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Prevalence of *Staphylococcus aureus* and Use of Antistaphylococcal Therapy in Children Hospitalized with Pneumonia

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Abstract

Within a cohort of >2,000 children hospitalized with community-acquired pneumonia, staphylococcal pneumonia was rare (1%) but associated with adverse in-hospital outcomes. Despite this low prevalence, use of antistaphylococcal antibiotics was common (24%). Efforts are needed to minimize overuse of antistaphylococcal antibiotics while also ensuring adequate treatment for pathogen-specific diseases.

Although *Staphylococcus aureus* pneumonia is common in children with cystic fibrosis and those with healthcare-associated infections (eg, ventilator-associated pneumonia),^{1,2} *S.*

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aureus is an uncommon cause of community-acquired pneumonia in children. In recent years, concerns have arisen about the increasing frequency and severity of staphylococcal pneumonia, largely fueled by the emergence of community-associated methicillin-resistant *S. aureus* (MRSA).^{3,4} Thus, therapy with clindamycin or vancomycin, both active against MRSA, has been recommended when *S. aureus* is suspected.⁵ Given the lack of rapid and sensitive approaches to the detection of the etiologies of pneumonia, antibiotic selection is most often empirical, contributing to overuse of anti-MRSA antibiotics. In addition, resistance against these antibiotics, especially clindamycin, has been increasing.^{6,7}

A better understanding of the likelihood of staphylococcal pneumonia would help to optimize empirical antibiotic selection, allowing for judicious use of antistaphylococcal antibiotics, while also avoiding poor outcomes due to delays in effective treatment when *S. aureus* is present.⁸ Using data from a multicenter, population-based study of pneumonia hospitalizations in children, we sought to describe the prevalence, clinical characteristics, and in-hospital outcomes of staphylococcal pneumonia and the prevalence of antistaphylococcal antibiotic use.

METHODS

The Etiology of Pneumonia in the Community (EPIC) study was a prospective, active, population-based surveillance study of pneumonia hospitalizations among children (age <18 years) conducted between 2010 and 2012 at three children's hospitals, including two in Tennessee and one in Utah.⁹ Children hospitalized with clinical evidence of pneumonia and radiographic evidence confirmed by a blinded review by study radiologists were enrolled. Etiologic assessments included blood analysis for bacterial culture, serology for eight respiratory viruses, pneumococcal and group A streptococcal polymerase chain reaction (PCR), and naso/oro-pharyngeal swabs for PCR for 13 respiratory viruses, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. Data from other clinical specimens (pleural fluid, high-quality endotracheal aspirate, or quantified bronchoalveolar lavage fluid) were also recorded. For this study, we included only children with at least one bacterial culture and complete information about antibiotic use. Those with confirmed fungal pneumonia were excluded. Additional details regarding the study population and methods have been published previously.⁹

Staphylococcal pneumonia was defined based on the detection of *S. aureus* by culture (any site) or PCR (pleural fluid only), regardless of codetection of other pathogens. Antibiotic susceptibility profiles were used to classify *S. aureus* isolates as MRSA or methicillin-sensitive *S. aureus* (MSSA). The remaining children were classified as nonstaphylococcal pneumonia including children with other bacterial pathogens detected (classified as other bacterial pneumonia, excludes atypical bacteria), atypical bacteria, viruses, and no pathogens detected.

Use of anti-MRSA antibiotics (vancomycin, clindamycin, linezolid, doxycycline, and trimethoprim-sulfamethoxazole) and any antistaphylococcal antibiotics (anti-MRSA agents plus oxacillin, nafcillin, and cefazolin) during and after the first two calendar days of admission was identified by medical record review.

Descriptive statistics included number (%) and median (interquartile range, [IQR]) for categorical and continuous variables, respectively. Baseline clinical characteristics and outcomes were compared between children with staphylococcal versus nonstaphylococcal pneumonia, those with staphylococcal versus other bacterial pneumonia, and those with MRSA versus MSSA pneumonia using Wilcoxon rank-sum and Pearson's chisquare tests where appropriate. To account for multiple comparisons, we used a Bonferroni corrected P value threshold of $<.001$ to determine statistical significance.

RESULTS

Of the 2,358 children enrolled in the EPIC study hospitalized with radiographically confirmed pneumonia, 2,146 (91.0%) had 1 bacterial culture obtained. Two children with *Histoplasma capsulatum* fungal infection and six children with incomplete antibiotic utilization data were excluded, yielding a final study population of 2,138 children. Among these, blood samples were obtained from 2,134 (>99%) children for culture, pleural fluid from 87 (4%) children, bronchoalveolar lavage fluid from 31 (1%) children, and endotracheal aspirate from 80 (4%) children. Across all culture types, there were 2,332 initial cultures; 2,150 (92%) were collected within the first 24 hours.

Staphylococcal pneumonia was detected in 23 of the 2,138 children (1% [95% CI 0.7, 1.6]; 17 MRSA, 6 MSSA). Of these, 6/23 (26%) had bacteremia, 12/23 (52%) had a positive pleural fluid, and 9/23 (39%) had a positive culture from bronchoalveolar lavage fluid or endotracheal aspirate; 4/23 (17%) children had *S. aureus* detected from more than one site. Three children (13%) with *S. aureus* had a viral codetection, including two with influenza.

Compared with children with nonstaphylococcal pneumonia, those with staphylococcal pneumonia were more likely to have a parapneumonic effusion (78% vs 12%, $P < .001$), but less likely to have cough (78% vs 95%, $P < .001$). Other baseline characteristics were similar between the two groups. Children with staphylococcal pneumonia had more adverse outcomes than those without (Table), including longer median length of stay (10 vs 3 days, $P < .001$), more frequent admission to intensive care (83% vs 21%, $P < .001$), and more frequent invasive mechanical ventilation (65% vs 7%, $P < .001$). Similar findings were noted when staphylococcal pneumonia was compared with pneumonia caused due to other bacterial pathogens ($n = 124$). There were no significant differences in baseline characteristics or clinical course between children with MRSA and MSSA pneumonia, although the numbers were small. Overall, *S. aureus* was detected in 18/267 (7%) children with parapneumonic effusion and 19/462 (4%) children admitted to intensive care. Importantly, there were no confirmed *S. aureus* cases among children with less severe pneumonia, defined as lacking both parapneumonic effusion and intensive care admission ($n = 1,488$).

Overall, 519 children (24%) received antistaphylococcal therapy during their hospitalization (512/519, 99% received anti-MRSA therapy), including 22 of the 23 children with *S. aureus* detected (the only child without antistaphylococcal therapy had *S. aureus* detected from a high-quality endotracheal tube aspirate only and also had respiratory syncytial virus detected). Clindamycin was most often used ($n = 266$, 51%), followed by vancomycin ($n =$

128, 24%), clindamycin plus vancomycin (n = 83, 16%), and others (n = 42, 8%). During the first two days of hospitalization, 479 children (22%) received antistaphylococcal therapy (477 received anti-MRSA therapy). After the first two days, 351 children (16%) received antistaphylococcal therapy (346/351, 99% received anti-MRSA therapy). Use of antistaphylococcal therapy was very common in those admitted to intensive care (182/462, 39%; all but two received anti-MRSA therapy) and in those requiring invasive mechanical ventilation (103/159, 65%). Among those lacking both parapneumonic effusion and intensive care admission (n = 1,488), 232 (16%) received antistaphylococcal therapy.

DISCUSSION

In our large, population-based study of >2,000 children hospitalized with community-acquired pneumonia, *S. aureus* was identified in only 1% of children. Compared with children with other pneumonia etiologies, staphylococcal pneumonia was associated with increased disease severity. Among the small numbers studied, no differences in outcomes were found between children with MRSA and MSSA disease. Despite the low prevalence of staphylococcal pneumonia, almost one in four children received antistaphylococcal antibiotic therapy; anti-MRSA therapy was used almost exclusively.

The severity of staphylococcal pneumonia was striking, with >80% of children with *S. aureus* detected being admitted to intensive care, about 65% requiring invasive mechanical ventilation, and >75% with parapneumonic effusion. These findings are similar to those of prior retrospective studies.^{4,10} The association between staphylococcal pneumonia and adverse outcomes underscores the importance of prompt institution of antimicrobial therapy targeting *S. aureus* in high-risk patients. This is noteworthy given recent epidemiological data demonstrating increases in MSSA relative to MRSA infections in children,⁶ and the known superiority of beta-lactam versus vancomycin for MSSA infections, including pneumonia.¹¹

Although detection of staphylococcal infection was rare, almost a quarter of children received antistaphylococcal therapy; nearly all of these children received anti-MRSA therapy. Confirming a bacterial etiology of pneumonia, however, is challenging. Given the severity associated with staphylococcal pneumonia, it is not surprising that use of antistaphylococcal therapy outpaced staphylococcal detections. Antistaphylococcal therapy was especially common in those with severe pneumonia, suggesting that disease severity is an important factor that influences initial antibiotic treatment decisions. Even so, two children with MRSA detected did not initially receive anti-MRSA therapy, highlighting the challenge of balancing judicious antibiotic selection along with ensuring effective treatment. Perhaps more striking is the finding that 16% of children received antistaphylococcal therapy beyond the first two days of hospitalization, presumably after the initial culture results were available. This suggests that clinicians are reluctant to stop antistaphylococcal therapy when the etiology is unknown, although certain features, such as negative cultures, rapid clinical improvement, and lack of risk factors for staphylococcal disease, may provide important clues to support de-escalation of empiric antibiotic therapy. It is also possible that some antibiotics with antistaphylococcal activity were used for alternative indications (eg, clindamycin for penicillin allergy or concern for aspiration pneumonia).

A simple strategy for tailoring antibiotic treatment is maximizing opportunities to identify a causative pathogen. Despite the very low yield of blood cultures in children with pneumonia overall, bacteremia is more common in children with severe pneumonia and those with parapneumonic effusion, especially when cultures are obtained prior to antibiotic use.^{12,13} Similarly, obtaining pleural fluid is often therapeutic and significantly improves the chances of identifying a bacterial pathogen.¹⁴ Moreover, at least one study suggests that *S. aureus* is much less likely in cases of culture-negative parapneumonic effusions.¹⁵ Institutional guidelines, order sets, and antimicrobial stewardship teams are also effective strategies that can facilitate judicious antibiotic use. In particular, stewardship experts can be very useful in assisting clinicians around de-escalation of therapy.¹⁶ Use of procalcitonin, a biomarker associated with bacterial infections,¹⁷ and prognostic tools to identify risk for adverse outcomes,¹⁸ may also inform treatment decisions and are deserving of further study.

Our study must be considered in the light of its strengths and limitations. Analysis was derived from a population-based surveillance study of community-acquired pneumonia hospitalizations in three children's hospitals and may not be generalizable to other settings. Nevertheless, the antibiotic-prescribing practices identified in our study are consistent with those from a larger network of children's hospitals in the United States.¹⁹ The relatively small number of children with *S. aureus* identified limited our ability to control for potential confounding factors. Some cases of staphylococcal pneumonia may not have been identified. All study children, however, were prospectively enrolled and had samples systematically collected and tested for etiology, likely leading to few cases of misclassification for this pathogen.

Our study demonstrates a very low prevalence of *S. aureus* detection among children hospitalized with pneumonia and highlights the association between staphylococcal disease and adverse in-hospital outcomes. We also document important discrepancies between disease prevalence and utilization of antistaphylococcal therapy, especially anti-MRSA therapy. Improved approaches are needed to minimize overuse of antistaphylococcal antibiotics while also ensuring adequate therapy for those who need it.

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TABLE. Clinical Characteristics, Outcomes, and Antibiotic Use among Children Hospitalized with Staphylococcal and Nonstaphylococcal Community-Acquired Pneumonia

Characteristic	Staphylococcal Pneumonia			Nonstaphylococcal Pneumonia		
	MRSA, n = 17	MSSA, n = 6	All <i>S. aureus</i> , n = 23	All non <i>S. aureus</i> , n = 2,115	Other Bacterial ¹ , n = 124	
Demographics						
Age in months, median (IQR)	15 (9–55)	99 (18–170)	25 (10–66)	28 (12–73)	24 (14–64)	
Male sex	12 (71)	5 (83)	17 (74)	1153 (55)	82 (66)	
Race/Ethnicity						
White nonhispanic	9 (53)	4 (67)	13 (57)	818 (39)	51 (41)	
Black nonhispanic	6 (35)	1 (17)	7 (30)	728 (34)	31 (25)	
Hispanic	1 (6)	1 (17)	2 (9)	398 (19)	28 (23)	
Other	1 (6)	0 (0)	1 (4)	171 (8)	14 (11)	
Comorbidities						
Asthma/reactive airway disease	1 (6)	1 (17)	2 (9)	692 (33)	29 (23)	
Other Pulmonary (excludes asthma)	1 (6)	1 (17)	2 (9)	54 (3)	2 (2)	
Prematurity	1 (6)	1 (17)	2 (9)	198 (9)	9 (7)	
Neurological	0 (0)	1 (17)	1 (4)	164 (8)	3 (2)	
Cardiovascular	0 (0)	0 (0)	0 (0)	128 (6)	8 (6)	
Genetic/metabolic	0 (0)	0 (0)	0 (0)	122 (6)	6 (5)	
Other	1 (6)	0 (0)	1 (4)	123 (6)	9 (7)	
Clinical Signs/Symptoms						
Illness duration in days, median (IQR)	5 (2–7)	3 (3–4)	4 (2.5–6)	3 (2–6)	4 (2–7)	
Fever	16 (94)	6 (100)	22 (96)	1933 (91)	111 (90)	
Cough	13 (76)	5 (83)	18 (78)	2002 (95) ³	113 (91)	
Upper respiratory symptoms ²	13 (76)	4 (67)	17 (74)	1690 (80)	87 (70)	

Characteristic	Staphylococcal Pneumonia			Nonstaphylococcal Pneumonia		
	MRSA, n = 17	MSSA, n = 6	All <i>S. aureus</i> , n = 23	All non <i>S. aureus</i> , n = 2,115	Other Bacterial ¹ , n = 124	
Shortness of breath	14 (82)	6 (100)	20 (87)	1481 (70)	85 (69)	
Chest indrawing	12 (71)	3 (50)	15 (65)	1130 (53)	52 (42)	
Wheezing	3 (18)	1 (17)	4 (17)	848 (40)	25 (20)	
<i>Radiographic features</i>						
Infiltrate pattern						
Consolidation, single lobar	3 (18)	0 (0)	3 (13)	477 (23)	30 (24)	
Consolidation, multilobar	10 (59)	2 (33)	12 (52)	621 (29)	51 (41)	
Other infiltrate	4 (24)	3 (50)	7 (30)	857 (41)	32 (26)	
Mixed	0 (0)	1 (17)	1 (4)	156 (7)	11 (9)	
Parapneumonic effusion	15 (88)	3 (50)	18 (78)	249 (12) ³	65 (52)	
<i>Clinical Course</i>						
Hospital length of stay in days, median (IQR)	10 (6–14)	12 (8–16)	10 (7–14)	3 (2–5) ³	7 (3–10)	
Intensive care admission	14 (82)	5 (83)	19 (83)	443 (21) ³	46 (37) ⁴	
Invasive mechanical ventilation	11 (65)	4 (67)	15 (65)	145 (7) ³	25 (20) ⁴	
In-hospital death	1 (6)	0 (0)	1 (4)	2 (<1) ³	0 (0)	
<i>Antibiotic use, 1st two calendar days</i>						
Antistaphylococcal, any	15 (88)	6 (100)	21 (91)	458 (22) ³	76 (61)	
AntiMRSA	15 (88)	6 (100)	21 (91)	456 (22) ³	76 (61)	
<i>Antibiotic use, after 1st two calendar days</i>						

Characteristic	Staphylococcal Pneumonia		Nonstaphylococcal Pneumonia	
	MRSA, n = 17	MSSA, n = 6	All <i>S. aureus</i> , n = 23	All non <i>S. aureus</i> , n = 2,115
Antistaphylococcal, any	16 (94)	5 (83)	21 (91)	330 (16) ^{1,3}
AntiMRSA	16 (94)	4 (67)	20 (87)	326 (15) ³

Other Bacterial¹, n = 12463 (51)⁴

63 (51)

Data presented as no. (%) unless otherwise specified; Tests of association included Wilcoxon rank-sum and Pearson chi-squared tests where appropriate;

¹ Does not include atypical bacteria;

² Includes conjunctivitis, congestion/rhinorrhea, otalgia, and sore throat

³ Bonferroni corrected $P < .001$ comparing *S. aureus* vs. non-*S. aureus*;

⁴ Bonferroni corrected $P < .001$ comparing *S. aureus* vs other bacterial.

Abbreviations: CAP, community-acquired pneumonia; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.