CRP, procalcitonin determination and blood culture were performed at the same time. The concentrations of IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ in the sera were quantitatively determined immediately after clotting (the sera were usually available 1 hour after blood sampling) with the CBA Human Th1/Th2 Cytokine kit II through flow cytometry (FCM), as previously described in the literature.[9] A standard calibration curve was established for each kit. The maximum and minimum limits of detection for all six cytokines were 1.0 and 5000 pg/mL, respectively. The investigators performed the assays while blinded to the clinical status of the patients. If the results were very unusual, with the levels of all six cytokines being significantly elevated, the samples were retested. The results were available to clinicians within 5 hours after sample collection.

Statistical Analysis

All of the data were input into STATA software, version 9.0. Variables were analysed by χ^2 test, rank-sum, *t* test and Fisher's exact test. A two-sided *P* value of ≤0.05 was statistically significant.

Results

Incidence of the BSI and Rate of MDI

In 1500 hospitalised children, 161 patients were diagnosed as BSI. The incidence was 10.73% (161/1500), in which only 79 show positive pathogenic culture. The rate of MDI for BSI was 49.06% (79/161).

Clinical Characteristics

Features of Temperature

All of the patients with BSI had fever. The incidence was 100%. Total 55 cases were complicated with shivering and/or decreased blood pressure (BP). The incidence of complications was 34.16% (55/161). The fever duration, maximum temperature and complications of chill and/or decreased BP among the non-MDI and MDI groups were listed in Table 1, and no statistical significance was revealed.

Comparison of the C-reactive Protein and Inflammatory Factors

CRP (C-reactive protein) in 161 BSI patients was all increased. The rate was 100% (161/161). FCM analysis of cytokines showed that human IL-6 in 90 patients increased evidently. The rate was 55.9% (90/161). Human IL-10 increased distinctly in 85 cases. The rate was 52.8% (85/161). Eleven patients showed increased TNF-α (11/161, 6.8%). Heightened IFN-γ was detected in 8 patients (4.97%, 8/161). Human IL-4 were increased in 4 patients (2.5%, 4/161). Procalcitonin was increased in 8 patients (4.97%, 8/161). The CRP values, cytokines and procalcitonin of the groups were compared in Table 2. There was no statistically significant differences between the two groups.

Predisposing Factors

Total 156 patients had bone marrow suppression, accounting for 96.89% (156/161). The predisposing factors for BSI such as neutropenia (123/161, 76.4%), pneumonia (17/161, 10.6%), oral infection (16/161, 9.94%), other infections (gastroenteritis, otitis media, pancreatitis) (8/161, 4.97%), flare in puncture site (22/161, 13.66%) and deep vein thrombosis (5/161, 3.11%) were analysed in Table 3, and no significant difference was found between the two groups. There was no significant differences in age, gender and disease distribution in the 70 patients with MDI compared to the remaining 1430 patients admitted during the same period.

Pathogenic Characteristics

Distribution of Pathogens

Total 79 strains were detected from 70 blood samples. Nine patients (9/70, 12.86%) had mixed infection. The co-existing organisms were *Klebsiella pneumoniae* and *Staphylococcus epidermidis* (4 patients), *Escherichia coli* and *Staphylococcus aureus* (3 patients), *Pseudomonas aeruginosa* and *Enterococcus* (1 patient), *Klebsiella*

Table 1 Comparison of fever duration, maximum temperature and complications between non-MDI and MDI groups

Groups	Patients	Fever duration (hour)			Maximum temperature (centigrade)			Complications	
		<24	24~96	>96	<38.5	38.5~39.4	>39.5	Chill	Decreased BP
Non-MDI	91	41	42	8	36	40	15	14	13
MDI	70	23	35	12	17	38	15	19	11
χ^2/Q			3.53			3.46		3.36	0.064
P			0.060			0.063		0.067	0.801

Non-MDI: BSI patients with negative blood culture; MDI: BSI patients with positive blood culture; BP: blood pressure.

Table 2 Comparison of the CRP, cytokines and procalcitonin between non-MDI and MDI groups

Groups	Patients	CRP value		Cytokines					Procalcitonin
		<100	>100	IL-6	IL -10	IL -4	TNF-α	IFN-γ	
Non-MDI	91	73	18	48	42	3	5	5	3
MDI	70	47	23	42	43	1	6	3	5
χ^2		3.56		0.844	3.70				
P		0.059		0.358	0.054	0.535	1.0	0.633	0.296

Non-MDI: BSI patients with negative blood culture; MDI: BSI patients with positive blood culture; CRP: C-reactive protein.

Table 3 Comparison of the predisposing factors in non-MDI and MDI groups

Groups	Patients	ANC		Topical infections				
		<0.1	0.1-0.5	Pneumonia	Oral infection	Flare in puncture site	Deep vein thrombosis	Other infections
Non-MDI	91	41	21	7	14	16	1	5
MDI	70	44	17	10	4	6	4	3
χ^2		3.41		1.821	3.726	2.723	2.80	0.122
p		0.065		0.177	0.054	0.099	0.094	0.726

Non-MDI: BSI patients with negative blood culture; MDI: BSI patients with positive blood culture; ANC: absolute neutrophilic cells.

pneumoniae and *Enterococcus* (1 patient), and the results were not due to the bacterial contamination. Gram-positive bacteria, gram-negative bacteria and fungi accounted for 55.70% (44/79), 43.04% (34/79) and 1.27% (1/79), respectively. The most common pathogens were *Staphylococcus epidermidis*, *Escherichia coli* and *Klebsiella pneumoniae*, accounting for 20.25%, 15.19% and 15.19%, respectively. The distribution of pathogens was shown in Table 4.

Drug Resistance Results of Common Pathogens

Total 27 β-lactamase-positive strains were detected from the collected 31 *staphylococcus aureus*, accounting for 87.1% (27/31). All of the 16 *Staphylococcus epidermidis* showed 100% resistance to oxacillin. 72.73% of 11 strains of other coagulase-negative staphylococci (CoNS) were resistant to oxacillin. All 4 strains of *Staphylococcus aureus* were not found to be resistant to oxacillin. Total 9 extended spectrum β-lactamase (ESBL) producing strains were

Table 4 Distribution of hospital-acquired BSI pathogens

Pathogens	Number of strains	Proportion(%)
Gram-positive bacteria	**44**	**55.70**
Staphylococcus epidermidis	16	20.25
Other CoNS	11	13.92
Streptococcus	6	7.59
Staphylococcus aureus	4	5.06
Enterococcus	4	5.06
Micrococcus	2	2.53
Bacillus	1	1.27
Gram-negative bacteria	**34**	**43.04**
Escherichia coli	12	15.19
Klebsiella pneumoniae	12	15.19
Pseudomonas aeruginosa	5	6.33
Sphingomonas paucimobilis	2	2.53
Aeromonas hydrophila	2	2.53
Salmonella thompsoni	1	1.27
Fungus	**1**	**1.27**
Candida albicans	1	1.27
Total	**79**	**100.00**

CoNS: coagulase negative staphylococcus.

detected from 12 strains of *Escherichia coli* (75%); total 5 ESBL-producing strains were detected from 12 strains of *Klebsiella pneumoniae* (41.7%). Staphylococcus and gram-negative bacteria resistant rates were shown in Table 5 and Table 6, respectively. The *Candida albicans* was sensitive to fluconazole according to the drug susceptibility.

Treatment and Outcome

All of the 161 BSI patients were treated with antimicrobial agents, which included β-lactams, carbapenems, glycopeptides, nitroimidazoles and anti-fungal. Single drug was used in 30 patients (18.63%). Two drugs were used in 63 patients (39.13%). Three or more drugs were used in 68 patients (42.24%). The top five antimicrobial agents were vancomycin, imipenem, cefoperazone/sulbactam, piperacillin/tazobactam and meropenem. The mean treatment time for the non-MDI group was 10.77±4.88 days, and it was 8.27±2.85 days for the MDI group (t=3.81, P=0.0002). Total 156 cases were successfully cured. Five patients (all MDI patients) passed away due to uncontrolled systemic infection. The organisms were *Pseudomonas aeruginosa* (2 patients), *Escherichia*

Table 5 Drug resistant pattern of staphylococci isolated from children's blood with bloodstream infection

Drugs	**Drug resistant rate (%)**		
	***Staphylococcus epidermidis* (16)**	**Other CoNS (11)**	***Staphylococcus aureus* (4)**
Clindamycin	50.00	45.45	50.00
Linezolid	0.00	0.00	0.00
Ampicillin/sulbactam	100.00	72.73	0.00
Gentamicin	37.50	27.27	25.00
Oxacillin	100.00	72.73	0.00
Rifampicin	12.50	9.09	0.00
Sulfamethoxazole	93.75	36.36	75.00
Vancomycin	0.00	0.00	0.00
Moxifloxacin	0.00	0.00	0.00
Erythromycin	93.75	54.55	75.00
Furantoin	0.00	0.00	0.00
Levofloxacin	0.00	27.27	25.00
Penicillin-G	100.00	81.82	75.00
Tetracycline	25.00	9.09	0.00

CoNS: coagulase negative staphylococcus.

Table 6 Drug resistant pattern of common gram-negative bacteria isolated from children's blood with bloodstream infection

Drugs	**Drug resistant rate (%)**		
	***Escherichia coli* (12)**	***Klebsiella pneumoniae* (12)**	***Pseudomonas aeruginosa* (5)**
Cefoperazone/sulbactam	0.00	0.00	100.00
Cephazoline	83.33	50.00	100.00
Cefoxitin	0.00	0.00	0.00
Amikacin	8.33	0.00	0.00
Levofloxacin	33.33	16.67	100.00
Cefuroxime	83.33	58.33	0.00
Ceftazidime	75.00	50.00	100.00
Ampicillin	100.00	83.33	0.00
Cefpiramide	75.00	50.00	0.00
Gentamicin	83.33	50.00	0.00
Imipenem	0.00	0.00	0.00
Meropenem	0.00	0.00	80.00
Cefotaxime	75.00	41.67	0.00
Piperacillin/tazobactam	0.00	25.00	0.00

coli (1 patient), *Klebsiella pneumoniae* and *Staphylococcus epidermidis* (1 patient), *Pseudomonas aeruginosa* and *Enterococcus* (1 patient), respectively. The mortality was 3.1% (5/161).

Discussion

The blood cancer patients were susceptibly complicated with infection, particularly bacterial sepsis. Besides low immune function caused by malignant tumours, impairment of physiological barrier defense function and local oedema, erosion, necrosis, compression and obstruction, bone marrow suppression resulting from chemotherapy and/or radiotherapy may be the directly single and most important risk factor responsible for the sepsis.[10] The data showed that incidence of BSI was 10.73% (161/1500) versus 5.2%-18.2% reported by other centers.[11,12] The positive blood culture rate of 43.48% in BSI patients was lower than that of other reports.[13,14] The reason maybe we only collected one tube of blood sample each time for bacterial culture instead of double samples in different sites.

All of the 161 BSI patients presented fever and increased CRP. There were no statistical significant difference between the non-MDI group and MDI group. Regarding cytokines determination, more than 50% had obviously elevated human IL-6 and IL-10, and there were no statistical significant difference between the two groups. Since there were no specific signs and symptoms while BSI occurred in blood cancer patients, the tests for infection such as CRP, relative cytokines IL-6 and IL-10[5] and blood culture should be performed immediately when patients got fever during neutropenia caused by chemotherapy, and powerful antibiotics should be administered ahead of the pathogenic isolation whether there was infectious foci identified.

The major original infection sites were catheter puncture sites, lungs, oral cavity and digestive tract among BSI patients. In our data, the rate of flare on the puncture sites was 13.66% (22/161), which was similar to another report of 13.6%.[15] We should pay more attention to the sterile care on the deep vein catheter, oral cavity, nasal cavity and peri-anus to avoid extra contamination. If the conditions permit, the neutropenic cases should be isolated in the sterile laminar flow room till the neutrophil recovery.

Our data showed that the distribution of gram positive bacteria, gram negative bacteria and fungi were 55.70%, 43.04% and 1.27%, respectively. The top three pathogens were *Staphylococcus epidermis*, *Escherichia coli* and *Klebsiella pneumoniae*. Celkan et al[16] reported that 60% of the pathogens separated from the blood culture of 159 cancer patients were gram positive bacteria, and the CoNS was the dominant. These results were similar to ours. Recently, the gram positive bacterial infection appeared to be increasing in cancer patients, especially, infections by CoNS and streptococcus.[17] All of these maybe due to the massive usage of broad spectrum antimicrobial agents against the gram negative bacteria and invasive operations such as deep vein catheter. The prolonged and massive use of broad spectrum antibiotics selected proliferation of the gram positive bacteria, and the catheter puncture resulted in mucocutaneous injury, which allowed conditional pathogenic infection. The main gram positive bacteria (staphylococcus) showed no/low drug resistance to vancomycin, linezolid and moxifloxacin, and the dominant gram negative bacteria had no/low drug resistance to cefoxitin, imipenem and piperacillin/tazobactam. According to the guideline of American Infectious Disease Association,[18,19] besides the supportive treatment, we administered antibiotics early, such as imipenem associated with vancomycin or piperacillin/tazobactam combined with vancomycin. The choice of initial empirical antibiotics for the treatment of neutropenic fever was based on the clinical conditions of the patients without any protocol. As soon as the results of antibiotic susceptibility test were available, we adjusted the antibiotics properly. The mean treatment time for MDI group was less than that of the non-MDI group, which was statistically significant (t=3.81, P=0.0002). It showed that the antibiotics selection according to the susceptibility test was superior to the empirical treatment.

Although the fungal infection accounted for 1.27% (1/79) from our data, but various pathogens, such as fungi, virus and parasite, may infect the patients who suffered from neutropenia, and the fungemia maybe the pivotal cause to mortality.[20] We only detected 1 patient infected with candida albicans although receiving previous fluconazole prophylaxis. The pathogen was sensitive to fluconazole and the fungemia was cured under the treatment of fluconazole. Mor et al[21] reported that 7.2% of 1,047 children hospitalised in their haematology/oncology department were diagnosed with a proven invasive fungal infection. Our low detection rate of invasive fungal infection might be the difficult culture of fungi and lack of sensitive and specific detection methods, and probably contributed to the prophylaxis usage of oral fluconazole when the ANC was less than 1.0×10^9/L.

In summary, there were no specific signs and symptoms clinically, and the values of CRP and relative cytokines had no significant difference statistically between the MDI group and non-MDI group. Till now the isolation of

pathogen by culture is the 'gold' diagnostic criteria for BSI. Gram-positive bacteria were the dominant pathogens in blood cancer children with BSI. Antibiotics susceptibility test was very important in drug adjustment. In order to decrease the incidence and improve the outcome of BSI, improved prevention, early detection, and advanced therapeutic strategies should be focused on.

Declaration of Conflicts of Interest

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Ethical approval: This study was approved by the institutional ethical review board.

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to this study.

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