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Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes

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Background. Prevalence of *Staphylococcus aureus* community-acquired pneumonia (CAP) and its clinical features remain incompletely understood, complicating empirical selection of antibiotics.

Methods. Using a multicenter, prospective surveillance study of adults hospitalized with CAP, we calculated the prevalence of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) among all CAP episodes. We compared the epidemiologic, radiographic, and clinical characteristics of *S. aureus* CAP (per respiratory or blood culture) with those of pneumococcal (per respiratory or blood culture or urine antigen) and all-cause non-*S. aureus* CAP using descriptive statistics.

Results. Among 2259 adults hospitalized for CAP, 37 (1.6%) had *S. aureus* identified, including 15 (0.7%) with MRSA and 22 (1.0%) with MSSA; 115 (5.1%) had *Streptococcus pneumoniae*. Vancomycin or linezolid was administered to 674 (29.8%) patients within the first 3 days of hospitalization. Chronic hemodialysis use was more common among patients with MRSA (20.0%) than pneumococcal (2.6%) and all-cause non-*S. aureus* (3.7%) CAP. Otherwise, clinical features at admission were similar, including concurrent influenza infection, hemoptysis, multilobar infiltrates, and prehospital antibiotics. Patients with MRSA CAP had more severe clinical outcomes than those with pneumococcal CAP, including intensive care unit admission (86.7% vs 34.8%) and in-patient mortality (13.3% vs 4.4%).

Conclusions. Despite very low prevalence of *S. aureus* and, specifically, MRSA, nearly one-third of adults hospitalized with CAP received anti-MRSA antibiotics. The clinical presentation of MRSA CAP overlapped substantially with pneumococcal CAP, highlighting the challenge of accurately targeting empirical anti-MRSA antibiotics with currently available clinical tools and the need for new diagnostic strategies.

Keywords. pneumonia; *Staphylococcus aureus*; antibiotics.

During the past decade, several reports described the emergence of community-acquired pneumonia (CAP) caused by *Staphylococcus aureus* and, specifically, methicillin-resistant *S. aureus* (MRSA) as a cause of severe pneumonia that leads to critical illness and death [1–6]. Although the prevalence of MRSA among acute cases of CAP has not been fully elucidated, recent studies suggest MRSA is an uncommon cause of CAP in the United States [7–11]. Nonetheless, clinicians often use vancomycin or linezolid empirically to treat adults with CAP due to concerns about the potential of MRSA pneumonia [12–16].

Although current guidelines from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) do not recommend routine empirical anti-MRSA antibiotics for CAP, addition of vancomycin or linezolid to standard therapy is recommended if MRSA pneumonia is clinically suspected [17]. Prior studies have described clinical features associated with MRSA CAP, such as hemodialysis, influenza infection, hemoptysis, multifocal or cavitary infiltrates, and recent antibiotic use [1–3, 7, 17–19]. However, these associations have not been rigorously evaluated, and whether the clinical syndrome of MRSA CAP is distinct from other types of CAP remains unclear [14]. Therefore, we estimated the prevalence of MRSA and methicillin-susceptible *S. aureus* (MSSA) among adults hospitalized with CAP and compared their clinical features with those of CAP patients without *S. aureus*, including all-cause CAP and pneumococcal CAP.

METHODS

We used data from the Etiology of Pneumonia in the Community (EPIC) study, a multicenter prospective active surveillance study of patients hospitalized with CAP funded by the Centers for Disease Control and Prevention (CDC) [9]. Enrollment of adult patients was conducted from 1 January 2010 to 30 June

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2012 at 3 hospitals in Chicago, Illinois, and 2 hospitals in Nashville, Tennessee. Ethics approval for the study protocol was obtained at the CDC and each enrolling institution. Written informed consent was obtained from all participants or their representatives.

Population

Detailed inclusion and exclusion criteria for the EPIC study cohort have been previously described [9]. In brief, adults (aged ≥18 years) were eligible if they were admitted to a study hospital, resided in the study catchment area, had clinical evidence of an acute respiratory infection, and had radiographic evidence of pneumonia as interpreted by a study-dedicated thoracic radiologist. Patients with any of the following criteria were excluded: recent hospitalization (<28 days for immunocompetent patients and <90 days for immunosuppressed patients), nursing home resident not functionally independent [20], tracheostomy, gastrostomy, cystic fibrosis, cancer with neutropenia, solid organ or hematopoietic stem-cell transplant within the previous 90 days, active graft-vs-host disease, bronchiolitis obliterans, or human immunodeficiency virus infection with a CD4 cell count <200 mm^3. The study population for the current analysis included adults in the EPIC study cohort who underwent at least 1 diagnostic test for both bacteria and viruses, which are outlined below.

Diagnostic Testing

As previously described [9], specimens were systematically evaluated for pathogen detection using blood, respiratory, and urine samples collected as soon as possible after hospital presentation.

Bacterial testing included blood cultures, sputum cultures (limited to high-quality samples [21]), urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* (BinaxNow, Alere) [22, 23], and detection of *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* by real-time polymerase chain reaction (RT-PCR) of naso/oropharyngeal (NP/OP) swabs [24]. Sputum was also tested for *Legionella* with a RT-PCR assay regardless of sputum quality [24]. Additionally, endotracheal aspirates, pleural fluid, and bronchoalveolar lavage (BAL) specimens obtained for routine clinical care underwent bacterial culturing. Pleural fluid samples obtained as part of clinical care also underwent testing with RT-PCR assays targeting *S. aureus*, *S. pneumoniae*, other streptococcus species, *Enterobacteriaceae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [25–27].

Viral testing included RT-PCR assays on NP/OP swab specimens for adenovirus, coronaviruses, human metapneumovirus, human rhinovirus, influenza, parainfluenza, and respiratory syncytial virus [28, 29]. Paired acute and convalescent serology was conducted for adenovirus, human metapneumovirus, influenza, parainfluenza, and respiratory syncytial virus [30, 31].

Etiology Group Definitions

Staphylococcus aureus CAP was defined as detection of *S. aureus* from a respiratory or blood specimen as described above. Patients with codetection of *S. aureus* and other pathogens were included in the *S. aureus* CAP group. Methicillin resistance was defined according to Clinical and Laboratory Standards Institute interpretive criteria for results of *S. aureus* in vitro antimicrobial susceptibility testing [32, 33]. Both MRSA and MSSA were included in the *S. aureus* CAP group. Additionally, MRSA and MSSA CAP subgroups were also reported separately.

Initially, the characteristics of *S. aureus* CAP and MRSA CAP were compared with characteristics of all CAP patients without *S. aureus*, defined as the all-cause non-*S. aureus* CAP group. This group included patients with other bacteria, viruses, fungi, mycobacteria, and unknown etiology. This comparison aimed to determine if MRSA CAP had clinical features distinctive enough to identify MRSA cases among a heterogeneous group of CAP patients.

Because certain clinical features may be associated with bacterial pneumonia in general, we also used pneumococcal CAP, the most common bacterial CAP detected in adults, as a second comparison group. Pneumococcal CAP was defined as a positive culture for *S. pneumoniae* in blood or respiratory specimen or a positive urinary antigen test as described above. Pneumococcal CAP was a subgroup of all-cause non-*S. aureus* CAP.

Prevalence and Seasonality

Prevalence of MRSA and MSSA was calculated by dividing the number of cases with each of these bacteria by the total study population of hospitalized adults with CAP. Prevalence calculations were also performed after stratifying the study population by age group (18–49, 50–64, 65–79, and ≥80 years), site of hospitalization (intensive care unit [ICU] vs general floor), and chronic hemodialysis use. Binomial 95% confidence intervals (CIs) were calculated for prevalence estimates. MRSA and MSSA prevalences were compared with *S. pneumoniae* prevalence, which has been previously reported in this study population [9].

To examine variation in *S. aureus* CAP across seasons and its temporal association with influenza activity, we plotted the number of *S. aureus* CAP and influenza-associated CAP cases by month during the study.

Clinical Characteristics and Outcomes

Patient characteristics, antibiotics administered, and clinical outcomes were systematically ascertained via patient interviews and medical chart abstractions using standardized definitions and data collection instruments [9]. For this analysis, use of empirical anti-MRSA antibiotics was defined as the administration of ≥1 dose of vancomycin or linezolid during the first 3 days of hospitalization, a time when culture results are typically incomplete and thus antibiotic selection is empirical.

Chest radiography findings were based on interpretations of study-dedicated thoracic radiologists. Pneumonia severity scores, including the pneumonia severity index (PSI) [34], CURB-65

(confusion, blood urea nitrogen ≥20 mg/dL, respiratory rate ≥30, systolic blood pressure <90 mmHg, age ≥65 years) [35], and ATS severe CAP minor criteria [17], were calculated from data at the time of initial hospital presentation.

Clinical characteristics and outcomes were compared among the CAP etiology groups. We compared the MRSA group with the pneumococcal and all-cause non-*S. aureus* groups for specific clinical features previously reported as potential risk factors for MRSA, including hemodialysis use [17, 18], seizure disorder [17], diabetes mellitus [17], recurrent soft tissue infections [1, 3], hemoptysis [1, 3], daily alcohol use [17], multilobar or cavitary infiltrates [1–3, 7, 19], pleural effusions [2, 3, 19], concurrent influenza infection [1–3, 17], proton pump inhibitor use [18], and use of antibiotics prior to hospital presentation [17]. Comparisons were conducted with the Wilcoxon rank-sum, χ^2, or Fisher exact test as appropriate. Analyses were performed with Stata 12.0 (StataCorp, College Station, Texas).

RESULTS

During the 2.5-year study period, 3634 potentially eligible adults were identified; 2259 (62.2%) of these were enrolled, confirmed to have radiographic pneumonia, and underwent etiologic testing for both bacteria and viruses (study population). Eighty-seven (3.2%) patients within this study population chronically used hemodialysis and 12 (0.5%) were independently functioning nursing home residents.

Prevalence

Overall, 37 (1.6%; 95% CI, 1.2, 2.3) patients were identified as having *S. aureus* CAP, including 15 (0.7%; 95% CI, .4, 1.1) with MRSA and 22 (1.0%; 95% CI, .6, 1.5) with MSSA (Table 1). These *S. aureus* cases included 21 with *S. aureus* cultured from blood, 13 from high-quality sputum, 6 from BAL, and 2 from pleural fluid; 4 patients had *S. aureus* cultured from multiple sample types.

Streptococcus pneumoniae was identified in 115 (5.1%; 95% CI, 4.2, 6.1) patients. These detections included 26 by blood culture, 8 from high-quality sputum, 3 from BAL, 1 from pleural fluid, 56 by urine antigen, and 21 by multiple modalities.

Prevalence of MRSA CAP was <1% in each age group, among patients admitted to the general medical floor, and among those who did not chronically use hemodialysis (Table 1). Prevalence of MRSA was lower than pneumococcus among CAP patients admitted to an ICU (2.7% vs 8.3%; $P < .01$) and similar among those chronically using hemodialysis (3.5% vs 3.5%; $P = 1.0$). None of the 12 independently functioning nursing home residents were found to have MRSA, MSSA, or pneumococcal CAP.

Seasonality and Codetections

Staphylococcus aureus CAP cases were identified sporadically throughout the study, with 3 peaks of increased activity, including December 2010–February 2011, May 2011, and January–March 2012. Two of these peaks closely coincided with increased numbers of influenza CAP (Figure 1).

Prevalence of codetection of another pathogen was similar in *S. aureus* CAP (13 of 37 patients, 35.1%) and pneumococcal CAP (35 of 115 patients, 30.4%; $P = .68$). Influenza virus was the most common copathogen in *S. aureus* CAP, codetected in 3 (8.1%) cases (Table 2). None of the influenza–*S. aureus* or influenza–*S. pneumoniae* codetections occurred in patients on chronic hemodialysis. Four (10.8) patients with *S. aureus* CAP had codetection of a gram-negative rod (2 with *Klebsiella pneumoniae*, 1 with *Escherichia coli*, and 1 with *Pseudomonas aeruginosa*).

Clinical Characteristics and Outcomes

Overall, patients with *S. aureus* CAP, including those with both MRSA and MSSA, had similar demographic characteristics,

Table 1. Prevalence of *Staphylococcus aureus* Community-Acquired Pneumonia (CAP), Including Methicillin-Resistant *S. aureus* and Methicillin-Susceptible *S. aureus* Subgroups, and Pneumococcal CAP Among Adults Hospitalized With CAP

		Staphylococcus aureus CAP, n (row %)			
Population	Total CAP Cases	Methicillin-Resistant *S. aureus*	Methicillin-Susceptible *S. aureus*	All *S. aureus*	Pneumococcal CAP, n (row %)
All adults	2259	15 (0.7)	22 (1.0)	37 (1.6)	115 (5.1)
By age group, y					
18–49	681	2 (0.3)	7 (1.0)	9 (1.3)	31 (4.6)
50–64	773	7 (0.9)	11 (1.4)	18 (2.3)	41 (5.3)
65–79	506	4 (0.8)	2 (0.4)	6 (1.2)	34 (6.7)
≥80	299	2 (0.7)	2 (0.7)	4 (1.3)	9 (3.0)
By admission type					
Intensive care unit	482	13 (2.7)	10 (2.1)	23 (4.8)	40 (8.3)
General floor	1777	2 (0.1)	12 (0.7)	14 (0.8)	75 (4.2)
By chronic hemodialysis use					
Hemodialysis user	87	3 (3.5)	2 (2.3)	5 (5.8)	3 (3.5)
Not hemodialysis user	2172	12 (0.6)	20 (0.9)	32 (1.5)	112 (5.2)

Abbreviation: CAP, community-acquired pneumonia.

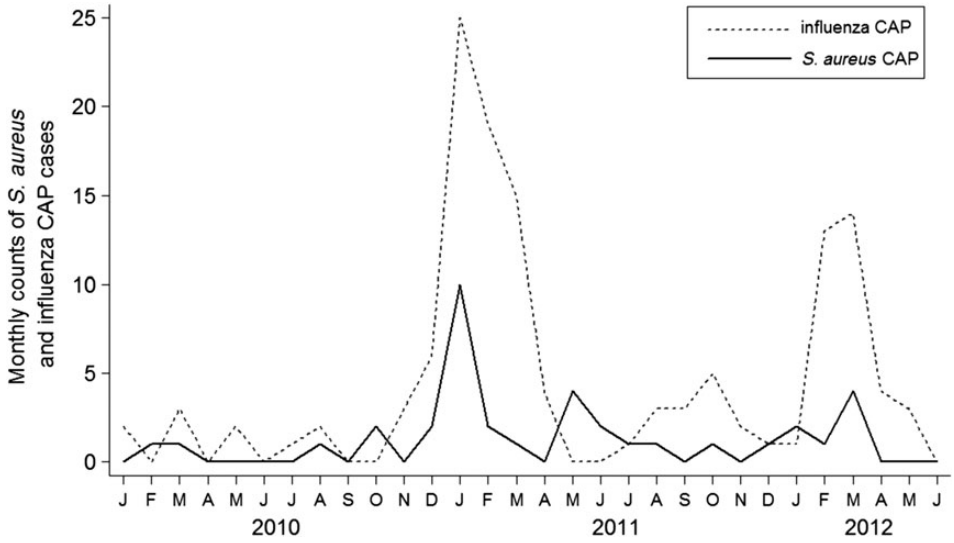

Figure 1. Counts of *Staphylococcus aureus* and influenza community-acquired pneumonia (CAP) hospitalizations by month.

comorbidities, and presenting signs and symptoms compared with patients with all-cause non-*S. aureus* and pneumococcal CAP (Table 3). However, patients with *S. aureus* CAP, especially MRSA, tended to have higher severity scores than patients with non-*S. aureus* and pneumococcal CAP (Table 3). For example, 73.3% of MRSA and 45.2% of pneumococcal CAP patients had a PSI risk class ≥4 ($P = .04$). Among clinical characteristics previously described as potential risk factors for MRSA CAP, only

Table 2. Pathogen Codetections Among Adults Hospitalized With Community-Acquired Pneumonia, by Etiology Group

	Staphylococcus aureus CAP, n (Column %)			
Pathogen	Methicillin-Resistant *S. aureus* (n = 15)	Methicillin-Susceptible *S. aureus* (n = 22)[a]	All *S. aureus* (n = 37)[a]	Pneumococcal CAP, n (Column %); n = 115[b]
Any codetection	3 (20.0)	10 (45.5)	13 (35.1)	35 (30.4)
Viruses				
Influenza	1 (6.7)	2 (9.1)	3 (8.1)	4 (3.5)
Parainfluenza	1 (6.7)	1 (5.4)	2 (5.4)	7 (6.1)
Coronavirus	0	1 (4.6)	1 (2.7)	2 (1.7)
Human metapneumovirus	0	1 (4.6)	1 (2.7)	7 (6.1)
Respiratory syncytial virus	0	1 (4.6)	1 (2.7)	2 (1.7)
Human rhinovirus	0	0	0	14 (12.2)
Bacteria				
Klebsiella pneumoniae	1 (6.7)	1 (4.6)	2 (5.4)	0
Escherichia coli	0	1 (4.6)	1 (2.7)	0
Mycoplasma pneumoniae	0	1 (4.6)	1 (2.7)	0
Pseudomonas aeruginosa	0	1 (4.6)	1 (2.7)	0
Viridans group *Streptococcus*	0	1 (4.6)	1 (2.7)	0
Haemophilus influenzae	0	0	0	1 (0.87)
Legionella pneumophila	0	0	0	1 (0.87)
Neisseria meningitidis	0	0	0	1 (0.87)

Abbreviation: CAP, community-acquired pneumonia.

[a] One patient with methicillin-susceptible *S. aureus* (MSSA) CAP had the following 3 pathogens detected: *MSSA*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Therefore, among the 22 patients with MSSA CAP there were 11 codetections in 10 patients. Among 37 patients with all *S. aureus* CAP, there were 14 codetections in 13 patients.

[b] Four patients with pneumococcal CAP had 3 pathogens detected; these coinfections included 1 of each of the following combinations: *Streptococcus pneumoniae/Haemophilus influenzae/Neisseria meningitidis*; *Streptococcus pneumoniae*/influenza/human rhinovirus; *Streptococcus pneumoniae*/coronavirus/human rhinovirus; *Streptococcus pneumoniae*/human metapneumovirus/human rhinovirus. Therefore, among the 115 patients with pneumococcal CAP, there were 39 codetections in 35 patients.

Table 3. Presenting Clinical Characteristics of Adults Hospitalized With Community-Acquired Pneumonia, by Etiology Group

Characteristic	*Staphylococcus aureus* CAP			CAP Without *Staphylococcus aureus*	
	Methicillin-Resistant *S. aureus* (n = 15)	Methicillin-Susceptible *S. aureus* (n = 22)	All *S. aureus* (n = 37)	Pneumococcal (n = 115)	All-Cause non-*S. aureus* (n = 2222)
Demographics					
Median age (IQR), y	62 (54, 76)	56 (48, 64)	60 (50, 65)	59 (48, 67)	57 (46,71)
Female, n (%)	9 (60.0)	12 (54.6)	21 (56.8)	55 (47.8)	1134 (51.0)
Independently functioning nursing home resident	0	0	0	0	12 (0.5)
Race/Ethnicity, n (%)					
White non-Hispanic	8 (53.3)	13 (59.1)	21 (56.8)	54 (47.0)	1033 (46.5)
Black non-Hispanic	3 (20.0)	8 (36.4)	11 (29.7)	44 (38.3)	863 (38.8)
Hispanic	3 (20.0)	1 (4.6)	4 (10.8)	14 (12.2)	234 (10.5)
Other	1 (6.7)	0	1 (2.7)	3 (2.6)	92 (4.1)
Medical conditions, n (%)					
Asthma	4 (26.7)	3 (13.6)	7 (18.9)	24 (20.9)	577 (26.0)
Chronic obstructive pulmonary disease	3 (20.0)	4 (18.2)	7 (18.9)	34 (29.6)	513 (23.1)
Chronic heart failure	4 (26.7)	6 (27.3)	10 (27.0)	21 (18.3)	420 (18.9)
Diabetes mellitus	7 (46.7)	8 (36.4)	15 (40.5)	23 (20.0)	569 (25.6)
Chronic kidney disease	4 (26.7)	6 (27.3)	10 (27.0)	25 (21.7)	346 (15.6)
Chronic hemodialysis	3 (20.0)	8 (36.4)	11 (29.7)	3 (2.6)	82 (3.7)
Chronic liver disease	0	1 (4.6)	1 (2.7)	6 (5.2)	125 (5.6)
Any immunodeficiency	3 (20.0)	4 (18.2)	7 (18.9)	16 (13.9)	361 (16.3)
Human immunodeficiency virus infection	0	1 (4.6)	1 (2.7)	2 (1.7)	65 (2.9)
Cancer	5 (33.3)	3 (13.6)	8 (21.6)	22 (19.1)	397 (17.9)
Seizure disorder	1 (6.7)	1 (4.6)	2 (5.4)	4 (3.5)	85 (3.8)
Current smoker	1 (6.7)	3 (13.6)	4 (10.8)	46 (40.0)	591 (26.6)
Body mass index ≥30 kg/m^2	5 (33.3)	9 (40.9)	14 (37.8)	26 (22.6)	789 (35.5)
Symptoms					
Median duration of symptoms prior to presentation (IQR), days	4.7 (3.7, 7.5)	4.8 (2.5, 8.7)	4.7 (2.9, 7.8)	4.8 (2.8, 8.8)	4.8 (2.8, 8.8)
Fever	9 (60.0)	14 (63.6)	23 (62.2)	81 (70.4)	1523 (68.5)
Cough with sputum production	8 (53.3)	8 (36.4)	16 (43.2)	69 (60.0)	1235 (55.6)
Hemoptysis	2 (13.3)	3 (13.6)	5 (13.5)	13 (11.3)	192 (8.6)
Shortness of breath	11 (73.3)	16 (72.7)	27 (73.0)	86 (74.8)	1733 (78.0)
Chest pain	5 (33.3)	8 (36.4)	13 (35.1)	60 (52.2)	1100 (49.5)
Rash	2 (13.3)	1 (4.5)	3 (8.1)	4 (3.5)	73 (3.3)
Clinical signs at hospital presentation					
Confusion	1 (6.7)	3 (13.6)	4 (10.8)	7 (6.1)	149 (6.7)
Wheezing	4 (26.7)	7 (31.8)	11 (29.7)	33 (28.7)	636 (28.6)
Median Temperature (IQR), °F	99.9 (97.9, 101.2)	98.2 (97.2, 99.8)	98.7 (97.8, 100.9)	99.4 (98.1, 100.6)	98.9 (98.0, 100.4)
Median systolic blood pressure (IQR), mmHg	142 (110, 159)	113 (101, 157)	119 (102, 159)	120 (103, 139)	131 (115, 149)
Median oxygen saturation (IQR), %	93 (88, 95)	94 (91, 96)	93 (89, 96)	95 (92, 98)	95 (93, 97)
Laboratory results at hospital presentation					
Median white blood cell count (IQR), 10^3 cells/μL	12.7 (7.7, 16.8)	13.4 (9.6, 17.2)	12.8 (9.6, 16.8)	13.5 (9.0, 19.9)	11.4 (7.9, 14.9)
Median hematocrit (IQR), %	36.0 (35.0, 40.0)	37.8 (33.0, 39.5)	38.0 (34.6, 39.6)	37.0 (33.1, 41.0)	38.0 (34.1, 41.5)
Median platelet count (IQR), 10^3 cells/μL	168 (130, 305)	225 (194, 295)	219 (161, 295)	216 (165, 276)	237 (179, 306)
Median blood urea nitrate concentration (IQR), mg/dL	34 (17, 62)	17 (11, 43)	29 (15, 43)	20 (13, 32)	15 (10, 23)
Median glucose concentration (IQR), mg/dL	130 (111, 170)	141 (115, 174)	137 (115, 170)	115 (100, 151)	115 (99, 144)
Chest X-ray findings					
Cavitation/Necrosis, n (%)	0 (0)	0	0 (0)	0 (0)	34 (1.5)
Multilobar infiltrates, n (%)	5 (33.3)	7 (31.8)	12 (32.4)	39 (33.9)	647 (29.1)
Pleural effusion, n (%)	4 (26.7)	5 (22.7)	9 (24.3)	41 (35.7)	687 (30.9)

Table 3 continued.

Characteristic	*Staphylococcus aureus* CAP			CAP Without *Staphylococcus aureus*	
	Methicillin-Resistant *S. aureus* (n = 15)	Methicillin-Susceptible *S. aureus* (n = 22)	All *S. aureus* (n = 37)	Pneumococcal (n = 115)	All-Cause non-*S. aureus* (n = 2222)
Pneumonia severity scores					
Median pneumonia severity index score (IQR)	107 (98, 132)	88 (74, 115)	99 (76,118)	83 (61.11)	75 (52, 102)
Pneumonia severity index risk class 4 or 5, n (%)	11 (73.3)	11 (50.0)	22 (59.5)	52 (45.2)	762 (34.3)
≥3 CURB-65 criteria, n (%)	6 (40.0)	3 (13.6)	9 (24.3)	20 (17.4)	243 (10.9)
≥3 American Thoracic Society CAP minor criteria, n (%)	3 (20.0)	4 (18.2)	7 (18.9)	13 (11.3)	153 (6.9)

Abbreviations: CAP, community-acquired pneumonia; CURB-65IQR, confusion, blood urea nitrogen ≥20 mg/dL, respiratory rate ≥30, systolic blood pressure <90 mmHg, age ≥65 years; IQR, interquartile range.

chronic hemodialysis use and diabetes mellitus were significantly more common in MRSA CAP compared with pneumococcal CAP (Table 4).

Empirical use of anti-MRSA antibiotics was common, with 29.8% of all enrolled patients receiving vancomycin or linezolid within the first 3 days of hospital admission despite only 0.7% ultimately found to have MRSA (Table 5). Anti-MRSA antibiotics were administered within the first 3 days of admission in 93.3% of patients with MRSA CAP compared with 47.0% with pneumococcal CAP ($P = .001$).

Analyses to evaluate the prevalence of traditional MRSA risk factors and use of anti-MRSA antibiotics were repeated after excluding the 87 patients who chronically used hemodialysis and 12 independently functioning nursing home residents. These results (Supplementary Tables 1 and 2) were similar to the results with the full study population.

Among the 37 patients with *S. aureus* CAP, 4 (10.8%) died during the index hospitalization (Table 6). These 4 deaths included 1 patient with codetection of MRSA and *K. pneumoniae*, 1 with codetection of MSSA and viridans group *Streptococcus*, 1 with detection of MRSA alone, and 1 with detection of MSSA alone.

In-patient mortality for MRSA CAP (13.3%) was similar to that for MSSA CAP (9.1%; $P = 1.00$) but was higher than that for pneumococcal (4.4%; $P = .19$) and all-cause *non*-S. *aureus* (2.0%; $P = .04$) CAP. Patients with both MRSA and MSSA

Table 4. Prevalence of Previously Reported Potential Risk Factors for Methicillin-Resistant *Staphylococcus aureus* Community-Acquired Pneumonia, by Etiology Group

Characteristic	MRSA CAP, n (%) (n = 15)	Methicillin-Susceptible *Staphylococcus aureus* CAP, n (%) (n = 22)	Pneumococcal CAP, n (%) (n = 115)	*P* Value[a] (MRSA vs Pneumococcal)	All-Cause non-*Staphylococcus aureus* CAP, n (%) (n = 2222)	*P* Value[a] (MRSA vs All-Cause non-*Staphylococcus aureus*)
Hemodialysis use	3 (20.0)	2 (9.1)	3 (2.6)	0.02	82 (3.7)	0.02
Seizure disorder	1 (6.7)	1 (4.6)	4 (3.5)	0.46	85 (3.8)	0.45
Diabetes mellitus	7 (46.7)	8 (36.4)	23 (20.0)	0.04	569 (25.6)	0.08
Recurrent soft tissue infections	1 (6.7)	4 (18.2)	9 (7.8)	1.00	145 (6.5)	1.00
Hemoptysis	2 (13.3)	3 (13.6)	13 (11.3)	0.68	192 (8.6)	0.38
Daily alcohol use	1 (6.7)	3 (13.6)	11 (9.6)	1.00	156 (7.0)	1.00
Multilobar or cavitary infiltrates	5 (33.3)	7 (31.8)	39 (33.9)	1.00	667 (30.0)	0.78
Pleural effusion	4 (26.7)	5 (22.7)	41 (35.7)	0.58	687 (30.9)	1.00
Concurrent influenza infection	1 (6.7)	2 (9.1)	4 (3.5)	0.46	129 (5.8)	0.59
Current proton pump inhibitor use prior to admission	5 (33.3)	5 (22.7)	18 (15.6)	0.14	505 (22.7)	0.35
Outpatient antibiotic use prior to admission	2 (13.3)	0	15 (13.0)	1.00	440 (19.8)	0.75

Abbreviations: CAP, community-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] *P* values calculated using Fisher exact test.

Table 5. Use of Anti-Methicillin-Resistant *Staphylococcus aureus* Antibiotics (Vancomycin or Linezolid) Within 3 Days of Hospital Presentation, by Etiology Group

Etiology Group	Patients, n	Anti-MRSA Antibiotics, n (row %)
All community-acquired pneumonia	2259	674 (29.8)
Staphylococcus aureus	37	34 (91.9)
MRSA	15	14 (93.3)
MSSA	22	20 (90.9)
All-cause non-*Staphylococcus aureus*	2222	640 (28.8)
Pneumococcal	115	54 (47.0)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

CAP also had longer hospital length of stay and were more likely to be admitted to the ICU than those with all-cause non-*S. aureus* CAP (Table 6).

DISCUSSION

In this multicenter, prospective active surveillance study at 5 US hospitals with systematic testing for pneumonia pathogens, *S. aureus* infection was uncommon among adults hospitalized with CAP, accounting for <2% of hospitalized CAP cases. MRSA was identified in <1% of adults hospitalized with CAP. Although clinical outcomes of MRSA CAP tended to be more severe than of other types of CAP, the initial presentation of MRSA and MSSA CAP overlapped substantially with one another and also with all-cause non-*S. aureus* CAP, especially that caused by *S. pneumoniae*.

Although the identification of risk factors and development of clinical prediction models for MRSA CAP have generated great interest recently [16, 18, 36–39], our results suggest it is unlikely that a clinical prediction model could be developed that accurately identifies MRSA CAP at hospital admission due to the nonspecificity of common MRSA features (influenza coinfection, multilobar infiltrates) and uncommon occurrence of more specific features (massive hemoptysis, cavitary pneumonia).

Despite the low prevalence of MRSA CAP, empirical anti-MRSA antibiotics were frequently used, with 29.8% of all patients in this study receiving vancomycin or linezolid during the first 3 days of hospitalization. MRSA CAP was uncommon among patients not admitted to an ICU, with a prevalence of 2 (0.1%) MRSA cases out of 1777 patients in this study, providing support for the current IDSA/ATS CAP guidelines [17] that do not recommend routine anti-MRSA antibiotics for patients admitted to a general medical floor. The prevalence of MRSA CAP among patients admitted to an ICU was 2.7%, and their clinical outcomes were particularly severe. Therefore, empirical anti-MRSA therapy for critically ill CAP patients appears to be an important consideration until results of diagnostic testing are available, especially since failure of initial empirical antibiotics to cover for the infecting pathogen appears to be associated with increased mortality in sepsis [40].

Overuse of antibiotics has been linked to several negative outcomes, including antibiotic resistance, medication-related toxicities, *Clostridium difficile* infections, and increased cost [41]. The difficulty of identifying MRSA CAP based on epidemiologic and clinical features and the overuse of anti-MRSA antibiotics highlight the need for the rapid diagnostic tests to help guide antibiotic selection [42] and stewardship programs to minimize the use of unnecessary antibiotics [12].

Prevalence of *S. aureus* and MRSA CAP in our study was comparable to that found by Moran et al [7], who reported a 3.9% prevalence of *S. aureus* and a 2.4% prevalence of MRSA among 595 adults hospitalized with CAP at 12 US hospitals during the 2005–2006 and 2006–2007 influenza seasons. Our results complement and expand on those published by Moran et al [7] in several important respects; namely, we studied a

Table 6. Clinical Outcomes of Adults Hospitalized With Community-Acquired Pneumonia, by Etiology Group

	Staphylococcus aureus CAP			CAP without *Staphylococcus aureus*	
Outcome	Methicillin-Resistant *S. aureus* (n = 15)	Methicillin-Susceptible *S. aureus* (n = 22)	All *S. aureus* (n = 37)	Pneumococcal (n = 115)	All-cause non-*S. aureus* (n = 2222)
Median hospital length of stay (IQR), days	9 (8, 13)	6 (4, 10)	8 (4, 11)	4 (2, 7)	3 (2, 6)
Intensive care unit admission, n (%)	13 (86.7)	10 (45.5)	23 (62.2)	40 (34.8)	459 (20.7)
Empyema, n (%)	4 (26.7)	4 (18.2)	8 (22.2)	17 (14.8)	187 (8.4)
Invasive mechanical ventilation, n (%)	5 (33.3)	4 (18.2)	9 (24.3)	14 (12.2)	108 (4.8)
Acute respiratory distress syndrome, n (%)	1 (6.7)	1 (4.5)	2 (5.4)	5 (4.3)	71 (3.2)
Septic shock with vasopressor use, n (%)	3 (20.0)	3 (13.6)	6 (16.2)	13 (11.3)	81 (3.6)
In-hospital mortality, n (%)	2 (13.3)	2 (9.1)	4 (10.8)	5 (4.4)	45 (2.0)

Abbreviations: CAP, community-acquired pneumonia; IQR, interquartile range.

larger population 4–6 years later in 2 cities not evaluated in the prior study, enrolled a population-based cohort year-round for 2.5 consecutive years, and performed systematic influenza testing to understand the frequency of *S. aureus* and influenza coinfections. Similar to our results, Moran et al [7] also found that patients with MRSA CAP had high pneumonia severity scores at presentation, but that epidemiologic and clinical features were not particularly helpful for identifying MRSA cases for the purposes of guiding empirical antibiotic selection. Interestingly, in-patient mortality for MRSA CAP in our study (13.3%) and that of Moran et al [7] (14%) was similar and substantially lower than in older MRSA CAP case series [2, 3, 43, 44].

Prior studies emphasized the potential role of influenza infection as a predisposing factor for *S. aureus* CAP and frequent coinfection with influenza and *S. aureus* [1–3, 44]. We systematically tested for influenza, allowing direct evaluation of influenza–*S. aureus* coinfection in individual patients and seasonal variation in the detection of these pathogens. As illustrated in Figure 1, the highest levels of detection for influenza and *S. aureus* tended to cluster together in the same months, but cases of *S. aureus* CAP occurred year-round. Influenza was codetected in only 3 (8.1%) patients with *S. aureus* CAP. This pattern suggests that while *S. aureus* CAP may be more common during influenza peaks, the disease is not limited to patients with active influenza infection.

The distinction between CAP and pneumonia that developed as a result of exposure to the healthcare system, termed healthcare-associated pneumonia (HCAP) [45], has not been fully delineated [46, 47]. In this study, we standardized enrollment criteria, aiming to capture patients who developed pneumonia outside the healthcare environment [9]. Patients with strong risk factors for multidrug-resistant pathogens, including recent hospitalization, tracheostomy, gastrostomy, and nursing home residents unable to perform activities of daily living, were excluded from this study [18, 36–38]. However, some patients with traditional HCAP criteria outlined by the IDSA/ATS pneumonia guidelines [45] were eligible for inclusion, including functionally independent nursing home residents and patients with chronic hemodialysis use. These patients were included to allow for more comprehensive evaluation of characteristics associated with *S. aureus* CAP. Hemodialysis use was significantly associated with *S. aureus* infection, supporting the recommendation to consider empiric anti-MRSA antibiotics in hemodialysis patients who are hospitalized for pneumonia [45]. Importantly, when analyses were repeated after patients with these traditional HCAP risk factors (hemodialysis use and nursing home residency) were excluded, the prevalence of MRSA was very low (0.6%) and the use of anti-MRSA antibiotics remained high (28.0%).

This study had limitations. First, 68% of patients identified as eligible were enrolled; among these, 91% of patients met the final radiographic criteria and also had appropriate testing for both bacteria and viruses and thus were included in this analysis. Nonenrollment was largely due to patients or surrogates declining participation in the study; nonenrolled patients were older, more likely to require invasive mechanical ventilation, and more likely to die in the hospital [17]. Whether patients with *S. aureus* CAP were differentially enrolled in the study is unknown. Second, detection of *S. aureus* was based on cultures of blood and respiratory secretions, which may have missed the presence of *S. aureus* at the site of disease pathology in the lung. Results from invasive sampling, such as BAL and pleural fluid, were only included when these specimens were obtained for routine clinical care. This may have contributed to more *S. aureus* detection in patients with ICU admission and higher severity scores. Third, *S. aureus* can colonize the respiratory tract without causing illness. We attempted to minimize misclassification of colonizing *S. aureus* as *S. aureus* CAP by only including sputum and endotracheal samples that met high-quality criteria and BAL cultures with moderate or heavy growth [9]. Fourth, the number of *S. aureus* cases was small, limiting the precision of statistical comparisons and precluding more robust multivariable analyses. Fifth, we evaluated for concurrent influenza and *S. aureus* infections but could not assess for influenza infection as a precipitating event before *S. aureus* CAP because we did not obtain samples prior to hospital presentation. Sixth, our study population may not be fully representative of other geographic regions or time periods.

In conclusion, *S. aureus* (1.6%), including MRSA (0.7%), was uncommon in this large population-based study of adults hospitalized with CAP. Despite this low prevalence, anti-MRSA antibiotics were frequently used (29.8%). While MRSA CAP patients generally had high severity of illness, clinical and epidemiologic characteristics overlapped substantially with non-*S. aureus* CAP, particularly pneumococcal CAP, making it difficult to distinguish between etiologic types of pneumonia clinically. Low prevalence of MRSA combined with a lack of highly distinctive clinical features make accurate targeting of empirical anti-MRSA antibiotics very difficult. Development of diagnostic tests capable of rapidly and accurately identifying *S. aureus* could greatly improve the current approach to CAP management and reduce overuse of anti-MRSA antibiotics.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author Contributions. *Study concept and design:* W. H. S., R. G. W., D. J. W., E. J. A., J. D. C., D. M. C., S. M., S. J., K. M. E., and C. G. G. *Acquisition of data:* W. H. S., R. G. W., D. J. W., R. A. B., S. S. F., J. D. C., D. M. C., C. T., G. W. W., A. B., S. J., and K. E. M. *Statistical analysis:* W. H. S., G. C., Y. Z., A. B., and C. G. G. *Interpretation of data:* W. H. S., R. G. W., D. J. W., G. C., Y. Z., E. J. A., R. A. B., S. S. F., J. D. C., D. M. C., C. T., G. W. W., S. M., S. J., K. M. E., and C. G. G. *Drafting of the initial*

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