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ORIGINAL ARTICLE

Risk factors for sepsis-related death in children and adolescents with hematologic and malignant diseases

Hirozumi Sano [a,*], Ryoji Kobayashi [a], Akihiro Iguchi [b], Daisuke Suzuki [a], Kenji Kishimoto [a], Kazue Yasuda [a], Kunihiko Kobayashi [a]

[a] *Department of Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan*
[b] *Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

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vancomycin

Background: The aim of this study was to elucidate risk factors for mortality after developing sepsis in pediatric patients with hematologic and malignant disorders.
Methods: A total of 90 patients (43 boys, 47 girls) with various hematologic and malignant diseases who experienced sepsis between June 2006 and March 2014 were enrolled. Clinical and laboratory features of 134 episodes of sepsis observed in the 90 patients were compared between those with and without sepsis-related death which was defined as death within 14 days after sepsis.
Results: Age at hospitalization, sex, and type of underlying disease did not differ between patients with and without sepsis-related death. Sepsis episode-based univariate analysis identified patients with a history of relapse or in a refractory state of underlying disease ($p < 0.01$), those with high C-reactive protein concentrations ($\geq$50 mg/L) at the beginning of fever ($p < 0.01$), those who had undergone hematopoietic stem cell transplantation ($p < 0.01$), and those who were forced to change initial antibiotics ($p = 0.02$) because of being at high risk of sepsis-related death. The former two factors were further confirmed by multivariate analysis. More than half (52.9%) the isolates from sepsis-related death were Gram-positive cocci resistant to β-lactam antibiotics, but susceptible to vancomycin.
Conclusion: It was found that a history of relapse, a refractory state of underlying disease, and high C-reactive protein concentrations at the beginning of fever were significant risk factors

* Corresponding author. Department of Pediatrics, Sapporo Hokuyu Hospital, Higashi-Sapporo 6-6, Shiroishi-ku, Sapporo 003-0006, Japan.
E-mail address: hirozumi.sano@gmail.com (H. Sano).

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for mortality after developing sepsis. Survival rate of patients with risk factors raised in this study might be improved by early introduction of vancomycin.

Introduction

Recent advances in chemotherapy and hematopoietic stem cell transplantation (HSCT) have improved the survival rate of pediatric patients with hematologic and malignant disorders and bone marrow failure syndrome. Nonetheless, the accompanying intensification of therapy, such as multidrug chemotherapy and HSCT, has led to an increased incidence of severe infection including sepsis. Sepsis is still a major cause of morbidity and mortality in patients with hematologic and malignant diseases, although various antibacterial/antifungal treatments have been developed. Limited data characterizing mortality after developing sepsis have been reported for children and adolescents.[1–4] New medical treatment strategies might be produced by the identification of risk profiles, and may lead to better survival. Thus, the aim of this study was to elucidate the risk factors for mortality after developing sepsis in children and adolescents with hematologic and malignant disorders receiving chemotherapy, immunosuppressive therapy, and HSCT.

Methods

Patients

A total of 90 consecutive patients (43 boys, 47 girls) at Sapporo Hokuyu Hospital, Sapporo, Japan with various hematologic malignancies, aplastic anemia, or solid tumors who experienced sepsis following chemotherapy, immunosuppressive therapy, and HSCT between June 2006 and March 2014 were enrolled in this study. The age at admission ranged from 4 months to 24 years (median, 8 years). Forty-three patients had acute lymphoblastic leukemia, 25 had acute myeloid leukemia, four had neuroblastoma, three had aplastic anemia, three had myelodysplastic syndrome (including juvenile myelomonocytic leukemia), two had non-Hodgkin lymphoma, two had hepatoblastoma, two had rhabdomyosarcoma, one had congenital dyserythropoietic anemia, and five had other malignant diseases including retinoblastoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, epithelioid sarcoma, and pancreatic neuroendocrine tumor. During the study period, 22 patients received HSCT: 21 of them received allogeneic HSCT and one received autologous HSCT. A total of 134 episodes of sepsis were observed in the 90 patients during the study period.

Informed consent was obtained from the patients and/or their parents, according to guidelines based on the tenets of the revised Helsinki protocol. The institutional review board of Sapporo Hokuyu Hospital approved this project.

Definitions of sepsis, fever, neutropenia, and sepsis-related death

Sepsis is defined as systemic inflammatory response syndrome in the presence of suspected or proven infection and organ dysfunction according to international consensus guideline[5,6]; however, in this study, we dealt with the cases in which bacterial/fungal pathogens were isolated from blood of patients. When bacteria that typically colonize the skin, such as coagulase-negative staphylococci, corynebacteriae other than *Corynebacterium jeikeium*, and other skin contaminants, were isolated, at least two consecutive blood cultures were analyzed to confirm the pathogenicity of the isolates. Blood cultures were performed in response to a sign of infection, which was typically fever. Fever was defined in this study as an axillary temperature of $\geq$37.5°C on two occasions at least 1 hour apart or a single axillary temperature >38.0°C. Neutropenia was defined as an absolute neutrophil count of $<0.5 \times 10^9$/L.

When evaluating the prognosis of sepsis, it is difficult to distinguish strictly whether patients died from sepsis or not. The prognosis of sepsis is often evaluated by the death rate at 28 days after sepsis development in such as an intensive care area[7]; however, when an evaluation period becomes longer in patients with hematological and malignant disease, involvement of factors of death other than sepsis (for example, death due to underlying malignant disease) might increase. Therefore, we decided to analyze prognostic factors of sepsis using the concept of *sepsis-related death*, which was defined as death within 14 days after developing sepsis.

Analytic procedures

To evaluate the background of the enrolled patients, sex, age at hospitalization, and type of underlying disease were compared between patients (a total of 90 patients) with and without sepsis-related death.

Meanwhile, to evaluate the risk factors of sepsis-related death, a total of 134 sepsis episodes observed in the 90 patients were analyzed between patients with and without sepsis-related death for factors including laboratory data at the beginning of fever, condition of underlying disease (history of relapse or refractory state), insertion of a central venous catheter, history of HSCT, changes of initial antibiotics due to prolonged or recurrent fever, and type of isolated pathogen. Data were analyzed as of May 1, 2014.

Infection prophylaxis

Trimethoprim–sulfamethoxazole was prescribed to all patients for the prevention of *Pneumocystis jirovecii*

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pneumonia. Prophylactic administration of oral voriconazole at 5–10 mg/kg/d was used for patients with acute myeloid leukemia, whereas oral fluconazole at 10 mg/kg/d was used for all other patients. For stem cell transplantation patients, intravenous micafungin at 1 mg/kg/d was administered from the beginning of the conditioning regimen until neutrophil recovery, followed by the oral administration of fluconazole at 10 mg/kg/d from the time of neutrophil recovery until the date of discharge. Prophylactic administration of antibacterial agents was not routinely performed.

Identification and initial treatment of sepsis

All eligible patients were hospitalized. When patients developed fever during neutropenia, the following laboratory tests were performed: complete blood cell count, peripheral blood smear, quantitative C-reactive protein (CRP), liver and renal function, urinalysis, and blood cultures from specimens obtained via peripheral venous puncture and/or a central venous catheter, if in place. Antimicrobial therapy was begun as soon as possible without waiting for the result of blood culture. The initial antibacterial drugs at the onset of fever were as follows: ceftazidime plus piperacillin/tazobactum (PIPC/TAZ) or sulbactam/ampicillin plus aztreonam from June 1, 2004, to March 31, 2006;[8] ceftazidime plus PIPC/TAZ or cefozopran monotherapy from April 1, 2006, to March 31, 2008;[9] cefozopran monotherapy or cefepime monotherapy from April 1, 2008, to March 31, 2010;[10] PIPC/TAZ monotherapy or cefepime monotherapy from April 1, 2010, to March 31, 2012;[11] and PIPC/TAZ monotherapy or meropenem monotherapy from April 1, 2012, to March 31, 2014 (data not shown).

Initial antimicrobials were continued when a case of fever was alleviated following initiation of antimicrobials. In a case of fever continuing following initiation of antimicrobials, or once resolved fever and infectious signs subsequently recurred in spite of the continuation of the same antimicrobial therapy, the laboratory test including blood culture was reexamined and the antimicrobial therapy was changed to other antibacterial drugs or antifungal drugs (*changes of initial antimicrobial*). When a bacterial infection was suspected in a case without neutropenia, the laboratory test including blood culture was done before the initiation of antimicrobial therapy.

Statistical analysis

A χ^2 test or Mann–Whitney *U* test was used to compare patients with or without sepsis-related death. Risk factors for sepsis-related death were evaluated by univariate and multivariate analyses using the Cox regression model. A multivariate model was constructed by the forward stepwise method using threshold *p* values of 0.05 for removal or additions to the model. Values of $p < 0.05$ were considered significant. Measures of association are expressed as hazard ratios with a 95% confidence interval. The cut-off point for CRP level was determined based on the value of Youden Index by constructing a receiver–operating characteristic curve. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.[12]

Results

Isolated bacteria/fungi

A total of 136 pathogens were isolated at 134 episodes of sepsis which occurred in 90 patients (Table 1). Two organisms were detected at the same time in 2 patients (*Enterobacter cloacae* and *α–streptococcus* were isolated in one patient, whereas *Enterococcus* sp. and *Staphylococcus epidermidis* were isolated in the other patient). Gram-positive cocci were the most common pathogens among isolated organisms, constituting 72.8% of the total, followed by Gram-negative bacilli (18.4%), Gram-positive bacilli (7.4%), and fungi (*Candida* species, 1.5%). The most common pathogen among isolated organisms in patients with sepsis-related death was Gram-positive cocci (82.4%), followed by Gram-negative bacilli (17.6%). There were no patients with sepsis-related death caused by Gram-positive bacilli and fungi.

Gram-positive cocci were the most common pathogen among isolated organisms regardless of underlying diseases. The distribution of pathogen did not differ significantly in each underlying disease. Of 17 isolates from sepsis-related death, nine (52.9%) were Gram-positive cocci (*Staphylococcus epidermidis*, n = 6; *Enterococcus faecium*, *n* = 1; *Enterococcus* sp., *n* = 2] resistant to β–lactam antibiotics (penicillin derivatives, cephalosporins, monobactams, and carbapenems), but susceptible to vancomycin. Of seven patients who died from sepsis of *S. epidermidis*, five patients (71.4%) had history of relapse or were in refractory state of underlying disease.

Risk factors for sepsis-related death

Age at hospitalization, sex, and type of original disease did not differ between patients with and without sepsis-related death (Table 2).

Meanwhile, as a result of the risk factor analysis of sepsis-related death (Table 3), the frequency of cases with a history of relapse or in a refractory state of underlying disease (nonremission) was significantly higher in those with sepsis-related death than in those without (69.2% vs. 22.6%, $p = 0.0011$; the studied cases were 128 cases with malignant disease, excluding 4 cases with aplastic anemia and 2 cases with congenital dyserythropoietic anemia). In addition, the frequency of cases that had experienced HSCT was higher in those with sepsis-related death than in those without (60.0% vs. 16.0%, $p = 0.0015$). The frequency of cases with changes of initial antimicrobials was also higher in those with sepsis-related death than in those without (40.0% vs. 14.3%, $p = 0.0233$). In the laboratory data, values of CRP at the beginning of a sepsis episode were significantly higher in those with sepsis-related death than in those without (85 mg/L vs. 13.9 mg/L, $p = 0.0005$).

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Table 1 Isolated pathogens on blood culture.

Isolate	Total number[a]	Number of episodes with sepsis-related death[b]
Gram-positive cocci	99 (72.6)	14 (82.4)
Staphylococcus aureus	9 (6.6)	1 (5.9)
Staphylococcus epidermidis	44 (32.4)	7 (41.2)
Staphylococcus capitis	1 (0.7)	0
α-Streptococcus spp.	18 (13.2)	1 (5.9)
Streptococcus viridans	6 (4.4)	0
Streptococcus mitis	2 (1.5)	0
Streptococcus oralis	5 (3.7)	0
Streptococcus pneumoniae	1 (0.7)	1 (5.9)
Streptococcus sanguis	2 (1.5)	0
Streptococcus pyogenes	1 (0.7)	0
Streptococcus intermedius	1 (0.7)	0
Micrococcus species	2 (1.5)	0
Enterococcus faecium	2 (1.5)	1 (5.9)
Enterococcus faecalis	2 (1.5)	1 (5.9)
Enterococcus species	3 (2.2)	2 (11.8)
Gram-positive bacilli	10 (7.4)	0
Bacillus subtilis	4 (2.9)	0
Bacillus cereus	2 (1.5)	0
Bacillus species	4 (2.9)	0
Gram-negative bacilli	25 (18.4)	3 (17.6)
Escherichia coli	7 (5.1)	1 (5.9)
Enterobacter cloacae	5 (3.7)	1 (5.9)
Klebsiella pneumoniae	4 (2.9)	0
Pantoea agglomerans	3 (2.2)	0
Pseudomonas aeruginosa	3 (2.2)	1 (5.9)
Pseudomonas stutzeri	1 (0.7)	0
Pseudomonas species	1 (0.7)	0
Capnocytophaga species	1 (0.7)	0
Fungi	2 (1.5)	0
Candida spp.	2 (1.5)	0
Total	136	17

[a] A total of 136 bacteria/fungi in 134 episodes were isolated (2 organisms were isolated at the same time in 2 patients).
[b] A total of 17 bacteria in 15 episodes with sepsis-related death were isolated (2 organisms were isolated at the same time in 2 patients).
Data are presented as *n* (%).

Table 2 Background of the patients who experienced sepsis with and without sepsis-related death ($n = 90$).

	Patients with sepsis-related death ($n = 15$)	Patients without sepsis-related death ($n = 75$)	*p*
Age (y)	8 (0–18)	6 (0–24)	0.6565
Sex			> 0.99
Male	7 (46.7)	36 (48.0)	
Female	8 (53.3)	39 (52.0)	
Disease			0.0994
ALL	6 (40.0)	37 (49.3)	0.5796
AML	2 (13.3)	23 (30.7)	0.2192
MDS + JMML	2 (13.3)	1 (1.3)	0.7091
Solid tumor	3 (20.0)	12 (16.0)	0.7097
AA + CDA	2 (13.3)	2 (2.7)	0.1279

Data are presented as *n* (%) or median (range).
AA = aplastic anemia; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CDA = congenital dyserythropoietic anemia; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome.

The association with high values of CRP (>50 mg/L, which was determined by constructing a receiver–operating characteristic curve, with 78.8% sensitivity and 66.7% specificity) and a history of relapse or a refractory state of underlying disease in sepsis-related death was further confirmed by multivariate analysis (Table 4). Other laboratory data, including white blood cell count, neutrophil count at the beginning of fever in a sepsis episode, presence of central venous catheter, and type of isolated pathogen, did not differ between the two groups.

Discussion

Infectious diseases have been major causes of morbidity and mortality in immunocompromized patients with cancer. Approximately 10–30% of febrile neutropenic patients with cancer are reported to be complicated with sepsis at presentation.[13,14] Although advances in supportive care have permitted patients to recover successfully from the impact of cytotoxic cancer chemotherapy, HSCT, radiation therapy, aggressive surgical intervention, and intense immunosuppression, sepsis is still a major issue leading to unexpected death. However, there are limited data concerning morbidity and mortality after developing sepsis in children and adolescents.[1–4,15–17] To improve the survival of patients with sepsis, understanding the risk profile of death due to sepsis is important in the application of medical interventions for high-risk patients. Thus, we aimed to elucidate the risk factors for mortality after developing sepsis in children and adolescents with hematologic and malignant disorders receiving chemotherapy, immunosuppressive therapy, and/or HSCT.

In this study, high CRP concentrations (≥50 mg/L) at the beginning of a sepsis episode and a history of relapse or a refractory state of underlying disease were identified as risk factors of sepsis-related death by multivariate analysis.

A high CRP concentration is acknowledged as an indicator of significant systemic bacterial/fungal infection. Santolaya et al[15] reported that a CRP level of ≥90 mg/L and the presence of hypotension were indicators of invasive systemic bacterial infection; however, the cut-off point for CRP level (≥50 mg/L) identified in the present analysis as a risk factor for sepsis-related death was much lower than in the above-mentioned report. Critical cut-off threshold CRP concentration varies widely because it is primarily determined by the sensitivity of the test.[18] CRP can be elevated from infectious and noninfectious causes such as tissue inflammation or necrosis, or advanced stage of malignant disease[19]; therefore, specificity of CRP tends to be low. The discrepancy in cut-off CRP concentration between our study and past reports might be simply due to differences in timing for checking CRP. CRP, an acute phase protein, usually elevates within 12–24 hours after the onset of fever, however, it often does not rise at the beginning of fever even in the case of true bacterial infections. Unlike

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Table 3 Risk factors for sepsis-related death: sepsis episode-based, univariate analysis ($n = 134$).

	Cases with sepsis-related death ($n = 15$)	Cases without sepsis-related death ($n = 119$)	p
Laboratory data at the beginning of sepsis episode			
WBC ($\times 10^6$/L)	200 (10–115,180)	270 (10–13,900)	0.6578
Neutrophils ($\times 10^6$/L)	17 (0–30,422)	37 (0–11,049)	0.8060
CRP (mg/L)	85 (4.2–376.9)	13.9 (0.5–205.1)	0.0005
History of relapse/refractory state[a]	9 (69.2)	26 (22.6)	0.0011
Presence of CVC	12 (80.0)	57 (52.1)	0.0536
History of HSCT	9 (60.0)	19 (16.0)	0.0015
Changes of initial antibiotics	6 (40.0)	17 (14.3)	0.0233
Types of pathogen[b]			0.7877
Gram-positive cocci	14 (82.4)	85 (71.4)	0.5603
Coagulase-negative staphylococci	7 (41.2)	45 (37.8)	0.7951
Gram-positive bacilli	0	10 (8.8)	0.3622
Gram-negative bacilli	3 (17.6)	22 (18.5)	> 0.99
Fungi (*Candida*)	0	2 (1.8)	> 0.99

[a] Excluding those with nonmalignant disease (4 cases with aplastic anemia and 2 cases with congenital dyserythropoietic anemia).
[b] Two organisms were isolated at the same time in two patients (both were included in cases with sepsis-related death); thus, the total number of primary causative organisms was defined as 136.
Data are presented as n (%) or median (range).
CRP = C-reactive protein; CVC = central venous catheter; HSCT = hematopoietic stem cell transplantation; WBC = white blood cell count.

our recruitment of CRP concentrations at the beginning of fever, others employed CRP concentrations taken at different timing; CRP concentration on the next day or the day after next of the fever,[18] peak CRP concentration throughout the whole course of fever,[16] peak CRP concentration within 48 hours after the onset of fever,[4] and increase rate of CRP from 24 hours to 48 hours after the onset of fever.[20]

In cases in which CRP is already elevated at the beginning of fever, a stronger inflammatory reaction might be induced compared with cases with a lower CRP concentration. Moreover, the tissue damage induced by cytokine storm might become obvious in such cases. Meanwhile, cases in which CRP is already elevated at the beginning of fever included more cases with a history of relapse or refractory underlying disease than those with low CRP concentration (41.2% vs. 22.3%, respectively, $p = 0.0441$). Patients with elevated CRP possibly due to poor-controlled underlying disease might progressively deteriorate in general condition as a result of subsequent septic events, leading to death, which could explain the strong association between the high value of CRP and sepsis-related death.

Table 4 Multivariate analysis of risk factors for sepsis-related death extracted by univariate analysis.

	Hazard ratio	p	95% CI
CRP $\geq$ 50 mg/L[a]	4.750	0.0269	1.20–18.90
History of relapse/ refractory state	4.170	0.0464	1.02–17.00
History of HSCT	2.890	0.1600	0.66–12.70
Changes of initial antibiotics	1.640	0.5020	0.39–6.98

[a] The cut-off point for CRP level was determined by constructing a receiver operator curve.
CI = confidence interval; CRP = C-reactive protein; HSCT = hematopoietic stem cell transplantation.

Patients with a history of relapse or in a refractory state of underlying disease might receive repeated and intensive chemotherapy, causing severe bone marrow suppression and/or organ dysfunction, such as liver and/or renal dysfunction. Prolonged neutropenia[21] and organ dysfunction[22] have been reported to be prognostic factors of severe sepsis. Organ dysfunction might get worse owing to deteriorating infection during prolonged neutropenia, leading to death. To the best of our knowledge, there have been no reports identifying a history of relapse or a refractory state as a prognostic factor of sepsis.

The mortality rate of sepsis in this study was 11.2% (15/134), which was higher than those of previous reports (1–4%).[1–4,15] This discrepancy might be due to differences in the studied patients. Although cases with a history of relapse or in a refractory state, which were among the potent risk factors for sepsis-related death as defined in this study, were not included in the studies described in previous reports,[1–4,15] such cases constituted 26.1% of our analyzed patients. The mortality rate of patients with sepsis excluding those with a history of relapse or in a refractory state in this study was almost the same as in previous studies[1–4,15]; thus, the higher mortality rate in our study could be explained simply by the higher rate of cases with a history of relapse or in a refractory state in the study population. In other research that included many cases with a history of relapse or in a refractory state like in our study, a higher mortality rate (23.7%) was reported.[23]

Among isolated pathogens of sepsis in this study, Gram-positive cocci were the most common, regardless of the underlying disease. Until the late 1970s, aerobic Gram-negative bacilli (especially *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) were the most frequently isolated pathogens. Subsequently, the pattern

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of infections shifted towards Gram-positive bacteria, which are now isolated more often than Gram-negative bacteria in most oncology institutes.[13,14] The main reasons for this shift to Gram-positive isolates could be the recent increase in the use of indwelling central venous catheters and fluoroquinolone prophylaxis, and the recent prevalence of oral mucositis induced by intensive chemotherapy. Although the attributable morbidity and mortality rates associated with infections due to coagulase-negative staphylococci and enterococci have been reported to be lower than those caused by Gram-negative bacilli,[24] sepsis caused by α-hemolytic streptococci, most commonly *S.*, may cause sudden onset of hypotension, with progression in approximately one-quarter of cases to a syndrome that can include shock, respiratory failure due to adult respiratory distress syndrome, acute renal failure, and neurologic manifestations.[25,26] Fortunately, no fatal cases due to *Streptococcus mitis* were observed in this study period; however, special caution is now warranted for its association with sepsis.

Although infection due to coagulase-negative staphylococci is generally treatable and known to cause less mortality,[24] *S. epidermidis* was the leading cause of sepsis-related death in this study. Of seven patients who died from sepsis of *S. epidermidis*, five (71.4%) had history of relapse or were in refractory state of underlying disease. These patients might have organ dysfunctions, and prolonged myelosuppression potentially due to repeated and intensive chemotherapy; therefore, even the mild pathogen, *S. epidermidis,* could be a cause of unexpected death. Meanwhile, more than half (52.9%) the isolates from sepsis-related death were Gram-positive cocci resistant to β-lactam antibiotics, but susceptible to vancomycin. From this point of view, survival rate of the patients with risk factors raised in this study could be improved by introducing vancomycin from an early phase of fever.

We had worked on prospective, randomized studies to compare the effectiveness of various antimicrobial regimens against sepsis in the patients of this study period[8–11] and found that there was no difference in the mortality rate for each regimen (data not shown). Thus, it seems feasible to say that findings of this research are not influenced by difference of the first line antibiotics.

In conclusion, we identified a history of relapse or a refractory state of underlying disease, as well as a high CRP concentration ($\geq$50 mg/L) at the beginning of fever, as significant risk factors of mortality after developing sepsis in children and adolescents with hematologic and malignant diseases. Early introduction of vancomycin to the patients with risk factors raised in this study might improve their survival rate.

Conflicts of interest

The authors have no conflicts of interest to declare.

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