

Epidemiology of Readmissions After Sepsis Hospitalization in Children

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ABSTRACT

BACKGROUND AND OBJECTIVES: The decline in hospital mortality in children hospitalized with sepsis has increased the number of survivors. These survivors are at risk for adverse long-term outcomes, including readmission and recurrent or unresolved infections. We described the epidemiology of 90-day readmissions after sepsis hospitalization in children. We tested the hypothesis that a sepsis hospitalization increases odds of 90-day readmissions.

METHODS: Retrospective cohort analysis of the Nationwide Readmissions Database. We included index unplanned admissions of non-neonatal pediatric patients and described the proportion of readmissions, including those involving infection or sepsis. We performed multivariable analysis to determine the odds of readmission after a sepsis and nonsepsis admission and compared costs of readmission after sepsis and nonsepsis admissions.

RESULTS: Of 562 817 pediatric admissions, 7634 (1.4%) and 555 183 (98.6%) were discharged alive after admissions with and without sepsis. The rate of 90-day readmission after sepsis was 21.4%: 7.2% and 25.5% in previously healthy and chronically ill patients. The adjusted mean cost during readmission was \$7385. Half of readmissions (52.9%) involved recurrent infection or sepsis. Sepsis admissions were associated with higher odds of readmission at 90 days compared with nonsepsis admissions (adjusted odds ratio 1.15, 95% confidence interval 1.08–1.23). The results remained unchanged for 30-day and 6-month readmissions.

CONCLUSIONS: Readmissions occur after 1 in 5 pediatric sepsis hospitalizations and increase health care costs. Sepsis hospitalization increased odds of readmission and commonly involved recurrent infection or sepsis. Clinicians caring for these patients should consider surveillance for recurrent or unresolved infection, and researchers should explore underlying mechanisms and potential interventions to reduce readmissions.



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Drs Yende and Prout conceived the project, interpreted the data, and wrote and revised the manuscript; Drs Carcillo and Angus reviewed and revised the manuscript, provided expert guidance and consultation, and assisted with the design of the study and interpretation of the results; Mr Talisa and Dr Chang performed and contributed to statistical analyses; and all authors approved the final manuscript as submitted and agree to be responsible for all aspects of the work.

Sepsis is the leading cause of death among children worldwide.¹ Advances in early resuscitation and critical care have reduced hospital mortality and increased the number of survivors.^{2,3} Adults who survive a sepsis hospitalization often have adverse long-term outcomes, including frequent readmissions⁴ and reduced long-term survival,⁵ but little is known about long-term outcomes in children. Thirty-day readmissions are common after pediatric hospitalizations and occur after ~6% of admissions.⁶ Readmissions increase the risk of hospital-acquired infections,⁷ impair quality of life, and increase health care spending.⁸ They are also a key measure for the Centers for Medicare and Medicaid Services⁹ value-based program for adults and a core quality measure for children.¹⁰ Recent work has revealed that sepsis is the leading cause of readmissions in adults,⁴ but the epidemiology, causes, and health care spending for readmissions after pediatric sepsis remain poorly understood. In particular, the frequency of readmissions due to infections is of interest because previous studies indicated that immunosuppression,¹¹ alterations in the microbiome,¹² and partially treated infections¹³ may be common among patients with sepsis.

Several pediatric studies revealed that chronic diseases are associated with increased risk of readmissions,^{14–16} and these readmissions are often due to exacerbations of the underlying chronic disease.¹⁷ Most children hospitalized with sepsis have an underlying chronic disease.^{18–20} Whether the high readmission rates are a consequence of sepsis or sepsis is simply a marker for children with a high burden of chronic diseases is not known. Understanding this relationship is critical to design future studies to determine underlying mechanisms and develop interventions such as novel care transition models to improve surveillance during the postdischarge period. Therefore, we sought to describe the epidemiology of readmission in a large, nationally representative sample of pediatric admissions. We tested the hypothesis that sepsis admissions are associated with higher odds of readmission compared with nonsepsis admissions.

METHODS

Study Design

We conducted a retrospective analysis of admissions of non-neonatal pediatric patients in the 2014 Nationwide Readmissions Database (NRD), which includes 49% of all hospital discharges in the United States. We examined the epidemiology of readmissions within 90 days in patients hospitalized for sepsis, including their clinical characteristics, costs, and proportion with an infection. Although 30-day readmission is a common quality metric for hospitals, we chose to focus on 90-day readmissions because they may better reflect readmissions due to changes in the microbiome and persistent immune suppression or organ failure.^{12,20} To determine the association between sepsis and readmission, we conducted an unmatched multivariable analysis comparing the odds of readmission between sepsis and nonsepsis admissions. We also performed sensitivity analyses with multiple matching strategies to address potential covariate imbalances and used different time frames to identify index admissions that were not preceded by an admission in the previous quarter and to allow for longer follow-up. This study was deemed exempt by our institutional review board.

Patients

Our analyses were conducted among non-neonatal pediatric patients (≤ 18 years) who were discharged alive. To classify patients as either readmitted or not readmitted within a given time frame, we identified a unique index admission for each patient. We defined index admissions as the first chronological admission in the calendar year that did not meet the following exclusion criteria: neonates identified by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 760 to 779, planned and surgical admissions using previously described approaches,¹⁶ those discharged against medical advice, and those discharged on or after October first.

After identifying index admissions, we stratified admissions by presence or absence of sepsis using ICD-9-CM codes for sepsis, severe sepsis or septic shock, or with diagnoses of infection and organ

failure as previously described.^{21–23} We then determined if they were readmitted to any hospital in the NRD for an unplanned reason within 90 days of the discharge day of the index admission.

Covariates

We stratified index admissions by age as <1, 1 to 4, 5 to 12, and 13 to 18 years. We also described demographic data and illness severity (Supplemental Information). We defined readmission with infection as readmission of patients after sepsis with any infection code in any discharge diagnosis field (Supplemental Information). We conducted multiple sensitivity analyses. First, we conducted matched analyses to estimate excess odds of readmission while accounting for potential confounders between the sepsis and nonsepsis groups. We performed matched analyses because unmatched analyses may not adequately control for confounders if there are large differences between the 2 groups. We matched admissions on demographics alone as well as demographics and chronic disease profile using 2 strategies: a more and less exact chronic disease matching strategy. We defined chronic diseases using the pediatric complex chronic conditions and Harlelid classification systems (Supplemental Information).^{24,25} Second, we determined the excess odds of readmission within 30 days and 6 months of discharge; the latter analysis was restricted to patients discharged by June first. Finally, because we were unsure if patients admitted in the first quarter of the year had been admitted in the last 3 months of the preceding year, we performed an analysis of only those patients discharged between April 1 and October 1 (Supplemental Information).

Statistical Analyses

We examined the epidemiology of readmissions after sepsis by describing 90-day readmissions overall and stratified by age and chronic disease status. We constructed failure plots to examine the cumulative rates of readmission over the 90-day period. We described sepsis and infection on readmission as well as infection involving the same pathogen as the index admission. We identified readmissions with infection using the infection codes

from the combination coding strategy.^{21–23} We calculated cost per readmission using the cost-to-charge ratios used by the Agency for Healthcare Research and Quality. We compared the adjusted mean cost of readmissions for each patient after a sepsis and nonsepsis admission using LSMEANS (SAS Institute, Inc, Cary, NC) with a γ regression of the log-transformed data.

We estimated excess odds of readmission after a sepsis hospitalization compared with nonsepsis hospitalization for the primary and sensitivity analyses using mixed-effects logistic regression models. Adjusted odds ratios (OR) were calculated by using LSMEANS. All models included fixed effects for sepsis status, chronic disease groups, age, sex, insurance type, zip code income quintile, and hospital type, in addition to hospital-specific random effects.

RESULTS

Clinical Characteristics

Of the 14 894 613 admissions, there were 897 179 index admissions among patients

≤ 18 years who were discharged alive and not against medical advice before October 1, 2014 (Fig 1). An additional 282 935 (31.5%) were among neonates and excluded. Of the remaining 614 244 admissions, we selected the 562 817 first index admissions for inclusion in the unmatched analysis sample; of these, 7634 (1.4%) were admissions involving sepsis and 555 183 (98.6%) were nonsepsis admissions.

The demographics, distribution of chronic disease, and hospital, insurance, and illness characteristics, including organ failure, are presented in Table 1 for the sepsis and nonsepsis admissions. Among index admissions without sepsis, 375 340 (67.6%) were previously healthy and 179 843 (32.4%) had a chronic disease. In contrast, of the 7634 index admissions with sepsis, 1564 (20.5%) were previously healthy and 6070 (79.5%) had at least 1 chronic disease. Among patients with sepsis, 1960 (25.7%) required mechanical ventilation and 1463 (19.2%) had shock. Most ($n = 6510$; 85.3%) were admitted to metropolitan academic

hospitals. Among index admissions with sepsis, 3095 (40.5%) had a bacterial or fungal pathogen identified, and the most common pathogens were *Escherichia coli* (10.3%), *Staphylococcus aureus* (9.9%), and *Streptococcus* species (9.8%).

Readmissions

Of the 7634 index admissions with sepsis, 1657 (21.7%) patients were readmitted at least once, 384 (5.0%) were readmitted twice, and 168 (2.2%) were readmitted 3 or more times within 90 days. Figure 2 displays the cumulative readmission rates at 90 days for patients after sepsis and nonsepsis admissions for the primary (unmatched) and matched sensitivity analyses. In the primary analysis, approximately one-third of all readmissions occurred in the first 2 weeks after discharge (4.1% [$n = 311$] at 7 days and 7.1% [$n = 539$] at 14 days) and the remaining two-thirds occurring over the remaining 10 weeks (11.7% [$n = 896$] at 30 days, 18.2% [$n = 1387$] at 60 days, and 22.1% [$n = 1687$] at 90 days). After

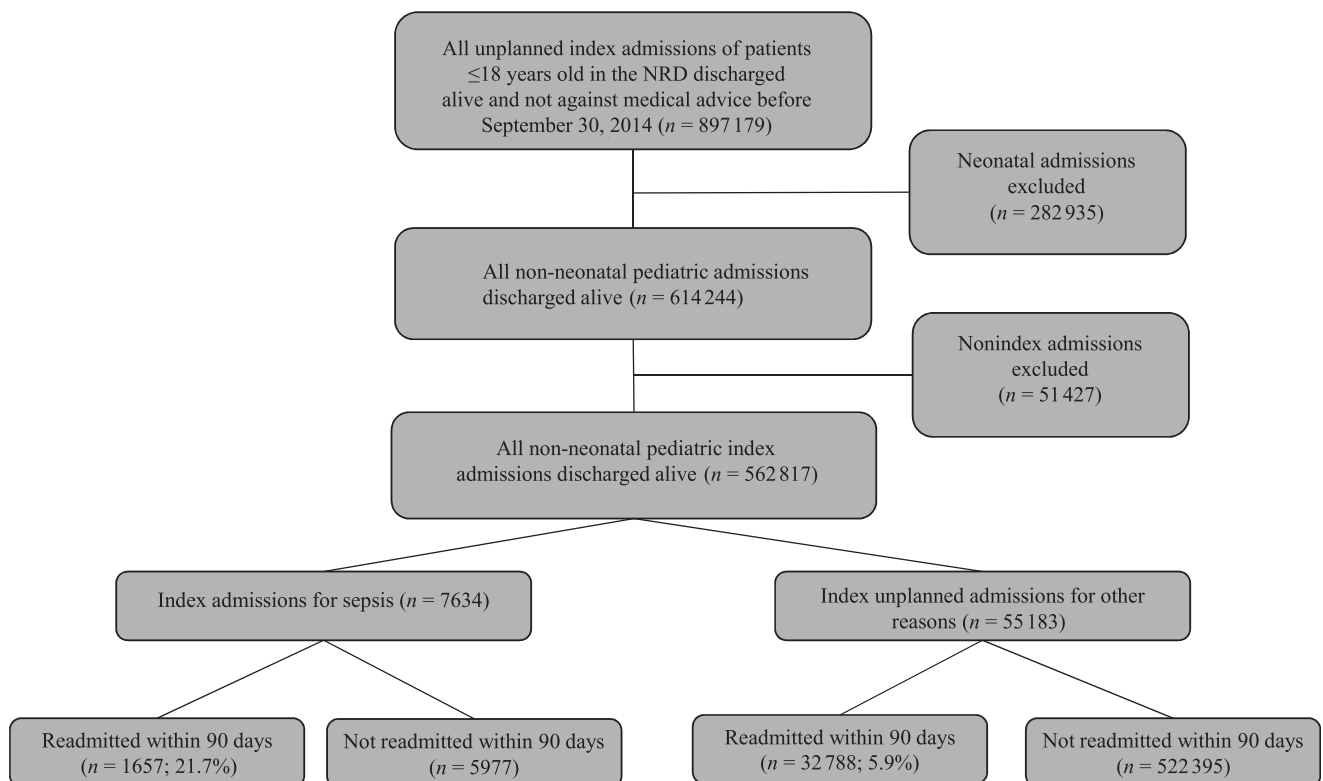


FIGURE 1 Enrollment of the primary cohort: cohort selection and inclusion criteria for index admissions with and without sepsis. These admissions were not the first admissions of the year for these patients.

TABLE 1 Clinical Characteristics of Patients Admitted With Sepsis and for Other Reasons

Variable	Index Nonsepsis Admissions (N = 555 183)	Index Sepsis Admissions (N = 7634)
Demographic		
Age <1 y, non-neonate	308 183 (55.5)	739 (9.7)
Age 1–5 y	60 049 (10.8)	1719 (22.5)
Age 6–12 y	66 922 (12.1)	1910 (25.0)
Age 13–18 y	120 029 (21.6)	3266 (42.8)
Female	292 457 (52.7)	4064 (53.2)
Public insurance	289 773 (52.3)	4351 (57.1)
Chronic disease ^a		
Previously healthy	375 340 (67.6)	1564 (20.5)
Any chronic disease	179 843 (32.4)	6070 (79.5)
Neurologic or neuromuscular conditions	83 135 (15.0)	3015 (39.5)
Cardiovascular conditions	13 668 (2.5)	1353 (17.7)
Respiratory conditions	57 690 (10.4)	1980 (25.9)
Renal and urologic conditions	14 844 (2.7)	1778 (23.3)
Gastrointestinal and hepatologic conditions	38 541 (6.9)	2672 (35.0)
Hematologic and immunologic conditions	11 745 (2.1)	791 (10.4)
Metabolic conditions	21 555 (3.9)	1429 (18.7)
Congenital and genetic conditions	5436 (1.0)	582 (7.6)
Oncologic conditions	4426 (0.8)	202 (2.6)
Technology dependence	17 901 (3.2)	2188 (28.7)
Solid organ transplant	2208 (0.4)	213 (2.8)
Organ failure		
Need for mechanical ventilation	2771 (0.5)	1960 (25.7)
Presence of shock	1322 (0.2)	1463 (19.2)
Acute renal failure	1451 (0.3)	1080 (14.1)
Neurologic failure	2209 (0.4)	587 (7.7)
Hepatic failure	140 (0.0)	70 (0.9)
Hematologic failure	2065 (0.4)	1341 (17.6)
Sepsis definition ^b		
Explicit criteria	N/A	3554 (46.6)
Combined criteria	N/A	5389 (70.6)
APRDRG illness severity ^c		
Mild and/or moderate severity	523 030 (94.2)	2489 (32.6)
Major severity	26 944 (4.9)	2829 (37.1)
Extreme severity	5067 (0.9)	2302 (30.2)
APRDRG risk of mortality		
Mild and/or moderate risk	548 405 (98.8)	4482 (58.7)
Major risk	3632 (0.7)	1989 (26.1)
Extreme risk	3004 (0.5)	1149 (15.1)
Hospital type		
Metropolitan teaching hospital	100 494 (18.1)	810 (10.6)
Metropolitan nonteaching hospital	403 458 (72.7)	6510 (85.3)
Nonmetropolitan hospital	51 231 (9.2)	314 (4.1)
Length of stay, median (IQR)	2 (2–3)	4 (2–9)

Cohort consists of children 18 y or younger and discharged alive and excluded neonates and those discharged against medical advice. All values expressed as frequency and percentage in parenthesis unless stated otherwise. APRDRG, all-patients refined diagnosis related group; IQR, interquartile range; N/A, not applicable.

^a Because patients could have >1 chronic disease, percentages add to >100%.

^b Because patients could meet either or both criteria, percentages add to >100%.

^c APRDRG illness severity and mortality risk are proprietary and validated method of illness severity stratification by using administrative data.

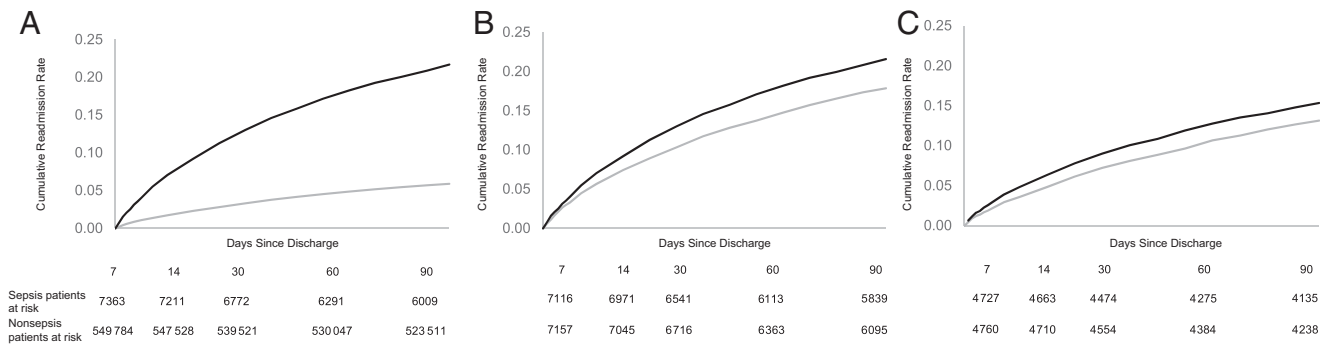


FIGURE 2 Failure plots with time to readmission within primary and matched sensitivity analysis cohorts. A, Failure plots for unadjusted readmission rate after sepsis and nonsepsis admissions in primary unmatched analysis. B, Failure plots for unadjusted readmission rate after sepsis and nonsepsis admissions in less exact matching analysis. C, Failure plots for unadjusted readmission rate after sepsis and nonsepsis admissions in more exact matching analysis. Sepsis admissions are in black, and nonsepsis admissions are in gray.

nonsepsis admission, the corresponding readmission rates were 1.1% ($n = 6044$), 1.7% ($n = 9623$), 3.0% ($n = 16464$), 4.7% ($n = 26236$), and 5.9% ($n = 32788$), respectively. The cost per patient for all 90-day readmissions after sepsis was higher compared with nonsepsis admissions (adjusted mean costs \$7385 and \$5810 after sepsis and nonsepsis admissions, $P < .0001$).

Over half of readmissions among patients with an index admission with sepsis involved recurrent sepsis or infection (52.9%, 876 of 1657 patients). Of the 876 patients with a readmission involving sepsis or infection, 499 (57.0%) had sepsis or infection in the primary discharge diagnosis field. Among all patients with readmission with sepsis or infection, 169 (19.3%) involved the same pathogen as the index sepsis admission, and the most common pathogens were *S aureus* ($n = 38$, 22.5%), *Pseudomonas aeruginosa* ($n = 31$, 18.3%), and *E coli* ($n = 29$, 17.2%). The high

proportion of patients readmitted with sepsis or an infection were observed in both previously healthy patients and those with chronic diseases (57.1% [64 out of 112 patients] and 52.6% [813 out of 1545 patients], respectively). In contrast, 26.2% (8616 out of 32788) of patients with nonsepsis admissions were readmitted for sepsis or an infection, and 30.2% (2632 out of 8684) and 24.8% (5984 out of 24104) were among previously healthy patients and those with chronic diseases. Among all index admissions that did not involve sepsis ($n = 555183$), 17098 (3.1%) involved infection.

Excess Odds of 90-Day Readmission After Sepsis

In the primary analysis, 1657 (21.7%) of patients with sepsis were readmitted compared to 32788 (5.9%) of other admissions. The higher odds persisted in multivariable analysis, and the sepsis group had a 15% higher odds of readmission

compared with other admissions (unadjusted OR 4.42, 95% confidence interval [CI] 3.08–6.33; adjusted OR: 1.15, 95% CI 1.08–1.23; Fig 3). All sensitivity analyses had similar point estimates and CIs (Fig 3).

We also calculated 90-day readmission rates in 6 sensitivity analyses. First, 7510 (98.4%) of patients with sepsis were matched to controls on the basis of demographics alone and had higher odds of readmission (adjusted OR: 1.23, 95% CI 1.11–1.38). Second, we matched most patients on the basis of a less exact chronic disease matching strategy (we were able to match 7376 [96.6%] of the 7634 index admissions in the primary analysis sample for sepsis to nonsepsis admissions). Third, we matched 4853 (63.6%) index admissions with sepsis using the more exact strategy. The characteristics of the matched samples are presented in Supplemental Table 2, which shows some imbalance in acute illness severity. However, the results of both matching strategies were similar to the primary unmatched analysis (Fig 3).

The excess odds of 30-day readmission in the unmatched sample were 13% (unadjusted OR: 4.35, 95% CI 2.74–6.91; adjusted OR: 1.13, 95% CI 1.04–1.23). Among only those index admissions with 6 months of follow-up, the 6-month readmissions rate was 19% higher after sepsis compared with nonsepsis admission (adjusted OR: 1.19, 95% CI 1.11–1.28). Finally, the association between a sepsis admission and higher

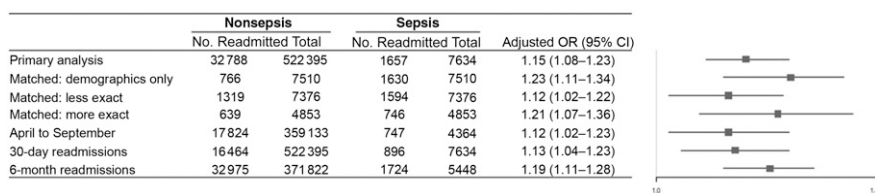


FIGURE 3 Multivariable models for primary and sensitivity analyses of adjusted odds of readmission after sepsis. Sepsis admissions were associated with higher adjusted odds of readmissions compared with nonsepsis admissions in primary and sensitivity analyses. Adjusted ORs with CIs, number of sepsis cases able to be matched, and cohort size for sensitivity analyses are shown (see text for additional details).

odds of readmission persisted among the 363 497 index admissions admitted between April 1 and September 30 (adjusted OR: 1.12, 95% CI 1.02–1.25; Fig 3).

DISCUSSION

In a nationally representative cohort of pediatric patients with sepsis, we showed that 1 in 5 patients were readmitted within 90 days after hospitalization, and these readmissions were associated with increased health care costs. The odds of readmission were higher among those with chronic disease compared with previously healthy patients but were elevated in both populations after sepsis admission. Finally, patients with an index admission for sepsis had higher odds of readmissions compared with nonsepsis admissions, and this association was robust across multiple sensitivity analyses.

The higher odds of readmission among patients with sepsis was explained in part by the higher burden of chronic disease among patients with sepsis. The association persisted in sensitivity analyses adjusting for demographics and chronic diseases, suggesting that other mechanisms may explain the higher odds among patients with sepsis. Potential mechanisms include residual organ failure, increased medical frailty, or worsening of preexisting chronic disease. In addition, a significant proportion of readmissions involved infection, with a substantial minority involving the same organism described during the index admission. Although some of these infections may have been hospital acquired during the readmission, over half of readmissions with sepsis or an infection had these diagnoses listed as the primary discharge diagnosis. Thus, infection or sepsis are likely to be the leading causes of readmission in pediatric sepsis survivors, a finding consistent with previous studies in adults.¹³ Potential reasons include inadequate duration of antimicrobial therapy (an unrecognized reservoir of infection) and preexisting or persistent immune dysfunction. The latter may be due to epigenetic changes or persistent alterations in the microbiome.^{11,12} Pediatricians caring for children during recovery from and after an episode of

sepsis should consider close follow-up and evaluation for recurrent or persistent infection in both previously healthy and chronically ill children when planning transitions of care²⁶ because approximately one-third of all readmissions occur within 2 weeks after hospital discharge. In addition, further research dedicated to understanding the underlying mechanisms of these adverse outcomes and developing effective interventions to prevent them may improve outcomes in survivors of pediatric sepsis.

Our study has several strengths. The NRD is a nationally representative data set with good follow-up for the primary outcome of interest and includes both children's and nonchildren's hospitals. The large sample size allowed for a more detailed description of subgroups of pediatric patients with chronic disease and the excess adverse outcomes among these patients.

Our study has several limitations. First, the NRD is not designed to track admissions and readmissions across different states and does not include reliable measures of ICU admission. Although little data exist about children crossing state lines for recurrent episodes of care, most children who are chronically ill and those who go to academic medical centers are less likely to visit different hospitals.²⁷ Second, the NRD does not allow tracking patients across different years. Although we may have misclassified some index admissions early in the year that involved an admission near the end of the preceding year, our findings were robust when we analyzed patients who were not admitted within the first quarter of 2014 but incurred an admission subsequently. Third, we used administrative data, and we may have misclassified sepsis and nonsepsis cases^{25,28,29} and reasons for readmission due to an infection. Fourth, given the design of the database, we were unable to describe out-of-hospital mortality or recurrent infections that did not result in readmission. Fifth, we cannot exclude unmeasured confounding in our study design given the limitations of using discharge diagnoses. However, we used stringent criteria to identify previously healthy patients. The 7.2% readmission rate in this group is higher than the readmission

rate after many other common pediatric admissions³⁰ that include a high proportion of previously healthy patients. In addition, we used multiple matching strategies among patients with chronic disease to describe the independent effect of sepsis on readmission odds and found a robust effect.

CONCLUSIONS

In this large, nationally representative sample of pediatric patients with sepsis, we showed persistently increased odds of readmission among both previously healthy patients and those with chronic disease, with a large proportion of readmission involving infection. Clinicians caring for pediatric patients after an episode of sepsis should consider close follow-up and targeted evaluation for recurrent infection in these patients. Researchers should aim to understand the biologic mechanisms that underlie these adverse outcomes and develop effective models for postacute care management of these patients.

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