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Staphylococcus aureus community-onset pneumonia in patients admitted to children's hospitals during autumn and winter of 2006–2007

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SUMMARY

Staphylococcus aureus is a relatively uncommon cause of community-onset pneumonia (COP) that may complicate influenza infection. We reviewed admissions to children's hospitals to describe more systematically this entity. Records of patients hospitalized at three children's hospitals between 1 October 2006 and 30 April 2007 who had a positive *S. aureus* culture from a sterile site or respiratory specimen were reviewed and data were abstracted for episodes of primary *S. aureus* COP. Overall, 30 episodes met criteria for primary *S. aureus* COP; 12 (41%) involved methicillin-resistant *S. aureus*. Patients in 11 (37%) episodes were seen by a healthcare provider for their symptoms prior to hospital admission; three received an antimicrobial, none of which had activity against the *S. aureus* isolated. Mechanical ventilation was required in 21 (70%) episodes; five (17%) patients died. When evaluating patients with severe COP, providers should be aware of the potential for *S. aureus*, including methicillin-resistant strains.

Key words: Antimicrobial resistance, paediatric pneumonia, *S. aureus*.

INTRODUCTION

Staphylococcus aureus is believed to account for only 3–5% of pneumonia acquired in the community [1, 2]. *S. aureus* pneumonia is, however, a well-recognized complication of influenza in children and young adults following both seasonal and pandemic influenza where it has accounted for a large number of deaths [3–6]. Although it is unclear whether the overall frequency of *S. aureus* pneumonia is changing, reports of paediatric influenza deaths complicated by *S. aureus* infection appear to be increasing [7]. There is also evidence to suggest that *S. aureus* community-onset pneumonia (COP) may not be uncommon [8]. A recent Emerging Infections Network survey following the 2006–2007 influenza season found that 47% of responding infectious disease providers reported caring for a hospitalized *S. aureus* COP patient during the preceding influenza season.

The Centers for Disease Control and Prevention (CDC) has received a number of case reports from

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state and local health departments over the last several influenza seasons describing previously healthy children with severe *S. aureus* COP [9]. In addition, three recently published case series of severe *S. aureus* pneumonia similarly describe younger, often previously healthy patients with case-fatality rates as high as 50% [10–12]. It is unclear if these reports are representative of all *S. aureus* pneumonia as the most severe cases are more likely to be reported to public health officials. In order to gain a more complete understanding of *S. aureus* COP, we conducted a systematic review of a cohort of children with positive *S. aureus* cultures presenting to three paediatric hospitals.

METHODS

All patients admitted to three Atlanta-area children's hospitals from 1 October 2006 to 30 April 2007 who had a positive culture for *S. aureus* from either a normally sterile site or a respiratory specimen (i.e. sputum, tracheal aspirate, or bronchoscopy specimen) were identified from microbiology records. Medical records for episodes were reviewed and data were abstracted by one of three reviewers using a standardized data abstraction form to identify cases of primary *S. aureus* COP. Data collected included patient demographics, clinical characteristics, laboratory values, concurrent illnesses, past medical history, and prior and concurrent medications including antimicrobials, and outcomes.

Definitions

Pneumonia was defined as pulmonary infection including signs or symptoms of a respiratory process (i.e. new or worsened cough, new or worsened sputum production, rales, or worsened gas exchange), with a new or changed infiltrate on chest imaging, and signs or symptoms of infection [i.e. fever, hypothermia, leukocytosis ($>10\,000/mm^3$), or leukopenia ($<4000/mm^3$)]. Primary pneumonia was defined as pneumonia that did not develop from another preceding or concurrent site of infection, including a primary bacteraemia. Pneumonias were classified as community-onset if onset of symptoms was in the community and the patient had not been admitted overnight to a hospital or long-term care facility within the preceding three calendar days. *S. aureus* was considered the cause of the pneumonia if specimens (sterile site or respiratory) obtained before the end of the third calendar day after admission (when the day of admission is day 1) grew the organism.

Further analysis included a focus on methicillin-resistant *S. aureus* (MRSA) cases, which were subdivided into two classes based on their antimicrobial resistance phenotype. Isolates that were susceptible to clindamycin and trimethoprim–sulfamethoxazole were considered more consistent with the community phenotype, while those with resistance to either of these agents were considered more consistent with the healthcare phenotype.

Patients with cystic fibrosis were excluded because it was difficult to discern changes in chest imaging consistent with acute pneumonia *vs.* worsening chronic lung infection. Furthermore, the respiratory tract of children with cystic fibrosis is commonly colonized with *S. aureus*.

Statistical analysis

Data analysis was primarily descriptive and was performed using Stata 9.2 (StataCorp., USA). Proportions were compared using χ^2 or Fisher's exact test. The unit of analysis for this evaluation was a *S. aureus* COP episode. The activities involved in this investigation constituted a public health response to evaluate an emerging problem and as such, were not considered research and were not subject to review by a CDC institutional review board.

RESULTS

Overall, 274 episodes were identified in which patients had positive cultures for *S. aureus* from a sterile site or a respiratory specimen (Fig. 1). Of these, 86 (31%) episodes met the criteria for pneumonia and 79 (29%) met the criteria for primary pneumonia. Forty-six of these episodes were community-onset but 16 episodes were in patients with cystic fibrosis. Ultimately, 30 patients had 30 episodes of a positive *S. aureus* culture as an outpatient or within the first three calendar days after admission and met the definition for primary *S. aureus* COP. Demographic information for the 30 COP episodes is presented in Table 1. The median age of patients was 4 years and six patients (20%) were aged <1 year. The majority (67%) of episodes involved patients with at least one comorbidity.

Of the 29 isolates for which antimicrobial susceptibility results were known, 12 (41%) were methicillin-resistant. Isolates were not available for

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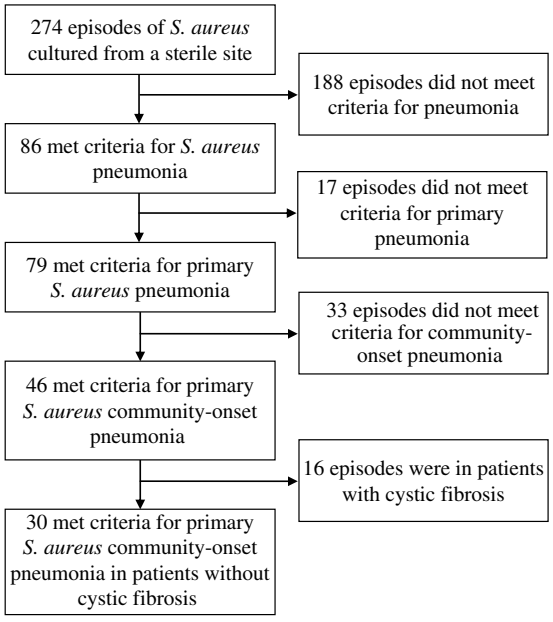

Fig. 1. *S. aureus* community-onset pneumonia episode selection process.

strain typing; however, antibiograms were available for 10/12 MRSA isolates. All 10 were susceptible to trimethoprim–sulfamethoxazole, linezolid and vancomycin, nine were susceptible to tetracycline and rifampin, six were susceptible to clindamycin and three to ciprofloxacin. Based on these susceptibilities six MRSA isolates had an antibiogram more consistent with the community phenotype.

Patients in 11 (37%) episodes were seen by a healthcare provider in the 7 days prior to admission (median 3 days, range 1–5 days). Three of these 11 received a prescription for an antimicrobial; two received azithromycin, one erythromycin, and all three patients had MRSA isolated from culture. None of these patients with MRSA received an antimicrobial to which their *S. aureus* isolate was susceptible. The diagnosis made by the healthcare provider was available for eight episodes and in all eight it included some form of acute viral or respiratory illness (e.g. croup, viral respiratory infection, etc.).

On the first calendar day of admission, 16 patients (53%) received either intravenous vancomycin or intravenous or oral linezolid, the two recommended antimicrobials for empiric treatment of adults with community-acquired or healthcare-associated pneumonia when MRSA is suspected [13, 14]. Of those 12 who ultimately had a positive culture for MRSA, half received empiric treatment with vancomycin or linezolid.

Table 1. *Characteristics of primary* Staphylococcus aureus *community-onset pneumonia episodes resulting in admission to an Atlanta area children's hospital for all patients*

Characteristic	Overall: number (%) or median (range)
Age (years)	3·8 (<1–23·8)
Female (%)	20 (67%)
Race	
White (%)	16 (53%)
Black	7 (23%)
Hispanic ethnicity	7 (23%)
Total household members	4 (2–8)
Transfer from outside facility	9 (30%)
Reside in Atlanta metropolitan statistical area	26 (87%)
Reside in Georgia	30 (100%)
Comorbidities*	20 (67%)
No comorbidities	10 (33%)
Developmental delay	8 (27%)
Neuromuscular disease	8 (27%)
Seizure disorder	6 (20%)
Asthma	5 (17%)
Other chronic lung disease	5 (17%)
History of prematurity	4 (13%)
Resides in home with smoker ($n=24$)	8 (33%)
Medications at admission	
Aspirin	0 (0%)
Non-steroidal anti-inflammatory	5 (17%)
Steroids (inhaled, oral or intravenous)	7 (23%)
Other immune-suppressing medications	0 (0%)

* For those comorbidities found in more than 10% of the sample.

A number of signs and symptoms were associated with the *S. aureus* COP episodes; however, the most commonly reported symptoms were cough and fever (Table 2). A history of skin or soft tissue infection (SSTI) was found in 3/15 episodes for which information about prior illnesses was available, and no COP episode involved a patient with a family member with a known history of SSTI. Testing for influenza was performed in 18 patients and three were positive. The initial chest X-ray was reported as abnormal in all but one of 30 *S. aureus* COP episodes – the types of abnormalities varied greatly and prevented specific categorization. However, cavitation was seen in two episodes and pleural effusions in seven. The single

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Table 2. *Presenting signs, symptoms, and selected laboratory findings for* Staphylococcus aureus *community-onset pneumonia episodes resulting in admission to an Atlanta area children's hospital for all patients*

Sign/symptom*	Overall: number (%) or median (range)
Cough	20 (67%)
Reported fever	18 (60%)
Dyspnoea	17 (57%)
Vomiting	10 (33%)
Tachypnoea	9 (30%)
Wheezing	6 (20%)
Lethargy	6 (20%)
Rhinorrhoea	5 (17%)
Increased difficulty in breathing	5 (17%)
Congestion	4 (13%)
Temperature >38 °C at admission	12 (30%)
Selected admission laboratory tests ($n=29$)	
White blood cell count (WBC) (mm^3)	14·9 (0·4–41·4)
WBC <4000 mm^3	5 (17%)
WBC >10 000 mm^3	18 (62%)
Platelets (mm^3)	251 (10–917)

* For signs/symptoms found in at least 9% of episodes.

patient with a normal initial chest X-ray had a follow-up chest X-ray during admission that was abnormal.

Overall outcomes, including the proportion requiring intensive care unit admission, mechanical ventilation, or extracorporeal membrane oxygenation; the median length of stay; and the proportion of in-hospital deaths are given in Table 3. These results were stratified further excluding those with any comorbidity. Five patients (17%) died and the median time from symptom onset to death was 9 days (range 4–24 days).

DISCUSSION

This systematic evaluation of patients hospitalized with a broadly defined syndrome of primary *S. aureus* COP provides a more complete description of this condition. Characteristics in this review differed from those seen in recent *S. aureus* pneumonia case reports and case series [10–12]. Specifically, underlying comorbidities were common and in-hospital mortality, although high, was lower than previously described. Methicillin-resistant isolates were found in about 40% of COP episodes. In about one-third of COP episodes, patients were evaluated as outpatients before their admission and none was treated with an antimicrobial to which their *S. aureus* isolate was susceptible.

Although the true incidence of *S. aureus* COP in children is unknown, recent reports of *S. aureus* infection associated with paediatric influenza-related deaths have raised concerns that this syndrome is growing in frequency. Bhat *et al.* [6] reported that during the 2003–2004 influenza season 11 (7%) of 153 influenza-related paediatric deaths were associated with *S. aureus* co-infection; one (2%) of 47 influenza-related paediatric deaths in 2004–2005 and three (7%) of 46 deaths in 2005–2006 were associated with *S. aureus* co-infection. However, in the 2006–2007 influenza season, 22 (30%) of 73 influenza-related paediatric deaths involved *S. aureus*, including 15 with MRSA [7]. Whether this increase represents an increase in disease or improved reporting is not clear. In addition, reports to state and local public health officials and CDC of severe *S. aureus* pneumonia, like those from Louisiana and Georgia published recently have also raised concerns about the role of *S. aureus*, especially MRSA, in COP [9].

Information on *S. aureus* pneumonia is available from a number of sources, most commonly case reports or case series. Reports of *S. aureus* infection after influenza have been common during influenza pandemics in the 20th century [3–5, 15, 16] mean age of case-patients from these reports (when reported) was between about 35–47 years [5, 15, 16], and reported case-fatality rates ranged from 7% to 55% [4, 5, 15, 16]. The presence of underlying comorbidities varied from 47% to 57% [4, 15, 16]. Fisher *et al.* [17] reviewed 21 'isolated' episodes of *S. aureus* pneumonia that did not occur during an outbreak of influenza. These patients had a mean age of 52 (range 15–81) years and a mortality rate of 67%. Eleven patients had 'serious debilitating diseases' that may have contributed to the high mortality rate. More recent case series and case reports have highlighted episodes of *S. aureus* pneumonia often in otherwise healthy children and adults (comorbidities present in 20–29%) with mortality rates of 30–50% [10, 11, 18].

The current investigation represents a systematically collected group of *S. aureus* COP episodes during a non-pandemic influenza season and differed somewhat from results in previous reports. First, although our series was limited to patients admitted to referral paediatric hospitals, the presence of comorbidities was high (67%) suggesting that disease in otherwise

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Table 3. *Outcomes in primary* Staphylococcus aureus *community-onset pneumonia episodes resulting in admission to three Atlanta area children's hospitals*

Outcome	All patients ($n=30$), number (%) or median (range)	Patients without known comorbidities ($n=10$), number (%) or median (range)
Extracorporeal membrane oxygenation	5 (17%)	2 (20%)
Duration (days)	3 (2–22)	3 (3–4)
Mechanical ventilation	21 (70%)	7 (70%)
Duration (days)	4 (<1–41)	2 (1–22)
Intensive care unit admission	25 (83%)	7 (70%)
Duration (days)	9 (<1–127)	5 (<1–22)
Length of stay (days)	13 (1–130)	5·5 (1–37)
In-hospital death	5 (17%)	2 (20%)

healthy patients makes up the minority of *S. aureus* COP at least at these facilities. In addition, while the mortality rate in our study was high, it was lower than that seen in prior case series. This might reflect a greater propensity for reports to be collected and published on patients who died. We also were unable, through retrospective record review, to comprehensively differentiate true community-acquired pneumonia from healthcare-associated pneumonia (COP in patients with healthcare risk factors). If mortality rates for *S. aureus* pneumonia differ in patients with and without healthcare risk factors then studies with different mixes of these patients may produce different mortality estimates.

Another important finding was the proportion of isolates that were resistant to methicillin (41%). MRSA as a cause for COP was highlighted in a 1999 report of deaths from MRSA in otherwise healthy children in Minnesota and North Dakota [19]. The proportion of isolates that were methicillin-resistant in our review, although high, was lower than that described by Hageman *et al*. [10] in their case series (88%); however, their estimate might have over-represented the contribution of MRSA as cases due to MRSA would have been more likely to be reported to public health officials. It is important to note that Atlanta has been previously characterized as an area with a high incidence of community-associated MRSA and therefore the proportion of MRSA observed here might not reflect that seen in many other parts of the USA [20, 21]. Further, about 60% of the MRSA isolates in this investigation had an antibiogram more consistent with that seen with community-associated MRSA isolates.

It is interesting to note that nearly 37% of patients sought care as outpatients in the week prior to admission and that very few of these patients (3/11) were treated with antimicrobials. In addition, those who did receive antimicrobials often received ones that did not have activity against the isolate that later grew from culture. All of these patients had MRSA. Further, about half of the patients were not treated empirically with antimicrobials recommended for the treatment of MRSA pneumonia on the calendar day of admission, including half the patients who eventually grew MRSA. These findings may in part reflect a failure to recognize MRSA as a potential cause of illness in these patients.

Further work is needed to identify characteristics that might alert clinicians to the possibility of *S. aureus* as a cause of COP in children. In this review, only cough, fever, and dyspnoea were reported to be present in at least half of patients and these symptoms are not specific for *S. aureus*. A white blood cell count $>10\,000/mm^3$ was found at admission in more than 62% of episodes and may be a clue to an underlying pneumonia although it is not clear if this finding would have been present at evaluations occurring prior to hospital admission. Chest imaging was abnormal at admission in almost all episodes although the clinical description varied greatly. Cavitation, which has been identified as a possible marker of *S. aureus* [13], was seen in only two episodes. Unfortunately, this evaluation was not able to examine thoroughly outpatient visits to determine if characteristics present during visits in the week prior to admission might have identified them as being at risk for subsequent hospital admission.

This investigation is subject to a number of limitations. First, our definition of *S. aureus* COP was broad and may have included patients who grew *S. aureus* from only a respiratory specimen and who may not have had a true lower respiratory tract infection with this organism. We attempted to minimize this by requiring that patients exhibit signs or symptoms of an infection, signs or symptoms of a respiratory process, and changes in chest imaging to be included as a *S. aureus* COP episode. Second, this investigation only evaluated patients who required hospitalization in one metropolitan area during a 7-month period; whether these results are representative of all *S. aureus* COP is unknown. Third, at least two of these facilities were primarily referral hospitals which may have led to over-representation of more severe cases of pneumonia or episodes of pneumonia in patients with a higher level of comorbidity. Fourth, we could not differentiate in this retrospective review between patients with true community-acquired pneumonia and those with healthcare-associated pneumonia (COP in patients with healthcare risk factors); however, the goal of this investigation was to define better the current spectrum of *S. aureus* pneumonia presenting from the community making this distinction, although important, less pertinent. The large number of patients in this investigation with underlying comorbidities suggests that many of these patients had significant healthcare exposures. Fifth, some patients with *S. aureus* COP may die at home and therefore would not be captured in this evaluation. Finally, this was a retrospective review of patient medical records and is subject to the limitations inherent in that process.

In summary, we describe the characteristics of patients admitted to three Atlanta paediatric hospitals for *S. aureus* COP during the influenza season. Overall, episodes appeared to frequently involve patients with comorbidities. In addition, MRSA made up a sizable proportion of the *S. aureus* isolated from these patients. *S. aureus* COP resulting in hospitalization resulted in significant morbidity and mortality. It is important that clinicians recognize *S. aureus*, including MRSA, as a potential cause of COP during the winter season.

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DECLARATION OF INTEREST

None.

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