Outcome of severe sepsis in pediatric oncology patients*

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LEARNNG OBJECTIVES

On completion of this article, the reader should be able to:

1. Recall that the Pediatric Risk of Mortality (PRISM) III score is independently associated with increased mortality among pediatric oncology patients with severe sepsis.
2. State the importance of the diagnoses of bone marrow transplantation and fungal sepsis and their impact on outcome in pediatric patients with severe sepsis.
3. Recall that profound neutropenia is not a key predictor of outcome from severe sepsis in pediatric oncology patients.

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Objective: **To describe survival to intensive care unit (ICU) discharge and 6-month survival in a large cohort of pediatric oncology patients with severe sepsis.**

Design: **Retrospective analysis.**

Setting: **The ICU of a single pediatric oncology center.**

Patients: **Patients with cancer admitted to the ICU of St. Jude Children's Research Hospital between January 1, 1990, and December 31, 2002, who met the following criteria: 1) severe sepsis by ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine) Consensus Conference criteria and 2) receipt of fluid boluses of ≥30 mL/kg to correct hypoperfusion or receipt of a dopamine infusion of >5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for inotropic support.**

Interventions: **None.**

Measurements and Main Results: **Data evaluated were demographic variables, oncologic diagnosis and time from diagnosis to ICU admission, Pediatric Risk of Mortality III score and absolute neutrophil count at admission, use of inotropes or pressors, use of mechanical ventilation, maximum organ system failure score, blood culture results, survival to ICU discharge, and 6-month survival. We identified 446 ICU admissions of 359 eligible patients. Overall ICU mortality was 76 of 446 (17%): 40 of 132 (30%) in post–bone marrow transplant (BMT) admissions and 36 of 314 (12%) in non-BMT admissions ($p < .0001$). In the 106 admissions requiring both mechanical ventilation and inotropic support, ICU mortality was 68 of 106 (64%). Regarding individual patients, 6-month survival was 170 of 248 (69%) among non-BMT patients vs. 43 of 111 (39%) for BMT patients ($p < .001$). When the 38 patients who survived to ICU discharge after requiring both mechanical ventilation and inotropic/vasopressor support are considered, 27 (71%) were alive 6 months after ICU discharge (22 of 27 [81%] non-BMT vs. 5 of 27 BMT [19%; $p < .001$]). ICU mortality varied by causative pathogen, from 63% for fungal sepsis (12 of 19) to 9% (5 of 53) for Gram-negative sepsis. Logistic regression analysis of factors significantly associated with ICU mortality in admissions requiring both mechanical ventilation and inotropic support identified four variables: BMT (odds ratio, 2.9; 95% confidence interval, 1.1–7.4; $p = .03$); fungal sepsis (odds ratio, 10.7; 95% confidence interval, 1.2–94.4; $p = .03$); use of multiple inotropes (odds ratio, 4.1; 95% confidence interval, 1.4–11.8; $p = .01$); and Pediatric Risk of Mortality III score (odds ratio, 1.1; 95% confidence interval, 1.0–1.2; $p = .04$).**

Conclusions: **In a large series of pediatric oncology patients with severe sepsis, ICU mortality was only 17% overall, although mortality remained quite high in the higher acuity patients. Mortality among the higher acuity patients was significantly associated with only a small number of variables. The number of patients alive at 6 months and the encouraging ICU survival rate further justifies the use of aggressive ICU interventions in this population. (Pediatr Crit Care Med 2005; 6:531–536)**

KEY WORDS: sepsis; oncology; bone marrow transplantation; pediatric; mechanical ventilation

***See also p. 610.**

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Through the use of aggressive treatment protocols that combine chemotherapy, radiation, and surgery, the prognosis for patients with childhood malignancies has improved substantially (1–7). However, these intensive treatment regimens can cause life-threatening complications, the most prominent of which are infections that result from treatment-associated immunosuppression. Historically, sepsis and septic shock in pediatric oncology patients have carried a poor prognosis (8–17). Earlier studies, however, used a variety of criteria to define sepsis and septic shock, and most included relatively small numbers of children. Some studies even excluded patients who had received bone marrow transplants (BMT) (8, 12–15).

In light of these findings, we attempted to develop a better understanding of the outcome of severe sepsis in pediatric cancer patients. To build on the available data, we sought to describe intensive care unit (ICU) and 6-month survival in a large group of pediatric patients with diverse malignant diseases by assessing a relatively large cohort of patients identified over a 13-yr time period defined by systematic application utilizing a uniform set of established diagnostic criteria (18, 19).

PATIENTS AND METHODS

Patients

Patients in this study were admitted to the ICU of St. Jude Children's Research Hospital, a freestanding, tertiary-care pediatric oncology center, with either clinically suspected or microbiologically proven sepsis. Study patients were identified by screening of an ICU admission log followed by chart review. Inclusion criteria for the study were: 1) age newborn through 25 yrs; 2) admission to the ICU between January 1, 1990, and December 31, 2002; 3) a primary diagnosis of cancer; 4) a diagnosis of severe sepsis based on the presence of fever, infection that was either clinically suspected or microbiologically proven, and at least two of the following signs—tachycardia, tachypnea, peripheral perfusion abnormalities, altered mental status, hypotension, or acidosis at the time of ICU admission (18); and 5) receipt of intravenous fluid boluses of ≥30 mL/kg (total volume) for hypoperfusion or receipt of a dopamine infusion of ≥5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for inotropic support.

Methods

Data Collection. After approval of this study by the St. Jude Institutional Review Board, which waived the need for informed consent, the following data were abstracted from an intensive care database and from the medical record: demographic variables, oncology diagnosis, time (months) between oncology diagnosis and ICU admission, Pediatric Risk of Mortality (PRISM) III score calculated for the first 24 hrs of admission (20), absolute neutrophil count at the time of ICU admission, use of inotropic/vasopressor support, use of mechanical ventilation (MV), maximum organ system failure (OSF) score (21) during ICU admission, results of blood and other body fluid cultures, survival to ICU discharge, and survival 6 months after ICU discharge.

Clinical Management Goals. Patients were managed by the attending intensivist in cooperation with an attending oncologist. In general, goals for clinical management were as described below, although data were not collected to monitor achievement of these goals. Fluid resuscitation comprised administration of crystalloids or colloids to restore normal central venous pressure. For inotropic support, a dopamine infusion was usually titrated to achieve blood pressure and perfusion goals. When a second inotropic agent or pressor was required, epinephrine or norepinephrine was generally used. In more recent years, patients with hypotension that seemed refractory to escalating doses of inotropic and pressor agents were often treated with "stress doses" of hydrocortisone. Dobutamine or milrinone infusion was given when there was echocardiographic and clinical evidence of poor cardiac contractility with normotension. MV was instituted for altered mental status with poor airway control, severe hemodynamic compromise, excessive work of breathing, or hypoxemic respiratory failure. Since approximately 1997, "lung protective" ventilatory strategies tended to be employed (22). Some patients with severe acute hypoxemic respiratory failure were treated with combinations of high-frequency oscillatory ventilation, inhaled nitric oxide, exogenous surfactant, and prone ventilation, although no patient received extracorporeal life support. Continuous venovenous hemofiltration was the preferred mode of renal replacement therapy (more frequently utilized in the latter half of the study period). Patients were treated with broad-spectrum intravenous antibiotics, antifungals, and antiviral agents at the discretion of the intensivist, oncologist, and infectious disease consultant. Enteral nutritional support was provided when possible, and parenteral nutrition was used otherwise. Patients generally received packed red blood cell transfusions to maintain a hemoglobin concentration of ≥10 g/dL and platelet transfusions to maintain goals set by the intensivist and oncologist. Patients were treated with hematopoietic colony-stimulating factors (granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) at the discretion of the attending oncologist or as specified by the oncology protocol. Coagulopathy was managed with transfusions of fresh frozen plasma, cryoprecipitate, and vitamin K. A few patients with documented fungal disease and profound neutropenia received granulocyte transfusions.

Statistical Analysis. Univariate statistical analysis was performed to compare characteristics of survivors and nonsurvivors. The chi-square test (Fisher's exact test when appropriate) was used to analyze categorical variables. Student's *t*-test (for parametric data) or Wilcoxon's rank-sign test (nonparametric data) were used to analyze continuous variables. In univariate analysis, a p value of $<.05$ was considered significant. For multivariable analysis, a logistic regression model was developed to identify variables significantly associated with survival. All variables with a p value of $<.10$ in univariate analysis were tested in the model, and those with a p value of $<.05$ after logistic regression analysis were considered significant and remained in the model. A Hosmer-Lemeshow test was performed to assess the goodness of fit of the model. Because of the heterogeneity of cancer diagnoses, therapy protocols, and definitions of disease status in this patient group, we used the number of months between oncology diagnosis and ICU admission as a rough surrogate indicator of patients' disease and treatment oncologic status (e.g., a shorter period would roughly indicate a greater likelihood of active disease and a lesser likelihood of cumulative toxicity, and vice versa). PRISM III scores were retrospectively assigned to patients admitted before the use of PRISM III scoring.

RESULTS

During the study period, 446 separate admissions were identified for 359 patients. Admissions in post-BMT patients accounted for 30% of study admissions (132 of 446). Roughly three fourths (341 of 446, 76%) of all admissions required at least single-agent inotropic support with a modest dose (≥5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of dopamine. ICU mortality for the study group as a whole was 76 of 446 (17%). ICU mortality was 40 of 132 (30%) after BMT vs. 36 of 314 (12%) for all other admissions ($p < .0001$). A smaller percentage of admissions (106 of 446, 24%) progressed to septic shock requiring both MV and inotropic support. This subgroup was further analyzed to determine factors associated with ICU mortality. In this subgroup, mortality was 68 of 106 (64%)—33 of 59 (56%) for non-BMT vs. 35 of 47 (74%) for post-BMT admissions ($p < .05$) (Fig. 1). Of 83 admissions that required multiple inotropic and vasopres-

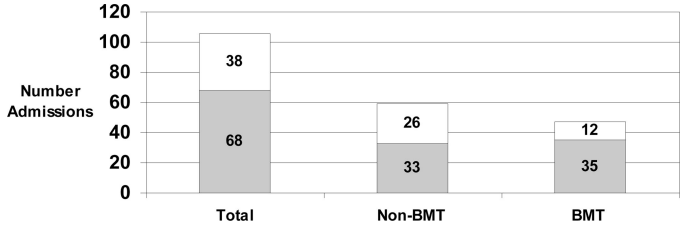

Figure 1. Intensive care unit (*ICU*) mortality in admissions requiring mechanical ventilation and inotropic support. *Column height* indicates number of admissions in which patients did (*white*) and did not (*gray*) survive to discharge. ICU mortality was 33 of 59 (57%) in non–bone marrow transplant (*BMT*) admissions vs. 35 of 47 (74%) in post-BMT admissions ($p < .05$).

sor agents and MV, ICU mortality was 60 of 83 (72%)—30 of 37 (81%) for post-BMT vs. 30 of 46 (65%) for non-BMT (p = not significant) admissions.

Table 1 reflects the results of a univariate analysis of factors potentially associated with mortality in the 106 admissions requiring both inotropic support and MV. Survival rate among BMT patients in this analysis was 12 of 47 (25.5%, $p = .048$), whereas survival for those with fungal sepsis was only 1 of 13 (7.7%, $p = .03$). Admissions requiring multiple inotropes for hemodynamic support had a survival rate of 23 of 83 (27.7%, $p = .0009$). Those admissions with either renal or hepatic failure as defined previously (21) had survival rates of 9 of 42 (21.4%, $p = .008$) and 4 of 22 (18.2%, $p = .044$), respectively. Table 2 includes only those factors found to be associated with mortality in multiple variable logistic regression analysis. Only a relatively small number of variables were significantly predictive of ICU mortality in a logistic regression model. In admissions already requiring both inotropic support and MV, the presence of fungal sepsis carried the highest odds ratio for ICU mortality. Time from oncologic diagnosis to ICU admission was not significantly associated with mortality from severe sepsis. In univariate analysis, the effect of era of ICU admission during the study period (arbitrarily defined as 1990–1997 vs. 1998–2002) had no significant effect on outcome ($p = .84$) and thus was not included in the logistic regression analysis. Further analysis of ICU survival of admissions requiring both MV and inotropic support as a factor of admission era, evaluating survival rates in 3- to 4-yr blocks, yielded no significant differences (Fig. 2).

Although maximal OSF score was not significantly associated with ICU mortality in multivariable analysis, its influence on ICU survival is demonstrated in Figure 3. For example, 10 of 33 (30%) admissions with a maximal OSF score of 4 at any point in the admission survived to ICU discharge; these included five BMT patients. Infection was microbiologically proven in 239 of 446 admissions (54%), with a positive blood culture in 153 admissions (34%). For admissions with no positive cultures of any sort, ICU mortality was 25 of 207 (12%) vs. 51 of 239 (21%) if at least one culture was positive ($p \leq .01$). The effect of a positive blood culture on ICU mortality was not significant—29 of 153 (19%) mortality in admissions with a positive blood culture vs. 47 of 293 (16%) mortality in those with negative blood cultures (p = not significant). However, when blood cultures were positive, the outcome varied widely with the type of organism isolated (Table 3).

For the entire study group admitted to the ICU with severe sepsis, 370 admissions resulted in survival to ICU discharge. Of these, 270 (73%) were alive 6 months after discharge. Six-month follow-up was not available for four admissions at the time of analysis. Regarding individual patients, 6-month survival was 170 of 248 (69%) among non-BMT patients vs. 43 of 111 (39%) for BMT patients ($p < .001$). When the 38 patients who survived to ICU discharge after requiring both MV and inotropic/vasopressor support are considered, 27 (71%) were alive 6 months after ICU discharge—22 of 27 (81%) non-BMT vs. 5 of 27 BMT (19%; $p < .001$).

DISCUSSION

This study seems to be the largest study of the outcome of severe sepsis in pediatric oncology patients. Our 13-yr retrospective review of 446 ICU admissions of pediatric oncology patients with severe sepsis revealed encouraging rates of survival at both ICU discharge and 6-month follow-up. Although patients progressing to septic shock and requiring both MV and inotropic support still had a depressingly high mortality rate, it was lower than has been previously reported (8–17). Moreover, for those patients who did survive severe sepsis and septic shock, outcome at 6 months was very encouraging, particularly among non-BMT patients.

Our study has several important limitations. First, the retrospective nature of the study renders it susceptible to potential flaws and bias. Second, this study group reflects the experience of a single center that deals almost exclusively with pediatric oncology patients. The application of these results to other pediatric ICUs, therefore, is open to question. In addition, the length of the study period may be questioned in view of changes in the nature of intensive care services over the 13-yr period (23). On the other hand, we were unable to demonstrate any significant change in the probability of survival during that period. Another potential concern is the inclusion of many admissions whose acuity of illness was relatively low. Three fourths of the study group did not receive MV. The median OSF score was only 2, when in fact almost all patients met the criteria for cardiovascular failure and most met the criteria for hematologic failure before ICU admission (21). Although the criteria for systemic inflammatory response syndrome and related conditions have been criticized as identifying a potentially low-acuity group of patients (19, 24), we used the well-established and widely accepted criteria for severe sepsis (18) systematically and also required a defined amount of fluid resuscitation or inotropic support. These inclusion criteria provided a uniform threshold of acuity for evaluation and allowed us to assess a broad range of patients. Moreover, the recent International Sepsis Definitions Conference chose to uphold the definitions of severe sepsis until new evidence is available to support changing them (19). Perhaps more importantly, the composition of the study group also reflects the clinical practice at this institution of early referral to the ICU of pediatric oncology patients with sepsis, a practice that may play a role in improving outcome. Early reversal of shock has recently been shown to halt progression toward multiple organ dysfunction and to improve the outcome of septic patients (25–27).

We suspected that the underlying malignancy and its associated therapy would influence outcome from severe sepsis.

Table 1. Univariate analysis of factors associated with intensive care unit mortality in admissions requiring both inotropic support and mechanical ventilation

Variable	Survivors	Nonsurvivors	*p* Value
BMT patients	31.6%	51.5%	.066
Fungal sepsis	2.6%	17.7%	.029
Multiple inotropes	60.5%	88.2%	.001
Renal failure[a]	23.7%	48.5%	.014
Hepatic failure[a]	10.5%	26.5%	.079
Months from oncology Dx	14.7 ± 2.9	25.8 ± 3.7	.019
Age, yrs	10.5 ± 1.1	14.2 ± 1.4	.048
PRISM III (median)	15.5 ± 0.9 (15)	18.9 ± 1.0 (17)	.016
Max OSF[a] (median)	3.3 ± 0.1 (3)	3.8 ± 0.1 (4)	.001
Positive blood culture	44.7%	42.7%	.841
Male sex	50.0%	63.2%	.219
Admission era[b]	44.7%	41.2%	.838
ANC < 500/μL	68.4%	72.1%	.824

BMT, bone marrow transplant; Dx, diagnosis; PRISM, Pediatric Risk of Mortality; OSF, organ system failure; ANC, absolute neutrophil count.

[a]Diagnosed by criteria of Wilkinson et al (21); [b] era 1 (1990–1997) vs. era 2 (1998–2002).

Table 2. Predictors of intensive care unit mortality using multivariate logistic regression analysis for admissions requiring both inotropic support and mechanical ventilation

Parameter	B Estimate	*p* Value	Odds Ratio	95% Confidence Interval
Bone marrow transplant	1.065	.002	2.9	1.1, 7.4
Fungal sepsis	2.372	.033	10.7	1.2, 94.4
Multiple inotropes	1.410	.010	4.1	1.4, 11.8
Pediatric Risk of Mortality III	0.072	.037	1.1	1.0, 1.2

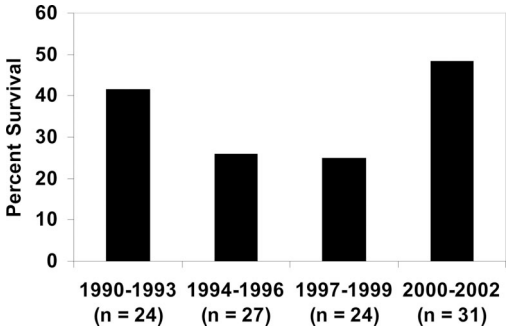

Figure 2. Intensive care unit survival compared with era of admission in admissions requiring mechanical ventilation and inotropic support (n = 106, *p* = not significant).

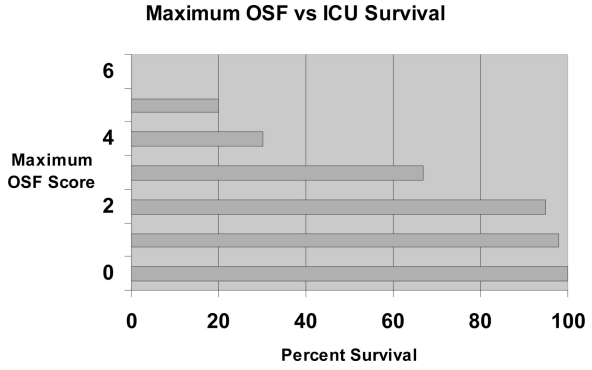

Figure 3. Maximum organ system failure (*OSF*) score vs. intensive care unit (*ICU*) survival for all admissions with severe sepsis.

However, defining this relationship proved difficult. A previous study in our unit demonstrated little difference between hematologic malignancies and solid tumors in the outcome of MV (28). Moreover, even within these two disease categories, there was little homogeneity among patients. Further, defining the status of oncologic disease at time of ICU admission was difficult because of the inconsistent use of definitions (stable disease, progressive disease, active disease, molecular relapse, partial remission, etc). In the absence of more specific variables, we postulated that the outcome of severe sepsis would be worse for patients who had experienced more cumulative treatment-related toxicity or for patients with more refractory malignant disease. Because virtually all patients studied had some form of active disease or were still undergoing protocol treatment at the time of ICU admission, we used the length of time between initial oncology diagnosis and ICU admission as a rough surrogate indicator of disease course or cumulative toxicity. Although the validity of this surrogate is open to question, it seems reasonable that a longer time after diagnosis implies a greater cumulative exposure to treatment-related toxicity or more refractory disease. This variable was indeed significant in a univariate analysis of the subgroup of patients with septic shock and higher acuity, but it did not remain significant in multivariable analysis.

The usefulness of PRISM scores in oncology patients has been debated (11, 15, 17, 29–30), with some authors suggesting that a severity of illness score more specific to oncologic disease would be more useful (29). However, PRISM III score was a significant predictor of outcome in our study, both in univariate and multivariable analysis. It is possible that the lack of association between PRISM and outcome in earlier studies of critically ill oncology patients was partially due to usage of an earlier version of the PRISM score and that the more recently developed PRISM III score is more accurately predictive of outcome. Any discussion of the utility of PRISM III in this study must be tempered by the fact that scores were retrospectively applied to patients admitted to the ICU before the advent of PRISM III.

The absence of an association between outcome of severe sepsis and severe neutropenia at the time of ICU admission is consistent with recent findings in criti-

Table 3. Survival to intensive care unit (ICU) discharge according to blood culture results

Isolated Pathogen	ICU Survival (%)
Fungal	7/19 (37)
Viral	1/3 (33)
Polymicrobial	22/27 (81)
Culture negative	246/293 (84)
Gram positive	46/51 (90)
Gram negative	48/53 (91)

cally ill adult cancer patients. In those studies, neutropenia at the time of ICU admission was not statistically associated with mortality, although the duration of neutropenia was found in some studies to be an independent predictor of mortality (31–35). The current study did not evaluate the persistence of profound neutropenia as a predictor of outcome.

The effect of respiratory failure requiring MV on outcome of severe sepsis in this population could not be evaluated by the current study design, as only those admissions progressing to septic shock requiring MV and inotropic support were analyzed for variables affecting outcome. Four admissions with severe sepsis died without MV support due to decisions by the family and medical team to limit aggressive support. Overall, only 34% of ventilated ICU admissions survived to discharge. Recent studies, including those of the authors, have reported higher survival rates for pediatric oncology patients requiring MV (8, 11, 28). However, these studies were not limited to patients with severe sepsis and septic shock. No previous study has evaluated a large group of pediatric oncology patients requiring MV for shock. In one recent study of ICU outcomes in pediatric oncology patients, all six patients who required both MV and inotropic support died (8). In a similar but larger series, 11 of 24 patients (46%) receiving both MV and inotropic support for shock died (11). Although this study's sample size was substantially smaller than ours, its findings are more in keeping with the 66% mortality reported here.

Not surprisingly, our findings indicate that BMT recipients are at a greater risk of death from severe sepsis than are other oncology patients. Although this finding is not a novel one (9, 10, 16, 17, 36, 37), it is interesting to note that 26% of BMT patients who required MV and inotropic support for septic shock survived to ICU discharge. This finding may be important information in view of the historically poor outcomes associated with critical illness (particularly with respiratory failure) in this population and the continuing debate regarding utilization of ICU resources for this group (9–11, 16, 17, 36, 37). Hallahan et al. reported the survival of 15/28 (54%) children admitted for a variety of causes to an ICU after BMT (11). Six deaths were attributed to septic shock, but it is unclear how many of these patients suffered from septic shock or severe sepsis at the time of ICU admission. Studies of acute respiratory failure in children after BMT have described a few patients with sepsis, who had a variety of outcomes (9–10, 16–17, 36–37).

As expected, cardiovascular failure requiring more than one inotropic agent or vasopressor predicted a poor outcome, as did an increasing OSF score. The relationship we observed between outcome and OSF score is consistent with that reported for general pediatric ICU populations (20, 38–40). Moreover, despite the progressive increase in mortality with each additional OSF, it is noteworthy that 30% and 20%, respectively, of patients with an OSF score of 4 and 5 survived. This finding suggests that multiple OSF, in and of itself, may not be a sufficient reason to limit intensive care support. However, one could argue that the criteria for OSF (21) may actually overestimate the acuity of illness. For example, a BUN $>$ 100 mg/dl or a creatinine $>$ 2 mg/dl is sufficient to meet the criteria for renal failure (21). It may be more pertinent to current pediatric ICU practice to evaluate renal failure based on need for renal replacement therapy rather than on a numeric value for serum creatinine or blood urea nitrogen. In addition, it is important to note that OSF as recorded for this study may have occurred at any point during the admission, and multiple OSFs may not have occurred simultaneously.

As previously reported, fungal sepsis was strongly associated with ICU mortality (41–43). On the other hand, the relatively low mortality rate (9%) associated with Gram-negative sepsis was somewhat unanticipated. Two thirds of the study group had no positive blood cultures, and a positive blood culture was not associated with mortality. The latter finding was also noted in the recent study of Hallahan et al. (11) but is contrary to the results of earlier studies of sepsis in pediatric oncology patients (12, 14). Moreover, given the extensive empirical use of broad-spectrum antimicrobial agents in this patient population, the high percentage of negative cultures is not surprising.

CONCLUSIONS

In this large, retrospective study of severe sepsis in pediatric oncology patients, outcomes were somewhat encouraging. Although those admissions progressing to septic shock requiring both inotropic/vasopressor support and MV demonstrated a high mortality rate, a substantial number did survive to ICU discharge. The high likelihood of survival to 6 months in those admissions surviving to ICU discharge is noteworthy. Although pediatric oncology patients with severe sepsis remain at very high risk, our findings suggest that their outcomes may not be as bleak as previously reported and that subsets of these patients may have a high likelihood of survival. Indeed, the mortality rate from severe sepsis among non-BMT admissions was not substantially different from the mortality rate for all pediatric patients with severe sepsis reported in a recent large epidemiologic study (44). Moreover, the identification of factors associated with outcome within this patient population may not only allow for more accurate prognostication but may also provide more precise stratification for prospective study. It is our hope that such study would lead to more prospective evaluation of therapeutic interventions for severe sepsis in pediatric oncology patients, ultimately resulting in further clinical improvement.

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