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Epidemiology of Sepsis in US Children and Young Adults

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Background. Most multicenter studies of US pediatric sepsis epidemiology use administrative data or focus on pediatric intensive care units. We conducted a detailed medical record review to describe sepsis epidemiology in children and young adults.

Methods. In a convenience sample of hospitals in 10 states, patients aged 30 days–21 years, discharged during 1 October 2014–30 September 2015, with explicit diagnosis codes for severe sepsis or septic shock, were included. Medical records were reviewed for patients with documentation of sepsis, septic shock, or similar terms. We analyzed overall and age group–specific patient characteristics.

Results. Of 736 patients in 26 hospitals, 442 (60.1%) had underlying conditions. Most patients (613 [83.3%]) had community-onset sepsis, although most community-onset sepsis was healthcare associated (344 [56.1%]). Two hundred forty-one patients (32.7%) had outpatient visits 1–7 days before sepsis hospitalization, of whom 125 (51.9%) received antimicrobials ≤30 days before sepsis hospitalization. Age group–related differences included common underlying conditions (<5 years: prematurity vs 5–12 years: chronic pulmonary disease vs 13–21 years: chronic immunocompromise); medical device presence ≤30 days before sepsis hospitalization (1–4 years: 46.9% vs 30 days–11 months: 23.3%); percentage with hospital-onset sepsis (<5 years: 19.6% vs ≥5 years: 12.0%); and percentage with sepsis-associated pathogens (30 days–11 months: 65.6% vs 13–21 years: 49.3%).

Conclusions. Our data suggest potential opportunities to raise sepsis awareness among outpatient providers to facilitate prevention, early recognition, and intervention in some patients. Consideration of age-specific differences may be important as approaches are developed to improve sepsis prevention, risk prediction, recognition, and management.

Keywords. children; epidemiology; sepsis; septic shock; severe sepsis.

Sepsis is recognized as an urgent global public health threat, with an estimated 48.9 million cases and 11.0 million deaths worldwide in 2017 [1]. In the United States (US), using a sepsis definition based on electronic health record (EHR) data, investigators estimated there were 1.7 million adults with sepsis and 270 000 in-hospital deaths in 2014 [2]. Although investigators have developed EHR definitions of sepsis for pediatric populations [3, 4], these definitions have not been used to estimate national pediatric sepsis cases and deaths, and additional work is needed to refine and validate a widely applicable EHR-based approach [5]. An analysis of administrative data from 2013 yielded an annual US estimate of 54 060 sepsis cases in children outside of the neonatal period and <19 years old; 3.7% of children with sepsis in this study died in the hospital [6]. Although there is robust literature on the epidemiology of sepsis in US adults [7–9], there are relatively few recent, multicenter studies of US pediatric sepsis epidemiology. Most previously published studies used administrative data [10–13] or were focused on patients admitted to pediatric intensive care units [14]. Through the Centers for Disease Control and Prevention's (CDC) Emerging Infections Program (EIP), we conducted a detailed medical record review of US children and young adults with hospital discharge codes of severe sepsis or septic shock to describe demographic and clinical characteristics, including by age group.

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METHODS

Hospitals and Patients

The methods have been described previously [15]. The EIP is a network of 10 state health departments (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) and academic partners [16]. Each EIP site recruited 2–4 hospitals. Trained EIP staff reviewed medical records of randomly selected patients with sepsis in these hospitals, with a goal of including approximately 100 adult (≥18 years old) and 100 pediatric patients (<18 years old) per EIP site. Patients were eligible for inclusion if they were discharged from a participating hospital between 1 October 2014 and 30 September 2015 and had an explicit diagnosis code for severe sepsis or septic shock (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 995.92 or 785.52). Only the first hospitalization per eligible patient during the period of interest was included. In some EIP sites there were fewer than 100 patients <18 years old with a sepsis-related hospital discharge during the time frame of interest across all participating hospitals. In these cases, sites were asked to review the records of all pediatric patients.

Patients without clinical documentation in the medical record of terms such as sepsis or septic shock and patients who were missing a sepsis diagnosis date were excluded. Results of the analysis of patients ≥18 years old with sepsis have been published [15]. For the current analysis, we included patients 30 days to 21 years old. Infants <30 days old or who were never discharged from the hospital after birth were excluded [5].

Patient Consent Statement

The human subjects advisor in the CDC's National Center for Emerging and Zoonotic Infectious Diseases determined the project to be a nonresearch activity. Institutional review boards in EIP sites and participating hospitals determined the project to be nonresearch or approved the project with waiver of informed consent.

Data Collection

EIP site staff collected medical record data using a standardized data collection form. Data collection focused on preadmission healthcare and information present in the medical record around the sepsis diagnosis date, defined as the first date a healthcare practitioner documented sepsis or a related term in the medical record. Preadmission healthcare data collection included (1) prehospital treatment or procedures (receipt of antimicrobial medications, chemotherapy, wound care, dialysis, or surgery in the 30 days before admission); (2) prehospital medical devices (urinary catheter, central line, mechanical ventilation, gastrostomy or jejunostomy tube, or tracheostomy in the 30 days before admission); and (3) stays of ≥2 days in a healthcare facility (such as a hospital or long-term care facility) in the 30 or 90 days before admission. Data were also collected on outpatient healthcare in the 7 days before sepsis hospital admission, including the visit date and setting type (eg, primary care or medical subspecialty clinic).

In addition, data were collected on (1) infections documented in the medical record as present within 7 days before or after sepsis diagnosis, including the subset documented to be associated with sepsis at the time of sepsis diagnosis or in the hospital discharge summary; (2) vital signs and laboratory data on the day before, day of, and day after sepsis diagnosis to determine the presence of the systemic inflammatory response syndrome using age-specific criteria [17, 18]; (3) cultures and nonculture microbiological tests collected during the 7 days before and after sepsis diagnosis; and (4) outcome at hospital discharge. Death certificate information was gathered from state vital statistics registries to identify patients who died within 90 days of sepsis diagnosis.

Indicators of organ dysfunction documented in the medical record in the 7 days before or after sepsis diagnosis were also collected. These indicators were generally consistent with criteria proposed by Hsu et al for consideration in an EHR definition of pediatric sepsis or sensitivity analyses [5], based on modifications of the pediatric Sequential Organ Failure Assessment (pSOFA) score [19]: invasive mechanical ventilation, noninvasive positive pressure ventilation, receipt of vasopressor medications, systolic blood pressure <90 mm Hg, documented altered mental status, lactate ≥2 mmol/L, platelets <100 000/μL, creatinine ≥2 times baseline, and total bilirubin ≥2 times baseline and ≥2 mg/dL. Organ dysfunction evidenced by mechanical ventilation or noninvasive positive pressure ventilation, receipt of vasopressors, systolic blood pressure <90 mm Hg, or altered mental status had to be new or worsening during the 7 days before or after sepsis diagnosis. Baseline values of total bilirubin and creatinine were defined as the lowest value during the 7 days before or after sepsis diagnosis.

Analysis

To determine which organisms were associated with sepsis, we developed an algorithm based on the specimen type (sterile or nonsterile body site), diagnostic test (culture or nonculture), organism, and infection site documented in the medical record (Supplementary Table 1). This approach was adapted from the previously published analysis of adult patients with sepsis [15]. Sepsis cases were classified as hospital-onset, healthcare-associated community-onset, or community-associated. Hospital-onset cases were defined as occurring in patients with a sepsis diagnosis date on hospital day 4 or later. Healthcare-associated community-onset cases were defined as sepsis events with diagnosis dates on hospital days 1–3, and occurring in (1) patients in a hospital or other healthcare facility (such as a nursing home) 4 days before admission and in a community location or

nonhospital facility immediately prior to admission; or (2) patients with a medical device, treatment, or procedure in the 30 days before sepsis hospital admission, or a ≥2-day healthcare facility stay in the 90 days before sepsis hospital admission. Community-associated cases were defined as sepsis events with diagnosis dates on hospital days 1–3, occurring in patients who were (1) in a private residence or other community location 4 days before the sepsis hospital admission, regardless of patient location immediately before sepsis hospital admission; and (2) reported to have no medical devices, treatments, or procedures in the 30 days before sepsis hospital admission and no ≥2-day healthcare facility stay in the 90 days before sepsis hospital admission. Patients who were in a hospital other than the sepsis hospital 4 days before sepsis hospital admission, and also in a hospital other than the sepsis hospital immediately prior to admission (such as patients transferred from another hospital), with a sepsis diagnosis date on days 1–3 in the sepsis hospital, were considered to have sepsis of unknown onset.

We conducted a descriptive analysis of demographic and clinical variables stratified by age group: 30 days–11 months, 1–4 years, 5–12 years, and 13–21 years. Analyses were performed using SAS version 9.4 software (SAS Institute). Data were analyzed between 1 May 2018 and 12 October 2022.

RESULTS

Patient Characteristics

Among 900 patients ≤21 years old at hospital admission, 736 patients in 26 hospitals met inclusion criteria. Of 164 excluded patients, 133 were <30 days old; 13 were never discharged from the hospital after birth; 17 did not have documentation of sepsis, septic shock, or similar terms in the medical record; and 1 was missing the sepsis diagnosis date.

Of 736 patients with sepsis who met inclusion criteria, 386 patients (52.4%) were female, 355 (48.2%) were non-Hispanic White, 144 (19.6%) were Hispanic, and 129 (17.5%) were non-Hispanic Black ethnicity and race. The distribution of ethnicity and race varied by age, with a higher percentage of children <5 years old reported to be of non-Hispanic Black ethnicity and race (53/235 [22.6%]) compared with older children (76/501 [15.2%]). Four hundred sixteen (56.5%) were reported to have Medicaid as the primary insurer.

Most patients (442 [60.1%]) had ≥1 underlying condition (Table 1). The distribution of underlying conditions varied by age, with prematurity the most common condition among children 30 days–11 months old (30 [33.3%]) and 1–4 years old (34 [23.4%]), chronic pulmonary disease among children 5–12 years old (51 [23.3%]), and chronic immunocompromise among patients 13–21 years old (54 [19.1%]).

Treatment, Procedures, and Devices Before the Sepsis Hospitalization

Three hundred thirteen patients (42.5%) received a treatment or procedure in the 30 days before hospital admission, among which antimicrobial medications were the most common in all age groups (263 patients [35.7%]). Medical devices were present in the 30 days before hospital admission in 264 patients (35.9%) overall, ranging from 23.3% in the age group 30 days to 11 months to 46.9% in those aged 1–4 years (Table 2). Among 442 patients with underlying conditions, 327 (74.0%) had a medical device, treatment, or procedure in the 30 days before sepsis hospital admission, or a healthcare facility stay in the 90 days before sepsis hospital admission.

Almost three-quarters of all patients with sepsis (548 [74.5%]) had an underlying condition, treatment, or procedure in the 30 days before admission, medical device in the 30 days before admission, or ≥2-day stay in a healthcare facility in the 90 days before admission. One hundred seventy-five patients (23.8%) had no underlying conditions and none of these healthcare interactions before hospital admission (data were incomplete for 13 patients [1.8%]).

Outpatient Visits Before the Sepsis Hospital Admission

Two hundred forty-one patients (32.7%) were identified as having outpatient visits from 1 to 7 days before hospital admission (not including the day of admission), with visits to a medical subspecialty (74 patients [10.1%]) or primary care clinic (74 patients [10.1%]) being the most common overall (Table 2).

The percentage of patients with underlying conditions who had an outpatient visit from 1 to 7 days before hospital admission (151/442 patients [34.2%]) was only slightly higher than in patients with no or unknown underlying conditions (90/294 patients [30.6%]). Among the subset of patients with underlying conditions and devices, treatments, or procedures in the 30 days before admission, or another healthcare facility stay in the 90 days before admission, the percentage with an outpatient visit in the 7 days before admission was 37.3% (122/327 patients). Among the 241 patients with outpatient visits 1 to 7 days before sepsis hospitalization, 125 (51.9%) received antimicrobials in the 30 days before sepsis hospitalization.

Infections and Pathogens

At least 1 infection (including infection of unknown type) was reported for 712 patients (96.7%) (Table 3). Infection types varied by age group; among patients 30 days to 11 months old, bloodstream infections were most common (26 [28.9%]), whereas pneumonia was the most common infection in all other age groups (in 30.3% of patients 1–4 years old, 24.2% of patients 5–12 years old, and 27.0% of patients 13–21 years old).

Almost all patients (732 [99.5%]) had ≥1 culture or nonculture microbiology test in the 7 days before or after the date of sepsis diagnosis; 518 (70.4%) had ≥1 positive test, and 427 (58.0%) had ≥1 positive test for a pathogen associated with

Table 1. Demographic and Clinical Characteristics of Children and Young Adults With Sepsis, by Age Group

Characteristic	Total (N = 736)	Age Group			
		30 Days–11 Months (n = 90)	1–4 Years (n = 145)	5–12 Years (n = 219)	13–21 Years (n = 282)
State of residence					
California	67 (9.1)	6 (6.7)	16 (11.0)	20 (9.1)	25 (8.9)
Colorado	94 (12.8)	5 (5.6)	18 (12.4)	30 (13.7)	41 (14.5)
Connecticut	82 (11.1)	6 (6.7)	14 (9.7)	22 (10.0)	40 (14.2)
Georgia	105 (14.3)	19 (21.1)	24 (16.6)	34 (15.5)	28 (9.9)
Maryland	94 (12.8)	13 (14.4)	24 (16.6)	34 (15.5)	23 (8.2)
Minnesota	87 (11.8)	20 (22.2)	13 (9.0)	28 (12.8)	26 (9.2)
New Mexico	38 (5.2)	5 (5.6)	4 (2.8)	8 (3.7)	21 (7.4)
New York	47 (6.4)	7 (7.8)	9 (6.2)	9 (4.1)	22 (7.8)
Oregon	59 (8.0)	3 (3.3)	13 (9.0)	14 (6.4)	29 (10.3)
Tennessee	63 (8.6)	6 (6.7)	10 (6.9)	20 (9.1)	27 (9.6)
Sex					
Female	386 (52.4)	48 (53.3)	75 (51.7)	123 (56.2)	140 (49.6)
Male	350 (47.6)	42 (46.7)	70 (48.3)	96 (43.8)	142 (50.4)
Race/ethnicity[a]					
American Indian, non-Hispanic	16 (2.2)	5 (5.6)	2 (1.4)	4 (1.8)	5 (1.8)
Asian, non-Hispanic	29 (3.9)	6 (6.7)	4 (2.8)	11 (5.0)	8 (2.8)
Black, non-Hispanic	129 (17.5)	21 (23.3)	32 (22.1)	33 (15.1)	43 (15.2)
Hispanic/Latino	144 (19.6)	18 (20.0)	25 (17.2)	47 (21.5)	54 (19.1)
Pacific Islander, non-Hispanic	4 (0.5)	1 (1.1)	0	1 (0.5)	2 (0.7)
White, non-Hispanic	355 (48.2)	34 (37.8)	66 (45.5)	104 (47.5)	151 (53.5)
Other or multiple races, non-Hispanic	29 (3.9)	0	9 (6.2)	13 (5.9)	7 (2.5)
Unknown race, non-Hispanic	30 (4.1)	5 (5.6)	7 (4.8)	6 (2.7)	12 (4.3)
Primary insurance type					
Medicaid	416 (56.5)	55 (61.1)	89 (61.4)	128 (58.4)	144 (51.1)
Private	254 (34.5)	24 (26.7)	36 (24.8)	74 (33.8)	120 (42.6)
Other	47 (6.4)	7 (7.8)	17 (11.7)	11 (5.0)	12 (4.3)
Unknown	19 (2.6)	4 (4.4)	3 (2.1)	6 (2.7)	6 (2.1)
Location immediately before sepsis admission					
Private residence	378 (51.4)	44 (48.9)	77 (53.1)	116 (53.0)	141 (50.0)
Another acute care hospital or emergency department	271 (36.8)	41 (45.6)	46 (31.7)	82 (37.4)	102 (37.6)
Outpatient clinic or urgent care	73 (9.9)	5 (5.6)	21 (14.5)	20 (9.1)	27 (9.6)
Nursing home	4 (0.5)	0	0	0	4 (1.4)
Other	6 (0.8)	0	0	1 (0.5)	5 (1.8)
Unknown	4 (0.5)	0	1 (0.7)	0	3 (1.1)
Location 4 days before sepsis admission					
Private residence	676 (91.8)	85 (94.4)	135 (93.1)	200 (91.3)	256 (90.8)
Another acute care hospital	38 (5.2)	5 (5.6)	7 (4.8)	13 (5.9)	13 (4.6)
Nursing home	5 (0.7)	0	1 (0.7)	0	4 (1.4)
Other[b]	11 (1.5)	0	1 (0.7)	3 (1.4)	7 (2.5)
Unknown	6 (0.8)	0	1 (0.7)	3 (1.4)	2 (0.7)
Underlying conditions					
Any underlying condition[c]	442 (60.1)	49 (54.4)	93 (64.1)	132 (60.3)	168 (59.6)
Chronic pulmonary disease[d]	137 (18.6)	6 (6.7)	33 (22.8)	51 (23.3)	47 (16.7)
Chronic cognitive deficit	118 (16.0)	8 (8.9)	31 (21.4)	40 (18.3)	39 (13.8)
Chronic immunocompromise[e]	109 (14.8)	5 (5.6)	17 (11.7)	33 (15.1)	54 (19.1)
Hematologic or oncologic disease	108 (14.7)	3 (3.3)	22 (15.2)	37 (16.9)	46 (16.3)
History of prematurity	90 (12.2)	30 (33.3)	34 (23.4)	14 (6.4)	12 (4.3)
Congenital heart disease	63 (8.6)	23 (25.6)	17 (11.7)	10 (4.6)	13 (4.6)
Hemiplegia, paraplegia, quadriplegia	42 (5.7)	0	4 (2.8)	16 (7.3)	22 (7.8)
Chronic kidney disease	31 (4.2)	2 (2.2)	7 (4.8)	10 (4.6)	12 (4.3)
Chronic mental illness	18 (2.4)	0	0	4 (1.8)	14 (5.0)
Other cardiovascular disease	17 (2.3)	2 (2.2)	6 (4.1)	5 (2.3)	4 (1.4)
Chronic liver disease	15 (2.0)	1 (1.1)	7 (4.8)	2 (0.9)	5 (1.8)

Table 1. Continued

Characteristic	Total (N = 736)	Age Group 30 Days–11 Months (n = 90)	1–4 Years (n = 145)	5–12 Years (n = 219)	13–21 Years (n = 282)
Diabetes mellitus[f]	12 (1.6)	0	1 (0.7)	3 (1.4)	8 (2.8)
Chronic wound	10 (1.4)	2 (2.2)	2 (1.4)	0	6 (2.1)
Connective tissue disease	6 (0.8)	0	0	3 (1.4)	3 (1.1)
Pregnancy	2 (0.3)	…	…	0	2 (0.7)
Peptic ulcer disease	1 (0.1)	0	0	0	1 (0.4)
Unknown	9 (1.2)	1 (1.1)	1 (0.7)	3 (1.4)	4 (1.4)
Substance use[g]	15 (2.0)	…	…	0	15 (5.3)

Data are presented as No. (%).

[a]Persons with unknown ethnicity are grouped with persons reported as non-Hispanic.

[b]Including persons experiencing homelessness or incarceration.

[c]Includes any of the conditions listed.

[d]Including asthma in 91 of 137 patients.

[e]Defined as asplenia, neutropenia, hematopoietic stem cell transplant, solid organ transplant, human immunodeficiency virus infection, primary immunodeficiency, or chronic steroid or other immunosuppressive therapy.

[f]Includes type 1 and type 2 diabetes mellitus and gestational diabetes.

[g]Includes alcohol use disorder, injection drug use, and smoking.

sepsis. The percentages of patients with any microbiological testing, positive tests, and positive tests for pathogens associated with sepsis decreased as patient age increased (Supplementary Table 2). For example, 65.6% of patients 30 days to 11 months old had ≥1 pathogen identified that was associated with sepsis compared with 49.3% of patients 13–21 years old.

Among patients in whom a sepsis-associated pathogen was detected, gram-positive bacteria were most common (215/427 patients [50.4%]), followed by gram-negative bacteria (193/427 [45.2%]) and viruses (123/427 [28.8%]) (Supplementary Table 2). Pathogen distribution varied by age group, although *Staphylococcus aureus* was the most common pathogen overall (89 patients, 12.1% of all patients and 20.8% of those with a sepsis-associated pathogen) and in all age groups except patients 1–4 years old in whom respiratory syncytial virus was most common (13 patients, 9.0% of all patients in this age group and 14.0% of those with a sepsis-associated pathogen) (Table 4).

Sepsis Hospitalization and Outcome

Most patients had community-onset sepsis (613/736 [83.3%]); most community-onset sepsis was healthcare associated (344/613 [56.1%]) (Table 5). Hospital-onset sepsis was more common among patients <5 years old (46/235 [19.6%]) than among older patients (60/501 [12.0%]).

Patients with sepsis had prolonged hospitalizations, ranging from a median of 7 days (interquartile range [IQR], 4–17 days) in those 13–21 years old to 14 days (IQR, 7–30 days) in those 1–4 years old (Table 5). Most patients (647 [87.9%]) spent at least part of their hospitalization in the intensive care unit, and ≥1 indicator of organ dysfunction was present in the 7 days before or after sepsis diagnosis in 682 patients (92.7%). Indicators of cardiovascular dysfunction (systolic blood pressure <90 mm Hg or receipt of vasopressors) or perfusion dysfunction (lactate ≥2 mmol/L) were documented for 627 patients (85.2%).

Overall, 74 patients (10.1%) died during their hospitalization (71 within 90 days of sepsis diagnosis). Eighty-four patients (11.4%) died within 90 days of sepsis diagnosis; 13 of these patients (15.5%) died after discharge from their sepsis hospitalization. The youngest age group, patients 30 days to 11 months old, had the highest percentage of patients who died during their hospitalization (15.6%) or within 90 days of diagnosis (18.9%). Patients with underlying conditions were more likely to die during their hospitalizations (55/442 [12.4%]) and during the 90 days after sepsis diagnosis (62/442 [14.0%]) than patients without or with unknown underlying conditions (in-hospital death: 19/294 [6.5%]; 90 days after sepsis diagnosis: 22/294 [7.5%]). Patients with hospital-onset sepsis were more likely to die (in-hospital death: 26/106 [24.5%]; 90 days after sepsis diagnosis: 26/106 [24.5%]) than patients with community-onset sepsis (in-hospital death: 46/613 [7.5%]; 90 days after sepsis diagnosis: 56/613 [9.1%]).

DISCUSSION

In our analysis of medical record data from 736 children and young adults with explicit *ICD-9-CM* codes for severe sepsis or septic shock during hospitalizations in 2014–2015, 60% of patients had at least 1 underlying condition and almost one-third of all patients with sepsis, including those without underlying conditions,

Table 2. Healthcare Received by Children and Young Adults With Sepsis Before the Sepsis Hospitalization, by Age Group

Characteristic	Total (N = 736)	Age Group			
		30 Days–11 Months (n = 90)	1–4 Years (n = 145)	5–12 Years (n = 219)	13–21 Years (n = 282)
Outpatient visit in the 7 d before sepsis hospitalization[a]					
Any of the included visits	241 (32.7)	33 (36.7)	52 (35.9)	71 (32.4)	85 (30.1)
Medical or pediatric subspecialty	74 (10.1)	7 (7.8)	21 (14.5)	21 (9.6)	25 (8.9)
Primary care	74 (10.1)	12 (13.3)	16 (11.0)	17 (7.8)	29 (10.3)
Emergency department	65 (8.8)	14 (15.6)	8 (5.5)	16 (7.3)	27 (9.6)
Urgent care	13 (1.8)	1 (1.1)	5 (3.4)	3 (1.4)	4 (1.4)
Surgery	6 (0.8)	0	0	6 (2.7)	0
Physical, occupational, or speech therapy	3 (0.4)	0	2 (1.4)	1 (0.5)	0
Dental	1 (0.1)	0	1 (0.7)	0	0
Other[b]	25 (3.4)	2 (2.2)	3 (2.1)	12 (5.5)	8 (2.8)
Unknown type of visit	1 (0.1)	0	0	0	1 (0.4)
Treatments or procedures in the 30 d before sepsis hospitalization					
Any of the included treatments or procedures	313 (42.5)	29 (32.2)	73 (50.3)	96 (43.8)	115 (40.8)
Antimicrobial medications	263 (35.7)	27 (30.0)	62 (42.8)	78 (35.6)	96 (34.0)
Cancer chemotherapy	76 (10.3)	2 (2.2)	16 (11.0)	28 (12.8)	30 (10.6)
Surgery	35 (4.8)	5 (5.6)	12 (8.3)	12 (5.5)	6 (2.1)
Wound care	14 (1.9)	2 (2.2)	2 (1.4)	6 (2.7)	4 (1.4)
Chronic dialysis	4 (0.5)	0	2 (1.4)	1 (0.5)	1 (0.4)
Devices present in the 30 d before sepsis hospitalization					
Any of the included devices	264 (35.9)	21 (23.3)	68 (46.9)	83 (37.9)	92 (32.6)
Gastrostomy or jejunostomy tube	159 (21.6)	13 (14.4)	53 (36.6)	50 (22.8)	43 (15.2)
Central line	132 (17.9)	8 (8.9)	33 (22.8)	41 (18.7)	50 (17.7)
Mechanical ventilator	33 (4.5)	5 (5.6)	9 (6.2)	9 (4.1)	10 (3.5)
Tracheostomy	27 (3.7)	1 (1.1)	10 (6.9)	11 (5.0)	5 (1.8)
Urinary catheter	17 (2.3)	1 (1.1)	1 (0.7)	6 (2.7)	9 (3.2)
Admission for ≥2 d to a healthcare facility in the 30 d before sepsis hospitalization					
Hospital	164 (22.3)	29 (32.2)	35 (24.1)	47 (21.5)	53 (18.8)
Long-term acute care hospital	1 (0.1)	0	0	0	1 (0.4)
Nursing home	4 (0.5)	0	0	0	4 (1.4)
Admission for ≥2 d to a healthcare facility in the 90 d before sepsis hospitalization					
Hospital	217 (29.5)	39 (43.3)	52 (35.9)	65 (29.7)	61 (21.6)
Long-term acute care hospital	1 (0.1)	0	0	0	1 (0.4)
Nursing home	4 (0.5)	0	0	0	4 (1.4)

Data are presented as No. (%).

[a]Includes outpatient encounters that occurred from 1 to 7 days before the day of admission. Excludes encounters that were reported to occur on the same day as hospital admission and encounters with missing dates.

[b]Other visits include visits to infusion clinics, laboratories, or radiology. Seven patients were reported to have visited a hospital; these were included since the specific type of location visited within the hospital was not reported and could have been an outpatient location.

had an outpatient visit in the week prior to the sepsis hospitalization. Although most sepsis had its onset in the community, more than half of cases of community-onset sepsis occurred in patients who had received recent prehospital healthcare.

Our finding that almost one-third of patients had an outpatient visit in the week before sepsis hospitalization has also been observed in studies of adult patients with sepsis [20, 21]. Flannery and colleagues reviewed observational studies of adult patients with sepsis and found that an average of 32.7% of patients had outpatient encounters in the week before sepsis hospitalization [20]. In a study of 1150 adult patients with a sepsis hospital discharge and an established outpatient provider in 2017, 118 patients (10.3%) were seen in clinic on the day of or day before sepsis hospitalization. Most of these patients (80.5%) had symptoms of infection or sepsis in clinic, but 44 patients (37.3%) were either treated as an outpatient or sent home without intervention. Upon subsequent presentation to the hospital or emergency department, 77.3% of the patients treated as an outpatient or sent home from clinic were noted to have worsening illness severity, compared with 37.8% of those who were referred directly to the emergency department [22]. These observations suggest that for some patients, there may be opportunities to intervene earlier, although more data are needed [23], including studies describing the reasons for and quality of prehospital care in children who are subsequently admitted for sepsis.

Table 3. Infections Present During the Period Defined by the 7 Days Before or After Sepsis Diagnosis[a] and Documented as the Cause of Sepsis[b], by Age Group

		Age Group			
Infection Type	Total (N = 736)	30 Days–11 Months (n = 90)	1–4 Years (n = 145)	5–12 Years (n = 219)	13–21 Years (n = 282)
Pneumonia	193 (26.2)	20 (22.2)	44 (30.3)	53 (24.2)	76 (27.0)
Documented as the cause of sepsis	152/193 (78.8)	17/20 (85.0)	29/44 (65.9)	46/53 (86.8)	60/76 (78.9)
Bloodstream	154 (20.9)	26 (28.9)	37 (25.5)	38 (17.4)	53 (18.8)
Documented as the cause of sepsis	123/154 (79.9)	22/26 (84.6)	29/37 (78.4)	34/38 (89.5)	38/53 (71.6)
Undetermined or unknown[c]	107 (14.5)	11 (12.2)	21 (14.5)	31 (14.2)	44 (15.6)
Documented as the cause of sepsis	72/107 (67.3)	8/11 (72.7)	12/21 (57.1)	20/31 (64.5)	32/44 (72.7)
Urinary tract	101 (13.7)	13 (14.4)	10 (6.9)	31 (14.2)	47 (16.7)
Documented as the cause of sepsis	77/101 (76.2)	9/13 (69.2)	9/10 (90.0)	22/31 (71.0)	37/47 (78.7)
Lower respiratory (other than pneumonia)	84 (11.4)	23 (25.6)	22 (15.2)	22 (10.0)	17 (6.0)
Documented as the cause of sepsis	36/84 (42.9)	12/23 (52.2)	8/22 (36.4)	9/22 (40.9)	7/17 (41.2)
Ear, eye, mouth, nose, or throat	64 (8.7)	9 (10.0)	12 (8.3)	27 (12.3)	16 (5.7)
Documented as the cause of sepsis	36/64 (56.3)	4/9 (44.4)	5/12 (41.7)	16/27 (59.3)	11/16 (68.8)
Skin or soft tissue	51 (6.9)	5 (5.6)	4 (2.8)	20 (9.1)	22 (7.8)
Documented as the cause of sepsis	29/51 (56.9)	2/5 (40.0)	2/4 (50.0)	11/20 (55.0)	14/22 (63.6)
Gastrointestinal tract (other than CDI)	50 (6.8)	5 (5.6)	7 (4.8)	14 (6.4)	24 (8.5)
Documented as the cause of sepsis	36/50 (72.0)	3/5 (60.0)	3/7 (42.9)	11/14 (78.6)	19/24 (79.2)
Intra-abdominal	39 (5.3)	2 (2.2)	9 (6.2)	15 (6.8)	13 (4.6)
Documented as the cause of sepsis	27/39 (69.2)	2/2 (100)	5/9 (55.6)	11/15 (73.3)	9/13 (69.2)
Central nervous system	36 (4.9)	10 (11.1)	10 (6.9)	8 (3.7)	8 (2.8)
Documented as the cause of sepsis	27/36 (75.0)	8/10 (80.0)	7/10 (70.0)	6/8 (75.0)	6/8 (75.0)
CDI	19 (2.6)	NA	7 (4.8)	4 (1.8)	8 (2.8)
Documented as the cause of sepsis	5/19 (26.3)	NA	1/7 (14.3)	1/4 (25.0)	3/8 (37.5)
Bone or joint	16 (2.2)	0	1 (0.7)	8 (3.7)	7 (2.5)
Documented as the cause of sepsis	12/16 (75.0)	0	0	7/8 (87.5)	5/7 (71.4)
Disseminated	16 (2.2)	0	3 (2.1)	4 (1.8)	9 (3.2)
Documented as the cause of sepsis	11/16 (68.8)	0	2/3 (66.7)	2/4 (50.0)	7/9 (77.8)
Cardiovascular	9 (1.2)	1 (1.1)	1 (0.7)	3 (1.4)	4 (1.4)
Documented as the cause of sepsis	7/9 (77.8)	1/1 (100)	1/1 (100)	2/3 (66.7)	3/4 (75.0)
Reproductive	7 (1.0)	0	0	1 (0.5)	6 (2.1)
Documented as the cause of sepsis	6/7 (85.7)	0	0	0	6/6 (100)
Hepatobiliary	6 (0.8)	0	3 (2.1)	0	3 (1.1)
Documented as the cause of sepsis	2/6 (33.3)	0	0	0	2/3 (66.7)
No infection documented	24 (3.3)	2 (2.2)	6 (4.1)	8 (3.7)	8 (2.8)

Data are presented as No. (%).

Abbreviations: CDI, *Clostridioides difficile* infection; NA, not applicable.

[a]Patients could have >1 infection type. In 14 patients, 1 infection type was reported >1 time (for example, 2 lower respiratory tract infections were reported for the same patient). Duplicate records for 8 of these patients (records with identical data) were deleted. For 6 of the 14 patients with multiple unique infections of the same type, we kept the infection that was reported to have caused sepsis and/or the infection with onset before the sepsis diagnosis date.

[b]Documented in the medical record as the cause of sepsis at the time of sepsis diagnosis or in the discharge summary.

[c]Infections were reported as undetermined site if there was medical record documentation that the source of infection was not yet known. Infections were reported as unknown site when there was insufficient or incomplete documentation in the medical record to determine the site of infection. In total, there were 106 patients with infections of undetermined site and 10 patients with infections of unknown site.

Guidelines for the care of pediatric patients with sepsis and septic shock, as for adult patients, have primarily focused on providing recommendations for the recognition and treatment of sepsis in the emergency department and after hospital admission [24, 25], although the importance of educating the public, including parents and healthcare providers, to improve sepsis early recognition and response in the prehospital setting has been acknowledged [26, 27]. In a study of 114 children with severe bacterial infection, 21 of whom died, children whose initial medical contact was with a general practitioner were more likely to receive suboptimal care compared with those who were evaluated by a pediatric emergency physician or mobile medical unit, and suboptimal care was associated with increased odds of death. Although not statistically significant, children who died were also more likely to have had parental delays in seeking medical care compared with those who survived [28]. Investigators are studying whether assessing the level of parent and healthcare provider concern for severe infection in the emergency department can lead to earlier recognition of sepsis [29]. CDC and organizations such as Sepsis Alliance and End Sepsis have developed campaigns and materials to educate the public and healthcare providers about sepsis

Table 4. Common Pathogens Associated With Sepsis, by Patient Age Group

Pathogen	Total (N = 736)	Age Group			
		30 Days–11 Months (n = 90)[a]	1–4 Years (n = 145)[b]	5–12 Years (n = 219)[c]	13–21 Years (n = 282)[d]
Staphylococcus aureus	89 (12.1)	10 (11.1)	12 (8.3)	26 (11.9)	41 (14.5)
Escherichia coli	61 (8.3)	6 (6.7)	8 (5.5)	21 (9.6)	26 (9.2)
Pseudomonas aeruginosa	32 (4.3)	5 (5.6)	11 (7.6)	11 (5.0)	5 (1.8)
Viridans streptococci	30 (4.1)	9 (10.0)	2 (1.4)	11 (5.0)	8 (2.8)
Klebsiella pneumoniae	29 (3.9)	3 (3.3)	11 (7.6)	7 (3.2)	8 (2.8)
RSV	27 (3.7)	8 (8.9)	13 (9.0)	4 (1.8)	2 (0.7)
Streptococcus pneumoniae	27 (3.7)	5 (5.6)	8 (5.5)	9 (4.1)	5 (1.8)
Streptococcus, group A	27 (3.7)	2 (2.2)	10 (6.9)	11 (5.0)	4 (1.4)
Rhinovirus	26 (3.5)	5 (5.6)	5 (3.4)	10 (4.6)	6 (2.1)
Enterovirus	18 (2.4)	6 (6.7)	5 (3.4)	6 (2.7)	1 (0.4)
Clostridioides difficile	15 (2.0)	NA	5 (3.4)	3 (1.4)	7 (2.5)
Influenza A	15 (2.0)	1 (1.1)	2 (1.4)	7 (3.2)	5 (1.8)
Haemophilus influenzae	14 (1.9)	6 (6.7)	2 (1.4)	2 (0.9)	4 (1.4)
Adenovirus	13 (1.8)	4 (4.4)	4 (2.8)	4 (1.8)	1 (0.4)
Enterococcus faecalis	13 (1.8)	1 (1.1)	5 (3.4)	3 (1.4)	4 (1.4)
Human metapneumovirus	13 (1.8)	0	6 (4.1)	5 (2.3)	2 (0.7)

Data are presented as No. (%).

Abbreviations: NA, not applicable; RSV, respiratory syncytial virus.

[a]Among patients 30 days to 11 months old, other organisms detected in 3 or more patients included *Moraxella catarrhalis* (7 [7.8%]) and *Serratia marcescens* (3 [3.3%]).

[b]Among patients 1–4 years old, other organisms detected in 3 or more patients included *Enterobacter cloacae* (5 [3.4%]), coagulase-negative staphylococci (3 [2.1%]), and *Streptococcus* spp (3 [2.1%]).

[c]Among patients 5–12 years old, other organisms detected in 3 or more patients included coagulase-negative staphylococci (5 [2.3%]), *Streptococcus* spp (4 [1.8%]), *Citrobacter freundii* (3 [1.4%]), cytomegalovirus (3 [1.4%]), *Enterobacter cloacae* (3 [1.4%]), and *Enterococcus* spp (3 [1.4%]).

[d]Among patients 13–21 years old, other organisms detected in 3 or more patients included *Enterococcus faecium* (4 [1.4%]), influenza B (4 [1.4%]), *Candida albicans* (3 [1.1%]), cytomegalovirus (3 [1.1%]), *Enterococcus* spp (3 [1.1%]), and *Proteus mirabilis* (3 [1.1%]).

[30–32]. Further research is needed to determine whether educational efforts facilitate earlier recognition and treatment of sepsis and improve patient outcomes [33].

We observed differences in sepsis epidemiology among children in different age groups outside the neonatal period, including differences in underlying conditions, prehospital healthcare, common infections and pathogens, and outcomes. For example, children between 30 days and 4 years old with sepsis tended to be more medically complex with longer hospitalizations and higher mortality than children ≥5 years old with sepsis. Our findings suggest that different approaches to prevention, early recognition, and management of nonneonatal pediatric sepsis may be needed in children of different ages. To optimize care and outcomes, investigators have proposed grouping patients into various subclasses of sepsis based on factors such as clinical or biological features [34]. Our findings indicate that there may be sepsis subclasses in children outside the neonatal period that are dependent, at least in part, on patient age.

This analysis has several limitations. First, we included a convenience sample of hospitals and relatively small number of patients in a limited number of geographic areas; therefore, our results might not be generalizable to all children and young adults with sepsis in the US. Second, because there is currently no widely accepted pediatric sepsis surveillance definition, we identified patients with sepsis using explicit administrative codes for sepsis and septic shock. This may have resulted in the exclusion of patients with sepsis who were less severely ill. Third, we relied on medical record documentation of healthcare interactions that occurred prior to hospital admission, and this documentation was likely incomplete. Fourth, we did not collect information about the reason for these healthcare interactions, nor did we collect information about infections diagnosed or treated before hospital admission. Fifth, we had limited data to use in determining whether sepsis was hospital or community onset, and it is possible some cases were misclassified. Finally, we used an algorithm to determine which organisms were likely to be associated with sepsis, which also may have resulted in misclassification.

CONCLUSIONS

A large percentage of US children and young adults hospitalized with sepsis have underlying chronic medical conditions or healthcare interactions, including visits with outpatient providers, in the days or weeks leading up to their sepsis hospital admission. Approaches to raise awareness among outpatient providers of the risk of sepsis in these patients and improve early recognition and appropriate clinical intervention should be developed and studied. In addition, our data demonstrate differences in the epidemiology of sepsis among children of different ages, which may be important to consider as approaches are developed to improve sepsis prevention, risk prediction, early recognition, and management.

Table 5. Characteristics of Sepsis Events and Hospitalization in Children and Young Adults, by Age Group

Characteristic	Total (N = 736)	Age Group: 30 Days–11 Months (n = 90)	1–4 Years (n = 145)	5–12 Years (n = 219)	13–21 Years (n = 282)
Patient location at the time the sepsis diagnosis was first documented in the medical record					
ICU	324 (44.0)	48 (53.3)	79 (54.5)	94 (42.9)	103 (36.5)
Emergency department	295 (40.1)	28 (31.1)	46 (31.7)	91 (41.6)	130 (46.1)
Inpatient ward	104 (14.1)	12 (13.3)	19 (13.1)	32 (14.6)	41 (14.5)
Other	2 (0.3)	0	0	1 (0.5)	1 (0.4)
Unknown	11 (1.5)	2 (2.2)	1 (0.7)	1 (0.5)	7 (2.5)
Days from admission to sepsis diagnosis, median (IQR)[a]	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)
Epidemiologic classification of sepsis episode					
Community onset	613 (83.3)	65 (72.2)	112 (77.2)	182 (83.1)	238 (84.4)
Community associated	254 (34.5)	28 (31.1)	38 (26.2)	71 (32.4)	117 (41.5)
Healthcare associated	344 (46.7)	37 (41.1)	74 (51.0)	111 (50.7)	122 (43.3)
Unknown healthcare association	15 (2.0)	4 (4.4)	1 (0.7)	7 (3.2)	3 (1.1)
Hospital onset	106 (14.4)	18 (20.0)	28 (19.3)	25 (11.4)	35 (12.4)
Unknown onset	17 (2.3)	3 (3.3)	4 (2.8)	5 (2.3)	5 (1.8)
Admitted to the ICU during the sepsis hospitalization	647 (87.9)	80 (88.9)	129 (89.0)	197 (90.0)	241 (85.5)
Days in ICU, median (IQR)[b]	4 (2–11)	6 (3–14)	7 (2–15)	4 (2–9)	3 (2–8)
Indicators of organ dysfunction[c]					
Any indicator of organ dysfunction	682 (92.7)	86 (95.6)	135 (93.1)	204 (93.2)	257 (91.1)
Systolic blood pressure <90 mm Hg	516 (70.1)	55 (61.1)	103 (71.0)	165 (75.3)	193 (68.4)
Vasopressors	370 (50.3)	37 (41.1)	64 (44.1)	119 (54.3)	150 (53.2)
Lactate ≥2 mmol/L	345 (46.9)	40 (44.4)	68 (46.9)	109 (49.8)	128 (45.4)
Platelets <100 000/μL	287 (39.0)	27 (30.0)	69 (47.6)	86 (39.2)	105 (37.2)
Invasive mechanical ventilation	273 (37.1)	59 (65.6)	66 (45.5)	78 (35.6)	70 (24.8)
Creatinine ≥2 times baseline	252 (34.2)	33 (36.7)	52 (35.9)	66 (30.1)	101 (35.8)
Altered mental status	175 (23.8)	29 (32.2)	35 (24.1)	57 (26.0)	54 (19.1)
Noninvasive positive pressure ventilation	104 (14.1)	12 (13.3)	20 (13.8)	32 (14.6)	40 (14.2)
Total bilirubin ≥2 times baseline and ≥2 mg/dL	72 (9.8)	7 (7.8)	12 (8.3)	14 (6.4)	39 (13.8)
SIRS[d]	727 (98.8)	88 (97.8)	144 (99.3)	217 (99.1)	278 (98.6)
Days in hospital, median (IQR)[e]	10 (5–22)	12 (5–29)	14 (7–30)	10 (6–20)	7 (4–17)
Sepsis listed in the discharge summary[f]	483 (65.6)	54 (60.0)	76 (52.4)	153 (69.9)	200 (70.9)
Location to which patient was discharged from the hospital					
Private residence	587 (79.8)	65 (72.2)	112 (77.2)	185 (84.5)	225 (79.8)
Deceased	74 (10.1)	14 (15.6)	16 (11.0)	17 (7.8)	27 (9.6)
Another acute care hospital	33 (4.5)	8 (8.9)	10 (6.9)	5 (2.3)	10 (3.5)
Long-term acute care hospital or long-term care facility	21 (2.9)	1 (1.1)	2 (1.4)	7 (3.2)	11 (3.9)
Other or unknown	21 (2.9)	2 (2.2)	5 (3.4)	5 (2.3)	9 (3.2)
Died within 90 d of sepsis diagnosis	84 (11.4)	17 (18.9)	18 (12.4)	17 (7.8)	32 (11.3)

Data are presented as No. (%).

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SIRS, systemic inflammatory response syndrome.

[a]Three patients had sepsis diagnosis dates predating the day of admission; for 2 patients, the sepsis diagnosis date was the day before hospital admission. These were included in the analysis. For 1 patient the day of sepsis diagnosis was reported to be 6 days before admission. This appeared to be a data entry error and was changed to the day of hospital admission for analysis purposes.

[b]Admission and/or discharge dates from the ICU were missing for 11 patients: 1 patient in the age group 30 days–11 months, 3 patients in the age group 1–4 years, 5 patients in the age group 5–12 years, and 2 patients in the age group 13–21 years.

[c]During the period defined by the 7 days before and 7 days after sepsis diagnosis.

[d]Criteria of the systemic inflammatory response syndrome (SIRS) were assessed each day during the 3-day period defined by the day before sepsis diagnosis through the day after sepsis diagnosis. SIRS was defined as described by Goldstein and colleagues [17]. Patients aged 30 days–17 years had to meet either the temperature criterion (>38.5°C or <36°C) or the age-based white blood cell count criterion, plus 1 additional age-based criterion. Adult SIRS criteria were used for patients who were 18–21 years old [18].

[e]Hospital discharge date missing for 2 patients.

[f]Data missing for 6 patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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