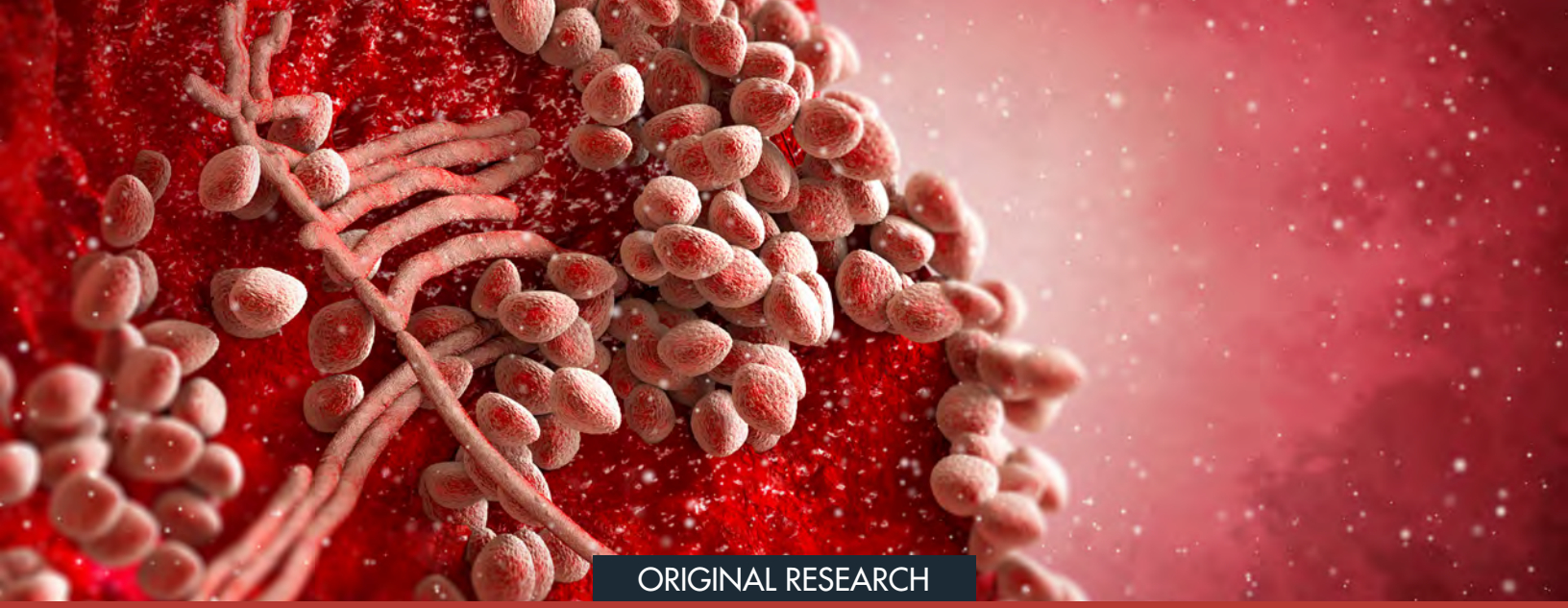

ORIGINAL RESEARCH

Staphylococcus aureus Resistance in Florida

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ABSTRACT

Background: *Staphylococcus aureus* antibiotic resistance is dynamic and local efforts to understand its patterns are the cornerstone for developing mitigation strategies. We aim to describe the antibiotic susceptibility of *Staphylococcus aureus* isolates from 2008 to 2019 and determine the rate and frequency of antibiotic prescribing in a tertiary care pediatric center in South Florida.

Methods: We conducted a retrospective observational study of 11,964 clinical isolates collected from 2008 to 2019 of *Staphylococcus aureus* in our center. We compared antibiotic resistance patterns between MRSA and MSSA isolates. We evaluated antibiotic prescribing practices from 2013 to 2019 using electronic medical records.

Results: Methicillin resistance was present in 47.9% (±0.63) isolates with no significant temporal trend. Resistance to clindamycin was, on average, 24.8% (±1.08), to erythromycin 66.9% (±1.68), to levofloxacin 35.5% (±1.61), and gentamicin 6.8% (±1.11). MRSA isolates had higher resistance rates to most antibiotics than MSSA ($p<0.05$) except for clindamycin, which both had similar rates. Resistance to clindamycin and gentamicin increased significantly from 20% to 25% and from 5 to 15%, respectively, among MRSA and quinolone resistance rose among MSSA from 7% to 13%. Antibiotic prescription rate increased from 56 prescriptions per 1,000 patients to 136 prescriptions per 1,000 patients from 2013 to 2019. There was a positive correlation between erythromycin resistance rate among MRSA and macrolide prescription frequency ($p<0.05$).

Conclusion: Pediatric *Staphylococcus aureus* isolates showed high and stable rates of methicillin resistance with growing clindamycin and gentamicin resistance among MRSA and levofloxacin resistance in MSSA in a tertiary care pediatric center in South Florida.

INTRODUCTION

Staphylococcus aureus is the causative agent of many childhood infections, including endocarditis, bacteremia, osteoarticular, and skin and soft tissue infections (SSTI).[1] Treating these infections has become a global challenge due to the development of antimicrobial resistance (AMR) to multiple antibiotics.[2] In 2019, bacterial AMR caused more than one million deaths worldwide, where *S. aureus* was the second most common pathogen. Over one hundred thousand deaths were attributed to methicillin-resistant *S. aureus* (MRSA) alone.[3]

Methicillin resistance, which confers resistance to most beta-lactams, appeared soon after the introduction of anti-staphylococcal

penicillin. For years, cases of MRSA were limited to hospital-acquired infections. Decades later, with the appearance of USA-300 strains, community-acquired MRSA displaced hospital-acquired MRSA as the most common form of MRSA and rapidly spread among communities making it the most isolated strain in several US regions.[2,4,5] Changes in the epidemiology of MRSA across the country led to the switch to clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX) in suspected or proven MRSA infections as first-line therapies.[6] Now, clindamycin and, to a lesser degree, TMP-SMX resistance rates have started to rise in some regions of the US, bringing new concerns in managing *S. aureus* infections.[4,5,7-9]

S. aureus antibiotic resistance is not a homogenous phenomenon, as it varies widely and depends on multiple factors specific to certain regions, patients, and centers.[2] Evaluating and understanding local resistance patterns can help clinicians make better antibiotic selections and take actions to stop or reduce AMR. This study aims to describe the antibiotic susceptibility of *Staphylococcus aureus* isolates from 2008 to 2019, compare antibiotic resistance patterns between MRSA and MSSA isolates, determine the rate and frequency at which certain antibiotics are prescribed, and explore the relation between antibiotic resistance rates and antibiotic prescription in a tertiary care pediatric center in South Florida.

MATERIALS AND METHODS

This is a retrospective observational study performed at Nicklaus Children's Hospital (NCH), a 300-bed tertiary pediatric care center that serves an average of ten thousand inpatient admissions and more than 75,000 ED visits yearly in Miami and South Florida. All non-duplicated *Staphylococcus aureus* clinical isolates from various body and tissue sites as well as hospital locations, comprising the emergency department (ED), urgent care centers, inpatient, and outpatient settings, were included for the elaboration of the annual institutional antibiograms from 2008 to 2019 by the Microbiology Laboratory at NCH. Antibiograms were elaborated based on the Clinical and Laboratory Standards Institute (CLSI) Guidelines from the isolates obtained the year prior.[10] Antibiotic susceptibility to clindamycin, erythromycin, levofloxacin, ciprofloxacin, gentamicin, oxacillin, rifampin, TMP-SMX, vancomycin and linezolid was performed on all isolates via disc diffusion method.

Outpatient and ED antibiotic prescription data from 2013 to 2019 and patient encounter visits were collected from electronic medical records. Only complete prescriptions were included, and all duplicates were removed from the analysis. The extracted data were entered into a database using Microsoft Office Excel®. The statistical analysis included descriptive statistics such as frequency distribution, means, and proportions; student's t-test to compare the resistance rate means; Pearson's correlation coefficient was used for temporal antibiotic resistance trends; and linear regression for the association between resistance rates and antibiotic prescription frequency the year preceding the antibiogram report. GraphPad® was used for statistical analysis. The antibiotic prescription rate was estimated by dividing the number of prescriptions for a specific antibiotic by the total number of hospital visits per year, and the antibiotic prescription frequency was estimated as the rate at which each antibiotic group was prescribed from the total number of antibiotics prescribed annually. Statistical significance was considered when a two-tailed $p<0.05$.

RESULTS

A total of 11,964 *Staphylococcus aureus* isolates were included in this study. Resistance to rifampin, TMP-SMX, vancomycin, and linezolid varied over time but remained at <2% with no significant temporal trends and were not included in Figure 1. No cases of vancomycin-intermediate *S. aureus* (VISA) or vancomycin-resistant *S. aureus* (VRSA) were detected. Resistance to clindamycin was, on average, 24.8% (±1.08), to erythromycin 66.9% (±1.68), to levofloxacin 35.5% (±1.61), and gentamicin 6.8% (±1.11). Resistance to methicillin among all isolates ranged between 49% and 56%, with an average of 47.9% (±0.63) with no significant temporal trend (Figure 1).

MRSA isolates had higher resistance rates to erythromycin, levofloxacin, and gentamicin than MSSA. Resistance to clindamycin was not different within groups ($p>0.05$). Among MSSA isolates, resistance to levofloxacin increased significantly from 7% to 13%, whereas resistance to other antibiotics did not change significantly over time. Regarding MRSA isolates, resistance to clindamycin and gentamicin increased from 20% to 25% and 5 to 15%, respectively, whereas resistance to erythromycin decreased significantly from 92% to 80% in the same period (Figure 2).

The antibiotic prescription rate increased from 56 prescriptions per 1,000 patients to 136 prescriptions per 1,000 from 2013 to 2019. During that period, penicillin prescription frequency increased significantly from 47.1% to 55.6% ($p<0.05$), while cephalosporin prescription frequency decreased from 25.5% to 21.9% ($p<0.05$), maintaining the overall beta-lactam prescription rate unchanged ($p>0.05$). Macrolide prescription frequency declined significantly from 16.9% to 8.8% ($p<0.05$). The frequency at which lincosamides and quinolones were prescribed did not vary significantly during this time ($p>0.05$) (Figure 3).

The erythromycin resistance rate among MRSA isolates decreased proportionally to the frequency at which macrolides were prescribed ($p<0.05$). There was no relation between erythromycin resistance rate and the prescription frequency of beta-lactams, quinolones, or lincosamides. The clindamycin and methicillin resistance rates among *S. aureus* isolates showed no relation with the prescription frequency of the antibiotics mentioned above.

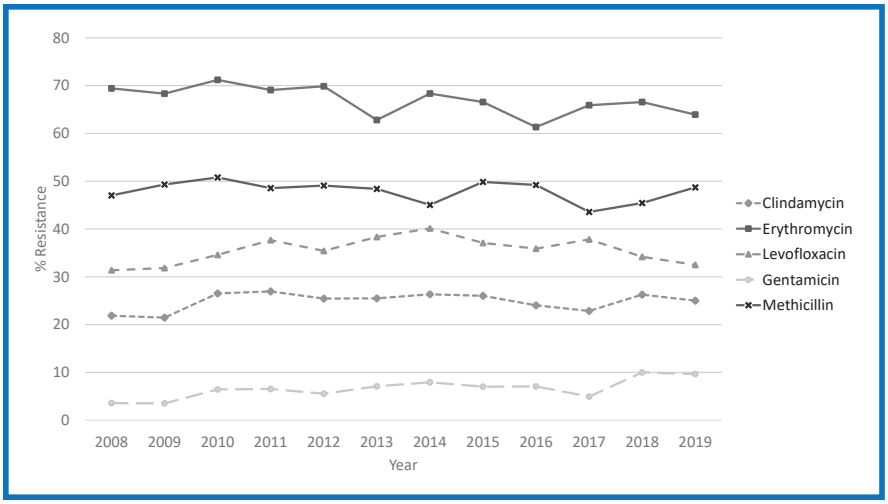

Figure 1. Antibiotic resistance in S aureus isolates from pediatric patients between 2008 and 2019. The trend in erythromycin and gentamicin resistance were statistically significant ($p<0.05$); all other trends shown were not significant.

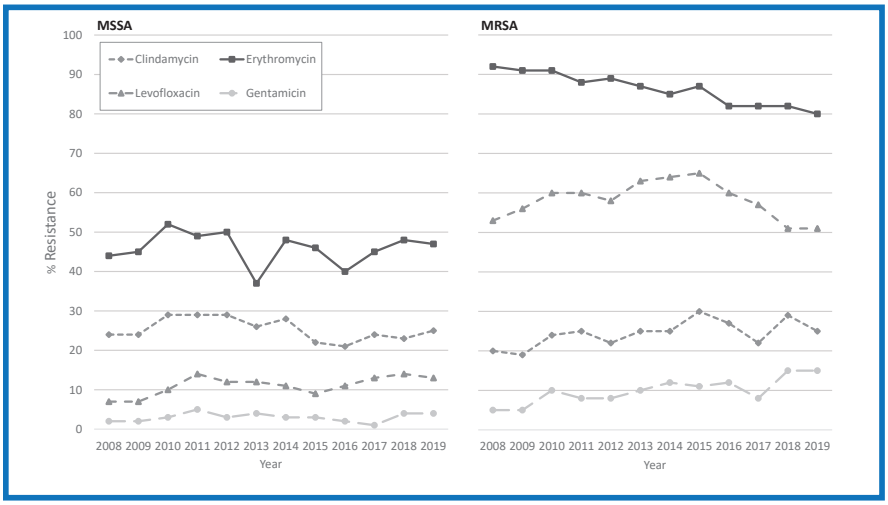

Figure 2. Comparative annual resistance rate among MSSA and MRSA isolates from pediatric patients between 2008 and 2019. The trend in levofloxacin resistance among MSSA was statistically significant, as well as the trends in erythromycin, clindamycin, and gentamicin in MRSA; all other trends were not significant.

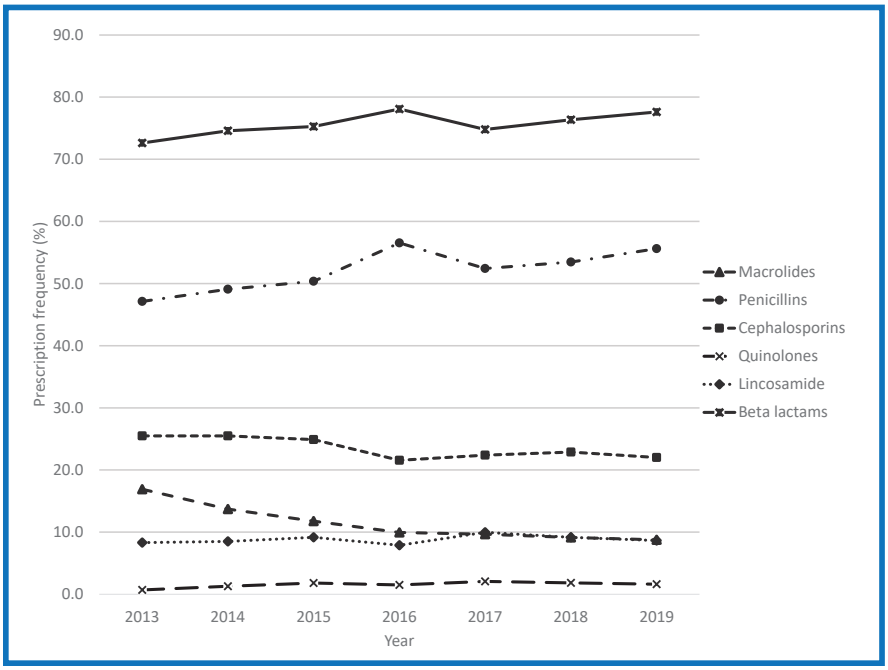

Figure 3. Annual antibiotic prescription frequency as a percentage of all antibiotics prescribed in outpatient facilities and Emergency Department at Nicklaus Children's Hospital between 2013 and 2019. Beta-Lactams are expressed as the summation of cephalosporins and penicillins. The frequency at which penicillins, cephalosporins, and macrolides were prescribed changed significantly; all other frequencies did not change significantly.

DISCUSSION

Methicillin resistance rates vary widely within studies due to differences in study periods, location, prevalent *S. aureus* strains, population characteristics, and site of infection, among others. Prior studies consistently identified an increasing rate of methicillin resistance from the early 2000s up to the end of the decade across the US.[4, 11] Since then, several other reports have shown declining rates of methicillin resistance among *S. aureus* isolates from around 50% to levels below 30% or even 15% in the Midwest[4,5,8,9] which has been attributed, at least in part, to an equivalent decline of MRSA infection incidence across the country.[5,12] Rates of methicillin resistance also seem to be higher in samples collected from children 1 to 5 years of age compared to other age groups, including adults, as well as from SSTI when compared to invasive disease and from community-acquired infections when compared to healthcare-associated infections.[4,8,9,12,13]

In our study, the methicillin resistance rate among *S. aureus* isolates remained stable at nearly 50% throughout the study period. We conclude that this reflects not only the antibiotic resistance pattern of *S. aureus* in this hospital system but also the resistance pattern of this bacterium in South Florida. Antibiotic overuse may play a significant role, as it has been depicted in prior studies[14] where antibiotic prescribing is up to three times higher in the South than in other US regions.[15] In our center, antibiotic prescriptions per hospital visit more than doubled during the study period. During this time, penicillins' prescription frequency significantly increased while cephalosporins' decreased, maintaining the overall beta-lactam prescription rate unchanged and making it the antibiotic group most frequently prescribed in the ED and outpatient settings. This variation in antibiotic prescribing practices aligns with the American Academy of Pediatrics (AAP) and Infectious Diseases Society of America (IDSA) recommendations for managing upper and lower respiratory infections, favoring penicillins over cephalosporins.[16,17] Exposure to specific antibiotic groups for extended periods, such as beta-lactams, can serve as a selective pressure in the community and help maintain non-susceptible *S. aureus* strains in the area, as it has been seen in other community and hospital-wide studies[18,19], which could explain the persistently elevated levels of methicillin resistance.

Clindamycin remains one of the first-line treatments for SSTI in children in most centers[20]; however, rising resistance threatens the suitability of this antibiotic to treat *S. aureus* infections, and it challenges its role as the antibiotic of choice for initial empiric treatment. The AAP's Red Book® recommends clindamycin as first-line empiric therapy in nonlife-threatening infections in areas where resistance to clindamycin remains below 15% [21], making clindamycin a poor antibiotic selection at our center. Resistance to clindamycin can be inducible or constitutive depending on the mechanism and phenotypic expression of the isolates relative to macrolides, lincosamides, and streptogramins B.[22] Clindamycin nonsusceptibility appears to be more common among MSSA isolates, community-acquired infections, USA 300 strains, and in SSTI.[4,5,7-9] In our study, both MRSA and MSSA isolates showed comparable rates of resistance to clindamycin, with a significantly increased rate among MRSA isolates. Resistance was not associated with any antibiotic prescription frequency in our study. However, it is worth noting that as clindamycin resistance rose among MRSA, erythromycin resistance declined within the same group. This, coupled with the fact that erythromycin resistance decreased directly proportional to the prescription frequency of macrolides, might be indicative of increasing macrolide-independent constitutive resistance rather than inducible resistance in our isolates.

Staphylococcus aureus resistance to other antibiotics has been dynamic, and even though quinolones remain an acceptable option for the treatment of MSSA infections, quinolone resistance can easily develop among *S. aureus*, and it has been increasing significantly among MSSA isolates during our study period. Similarly, gentamicin, used for its synergistic effect with beta-lactams in treating infective endocarditis[23] and other invasive infections, has also demonstrated increasing resistance rates among MRSA isolates. On the other hand, despite the growing TMP-SMX resistance in other centers in the US, especially among MRSA isolates and long-term care facilities[4,8,24], resistance rates have remained consistently below 2% in our center and make it a suitable option for the treatment of MRSA infections. Equally important, MRSA isolates remained broadly susceptible to vancomycin and linezolid without any VISA or VRSA isolates found.

Our study is one of the first to evaluate *Staphylococcus aureus* antibiotic susceptibilities from pediatric samples in South Florida. This helps us to understand the need for better antibiotic stewardship initiatives and could guide pediatricians to make a better empiric antibiotic selection for staphylococcal infections in the region. However, certain limitations may reduce the impact of our findings. First, this is a retrospective review of laboratory data; no clinical or demographic data could be included in the analysis. Second, as a single-center study, the findings may only be representative of some *S. aureus* susceptibility patterns in the region, and caution should be taken when extrapolated to other centers. Additionally, susceptibility data did not differentiate between inducible and constitutive clindamycin resistance and did not include genotyping for resistance gene identification. Lastly, we did not account for possible changes in the practice of collecting cultures from sites of infection or empiric antibiotic selection at NCH during this time.

CONCLUSION

In conclusion, the susceptibility of pediatric *Staphylococcus aureus* isolates has changed in recent years. Methicillin resistance is present in almost half of all isolates and may limit the use of beta-lactams as first-line treatment options. Clinicians should consider MRSA and MSSA's different resistance patterns when treating these infections. Clindamycin is no longer an acceptable first-line option for treating *S. aureus* infections at our institution. Trimethoprim-sulfamethoxazole, vancomycin, and linezolid remain acceptable alternatives for treating MRSA infections in our center. Antibiotic prescribing is rising in our center, and efforts to limit them should be implemented.

FUNDING

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

We thank everyone involved in the Antimicrobial Stewardship Program at Nicklaus Children's Hospital and the microbiology laboratory personnel who made this study possible.

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