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Clinical Characteristics and Antibiotic Utilization in Pediatric Patients Hospitalized with Acute Bacterial Skin and Skin Structure Infection

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Abstract

Background—Hospitalizations for acute bacterial skin and skin structure infection (ABSSSI) in children are increasingly frequent, but little is known about antibiotic utilization. In adults, recent studies suggest substantial opportunity to reduce broad-spectrum antibiotic use and shorten therapy. We sought to determine whether similar opportunity exists in children.

Methods—This was a planned secondary analysis of a pediatric cohort taken from a multicenter, retrospective cohort of patients hospitalized for ABSSSI between June 1, 2010 and May 31, 2012. The pre-specified primary endpoint was a composite of two prescribing practices: 1) use of antibiotics with broad Gram-negative activity, or 2) treatment duration >10 days.

Results—102 patients 18 years old were included: 43 had non-purulent cellulitis, 19 had wound infection or purulent cellulitis, and 40 had cutaneous abscess. The median age was 5 years (range 45 days to 18 years). Clindamycin was the most frequently prescribed antibiotic during hospitalization (67% of cases) and at discharge (66% of cases). The median duration of therapy was 11 days (interquartile range 10 – 12) and was similar for all three types of ABSSSI. The

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primary endpoint occurred in 67% of cases, including broad Gram-negative therapy in 25% and treatment duration >10 days in 61%. By multivariate logistic regression, admission via an emergency department and management by a medical (vs. surgical) service were independently associated with the primary endpoint.

Conclusions—Children hospitalized for ABSSSI are frequently exposed to antibiotics with broad Gram-negative activity or treated longer than 10 days suggesting opportunity to reduce antibiotic use.

Keywords

Acute bacterial skin and skin structure infection; skin and soft tissue infection; cellulitis; cutaneous abscess; antimicrobial stewardship

Introduction

Acute bacterial skin and skin structure infections (ABSSSI) are among the most common infections requiring hospitalization and exert a substantial burden on the health care system. In the United States, ABSSSI result in approximately 3 million pediatric health care visits per year.¹ With the emergence and epidemic of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), hospitalizations for ABSSSI among children have more than doubled over the last 15 years,^{2,3} now exceeding over 70,000 per year.³ Such hospitalizations have been associated with an increasing cost of care and need for invasive procedures.³

Understanding current antibiotic prescribing patterns for common infections is essential to improving antibiotic use in hospitals. Despite the increasing frequency of hospitalizations for ABSSSI among children, there are limited data regarding antibiotic utilization in such cases. One study demonstrated that in children hospitalized with *S. aureus* skin and soft tissue infections, use of clindamycin has substantially increased while use of β -lactams has declined in the era of CA-MRSA.⁴ In adults, recent studies have demonstrated frequent use of overly broad-spectrum antibiotic regimens and prolonged treatment durations suggesting substantial opportunity to reduce unnecessary antibiotic use.^{5–8} We sought to evaluate whether similar opportunity existed in pediatric patients. The objectives of this study were to describe antibiotic prescribing practices in pediatric patients hospitalized with ABSSSI and identify factors associated with use of broad-spectrum and prolonged treatment courses.

Methods

Study Design

We performed a multicenter, retrospective cohort of patients hospitalized for ABSSSI between June 1, 2010 and May 31, 2012 in seven academic and community hospitals in Colorado.⁹ The present study represents a planned subgroup analysis of pediatric patients.

Study Setting and Population

Of the seven hospitals that participated in the study, four provide pediatric care including a free-standing children's hospital, a public safety-net hospital with pediatric wards, and two

private community hospitals. Children aged 18 years or less with a principal discharge diagnosis of cellulitis, wound infection, or cutaneous abscess¹⁰ during the designated study period were included in the pediatric cohort. Cases were classified as (i) non-purulent cellulitis, (ii) wound infection or purulent cellulitis, or (iii) cutaneous abscess. The following cases were excluded: those with a co-existing infection requiring antibacterial therapy, surgical site infection, infected ulcer or bite, lymphadenitis, periorbital, perineal, or odontogenic infection, hospital-acquired infection, infected hidradenitis suppurativa, or involvement of deep tissue including fascia, muscle, bone, joint, or organ space. Patients who were less than 30 days old, refused medical care, transferred to or from another institution, pregnant, or incarcerated were also excluded.

Cohort Identification and Data Collection

Eligible cases were identified by casting a broad net of *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes (680.*, 681.*, 682.*, 686, 035). Cases were manually reviewed, and for those meeting study entry criteria, data on clinical characteristics, diagnostic tests, and treatment were abstracted using a standardized data collection instrument. Antibiotics prescribed at the time of hospital discharge were captured by pharmacy fill data, when available, or discharge medication lists. All available records of hospital and ambulatory care visits within a 45-day follow-up period from the date of hospitalization were reviewed to assess clinical outcomes.

Definitions and Study Outcomes

The pre-specified primary endpoint was a composite of two antibiotic prescribing practices suggestive of opportunity to reduce antibiotic use: 1) use of antibiotics with a broad spectrum of activity against aerobic Gram-negative pathogens, including β -lactam/ β -lactamase inhibitor combinations, 2nd through 5th generation cephalosporins, fluoroquinolones, carbapenems, tigecycline, aminoglycosides, or colistin, or 2) total treatment duration greater than 10 days. Given that short courses of antibiotics with Gram-positive activity are generally effective for ABSSSI, these two prescribing practices were selected as surrogate markers for opportunity to reduce unnecessary antibiotic use. Antibiotic therapy was analyzed by provider intention to treat, irrespective of what treatment actually occurred. Clinical failure was defined as any of the following within 45 days of hospitalization: (i) treatment failure, defined as a change in antibiotic therapy or unplanned drainage procedure due to inadequate clinical response more than 5 days after hospital admission; (ii) recurrence, defined as re-initiation of antibiotics for skin infection after completion of the initial treatment course; or (iii) re-hospitalization due to skin infection.⁵ Transitions from intravenous to oral antibiotic therapy and changes in therapy as a result of allergy, intolerance, or adverse drug effects were not classified as treatment failure.

Statistical Analysis

Comparisons between the three classifications of ABSSSI were performed using the Cochran-Mantel-Haenszel, ANOVA, or Kruskal-Wallis test. Multivariate logistic regression models were developed to identify factors associated with the composite primary endpoint and factors associated with use of antibiotics with broad Gram-negative activity and

treatment duration greater than 10 days separately. We performed bivariate analyses and retained variables with a P value ≤ 0.25 for inclusion in the regression models. We assessed for multicollinearity by calculating the variance inflation factor for each variable included in the final model. A P value of $< .05$ was considered significant. We used SAS Version 9.3 (SAS Institute, Cary, NC) for data analysis.

Results

Demographic and Clinical Characteristics

2842 eligible cases were initially identified by ICD-9-CM search. Of 1030 cases manually reviewed, 533 met study entry criteria. 102 of these patients were 18 years old or less and included in the pediatric cohort: 43 (42%) had non-purulent cellulitis, 19 (19%) had wound infection or purulent cellulitis, and 40 (39%) had cutaneous abscess (see Figure, Supplemental Digital Content 1). Eighty-four of these cases were reported from the free-standing children's hospital. The median age was 5 years (range 45 days to 18 years) (see Table, Supplemental Digital Content 2). Comorbid conditions assessed in this study were infrequent; however, prior skin infection was documented in 15% of cases and was particularly common among those with cutaneous abscess. Anatomical sites of infection varied, with the lower extremities and head or neck being most common (44% and 23%, respectively). Upper extremity involvement was more common in cases of non-purulent cellulitis ($p = .02$), while inguinal involvement was more common in cases of cutaneous abscess ($p = .008$). Most patients were admitted to a medical service (87 General Pediatrics, 4 Medicine), and surgical consultation was frequent. Infectious Diseases consultation did not occur in any cases.

Resource Utilization and Microbiology

Laboratory, radiographic, and microbiological data are presented in Supplemental Digital Content 3 (table). A microorganism was identified in 59 (67%) of 88 cases where at least one microbiological culture was obtained. Among cases with a positive culture, *S. aureus* was the most frequently identified pathogen (41 of 59, 69%), with a similar frequency of methicillin-susceptible *S. aureus* (MSSA) (32%) and MRSA (34%). Only one case was complicated by bacteremia (β -hemolytic streptococcus). In total, a Gram-positive organism was identified in 56 (95%) cases. A Gram-negative organism was identified in 5 (8%) cases; only one of these cases involved culture of a single organism. In the other four cases, Gram-negative organisms were isolated along with staphylococci (2), streptococci (1), or normal skin flora (1).

Antibiotic Utilization

In 35% of cases, an initial attempt at outpatient antibiotic therapy prior to hospitalization had failed, most commonly with cephalexin (17%), trimethoprim-sulfamethoxazole (10%), or clindamycin (10%) (see Table, Supplemental Digital Content 4). During the hospitalization, the initial empiric antibiotic regimen consisted of a combination of antibiotics in 21% of cases. Clindamycin or vancomycin were included in the initial regimen in 67% and 20% of cases, respectively. Vancomycin was more likely to be utilized in cases involving cutaneous abscess ($p = .005$). At the time of hospital discharge, a single antibiotic was prescribed in

87% of cases, most commonly clindamycin (66%), cephalexin (20%), or trimethoprim-sulfamethoxazole (11%). The median total duration of therapy was 11 days (interquartile range 10 – 12) and was similar for all three types of infection. Only 3% of patients were treated for 7 or fewer days, and only 7% were treated for more than 14 days.

The composite primary endpoint of use of antibiotics with broad Gram-negative activity or treatment duration greater than 10 days occurred in 67% of cases and was predominantly driven by treatment duration greater than 10 days (61% of cases) (Table 1). Although common among all three types of infection, the primary endpoint occurred somewhat more frequently in cases of wound infection or purulent cellulitis ($p = .08$). Antibiotics with broad Gram-negative activity were prescribed in 25% of cases, including only one of the five cases where a Gram-negative organism was identified. In cases where an antibiotic with broad Gram-negative activity was prescribed, these agents accounted for 32% of the total days of antibiotic therapy. The results of the primary endpoint and its individual components were unchanged when excluding 5 patients with immunosuppression from a hematologic malignancy, connective tissue disease or vasculitis, or an immunosuppressing medication (data not shown).

Logistic Regression Models

The multivariate logistic regression model revealed that admission via an emergency department and primary management by a medical (vs. surgical) service were independently associated with the composite primary endpoint (Figure 1). In separate models, head or neck involvement was independently associated with the use of antibiotics with broad Gram-negative activity (see Figure, Supplemental Digital Content 5), and admission via an emergency department and management by a medical service were independently associated with treatment duration longer than 10 days (see Figure, Supplemental Digital Content 6).

Clinical Outcomes

All patients survived to hospital discharge; follow-up medical encounters were documented most frequently in cases of cutaneous abscess ($p = .04$) (Table 2). Clinical failure occurred in 6% of all cases; incidence of treatment failure was significantly higher in cases of abscess than in the other types of ABSSSI ($p = .04$).

Discussion

In this cohort of pediatric patients hospitalized for ABSSSI, prescription of antibiotics with broad Gram-negative activity or treatment for longer than 10 days occurred in two-thirds of cases. Admission via an emergency department and primary management by a medical (vs. surgical) service were associated with broad Gram-negative therapy or treatment for longer than 10 days. Since the emergence of CA-MRSA, few studies have evaluated antibiotic utilization in pediatric patients hospitalized with ABSSSI. In one such study of children admitted to U.S. hospitals for *S. aureus* skin infections between 1999 and 2008, Herigon and colleagues demonstrated that use of clindamycin increased 3-fold while use of β -lactams markedly declined.⁴ However, this study was limited to *S. aureus* infections and only reported the use of oxacillin/nafcillin, cefazolin, and antibiotics with activity against MRSA.

In Canada, where the incidence of CA-MRSA was low, Kam and colleagues demonstrated frequent use of first-generation cephalosporins and other anti-staphylococcal penicillins, with less frequent use of clindamycin.¹¹ Neither of these studies reported the duration of therapy. Our study therefore adds to the prior literature through the inclusion of various types of ABSSI, providing more detailed data regarding antibiotic selection and duration of therapy, and identifying factors that influence prescribing patterns. Similar to the findings by Herigon and colleagues, clindamycin was the most commonly prescribed antibiotic in our study, with less frequent use of vancomycin.⁴ However, we also observed frequent use of agents with broad Gram-negative activity such as higher-generation cephalosporins (18% of cases) and β -lactam/ β -lactamase inhibitor combinations (15% of cases). In cases where antibiotics with broad Gram-negative activity were prescribed, they accounted for nearly one third of all antibiotic-days demonstrating that exposure to these agents was not trivial. This is particularly notable in that Gram-negative organisms were identified in only five cases. The fact that of these five cases, four involved polymicrobial growth, three involved cultures of wounds, and antibiotics with Gram-negative activity were administered in only one suggests that these Gram-negative organisms may not have been clinically relevant. Regardless, our findings do not support the routine use of antibiotics with broad Gram-negative activity and suggest the need to better educate pediatric providers regarding the microbiology of ABSSI and to develop interventions to promote the appropriate spectrum of therapy.

Several pediatric studies have suggested that adjunctive antibiotic therapy may not be necessary after abscess drainage in outpatients.^{12,13} To the best of our knowledge, there have been no clinical trials evaluating the appropriate duration of antibiotic therapy in children hospitalized with cutaneous abscess or other types of ABSSI. We found that treatment durations were relatively prolonged (median 11 days) in all three types of ABSSI, perhaps reflecting the lack of data to promote shorter durations of therapy. In adults, the available evidence suggests that courses of less than 7 days are as effective as longer courses.^{14,15} Although it is not known whether these findings can be extrapolated to children, shorter courses may be adequate since children with ABSSI have relatively few comorbid conditions and a low rate of clinical failure. Shortening the duration of therapy therefore represents an attractive option to reduce unnecessary antibiotic exposure in children. Our findings underscore the need to include children in future randomized trials to delineate the shortest effective duration of therapy for ABSSI.

We found it noteworthy that not a single pediatric case involved Infectious Diseases consultation, a sharp contrast to adult cases where Infectious Diseases consultation is common.⁹ This suggests that the vast majority of pediatric cases were uncomplicated and responded rapidly to treatment, supporting the assertion that antibiotic use might be safely reduced in this population. A co-management model between primary and Infectious Diseases services may represent one method to optimize antibiotic use and outcomes for ABSSI, as has been shown with other infectious diseases.^{16–19} Antimicrobial stewardship interventions are another approach to improve antibiotic use and have been shown to impact prescribing practices in adults hospitalized with ABSSI.⁸ The results of our logistic regression models suggest that children admitted through emergency departments, those with head or neck involvement, and those treated by non-surgical services may be at

increased risk for exposure to antibiotics with Gram-negative activity or prolonged treatment courses and may warrant particular attention as stewardship interventions are developed. Furthermore, since the majority of antibiotic therapy for ABSSSI occurs after hospital discharge, review of prescriptions written at discharge may improve antibiotic selection and reduce treatment durations.

In addition to the limitations previously outlined,⁹ this study has at least four other limitations. First, this is a secondary analysis from a larger cohort study that was not specifically designed to evaluate antibiotic utilization in pediatric cases. Despite this, the findings suggest there may be opportunity to reduce antibiotic use in children hospitalized with ABSSSI. Second, the sample size was relatively small which limited the statistical power of the logistic regression models. Furthermore, due to the retrospective nature of the study, the results of the regression models cannot be assumed to represent causation. Third, the majority of cases were reported from a free-standing children's hospital, potentially limiting the generalizability of the findings. Finally, as discussed above, no studies have been performed to delineate the appropriate duration of therapy in children hospitalized with ABSSSI. Our endpoint concerning duration of therapy was therefore based on data from adult studies.^{14,15}

In summary, pediatric patients hospitalized with ABSSSI are frequently exposed to antibiotics with a broad spectrum of Gram-negative activity or prolonged treatment durations. Antibiotic use in such cases could potentially be reduced through prescription of shorter durations of antibiotics with Gram-positive activity, although the greatest opportunity appears to lie in reducing treatment durations. These findings highlight the need for studies to determine the shortest effective duration of therapy in pediatric patients hospitalized with ABSSSI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Multivariate logistic regression model of factors associated with the composite primary endpoint.

Table 1Primary endpoint^a

	Non-purulent cellulitis	Wound infection or purulent cellulitis	Cutaneous abscess	Total
	n = 42	n = 18	n = 39	n = 99
Prescribed antibiotic with broad Gram-negative activity or treatment >10 days	27 (64)	16 (89)	23 (59)	66 (67)
Prescribed antibiotic with broad Gram-negative activity	12 (29)	7 (39)	6 (15)	25 (25)
Treatment duration >10 days	24 (57)	13 (72)	23 (59)	60 (61)

^a analysis limited to 99 patients with complete data for antibiotics prescribed and duration of therapy

Table 2

Clinical outcomes

	Non-purulent cellulitis n = 43	Wound infection or purulent cellulitis n = 19	Cutaneous abscess n = 40	Total n = 102
Length of hospital stay, median days (IQR)	3 (2 – 4)	3 (3 – 4)	3 (3 – 4)	3 (3 – 4)
Survived to discharge	43 (100)	19 (100)	40 (100)	102 (100)
Follow-up medical encounter documented	18 (42)	5 (26)	24 (60)	47 (46) ^a
Clinical failure	2 (5)	0	4 (10)	6 (6)
Treatment failure	0	0	4 (10)	4 (4) ^a
Recurrence	1 (2)	0	1 (3)	2 (2)
Rehospitalization due to skin infection	2 (5)	0	1 (3)	3 (3)
Rehospitalization for reason other than skin infection	1 (2)	0	0	1 (1)

^a *P* value <.05 for comparison among the three classifications of ABSSSI