Clinical Spectrum of Shock in the Pediatric Emergency Department

Jay D. Fisher, MD, David G. Nelson, MD,* Heidi Beyersdorf, MD,* and Lawrence J. Satkowiak, MD†*

Objective: The objective of this study was to describe the clinical spectrum of patients presenting with shock or developing shock in a pediatric emergency department (ED) during an 8-year period.

Methods: An observational study of all pediatric ED patients with shock between September 1998 and September 2006 was performed. Trauma activations were excluded. A structured, explicit chart review using a standardized abstraction form and case definition was completed by 3 physicians board certified in pediatric emergency medicine. Inter-rater reliability was monitored.

Results: A total of 147 cases of shock were identified. Septic shock was the underlying physiology in 57% of cases. A pathogen was identified in 45% of these cases. Hypovolemic shock due to gastroenteritis, metabolic disease, surgical emergencies, or hemorrhage was the cause in 24% of cases. Distributive shock represented 14% of cases. Cardiogenic shock contributed to 5% of cases. Patients with septic shock received a mean of 58 mL/kg of crystalloid or colloid versus 50 mL/kg in patients with other causes. Intubation and vasopressor use was required in 41% and 21% of cases, respectively. Clinical signs of shock developed in the ED after initially presenting without clinical signs of shock in 14% of study subjects. Nearly half of these episodes occurred after the administration of antimicrobials or performance of a lumbar puncture. Mortality was 6% overall and 5% in septic shock patients.

Conclusions: Pediatric ED patients with shock represent a diverse population with substantial mortality. Of 147 patients, 21 presented without clinical signs of shock and deteriorated to a clinical condition meeting the definition of shock during the ED course.

Key Words: shock, cause, deterioration

(*Pediatr Emer Care* 2010;26: 622–625)

Twenty-five years after the development of the pediatric emergency medicine fellowship, systematic research on the clinical spectrum of shock in the pediatric emergency department (ED) has been limited.[1–3] Research on pediatric shock has focused primarily on patients with shock due to sepsis and has come from the intensive care perspective.[4–9] The reasons for this are manifold. Although cardiopulmonary arrest in children can occur because of respiratory or circulatory insufficiency, respiratory compromise occurs with much greater frequency. On initial presentation, there is a significant clinical overlap between pediatric patients with and without shock and those with shock because of different physiologic categories. This creates a challenge for both clinicians and researchers.

A fundamental appreciation of the clinical variability of shock is essential for pediatric emergency providers. Research from the critical care setting suggests that children with decompensated shock due to sepsis have a mortality rate as high as 50%[8] and that early identification and aggressive management can significantly reduce mortality.[4–7,9] Case reports of significant morbidity and mortality of shock due to cardiogenic, distributive, and hypovolemic etiologies are also abundant.[10–13]

For the clinician at the bedside, identification and management of children during the nascent stages of shock are difficult because of the low incidence of disease, the wide etiology spectrum, and variable physical findings. Each case of pediatric shock possesses unique features for the initial examiner and is capable of confounding even experienced physicians. The clinical course of shock is also a dynamic process, yet there are few published studies describing children who present to the ED without shock and deteriorate to a state of circulatory compromise later in their ED course.[4,14] In an effort to supplement the published experience with pediatric emergency patients with shock, the following study was performed.

METHODS

Data extraction on a consecutive series of patients with shock presenting to the pediatric ED at Children's Hospital of Nevada at University Medical Center from September 1998 to September 2006 was performed. The department is a stand-alone pediatric ED in the setting of a large, general university hospital, seeing all patients presenting for emergency care younger than 18 years. Annual volume averaged 30,000 visits during the study period. All patients presenting with shock, or deteriorating to a state of shock while in the pediatric ED, were identified for study. The pediatric emergency physicians used the shock definitions and practice parameters detailed in the Pediatric Advanced Life Support guidelines in identifying and managing patients with shock during the study period.[15] Changes to the Pediatric Advanced Life Support guidelines during the study period were reviewed. The patient history, physical examination, and hospital course of all study subjects were documented by a dictated record by the pediatric emergency attendants, all of whom were board certified in pediatric emergency medicine. Our standard practice during the study period was to specifically dictate the clinical criteria classifying the patients as having shock, with specific attention to peripheral pulse quality, skin perfusion, capillary refill, and blood pressure. The pediatric emergency physicians providing clinical care on study patients met monthly for peer review during the study period and routinely discussed the diagnosis and management of patients with shock. The standard of care in our department for all patients presenting with signs and symptoms of shock included the administration of at 20 to 40 mL/kg of crystalloid within the first hour based on the patients' peripheral perfusion. Patients presenting with circulatory compromise status after a prehospital cardiac arrest were excluded from analysis, as were patients requiring trauma team activation.

From the *Department of Emergency Medicine; University Medical Center, University of Nevada School Medicine, Las Vegas, NV; and †Department of Pediatrics, Children's Hospital of Central California, University of California, San Francisco, Madera, CA.

Reprints: Jay D. Fisher, MD, Department of Emergency Medicine; University Medical Center, University of Nevada School Medicine, Las Vegas, NV (e-mail: jdfisher1@cox.net).

The study was presented at the American Academy of Pediatrics National Conference and Exhibition, Boston, MA, October 10, 2009

ISSN: 0749-5161

TABLE 1. Age Distribution

Age	n (%), n = 147
0–3 mo	46 (31)
3–36 mo	47 (32)
3–12 yr	31 (21)
>12 yr	23 (16)

Patient capture was ensured as part of an ongoing mandatory peer review of all pediatric intensive care unit (PICU) admissions by the primary author on a monthly basis. During the study period, no patient admitted to the ward required emergent transfer to the PICU for circulatory compromise within 4 hours of admission. Beginning in 2001, a computerized patient tracking system (EMSTAT) was used to cross check patient capture. Data extraction was performed on each ED chart by 2 of 3 physicians board certified in pediatric emergency medicine (J.F., D.N., and L.S.). The physicians were instructed on explicit data extraction, and a standardized form was used. The primary author submitted and reviewed a precise set of operational definitions for the extracted variables with each data extractor. Physicians extracted the following variables: vital signs, oxygen saturation, peripheral pulse quality, extremity perfusion, capillary refill time, mental status, overall impression on the presence or absence of shock, whether shock was manifest at presentation or occurred later in the ED course, the predominant clinical sign of shock, amount of fluid resuscitation, antibiotic use, pressor use, need for endotracheal intubation, and ED diagnosis. The physician extractors met regularly and reviewed the details of the chart review. Final diagnosis was determined by review of the hospital course by the primary author, in conjunction with the extracted ED diagnosis. The final determination of the most significant contributing pathophysiologic category (septic, cardiac, distributive, or hypovolemic) was made by the primary author. The level of agreement between reviewers was monitored. The study was approved by the hospital's institutional review board.

RESULTS

One hundred fifty-three cases were identified. There was agreement on the presence of shock between extractors in 96% of cases, resulting in 147 cases for analysis. This represented approximately 1 case for every 1600 pediatric ED patients during the study period. The presence or absence of shock and the predominant clinical sign suggestive of shock could be determined in all 147 cases. The age distribution of the cohort was as follows: 0 to 90 days, 31%; 3 months to 3 years, 32%; 3 to 12 years, 21%; and older than 12 years, 16% (Table 1). Twenty-two patients (15%) had underlying medical conditions. Sepsis was determined to be the cause of shock in 57% cases (Table 2). A pathogen was identified in 38 of these cases; bacterial pathogens were identified by blood culture, and respiratory syncitial virus (RSV) was identified by nasal washings. Respiratory syncitial virus, *Streptococcus pneumoniae*, *Escherichia coli*, *Streptococcus pyogenes*, *Enterococcus*, and *Neisseria meningitidis* accounted for most of the pathogens.

Hypovolemic shock due to gastroenteritis, metabolic disease, surgical emergencies, or nontraumatic hemorrhage was the cause in 24% of cases. Distributive shock due to neurologic, anaphylactic, environmental, and collagen vascular

TABLE 2. Shock Classification

Shock Physiology	n (%), n = 147	Delayed,* n = 21
Septic	84 (57)	11
Hypovolemic	35 (24)	5
Distributive	21 (14)	4
Cardiogenic	7 (5)	1

*Number of patients who presented without signs of shock and developed them later in their ED course.

TABLE 3. Shock Etiologies

	n
Septic (n = 84)	
Pathogen identified	38
RSV	7
E. coli	5
S. pneumoniae	4
Group A *Streptococcus*	4
Enterococcus	3
N. meningitidis	3
Staphylococcus aureus (toxic shock)	3
Group B *Streptococcus*	2
Pseudomonas aeruginosa	2
Enterobacter cloaca	1
Methicillin-resistant *S. aureus*	1
Acinetobacter	1
Clostridium difficile	1
Varicella	1
Hypovolemic (n = 35)	
Gastroenteritis	10
DKA/metabolic	9
Nontraumatic hemorrhage	10
Epistaxis	4
Aortoenteric fistula	2
Hemorrhagic disease of newborn	1
Upper GI bleed	2
Vaginal bleed	1
Surgical	5
Volvulus	2
Intussusception	1
Toxic megacolon	1
Appendicitis	1
Malignancy	1
Distributive (n = 21)	
Neurologic	9
Status epilepticus	4
Nonaccidental trauma	4
Encephalopathy	1
Toxin/Env	6
Collagen vascular	3
Anaphylactic	3
Cardiogenic (n = 7)	
Congenital heart disease	3
Myocarditis	3
Cardiomyopathy	1

DKA indicates diabetic ketoacidosis; GI, gastrointestinal.

TABLE 4. Predominant Cardiovascular Sign

Age	Poor Perfusion/Pulses, n (%)	Hypotension, n (%)
0–90 d (n = 46)	40 (87)	6 (13)
3–36 mo (n = 47)	41 (87)	6 (13)
3–12 yr (n = 31)	15 (48)	16 (52)
>12 yr (n = 23)	7 (30)	16 (70)

diseases represented 14% of cases. Cardiogenic shock contributed 5% of cases (Table 3). The predominant clinical sign of circulatory compromise differed among age groups (Table 4). Younger patients presented with poor extremity perfusion and pulses, whereas adolescents were more likely to manifest hypotension.

Patients with septic shock received a mean of 58 mL/kg of crystalloid or colloid versus 50 mL/kg in patients with other causes. Endotracheal intubation and vasopressor administration were required in 41% and 21% of cases, respectively. Fourteen percent of patients presented without clinical signs of shock, and their conditions deteriorated to shock during their ED course (Table 5). Nearly half of these episodes occurred after the administration of antimicrobials or performance of a lumbar puncture. Most of these patients were younger than 2 years. One third (7/21) of patients in the deterioration group had isolated tachycardia on presentation, with normal perfusion. Of the 7 patients with isolated tachycardia on presentation, 6 were older than 10 years. All but 1 patient in the series survived to PICU admission. Subsequent mortality was 6% overall and 5% in septic shock patients.

DISCUSSION

Our study adds to what is known about the presentation of pediatric shock in the ED. Clinical research on the entire spectrum of pediatric shock presenting for emergency care has been limited. Most research on pediatric shock has been from the intensive care unit perspective and has focused on patients with shock due to sepsis. Many authoritative references cite hypovolemia, often due to gastroenteritis, as the most common pathophysiologic mechanism of shock in children.[14,16] Our survey, however, found sepsis to be the most common form of shock, representing 57% of patients. In the United States, where access to emergency care is abundant and the use of intravenous fluids is liberal, it is likely that shock due to isolated hypovolemia is less common. Isolated hypovolemia was responsible for just 24% of patients in our series.

Of 147 patients, 21 presented without clinical signs of shock and deteriorated to a clinical condition meeting the definition of shock during the ED course. Nearly half of these episodes occurred after the administration of antibiotics or performance of a lumbar puncture, and most of these cases were in children younger than 2 years. Toxin release or physical stress may have contributed to circulatory decompensation in these patients. The evolving nature of shock in children has been noted by other authors,[4,8,14] and this emphasizes the importance of repeat assessment in pediatric emergency patients at risk for deterioration. One third of patients whose conditions deteriorated to the shock state while in the ED had isolated tachycardia on presentation. Nearly all of these children were in the older school age or adolescent age range. This may be because older children are less able than younger children to constrict their peripheral vasculature in the face of a decreased cardiac output.

We chose to evaluate the frequency of altered peripheral perfusion, pulses, and blood pressure in our patients with shock.

TABLE 5. Characteristics of Patients With Deterioration to Shock Later in ED Course (n = 21)

Age	Diagnosis	Shock Type	Precipitant	Survival	Triage Heart Rate, beats/min
2 mo	Pneumonia	Septic	No	Yes	162
2 yr	Meningococcemia	Septic	abx	Yes	188*
15 yr	Collagen vascular disease	Distributive	No	Yes	150*
2 mo	Thoracic neuroblastoma	Hypovolemic	LP	Yes	118
1 d	Upper GI bleed	Hypovolemic	No	Yes	160
2 mo	Hyperthermia/environmental	Distributive	No	Yes	100
8 mo	Intussusception	Hypovolemic	EJ line	Yes	186
2 mo	Pyelonephritis	Septic	abx	Yes	134
7 mo	Pneumonia	Septic	LP	Yes	102
8 mo	Pneumococcal meningitis	Septic	No	Yes	172
10 yr	Epistaxis	Hypovolemia	No	Yes	190*
13 yr	Pneumonia	Septic	No	Yes	112*
14 d	Hemorrhagic disease of newborn	Hypovolemic	No	Yes	150
16 yr	Terbutaline ingestion	Distributive	No	Yes	215*
11 yr	Pneumonia	Septic	abx	Yes	150*
12 yr	Acute encephalopathy	Distributive	No	Yes	200*
23 d	Pneumonia	Septic	LP	Yes	99
2 mo	RSV/sepsis	Septic	abx	Yes	119
23 d	*E. cloaca* UTI/meningitis	Septic	abx	Yes	168
2 yr	Myocarditis	Cardiogenic	No	No	120
1 mo	Meningitis	Septic	abx	Yes	158

*Patients with tachycardia at presentation as defined by Pediatric Advanced Life Support ranges for age.

UTI indicates urinary tract infection; abx, antibiotics; EJ line, external jugular line placement; LP, lumbar puncture.

Our experience has been that isolated tachycardia is of limited clinical value in identifying children with shock because of the frequency with which patients without shock have this finding. The predominant clinical manifestations of shock in our study varied between age groups, with hypotension becoming a more prevalent finding in older children and adolescents. This suggests a change in the cardiovascular response to shock as children age. An extended period of compensation with elevated cardiac output and increased peripheral vascular resistance has long been described in young children.[15] Our data suggest that as children reach adolescence, hypotension as a clinical sign of shock becomes more prevalent as their cardiovascular responses to shock become more adult in nature.

The mortality from septic shock in our series was low compared with those in other series. Although our use of early and aggressive therapy may have contributed to this finding, other factors were operative. Our population had a lower prevalence of underlying disease compared with other studies. In addition, several previous studies were performed in parts of the world where delays seeking medical care were likely. This would tend to make those populations sicker on presentation and more likely to have a higher mortality.[3,7] Mortality from hypovolemic, cardiogenic, and distributive mechanism was similar to those with sepsis in our study. These patients also received fluid volumes similar to those with sepsis.

The diagnostic spectrum of shock found in our study was notable, consistent with the protean mechanisms described in published case reports. The frequency of shock cases was relatively low in our patient population. A physician working an average number of monthly clinical hours would be expected to see approximately 2 such cases annually. This emphasizes the need for pediatric emergency physicians to study the experience of others, optimize their learning in each of their own cases, and carefully assess the peripheral perfusion of each patient they examine.

The strength of our study is limited by several factors. Patients were collected at a single pediatric facility with a modest annual volume, which could limit the external validity of our data. In addition, although patients were identified prospectively, data elements were extracted from medical records. Although the data extraction methods were explicit and the accuracy was monitored, this method of data acquisition has inherent limitations.

CONCLUSIONS

Pediatric ED patients with shock represent a diverse population with substantial mortality. One in 7 cases presented without signs of shock and deteriorated to a condition meeting the definition of shock during their ED course. Research on the optimal management of shock in this population will require a multicenter design.

REFERENCES

1. Chang P, Hsu Y, Chang MH, et al. Shock in the pediatric emergency service: five years' experience. *Acta Paediatr Taiwan.* 1999;40(1):9–12.
2. Singh D, Chopra A, Pooni PA, et al. A clinical profile of shock in children in Punjab, India. *Indian Pediatr.* 2006;43:619–622.
3. Santhanam I, Sangareddi S, Venkataraman S, et al. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. *Pediatr Emerg Care.* 2008;24(10):647–655.
4. Inwald DP, Tasker RC, Peters MJ, et al. Paediatric Intensive Care Society Study Group. Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society audit. *Arch Dis Child.* 2009;94(5):348–353.
5. Oliveira C, Nogueira de Sa FR, Oliveira D, et al. Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: barrier to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support guidelines in a pediatric intensive care unit in a developing world. *Pediatr Emerg Care.* 2008;24(12):810–815.
6. de Oliveira C, de Oliviera D, Gottschald A, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med.* 2008;34:1065–1075.
7. Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics.* 2003;112:793–799.
8. Proulx F, Fayon, M, Farrell CA, et al. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest.* 1996;109:1033–1037.
9. Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitaiton in pediatric septic shock. *JAMA.* 1991;266:1242–1245.
10. Bay TA, Walter FG, Lober W, et al. *Loxosceles arizonica* bite associated with shock. *Ann Emerg Med.* 1997;30(5):701–703.
11. Bonadio WA, Losek JD. Infants with myocarditis presenting with severe respiratory distress and shock. *Pediatr Emerg Care.* 1987;3(2):110–113.
12. Lucking SE, Pollack MM, Fields AI. Shock following generalized hypoxic ischemic injury in previously healthy infants and children. *J Pediatr.* 1986;108(3):359–364.
13. Griggs JR, Bricker JT, Mariscalco M, et al. Back pain with cardiovascular collapse in pediatric emergency department. *Pediatr Emerg Care.* 1990;6(1):17–20.
14. Byer RL, Bachur RG. Clinical deterioration among patients with fever and erythroderma. *Pediatrics.* 2006;118(6):2450–2460.
15. Ralston M, Hazinski MF, Zaritsky AL, Schexnayder SM, Kleinman ME, eds. *Pediatric Advanced Life Support.* Dallas, Tex: American Heart Association; 2006.
16. Fleisher GR, Ludwig S, Henretig FM. *Textbook of Pediatric Emergency Medicine.* Philadelphia, PA: Lippincott Williams and Wilkins; 2006, 5th ed. 55.

been suggested in fatal cases of HHV-6–associated myocarditis.[8] On the other hand, HHV-6 increases the synthesis of several cytokines including tumor necrosis factor-α,[10] which is capable of causing acute proteolysis in a variety of organs including the liver, central nervous system and skeletal muscle.[11] Although intensive care, including dialysis, is sometimes necessary for the treatment of rhabdomyolysis, this was not required for our patient. Further studies to elucidate the pathophysiology of HHV-6–associated rhabdomyolysis are necessary, and may shed light on the therapeutic efficacy of antiviral drugs or anticytokine drugs for treatment of this disease.

REFERENCE

1. Tanaka N, Kimura H, Hoshino Y, et al. Monitoring four herpesviruses in unrelated cord blood transplantation. *Bone Marrow Transplant.* 2000;26:1193–1197.
2. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. *Muscle Nerve.* 2002;25:332–347.
3. Singh U, Scheld WM. Infectious etiologies of rhabdomyolysis: three case reports and review. *Clin Infect Dis.* 1996;22:642–649.
4. Ebbeson RL, De Kock MJ, Penny N, et al. Rhabdomyolysis, acute renal failure, and compartment syndrome in a child with parainfluenza type 1 infection. *Pediatr Infect Dis J.* 2009;28:850–852.
5. Asano Y, Yoshikawa T, Suga S, et al. Clinical features of infants with primary human herpesvirus 6 infection (exanthem subitum, roseola infantum). *Pediatrics.* 1994;93:104–108.
6. Asano Y, Yoshikawa T, Kajita Y, et al. Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection. *Arch Dis Child.* 1992;67:1484–1485.
7. Huang LM, Lee CY, Lin KH, et al. Human herpesvirus-6 associated with fatal haemophagocytic syndrome. *Lancet.* 1990;336:60–61.
8. Yoshikawa T, Ihira M, Suzuki K, et al. Fatal acute myocarditis in an infant with human herpesvirus 6 infection. *J Clin Pathol.* 2001;54:792–795.
9. Qin H, Cha SC, Neelapu SS, et al. Generation of an immune microenvironment as a novel mechanism for myotoxins to potentiate genetic vaccines. *Vaccine.* 2010;28:7970–7978.
10. Ohashi M, Sugata K, Ihira M, et al. Human herpesvirus 6 infection in adult living related liver transplant recipients. *Liver Transpl.* 2008;14:100–109.
11. Flores EA, Bistrian BR, Pomposelli JJ, et al. Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. *J Clin Invest.* 1989;83:1614–1622.

ETIOLOGIES OF SEPTIC SHOCK IN A PEDIATRIC EMERGENCY DEPARTMENT POPULATION

Nakia N. Gaines, MD, Binita Patel, MD,* Eric A. Williams, MD, MS,† and Andrea T. Cruz, MD, MPH*‡*

Abstract: Knowledge of pediatric sepsis etiologies is needed to optimize empiric therapy. A retrospective cross-sectional review of 428 children with clinically diagnosed sepsis found that 13% had lobar pneumonia, 12% bacteremia and 10% viral infections. No etiologies were found in 76%. Empiric antibiotic coverage of vancomycin/piperacillin-tazobactam/gentamicin for immunocompromised children and vancomycin/nafcillin/cefotaxime for previously healthy children would have covered all bacteremic children.

Key Words: septic shock, etiologies, emergency department, pediatric

Accepted for publication June 30, 2012.

From the *Sections of Emergency Medicine, †Critical Care Medicine and ‡Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, TX.

This study was supported by internal funding. The authors have no other funding or conflicts of interest to disclose.

Address for correspondence: Andrea T. Cruz, MD, MPH, 6621 Fannin Street, Suite A2210, MC 1-1481 Houston, TX 77030. E-mail: acruz@bcm.edu.

DOI: 10.1097/INF.0b013e3182678ca9

Septic shock occurs in more than 40,000 children annually in the United States.[1] Prompt administration of broad-spectrum antibiotics is incorporated into national guidelines.[2] Although empiric antibiotic therapy should be based on treatment of prevalent bacterial pathogens, few studies have analyzed bacteremia etiologies in the pediatric emergency department (ED) population, the first venue of care for most of these children. Instead, much of the existing literature addresses specific populations.[3] The goal of this cross-sectional study was to describe the etiology of bacteremia in children presenting to the ED in shock to optimize antibiotic selection.

MATERIALS AND METHODS

This was a retrospective, single-center review of data obtained as part of a quality improvement (QI) project (the "shock protocol") to increase recognition and augment management of children with suspected septic shock in the ED.[4] This QI project used a combination of tachycardia out of proportion to fever and presence of medical conditions predisposing to sepsis to enable rapid identification of children with compensated shock. High-risk medical conditions identified a priori included asplenia, bone marrow transplantation (BMT) or solid organ transplantation, presence of central venous catheter, immunodeficiency and malignancy. The shock protocol did not dictate microbiologic, laboratory or radiographic evaluation, but recommended standardized antibiotic use in children for whom prior blood cultures were unavailable. For children with prior blood cultures, these were reviewed to see whether modifications were required based on past bacteremic episodes. For children with high-risk medical conditions, vancomycin, piperacillin/tazobactam and gentamicin were recommended. For otherwise healthy children, vancomycin, cefotaxime and nafcillin were recommended. Antifungal drugs were not empirically used.

The study was conducted in the Texas Children's Hospital ED in Houston, TX, where the annual ED volume is more than 85,000. All patients ≥2 months of age clinically diagnosed with sepsis from February 1, 2010 to January 31, 2011, were included; case definitions[5] were not used as inclusion criteria. Medical record abstraction was performed. Microbiologic data included cultures, rapid viral assays and polymerase chain reaction. Urine cultures were considered positive if >50,000 cfu/mL of a single urinary pathogen was isolated from a catheterized urine specimen or >100,000 cfu/mL in a clean-catch specimen.[6] Any growth from a blood culture obtained from a central venous catheter was considered positive. For peripheral cultures, a positive culture was defined as at least 1 positive blood culture for a nonskin flora pathogen in a child with clinical manifestations of infection.[7] Quantitative blood cultures were unavailable. The microbiology laboratory followed Clinical and Laboratory Standards Institute guidelines.

Frequencies and percentages were calculated for demographic variables, microbiology results and radiographic findings. Continuous and categoric variables were analyzed using t tests and χ^2, respectively. Significance was defined as $P < 0.05$. Data were analyzed using Stata 10 (Stata, Inc., College Station, TX). Before initiation, institutional review board approval was obtained.

RESULTS

Clinical sepsis was diagnosed in 428 patients; the demographic characteristics and laboratory/radiographic findings of the study population are presented in the Table. Ninety-nine percent of children received blood cultures, 48% viral respiratory cultures, 42% urine cultures, 7% tracheal aspirate cultures and 2% cerebrospinal fluid cultures. Neutropenia was seen in 19% of children; 180

TABLE. Demographic, Laboratory and Radiographic Characteristics of the Study Population

Variable		Complete Study Population (n = 428) n (%)	Population With Bacterial Etiology[a] (n = 68)
Gender	Male	221 (48%)	32
Age	Median (years)	6.1	6.4
	<7 days	0	0
	7–30 days	3 (1%)	1 (33%)
	31–364 days	24 (6%)	7 (29%)
	1–4 years	152 (36%)	22 (14%)
	5–12 years	145 (34%)	17 (12%)
	>12 years	104 (24%)	21 (20%)
Medical comorbidity	None	38 (9%)	7 (18%)
	Malignancy	206 (48%)	22 (11%)
	SOT recipient	38 (9%)	5 (13%)
	Other immunodeficiency	34 (8%)	7 (21%)
	BMT recipient	30 (7%)	10 (33%)
	Asplenia	11 (3%)	1 (9%)
	Short-gut syndrome	10 (2%)	6 (60%)
	Chronic, nonimmunocompromising condition	61 (14%)	10 (16%)

Variable, medians	Percentage of Population in Which Laboratory Obtained	Complete Study Population (n = 428)	Population With Bacterial Etiology (n = 68)	Statistical Test
CVC	Present	258 (60%)	50 (19%)	
WBC (cells/μL)	99%	n = 424 6.3 (5.5–7.2)	n = 68 4.8 (3.4–6.3)	$P = 0.03$
ANC (cells/μL)	99%	n = 424 4.7 (4–5.5)	n = 68 3.4 (1.8–5)	$P = 0.03$
Hemoglobin (g/dL)	99%	n = 424 10.6 (10.3–10.8)	n = 68 9.8 (8.8–10.5)	$P = 0.08$
Platelets (cells/μL)	99%	n = 424 192 (280–309)	n = 68 134 (109–169)	$P < 0.001$
BUN/Cr	86%	n = 368 27 (25–28)	n = 63 28 (24–31)	$P = 0.35$
pH	81%	n = 347 7.41 (7.4–7.41)	n = 62 7.41 (7.39–7.43)	$P = 0.79$
AST (IU/L)	63%	n = 269 42 (40–47)	n = 54 49 (33–67)	$P = 0.47$
ALT (IU/L)	63%	n = 269 38 (33–41)	n = 54 44 (34–59)	$P = 0.69$
Lactate (mg/dL)	62%	n=176 1.6 (1.4–1.7)	n = 35 1.7 (1.5–2)	$P = 0.2$
D-dimer (μg/L)	61%	n = 2590. 7 (0.6–0.8)	n = 44 1.1 (0.7–1.9)	$P = 0.02$
CRP (mg/L)	27%	n = 116 2.3 (1.7–3.2)	n = 17 4.3 (0.6–11.2)	$P = 0.79$

	Finding	Complete Study Population (n = 428)	Population With Bacterial Etiology (n = 68)	Statistical Test
CXR (n = 293)	Normal	183	32	$P = 0.77$
	Lobar infiltrate	55	10	
	Atelectasis	27	4	
	Effusion	3	0	
	Other findings[c]	25	0	
	Not Done	135	22	

Numbers may not sum to 100% due to rounding; percentages for first data column express within-column percentages; percentages in latter 2 columns express within-row percentages.

[a]Bacterial culture from a normally sterile site.

[c]Other radiographic findings included pulmonary edema, peribronchial thickening and cardiomegaly.

ALT indicates alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BMT, bone marrow transplant; BUN, blood urea nitrogen; CRP, C-reactive protein; CVC, central venous catheter; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; SOT, solid organ transplant; WBC, white blood cell count.

(42%) had a white blood cell count under 5000 cells/mm^3, and 53% of children with a confirmed bacterial infection had a white blood cell count under 5000 cells/mm^3. Although pancytopenia and elevated D-dimer were associated with documented bacterial infection in univariate analysis, none were significant in regression analyses.

Bacteremia was found in 13% of patients, of whom 82% had CVCs and 91% had comorbidities. The most common isolates were coagulase-negative staphylococci (CONS; 17), *Staphylococcus aureus* (9), *Pseudomonas* (7), *Enterococcus* (4), *Klebsiella* (3) and 2 isolates each of *Streptococcus pneumoniae*, *Bacillus*, *Enterobacter* and *Serratia*; 2 children had candidemia. Five children had polymicrobial bacteremia. The most common pathogens identified in previously healthy children were *Staphylococcus aureus* (2; 5%), pneumococcus (1; 2.6%) and group B streptococcus (1; 2.6%). The highest rates of bacteremia were seen in short-gut (6/10) and BMT (11/30) patients. For these patients,

the most common pathogens were CONS (5; 12.5%), *Staphylococcus aureus* (3; 7.5%), *Pseudomonas* (2; 5%) and *Enterobacter* (2; 5%). In non-BMT oncology patients, the most common pathogens causing bacteremia were CONS (5; 2.4%), *Bacillus* (2; 1%) and *Pseudomonas* (2; 1%).

Urinary tract infections were present in 9 (2%) children (4 *Escherichia coli*, 3 *Klebsiella pneumoniae*, 1 *Enterococcus faecalis*, 1 *Proteus mirabilis*). Urinary tract infections were associated with central venous catheter–associated bacteremia in 4 instances, including 1 piperacillin/tazobactam-resistant *Klebsiella* isolate. Chest radiographs were obtained in 68% of cases. Lobar pneumonia was present in 13%. In 10 instances, pneumonia was associated with bacteremia and in 4 cases with a documented respiratory virus. Viral pathogens were identified in 44 (10%) children. The viruses isolated included influenza A (11) and B (4), parainfluenza virus (9), human metapneumovirus (6), picornaviruses (5), adenovirus (3), herpes simplex virus type 1 (3), respiratory syncytial virus (2) and cytomegalovirus (1). No pathogen was isolated in 76% of cases.

The empiric antibiotic regimen would have covered all bacteremic children. For our a priori definition of high-risk patients, the addition of gentamicin provided the only effective coverage in 3 cases where piperacillin-tazobactam resistance was documented. All 3 children had medical comorbidities and had received recent courses of piperacillin-tazobactam for empiric therapy during prior admissions; in each case, this was the first time they had grown a pathogen resistant to this antibiotic.

DISCUSSION

Prompt antibiotic administration is essential to early treatment of suspected sepsis and shock. Our QI project aimed to help minimize provider variation in antibiotic selection while providing broad-spectrum antibiotic coverage for potential pathogens. Consistent with prior studies of bacteremia, CONS and Gram-negative enterics were the most common organisms isolated from children with CVCs, whereas *Staphylococcus aureus* was the most common isolate from previously healthy children. Our protocol targeted children with medical comorbidities predisposing to sepsis. The populations with highest risk for bacterial etiologies for shock were children with short-gut syndrome and BMT recipients, with bacteremia rates of 60% and 33%, respectively. Of note, the majority of children presenting to the ED with compensated or decompensated shock had no etiologies identified; in part, this may have been due to variations in diagnostic approaches (eg, decision to initiate viral diagnostics).

The pretest probability of bacteremia should drive institutional decisions about empiric antibiotic regimens rather than diagnostic testing. Laboratory findings would not have enabled children to be risk stratified for bacteremia. For example, C-reactive protein and lactate were not significantly different in bacteremic and nonbacteremic children. The inconsistencies in association between lactate and shock have been demonstrated in adults, with some studies showing that almost half of adults with vasopressor-dependent septic shock did not have elevated lactate levels.[8]

Vancomycin was added to a third generation cephalosporin for previously healthy children, recognizing that *Staphylococcus aureus* and *Streptococcus. pneumoniae* would be the most common pathogens in these children. Therapy was broadened for immunocompromised children to augment Gram-negative (including antipseudomonal) coverage for children with substantial preceding antibiotic exposure that may have been selected out for resistant pathogens. Although our empiric antibiotic regimens covered all pathogens identified in both populations during the study period, this will require monitoring as resistance patterns may change.

One additional concern may be the empiric addition of an aminoglycoside to children at risk for acute kidney injury. Limited data exist on this topic for children with differing medical comorbidities. One meta-analysis of children with febrile neutropenia (without shock) demonstrated that combination therapy with an aminoglycoside combined with either antipseudomonal penicillin or antipseudomonal cephalosporin was safe and efficacious.[9] Risk-benefit analysis may be necessary for children with preexisting renal insufficiency. However, the risk of short-term (48–72 hours) use pending cultures needs to be balanced against the risk of inadequately treating a resistant Gram-negative enteric pathogen in an immunocompromised child with shock. For 3 children enrolled in our study with recent prior antibiotic exposure (but no history of drug-resistant pathogens), the only effective antimicrobial coverage was offered by an aminoglycoside.

Our study has limitations. Children did not receive uniform microbiologic or radiographic evaluation, particularly for viral studies. However, as there was not 100% sampling of blood, urine and respiratory secretions as well, we cannot be completely confident of the "population without bacteremia." The incomplete collection of urine cultures might have been in part due to the policy of not catheterizing neutropenic children and that many children did not void while in the ED. Some children had prior blood cultures available to ED clinicians, which may have (appropriately) altered clinical decisions. Finally, the QI project tried to facilitate recognition of compensated shock; these children may have had lower rates of bacteremia than children in decompensated shock.

Although many children presenting to the ED with shock did not have identifiable bacterial etiologies, certain subpopulations had high rates of bacteremia. These populations included children with short-gut syndrome and BMT recipients. Knowledge of the most common bacterial etiologies in these high-risk populations can inform empiric antibiotic selection. Multicenter evaluation of our single-center findings is warranted.

REFERENCES

1. Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med.* 2003;167:695–701.
2. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med.* 2009;37:666–688.
3. Fiser RT, West NK, Bush AJ, et al. Outcome of severe sepsis in pediatric oncology patients. *Pediatr Crit Care Med.* 2005;6:531–536.
4. Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics.* 2011;127:e758–e766.
5. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6:2–8.
6. American Academy of Pediatrics, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of initial UTI in febrile infants and children 2 to 24 months. *Pediatrics.* 2011;128:595–610.
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1–45.
8. Dugas AF, Mackenhauer J, Salciccioli JD, et al. Prevalence and characteristics of nonlactate and lactate expressors in septic shock. *J Crit Care.* 2012;27:344–350.
9. Manji A, Lehrnbecher T, Dupuis LL, et al. A meta-analysis of antipseudomonal penicillins and cephalosporins in pediatric patients with fever and neutropenia. *Pediatr Infect Dis J.* 2012;31:353–358.