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Antibiotic Management of Staphylococcus aureus Infections in US Children's Hospitals, 1999 –2008

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WHAT'S KNOWN ON THIS SUBJECT: An increase in the incidence of *S aureus* infection among hospitalized children has been observed as a result of the increase in community-associated MRSA infections. Data are lacking regarding the impact of changing *S aureus* epidemiology on antibiotic use.

WHAT THIS STUDY ADDS: This study shows a significant shift in the use of antibiotics to treat *S aureus* infections. Clindamycin now represents the most commonly used antibiotic among hospitalized children with *S aureus* infections.

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KEY WORDS

Staphylococcus aureus, epidemiology, pediatric, antibiotic use

ABBREVIATIONS

SSTI—skin and soft tissue infection
MRSA—methicillin-resistant *Staphylococcus aureus*
CA-MRSA—community-associated MRSA
MSSA—methicillin-susceptible *S aureus*
TMP/SMX—trimethoprim/sulfamethoxazole
PHIS—Pediatric Health Information System
CHCA—Child Health Corporation of America
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
DOT—days of therapy

abstract

OBJECTIVES: The objective of this study was to describe trends in antibiotic management for *Staphylococcus aureus* infections among hospitalized children from 1999 to 2008.

METHODS: A retrospective study was conducted by using the Pediatric Health Information Systems database to describe antibiotic treatment of inpatients with *S aureus* infection at 25 children's hospitals in the United States. Patients who were admitted from 1999 to 2008 with *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for *S aureus* infection were included. Trends in the use of vancomycin, clindamycin, linezolid, trimethoprim-sulfamethoxazole, cefazolin, and oxacillin/nafcillin were examined for percentage use and days of therapy per 1000 patient-days.

RESULTS: A total of 64 813 patients had a discharge diagnosis for *S aureus* infection. The incidence of methicillin-resistant *S aureus* (MRSA) infections during this period increased 10-fold, from 2 to 21 cases per 1000 admissions, whereas the methicillin-susceptible *S aureus* infection rate remained stable. Among patients with *S aureus* infections, antibiotics that treat MRSA increased from 52% to 79% of cases, whereas those that treat only methicillin-susceptible *S aureus* declined from 66% to <30% of cases. Clindamycin showed the greatest increase, from 21% in 1999 to 63% in 2008. Similar trends were observed by using days of therapy per 1000 patient-days.

CONCLUSIONS: Antibiotic prescribing patterns for the treatment of *S aureus* infections have changed significantly during the past decade, reflecting the emergence of community-associated MRSA. Clindamycin is now the most commonly prescribed antibiotic for *S aureus* infections among hospitalized children. The substantial use of clindamycin emphasizes the importance of continuous monitoring of local *S aureus* susceptibility patterns. *Pediatrics* 2010;125:e1294–e1300

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Staphylococcus aureus is a significant cause of skin and soft tissue infections (SSTIs) as well as a variety of invasive diseases in both children and adults.[1,2] Although first successfully treated with β-lactam antibiotics >60 years ago, *S aureus* developed resistance relatively quickly, leading to the isolation of methicillin-resistant *S aureus* (MRSA) within 1 year of exposure to this class of antibiotics.[3–6] Initial MRSA infections were almost exclusively nosocomial, confined to patients with a history of repeated hospitalizations, lengthy or repeated antibiotic treatments, or close contact with health care workers.[7,8] More recently, however, an epidemic of MRSA infections that affect individuals without such risk factors has emerged.[9] These community-associated MRSA (CA-MRSA) infections have primarily manifested as SSTIs among previously healthy children and adults. This evidence, coupled with molecular and genetic studies demonstrating the emergence of genetically unique strains, suggested novel transmission routes outside of health care settings.[10] More recent evidence suggests that this trend has led to an increase in MRSA infections among hospitalized children.[11]

Before this shift in epidemiology, empiric β-lactam therapy for hospitalized patients with suspected *S aureus* infection remained commonplace. The rapid emergence of CA-MRSA, however, has led to recommendations for targeting both methicillin-susceptible *S aureus* (MSSA) and MRSA in patients with suspected *S aureus* infections.[12–16] This approach is complicated by the absence of an antibiotic that is ideally suited for this goal. For example, although vancomycin, clindamycin, trimethoprim-sulfamethoxazole (TMP/SMX), and linezolid each provide adequate coverage against most *S aureus* strains, including MRSA,[14] each drug has limitations: despite broad-spectrum coverage, vancomycin has poor antistaphylococcal activity relative to β-lactams and is available only intravenously; clindamycin is limited by increasing resistance in certain regions of the United States[17]; TMP/SMX is variably active against *Streptococcus* species (coverage of which is often desirable for such infections); and linezolid is prohibitively expensive. Accordingly, the extent to which antibiotics with activity against MRSA have supplanted β-lactams in the treatment of *S aureus* infections, in hospitalized children and the preferred anti-MRSA agent chosen in such circumstances is unknown. The objective of this study was to describe national trends in antibiotic management of *S aureus* infections from 1999 to 2008 in US children's hospitals.

METHODS

Study Design

We conducted a retrospective observational study to examine the use of commonly prescribed antimicrobial agents for *S aureus* infections among inpatients at 25 freestanding, tertiary care children's hospitals throughout the United States from 1999 to 2008.

Data Source and Quality

We used data from the Pediatric Health Information System (PHIS), an administrative database that is maintained by the Child Health Corporation of America (CHCA) located in Mission, Kansas. The CHCA is a collaboration of 43 not-for-profit, tertiary care pediatric hospitals across the United States aimed at improving outcomes and reducing costs. Member hospitals represent 17 of the 20 major metropolitan areas across the United States. The PHIS database contains patient-level demographic, diagnostic, procedural, and resource use (eg, pharmaceuticals, laboratory and imaging studies, other patient services) data from CHCA member hospitals. To date, data on >19 million patient encounters are included in the PHIS database.

Data quality and reliability are ensured through a joint effort among the CHCA, Thomson Healthcare (contracted data manager), and contributing hospitals. Data are accepted into the database once classified errors occur in <2% of a hospital's quarterly data. When a hospital's quarterly data are unacceptable according to these limits, all of their quarterly data are rejected; however, these data can be corrected, then resubmitted and reevaluated before inclusion in the database. Hospitals were excluded from our study when they did not contribute complete resource use data for the entire study period. Twenty-five hospitals had complete data and were included in our analysis.

Study Population

The cohort for this investigation included patients who were younger than 18 years at time of admission to 1 of the 25 study hospitals between January 1, 1999, and December 31, 2008, with an *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) code for *S aureus* infection (041.11), *S aureus* septicemia (038.11), pneumonia caused by *S aureus* (482.41), or MRSA (041.12, 038.12, 482.42, or V09.0) infection at discharge. Thus, patients were classified as having a *S aureus* infection when ≥1 of the aforementioned codes was in the patient's discharge data, with additional classification of *S aureus* as MRSA or MSSA on the basis of the presence (or absence) of a discharge code for MRSA infection. Patient encounters that contained multiple *S aureus*–related codes were counted only once. Patients with *S aureus* infections were further subdivided into those with

SSTIs, osteomyelitis, endovascular infections (endocarditis and septic thrombophlebitis), and pneumonia by using additional ICD-9-CM codes. This approach was previously implemented by using the PHIS database.[11] Site-of-infection codes were available for 57% of the study population.

Antibiotic Use Measures

Antibiotics that were selected for investigation included the anti-MRSA antibiotics vancomycin, clindamycin, TMP/SMX, and linezolid and the anti-MSSA β-lactam antibiotics oxacillin, nafcillin, and cefazolin. Two measures were used to examine antibiotic use for each agent: (*1*) percentage use and (2) days of therapy (DOT) per 1000 patient-days. Percentage use was defined as the proportion of patients who had *S aureus* infections and received 1 of the specified antibiotics at any time during the hospitalization; this measure assigns equal weight to a single antibiotic dose or multiple days of therapy and is therefore independent of therapy duration. To account for variations in therapy duration, we also measured antibiotic use by calculating DOT, normalized to 1000 patient-days. One day of therapy was defined as receiving ≥1 dose in a given day; patients were counted as having 1 day of therapy regardless of the number of doses administered. By using these measures, we examined antibiotic use for all patients with *S aureus* and subsequently stratified them by the presence of codes for MRSA and site of infection. All trends were examined annually.

Statistical Analysis

Summary statistics were constructed by using frequencies and proportions for categorical data elements and medians or means for continuous variables. All temporal trends were examined by using the Mantel-Haenszel χ^2 test. Because of large sample sizes, significance was determined on the basis of $P < .001$. SPSS Base 16.0 (SPSS, Inc, Chicago, IL) was used for all statistical analyses.

TABLE 1 Demographic and Clinical Characteristics for All Patients With *S aureus* Infections Between 1999 and 2008

Characteristic	MRSA ($n = 29\,571$)	MSSA ($n = 35\,242$)	All *S aureus* ($N = 64\,813$)	*P*
Age, median (IQR), y	2.6 (0.9–10.7)	3.4 (0.7–11.1)	3.0 (0.8–10.9)	.261
Male gender, *n* (%)	15 644 (53)	19 616 (56)	35 260 (54)	<.001
Race, *n* (%)				
White	17 955 (61)	22 782 (65)	40 737 (63)	<.001
Black	8250 (28)	7458 (21)	15 708 (24)	
Other[a]	3366 (11)	5002 (14)	8368 (13)	
LOS, median (IQR), d	5 (3–12)	6 (3–15)	5 (3–14)	<.001
Disposition, *n* (%)				
Home	27 037 (91)	30 796 (88)	57 833 (89)	<.001
Died in hospital	374 (1)	833 (2)	1207 (2)	
Other[b]	2160 (8)	3613 (10)	5773 (9)	
Type of infection, *n* (%)				
Skin/soft tissue	13 809 (75)	11 263 (61)	25 072 (68)	<.001
Osteomyelitis	1733 (9)	2682 (15)	4415 (12)	
Endovascular	197 (1)	356 (2)	553 (2)	
Pneumonia	2678 (15)	4028 (22)	6706 (18)	

P values are for differences between patients with MRSA and with MSSA. IQR indicates interquartile range. LOS indicates length of stay.

[a] Asian, American Indian, other, missing.

[b] Transferred to another care facility, discharged to home health care, left against medical advice, or data were missing.

RESULTS

Patient Characteristics

Of the 2.4 million patient discharges examined from 1999 to 2008, a total of 64 813 (3%) children had a discharge diagnosis code for *S aureus* infection. Overall, the majority of patients with *S aureus* infections were male and white, with a median age of 3.0 years (interquartile range: 0.8–10.9 years). Black children were more commonly infected with MRSA than MSSA ($P < .001$). The most common type of *S aureus* infection was SSTI, occurring in 39% of all *S aureus* cases. SSTIs occurred more frequently among patients with MRSA compared with MSSA ($P < .001$), whereas pneumonia was more commonly observed in children with MSSA ($P < .001$; Table 1).

Trends in *S aureus* Infection

During the 10-year study period, the incidence of *S aureus* infection more than doubled, increasing from 14.8 per 1000 admissions in 1999 to 35.7 per 1000 admissions in 2008 (Fig 1). The incidence of MRSA infections during this period increased 10-fold, from 2.0 cases per 1000 admissions in 1999 to 20.7 cases per 1000 admissions in 2008 ($P < .001$ for trend), whereas the MSSA infection rate remained relatively stable. By 2008, MRSA accounted for 58% of all *S aureus* infections in hospitalized children.

Temporal Trends in Antibiotic Use for All Patients With *S aureus*

Concurrent with this shift in *S aureus* epidemiology in hospitalized children, antibiotic use changed significantly.

Percentage Use

Measured as percentage use, the overall use of anti-MRSA antibiotics for patients with *S aureus* infections increased from 52% to 79% of cases. Clindamycin showed the greatest overall increase, with percentage use increasing threefold (21% in 1999 to 63% in 2008; $P < .001$ for trend; Fig 2). Vancomycin use remained stable (36% in 1999 vs 37% in 2008; $P = .003$ for trend), whereas TMP/SMX (9% vs 12%; $P < .001$ for trend) and linezolid (0% vs 5%; $P < .001$ for trend) showed small increases. In contrast, β-lactam antibiotic use declined signifi-

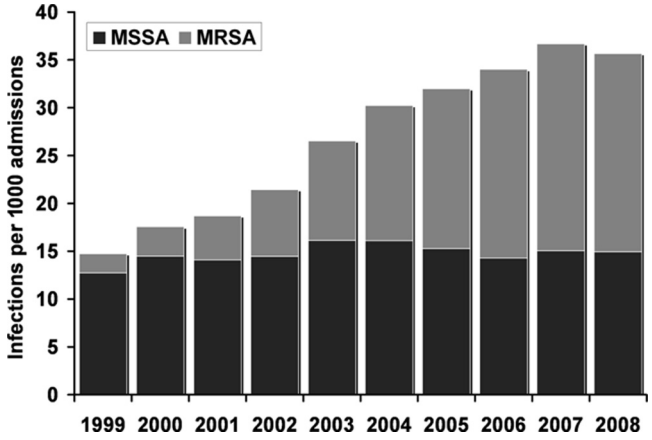

FIGURE 1
Rate of *S aureus* infections in 25 US children's hospitals from 1999 to 2008.

cantly during the study period, from 66% of *S aureus* cases in 1999 to <30% in 2008 ($P < .001$ for trend).

DOT per 1000 Patient-days

Overall, similar trends were evident when antibiotic selection was examined in terms of DOT per 1000 patient-days (Fig 2). Clindamycin use increased from 53 DOT per 1000 patient-days in 1999 to 192 DOT per 1000 patient-days in 2008 ($P < .001$ for trend). Smaller increases occurred for TMP/SMX (37 vs 53 DOT per 1000 patient-days; $P < .001$ for trend) and linezolid (1 vs 27 DOT per 1000 patient-days; $P < .001$ for trend). Also consistent with the results observed for percentage use, there was a substantial decline in DOT for β-lactam antibiotics, from 33 to 18 DOT per 1000 patient-days ($P < .001$ for trend). Vancomycin use, however, increased from 152 to 204 DOT per 1000 patient-days during the study period ($P < .001$ for trend), an increase not apparent when calculated by percentage use.

Temporal Trends in Antibiotic Use Only for Patients With MRSA

When antibiotic selection was examined for the subset of patients with MRSA infections, generally similar trends emerged across both measures of antibiotic use (Fig 2). When measured by either percentage use or

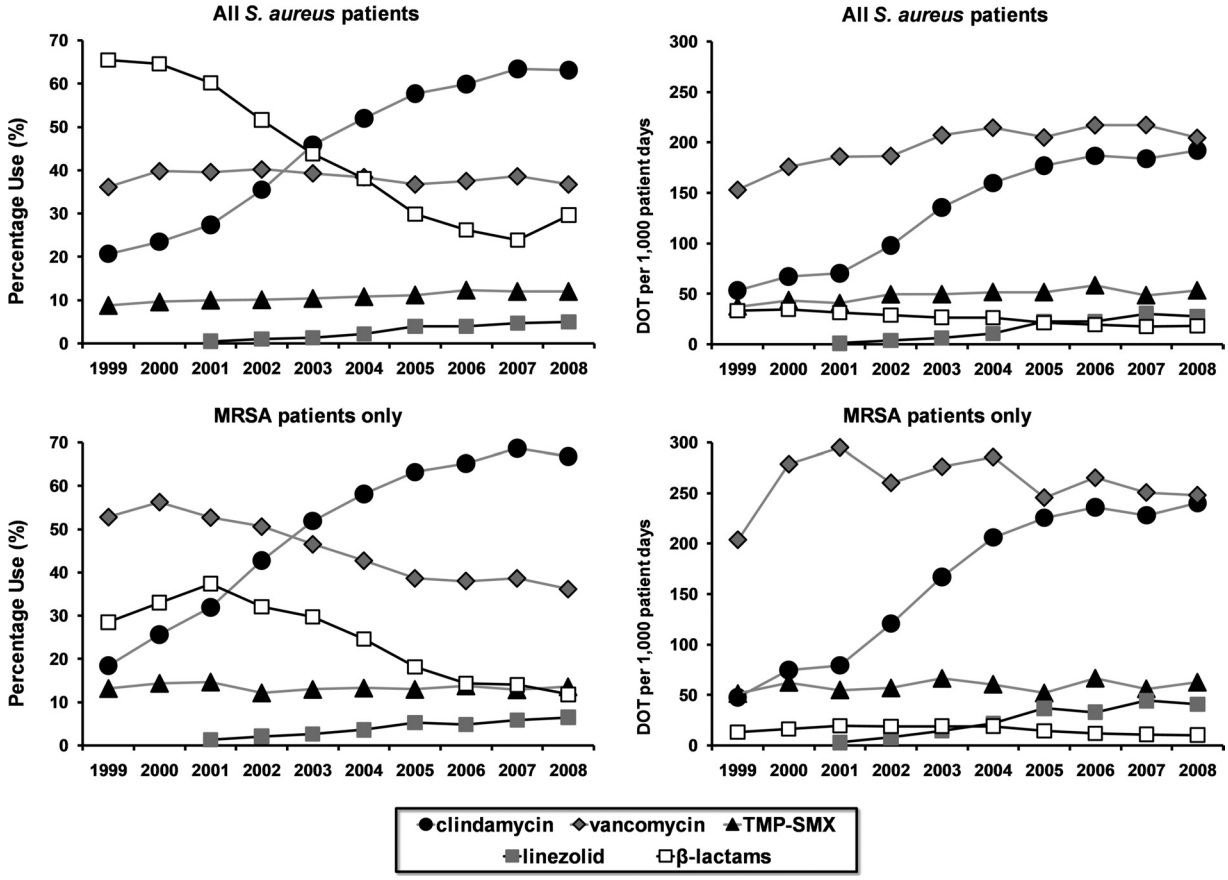

FIGURE 2
Antibiotic use in patients with *S aureus* infection at 25 US children's hospitals from 1999 to 2008. β-Lactams include cefazolin, nafcillin, and oxacillin.

DOT, clindamycin use increased more than three-fold (19% to 67% for percentage use and 48–240 DOT per 1000 patient-days; both $P < .001$ for trend). Smaller increases occurred for TMP/SMX and linezolid (Fig 2). Although we observed a decline in percentage use of vancomycin from 53% in 1999 to 36% of patients in 2008 ($P < .001$ for trend), we observed an increase in DOT with vancomycin (204–248 per 1000 patient-days; $P < .001$ for trend). A significant decline occurred for β-lactam antibiotics ($P < .001$ for trend) with both measures of antibiotic use.

Antibiotic Use on the Basis of Site of Infection

Among the 64 813 children with a diagnosis of *S aureus* infection, 36 746 (57%) had an associated code indicating the type of *S aureus* infection. Although use of anti-MRSA antibiotics—clindamycin in particular—increased overall, we observed differential trends across the various types of *S aureus* infection. The most substantial increases in clindamycin use were for SSTIs (30% in 1999 vs 89% in 2008; $P <$ .001 for trend) and osteomyelitis (17% in 1999 vs 72% in 2008; $P < .001$ for trend). Although linezolid was not available during the first 2 years of the study period, its use substantially increased between 2001 and 2008. Linezolid use in 2008 was relatively limited for SSTIs (3%) when compared with osteomyelitis (9%), endovascular infection (21%), and pneumonia (10%). Consistent with aggregated trends, use of β-lactams dropped significantly across all infection sites during the study period, the biggest drop seen in SSTIs (78% in 1999 vs 11% in 2008; $P <$ .001 for trend; Table 2).

TABLE 2 Antibiotic Use in Terms of Percentage Use Stratified by Infection Site at 25 US Children's Hospitals From 1999 to 2008

	S aureus			MRSA		
	1999	2008	*P*	1999	2008	*P*
Skin/soft tissue						
Clindamycin	29.7	89.3	<.001	34.2	90.5	<.001
Vancomycin	19.1	22.9	.320	42.1	24.2	<.001
TMP/SMX	4.5	9.0	<.001	5.3	10.3	.074
Linezolid	0.5[a]	2.7	<.001	1.6[a]	3.3	<.001
β-Lactams	77.6	11.4	<.001	63.2	6.4	<.001
Osteomyelitis						
Clindamycin	16.9	71.9	<.001	12.5	77.5	<.001
Vancomycin	22.2	52.2	<.001	62.5	62.4	.112
TMP/SMX	2.7	3.3	.122	0.0	4.3	.609
Linezolid	0.3[a]	9.4	<.001	2.3[a]	15.9	<.001
β-Lactams	87.6	47.6	<.001	37.5	27.7	<.001
Endovascular						
Clindamycin	22.5	45.7	<.001	33.3	58.3	.001
Vancomycin	72.5	79.3	.097	66.7	87.5	.243
TMP/SMX	5.0	3.3	.784	0.0	6.2	.599
Linezolid	0.0[a]	20.7	<.001	0.0[a]	25.0	.003
β-Lactams	87.5	52.2	<.001	66.7	33.3	.095
Pneumonia						
Clindamycin	27.1	40.6	<.001	23.7	45.3	<.001
Vancomycin	36.1	61.8	<.001	61.0	64.6	.296
TMP/SMX	10.8	20.9	<.001	16.9	25.5	.227
Linezolid	0.3[a]	10.1	<.001	1.4[a]	14.7	<.001
β-Lactams	40.0	30.1	<.001	22.0	18.0	.752

β-Lactams include cefazolin, nafcillin, and oxacillin.
[a] Percentage use in 2001, the first year linezolid was available.

DISCUSSION

Epidemiologic studies of both children and adults have documented an increase in *S aureus* infections that largely were attributable to the emergence of CA-MRSA.[11,18–20] This study is the first to evaluate the change in antibiotic use in hospitalized children with *S aureus* infections during the decade in which CA-MRSA emerged. Consistent with clinical recognition of this epidemic, we identified a dramatic increase in the use of MRSA-active agents—particularly clindamycin—in conjunction with a significant decrease in β-lactam use.

Although use of all MRSA-active antibiotics significantly increased during the study period, the use of clindamycin increased most dramatically, representing use in almost two-thirds of hospitalized patients with *S aureus* infection. Considering DOT per 1000 patient-days, clindamycin use for children with *S aureus* infection increased four-fold, becoming equivalent by this measure to that of vancomycin. In addition, increases in use of clindamycin across various sites of *S aureus* infection (osteomyelitis: six-fold increase; pneumonia: 1.5-fold increase; and endocarditis: two-fold increase) suggest that clinicians are becoming more comfortable prescribing clindamycin for serious invasive *S aureus* infections. Although clindamycin is not Food and Drug Administration–approved for these indications, pediatric studies have demonstrated effectiveness in treating osteomyelitis and pneumonia with this agent.[21,22] Despite this expanding pattern of use, it is noteworthy that the American Heart Association discourages the use of clindamycin in the treatment of *S aureus* endocarditis.[23] In our study, 87% of patients with documented MRSA endocarditis were treated with vancomycin in 2008.

The observed decrease in β-lactam use in the context of unchanged MSSA incidence rates suggests that another antibiotic—likely clindamycin—may be replacing β-lactams as the preferred empiric therapy for presumed *S*

aureus infections. Although these data do not allow us specifically to distinguish between empiric and culture-directed therapies, it is probable that clindamycin is often the empiric therapy for both SSTIs and more invasive infections. Given this dramatic increase in clindamycin use, practitioners must become aware of its limitations. These include both constitutive and inducible resistance, each of which varies significantly by geography (with rates as high as 80% in some regional reports).[17] Furthermore, this surge of antibiotic pressure has the potential to facilitate the development of resistance among circulating clindamycin-sensitive CA-MRSA strains; therefore, it is essential that clinicians be aware of and continue to monitor their institution's antibiograms. Unfortunately, a recent study that evaluated the use of institution-based antibiograms among house officers revealed that 60% never used this information, with the main reason being not knowing where to find it.[24] It is imperative that infectious diseases physicians and microbiologists make this information readily available, because it will affect the future treatment of patients with *S aureus* infection. Ultimately, prospective studies that compare both empiric and definitive antibiotic therapy for MRSA infections in children are required to define the appropriate approach.

We evaluated temporal trends in antibiotic use by measuring both percentage use and DOT per 1000 patient-days. This combination of metrics allowed us to compute a more accurate description of antibiotic use within this setting. Percentage use evaluates how often the antibiotics are being prescribed irrespective of whether the choice is empiric or culture-directed. Although this provides a broad overview of antibiotic choices, percentage use ignores length of antibiotic therapy and, consequently, gives equal weight to empiric (often brief) and culture-directed (generally longer and more definitive) therapy. To account for variations in length of therapy, we also calculated DOT. This measure describes how many days a patient was on a given antibiotic, standardizing to 1000 patient-days. This approach not only addresses variable lengths of therapy but also provides a more accurate picture of use when compared with another common measure—the defined daily dose—especially in pediatric populations.[25]

The difference between these 2 measures is exemplified by the calculated vancomycin use in our study; although percentage use was unchanged over time, DOTs per 1000 patient-days increased substantially. Given that vancomycin is the empiric antibiotic of choice for patients with suspected severe *S aureus* infections, this difference may be reconciled by considering the epidemiology of MRSA: in the early study period, we speculate that patients were empirically treated with vancomycin but it was discontinued after the patient's culture and susceptibility results revealed MSSA; however, given that MRSA is more prevalent today, use of MRSA-active drugs such as vancomycin should increase as patients require continuation of this initial empiric therapy, leading to increases in vancomycin DOT.

A strength of this study is the ability to evaluate the antibiotic treatment of a large number of hospitalized children from across the United States with *S aureus* infections by using the PHIS database. The PHIS database provides national-level pediatric data, combining patient records from 43 large, tertiary care children's hospitals. PHIS provides up to 21 diagnosis codes per hospitalization, providing more diagnosis data per patient than other administrative data sets. In this study, only 25 of the CHCA hospitals were included because of lack of complete data from 18 of the hospitals. Although the hospitals excluded were similar in that they are freestanding children's hospitals, the exclusion of these hospitals led to a lack of significant representation from the Pacific Northwest and the Northeast. This is potentially important because the rates of MRSA vary on the basis of geographic region; however, a recent study that used PHIS hospitals with a more uniform geographic representation noted a similar increase in MRSA infection.[11] Although it is possible that these areas are using antibiotics differently, anecdotal reports suggested that their prescribing practices are likely similar.

Despite the advantages of administrative data, they are limited by the possibility of miscoded information. The accuracy of ICD-9-CM codes for diagnosing either *S aureus* or MRSA infection has not been validated for this large population, and, although generally specific, ICD-9-CM code–based searches may not have ideal sensitivity, as evidenced by our identification of site codes for less than two-thirds of *S aureus* infections; therefore, this analysis might underrepresent the actual disease burden. Also, because we were unable to assess microbiologic data, we are limited in distinguishing empiric therapy from culture-directed regimens. Furthermore, we cannot verify that patients received medications for which bills were generated—the source of antibiotic use data. Finally, because the analysis was limited to freestanding children's hospitals, generalizing these findings to other inpatient pediatric settings (eg, general hospitals with pediatric wards) and outpatient settings may not be warranted.

CONCLUSIONS

Antibiotic prescribing for hospitalized children with *S aureus* infections has changed dramatically since the emergence of CA-MRSA, reflecting an increase in MRSA-active therapy coincident with a decrease in β-lactam use. Clindamycin has become the primary antibiotic for the treatment of *S aureus* infections, including both SSTIs and invasive diseases such as osteomyelitis and pneumonia. It is essential that clinicians be vigilant in monitoring antibiotic susceptibilities as well as patient outcomes to ensure appropriate empiric and culture-directed therapy for *S aureus* infections.

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