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Concise Communication

Epidemiology of *Staphylococcus aureus* infections in patients admitted to freestanding pediatric hospitals, 2009–2016

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Abstract

We observed pediatric *S. aureus* hospitalizations decreased 36% from 26.3 to 16.8 infections per 1,000 admissions from 2009 to 2016, with methicillin-resistant *S. aureus* (MRSA) decreasing by 52% and methicillin-susceptible *S. aureus* decreasing by 17%, among 39 pediatric hospitals. Similar decreases were observed for days of therapy of anti-MRSA antibiotics.

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Staphylococcus aureus (S. aureus) causes a substantial number of pediatric infections each year in the United States, with potential for severe complications including death.[1–4] Although the emergence of methicillin-resistant *S. aureus* (MRSA) led to a rapid increase in the number of *S. aureus* infections in children,[5] recent data suggest that *S. aureus* infections are declining in adults, driven primarily by decreases in MRSA.[6,7] Similar findings have been reported in pediatric populations, but these studies were limited to single centers and unique populations, such as military members or infants.[4,5,8–10] A nationally representative and contemporary characterization of epidemiologic trends in *S. aureus* infections has not been conducted. The objective of this study was to describe recent trends in pediatric *S. aureus* hospitalizations and associated antibiotic prescribing patterns.

Patients and Methods

Data source and quality

We conducted a retrospective cohort study using the Pediatric Health Information Systems (PHIS) administrative database, maintained by the Children's Hospital Association (Overland Park, KS). PHIS includes clinical and resource utilization data from inpatient, emergency, ambulatory surgery, and observation units at more than 45 tertiary-care freestanding children's hospitals in the United States. The data are subject to numerous validity and reliability checks before incorporation into the database. The data warehouse function was provided by Truven Health Analytics (Ann Arbor, MI).

Study population

All inpatient encounters for patients <18 years of age hospitalized between January 1, 2009, and December 31, 2016, at a PHIS hospital with continuous reporting were included. The study population was limited to patients with an *S. aureus* infection indicated in the electronic medical record, defined as (1) having ≥1 *International Classification of Disease, Clinical Modifications version 9* or *version 10* discharge code for MRSA (038.12, 041.12, 482.42, A41.02, A49.02, B95.62, J152.12, V02.54) or methicillin-susceptible *S. aureus* (MSSA) (038.11, 041.11, 482.41, A41.01, A49.01, B95.61, J152.11, V02.53) present on admission or occurring during the admission; and (2) receiving ≥1 anti-staphylococcal antibiotic (list available upon request). Using additional discharge codes when present, *S. aureus* infections were further stratified into 4 infection categories: (1) skin or soft-tissue infection (SSTI); (2) myositis/osteomyelitis/septic arthritis;

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(3) bacteremia/endocarditis; or (4) pneumonia.[10] Patients could be assigned >1 category.

Data analysis

The annual rates for *S. aureus* overall, MRSA, and MSSA were calculated per 1,000 hospital admissions. Trends in hospitalization rates over time were analyzed using the Cochran-Armitage trend test, with 2-sided *P* values reported and statistical significance set at $P < .05$. Median and interquartile ranges (IQR) are reported for continuous variables. Antibiotic days of therapy (DOT) per 1,000 patient days were evaluated, where the DOT numerator is the aggregate sum of anti-staphylococcal antibiotics used per patient with *S. aureus* infections per day and the denominator is the total hospital inpatient days for all hospitalized patients, analyzed separately for antibiotics with activity against MRSA. Data analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC). The Institutional Review Board of Children's Minnesota Hospital deemed this study exempt from review.

Results

Among 39 hospitals with continuous reporting to PHIS from 2009 to 2016, we identified 116,152 *S. aureus* hospitalizations. Among patients with *S. aureus* hospitalizations, the median age was 3 years (IQR, 0–11 years), 53.7% were male, 52.5% were white, and 18.8% were African American. The median length of hospital stay was 5 days (IQR, 2–13 days), with intensive care unit admissions occurring in 26.3% of MSSA hospitalizations compared with 22.3% of MRSA hospitalizations (Table 1).

From 2009 to 2016, pediatric *S. aureus* hospitalizations decreased 36% from 26.3 to 16.8 infections per 1,000 admissions ($P < .001$) (Fig. 1A). Overall, there was a 52% decrease in MRSA infections (14.4 to 6.9 infections per 1,000 admissions; $P < .001$) and a 17% decrease in MSSA infections (11.9 to 9.9 infections per 1,000 admissions; $P < .001$). In 2009, 55% of all *S. aureus* infections were MRSA, and this rate decreased to 41% in 2016.

MRSA infections were most often categorized as SSTIs (44.7%), followed by myositis/osteomyelitis/septic arthritis (7.1%), bacteremia/endocarditis (4.5%), and pneumonia (4.8%); 44.3% of MRSA infections were not categorized. Although rates in all MRSA categories decreased over time, the decrease was most notable among SSTIs, which decreased from 7.3 in 2009 to 2.9 infections per 1,000 admissions in 2016 ($P < .001$); other MRSA categories remained relatively unchanged. Notably the proportion of MRSA infections decreased among non-Hispanic African Americans (22.9% to 19.1% from 2009 to 2016; $P < .001$), 1–5-year-olds (39% to 32.1% from 2009 to 2016; $P < .001$), and among patients from the South (47.2% to 43.8%; $P < .001$).

MSSA infection categories were similar to MSRA in distribution. Over time, these decreases were most notable among SSTIs (from 4.1 in 2009 to 2.9 in 2016; $P < .001$) and bacteremia/endocarditis infections (from 1.2 in 2009 to 0.6 in 2016; $P < .001$).

The antibiotics most commonly used to treat *S. aureus* infections were vancomycin (14.9% of DOT per 1,000 patient days), clindamycin (11.3%), cefazolin (4.1%), trimethoprim/sulfamethoxazole (TMP/SMX) (4.1%), and ceftriaxone (2.4%). Vancomycin and clindamycin remained the 2 most commonly prescribed antibiotics over the study period. Days of therapy per 1,000 patient days among antibiotics with activity against MRSA specifically decreased from 38.0 to 24.5, with the most notable

Table 1. Demographics of Pediatric Patients With *Staphylococcus aureus* Infections in 39 PHIS Hospitals With Continuous Reporting, 2009–2016.[a]

Variable	All *S. aureus* (n = 116,152) No. (%)[b]	MRSA (n = 59,762) No. (%)[b]	MSSA (n = 56,390) No. (%)[b]
Demographic variables			
Gender			
Female	53,773 (46.3)	28,582 (47.8)	25,191 (44.7)
Male	62,379 (53.7)	31,180 (52.2)	31,199 (55.3)
Age			
Median (IQR), y	3 (0–11)	3 (1–11)	4 (0–11)
<1 y	29,336 (25.3)	14,453 (24.2)	14,883 (26.4)
1–5 y	37,509 (32.3)	21,446 (35.9)	16,063 (28.5)
6–12 y	26,092 (22.5)	12,462 (20.9)	13,630 (24.2)
13–17 y	23,215 (20)	11,401 (19.1)	11,814 (21)
Race and ethnicity			
White	61,020 (52.5)	31,823 (53.2)	29,197 (51.8)
African American	21,855 (18.8)	12,316 (20.6)	9,539 (16.9)
Hispanic	20,366 (17.5)	9,738 (16.3)	10,628 (18.8)
Asian American	2,387 (2.1)	839 (1.4)	1,548 (2.7)
Other	10,524 (9.1)	5,046 (8.4)	5,478 (9.7)
Census region			
Midwest	31,285 (26.9)	16,166 (27.1)	15,119 (26.8)
Northeast	13,818 (11.9)	6,122 (10.2)	7,696 (13.6)
South	46,462 (40)	26,446 (44.3)	20,016 (35.5)
West	24,587 (21.2)	11,028 (18.5)	13,559 (24.0)
Health insurance payer			
Private	37,297 (32.1)	17,041 (28.5)	20,256 (35.9)
Government	72,619 (62.5)	39,370 (65.9)	33,249 (59)
Other payer	6,236 (5.4)	3,351 (5.6)	2,885 (5.1)
Hospital-encounter variables			
Length of hospital stay			
Median (IQR), d	5 (2–13)	4 (2–12)	5 (3–14)
ICU or NICU stay	28,137 (24.2)	13,321 (22.3)	14,816 (26.3)
Primary reason for visit			
Medical	85,895 (74)	45,466 (76.1)	40,429 (71.7)
Surgical	30,257 (26)	14,296 (23.9)	15,961 (28.3)
Any complex chronic condition	54,517 (46.9)	26,569 (44.5)	27,948 (49.6)
Crude mortality	1,850 (1.6)	754 (1.3)	1,096 (1.9)
30-day all-cause readmission rate	13,858 (11.9)	6,604 (11.1)	7,254 (12.9)

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Table 1. (*Continued*)

Variable	All *S. aureus* (n = 116,152) No. (%)[b]	MRSA (n = 59,762) No. (%)[b]	MSSA (n = 56,390) No. (%)[b]
S. aureus infection category			
SSTI	45,148 (38.9)	26,709 (44.7)	18,439 (32.7)
Myositis/osteomyelitis/ septic arthritis	11,750 (10.1)	4,231 (7.1)	7,519 (13.3)
Bacteremia/endocarditis	8,140 (7)	2,717 (4.5)	5,423 (9.6)
Pneumonia	9,174 (7.9)	2,861 (4.8)	6,313 (11.2)
Not specified	49,971 (43)	26,450 (44.3)	23,521 (41.7)
Treatment-related variables			
MRSA treatment coverage, DOT/1,000 patient days	36.9	20.1	16.8
Top 5 antibiotics prescribed during hospital admission			
Clindamycin	64,059 (55.2)	35,874 (60)	28,185 (50)
Vancomycin	51,047 (43.9)	26,967 (45.1)	24,080 (42.7)
Cefazolin	25,131 (21.6)	7,111 (11.9)	18,020 (32)
Ceftriaxone	17,732 (15.3)	7,846 (13.1)	9,886 (17.5)
TMP/SMX	15,856 (13.7)	9,712 (16.3)	6,144 (10.9)

Note. IQR, interquartile range; ICU, intensive care unit; NICU, neonatal intensive care unit; SSTI, skin and soft-tissue infection; DOT, days of therapy; TMP/SMX, trimethoprim/sulfamethoxazole.
[a]All differences between groups were statistically significant.
[b]Unless otherwise specified.

decreases for clindamycin (14.32 to 7.5) and vancomycin (16.6 to 10.8) (Fig. 1B).

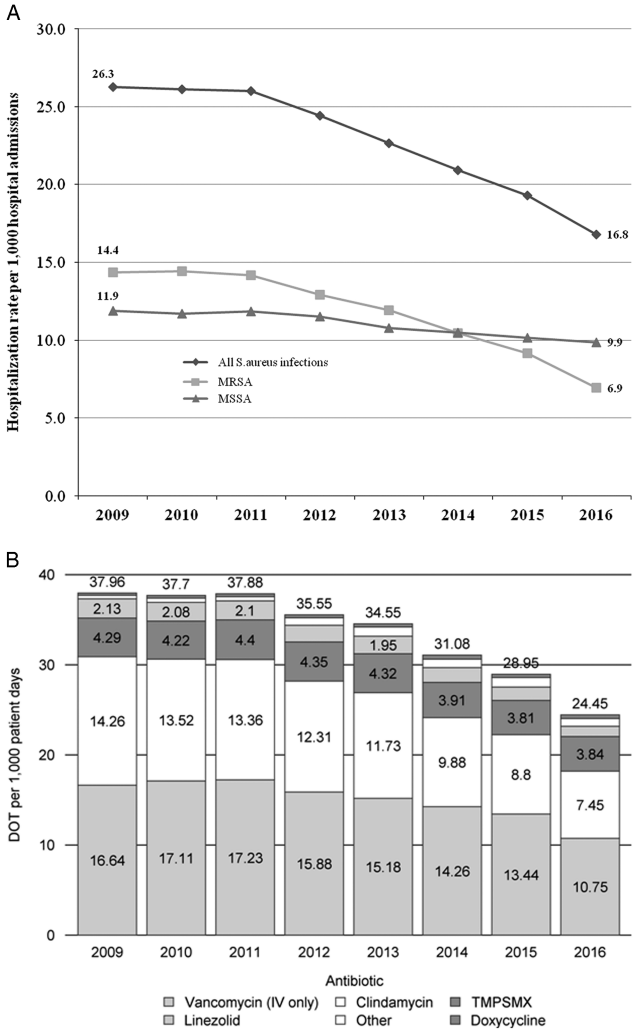

Fig. 1. (A) *S. aureus* hospitalization rate per 1,000 hospital admissions in 39 PHIS hospitals with continuous reporting, 2009–2016. (B) Days of therapy for the most commonly used antibiotics per patient day among *S. aureus* hospital admissions.

Discussion

In this study, we observed a 36% decrease for *S. aureus* hospitalizations between 2009 and 2016. Notably, MRSA hospitalizations decreased 52%, including a corresponding decrease in DOT for anti-MRSA antibiotics during the same period.

Decreases in *S. aureus* hospitalizations detected in this study were similar to findings from studies performed in other adult and pediatric inpatient populations.[6,7] A number of factors may contribute to these decreases: (1) earlier recognition of *S. aureus* infections (especially SSTIs) and initiation of appropriate therapy in outpatient settings, such as incision and drainage and/or targeted antibiotic therapy which might prevent hospitalization and/or recurrences; (2) changes in the tendency to hospitalize patients with suspected staphylococcal infections such as SSTIs presenting to emergency departments; (3) increased provider confidence to manage infections in the outpatient settings, and (4) the possibility of reductions in transmission of MRSA due to better infection control strategies especially in community settings or due to changes in circulating MRSA clones or lower prevalence in the community. Future studies are warranted to determine whether MRSA infections at the community-level are also decreasing, how to best measure the impact of infection control practices, and how SSTI visits in the emergency department might have also changed over time.

This study has several limitations. First, we identified cases of *S. aureus* using administrative coding and, though this method has been used in other studies, it has not been validated. To enhance specificity, we included an additional requirement of receipt of an antibiotic with activity against *S. aureus* during the hospitalization. Second, PHIS only includes hospitalized patients and therefore does not allow us to distinguish between hospital-onset versus community-onset infections or to address concurrent trends in outpatient care settings that might have contributed to our findings. When we looked at our "present on admission" flag, we found only 9.3% of all *S. aureus* infections were marked as "no." Third, the generalizability of our findings to pediatric hospitalizations outside of freestanding children's hospitals is uncertain including the possibility that some *S. aureus* hospitalizations may have shifted to hospitals not captured by PHIS.

Despite these limitations, these results provide evidence of substantial and sustained decreases in pediatric *S. aureus* hospitalizations, driven by declining MRSA hospitalizations. Further

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research is necessary to better understand the factors driving these epidemiologic changes.

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