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Article *in* American Journal of Respiratory and Critical Care Medicine · March 2003
DOI: 10.1164/rccm.200207-682OC · Source: PubMed

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The Epidemiology of Severe Sepsis in Children in the United States

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Despite extensive research into the etiology and treatment of severe sepsis, little is known about its epidemiology in children. We sought to determine the age- and sex-adjusted incidence, outcome, and associated hospital costs of severe sepsis in United States children using 1995 hospital discharge and population data from seven states (24% of the United States population). Of 1,586,253 hospitalizations in children who were 19 years old or less, 9,675 met International Classification of Diseases, 9th revision, clinical modification–based severe sepsis criteria or 42,364 cases of pediatric severe sepsis per year nationally (0.56 cases per 1,000 population per year). The incidence was the highest in infants (5.16 per 1,000), fell dramatically in older children (0.20 per 1,000 in 10 to 14 year olds), and was 15% higher in boys than in girls (0.60 versus 0.52 per 1,000, $p < 0.001$). Hospital mortality was 10.3%, or 4,383 deaths nationally (6.2 per 100,000 population). Half of the cases had underlying disease (49.0%), and over one-fifth (22.9%) were low-birth-weight newborns. Respiratory infections (37%) and primary bacteremia (25%) were the most common infections. The mean length of stay and cost were 31 days and $40,600, respectively. Estimated annual total costs were $1.97 billion nationally. Severe sepsis is a significant health problem in children and is associated with the use of extensive healthcare resources. Infants are at highest risk, especially those with a low birth weight.

Keywords: outcome; mortality; pediatrics; intensive care

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference arrived at the current definition of severe sepsis as a systemic inflammatory syndrome in response to infection that is associated with acute organ dysfunction (1). These criteria have been widely adopted in clinical practice and research (2–4). However, most research has focused on adults, and information about the epidemiology of sepsis in children is limited. In 1990, the Centers for Disease Control released an epidemiologic study of United States septicemia ("a systemic disease associated with organisms or their toxins in the blood") that included children (5). However, that study did not examine severe sepsis. Infants were excluded, and pediatric-specific results were not presented. Other studies in neonates and older children were limited to only a few hospitals or to the epidemiology of specific infections (6–11).

In a recent US epidemiologic study, we found evidence of differences in incidence and mortality between children and adults with severe sepsis (12). This is not surprising given age-dependent differences between adults and children in physiology, predisposing diseases, and management strategies. For example, premature birth is an obvious risk factor for pediatric sepsis that is not relevant in adults. Similarly, national vaccination programs may have larger effects on sepsis in pediatric versus adult patients. However, there is no detailed analysis of the epidemiology of pediatric sepsis in the United States. We therefore sought to explore the pediatric subset of our national sample of severe sepsis in more depth. Specifically, we analyzed the impact of age, gender, birth weight, underlying pediatric disease, and microbiologic etiology on the incidence, mortality, and hospital costs of children who develop severe sepsis. Some of the results of this study have been previously reported in the form of abstracts (13, 14).

METHODS

Data Sources

We constructed a patient database for the calendar year 1995 (the most recent year from which complete data were available) from seven state hospital discharge databases (Florida [15], Maryland [16], Massachusetts [17], New Jersey [18], New York [19], Virginia [20], and Washington [21]). These databases include all discharge abstracts from the 942 nonfederal hospitals in those states (6.62 million discharges, of which 1.59 million [26%] were in patients who were 19 years old or less). We selected states by data quality, availability, and inclusion of centers in which we could assess the validity of our selection criteria for severe sepsis. We extracted demographic characteristics; principal discharge diagnosis, up to 14 secondary discharge diagnoses, and 15 procedures classified by the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) (22) codes; hospital discharge status; and charge items. We obtained population data from the United States Census (23) and the National Center for Health Statistics natality report (24).

Case Selection and Definitions

As previously described (12), we identified cases with severe sepsis by selecting all acute care hospitalizations with ICD-9-CM codes for a bacterial or fungal infectious process and a diagnosis of acute organ dysfunction (25). We validated our procedure by comparing results from a subset of the Sands and colleagues (26) cohort with our results from the same hospitals in 1995. Both techniques identified cohorts with a similar incidence, ages, sex, and sites of infection. Specific ICD-9-CM codes and validation results can be found in our previous study (12).

We defined children as patients who are 19 years old or less to take advantage of 5-year age groupings by the United States Census (23), the oldest of which in the pediatric age range is 15 to 19 years old. Some of the seven states provided data allowing identification of important subgroups of infants. Definitions of these subgroups and the states in which they could be identified are provided in Table 1. To identify the presence of underlying diseases, we used the Pediatric Complex Chronic Conditions score (27). The Pediatric Complex Chronic Conditions score uses administrative data to classify underlying disease into nine categories: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic and immunologic, metabolic, neoplastic, and other congenital or genetic defects.

(*Received in original form July 10 2002; accepted in final form November 8 2002*)

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Am J Respir Crit Care Med Vol 167. pp 695–701, 2003
Originally Published in Press as DOI: 10.1164/rccm.200207-682OC on November 14, 2002
Internet address: www.atsjournals.org

TABLE 1. DEFINITIONS AND SOURCES OF DATA FOR BABIES WHO ARE LESS THAN 1 YEAR OLD

	Description	Age at Hospital Admission (*Days*)	States with Sufficient Data to Allow Identification	US Population Represented by States (23) (*%*)
Infants	All children admitted in the first year of life	0–364	FL, MD, MA, NJ, NY, VA, WA	24
Neonates	Infants admitted in the first 28 days of life	0–28	MD, MA, NJ, NY, VA	17
LBW neonates	Neonates less than 2,500 g birth weight	0–28	MA, NJ, NY	12
VLBW neonates	Neonates less than 1,500 g birth weight	0–28	MA, NJ, NY	12
Newborns	Neonates admitted on the first day of life	0	MD, NJ, NY, VA	14
LBW newborns	Newborns less than 2,500 g birth weight	0	NJ, NY	10
VLBW newborns	Newborns less than 1,500 g birth weight	0	NJ, NY	10

Definition of abbreviations: FL = Florida; g = grams; LBW = low birth weight; MA = Massachusetts; MD = Maryland; NJ= New Jersey; NY = New York; VA = Virginia; VLBW = very low birth weight; WA = Washington.

We defined cases as surgical if they had a major surgical procedure other than tracheostomy. We estimated costs by multiplying charges by hospital-specific cost-to-charge ratios derived from the Centers for Medicare and Medicaid Services Provider Specific File. Costs were adjusted to 2001 dollars using the consumer price index. We explored subgroups of patients whose severe sepsis was due to the following etiologies and for which ICD-9 codes were available: *Streptococcus*, *Staphylococcus*, *Haemophilus influenza*, *Neisseria meningitidis*, *Pseudomonas*, and fungus (all types).

Statistical Analyses

We compared categorical data by chi-square or Fisher's exact test as appropriate and continuous data by the Wilcoxon rank sum test. We generated national estimates using cohort age- and sex-specific rates. We constructed the databases in Foxpro (Microsoft Corp., Redmond, WA) and conducted analyses in STATA (Stata Corp., College Station, TX) and SPSS (SPSS, Inc., Chicago, IL).

RESULTS

Incidence and Case Mix

We identified 9,675 cases of severe sepsis in the seven states (0.6 cases per 100 hospital discharges). Of these 9,675 cases, 66% (n = 6,349) occurred in the five states in which we could identify neonates, 57% (n = 5,497) in the four in which we could identify newborns, 50% (n = 4,844) in the three in which we could classify neonates by birth weight, and 41% (n = 3,992) in the two in which we could classify newborns by birth weight.

There were 17,136,365 children in the seven states (22.7% of the United States population who were 19 years old or less) and 899,000 live births. Nationally, the age- and sex-adjusted annual incidence was 0.56 cases per 1,000 children or 42,364 cases per year (Table 2). The incidence was highest in infants (5.16 per 1,000) and fell dramatically in older children (0.20 per 1,000 in 10–14 year olds). The mean age was 4.7 years (median, 1.0 year); 48.0% were less than 1 year of age, and 55.1% of cases were male. Half of all children (49.0%) had underlying comorbidity, ranging from 36.1% in 15–19 year olds to 59.1% in 5–9 year olds. Neuromuscular (12.4%), cardiovascular (11.1%), and respiratory (10.5%) disorders were the most common categories of comorbidity overall, and their distribution varied by age. Descriptive characteristics of the children with severe sepsis are provided in Table 3.

The high rate of severe sepsis in infants was largely due to neonatal severe sepsis (69.7% of infants). Two-thirds (69.3%) of neonates were low birth weight (LBW) and half (52.7%) were very LBW (VLBW). The annual incidence of severe sepsis in newborns was 0.3 of 100 live births. Four-fifths (81.1%) of newborns were LBW, and nearly two-thirds (63.6%) were VLBW. The most common underlying conditions in infants were respira-

TABLE 2. ANNUAL INCIDENCE, CASE FATALITY, AND NATIONAL ESTIMATES OF SEVERE SEPSIS BY AGE

Age	Incidence (*Per 1,000 Population*)	National Estimate of Cases	Case Fatality (*%*)	National Estimate of Deaths
Less than 1 Year*	5.16	20,145	10.6	2,135
0–28 Days†	3.60	14,049	10.3	1,361
29–364 Days†	1.56	6,096	13.5	774
1–4 Years*	0.49	7,583	10.4	786
5–9 Years*	0.22	4,168	9.9	413
10–14 Years*	0.20	3,836	9.6	368
15–19 Years*	0.37	6,633	9.7	644
All children	0.56	42,364	10.3	4,383

* National estimates are generated from the seven-state cohort using state and national age- and sex-specific population estimates from the National Center for Health Statistics and the United States Census.

† Results for these ages are based on data from the five states (MA, MD, NJ, NY, and VA) in which neonates could be identified (n = 6,349 or 66% of the entire seven-state cohort).

TABLE 3. CHARACTERISTICS OF THE STUDY COHORT (n = 9,675)

	Age Group					
	Less than 1 Year (n = 4,643)		1–9 Years (n = 2,724)		10–19 Years (n = 2,308)	
Characteristic	Cases (%)	Case Fatality (%)	Cases (%)	Case Fatality (%)	Cases (%)	Case Fatality (%)
Entire severe sepsis cohort	48.0	10.6	28.2	10.2	23.9	9.7
Gender						
Male	56.8	11.2	54.8	9.7	52.0	9.6
Female	43.2	9.9	45.2	10.9	48.0	9.7
Medical condition	68.5	11.8	79.5	9.6	67.4	8.4
Surgical condition	31.5	13.3	20.5	11.9	32.6	11.1
Underlying comorbidity						
Neuromuscular	6.6	13.7	21.2	8.5	13.8	9.4
Cardiovascular	17.1	14.5	7.3	22.2	3.3	31.2
Respiratory	19.0	9.2	3.9	5.7	1.1	23.1
Renal	1.6	24.7	1.3	5.6	1.9	18.2
Gastrointestinal	3.1	14.6	2.1	8.9	1.8	7.3
Hematologic/immunologic	2.5	21.9	15.7	18.5	6.2	20.3
Metabolic	1.1	15.1	1.6	11.6	2.3	11.1
Genetic	4.6	16.3	5.2	9.2	1.9	11.4
Neoplastic	0.9	26.2	12.8	15.8	17.4	16.0
Any underlying comorbidity	46.0	12.4	58.7	12.5	49.0	14.2
Site of infection						
Respiratory	26.9	9.7	51.1	8.6	41.3	9.8
Bacteremia	33.6	13.1	17.6	17.1	16.4	16.7
Genitourinary	4.1	3.7	2.4	4.7	5.8	3.0
Abdominal	2.8	9.9	5.8	4.4	8.6	7.5
Wound/soft tissue	5.9	7.7	4.2	9.6	6.3	6.2
Device related	3.6	8.5	4.7	11.0	3.9	13.2
Central nervous system	5.3	17.8	3.3	19.1	3.9	13.2
Endocarditis	0.6	19.2	0.2	25.0	0.4	25.0
Other/unspecified	17.3	7.7	10.8	7.8	13.4	4.2

tory (19.0%) and cardiovascular (17.1%). Chronic lung disease related to prematurity occurred in 16.5% of infants, and congenital heart malformations occurred in 15.0%.

In older children, neuromuscular disorders occurred most often in children aged 1–4 years (19.5%) and 5–9 years (24.3%). The most common neuromuscular conditions were seizure disorders (27.1% of children aged 1–9 years), cerebral palsy (9.4%), and developmental abnormalities (7.9%). Neoplastic disorders occurred most often in children aged 10–14 years (23.4%) and 15–19 years (13.8%). In these ages, the most common cancers were acute lymphoid leukemia (25.4% of those with neoplasm, 4.4% of all 10–19 year olds) and acute myeloid leukemia (19.2% of those with neoplasm, 3.3% of all 10–19 year olds).

Boys had a significantly higher incidence of severe sepsis than girls (0.60 versus 0.52 of 1,000, or an additional 3,300 boys per year nationally, $p < 0.0001$). The incidence difference was largest among infants (5.73 versus 4.57 of 1,000, or an additional 2,300 infant boys nationally, $p < 0.001$) but was also present among 1–4 year olds (0.51 versus 0.45 of 1,000, $p < 0.01$) and 5–9 year olds (0.24 versus 0.20 of 1,000, $p < 0.01$) (Figure 1). The incidence in children who were more than 9 years old did not vary significantly by sex. The rate of underlying disease was significantly, but not substantially, higher in girls than in boys (50.4% versus 48.1%, $p = 0.02$).

Mortality

Of the 9,675 children with severe sepsis, 993 (10.3%) died before discharge. Nationally, the annual age- and sex-adjusted mortality

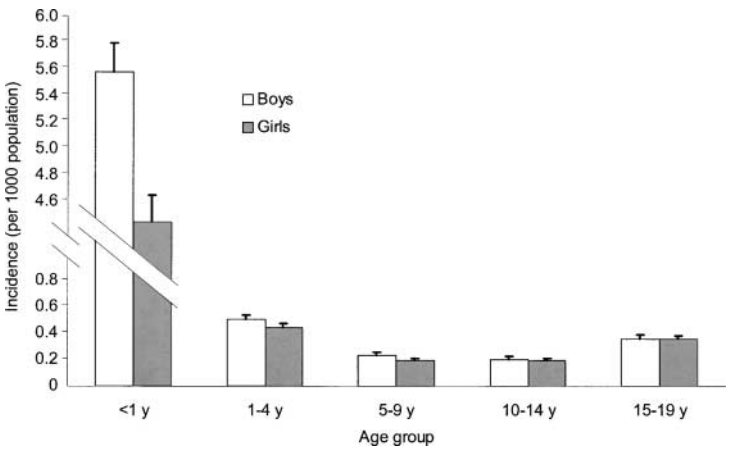

Figure 1. Incidence of severe sepsis by age and sex. The incidence was highest in the youngest patients and decreased until late adolescence (15–19 years old). A total of 48% of all patients were less than 1 year old, and 27% were admitted at birth. The incidence was significantly higher in boys than girls among infants and children aged 1–4 and 5–9 years; 95% confidence intervals are shown by *error bars*.

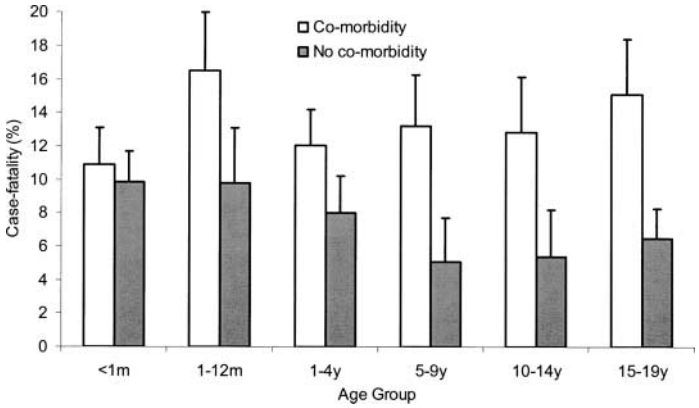

Figure 2. Case fatality of children with severe sepsis by age and comorbidity. Case fatality was highest in children 1–12 months old and was significantly higher among children with any underlying disease. Results for children who were less than 1 month old and 1–12 months old are from the five states (MA, MD, NJ, NY, and VA) in which neonates could be identified (n = 6,349 or 66% of the entire seven-state cohort). Results for children older than 1 year are from the entire seven-state cohort (n = 9,675); 95% confidence intervals are shown by *error bars*.

rate was 5.8 per 100,000 children, or 4,383 deaths during a hospitalization in which severe sepsis occurred (Table 2). Hospital mortality generally varied little with age except for the significantly higher rate (13.5%) among non-neonatal infants (those 1–12 months old). Because hospital mortality varied little with age, the number of deaths per population paralleled the incidence rate, with a high rate in infants that fell dramatically in older children and increased slightly in older adolescents. The only gender-related differences in hospital mortality occurred among infants. Because of similar overall hospital mortality and a higher incidence, infant boys had a higher mortality rate than infant girls (63.9 versus 45.1 per 100,000, $p < 0.002$). Among newborns, LBW babies had a higher hospital mortality than babies of normal birth weight (11.0% versus 6.1%, $p = 0.04$), and LBW boys had a higher hospital mortality than LBW girls (13.5% versus 7.8%, $p < 0.01$).

Hospital mortality was higher in children with underlying disease (Figure 2), surgical procedures, or human immunodeficiency virus infection. The risk of death increased with increasing numbers of failing organs, from 7.0% for those with single-organ system failure to 53.1% for those with four organ systems or more failing. A fifth (19.7%) of deaths occurred within 2 days of admission. Children with neoplastic disorders accounted for 13.1% of the deaths (580 nationally), and those with human immunodeficiency virus accounted for 10.8% of deaths (470 nationally).

Site of Infection and Microbiologic Etiology

The majority of infections causing severe sepsis were either respiratory (37.2%) or primary bacteremia (25.0%). Primary bacteremia was particularly common in neonates (41.8%) and less common in older children (18.9%), whereas respiratory infections predominated in older children (45.9%) and were less common in neonates (16.9%). Bacteremia was also more common in children with neoplastic disorders (41.5% versus 23.5%, $p < 0.001$). The frequency of respiratory infection was higher in children with human immunodeficiency virus than in children without human immunodeficiency virus (46.6% versus 36.6%, $p < 0.001$). The most deadly infections were endocarditis (case fatality 21.1%) and infections of the central nervous system (case fatality 17.1%).

The most common infecting organism was *Staphylococcus* (17.5% overall), especially among neonates (25.7% of all neonatal infections) (Table 4). Meningococcal infections were uncommon (1.2% of all infections) and much less common in patients with comorbidity than without comorbidity (0.2% versus 2.2%, $p < 0.001$). On the other hand, fungal infections were more common in children with comorbidity (14.9% versus 7.4%, $p < 0.001$), particularly in those with human immunodeficiency virus (47.4%). Case fatality was highest in children with pneumococcal (14.5%) or fungal (13.0%) infections.

Hospital Resource Use and Costs

The mean length of stay (LOS) and cost were 31 days and $47,050, yielding national estimates of 1.3-million hospital days and $1.97 billion. Forty percent of the total hospital days and 31% of the costs were incurred by VLBW newborns, who had a much higher mean LOS and mean cost than other children (74 versus 24 days, $p < 0.0001$; $86,910 versus $35,340, $p < 0.0001$). The mean LOS

TABLE 4. OCCURRENCE AND CASE FATALITY OF SELECT PATHOGENS AMONG CHILDREN WITH SEVERE SEPSIS BY AGE

	Age Group					
	Less than 1 Year (n = 4,643)		1–10 Years (n = 2,724)		11–19 Years (n = 2,308)	
Organism	Cases (%)	Case Fatality (%)	Cases (%)	Case Fatality (%)	Cases (%)	Case Fatality (%)
Meningococcus	0.3	20.0	8	10.4	2.3	15.1
H. influenza	1.6	4.2	2.4	1.6	1.9	6.8
Pseudomonas	3.6	14.6	7.7	12.4	6.9	9.4
Staphylococcus (all types)	22.7	8.6	11.2	7.9	14.4	7.8
Staphylococcus aureus	2.3	5.7	2.9	0	3.5	3.8
Streptococcus (all types)	12.1	10.2	9.8	13.9	6.9	8.8
Pneumococcus	1.7	12.8	4.0	19.1	2.0	6.4
Group A *streptococcus*	0.3	0	0.7	5.0	0.2	0
Group B *streptococcus*	3.1	7.6	0.1	50.0	0.8	5.6
Fungus	10.0	10.8	13.3	16.8	10.4	11.6

and cost were also high in surgical patients (46 days, $80,070) and in patients with comorbidity (37 days, $56,550). Mean LOS and cost were similar between boys and girls. Nonsurvivors had similar LOS, but higher costs, than survivors (30 versus 31 days; $63,730 vs. $45,190, $p < 0.0001$).

DISCUSSION

We found that severe sepsis is a major health problem in children, with more than 42,000 cases and 4,400 associated deaths per year in the United States. Infants were at highest risk, especially those of LBW. As with adults, underlying illness was very common in children who develop severe sepsis. Boys were much more likely to develop sepsis, and infant males of LBW were also much more likely to die. Children who developed severe sepsis consumed substantial healthcare resources, with average cost and length of stay in excess of all conditions examined in a recent federal report (28). The microbiologic etiology was quite diverse, implying that any preventive strategies must be multifaceted.

The number of children hospitalized with severe sepsis is roughly half of the number hospitalized with appendicitis (29). Our estimate of severe sepsis-associated deaths represents 7% of all deaths in children in 1995 (30) and is greater than the 2,275 pediatric deaths associated with cancer that year (31). Resource use was high, even compared with other costly pediatric illnesses. VLBW and LBW infants with severe sepsis consumed over twice the average resources of those with infant respiratory distress syndrome, a common and expensive complication of prematurity (28). However, sepsis is undoubtedly a marker as well as a cause of severe illness, and neither this nor other sepsis studies have determined to what extent patients die (or consume healthcare resources) from sepsis itself (32). For example, VLBW and LBW babies with severe sepsis may have prematurity-associated complications in addition to infant respiratory distress syndrome (such as intraventricular hemorrhage or chronic lung disease), which may not be sepsis-related but may be the main factors leading to the extremely high resource use in this population.

These findings are consistent with those of other studies (33, 34). Because sepsis occurs more frequently among children with underlying or severe diseases that may be fatal and costly in themselves, no study has determined what proportion of sepsis-associated deaths and resource use is a direct result of sepsis. For example, if a vaccine preventing sepsis were given to patients with cancer, it might merely delay death that will ultimately occur due to the cancer. On the other hand, the prevention of sepsis might allow timely therapy to be administered that ultimately eradicates the cancer.

More than any other single factor, age influences the epidemiology of severe sepsis. Infants and older children are two epidemiologically distinct pediatric populations with different incidences, underlying diseases, sites of infection, organ dysfunction, and infecting organisms. Severe sepsis among infants is dominated by perinatal events. The majority of newborns were of VLBW and were undoubtedly premature (95% of all VLBW babies born in 1995 were premature [24]). After infancy, epidemiologic borders between populations are less distinct; however, age-related differences continue to occur, especially regarding underlying diseases. Children 1 to 4 years old are clearly different than adults in terms of underlying disease, mortality, and sites of infection. Healthy older children, particularly adolescents, share many epidemiologic characteristics with healthy young adults, particularly those younger than 35 years of age (12). In fact, these two groups are more similar to each other than they are to either infants or adults over the age of 60 years.

Our findings have implications both for studying sepsis therapy in children and for determining best practice in pediatric critical care medicine. Recent randomized trials of sepsis therapies have either been performed in specific diseases in children (e.g. meningococcemia [34]) or in only adults (e.g., recombinant activated protein C [3]). The generalizability of these studies is a legitimate concern. Meningococcal sepsis affects healthy children almost exclusively, and differences in severe sepsis between children and adults, particularly in those with underlying disease, are not trivial. However, the lower incidence and case fatality of pediatric severe sepsis would require the enrollment of a large proportion of United States cases to power adequately a randomized trial in all-cause severe sepsis using mortality as the primary endpoint. The use of other endpoints, the study of populations at higher risk of death, the formation of multicenter study networks that can capture a substantial proportion of all critically ill children in the United States, and the inclusion of children in adult trials are all potential solutions to this difficult problem.

We found an important difference in severe sepsis incidence and outcome between infant boys and girls, consistent with prior studies showing that male gender is a risk factor for poor outcome in prematurity (38–41) and in some neonatal infections (35–38, 39). Gender differences beyond infancy are less striking and more difficult to interpret. The incidence of severe sepsis in boys less than 10 years old was higher than that in girls, with no difference in mortality. In children aged 10 years and older, there were no sex differences. We previously found that males over 30 years of age have a higher incidence of severe sepsis than females (12). These findings suggest that the sex-related differences in immunity and infection-related outcome that have been found in animal and adult studies (40–47) may also be relevant in children. However, if sex-related differences are hormonal in origin, it is unclear why we did not see a difference among adolescents, when sex hormones are most highly expressed.

The major limitations of our study relate to the use of administrative data to define severe sepsis. By using ICD-9-CM codes to identify severe sepsis, the temporal overlap between infection and organ dysfunction was not as tightly coupled as in clinical trials. However, we validated our approach as previously described (12), and our results are consistent with numerous smaller pediatric studies (11, 32–34, 48–55). Our definition of severe sepsis could also be considered more inclusive than others (e.g., a premature neonate requiring mechanical ventilation for neonatal respiratory distress syndrome with an infected central line would be considered to have severe sepsis). Even at the bedside, it is frequently difficult to determine definitively whether certain microbiologic findings (e.g., organisms cultured from tracheal aspirates in the workup of ventilator-associated pneumonia, coagulase negative staphylococci cultured from a central line) represent true infection. These limitations likewise apply to our data. Because we have no information about how a diagnosis was made, only that it was made, if clinicians overdiagnose ventilator-associated pneumonia or coagulase negative staphylococcal sepsis, then our estimates will be equally too high. However, large studies of nosocomial infection in critically ill children have also shown high rates of pulmonary infections and infections due to coagulase negative staphylococci (7, 56), and our rate of neonatal sepsis is similar to rates reported in smaller studies using physiologic data (11, 51–53). The states that we selected represent the most heavily populated areas of the United States (West, Northeast, Midatlantic, and Southeast regions), but not the Midwest or Southwest. Unfortunately, there are no statewide hospital databases from these regions with the appropriate level of detail and quality for this study. When generating national estimates, we adjusted for differences in population distribution between the seven-state cohort and the entire country and believe it un-

likely that additional data from the Midwest or Southwest would have substantially altered any of our national estimates.

Administrative data are not a good source of comprehensive microbiologic information. Discharge diagnoses may not include all microbiologic results from a hospitalization, and specific ICD-9-CM codes for some organisms (e.g., *H. influenza*, type B) do not exist. Furthermore, we did not examine specific viral pathogens, and thus, we may have missed some cases of viral sepsis and therefore underestimated the total number of pediatric cases. However, certain organisms appear to be reliably coded. For example, our results related to meningococcal (34, 54) and pneumococcal (55) severe sepsis are consistent with results reported in other studies. We were surprised by the relatively high rate of fungal sepsis. This may be related to the severe nature of systemic fungal infection, the frequent use of broad-spectrum antibiotics, the high rate of underlying disease in children with severe sepsis (which doubled the risk of fungal infection), or a paucity of vaccine-preventable bacterial sepsis. Further clarification of this issue using longitudinal and detailed clinical data could influence the prevention and empiric treatment of pediatric sepsis.

Using discharge data and diagnoses for infection and organ dysfunction to delineate the epidemiology of severe sepsis offers several advantages over previous approaches. As opposed to using the nonspecific discharge diagnosis of septicemia, we were able to examine a cohort of patients with illness that more closely resembles that in patients studied in clinical trials of therapeutic agents for sepsis (3, 57, 58). This large data set also allows the generation of national estimates while permitting exploration of various factors related to incidence, outcome, and resource use.

Recent and impending developments in the healthcare of children may affect pediatric severe sepsis. New vaccines could decrease the rate of severe sepsis in previously healthy children. Educational and monitoring programs regarding Group B *Streptococcus* (59, 60), fungal and nosocomial infections (61), and resuscitation (62–64) may decrease the incidence, change the etiology, and improve the outcome of severe sepsis in children. The growth of populations of children known to be at high risk for severe sepsis (e.g., premature babies, unimmunized or immunosuppressed children) could increase its incidence. Genetic and immunologic analysis (65) may identify other children at high risk of sepsis and could change many epidemiologic aspects. Finally, sepsis therapy approved in adults (3) may be used in children, possibly changing their outcome as well. Large discharge databases can be used with other approaches to follow the epidemiology of this complex syndrome over time, providing a coordinated picture that is easily accessible and can be a valuable tool against this complex syndrome.

Acknowledgment: The authors are indebted to Timothy Rickert, B.S., of Health Process Management, LLC, for his assistance with data management; to Tony T. Dremsizov, M.B.A., for his assistance with manuscript preparation; and to Chris Feudtner, M.D., Ph.D., M.P.H., for his assistance with data analysis related to the identification of underlying disease in children.

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