Children with Chronic Disease Bear the Highest Burden of Pediatric Sepsis

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Objective To describe the contemporary epidemiology of pediatric sepsis in children with chronic disease, and the contribution of chronic diseases to mortality. We examined the incidence and hospital mortality of pediatric sepsis in a nationally representative sample and described the contribution of chronic diseases to hospital mortality.

Study design We analyzed the 2013 Nationwide Readmissions Database using a retrospective cohort design. We included non-neonatal patients <19 years of age hospitalized with sepsis. We examined patient characteristics, the distribution of chronic disease, and the estimated national incidence, and described hospital mortality. We used mixed effects logistic regression to explore the association between chronic diseases and hospital mortality.

Results A total of 16 387 admissions, representing 14 243 unique patients, were for sepsis. The national incidence was 0.72 cases per 1000 per year (54 060 cases annually). Most (68.6%) had a chronic disease. The in-hospital mortality was 3.7% overall—0.7% for previously healthy patients and 5.1% for patients with chronic disease. In multivariable analysis, oncologic, hematologic, metabolic, neurologic, cardiac and renal disease, and solid organ transplantation were associated with increased in-hospital mortality.

Conclusions More than 2 of 3 children admitted with sepsis have ≥1 chronic disease and these patients have a higher in-hospital mortality than previously healthy patients. The burden of sepsis in hospitalized children is greatest in pediatric patients with chronic disease. *(J Pediatr 2018;■■:■■-■■).*

Sepsis and septic shock remain significant causes of morbidity and mortality for children in the US and around the world. An analysis of a 7-state dataset of pediatric patients with sepsis in 1995 estimated that there were 75 000 cases in the US annually.[1] A subsequent update using data from 2000 and 2005 showed a 1.6-fold increase in incidence from 0.56 per 1000 children to 0.89 per 1000 children,[2] but more recent estimates are not available. Conversely, the hospital mortality has decreased in some analyses. For example, the hospital mortality decreased from 10.3% in 1995 to 8.9% in 2005,[1,2] and a longitudinal analysis of a cohort of patients admitted to a pediatric intensive care unit with sepsis from 2004 to 2012 also showed a decrease from 18.9% to 12.0%.[3]

Recent reports have found that the majority of children with sepsis have ≥1 chronic disease,[4,5] but contemporary national estimates of the prevalence of sepsis and risk of hospital mortality in children with different chronic diseases are not available. Although prior studies showed increased hospital mortality in pediatric patients with sepsis and a history of cancer or hematopoietic stem cell transplantation[6] and congenital heart disease,[7,8] the interaction of other chronic diseases with mortality risk in pediatric sepsis has not been previously described. The Improving Pediatric Sepsis Outcomes initiative, recently implemented by the Children's Hospital Association,[9] incorporates special considerations for children with cancer, but no guidance exists for children with other chronic diseases. We sought to describe the proportion of children hospitalized with sepsis who had a chronic disease, and the in-hospital mortality in children with different chronic diseases as well as previously healthy children. We hypothesized that children with chronic disease would have higher in-hospital mortality than previously healthy children.

Methods

We used a retrospective cohort design and the Nationwide Readmissions Database (NRD)[10] from 2013, which includes 49% of all hospital admissions in the

APRDRG	All-patient refined diagnosis-related group
ECMO	Extracorporeal membrane oxygenation
ICD-9 CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
NRD	Nationwide Readmissions Database

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US. The NRD includes hospitalizations for children who were between 1 and 18 years of age from 21 states and hospitalizations for children <1 year of age from 9 states. This study was deemed exempt by the University of Pittsburgh Institutional Review Board.

We estimated the national incidence of sepsis using the weights provided by the NRD and described the hospital mortality and 90-day readmission rates for all pediatric hospitalizations and across different subgroups. We examined the proportion of sepsis cases among children with different chronic diseases and the relationship between individual chronic diseases and hospital mortality after adjusting for potential confounders.

Identification of Sepsis

We limited our study to admissions of non-neonatal pediatric patients <19 years of age because neonatal patients have different risk factors for sepsis and outcomes than pediatric patients.[11] We identified neonatal admissions using neonatal-specific diagnosis codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9 CM] 760.xx-779.xx). We included all non-neonatal pediatric patients discharged between January 1, 2013, and December 31, 2013. We identified patients admitted with sepsis or septic shock using ICD-9 CM codes for infection and ≥1 organ dysfunction using codes in the first 15 diagnosis fields (combination codes, **Appendix**; available at www.jpeds.com) or those with codes for sepsis, severe sepsis, or septic shock (ICD-9 CM codes 995.91, 995.92, and 785.52) in 25 diagnosis fields. We used both approaches because prior evaluations have found poor correlation and differential outcomes between cases identified using either approach.[12] We performed limited descriptive analyses in patients identified using sepsis codes and stratifying by sepsis without organ failure compared with sepsis with identified organ failure, severe sepsis, or septic shock.

Clinical Characteristics

We examined the clinical characteristics for each patient admitted, including demographics, chronic diseases, severity of illness, use of extracorporeal membrane oxygenation (ECMO) during hospital stay, and hospital characteristics. We used the pediatric complex chronic conditions classification system, version 2, to identify chronic diseases.[13] Briefly, this system incorporates ICD-9 CM codes for chronic conditions in children that are expected to last ≥12 months and involve 1 or multiple organ systems severely enough to require specialty pediatric care, or include technology or medical device dependence. We assessed illness severity using the all-patient refined diagnosis-related group (APRDRG), a proprietary and validated tool used across all Health Care and Utilization Project datasets. We assessed organ failure using ICD-9 CM codes for mechanical ventilation (96.7), shock including septic shock (458.8, 458.9, 785.50, 785.52, 785.59), acute kidney injury (584.X, 788.5), and failure of the neurologic (293.0, 293.1, 293.9, 348.3X, 780.09), hepatic (570.X, 573.4), and hematologic (286.6, 286.7, 286.9, 287.49, 287.5) systems. We assessed admissions that involved ECMO using procedure code 39.65. We described hospitals where patients received care using the predefined categorical variable from the NRD for metropolitan teaching, metropolitan nonteaching, or nonmetropolitan hospitals.

Statistical Analyses

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and R 3.3.3 (R Project, Vienna, Austria). The clinical characteristics of the sample of pediatric patients admitted with sepsis were quantified using frequencies and percentage of the total number of admissions.

We calculated the incidence of sepsis for all pediatric cases and stratified by age and coding criteria (combination and sepsis codes). We estimated the national incidence of sepsis in non-neonatal children <19 years of age by applying the sampling weights and strata provided by the NRD.[14] No other analyses used the NRD sampling weights. We reported hospital mortality for all pediatric sepsis cases and stratified by age, chronic diseases, and coding criteria.

We examined the relationship between individual chronic diseases and hospital mortality among children hospitalized with sepsis by fitting a multivariable mixed effects logistic regression model and adjusting for demographic features (age and sex) and admitting hospital type. Random intercepts were included to account for the correlation of outcomes among patients who received care within similar types of hospital and within the same hospital. We limited the logistic regression analysis to 1 admission per patient with sepsis using the unique patient linking identification in the NRD; specifically, only the first chronological admission involving sepsis in 2013 was included in the analysis.

Results

Of the 14 325 172 admissions in the NRD, 1 227 931 admissions were in patients <19 years of age, of which 309 675 (25.2%) were neonatal patients admitted. Of the 918 256 non-neonatal pediatric admissions, 16 387 met the criteria for sepsis. The estimated national incidence in the pediatric population was 0.72 per 1000, with an estimated 54 060 cases per year (**Figure 1**).

Clinical Characteristics

The clinical characteristics of the 16 387 pediatric admissions are shown in **Table I**. Among these admissions, 11 247 (68.6%) involved patients with ≥1 chronic disease. Furthermore, 6576 (40.1%) had explicit codes for sepsis, and 12 762 (77.9%) were identified using combination coding. Within the group identified using explicit codes, 3364 had sepsis without organ dysfunction identified, 964 had a sepsis code and an organ dysfunction code, and 2278 had severe sepsis or septic shock. Among the group with sepsis without organ dysfunction, 43.6% of admissions (n = 1465) had a chronic disease. Among admissions with sepsis codes and organ dysfunction, 73.2% (n = 684) had a chronic disease, and among those with severe sepsis or septic shock, 74.9% (n = 1706) had a chronic disease. Fewer than one-half of admissions (34.9%; n = 5712) received invasive mechanical ventilation, and 19.0% of admis-

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