Evaluating the Role of *Staphylococcus aureus* Nasal PCR in Pediatric Head and Neck Infections

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OBJECTIVE Vancomycin is often empirically used in the management of head and neck infections (HNIs) in children. The objective of this study was to determine the utility of *Staphylococcus aureus* (SA) nasal PCR to facilitate de-escalation of vancomycin for pediatric HNIs.

METHODS This was a single-center, retrospective cohort study of pediatric patients who received empiric intravenous vancomycin for a diagnosis of HNIs between January 2010 and December 2019. Subjects were excluded if they met any of the following: confirmed/suspected coinfection of another site, dialysis, immunocompromised status, admission to the NICU, alternative diagnosis that did not require antibiotics, or readmission for HNIs within 30 days of previous admission. The primary outcome was time to de-escalation of vancomycin. Total duration of antibiotics, treatment failure, hospital length of stay (LOS), and incidence of acute kidney injury (AKI) were also assessed.

RESULTS Of the 575 patients identified, 124 patients received an SA nasal PCR. The median time to de-escalation was 39.5 hours in those patients compared with 53.7 hours in patients who did not have a SA nasal PCR ($p = 0.002$). No difference was noted in total duration of all methicillin-resistant *Staphylococcus aureus* antibiotics, hospital LOS, treatment failure, and AKI.

CONCLUSIONS In a large cohort of pediatric patients with HNIs, those who underwent testing with an SA nasal PCR spent less time receiving intravenous vancomycin, although their LOS was not significantly reduced. Further investigation is needed to better define the role of SA nasal PCRs in determining antibiotic therapy for HNIs.

ABBREVIATIONS AKI, acute kidney injury; HNI, head and neck infection; IQR, interquartile range; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; SA, *Staphylococcus aureus*; SCr, serum creatinine

KEYWORDS blood culture panels; de-escalation; head and neck infection; methicillin resistance; rapid test; SA nasal PCR; vancomycin

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Introduction

Staphylococcus aureus (SA) is a Gram-positive bacteria that can be the cause of a number of infections, with methicillin-resistant *Staphylococcus aureus* (MRSA) specifically having a significant impact on length of stay (LOS), hospital costs, and mortality.¹ In recent years, the incidence of SA infections in pediatric patients has been rising, including those affecting the head and neck, which are usually preceded by underlying upper respiratory infections and can lead to abscess formation.^{2–4} As a result, patients admitted to the hospital for head and neck infections (HNIs) are commonly started on empiric antimicrobial therapy with vancomycin, a glycopeptide antibiotic used to treat SA infections. However, only a small portion of patients treated with empiric anti-MRSA therapy ultimately require it based on the microbiology of

their infection.⁵ A diagnostic tool capable of determining the need for MRSA therapy in HNI would provide benefit to patients and clinicians. One of the tests that can be used in this setting is a rapid diagnostic test known as the SA nasal PCR assay, which can help detect colonization with SA in the nares. Although some systems are limited to detection of MRSA isolates only, others can detect the presence of both methicillin-susceptible *S aureus* (MSSA) and MRSA isolates.^{6–8}

The use of SA nasal PCR has been studied in lower respiratory tract infections, with several studies demonstrating a beneficial role in reducing duration of empiric MRSA antimicrobial therapy in patients with pneumonia.^{9–11} Pediatric trials are limited; however, available studies in pediatric pneumonia have reported high negative predictive values with the nasal PCR test and a possible role in facilitating earlier discontinuation

Table 1. Baseline Characteristics

Characteristics	No Nasal SA PCR (n = 102)	Nasal SA PCR (n = 124)	p value
Age, median (IQR), yr	3.5 (1.7–6.8)	4.7 (1.7–8.1)	0.15
Weight, median (IQR), kg	16.2 (11.8–24.5)	18.7 (11.9–32.1)	0.20
Male, n (%)	52 (51)	76 (61.3)	0.12
Diagnosis, n (%)			
Orbital abscess	20 (19.6)	43 (34.7)	0.19
Lymphadenitis/adenitis	16 (15.7)	26 (21.0)	0.74
Parotid abscess	4 (3.9)	6 (4.8)	1.00
Retropharyngeal abscess	29 (28.4)	28 (22.6)	0.70
Peritonsillar abscess	11 (10.8)	4 (3.2)	0.34
Neck abscess/swelling	22 (21.6)	17 (13.7)	0.02
Prior to admission antibiotics, n (%)	62 (60.8)	68 (54.8)	0.37
Nasal swab positive, n (%)	—	23 (18.6)	NR
MSSA	—	19 (82.6)	NR
MRSA	—	4 (17.4)	NR
Surgical intervention, n (%)	54 (52.9)	42 (33.9)	0.004
Other culture obtained, n (%)	71 (69.6)	76 (61.3)	0.19
Blood culture	14 (19.7)	21 (27.6)	0.26
Wound culture	40 (56.3)	47 (61.8)	0.50
Both	17 (23.9)	8 (10.5)	0.03
Number of organisms from other cultures, n (%)			
Monomicrobial	20 (28.2)	25 (32.9)	0.43
Polymicrobial	26 (36.6)	18 (23.7)	0.09
No growth	25 (35.2)	33 (43.2)	0.39
Organisms from other cultures obtained, n (%)			
MRSA	6 (8.5)	5 (6.6)	0.84
MSSA	11 (15.5)	13 (17.1)	0.50
Mixed flora	10 (14.1)	8 (10.5)	0.71
<i>Streptococcus</i> spp.	22 (31.0)	14 (18.4)	0.14
<i>Haemophilus influenzae</i>	3 (4.2)	0 (0)	0.24
<i>Pseudomonas aeruginosa</i>	0 (0)	1 (1.3)	0.48

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NR, not relevant; SA, *Staphylococcus aureus*; spp., species

of empiric MRSA coverage.¹² There remains a relative paucity of studies reporting the use of SA nasal PCR for de-escalation of antibiotics in HNIs. One recent trial conducted by Bradford et al¹³ identified that SA nasal PCRs in pediatric patients with head and neck abscesses had a positive predictive value of 91.7% and a negative predictive value of 78.1%. Given the variable use of SA nasal PCR testing at our institution in the setting of pediatric HNIs, this study was designed to better understand its current utility and impact on time to de-escalation from vancomycin therapy and the number of total days of antibiotic therapy in pediatric patients with various HNIs at our institution.

Methods

Study Design and Patient Population. This was a single-center, retrospective cohort study conducted at

the University of Iowa Stead Family Children's Hospital, which is a 190-bed pediatric tertiary care center in Iowa City, IA. Pediatric patients identified as having specific HNIs by ICD-10¹⁴ codes from January 1, 2010 to December 31, 2019 were evaluated and grouped by whether or not they underwent testing with a SA nasal PCR (Xpert MRSA until July 2012; Xpert SA Nasal Complete, thereafter). Eligible patients were hospitalized pediatric patients ≤ 18 years of age who had 1 of the following primary diagnoses: orbital abscess, lymphadenitis/adenitis, parotid abscess, retropharyngeal abscess, or neck abscess, and who were treated empirically with intravenous vancomycin. Patients with confirmed or suspected coinfection of another site distal from the head/neck, receiving dialysis, having a primary or secondary immunodeficiency, admission to the NICU, having an alternative diagnosis that did not require

Table 2. Time to De-escalation Off Vancomycin (N = 226)

	De-escalation Off Vancomycin, hr*	p value
All patients (N = 226)		
No nasal SA PCR (n = 102)	53.7 (36.0–85.0)	0.002
Nasal SA PCR (n = 124)	39.5 (23.1–66.8)	
Nasal SA PCR testing (n = 124)		
Negative PCR (n = 101)	43.5 (25.2–67.4)	0.11
Positive PCR (n = 23)	29.8 (12.5–59.9)	
Positive nasal SA PCR test (n = 23)		
MSSA (n = 19)	24.8 (12.1–58.6)	0.06
MRSA (n = 4)	58.8 (57.5–84.3)	

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SA, *Staphylococcus aureus*

* Data presented as median (IQR).

antibiotic treatment, or being readmitted for HNIs within 30 days of a prior admission were excluded.

Data Collection. Data were collected retrospectively using the electronic medical record. The following information was collected and analyzed: age, sex, weight, diagnosis, SA nasal PCR test result (if applicable), other microbiological culture results, surgical intervention (if applicable), serum creatinine (SCr), antibiotics administered (including total days of therapy), and hospital LOS.

Outcomes. The primary outcome of this study was to determine the time to de-escalation of vancomycin in patients who underwent testing with an SA nasal PCR test compared with those who did not have the test. Secondary endpoints included total days of all antimicrobial therapy for a specified infection, LOS, treatment failure, and incidence of acute kidney injury (AKI) during hospitalization.

Study Definitions. The primary outcome of time to de-escalation of vancomycin was defined as the number of hours from vancomycin initiation to vancomycin discontinuation. A day of therapy was defined by a patient receiving at least 1 dose of a medication on a given day. Hospital LOS was calculated in hours from the admission date and time to the discharge date and time. Prior to admission, antibiotics were classified as any receipt of antibiotics in the 14 days prior to admission. Treatment failure was defined as hospital readmission within 30 days of previous admission for a HNI. Lastly, AKI was defined as any rise in SCr by 0.3 mg/dL or a 50% increase from the patient's baseline SCr during the patient's hospitalization.

Statistical Analysis. All categorical variables were tested using the Fisher exact test or χ^2 , as appropriate. For continuous variables, the Mann-Whitney *U* test was used. Statistical significance was defined as $p < 0.05$. Data were analyzed using Stata version 16.0 (StataCorp, College Station, TX). Medians were reported with an IQR.

Results

Of the 575 patients identified, a total of 226 were included in the study, with 124 in the SA nasal PCR group and 102 in the no SA nasal PCR group. Patients (n = 349) were excluded for the following reasons: immunocompromised (n = 190), confirmed or suspected coinfection of another site distal from the head/neck (n = 118), readmitted for HNIs within 30 days of previous admission (n = 14), admitted to the NICU (n = 13), alternate diagnosis that did not require antibiotic treatment (n = 9), and received dialysis or had end stage renal disease (n = 5).

A between-group comparison of demographic data and clinical characteristics is displayed in Table 1. There were no significant differences observed between groups, aside from surgical intervention, which occurred more commonly in the group that did not have an SA nasal PCR ($p = 0.004$).

When evaluating our primary outcome (i.e., time to de-escalation off vancomycin), there was a statistically significant difference between the 2 groups with patients in the SA nasal PCR group having a shorter median time to de-escalation compared with those patients who did not have a nasal PCR test (Table 2).

There was no statistically significant difference in the total duration of antibiotic therapy in those patients who underwent testing with an SA nasal PCR and those who did not (Table 3). Likewise, those who received non-MRSA- versus MRSA-targeted antibiotic therapy were not different (Table 3). Patients who had a nasal PCR positive for MRSA did receive more total days of MRSA-targeted antibiotic therapy than those who had a nasal PCR negative for MRSA ($p = 0.03$). Although there were more treatment failures among patients who underwent SA nasal PCR testing, this did not reach statistical significance (Table 4). Total hospital LOS was comparable between the 2 groups (Table 4). There was 1 patient in each group who experienced AKI during the hospitalization (Table 4).

Table 3. Days of Antimicrobial Therapy Among All Patients*

	Antibiotic Duration, days		
	All MRSA	All non-MRSA	All
All patients (N = 226)			
No nasal SA PCR (n = 102)	9 (4–16)	13.5 (6–17)	21 (15–31)
Nasal SA PCR (n = 124)	5.5 (2–18.5)	16 (11–19)	22 (18–32.5)
p value	0.36	0.03	0.1
Nasal SA PCR testing (n = 124)			
Negative test (n = 101)	5 (2–18)	15 (10–19)	21 (17–32)
Positive test (n = 23)	15 (2–20)	16 (15–20)	28 (19–36)
p value	0.5	0.24	0.11
Positive SA PCR testing (n = 23)			
MSSA (n = 19)	4 (2–19)	17 (16–20)	31 (18–36)
MRSA (n = 4)	25 (17.5–29)	2.5 (0.5–8.5)	27 (27–29.5)
p value	0.03	0.002	0.94

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SA, *Staphylococcus aureus*

* Data presented as median (IQR).

Table 4. Treatment Failure, Hospital LOS, and Acute Kidney Injury

	No Nasal SA PCR (n = 102)	Nasal SA PCR (n = 124)	p value
Treatment failure, n (%)	4 (3.9)	10 (8.1)	0.27
Hospital LOS, median (IQR), hr	90.5 (69.1–119.5)	87.3 (67.4–113.8)	0.71
Acute kidney injury, n (%)	1 (0.01)	1 (0.01)	0.71
Baseline serum creatinine, median (IQR), mg/dL	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.37

SA, *Staphylococcus aureus*

Discussion

This study provides novel data on the utility of SA nasal PCR as a tool in pediatric patients with HNIs for de-escalation of vancomycin. Though our study is the first pediatric study that has evaluated the time to de-escalation of vancomycin in patients who underwent testing with an SA nasal PCR for HNIs, our findings are not completely congruent with the characteristics of SA nasal PCR tests that have been reported in previous trials. A recent trial conducted at the Department of Veterans Affairs hospitals found a 97% negative predictive value of nasal swabs to rule out various MRSA infections.¹⁵ Furthermore, prior pediatric studies noted that the SA nasal PCR had negative predictive values of 100% and 78% in pneumonia and HNIs, respectively.^{11,12} In our study, there were 5 patients who had nasal PCR tests negative for the presence of MRSA but who grew MRSA from a wound culture, which equates to an approximate false negative rate of 4%. There are a few possible explanations for this observed false negative rate. Collection technique is important as an improperly collected nasal sample may lead to a false negative result. It has also

been shown that infants and children may be colonized with MRSA in their oropharynx rather than nasopharynx, which may also contribute to a negative nasal PCR test in a patient who has an MRSA infection.^{16–18}

Results of an SA nasal PCR can influence the duration of MRSA antimicrobial therapy. Our study supported this finding in that patients who had a nasal PCR positive for MRSA received a longer duration of MRSA-targeted antibiotics than those with a negative PCR test. As was demonstrated by Bradford et al,¹³ our results may support the superiority of the positive predictive value of SA nasal PCR over its negative predictive value in children with HNIs.

Additionally, our study also evaluated treatment failure as a secondary outcome. Therapy failed in 10 patients who received the SA nasal PCR. Of these patients, 1 had a nasal swab positive for MRSA on initial admission but did not grow MRSA on surgically obtained cultures on this visit. Nonetheless, this patient was treated with anti-MRSA therapy prior to readmission. However, among the 9 other patients who initially had negative SA nasal swabs and required surgical intervention

upon readmission, only 1 grew MRSA from a surgically obtained specimen; whereas, 1 patient grew *Streptococcus anginosus* and 1 other grew *Mycobacterium avium complex*. The remaining 7 patients who experienced failed treatment did not have microbial growth on blood or wound cultures. Failure of medical management can likely be attributed to the need for surgical intervention and source control upon initial admission rather than inadequate antimicrobial coverage, drug dosage, and duration of therapy. As reported elsewhere, the use of a SA nasal PCR was not associated with decreased hospital LOS. Finally, there was no difference in the rate of AKI between our studied groups.

The primary limitation of our study was its retrospective, single-center design that used chart reviewed and documented ICD-10¹⁴ codes to obtain clinical data. The results of this review could have been affected by inaccurate or incomplete documentation. Additionally, there are certain pieces of information such as adherence to post-discharge antibiotic therapy that would be difficult to assess in any study type. Microbiological confirmation of the causative pathogen, as well as antibiotics prescribed prior to admission for the HNIs in our review was often unattainable. Although studies assessing SA nasal PCR utility in other types of infections have been able to produce negative and positive predictive values associated with the diagnostic, the absence of a confirmed pathogen in many of our cases resulted in an inability to calculate similar metrics. Furthermore, without an institutional policy regarding use of SA nasal PCR in place prior to conducting this review, it was possible that provider decision making was influenced by patient's clinical status rather than solely on the result of the SA nasal PCR and this may have affected antibiotic choices. Finally, definition of AKI was based on rise in SCr rather than pediatric nephrotoxicity scales, such as pediatric Risk, Injury, Failure, Loss, End-stage kidney disease because these scores would have required additional information including urine output, which may not be accurately or frequently recorded in the chart.

In this study, pediatric patients with an HNI who underwent testing with an SA nasal PCR received less empiric intravenous vancomycin. These patients had a shorter MRSA antibiotic course, longer non-MRSA antibiotic course, and similar total days of antibiotics in comparison with patients who did not undergo SA nasal PCR testing. Though the results of an SA nasal PCR test may help guide the clinical decision to either initiate, continue, or stop MRSA-active antibiotic therapy in the setting of a pediatric HNI, the data from this study do not support their reliability as a definitive indicator of MRSA involvement. Therefore, further prospective studies are needed to assess the use of SA nasal PCR de-escalation and stewardship of antibiotics in children with HNIs.

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