Clinical course of sepsis in children with acute leukemia admitted to the pediatric intensive care unit*

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Objective: **To describe the clinical course, resource use, and mortality of patients with leukemia admitted to the pediatric intensive care unit with sepsis and nonsepsis diagnoses over a 10-yr period.**

Design: **Retrospective analysis.**

Setting: **Tertiary medical–surgical pediatric intensive care unit at C.S. Mott Children's Hospital, University of Michigan.**

Patients: **All patients with leukemia admitted to the pediatric intensive care unit from January 1, 1998, to December 31, 2008.**

Interventions: **None; chart review.**

Measurements and Main Results: **Clinical course was characterized by demographics, leukemia diagnosis, phase of therapy, leukocyte count on admission, presence of sepsis, steroid administration, intensity of care, and Pediatric Risk of Mortality score on admission to the pediatric intensive care unit. The primary outcome was survival to pediatric intensive care unit discharge. Among 68 single admissions to the pediatric intensive care unit with leukemia during the study period, 33 (48.5%) were admitted with sepsis. Admission to the pediatric intensive care unit for sepsis was associated with greater compromise of hemodynamic and renal function and use of stress dose steroids ($p = .016$), inotropic and/or vasopressor drugs ($p = .01$), and renal replacement therapy ($p = .028$) than nonsepsis admission. There was higher mortality among children with sepsis than other diagnoses (52% vs. 17%, $p = .004$). Also, mortality among children with sepsis was higher among those with acute lymphoblastic leukemia (60% vs. 44%) compared with acute myelogenous leukemia. Administration of stress dose steroids was associated with higher mortality (50% vs. 17%, $p = .005$) and neutropenia. Patients with acute lymphoblastic leukemia and sepsis showed the greatest mortality and resource use.**

Conclusions: **Patients with acute leukemia and sepsis had a much higher mortality rate compared with previously described sepsis mortality rates for the general pediatric intensive care unit patient populations. Patients who received steroids had an increased mortality rate, but given the retrospective nature of this study, we maintain a position of equipoise with regard to this association. Variation in mortality and resource use by leukemia type suggests further research is needed to develop targeted intervention strategies to enhance patient outcomes. (Pediatr Crit Care Med 2011; 12:649–654)**

KEY WORDS: sepsis; leukemia; mortality; severity of illness; length of stay; natural history

Sepsis is a leading cause of pediatric illness with an estimate of >42,000 hospitalizations in the United States annually (1). It is also among the leading causes of pediatric deaths with associated significant hospital resource consumption. Development of evidence-based guidelines for the management of sepsis has been limited by difficulty in performing randomized controlled trials in this patient population. The challenge in developing robust randomized controlled trials in pediatric sepsis also relates to the wide array of etiologies and confounding factors that play a role in treatment responses and ultimate clinical outcome (2). A potential step toward formulating standardized approaches to management of pediatric sepsis is to study pediatric subpopulations with specific comorbidities with the goal of gaining improved understanding of the clinical course of sepsis in hospitalized children and thus develop approaches that might ultimately lower mortality and reduce resource consumption among the most severely ill children. As such, high-risk patients who are anticipated to have greater mortality from sepsis may provide one potential cohort on which to target interventional randomized controlled trial studies.

Although historically the appropriate intensity of treatment for complicating illnesses during leukemia treatment was often unclear, there is current consensus that aggressive treatment of pediatric patients with leukemia is appropriate given current positive long-term outcomes (3). The last reported 5-yr mortality for acute lymphoblastic leukemia (ALL) was reported as 20% and for acute myelogenous leukemia (AML) was approximately 40% (4). Throughout the course of treatment, patients with acute leukemia are susceptible to overwhelming infectious illnesses, in part related to aggressive antileukemia therapies. Sepsis is a frequent cause of death in children with leukemia (5, 6). Other related risk factors for developing sepsis among children with leukemia include the use of central vascular catheters, frequent hospitalizations, and neutropenia (7). Prior studies have also

***See also p. 680.**

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shown that outcomes of sepsis in children are affected by the multiplicity of organ dysfunction, a common occurrence in patients with leukemia, even before the occurrence of sepsis (8). Current pediatric sepsis guidelines emphasize the need for early resuscitation in hopes of preventing multiorgan failure, but they do not address specific comorbid diagnoses such as leukemia (9).

Given the underlying immunosuppression and endocrine abnormalities caused both by leukemia and associated chemotherapy, treatment of sepsis in patients with leukemia frequently includes administration of "stress" dose steroids in addition to the mainstay of broad-spectrum antibiotic therapy. For instance, during induction therapy for patients with ALL, there is often administration of high doses of steroids with subsequent risk for adrenal insufficiency. On the other hand, patients with AML do not typically receive steroids during induction therapy and are expected to be at lower risk of adrenal suppression. Knowledge of the outcomes of patients subjected to steroid therapy is, however, very limited. Therefore, appropriate use of corticosteroid treatment in sepsis for these patients has long been debated (10). Specific studies have not been performed to address how the various treatment approaches according to the type of leukemia impact outcomes from sepsis (11).

Given the paucity of studies of sepsis in children with leukemia and the overall high mortality in patients with leukemia, we conducted a retrospective study to investigate the clinical course among critically ill children with leukemia according to the pediatric intensive care unit (PICU) admitting diagnosis of sepsis or no sepsis. We present a large case series of patients with leukemia admitted to a pediatric intensive care unit at C.S. Mott Children's Hospital at the University of Michigan from 1998 to 2008. Comparisons among patients with sepsis and those without sepsis were performed to formulate a description of clinical course including survival to PICU discharge and PICU resource use to try to identify factors that could be used for potential treatment stratification in the future.

MATERIALS AND METHODS

Subjects. A retrospective analysis with medical chart review was performed. Approval for the study was obtained from the institutional review board of the University of Michigan Medical School.

Data Source and Subject Identification. All children 0–20 yrs of age diagnosed with leukemia between January 1, 1998, and December 31, 2008, were identified in the University of Michigan Comprehensive Cancer Center Registry. Thereafter, their inpatient hospitalization records at the C.S. Mott Children's Hospital were searched for with the EMERSE (12) search program to identify those patients hospitalized in the PICU during the study period. Patients admitted to the neonatal intensive care unit were excluded.

Study Variables. Patients with culture-positive sepsis were identified using the following key terms: "sepsis," "infection," and "culture." To avoid potential bias toward overdiagnosing sepsis when these broader criteria are used, we decided *a priori* to report only on culture-positive sepsis to avoid potential capture of patients exhibiting a systemic inflammatory response as a result of nonspecific triggers other than systemic infection (e.g., adverse reaction to chemotherapy, viral upper respiratory illness, etc.) that is common in this cohort. Furthermore, given the retrospective nature of the study, it was not possible to ensure accurate identification of "culture-negative" sepsis patients on the basis of clinical judgment by the medical team. Data collected from the medical records included demographic information (age, gender, length of PICU stay, source of admission), leukemia diagnosis (ALL or AML), phase of therapy, white blood cell count on admission, and intensity of PICU care. Indicators of the intensity of care included use of mechanical ventilation, arterial catheterization, central venous catheterization, continuous renal replacement therapy, use of inotropic and/or vasopressor agents, and fluid resuscitation. Severity of patient illness was further characterized by the Pediatric Risk of Mortality (PRISM) score on admission to PICU when available (13). The primary outcome variable of the study was survival to PICU discharge or death.

Statistical Analysis. Continuous variables are presented as median values and categorical variables as frequencies. Comparisons among multiple groups of continuous variables were made using the Kruskal-Wallis test. Comparisons of proportions were made using Fisher's exact test. A p value of .05 was taken as the threshold for statistical significance. Calculations were performed on the Minitab software platform (Minitab 15, Minitab Inc., State College, PA).

RESULTS

During the 10-yr study period, 312 individual inpatients carried the diagnosis of acute leukemia and 68 of these were admitted to the PICU at varying time points in their treatment, including at diagnosis or relapse and during induction, maintenance, consolidation, or intensification phases of therapy. Thirty percent of patients with AML (34 of 114) and 17% of patients with ALL (34 of 199) had been admitted to the PICU. Among all patients with leukemia admitted to the PICU, 25% had relapsed leukemia and 75% were in initial treatment. As seen in Table 1, most of the patients with relapse (bone marrow, central nervous system, or testicular) were in the ALL sepsis subgroup. Of the 68 patients admitted to the PICU, 33 (48.5%) were diagnosed with sepsis by clinical symptoms and a positive blood culture with bacteria (*Enterobacter*, *Pseudomonas*, *Klebsiella*, *Enterococcus*, coagulase-positive *Staphylococcus*, *Streptococcus*), viruses (cytomegalovirus, parainfluenza), and fungi (*Aspergillus*, *Candida*). Fifteen of the 33 patients with sepsis had ALL and 18 had AML. Nineteen of the 35 patients without sepsis were diagnosed with ALL and 16 had AML. The nonsepsis admissions were for a variety of reasons, including 11% gastrointestinal, 11% postoperative, 23% hematologic, 29% pulmonary, 14% neurologic, 3% cardiac, 3% endocrine, and 6% immunologic.

Table 1. Relapse rates among patient groups

	Acute Lymphoblastic Leukemia	Acute Myelogenous Leukemia
Sepsis	73% (11/15)	6% (1/18)
Nonsepsis	26% (5/19)	0% (0/16)

No significant differences were observed in age, gender distribution, or length of stay among patients according to the diagnosis of sepsis or the type of leukemia (Table 2). The majority of patients were admitted from the hematology–oncology service on the ward, whereas others were admitted from other sources, including other intensive care units within the study hospital, referring hospitals, emergency departments, or clinics (Table 2).

Patients with ALL overall had a shorter PICU length of stay. To assess whether this was related to early death, subgroups were compared as depicted in Figure 1. Patients who died had longer PICU courses with a median length of stay of 10 days. The patients with ALL who were ill and died did have shorter average length of stay (7 days) compared with the AML group (17.5 days), indicating a likely difference in the course of sepsis between these populations

Neutropenia. Patients with sepsis were more likely to be neutropenic (absolute neutrophil count $<0.5 \times 10^9$/mL)

Table 2. Patient characteristics

	Acute Lymphoblastic Leukemia Nonsepsis	Acute Myelogenous Leukemia Nonsepsis	Acute Lymphoblastic Leukemia Sepsis	Acute Myelogenous Leukemia Sepsis	*p*
No. of subjects in each group	19	16	15	18	
Age, median yrs	12	10	12	14	.705
Gender, percent female	15.79	37.5	33.33	50	.175
Median length of stay	3.5	5.5	5.0	12.0	.144
Admission source, %	47 ward, 37 ED, 16 OSH	63 ward, 31 OSH, 6 ED	71 ward, 7 intensive care unit, 7 OSH, 7 ED, 7 clinic	82 ward, 18 OSH	
Median white blood cell count, $10^3/mm^3$	7.0	16.15	1	2.3	.009
Percent neutropenic	39	44	53	65	.444

ED, emergency department; OSH, outside hospital.

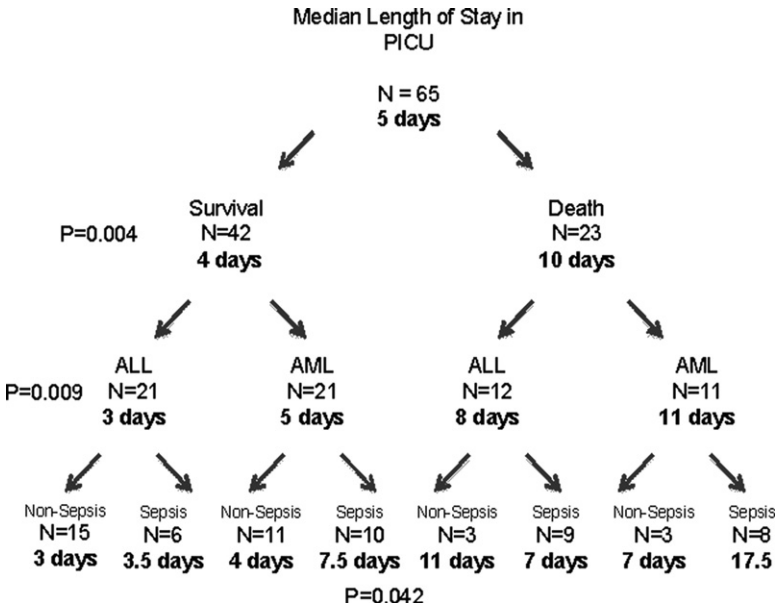

Figure 1. Median length of stay of patients admitted to the pediatric intensive care unit (*PICU*). *ALL*, acute lymphocytic leukemia; *AML*, acute myelogenous leukemia.

on PICU admission. However, the difference between the proportions of neutropenic patients in the sepsis group (19 of 32 [59%]) and in the nonsepsis group (14 of 34 [41%]) is not statistically significant ($p = .218$, Fisher's exact test). In assessing the incidence of neutropenia between the sepsis and nonsepsis cohort and the basis of receiving received steroids or not (Table 3), we found that neutropenia was more frequent among patients who received steroids and were septic (17 of 24 [71%]), which was significant compared with the other subclasses with neutropenia. The proportions of neutropenic patients in the four subgroups based on steroid and sepsis (non sepsis nonsteroid group ten of 20 [50%], nonsepsis steroid group four of 14 [29%], sepsis nonsteroid group two of eight [25%], sepsis steroid group 17 of 24 [71%]) are significantly different ($p = .033$, chi-square test, Supplemental Table 1 [see Supplemental Digital Content 1, http://links.lww.com/PCC/A33]). The proportions of neutropenic patients in the subgroups based on death and sepsis are not significantly different (Supplemental Table 2 [see Supplemental Digital Content 1, http://links.lww.com/PCC/A33]). The proportions of neutropenic patients in the four subgroups based on death (nonsepsis no death group 13 of 28 [46%], nonsepsis death one of six [17%], sepsis no death group eight of 15 [53%], sepsis death group 11 of 17 [65%]) are homogeneous ($p = .226$, chi-square test). Similarly, the proportions of neutropenic patients in the four subgroups (ALL no death group nine of 21 [43%], ALL death six of 12 [50%], AML no death group 12 of 22 [55%], AML death group six of 11 [55%]) are homogeneous ($p = .873$, chi-square test) (Supplemental Tables 3 and 4 [see Supplemental Digital Content 1, http://links.lww.com/PCC/A33]). There was a significantly higher median white blood cell count in patients with AML without sepsis compared with all other groups ($p = .009$; Kruskal-Wallis test) as shown in Table 2.

Intensive Care Unit Course. To better characterize the intensity of illness and requisite care in the PICU, use of PICU resources was compared among patients with and without sepsis. There were no significant differences in the use of mechanical ventilation, arterial catheterization, central venous catheterization, or fluid resuscitation among patients with and without sepsis (Table 4). However, a greater proportion of patients with sepsis received inotropic and/or vasopressor agents ($p = .001$), stress dose steroids ($p = .016$), and continuous renal replacement therapy ($p = .028$). This suggests that although there was significant illness in both groups, the sepsis group had a higher incidence of renal failure and more severe hemodynamic compromise.

The number of deaths among patients with sepsis was significantly higher than among those without sepsis (52% vs. 17%, $p = .0044$). This increased mortality and significant differences in use of intensive care unit resources is concordant with their increased severity of illness on admission. Use of steroids was also significantly associated with mortality ($p = .004$). This relationship appeared most pronounced among patients with sepsis, although it was not statistically significant (Table 5). Similar associations of increased mortality with steroid use were observed when patients with AML and ALL were considered separately; however, this association was made to unadjusted mortality because a severity

Table 3. Distribution of patients in subgroups of steroid use, neutropenia, and death

Nonsepsis 35/68 (51%)								Sepsis 33/68 (49%)							
No Steroids 20/35 (57%)				Steroids 15/35 (43%)				No Steroids 9/33 (27%)				Steroids 24/33 (73%)			
NN 10/20 (50%)		N 10/20 (50%)		NN 10/14[a] (71%)		N 4/14[a] (29%)		NN 6/8[a] (75%)		N 2/8[a] (25%)		NN 7/24 (29%)		N 17/24 (71%)	
ND	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND	D
8/10	2/10	10/10	0/10	7/10	3/10	3/4	1/4	4/6	2/6	2/2	0/2	3/7	4/7	6/17	11/17
80%	20%	100%	0%	70%	30%	75%	25%	67%	33%	100%	0%	43%	57%	35%	65%

NN, not neutropenic; N, neutropenic; ND, not death; D, death.

[a]In both the nonsepsis/steroid group and sepsis/no steroid group, a single patient had no absolute neutrophil count data recorded and thus was not carried forward in the analysis.

Table 4. Comparison of intensive care unit course in patients with and without sepsis

	Sepsis (n = 33)	Nonsepsis (n = 35)	*p*
Mechanical ventilation	58%	51%	.635
Arterial line	52%	40%	.465
Central venous catheter	94%	91%	1.000
Continuous renal replacement therapy	39%	14%	.028
Stress dose steroid	73%	43%	.016
Inotrope/vasopressor use	67%	26%	.001
Fluid resuscitation	82%	60%	.064
Death	52%	17%	.004
Median Pediatric Risk of Mortality severity of illness	12 (n = 22)	8 (n = 31)	.036
Median Pediatric Risk of Mortality-predicted mortality	0.25	0.16	.013

Table 5. Mortality rates among patients receiving steroids during the intensive care unit course

	Steroids (%)	No Steroids (%)	*p*
All patients	49	14	.004
Sepsis	63	22	.057
Nonsepsis	27	10	.367
Acute lymphocytic leukemia	56	13	.013
Acute myelogenous leukemia	43	15	.140

of illness measure was not available for all patients.

In the subset of patients for which PRISM scores were available (n = 22 in sepsis group, n = 31 in nonsepsis group), there was significantly increased severity of illness ($p = .036$) and predicted mortality ($p = .013$) among patients with sepsis vs. those without sepsis. This difference in predicted mortality was borne out in actual observed mortality differences among the groups. When subgroups of patients with AML and ALL were examined, differences in intensive care unit resource use were most pronounced among patients with ALL with and without sepsis. A significantly larger proportion of patients with ALL and sepsis received fluid resuscitation, continuous renal replacement therapy, inotropic and/or vasopressor agents, and stress dose steroids than those with ALL without sepsis (Table 6). Consequently, given the increased resource needs, it was not surprising that mortality was significantly higher in patients with ALL and sepsis compared with patients with ALL without sepsis (Table 6). Interestingly, no significant differences in intensive care unit resource use or mortality were observed among patients with AML with or without sepsis, although this series may have been underpowered to detect significant differences among this subgroup (Table 6). There were no significant differences in PRISM scores or predicted mortality scores in the subgroup analysis.

DISCUSSION

This single-center retrospective study describes the clinical course and outcomes of patients with acute leukemia admitted to the PICU at a single tertiary care center over a 10-yr period. Patients with leukemia who were admitted for sepsis had higher illness severity and predicted mortality as reflected by PRISM scoring and ultimately higher death rates than those admitted for other reasons. The mortality rate in this specific cohort was much higher than the mortality rate (approximately 10%) reported in prior sepsis studies, which encompassed a much broader, heterogeneous population (1, 8, 14). Studies of severe sepsis have reported higher mortality rates (17%), but the cohort studied here far exceeded that rate (15, 16). This subgroup mortality is also much higher then the reported C.S. Mott Hospital PICU mortality of 4.2% (17) and higher than the mortality in sepsis patients alone of 7.4% (18). When patients were grouped by leukemia diagnosis, patients with ALL and sepsis had significantly greater mortality and resource use than patients with ALL without sepsis, who still required intensive care. Interestingly, similar differences were not observed among patients with and without sepsis and AML as an underlying diagnosis although initial PRISM scores were similar. The differences between the AML and ALL groups require further investigation, but one potential contributor this observed difference we speculate may be related to is differences between lymphocytes and monocytes and their related cytokine expression profiles that may be activated in the setting of sepsis. A number of investigators have demonstrated distinct gene expression profiles with notable differences in cytokine and chemokine production between monocytes and lymphocyte

Table 6. Comparison of frequency of use of intensive care unit technology and outcomes among patient subgroups with acute myelogenous leukemia and acute lymphocytic leukemia

	Frequencies (*p* Values)	
	Acute Lymphocytic Leukemia Sepsis vs. Nonsepsis (No. of 15 vs. No. of 19)	Acute Myelogenous Leukemia Sepsis vs. Nonsepsis (No. of 18 vs. No. of 16)
Mechanical ventilation	60% vs. 42% (.491)	56% vs. 63% (.738)
Arterial line	47% vs 32% (.484)	56% vs. 50% (1.000)
Central venous catheter	93% vs. 89% (1.000)	94% vs. 94% (1.000)
Fluid	93% vs. 63% (.053)	72% vs. 56% (.475)
Continuous renal replacement therapy	47% vs. 16% (.068)	33% vs. 13% (.233)
Inotrope/vasopressor use	67% vs. 16% (.004)	67% vs. 38% (.168)
Steroid use	80% vs. 32% (.007)	67% vs. 56% (.725)
Death	60% vs. 16% (.012)	44% vs 19% (.152)
Median Pediatric Risk of Mortality score	11.00 vs. 8.00 (.079)	12.00 vs. 11.00 (.333)
Predicted mortality (median)	0.23 vs. 0.12 (.095)	0.27 vs. 0.16 (.129)

subsets when stimulated with microbial-associated molecular patterns (19–22). These observations raise the possibility that the type and quantity of cytokines produced by leukocytes in the different leukemia cohorts may differ to influence sepsis pathophysiology, particularly in the nonleukopenic cohorts.

Patients with sepsis in the ALL population were mostly in a relapse state and it is likely that they had more severe illness and hence were at risk for increased mortality. It is not surprising that this population used more resources, likely as a result of heightened severity of illness (23). There was discordance between PRISM-based predicted mortality and actual observed mortality with the latter being higher than predicted. Although this may suggest opportunities for improving PICU care in this targeted cohort, it is also likely that PRISM may be unable to accurately capture pathophysiological progression of organ failure occurring beyond the PRISM data-capturing timeframe of the initial 24 hrs of care in the PICU.

One of the key differentiating factors between ALL and AML is the use of steroids during induction therapy for the former diagnosis. Given the use of steroids at induction, it is possible that ALL subjects have a greater risk of adrenal insufficiency. Suppression of the hypothalamic–pituitary–adrenal axis occurs 6–8 wks after induction with high dose steroids in ALL treatment protocols, but previous studies have not demonstrated the clinical consequences of these changes (24, 25). The duration of hypothalamic–pituitary–adrenal axis suppression after induction therapy varies, but may be as long as 4–8 months (26–28). Assessment of the hypothalamic–pituitary–adrenal axis with the low-dose adrenocorticotropin test (27, 29), baseline cortisol (30), and urinary steroids (10) after therapy for leukemia has been suggested, but these studies were performed in small numbers of adult subjects and their applicability to the pediatric population remains unclear. Given our observations in this cohort, we propose such tests merit further investigation.

In patients without underlying risk factors for hypothalamic–pituitary–adrenal axis suppression, the use of corticosteroids in the treatment of septic shock has been long debated. Use of corticosteroids is often prompted by a state of "relative adrenal insufficiency" in which endogenous cortisol production is not appropriately elevated given the degree of physiological stress (31). Eighty-two percent of the patients with ALL in this study with sepsis who had received steroids during hospitalization died, although it is difficult to ascertain in this retrospective review when steroids were initiated and what doses of steroids were used. Overall, the group of patients with steroid use during PICU stay had higher mortality. Formal testing for adrenal insufficiency was not performed routinely and such testing early in PICU admission may yield more information about the adrenal axis, although the use of this testing remains controversial in light of other studies in sepsis. Recent meta-analyses in adult patients have come to conflicting conclusions, showing either evidence of short-term benefit (32, 33) or no benefit (34) from the use of corticosteroids in the treatment of septic shock. It is unclear what protocol to follow in children, and this question is the subject of ongoing debate, but our observations would strongly suggest such prospective inquiry merits further investigation, particularly in this high-risk cohort (35, 36). Although prior studies have suggested that low-dose or high-dose adrenocorticotropic hormone stimulation tests may help identify those with adrenal insufficiency and should be used in pediatric patients with refractory shock (37, 38), we suggest a position of clinical equipoise with regard to the association of steroids and mortality until further prospective studies are executed.

Finally, testing for adrenal insufficiency may serve as a stratification tool. Some studies have suggested the potential association between levels of C-reactive protein or interleukin-8 with patient outcomes and therefore serve as a stratification method for subsequent targeting of therapies (39, 40). However, interleukin-8 studies have excluded neutropenic patients and C-reactive protein studies have focused only on adult populations. Thus, further research is needed in patients with acute leukemia with sepsis for targeted intervention strategies.

CONCLUSIONS

Patients with acute leukemia and sepsis have much higher mortality in comparison to other populations of critically ill children with sepsis. This study suggests the need for further investigation of treatment approaches for critically ill children with leukemia and sepsis given the differential mortality and significant impact on resource use. There was on overall increased mortality in individuals receiving steroid treatment, but given the retrospective nature of this study, we maintain a position of equipoise with regard to this association. Patients with ALL with sepsis had increased mortality and as we seek to improve outcomes in leukemia treatment, targeted interventions in sepsis may lead to better patient outcomes.

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