Mortality rates in pediatric septic shock with and without multiple organ system failure

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Objectives: **To determine the current mortality rates for pediatric patients with septic shock and the frequency and outcome of associated multiple organ system failure.**

Design: **Retrospective chart review.**

Setting: **Multidisciplinary pediatric intensive care unit.**

Patients: **Children age 1 month to 21 yrs admitted to the pediatric intensive care unit from January 1, 1998, to December 31, 1999, with a diagnosis of septic shock.**

Interventions: **None.**

Measurements and Main Results: **A database of all admissions to the pediatric intensive care unit was queried, and cases with diagnoses of sepsis and septic shock were reviewed. The final study cohort consisted of 96 episodes of septic shock in 80 patients. Septic shock was defined as a clinical suspicion of sepsis manifested by hyperthermia or hypothermia accompanied by hypotension and/or alteration in perfusion. Multiple organ system failure was defined by established criteria. Data were analyzed by using Fisher's exact test. The overall mortality rate for the study cohort was 13.5%. There were differences in case mortality rates between patients requiring one inotropic agent (0%) and patients requiring multiple inotropic agents (42.9%), between oncology patients who had undergone bone marrow transplantation (38.5%) and oncology patients without bone marrow transplantation (5.5%), and between patients with multiple organ system failure (18.6%) and those without multiple organ system failure (0%); $p < .05$. There did not appear to be differences in the case mortality rates between oncology and nononcology patients or among patients with varying degrees of neutropenia.**

Conclusions: **The mortality rate in pediatric septic shock is lower than has been previously reported. Oncologic illness in the absence of bone marrow transplantation does not appear to be associated with an increased mortality rate in children with septic shock. Bone marrow transplantation patients have an increased mortality rate compared with other patients with septic shock. Mortality from septic shock occurs most frequently in the context of multiple organ system failure. (Pediatr Crit Care Med 2003; 4:333–337)**

KEY WORDS: sepsis; oncology; neutropenia; bone marrow transplantation

Sepsis, defined as the systemic response to infection (1), remains a significant cause of morbidity and potential mortality in the pediatric population. There are 400,000–500,000 cases per year of Gram-negative sepsis in children (2). Susceptibility to infection depends on age and preexisting medical conditions, such as immunologic disorders, cancer, neurologic/developmental disabilities, and congenital heart disease. Pathogens responsible for sepsis may be bacterial, viral, or fungal. In many cases, the offending pathogen cannot be isolated despite appropriate microbiological evaluation.

Severe sepsis causes a release of inflammatory mediators, maldistribution of intravascular volume, and depression of myocardial function, ultimately resulting in septic shock. The treatment of septic shock requires administration of antimicrobials, aggressive fluid resuscitation, and titration of appropriate inotropic and/or vasopressor agents. Five to 30% of pediatric patients with sepsis will develop septic shock (2). Several studies conducted in the 1980s and 1990s reported mortality rates >50% in children with septic shock (3, 4). More recent investigations have reported mortality rates of 20–30% (2, 5, 6).

Cases of septic shock in which the shock state is not reversed often progress to multiple organ system failure (MOSF). Wilkinson et al. (7) reported the overall mortality rate for patients with MOSF to be 54%. This rate was directly related to the number of organ systems involved. Additional studies have reported mortality rates of 46% in patients with MOSF and sepsis (8) and 52% in patients with MOSF and septic shock (9).

We retrospectively examined the medical records of children admitted to a multidisciplinary pediatric intensive care unit (PICU) who had septic shock at the time of admission or who developed septic shock during their hospitalization. A percentage of these children had MOSF. The objectives of this study were to determine the mortality rates for pediatric patients with septic shock with various comorbid conditions, to determine what proportion of patients with septic shock have associated MOSF, and to determine the impact of MOSF on mortality rate in septic shock.

METHODS AND MATERIALS

This study was conducted in a multidisciplinary PICU with an affiliation to a major pediatric cancer center. A computerized database and the raw data sheets of all admissions from January 1, 1998, through December 31,

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1999, were queried to identify patients with sepsis or septic shock. Medical records were reviewed; demographic and clinical data were collected. Data included patient age, gender, underlying diagnoses, pediatric risk of mortality score (PRISM), length of stay, presence of indwelling catheters and frequency of removal of those catheters, presence of neutropenia (absolute neutrophil count $<1500/mm^3$) (10, 11), presence of severe neutropenia (absolute neutrophil count $<500/mm^3$) (10, 11), vital signs, blood culture results, and the use of inotropic/vasopressor agents. Risk of mortality, based on PRISM score, age, and operative status, was calculated. Patients who were >21 yrs of age were excluded from the study. A positive blood culture was not required for the diagnosis of sepsis or septic shock.

Septic shock was defined by criteria adapted from the Task Force on Hemodynamic Support from the American College of Critical Care Medicine/Society of Critical Care Medicine (Table 1) (12). Patients had to meet criteria listed in I and II or I and III to be included in the study. Patients who had evidence of sepsis without evidence of shock were excluded.

The diagnosis of MOSF was made based on specific criteria adapted from Wilkinson et al. (7, 8), marking dysfunction of the cardiovascular, respiratory, neurologic, hematologic, renal, gastrointestinal, and hepatic systems (Table 2). Meeting one criterion from a given system qualified as failure of that system. MOSF was defined as having two or more organ system failures. This study was approved by the Institutional Review Board. Data were analyzed by using Fisher's exact test ($p < .05$).

Table 1. Criteria for diagnosis of septic shock

I.	Suspected infection manifested by	
	1. Hypothermia (temperature, ≤36.0°C) or	
	2. Fever (temperature, ≥38.0°C)	
II.	Clinical signs of altered perfusion (one of the following)	
	1. Depressed mental status	
	2. Capillary refill >2 secs	
	3. Flash capillary refill	
	4. Decreased pulses	
	5. Bounding pulses	
	6. Mottled, cool extremities	
	7. Decreased urine output (<1 mL/kg/hr)	
III.	Hypotension	
	1. Infants (birth–11 mos):	Systolic blood pressure, ≤65 mm Hg
	2. Children (12 mos–12 yrs):	Systolic blood pressure, ≤75 mm Hg
	3. Adolescents (13 yrs–21 yrs):	Systolic blood pressure, ≤85 mm Hg

Table 2. Criteria for diagnosis of multiple organ system failure

I.	Cardiovascular	
	1.	Systolic blood pressure, mm Hg
		≤65 in infants
		≤75 in children or
		≤85 in adolescents
	2.	Heart rate, beats/min
		<50 or >220 in infants
		<40 or >200 in children
	3.	Continuous infusion of inotropic agents
	4.	Serum pH <7.20 (with a normal $Paco_2$)
II.	Respiratory	
	1.	Respiratory rate, breaths/min
		>90 in infants or
		>70 in children
	2.	Pao_2/Fio_2 <200 (in the absence of congenital heart disease)
	3.	Mechanical ventilation (>24 hrs in a postoperative patient)
	4.	$Paco_2$ >65 torr
	5.	Pao_2 <40 torr (in the absence of congenital heart disease)
III.	Neurologic	
	1.	Glasgow Coma Scale score of <5
	2.	Fixed and dilated pupils
IV.	Hematologic	
	1.	Hemoglobin, <5 g/dL
	2.	White blood cell count, $<3000/mm^3$
	3.	Platelet count, $<20{,}000/mm^3$
	4.	Prothrombin time, >20 secs or Activated partial thromboplastin time, >60 secs
V.	Renal	
	1.	Blood urea nitrogen, >100 mg/dL
	2.	Creatinine, >2.0 mg/dL (in the absence of preexisting renal disease)
	3.	Dialysis
VI.	Gastrointestinal	
	1.	Blood transfusions >20 mL/kg in 24 hrs because of hemorrhage
VII.	Hepatic	
	1.	Total bilirubin >5 mg/dL and aspartate aminotransferase or lactate dehydrogenase greater than twice normal (without evidence of hemolysis)

RESULTS

In the period between January 1, 1998, and December 31, 1999, there were 2,346 admissions to the PICU. Of these, 147 (6.3%) were related to sepsis or septic shock. In 38 cases, the patients failed to meet criteria for septic shock as outlined in the clinical practice parameters (12). Four cases were excluded because the patients exceeded the study's upper age limit of 21 yrs. Two cases were excluded because the patients had had extended stays in a neighboring PICU before transfer to our unit. Seven cases were excluded because the medical records were unavailable for review. Of these seven cases, there was one mortality. In all, 51 cases were excluded.

The final study cohort consisted of 96 episodes (cases) of septic shock in 80 patients. The patients ranged in age from 1 month to 21 yrs. Ages, PRISM scores, risks of mortality, and lengths of stay are presented in Table 3 as means and SD.

Of the 96 patients, 68 (70.8%) involved patients with an oncologic illness. The oncologic diagnoses included neuroblastoma (n = 9), acute myelogenous leukemia (n = 8), acute lymphocytic leukemia (n = 5), osteogenic sarcoma (n = 4), non-Hodgkin's lymphoma (n = 5, 2 of which had underlying diagnoses of AIDS), Ewing's sarcoma (n = 3), other lymphomas (n = 3), malignant teratoma (n = 3), rhabdomyosarcoma (n = 3), synovial sarcoma (n = 2), desmoplastic small round cell tumor (n = 2), nasopharyngeal carcinoma (n = 2), and melanoma (n = 2). There was one case each of glioblastoma multiforme, medulloblastoma, rhabdoid sarcoma, and posterior fossa rhabdoid tumor. There was one patient with both a rhabdoid tumor of the kidney and a primitive neuroectodermal tumor of the posterior fossa. One patient had received an autologous bone marrow transplantation (BMT) for neuroblastoma and

subsequently developed acute lymphocytic leukemia. There were 11 episodes of septic shock in a single patient with Gardner's syndrome, multiple desmoplastic small round cell tumors of the abdomen, and multiple ostomies. Among the 68 cases involving oncology patients, 13 involved patients who had undergone BMT (19.1% of oncology cases and 13.5% of all cases). All BMT patients had an underlying oncologic diagnosis. Among the 28 cases of patients without an oncologic diagnosis, 13 (13.5%) were previously healthy, whereas the remaining 15 (15.6%) involved patients with underlying conditions including acquired immune deficiency syndrome (n = 4), complex congenital heart disease (n = 2), neurologic disorders/seizures (n = 2), burns/toxic epidermal necrolysis (n = 2), renal transplant (n = 1), dysrhythmias (n = 1), autoimmune lymphoproliferative syndrome (n = 1), Langerhans cell histiocytosis (n = 1), and aplastic anemia (n = 1).

Blood cultures were positive in 48 cases (50.0%). Of these, there were 35 cases in which one organism grew (23 Gram-positive organisms and 12 Gram-negatives) and 13 in which multiple organisms grew. In the cases where multiple organisms were cultured, there were five cases in which two organisms grew (two grew two different Gram-positive organisms, two grew one Gram-positive and one Gram-negative, and one grew one Gram-positive organism and a fungal species); three organisms grew in seven cases (in four there was at least one species of fungus and the remaining three grew a combination of Gram-positive and Gram-negative organisms). In one case involving a patient who developed septic shock after suffering significant burns, four different organisms grew.

Neutropenia was present in 46 cases (47.9%). In 56 cases (58.3%), an indwelling catheter was in place at the onset of illness. Twenty-eight (50.0%) of these catheters were removed. In 86 cases (89.6%), patients were hypotensive. Inotropic/vasopressor support was required in 64 cases (66.7%). Of these 64 cases of patients requiring inotropic/vasopressor support, 28 (43.8%) were treated with more than one agent. MOSF was present in 70 cases (72.9%) either at the time of presentation or at some time during the patients' PICU course. Treatment of septic shock included empirical antibiotic therapy, aggressive fluid resuscitation, and infusion of inotropic and vasopressor agents.

The overall mortality rate for the final study cohort was 13.5% (13 of 96 cases). There were no deaths among children who were previously healthy. The mortality rates for oncology patients who had undergone BMT compared with oncology patients without BMT are shown in Figure 1. The mortality rates for patients requiring more than one vasopressor/inotropic agent compared with patients requiring only one agent are shown in Figure 2. The mortality rate for the initial age-appropriate cohort of 143 patients was 12.6%, which was not statistically different from the final study cohort (p = nonsignificant). The mortality rates for patients with and without MOSF are shown in Figure 3. MOSF was present in 100% of the patients who died.

The study was insufficiently powered to detect differences in mortality rates for oncology patients (11.8%) vs. nononcology patients (17.9%), neutropenic patients (absolute neutrophil count $<1500/mm^3$) (17.4%) vs. nonneutropenic patients (10.0%), and severely neutropenic patients (absolute neutrophil count $<500/mm^3$) (20.0%) vs. nonseverely neutropenic patients (8.9%).

DISCUSSION

Mortality rates in pediatric septic shock have declined steadily over the past

Table 3. Demographics

	All Cases	Survivors	Nonsurvivors
Age, mos	127 ± 84	132 ± 83	95 ± 88
PRISM	11 ± 9	9 ± 6	24 ± 16
Risk of mortality, %	9.6 ± 18.7	6.0 ± 9.2	33.1 ± 38.9
Length of stay, days	9 ± 16	8 ± 16	15 ± 14

PRISM, pediatric risk of mortality score.

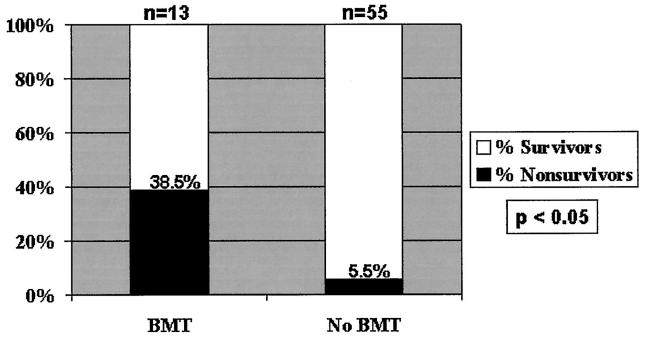

Figure 1. Mortality rates of patients with and without bone marrow transplantation (*BMT*). The mortality rates are presented as percentages of the total number of patients. The mortality rate for septic shock episodes in oncology patients who had undergone bone marrow transplantation (n = 13) was 38.5% compared with oncology patients who had not undergone bone marrow transplantation (n = 55), which was 5.5% ($p < .05$).

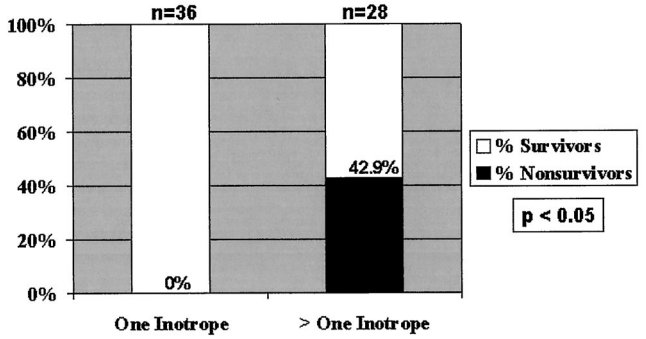

Figure 2. Mortality rates of septic shock episodes in patients requiring one inotropic/vasopressor agent vs. multiple inotropic/vasopressor agents. Mortality rates are presented as percentages of the total number of patients. The mortality rate for patients requiring one inotropic/vasopressor agent (n = 36) was 0% compared with patients requiring multiple inotropic/vasopressor agents (n = 28), where the mortality rate was 42.9% ($p < .05$).

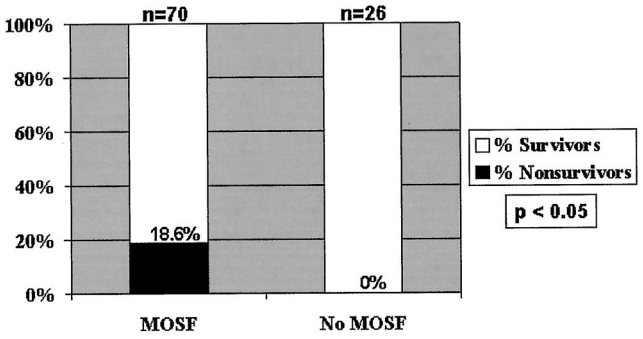

Figure 3. Mortality rates of septic shock episodes in patients with multiple organ system failure (*MOSF*) vs. patients without MOSF. Mortality rates are presented as percentages of the total number of patients. The mortality rate for patients with MOSF (n = 70) was 18.6%, which was significantly higher than the mortality rate in patients without MOSF (n = 26), where the mortality rate was 0% ($p < .05$).

Oncologic illness in the absence of bone marrow transplantation does not appear to be associated with an increased mortality rate in children with septic shock.

several decades. The improvement in survival may be attributed to a better understanding of the pathophysiology of the illness. Research has elucidated the roles of aggressive fluid resuscitation and of vasopressor and inotropic agents in the management of septic shock. Similar work has improved our understanding of the hemodynamic variations and their impact on end-organ function in septic shock (3, 4, 13–16).

We report a mortality rate of 13.5% in a cohort of patients with septic shock admitted to our PICU in 1998 and 1999, reflecting data collected in a case-by-case medical record review. This mortality rate is higher than would be predicted from the patients' PRISM scores and calculated risks of mortality. However, the generally lower PRISM scores may simply reflect improved resuscitation during the first 24 hrs of hospitalization. The mortality rate of 13.5% is consistent with recently published mortality rates in pediatric patients obtained from analyses of large, multiple-center, national databases. In 2001, Angus et al. (17) reported a 10% mortality rate in children with severe sepsis, reflecting analysis of hospital discharge databases from seven states in 1995. In this study, patients with severe sepsis were identified by using International Classification of Diseases, Ninth Revision, Clinical Modification codes for bacterial or fungal infections as well as acute organ dysfunction. In 1998, Stoll et al. (18) reported an infant sepsis mortality rate of 21%, reflecting data from 1992 to 1994 obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention.

In a majority of episodes of septic shock in our study (86.5%), the patients had a comorbid condition at presentation. No deaths occurred in previously healthy patients. There were no cases of meningococcemia, which continues to be a significant source of sepsis and septic shock in other geographic areas. In contrast to previous studies reporting mortality rates as high as 63% in oncology patients with septic shock (19,20), patients with preexisting oncologic conditions did not appear to have significantly different mortality rates from those without oncologic diagnoses. Additionally, patients with neutropenia did not appear to have a significantly different mortality rate from those without neutropenia. However, a larger study cohort would be needed to demonstrate that no true differences existed between these groups.

Although there did not appear to be a difference in mortality rate between cases involving oncology and nononcology patients, there was a difference in mortality rate between septic shock episodes in oncology patients who had undergone BMT compared with those who had not undergone BMT. Cases involving patients meeting criteria for MOSF, regardless of the premorbid condition, had a significantly higher mortality rate than those without MOSF. Of the 13 episodes of septic shock in patients who had undergone BMT, 12 had MOSF, which helps explain the higher mortality in this population. Some of the BMT patients had preexisting MOSF at the time of presentation with septic shock, whereas others developed MOSF in the course of the illness. Patients with refractory septic shock, as manifested by the need for more than one inotropic/vasopressor agent, had a significantly higher mortality rate than patients who responded to one agent. The general approach to the use of inotropic/vasopressor therapy in the study population involved employing dopamine as the first line therapy and then adding epinephrine or norepinephrine as the need arose based on hemodynamic variables and clinical examination. In some patients, vasopressin or dobutamine also was used. All deaths in the study were associated with MOSF.

The improved mortality rates in patients previously thought to be at high risk for poor outcomes (i.e., oncology and neutropenic patients) may be attributed to more aggressive resuscitation, aggressive inotropic support, and early removal of indwelling catheters when catheter-related sepsis was suspected. BMT patients continue to have a higher mortality rate than their non-BMT oncologic counterparts. This is undoubtedly related to the immunosuppressive regimen that these patients undergo in association with transplantation as well as the immunologic dysregulation that patients experience following BMT. Additionally, the increased mortality rate is related to the increased frequency of MOSF that exists in these patients in the context of septic shock. Further investigation is warranted.

CONCLUSIONS

The mortality rate in pediatric septic shock is lower than has previously been reported. Otherwise healthy children have good outcomes when they develop sepsis with septic shock. Oncologic illness, neutropenia, and the requirement for one inotropic agent do not appear to increase the mortality risk in children with septic shock. Oncology patients who have undergone BMT have an increased mortality rate from septic shock compared with non-BMT oncology patients,

as do patients who require two or more inotropic/vasopressor agents compared with patients requiring only one agent. Death from septic shock occurs most frequently in association with MOSF.

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