Changing Susceptibility of Staphylococcus aureus in a US Pediatric Population

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abstract

BACKGROUND: Staphylococcus aureus is a major cause of infection in both adult and pediatric populations. After several decades of increasing prevalence, the proportion of S aureus infections due to methicillin-resistant S aureus has been reported to be in decline in adults. Data for similar changes in pediatric populations are limited.

METHODS: Evaluation of S aureus susceptibility data for pediatric patients receiving care in the US Military Health System was performed. Microbiology and demographic data were collected for years 2005 through 2014. Trends in antibiotic susceptibility results were evaluated. Clinical and demographic characteristics were explored to assess for association with antibiotic susceptibilities.

RESULTS: In this study, 41 745 S aureus isolates from 39 207 pediatric patients were included. An overall increase in susceptibility of isolates to oxacillin was noted over this 10-year period; with over 60% of isolates oxacillin-susceptible in 2014. S aureus susceptibility to clindamycin declined over the study period; notably methicillin-susceptible S aureus susceptibility to clindamycin declined from 90% to 83% (P < .0001). Differences in oxacillin susceptibility between US regions decreased over time.

CONCLUSIONS: Similar to recent trends seen in adults, the proportion of pediatric S aureus infections secondary to methicillin-resistant S aureus appear to be decreasing, as is variability in US geographical resistance rates. Increasing clindamycin resistance among methicillin-susceptible S aureus should raise caution in the use of empirical clindamycin in presumed S aureus infection. Clinicians should be aware of regional susceptibility patterns when choosing empirical regimens.

WHAT’S KNOWN ON THIS SUBJECT: After several decades of increasing prevalence, the proportion of Staphylococcus aureus infections due to methicillin-resistant S aureus (MRSA) has been reported to be in decline in adults. Whether this decrease is also occurring in children is not well documented.

WHAT THIS STUDY ADDS: Our study documents decreasing oxacillin resistance (MRSA) in 41 745 S aureus isolates from pediatric patients, 2005–2014. Clindamycin resistance increased in methicillin-susceptible isolates (MSSA). MRSA was most common in age 1–5 years. Geographical differences in MRSA declined over the study period.

Dr Sutter conceptualized and designed the study, interpreted data, and drafted and edited the manuscript; Ms Milburn carried out analysis of data, interpreted data, prepared tables and figures, and reviewed and revised the manuscript; Ms Chukwuma conceptualized and designed the study, carried out analysis of data, interpreted data, prepared tables and figures, and reviewed and revised the manuscript; Ms Dzialowy carried out analysis of data, interpreted data, prepared tables and figures, and reviewed and revised the manuscript; Dr Maranich interpreted data and reviewed and revised the manuscript; Dr Hospenthal assisted in study design, interpreted data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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*Staphylococcus aureus* is associated with a wide range of disease presentations in hosts of all ages. Methicillin-resistant *S. aureus* (MRSA), traditionally a hospital-acquired pathogen, became an increasingly common cause of community-onset infections in the 1990s. These infections were attributed to a small number of clonal types, predominantly pulse-field type USA 300. MRSA rates increased worldwide over the next decade, with **β-lactam** resistance exceeding 60% in some populations. Although MRSA remains a common pathogen, recent studies have revealed a declining incidence of methicillin resistance among *S. aureus* in adult populations in the United States. A similar decline in children has not been well described, with some authors reporting increasing rates of MRSA infections in children.

Due to optimal tissue penetration and bactericidal action, antistaphylococcal β-lactam antibiotics are the treatment of choice for susceptible *S. aureus* infections. However, the MRSA epidemic has led clinicians to choose alternative therapies for empirical treatment of suspected *S. aureus* infections. Clindamycin is frequently used as first-line empirical therapy for pediatric patients with nonbacteremtic invasive infections, including necrotizing pneumonia and osteomyelitis. Although typically preferred over tetracyclines and trimethoprim/sulfamethoxazole (TMP/SMX), rates of resistance to clindamycin in *S. aureus* infections vary widely, whereas resistance to tetracycline and TMP/SMX is uncommon. A recent study comparing TMP/SMX to clindamycin in uncomplicated skin infections found these drugs comparable.

Several clinical and demographic factors may be associated with antibiotic susceptibility trends. Fundamental differences between pediatric and adult patient populations merit separate epidemiologic analysis of factors associated with *S. aureus* infections. Many studies have suggested that despite a high burden of *S. aureus* disease in children, resistance to non-β-lactam antibiotics is relatively uncommon. Our study evaluates annual antimicrobial susceptibility trends of *S. aureus* isolates from infections in pediatric patients receiving care in the Military Health System (MHS) treatment facilities from 2005 to 2014. Differences in antimicrobial susceptibility of *S. aureus* between age groups, infection types, patient status (inpatient versus outpatient), and geographical region were examined. Finally, susceptibility of MRSA and methicillin-susceptible *S. aureus* (MSSA) to non-β-lactam antibiotics was evaluated to assess for significant temporal trends over the study period.

**METHODS**

This retrospective observational surveillance study included susceptibility results from all *S. aureus* isolates recovered from pediatric patients in the MHS from January 1, 2005, to December 31, 2014. The MHS is composed of 266 fixed military treatment facilities (MTFs) in the United States. Data from overseas locations were not included in this study. Pediatric patients were defined as non-active duty beneficiaries less than 18 years of age.

Susceptibility data from *S. aureus* isolates were identified from the Navy and Marine Corps Public Health Center Health Level 7 formatted microbiology data from the Composite Health Care System. *S. aureus* isolates that were resistant to cefoxitin, methicillin, or oxacillin were classified as MRSA. MSSA isolates were identified as nonresistant to cefoxitin, methicillin, or oxacillin. Only the first *S. aureus* isolate per patient per year was included in the analyses. Isolates were included if culture type and site were consistent with *S. aureus* infection. Isolates classified as colonization or surveillance cultures (ie, from anatomic sites typically not indicative of a true infection) were excluded. These included nasal, mouth, oral cavity, nasopharynx, oropharynx, pharynx, throat, axilla, and groin cultures. Isolates with no oxacillin, cefoxitin, or methicillin susceptibility results were excluded from the analysis.

Antibiograms were constructed by using laboratory interpretation susceptibility results and included ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, penicillin, rifampin, tetracycline, and TMP/SMX. Clindamycin data were limited to the final interpretation entered by the clinical microbiology laboratory into the studied database. Isolates identified as susceptible to clindamycin but resistant to erythromycin had clindamycin “S” overridden to “R” by some laboratories. Others had comments noting inducible resistance with D-test (if performed) and others may have had no testing for inducible resistance performed at all. As a result, the data as a whole did not differentiate between constitutive and inducible resistance. Data for vancomycin were not included because no isolates with confirmed resistance were identified.

Age groupings consisted of neonates (birth through 27 days of age), infants (28 days but less than 12 months of age), early childhood (1 year through 5 years), and middle childhood/early adolescence (6 years through 17 years of age). Patients were categorized as inpatients or outpatients on the basis of patient status at the time of culture. Infections were classified into respiratory, skin and soft tissue infection (SSTI), sterile site, and other infections, as described
locations. Antibiotic susceptibility trends across the 10-year time period were analyzed by Cochrane-Armitage trend test. Trends were considered statistically significant at $P$ value $< 0.05$. Tetracycline, clindamycin, oxacillin, and TMP/SMX susceptibility trends were further investigated by analyzing covariates including age, patient type (inpatient versus outpatient), infection classification, and geographic location. To identify regional changes in oxacillin susceptibility, annual mean susceptibility rates were calculated by region. Ciprofloxacin, clindamycin, erythromycin, tetracycline, and TMP/SMX susceptibility trends for MRSA and MSSA isolates were also compared. A $\chi^2$ test was conducted to calculate $P$ values for each of these comparisons. Statistics were conducted by using SAS software version 9.2 (SAS Institute, Inc, Cary, NC).

**RESULTS**

Over the study period, 41 745 annual first positive *S aureus* isolates from 39 209 pediatric patients were identified. Throughout the study period, 42% of isolates were MRSA and 58% were MSSA. All covariates were well represented among identified isolates with the exception of the Northeast region of the United States. Over the study period, *S aureus* isolates from 2005 to 2014 demonstrated a significant overall trend of decreased susceptibility to clindamycin, ciprofloxacin, and TMP/SMX and an increase in susceptibility to erythromycin, gentamicin, and oxacillin (Table 1). Susceptibility to oxacillin declined from 59.4% in 2005 to a nadir of 53.6% in 2007. From 2007 to 2014, oxacillin susceptibility steadily increased, eventually reaching 68.4% susceptibility (a 14.8% increase). Ciprofloxacin susceptibility significantly decreased overall, although an initial decrease of 10.6% over the first 7 years of the study was subsequently followed by an increase of 6% between 2011 and 2014. Despite the statistically significant decline, *S aureus* remained highly susceptible to TMP/SMX (98.4% susceptible in 2014). Clindamycin susceptibility declined with 86% of isolates susceptible in 2014. Although susceptibility to erythromycin increased during the same period, most isolates remained erythromycin-resistant in 2014 (Table 1). Differences in antimicrobial susceptibility between MRSA and MSSA are presented in Figure 1. Overall, MSSA susceptibility to clindamycin declined from 90.7% to 83.8% ($P < 0.0001$), whereas MRSA rates remained stable. In 2014, 90.5% of MRSA and 83.8% of MSSA were reported as clindamycin-susceptible. MRSA and MSSA remained highly susceptible to TMP/SMX. Despite a small increase in susceptibility to tetracycline among MRSA and a decrease among MSSA, all *S aureus* remained highly susceptible to tetracycline. MSSA isolates had a 34.8% higher rate of susceptibility to ciprofloxacin when compared with MRSA isolates. Erythromycin susceptibility remained stable among MSSA isolates throughout the study period at 63.5%, whereas MRSA susceptibility to erythromycin increased from 12.1% to 20.5%.

The majority of *S aureus* isolates were isolated from outpatients with SSTIs (Tables 2 and 3). SSTI isolates were less likely to be oxacillin-susceptible than isolates from other infection types ($P < 0.0001$). Notably, isolates from young children aged 1 to 5 years had significantly lower rates of susceptibility to oxacillin than isolates from other age groups ($P < 0.0001$). Isolates cultured from inpatients were slightly more likely to be resistant to oxacillin and clindamycin ($P = 0.0129$).

**DISCUSSION**

This study included over 41 000 *S aureus* isolates from infections in children receiving care in the MHS, demonstrating temporal and demographic differences in antimicrobial susceptibility. From a low of 53% in 2007, susceptibility to oxacillin has continuously increased, with nearly 70% of *S aureus* isolates categorized as MSSA in 2014. This is consistent with several recent reports of declining rates of MRSA in both regional and geographically diverse epidemiologic studies. Before 2005, dramatic increases in rates of community-associated MRSA infection were reported, with most studies revealing oxacillin resistance in 40% to 60% of SSTIs. The rate of rise of MRSAs infections slowed by 2005–2006 and subsequently...
A parallel decline in MSSA infections has not been consistently reported, with some authors noting stable rates of MSSA during the same time period. Landrum et al. reported a significant decline in the rate of bacteremia, but not SSTIs, due to both MRSA and MSSA between 2005 and 2010. However, the proportion of MRSA among S. aureus community-onset SSTIs did significantly decrease.

Our study data are derived from the same population of military beneficiaries with S. aureus infections, and include an additional 4 years of data. Although our study was not designed to evaluate incidence of disease, we did document approximately a 46% decrease in the number of S. aureus isolates between 2008 (n = 5732) and 2014 (n = 3112) with an associated decline in the proportion that were MRSA.

Several investigators have described declines in the incidence or proportion of MRSA in pediatric populations. Iwamoto et al. described 876 cases of invasive MRSA infection in children across the United States, reporting a stable rate of health care-associated infection and an increasing incidence of community-associated infections from 2005 to 2010; however, the incidence of both subsets was noted to peak in 2009 and decline rapidly in 2010. Another study of pediatric inpatients in California noted a rapid rise in MRSA hospitalizations between 2002 and 2006, followed by a subsequent decrease in infections reported by a health care-associated infection surveillance system. Iwamoto et al. noted similarities between the trends in proportion of MRSA in our pediatric population and the trends noted in the national surveillance data.

The epidemic of SSTI and invasive MRSAs due to modifications in antimicrobial prescribings practices for suspected S. aureus infections.

Although incision and drainage alone...
may be employed for nonsevere cutaneous abscesses, health care providers often prescribe adjunctive antimicrobial agents, particularly in children.\textsuperscript{10} Despite these early reports, most community-associated isolates remain susceptible to non-β-lactam antibiotics, although drug resistance has developed in some clonal types.\textsuperscript{9, 28} Non-β-lactam therapy with tetracyclines and sulfonamides (TMP/SMX) are frequently prescribed for adults. These options are reasonable for nontoxic children with noninvasive infection as well, although the use of tetracyclines is generally limited to children over 8 years of age due to potential skeletal and dental toxicity. Fluoroquinolones are less preferred for \textit{S} \textit{aureus} due to baseline resistance rates and rapid development of resistance. In addition, fewer than 60\% of MRSA in the current study were susceptible, making ciprofloxacin a poor choice for empirical therapy for \textit{S} \textit{aureus} infections. Fluoroquinolones are used relatively infrequently in children, therefore limiting the relevance of susceptibility trends.

Clindamycin is commonly prescribed for children as empirical therapy for \textit{S} \textit{aureus} infections, to include SSTIs, pneumonia, osteomyelitis, and septic arthritis in clinically stable, nonbacteremic children.\textsuperscript{8, 10} Trends over the final 4 years of our study suggest a progressive decrease in clindamycin susceptibility among MSSA, with less than 84\% of isolates reported as clindamycin-susceptible by 2014. In contrast, MRSA susceptibility to clindamycin remained stable at >90\%. These findings differ from earlier studies noting higher rates of clindamycin resistance among MRSA than MSSA.\textsuperscript{16, 29} Recent reports of clindamycin susceptibility rates in the United States have varied widely, with many studies identifying resistance rates of less than 10\%.\textsuperscript{15, 30, 31} Other reports include clindamycin resistance exceeding 30\% to 50\%.\textsuperscript{11, 12} It is difficult to make direct comparisons between these studies due to significant variability in study dates, target populations, and methodology.

Further confounding any comparisons between studies is the variability in reporting isolates with inducible clindamycin resistance. Although clinical failures with use of clindamycin to treat inducibly resistant isolates are relatively uncommon, the Clinical and Laboratory Standards Institute has recommended testing erythromycin-resistant isolates for inducible clindamycin resistance since 2004.\textsuperscript{32} The microbiology data available in our study were limited to final reports of antibiotic susceptibility and do not distinguish between constitutive or inducible clindamycin resistant isolates. Over the study period, erythromycin susceptibility among MSSA remained stable, suggesting that declining clindamycin susceptibility is a result of an increase in inducible resistance (or recognition of inducible resistance). Poor compliance with D-testing in clinical microbiology laboratories has been reported, although the development of a automated testing for inducible resistance may improve compliance. In our experience, if erythromycin resistance was detected, some microbiology laboratories omitted clindamycin from susceptibility results, reported all erythromycin-resistant isolates as clindamycin-resistant, or warned clinicians about possible inducible resistance without performing testing for inducible resistance. These results may be included only in comments to providers and may not be in the data reviewed in this study.\textsuperscript{33, 34} Increasing rates of clindamycin-resistant MSSA have been reported elsewhere. Whether this is due to proliferation of individual clones or acquisition of the \textit{erm} gene due to antimicrobial pressure is unclear.\textsuperscript{35}

Despite these limitations, our data demonstrate a steady decline in clindamycin susceptibility among MSSA. This trend may lead to some concern about the continued reliance on clindamycin for the empirical treatment of presumptive \textit{S} \textit{aureus} infections although it is probably premature to abandon this effective antibiotic choice. It is crucial that clinicians remain knowledgeable about local susceptibility rates as it would be prudent to consider alternate antimicrobial agents for empirical use when the local clindamycin susceptibility rate drops below 85\%. In that situation, β-lactams, TMP/SMX, or tetracyclines may be used for less severe infections with intravenous vancomycin.
employed in severe cases. If overall MRSA rates continue to decline and clindamycin resistance among MSSA continues to increase, we may see a return to antistaphylococcal β-lactam antimicrobial agents such as oxacillin or first generation cephalosporins as preferred empirical therapy for presumed S. aureus infections.

The clinical covariates explored demonstrated significant associations with antibiotic susceptibility. S. aureus isolates in neonates, infants, and older children were significantly more likely to be susceptible to oxacillin than isolates from children aged 1 to 5 years. By 2014, 62% of isolates from this age group were susceptible, demonstrating an increase in susceptibility, but significantly lower than in older children. This may reflect higher rates of β-lactam antibiotic usage in this age group, but may also be due to intrinsic differences in disease epidemiology. A high burden of disease associated with MRSA infection has been reported in preschool-aged children. 2, 14, 30 Toddlers have a high incidence of MRSA buttock and perineal abscesses that may account for a portion of the higher SSTI rate. 15, 30, 36 Additionally, a recent meta-analysis suggested that the community-associated MRSA epidemic may have peaked earlier in children than in adults. 37 Evaluation of respiratory, sterile site, and other non-SSTI cultures suggests that MSSA predominates in these infections as compared with SSTIs. Although sterile site isolates were not analyzed in this study, these isolates were consistently more likely than SSTI isolates to be oxacillin-susceptible. These findings are in agreement with other pediatric studies, including a recent report in which two-thirds of S. aureus bloodstream isolates were MSSA. 38 In adult and pediatric populations, MRSA bacteremia is a return to antistaphylococcal β-lactam antibiotics such as oxacillin is recommended.

### Table 2: Demographic Characteristics of Pediatric Patients with Staphylococcus aureus Infections and Percent Susceptibilities of Tetracycline, Clindamycin, Oxacillin, and Trimethoprim/Sulfamethoxazole

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*P values were determined by using a χ² test.

b Includes 473 positive blood cultures.
declining, predominantly due to decreasing health care-associated infections. Improved infection control measures in intensive care units and enhanced surveillance for MRSA are potential reasons for this decline in health care-associated bacteremia, primarily in adult patients. Despite this, *S aureus* remains the number 1 hospital-acquired pathogen and still requires vigilance of current antimicrobial susceptibilities. Along with declining rates of MRSA bacteremia, 1 report has also revealed a similar decline in rates of community-associated MSSA bacteremia.

Regional differences in prevalent clonal *S aureus* types have been well described in the United States, with highest rates of MRSA consistently reported in southern and Midwestern states in both early reports and more recent data. In contrast, our study identified a recent convergence of rates of oxacillin susceptibility; by 2014 the southern United States, which in previous years had the highest percentage of MRSA, had only a 5% higher rate of oxacillin resistance than in the West, where oxacillin susceptibility remained high. This suggests that much of the overall increase in oxacillin susceptibility among *S aureus* was driven by decreasing resistance in these historically high MRSA regions.

There are some significant limitations to this study, most secondary to its design as a retrospective review of clinical laboratory data. As laboratory data are associated with only limited clinical data, categorization of infection types and sites may have inaccuracies secondary to local ordering practices. Susceptibility data did not differentiate between inducible and constitutive clindamycin resistance. We also have fewer isolates available from some regions (specifically the Northeast United States) secondary to the number of MTFs present in each region and the population of pediatric patients they serve. Additionally, isolates from inpatients may be underrepresented in regions without inpatient pediatric services that rely on referral to civilian hospitals.

**CONCLUSIONS**

The antimicrobial susceptibility of *S aureus* infections in children...
has changed significantly in the past decade, with increasing susceptibility to oxacillin, particularly in regions with historically high MRSA rates. These trends support the conclusion that the burden of MRSA infections is declining in the US pediatric population, similar to that described in adults. Children aged 1 to 5 years had the highest rates of MRSA, with the vast majority of infections associated with SSTIs. Although rates of resistance to other non-β-lactam antibiotics remain low, clindamycin resistance is increasing among MSSA, with over 16% of isolates identified as resistant. Clinicians should be aware of these trends and use caution when using clindamycin for empirical therapy.

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### ABBREVIATIONS

- MHS: Military Health System
- MRSA: methicillin-resistant *Staphylococcus aureus*
- MSSA: methicillin-susceptible *Staphylococcus aureus*
- MTF: military treatment facility
- SSTI: skin and soft tissue infection
- TMP/SMX: trimethoprim/sulfamethoxazole


20. Baron S, ed. Chapter 93: Infections


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