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Bacterial and fungal etiology of sepsis in children in the United States: reconsidering empiric therapy

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Abstract

Objective: Timely empiric antimicrobial therapy is associated with improved outcomes in pediatric sepsis, but minimal data exist to guide empiric therapy. We sought to describe the prevalence of four pathogens that are not part of routine empiric coverage (eg *Staphylococcus aureus, Pseudomonas aeruginosa, Clostridium difficile,* and fungal infections) in pediatric sepsis patients in a contemporary nationally representative sample.

Design: This was a retrospective cohort study using administrative data.

Setting: We used the Nationwide Readmissions Database from 2014, which is a nationally representative dataset that contains data from nearly half of all discharges from nonfederal hospitals in the United States.

Patients: Discharges of patients who were less than 19 years old at discharge and were not neonatal with a discharge diagnosis of sepsis.

Interventions: None

Measurements and Main Results: Of the 19,113 pediatric admissions with sepsis (6,300 [33%] previously healthy and 12,813 [67%] with a chronic disease), 31% received mechanical ventilation, 19% had shock, and 588 (3.1%) died during their hospitalization. Among all admissions, 8,204 (42.9%) had a bacterial or fungal pathogen identified. *Staphylococcus aureus* was the most common pathogen identified in previously healthy patients (n=593, 9.4%) and those

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with any chronic disease (n=1,430, 11.1%). Methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa, Clostridium difficile* and fungal infections all had high prevalence in specific chronic diseases associated with frequent contact with the healthcare system, early surgery, indwelling devices, or immunosuppression.

Conclusions: In this nationally representative administrative database, the most common identified pathogen was *Staphylococcus aureus* in previously healthy and chronically ill children. In addition, a high proportion of children with sepsis and select chronic diseases had infections with methicillin-resistant *Staphylococcus aureus,* fungal infections, *Pseudomonas* infections, and *Clostridium difficile*. Clinicians caring for pediatric patients should consider coverage of these organisms when administering empiric antimicrobials for sepsis.

Keywords

Sepsis; empiric antimicrobials; pediatric; chronic disease; immune suppression

Introduction

Appropriate broad-spectrum antimicrobial therapy remains a cornerstone of effective sepsis treatment (1) and is associated with lower mortality when administered with early fluid resuscitation (2). Administration of inappropriate antimicrobials is associated with higher mortality in adult patients with septic shock (3). A recent global point prevalence study limited to patients admitted to pediatric intensive care units (ICUs) with severe sepsis or septic shock (4) found that *Staphyloccocus aureus* (15%), *Pseudomonas* (7.9%), and fungi (13.4%) are common pathogens. The empiric coverage of these infections for all sepsis patients is not currently recommended in pediatric sepsis guidelines (5), and may increase the prevalence of multidrug resistant organisms and adverse drug-related events if administered inappropriately. Little data currently exist to guide empiric antimicrobial administration in pediatric sepsis, particularly with respect to previously healthy patients or those with specific chronic diseases, although implementation of a risk-based protocol based on chronic disease profile has shown improvement in appropriate empiric antimicrobial therapy for pediatric patients with sepsis in a single-center study (6).

The bacterial pathogens that cause sepsis in healthy children in the US have changed in the last twenty years, with a rising prevalence of *Staphylococcus aureus* and a falling prevalence of vaccine-preventable pathogens (7–9). In addition, most children with sepsis now have at least one chronic disease (4, 9, 10), prior exposure to healthcare, immunosuppression, or invasive devices. These patients are at high risk for colonization and infection with drug-resistant or hospital-acquired organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, *Pseudomonas* species, and fungal infections (11–13). We sought to describe the epidemiology of these infections in pediatric patients with sepsis to assist clinicians in determining which patients may need coverage for these pathogens, because these pathogens are not part of routine empiric antimicrobial coverage for sepsis in children. We used a threshold of 10% or higher prevalence of these pathogens to recommend empiric coverage of these pathogens. While there is minimal guidance for a specific threshold for empiric antimicrobials in sepsis, we chose 10% because the consequences of inappropriate antimicrobial therapy are high in this context and there is some survey-level

data to suggest that this is an acceptable threshold to clinicians caring for patients with sepsis(14).

Methods

Study design

We used a retrospective cohort design and the Nationwide Readmissions Database (NRD) (15) from 2014, which is a multi-state administrative Health Care Utilization Project (HCUP) dataset that includes data from 49% of all hospital admissions in the United States. The NRD includes data from 21 states for patients 1 through 18 years of age and data from 9 of these states for patients <1 year old. All admissions from the calendar year of 2014 were considered for inclusion. This study was deemed exempt by our institutional review board.

Clinical characteristics

We excluded neonatal patients using administrative codes 760-779 because neonatal sepsis is a distinct clinical entity. We described ages of patients by age group as <1 year old, 1-4 years old, 5-12 years old, and 13-18 years old. We described insurance as public, private, or other, and hospital type as urban academic, urban non-academic and rural using classifications in the dataset. We described organ failure using administrative codes and illness severity using the all patients refined diagnosis-related groups (APRDRG) methodology, a proprietary system for classifying illness severity and mortality risk in administrative datasets. Mechanical ventilation was defined as invasive mechanical ventilation by ICD-9 procedure codes, and shock was defined using explicit ICD-9 codes. We described in-hospital mortality among previously healthy patients and those with and without cancer or bone marrow transplant. We separated patients with cancer for mortality analysis because refractory or relapsed cancer is a known risk factor for mortality in these patients, which may reflect end-stage disease or alterations in goals of care (16). We defined sepsis in the cohort using previously described methods for identification of sepsis using administrative data, including International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes for infection and organ dysfunction (17) in the first 15 diagnosis fields and ICD-9 CM codes for sepsis, severe sepsis and septic shock (ICD-9 CM codes 995.91, 995.92 and 785.52) in the first 25 diagnosis fields.

Chronic disease classification

We classified patients with chronic diseases using the pediatric complex chronic conditions classification (PCCC) system, version 2 (18). We subclassified the chronic diseases in the PCCC into a total of 32 classifications based on presumed risk of infection with the identified pathogens of interest. We chose groups of diagnoses within the PCCC that were expected to result in immunosuppression because of disease treatment (i.e. cancer, solid organ transplant, inflammatory bowel disease), congenital or inherited immune deficiencies, indwelling devices, and congenital or structural anomalies that may lead to increased risk for infection with resistant or uncommon organisms. A complete list of groups of diagnoses identified and ICD-9 codes used for identification is in Supplemental Table 1.

Microbiologic etiology

Within the cohort, we described the incidence of admissions with diagnostic codes for *Staphylococcus aureus* including MRSA, *Clostridium difficile*, *Pseudomonas aeruginosa*, and fungal infections. We also evaluated infections with other organisms, including codes for other drug-resistant organisms and other common bacterial infections (Supplemental Table 2). We also classified site of infection and described the relative prevalence of the described organisms based on site of infection. We classified an organism as being a cause of infection in a particular site based on codes for site-specific infection (i.e. ICD-9 CM 481 for *Pneumococcal* pneumonia) or if there were separate codes for infection with a specific organism and infection of a specific site (i.e. ICD-9 CM 008.5 for bacterial enteritis with unspecified organism and ICD-9 code 038.43 for septicemia due to Pseudomonas). We counted the first three etiologic organisms and sites in the dataset.

Statistical analysis

Among admissions with sepsis, we reported frequencies of infections by causative pathogens using ICD-9 codes (Table 4). If there was more than one administrative code identifying the same pathogen in multiple sites, it was counted as a single etiology of infection. If multiple pathogens were identified, the first three distinct pathogens were counted individually. We followed the same strategy for site identification. We reported frequencies and percent of each infection and site of infection stratified by chronic diseases. We described the chronic disease groups with more than 10% prevalence of any of the pathogen groups of interest. Patients could have more than one admission within the dataset, and we described each admission separately.

We determined community-acquired sepsis in two sensitivity analyses. First, we restricted the cohort to only the first admission of the year for given patients. We also performed a sensitivity analysis restricted to those patients with an infection or sepsis as their primary discharge diagnosis and excluded patients who were admitted for a planned reason (19) because prior studies suggest that this approach has reasonable sensitivity for identification of community-acquired sepsis (20). We also described the subset of patients with septic shock identified with explicit coding (785.52) because these patients are more likely to receive broad-spectrum empiric coverage, have a high mortality if inappropriate antimicrobials are administered (21), and some have recommended empiric MRSA coverage for all septic shock patients (22).

Results

Cohort characteristics

There were 940,467 non-neonatal admissions among patients 18 years of age or younger in the NRD in 2014, and 19,113 (2.0%) met criteria for sepsis. Of these, 1,784 (9.3%), 4,515 (23.6%), 4,929 (25.8%), and 7,885 (41.3%) were admissions among patients <1 year, 1-4 years, 5-12 years and 13-18 years, respectively (Table 1). Most (58.2%, n=11,099) had public insurance, and 16,892 (88.4%) were admitted to an urban academic hospital. A total of 6,028 (31.5%) admissions required mechanical ventilation, and 3,707 (19.4%) had shock. The median length of stay was 6 days (interquartile range [IQR] 3-14 days) and the hospital

mortality was 3.1% (n=588), with 0.6% (n=35) among healthy patients, 3.6% (n=355) among those with non-cancer related chronic disease, and among patients with cancer or bone marrow transplant (n=2,916), hospital mortality was 6.8% (n=198). Using the APRDRG illness severity classification, 23.8% of the cohort had mild or moderate severity of illness, 35.6% had major severity of illness, and 40.5% had extreme severity of illness. Within the cohort, 10,908 (57.1%) of admissions did not have a bacterial or fungal pathogen identified, 5,890 (30.8%) had 1 pathogen, 1,683 (8.8%) had 2 pathogens, and 632 (3.3%) had 3 or more pathogens identified.

Among children hospitalized with sepsis, 67.0% (n=12,811) of admissions had at least one chronic disease (Table 1). Approximately 31% (n=6,025) had an indwelling device, 2,729 (14.3%) had congenital heart disease, 1,361 (7.1%) had a hematologic malignancy, 843 (4.4%) had a solid organ transplant, 668 (3.5%) had a congenital or acquired immune deficiency, 656 (3.4%) had dialysis-dependent renal failure, and 471 (2.5%) had undergone bone marrow transplant.

Common pathogens

Among admissions of previously healthy patients (n=6,300), the most common pathogen was *Staphylococcus aureus* (n=593, 9.4%) with 40.5% (n=240) identified as MRSA. Other common pathogens in this population included *Escherichia coli* (n=446, 7.1%) and *Streptococcus* species other than *Streptococcus pneumonaie* (n=399, 6.3%) (Table 2). Among admissions of patients with any chronic disease (n=12,811), the most common pathogen was also *Staphylococcus aureus* (n=1,410, 11.0%) with 38.6% (n=544) identified as MRSA, followed by *Candida* species (n=1,250, 9.8%) and *Pseudomonas aeruginosa* (n=1,034, 8.1%; Table 2).

Pathogens of interest among select chronic diseases

The chronic disease groups that had a prevalence of >10% of the pathogens of interest included patients with bone marrow transplant, hematologic or solid cancer, tracheostomy, ventriculoperitoneal shunt, congenital heart disease, congenital hematologic or immunologic disease, short bowel syndrome, and dialysis dependence (Table 3).

Devices

Among patients with tracheostomy (n=2,514, 13.1%), 594 (23.6%) had *Pseudomonas aeruginosa* infections. Admissions of patients with a neurologic shunt (n=1,050, 5.5%) also commonly involved *Pseudomonas aeruginosa* (n=130, 12.4%) and fungal infections (n=133, 12.7%). Patients with ventricular assist devices or pacemakers (n=631) commonly had fungal infections (n=122, 19.3%). Mortality for the pathogens of interest among patients with devices ranged from 1.3%-11.4%, with the highest among patients with cardiac devices and fungal infections.

Hematologic disease and cancer

Patients with bone marrow transplant (n=471) or hematologic cancer (n=1,361) commonly had *Clostridium difficile* (n=77, 16.3% and n=198,14.5% respectively) and fungal infections (n= 97, 20.6% and n=311, 22.9%, respectively). Among patients with other cancer

(n=1,084), *Clostridium difficile* and fungal infections were also common (n=126, 11.6% and n=198, 11.6% respectively). Patients with non-malignant hematologic or immunologic conditions (n=2,530) also had a high proportion of fungal infections (n=429, 17.0%). Mortality for the pathogens of interest among patients with these conditions ranged from 3.8%-12.4%, with the highest among patients with fungal infections and non-malignant hematologic or immunologic conditions.

Other chronic diseases

Patients with congenital heart disease (without cardiac devices or heart transplant, n=2,729) also had a high rate of fungal infections (n=300, 11.0%). Among patients with dialysis-dependent renal failure (n=467), 89 (19.1%), had a fungal infection. Patients with chronic respiratory disease without tracheostomy (n=1,448) commonly had infections with *Pseudomonas aeruginosa* (n=327, 22.6%). Patients with short bowel syndrome (n=634) had a high prevalence of fungal infections (n=149, 23.5%). Patients with chronic neurologic disease (n=4,595) also had a high rate of infection with *Pseudomonas aeruginosa* (n=645, 14.0%) and fungal infections (n=469, 10.2%). Mortality in these groups was above 10% in patients with congenital heart disease (11.3%) and dialysis-dependent renal failure (33.7%).

Sites of infection

In the overall cohort, the most common site of infection was the lower respiratory tract (n=5,553, 29.1% of the entire cohort). The next most common site was the urinary tract (n=3,846, 20.1% of the entire cohort). The most common bacterial organism isolated from the respiratory tract was *Staphylococcus aureus* (n=807, 14.5% of lower respiratory tract infection, with 42.2% classified as MRSA), followed by *Pseudomonas aeruginosa* (n=745, 13.4%). Additional details of infection types based on site of infection can be found in Table 4.

Because our methodology for identifying cause of infectious site by specific pathogens could have led to some misclassifications, we highlighted unusual and possibly erroneous identifications in Table 4, such as lower respiratory tract infections caused by *Clostridium difficile*. Because of the structure of the database, it was not possible to identify whether these represented coding errors, a second episode of infection during the same hospitalization, or unusual infections. Overall, 5.8% (1,102 of 19,113) were identified as unusual and possibly erroneous (Table 4).

Sensitivity analyses

Among admissions that were unplanned and the first of the year for patients (n=16,248, 85.0%), pathogen prevalence results were similar to the overall cohort across chronic disease strata (Supplemental Table 3). These patients had a slightly higher illness severity but similar mortality rates. We also observed similar results among patients with a sepsis or infection code in the primary discharge diagnosis field (n=10,299, 53.9%) (Supplemental Table 3), with the exception of fewer fungal pathogens noted. Similar pathogens were observed across chronic disease strata. While organ failure rates were similar, APRDRG illness severity was lower and hospital mortality was 2.2% (221 of 10,299). Similar to the overall cohort, 61.1%

(n=6,292) did not have a bacterial or fungal pathogen identified, 28.3% (n=2,910) had one, 7.8% (n=805) had two, and 2.8% (n=292) had three or more.

Among patients with an explicit diagnosis of septic shock (n=1,832), distribution of chronic disease was similar (n=495, 27.0% previously healthy and n=1,337, 73.0% with chronic disease). Hospital mortality was 10.3% (n=188), and 689 (37.6%) had at least one bacterial or fungal pathogen identified. Among pathogens of interest, 81 (4.4%) had MRSA, 55 (3.3%) had *Pseudomonas aeruginosa,* 74 (4.0%) had *Clostridium difficile*, and 56 (3.1%) had a fungal infection. The most common infection remained *Staphylococcus aureus* (n=193, 10.5%). The prevalence of other pathogens was similar across chronic disease strata in the septic shock group.

Discussion

This nationally representative pediatric cohort demonstrates a shift in infectious etiology from previously reported large cohorts of pediatric sepsis in the United States. *Staphylococcus aureus* was the most common documented infection in our overall cohort and most subgroups, including previously healthy patients, and all pediatric patients with evidence of sepsis and a compatible primary source should receive adequate coverage for *Staphylococcus aureus.* Prior studies using administrative data have noted poor correlation of administrative coding for MRSA with documented MRSA infection (23, 24). Most of our subgroups did not meet our threshold, but between a third and a half of patients with a *Staphylococcus aureus* infection were identified as having MRSA. Therefore, we do not recommend empiric MRSA coverage for all pediatric patients with sepsis, but given the high virulence of this pathogen (25–27), clinicians should consider empiric MRSA coverage based on local prevalence patterns and severity of illness.

Given that most pediatric patients with sepsis now have at least one underlying chronic disease (4, 8–10), empiric antimicrobial therapy should be tailored to the most likely pathogens in specific subpopulations. Among other pathogens of interest, our data suggest that empiric antimicrobials should include coverage for *Pseudomonas aeruginosa* in patients with indwelling devices and chronic respiratory and neurologic conditions, and *Clostridium difficile* in patients with cancer and bone marrow transplant patients and a compatible source. We identified patients with several chronic diseases that are at high risk for fungal infections, including congenital heart and hematologic disease, indwelling devices, and short bowel syndrome. While the prevalence of resistant Gram negative infections, including extended-spectrum beta-lactamase producing organisms, *Acinetobacter* species, and carbapanem-resistent *Enterobacteriaceae* organisms has been increasing in some studies, prior evaluations have shown poor identification of these pathogens in administrative datasets using ICD-9 codes, which we also observed in our data (28). While our findings suggest that coverage of Pseudomonas, *Clostridium difficile*, and fungal infections should be considered for select group of patients with sepsis, it is important to de-escalate antimicrobial therapy once culture results are obtained.

Our study has several strengths. We used a well-described and inclusive methodology for the identification of all pediatric patients with sepsis. The size of the database allows for

description of the etiology of sepsis in multiple subgroups of previously healthy and chronically ill children. This represents the first attempt to provide data for empiric antimicrobial selection in specific pediatric subpopulations.

Our study has several limitations. First, we used administrative codes and did not have culture results, site of culture, ICU admission status, or antimicrobial susceptibility data. We were unable to identify whether patients had received antimicrobials prior to the identification of an infection, or whether some infections were nosocomial. In addition, our methodology may have misclassified some positive cultures that were reflective of colonization as pathogenic. We also identified *Clostridium difficile* infections using administrative codes, some of which may represent colonization rather than gold-standard testing. Second, it is possible that mortality in some chronically ill patients, especially patients with cancer, was due to the underlying disease and not due to the sepsis episode. We therefore described mortality separately in patients with and without malignancy. Third, we identified sepsis using administrative data (29) and it is possible that some patients were misclassified. We attempted to address this limitation by performing a sensitivity analysis using only those admissions with an infection or sepsis as their primary diagnosis because prior studies suggest that approximately 90% of sepsis admissions identified using similar methodology in adults involved admissions for sepsis (30). Fourth, prior studies report higher hospital mortality when limited to patients with severe sepsis or septic shock and admitted to the PICU (4, 9). In contrast, we included all patients with sepsis. We did perform a sensitivity analysis of the group of patients with septic shock, and found similar results to the overall cohort, with a slightly higher rate of *Staphylococcus aureus* including MRSA. Fifth, we used the 10% threshold to identify chronic diseases where the prevalence of a pathogen was high. While this number is somewhat arbitrary, the prevalence in some cases exceeded 20%, and the consequences of inappropriate empiric antimicrobial therapy are high in this population. Finally, our results should serve as a guide to select initial antimicrobial therapy and local prevalence and antimicrobial resistance patterns should be considered whenever available. These data are from patients in the United States and may not be applicable internationally.

Conclusions

Clinicians caring for pediatric patients should consider empiric coverage for *Staphylococcus aureus* in seriously ill patients with sepsis, regardless of chronic disease status, who have a compatible primary source. In addition, they should consider the chronic disease profile in addition to the clinical presentation and primary site of infection when selecting initial antimicrobials for pediatric patients with sepsis. Coverage of MRSA, Pseudomonas, *Clostridium difficile*, and fungal infections may be appropriate in patients with select chronic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Singer M, Deutschman CS, Seymour CW, et al.: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315:801–10 [PubMed: 26903338]
2. Evans IVR, Phillips GS, Alpern ER, et al.: Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. JAMA 2018; 320:358 [PubMed: 30043064]
3. Kumar A, Ellis P, Arabi Y, et al.: Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock. Chest 2009; 136:1237–1248 [PubMed: 19696123]
4. Weiss SL, Fitzgerald JC, Pappachan J, et al.: Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015; 191:1147–57 [PubMed: 25734408]
5. Dellinger RP, Levy MM, Rhodes A, et al.: Surviving Sepsis Campaign. Crit Care Med 2013; 41:580–637 [PubMed: 23353941]
6. Karsies TJ, Sargel CL, Marquardt DJ, et al.: An Empiric Antibiotic Protocol Using Risk Stratification Improves Antibiotic Selection and Timing in Critically Ill Children. Ann Am Thorac Soc 2014; 11:1569–1575 [PubMed: 25402656]
7. Watson RS, Carcillo JA, Linde-Zwirble WT, et al.: The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003; 167:695–701 [PubMed: 12433670]
8. Hartman ME, Linde-Zwirble WT, Angus DC, et al.: Trends in the Epidemiology of Pediatric Severe Sepsis. Pediatr Crit Care Med 2013; 14:686–693 [PubMed: 23897242]
9. Balamuth F, Weiss SL, Neuman MI, et al.: Pediatric severe sepsis in U.S. children's hospitals. Pediatr Crit Care Med 2014; 15:798–805 [PubMed: 25162514]
10. Prout AJ, Talisa VB, Carcillo JA, et al.: Children with Chronic Disease Bear the Highest Burden of Pediatric Sepsis. J Pediatr 2018; 199:194–99 [PubMed: 29753542]
11. Toltzis P, Hoyen C, Spinner-Block S, et al.: Factors that predict preexisting colonization with antibiotic-resistant gram-negative bacilli in patients admitted to a pediatric intensive care unit. Pediatrics 1999; 103:719–23 [PubMed: 10103292]
12. Renk H, Stoll L, Neunhoeffer F, et al.: Suspicion of respiratory tract infection with multidrug-resistant Enterobacteriaceae: epidemiology and risk factors from a Paediatric Intensive Care Unit. BMC Infect Dis 2017; 17:163 [PubMed: 28222699]
13. Folgori L, Bernaschi P, Piga S, et al.: Healthcare-Associated Infections in Pediatric and Neonatal Intensive Care Units: Impact of Underlying Risk Factors and Antimicrobial Resistance on 30-Day Case-Fatality in Italy and Brazil. Infect Control Hosp Epidemiol 2016; 37:1302–09 [PubMed: 27511591]
14. Cressman AM, MacFadden DR, Verma AA, et al.: Empiric Antibiotic Treatment Thresholds for Serious Bacterial Infections: A Scenario-based Survey Study. Clin Infect Dis 2018; 69:930–37
15. NRD Overview [Internet]. [cited 2017 Mar 20] Available from: https://www.hcup-us.ahrq.gov/nrdoverview.jsp
16. Sano H, Kobayashi R, Iguchi A, et al.: Risk factors for sepsis-related death in children and adolescents with hematologic and malignant diseases. J Microbiol Immunol Infect 2017; 50:232–238 [PubMed: 26055687]
17. Angus DC, Linde-Zwirble WT, Lidicker J, et al.: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303–10 [PubMed: 11445675]

18. Feudtner C, Feinstein JA, Zhong W, et al.: Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 2014; 14:199 [PubMed: 25102958]
19. Nakamura MM, Zaslavsky AM, Toomey SL, et al.: Pediatric Readmissions After Hospitalizations for Lower Respiratory Infections. Pediatrics 2017; 140(2):e20160938 [PubMed: 28771405]
20. Gedeborg R, Furebring M, Michaëlsson K: Diagnosis-dependent misclassification of infections using administrative data variably affected incidence and mortality estimates in ICU patients. J Clin Epidemiol 2007; 60(2):155–62 [PubMed: 17208121]
21. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al.: Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003; 31:2742–51 [PubMed: 14668610]
22. Weiss S: Septic shock in children: Rapid recognition and initial resuscitation (first hour) - UpToDate [Internet]. www.uptodate.com [cited 2018 Aug 22] Available from: https://www.uptodate.com/contents/septic-shock-in-children-rapid-recognition-and-initial-resuscitation-first-hour
23. Schaefer MK, Ellingson K, Conover C, et al.: Evaluation of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Reporting Methicillin-Resistant Staphylococcus aureus Infections at a Hospital in Illinois. Infect Control Hosp Epidemiol 2010; 31:463–68 [PubMed: 20353360]
24. Schweizer ML, Eber MR, Laxminarayan R, et al.: Validity of ICD-9-CM coding for identifying incident methicillin-resistant Staphylococcus aureus (MRSA) infections: is MRSA infection coded as a chronic disease? Infect Control Hosp Epidemiol 2011; 32:148–54 [PubMed: 21460469]
25. Powers ME, Wardenburg JB: Igniting the Fire: Staphylococcus aureus Virulence Factors in the Pathogenesis of Sepsis. PLoS Pathog 2014; 10(2):e1003871 [PubMed: 24550724]
26. Powers ME, Becker REN, Sailer A, et al.: Synergistic Action of Staphylococcus aureus α-Toxin on Platelets and Myeloid Lineage Cells Contributes to Lethal Sepsis. Cell Host Microbe 2015; 17:775–87 [PubMed: 26067604]
27. Randolph AG, Xu R, Novak T, et al.: Vancomycin Monotherapy May Be Insufficient to Treat Methicillin-resistant Staphylococcus aureus Coinfection in Children With Influenza-related Critical Illness. Clin Infect Dis 2019; 18;68(3):365–372
28. Flokas ME, Karanika S, Alevizakos M, et al.: Prevalence of ESBL-Producing Enterobacteriaceae in Pediatric Bloodstream Infections: A Systematic Review and Meta-Analysis. PLoS One 2017; 12(1):e0171216 [PubMed: 28141845]
29. Balamuth F, Weiss SL, Hall M, et al.: Identifying Pediatric Severe Sepsis and Septic Shock: Accuracy of Diagnosis Codes. J Pediatr 2015; 167:1295–1300 [PubMed: 26470685]
30. Liu V, Escobar GJ, Greene JD, et al.: Hospital Deaths in Patients With Sepsis From 2 Independent Cohorts. JAMA 2014; 312(1):90–92 [PubMed: 24838355]

Table 1.

Characteristics of the cohort

Variable	Admissions (n=19,113, %)	Mortality (n=588, %)
Demographic		
<1 year old	1,784 (9.3)	65 (3.6)
1-4 years old	4,514 (23.6)	125 (2.8)
5-12 years old	4,927 (25.8)	177 (3.6)
13-18 years old	7,879 (41.2)	221 (2.8)
Female	9,659 (50.6)	282 (2.9)
Public insurance	11,094 (58.2)	346 (3.1)
Chronic disease *		
Any chronic disease	12,804 (67.0)	553 (4.3)
Previously healthy	6,300 (33.0)	35 (0.6)
Bone marrow transplant	471 (2.5)	42 (8.9)
Hematologic malignancy	1,361 (7.1)	85 (6.3)
Other malignancy	1,084 (5.7)	71 (6.6)
Solid organ transplant	843 (4.4)	26 (3.1)
Neurologic disease	4,595 (24.0)	243 (5.3)
Congenital heart disease	2,729 (14.3)	211 (7.7)
Pulmonary disease	1,448 (7.6)	68 (4.7)
Dialysis dependent renal failure	656 (3.4)	96 (14.6)
Other renal disease	1,160 (6.1)	28 (2.4)
Short bowel syndrome	636 (3.3)	29 (4.6)
Other gastrointestinal disease	653 (6.7)	24 (3.7)
Congenital or acquired immunodeficiency	668 (3.5)	44 (6.6)
Other hemato/immunologic disease	2,044 (10.7)	114 (5.6)
Any device	6,025 (31.5)	252 (4.2)
Tracheostomy	2,514 (13.2)	76 (3.0)
G or GJ tube	4,520 (23.6)	149 (3.3)
Neurologic shunt	1,050 (5.5)	69 (6.6)
Ventricular assist device or pacemaker	631 (3.3)	40 (6.3)
Other device	488 (2.6)	21 (4.3)
All other chronic diseases	4,448 (23.3)	219 (4.9)
Acute organ failure		
Mechanical ventilation	6,023 (31.5)	470 (7.8)
Shock	3,704 (19.4)	253 (6.8)
Acute kidney injury	2,718 (14.2)	162 (6.0)
Neurologic failure	1,616 (8.5)	76 (4.7)
Hepatic failure	222 (1.2)	54 (24.3)
Hematologic failure	3,550 (18.6)	185 (5.2)
APRDRG Illness Severity		
Mild/moderate severity	4,545 (23.8)	8 (0.2)

Variable	Admissions (n=19,113, %)	Mortality (n=588, %)
Major severity	6,793 (35.6)	34 (0.5)
Extreme severity	7,730 (40.5)	545 (7.1)

*Because patients could have more than one chronic disease, percentages add to more than 100%.

Table 2.

Prevalence of all pathogens among previously healthy patients and those with a chronic disease.

Pathogen	Previously healthy patients (n=6,300, %)	Any chronic disease (n=12,804, %)
Staphylococcus aureus	353 (5.6)	886 (6.9)
Methicillin-resistant *Staphylococcus aureus*	240 (3.8)	544 (4.2)
Other *Staphylococcus* species	57 (0.9)	258 (2.0)
Streptococcus pneumonaiae	102 (1.6)	220 (1.7)
Other *Streptococcus* species	399 (6.3)	907 (7.1)
Clostridium difficile	69 (1.1)	796 (6.2)
Klebsiella species	40 (0.6)	404 (3.2)
Escherichia coli	446 (7.1)	719 (5.6)
Haemophilus influenzae	89 (1.4)	180 (1.4)
Proteus mirabilis	13 (0.2)	87 (0.7)
Pseudomonas aeruginosa	51 (0.8)	1,034 (8.1)
Other Gram negative rods	111 (1.8)	775 (6.0
Fungal infections	234 (3.7)	1,512 (11.8)
Anaerobic infections	24 (0.4)	62 (0.5)

Table 3:

Prevalence of pathogens of interest among all admissions and chronic disease groups with greater than 10% occurrence*

	MRSA**	Pseudomonas aeruginosa	Fungal infections	Clostridium difficile
All patients	783 (4.1)	1,085 (5.7)	1,746 (9.1)	865 (4.5)
Previously healthy	240 (3.8)	51 (0.8)	234 (3.7)	69 (1.1)
Any chronic disease	543 (4.2)	1,034 (8.1)	1,512 (11.8)	796 (6.2)
Bone marrow transplant	17 (3.6)	8 (1.7)	97 (20.6)	77 (16.3)
Hematologic malignancy	20 (1.5)	21 (1.5)	311 (22.9)	198 (14.5)
Solid tumor	26 (2.4)	39 (3.6)	197 (18.2)	126 (11.6)
Solid organ transplant	15 (1.8)	34 (4.0)	72 (8.5)	54 (6.4)
Short bowel syndrome	15 (2.4)	26 (4.1)	149 (23.5)	27 (4.3)
Congenital heart disease	134 (4.9)	211 (7.7)	300 (11.0)	138 (5.1)
Chronic respiratory disease	144 (9.9)	327 (22.6)	139 (9.6)	60 (4.1)
Renal failure, dialysis-dependent	18 (2.7)	24 (3.7)	89 (13.5)	43 (6.6)
Chronic neurologic or neuromuscular disease	239 (5.2)	645 (14.0)	469 (10.2)	245 (5.3)
Hematologic or immunologic conditions	82 (3.2)	92 (3.6)	429 (17.0)	223 (8.8)
Tracheostomy	197 (7.8)	594 (23.6)	228 (9.1)	137 (5.4)
Cardiac devices	29 (4.6)	36 (5.7)	122 (19.3)	53 (8.4)
Neurologic shunt	66 (6.3)	130 (12.4)	133 (12.7)	56 (5.3)

*Chronic disease groups are not mutually exclusive between organ systems, but are exclusive within organ systems

**Methicillin-resistant *Staphylococcus aureus*

Table 4:

Common pathogens and associated sites of infection for the entire cohort (percent of the site of infection). Infections that could not be attributed to the pathogens are highlighted in red.

Organism	Bloodstream infection	Meningitis	Endocarditis	Skin and soft tissue infection	Pneumonia or tracheitis	Intestinal or peritoneal	UTI	Device	Osteomyelitis
Staphylococcus aureus (not MRSA)	116 (16.0)	35 (8.5)	36 (37.5)	205 (15.2)	466 (8.4)	77 (3.1)	125 (3.3)	250 (14.5)	104 (28.7)
Methicillin-resistant Staphylococcus aureus	46 (6.3)	14 (3.4)	11 (11.5)	193 (14.3)	341 (6.1)	37 (1.5)	86 (2.2)	95 (5.5)	81 (22.4)
Other Staphylococcus species	73 (10.1)	9 (2.2)	3 (3.1)	19 (1.4)	53 (1)	28 (1.1)	53 (1.4)	124 (7.2)	8 (2.2)
Streptococcus pneumonaie	17 (2.3)	36 (8.7)	2 (2.1)	3 (0.2)	219 (3.9)	18 (0.7)	25 (0.7)	18 (1)	3 (0.8)
Other streptococcus species	132 (18.2)	97 (23.5)	12 (12.5)	123 (9.1)	278 (5)	113 (4.6)	307 (8)	228 (13.2)	51 (14.1)
Clostridium difficile	24 (3.3)	11 (3.1)	1 (1.0)	31 (2.3)	154 (2.8)	865 (35.3)	98 (2.5)	95 (5.5)	5 (1.4)
Other anaerobic organisms	3 (0.4)	1 (0.2)	0 (0)	8 (0.6)	17 (0.3)	24 (1.0)	12 (0.3)	16 (0.9)	3 (0.8)
Klebsiella pneumonaie	56 (7.7)	7 (1.7)	1 (1)	16 (1.2)	178 (3.2)	45 (1.8)	198 (5.1)	79 (4.6)	7 (1.9)
Escherischia coli	81 (11.2)	9 (2.2)	2 (2.1)	28 (2.1)	188 (3.4)	124 (5.1)	879 (22.9)	78 (4.5)	10 (2.8)
Haemophilus influenzae	9 (1.2)	14 (3.4)	0 (0)	5 (0.4)	205 (3.7)	8 (0.3)	13 (0.3)	4 (0.2)	2 (0.6)
Proteus mirabilis	5 (0.7)	3 (0.7)	0 (0)	6 (0.4)	38 (0.7)	9 (0.4)	45 (1.2)	6 (0.3)	3 (0.8)
Pseudomonas aeruginosa	50 (6.9)	9 (2.2)	3 (3.1)	52 (3.8)	745 (13.4)	75 (3.1)	194 (5)	92 (5.3)	11 (3)
Other Gram negative rods	86 (11.9)	34 (8.2)	2 (2.1)	37 (2.7)	507 (9.1)	50 (2.0)	201 (5.2)	91 (5.3)	4 (1.1)
Candida species	65 (9)	35 (8.5)	6 (6.3)	95 (7)	363 (6.5)	160 (6.5)	182 (4.7)	218 (12.6)	17 (4.7)
Aspergillus species	3 (0.4)	4 (1)	0 (0)	7 (0.5)	15 (0.3)	7 (0.3)	7 (0.2)	12 (0.7)	0 (0)
Other fungal species	15 (2.1)	5 (1.2)	2 (2.1)	18 (1.3)	41 (0.7)	35 (1.4)	20 (0.5)	60 (3.5)	4 (1.1)
No known pathogen	N/A	88 (21.3)	15 (15.6)	506 (37.4)	1,742 (31.4)	782 (31.8)	1,399 (36.4)	259 (15.0)	49 (13.5)
Total (percentage of cohort)	**725 (3.8)**	**413 (2.2)**	**96 (0.5)**	**1,352 (7.1)**	**5,550 (29.1)**	**2,452 (12.9)**	**3,844 (20.1)**	**1,725 (9.0)**	**362 (1.9)**