Incidence, characteristics and outcomes of patients with severe community acquired-MRSA pneumonia

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ABSTRACT: We evaluated the published data for the incidence, characteristics and outcomes of patients with community-acquired pneumonia (CAP) due to methicillin-resistant *Staphylococcus aureus* (MRSA). The estimated incidence of MRSA CAP is 0.51–0.64 cases per 100,000.

We identified 74 articles reporting data on 114 patients. Influenza like symptoms was reported in 41% of patients. Pneumonia improved in 59 (54.1%) out of 109 patients; 49 (44.5%) out of 110 patients died. The duration of hospitalisation was 38.1 ± 24.9 and 8.3 ± 11.7 days, respectively. The duration of intensive care unit (ICU) stay was 18.9 ± 13.6 and 6.8 ± 9.7 days, respectively. 76 strains carried the Panton–Valentine leukocidin gene.

The univariate analysis showed that multi-organ failure ($p < 0.001$), leukopenia ($p < 0.001$), admission to ICU ($p < 0.001$), mechanical ventilation ($p < 0.001$), use of aminoglycosides after culture results ($p < 0.001$), shock ($p = 0.001$), acute respiratory distress syndrome ($p = 0.001$), influenza like symptoms ($p = 0.008$), disseminated intravascular coagulation ($p = 0.042$) and rash ($p = 0.04$) were the factors associated with death.

O ne of the common causes of infection of all organs of the human body is *Staphylococcus aureus*. It is armed with a variety of virulence factors that facilitate adherence of and invasion to host tissues in addition to structures that disable host defenses and toxins that induce septic syndromes [1]. Furthermore, *S. aureus* has acquired genes that promote resistance for several classes of antibiotics; the most important to date is the *mec*A gene that confers resistance to methicillin and almost all β-lactams [2]. From the clinical point of view, methicillin-resistant *S. aureus* (MRSA) has become the primary pathogen of skin and soft tissue infections, but invasive infections also occur [2–4]. Among them, nosocomial pneumonia (NP), healthcare-associated pneumonia (HCAP) and community-acquired pneumonia (CAP) are of major importance due to the morbidity and mortality attributed to them [5–7].

The strains associated with NP/HCAP and CAP have distinct characteristics. The former contains the staphylococcal cassette chromosome SCC*mec* types I–III, while the latter contains SCC*mec* types IV and V. In addition, community-acquired (CA)-MRSA strains are susceptible to more classes of antibiotics [8, 9]. Finally, toxins like Panton–Valentine leukocidin (PVL) have been identified more frequently in CA-MRSA strains.

Although the incidence of MRSA NP/HCAP has been evaluated in several studies [10], the incidence of MRSA CAP is unknown [8, 9, 11]. *S. aureus* is responsible for 1–10% of CAP cases reported in the literature [12–14]. Studies describing patients with *S. aureus* CAP included only a very small number of MRSA cases [15–17]. Therefore, we sought to study systematically the available evidence in order to identify the incidence, characteristics and outcomes of patients with MRSA CAP.

METHODS

Literature search

A systematic search of PubMed and Scopus was performed by two independent reviewers. A combination of the terms "*S. aureus*", "staphylococcal", "methicillin-resistant", "community-acquired pneumonia", "pneumonia", "necrotizing pneumonia", "sepsis" and "toxic shock syndrome" were used. We also searched reference lists of retrieved articles and review papers for relevant studies. A time limit was set to only include articles written after 1985, when the first reports of CA-MRSA infections were reported (January 1985 to September 2008).

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Study selection and data extraction

All articles reporting data on patients with MRSA CAP could be included (population based studies, case reports, case series, cohorts, case–control studies, cross-sectional, randomised controlled trials). A language restriction was set for articles published in English, French, German, Italian, Spanish, Greek and Scandinavian. Inclusion was stratified according to available data on *S. aureus* susceptibility; in the absence of such data, studies were excluded from the analysis. Studies were also excluded from the review if clinical, microbiological and outcome data regarding individual patients or groups of patients with MRSA pneumonia were not available. Studies evaluating animal models were not eligible for inclusion.

Subsequently, data on demographics, history, risk factors for CA-MRSA (close contact with CA-MRSA colonisation or infection [18], prison incarceration [19, 20], contact sports [21, 22], recent military service [23], males having sex with males [24], intravenous drug use [25–27], steam bath use [28, 29], recent antibiotic use before the current infection [8]), severity and course of the disease, antibiotic use or need for intensive care unit (ICU) treatment and/or outcome of the infection were extracted from the studies. Hospitalisation was not an inclusion criterion. Both primary and secondary cases of CAP (haematogenous spread from other sites of infection) could be included.

Definitions

MRSA CAP was defined according to the definition of the Center for Disease Control and Prevention (CDC). A case of CA-MRSA was defined as illness compatible with CAP, in which MRSA was cultured from sputum or blood in an outpatient setting or <48 h after hospital admission, and with none of the following healthcare risk factors: recent hospitalisation; surgery; dialysis; or residence in a long-term care facility <1 yr before the onset of illness; and permanent indwelling catheter or percutaneous medical device [30]. In addition, the definition was broadened to include cases in which the genotyping data (pulsed-field gel electrophoresis (PFGE), multilocus sequence typing or other techniques) provided evidence of a community strain.

CAP was defined as a baseline chest radiograph demonstrating new or progressive infiltrates, consolidation with or without effusion, and four of the following signs and symptoms: cough; new or worsened purulent sputum production; rales and/or signs of pulmonary consolidation; dyspnoea and/or hypoxemia; fever ($\geqslant 38^{\circ}C$); respiratory rate $\geqslant 20$ breaths·min^{-1}; systolic hypotension (<90 mmHg); heart rate $\geqslant 120$ beats·min^{-1}; altered mental status; requirement for mechanical ventilation; white blood cell (WBC) count $\geqslant 10,000$ cells·mm^{-3} with $\geqslant 15\%$ immature neutrophils; or leukopenia (WBC count $\leqslant 4,500$ cells·mm^{-3}). The severity of CAP was based either on the opinion of the author of each article or the need for ICU treatment. A patient received appropriate initial antibiotic therapy if the isolate recovered from blood or sputum was susceptible to at least one of the antibiotics included in the empirical regimen.

Statistical analysis

The extracted data was converted to variables and analysed accordingly. Data was analysed with SPSS 15.0 software (SPPS Inc, Chicago, IL, USA). For categorical variables, the Chi-squared test or Fisher's exact was used. For continuous variables, an independent sample t-test was used. For all tests performed, a two-tailed p-value <0.05 was considered as denoting statistical significance.

RESULTS

Selected studies

Figure 1 shows the process of screening and selection of studies included in the systematic review. The initial search revealed a total of 2,602 studies. Of which, 1,292 were published from 1985 and onwards. After screening according to the inclusion criteria,
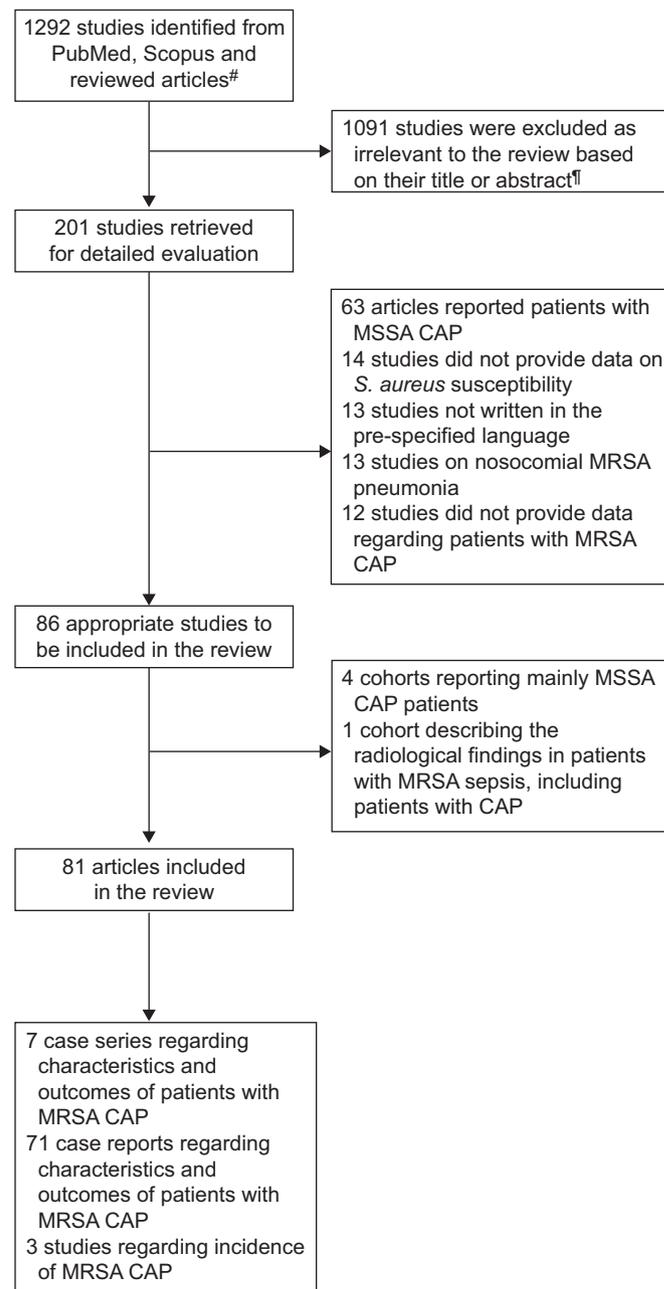

FIGURE 1. Flow diagram of the reviewed studies. MSSA: methicillin-sensitive *Staphylococcus aureus* (*S. aureus*); CAP: community-acquired pneumonia; MRSA: methicillin-resistant *S. aureus*. #: the majority of studies were found in both databases; ¶: include studies on nosocomial pneumonia, effectiveness of antimicrobial agents for CAP, cohorts of CAP patients without data regarding MRSA CAP, community acquired-MRSA infections other than CAP.

201 articles were retrieved for detailed evaluation. 115 were excluded for reasons shown in figure 1. Thus 81 studies were included in the systematic review [31–111]. Three of these reports provided data regarding the incidence of MRSA infections [31–33]. The remaining studies provided data regarding the characteristics and outcomes of patients with MRSA CAP (71 case reports and 7 case series) [34–111].

Incidence of MRSA CAP

We could not identify any study that sought to investigate the incidence of MRSA CAP. Two reviews reported that the evidence on epidemiology and characteristics of MRSA CAP is unknown and is extrapolated from studies on patients hospitalised with MSSA (methicillin-sensitive *S. aureus*) CAP (which is also scarce) [112, 113]. One of them also commented that ''this should be attributed to the lack of routine culture in patients with uncomplicated pneumonia'' [113]. Several studies reported that after the implementation of the anti-pneumococcal vaccine the incidence of *Streptococcus pneumoniae* CAP decreased with a simultaneous increase in MRSA CAP, especially in cases complicated with pleural effusions [114–116]. Accordingly, an increase in staphylococcal infections, caused primarily by an increase in MRSA infections, has been confirmed [117, 118].

However, we came across studies that reported the incidence of CA-MRSA infections and also included patients with MRSA CAP. FRIDKIN *et al.* [31] reported that the annual incidence of CA-MRSA infections (based on population-based surveillance in Baltimore (MD, USA) and Atlanta (GA, USA), and hospital-laboratory sentinel surveillance of 12 hospitals in Minnesota (USA) between 2001 and 2002) was 25.7 cases per 100,000 in Atlanta and 18.0 per 100,000 in Baltimore. In both areas, the incidence was higher among patients <2 yrs of age than in patients >2 yrs of age. In Atlanta the incidence was also higher among Blacks than Whites. CAP was responsible for 2% of these cases in Atlanta and 3% in Baltimore for an estimated incidence of 0.51 cases per 100,000 and 0.54 cases per 100,000, respectively. Clinical and outcome data regarding patients with MRSA CAP were not available.

KLEVENS *et al.* [32] also reported that the incidence of CA-MRSA infections (based on population-based surveillance in nine sites participating in the Active Bacterial Core surveillance from July 2004 through December 2005) was 4.6 cases per 100,000. Incidence varied among age groups. A lower incidence was found between the age group 2–17 yrs (median 0.7 per 100,000 cases), and a higher incidence was found among the age groups 35–64 yrs (median 6.5 per 100,000 cases) and >65 yrs (8.9 per 100,000 cases). CAP accounted for 14.0% of CA-MRSA infections for an estimated incidence of 0.64 cases per 100,000. Mortality among patients with CA-MRSA infections was 0.5 cases per 100,000. The corresponding figure for MRSA CAP was not reported. However, it was reported that the overall mortality was higher for patients with septic shock (55.6%) and pneumonia (32.4%) than patients with other CA-MRSA related infections (6.2–19.3%).

Finally, a survey in US hospitals between 2002 and 2003, which included ~2,200 patients with culture positive CAP requiring hospitalisation, reported that MRSA was responsible for 8.9% of all cases and 34.8% of staphylococcal CAP [33]; the characteristics and outcomes of these patients were not reported. The same study reported that *S. aureus* was responsible for 25.5% of cases, being the dominant pathogen, followed by *Pseudomonas aeruginosa* (17.1%), a figure similar to the one reported for nosocomial and ventilator associated pneumonia.

Case reports of MRSA CAP

Data for 114 patients were retrieved [34–104]; data on outcomes were available for 110 patients. 23 patients had CAP secondary to another infection. The demographical and clinical characteristics and outcomes of these patients are shown in table 1 (data were not available for all patients).

The mean±SD and median (range) age of patients with MRSA CAP was 25.5±20.3 and 21 (0–83), respectively. 75 (69%) out of 109 patients were aged <35 yrs and 59% were males. Risk factors for CA-MRSA colonisation were reported for 32 patients.

Influenza like illness and documented influenza infection was reported in 41% and 21% of patients, respectively. Tachypnoea was the most commonly reported symptom (92%), followed by fever (89%), shock (56%), cough (58%), haemoptysis (29%), chest pain (19%), gastro-intestinal symptoms (18%), rash (15%) and confusion (13%). All reported patients were admitted to the hospital. The reasons for admission are summarised in table 1. Pneumonia was considered severe for 85 (86%) out of 99 patients.

Laboratory findings were not reported consistently in these case reports. Leukopenia was reported in 26 (45%) patients, while thrombocytopenia was reported in 21 (68%) patients. Liver and kidney function tests, as well as arterial oxygen saturation or blood gases analyses, were rarely reported.

The majority of patients had multilobar consolidations or bilateral lung infiltrates (69 (75%) out of 92 patients) either at presentation or during the following days. Pleural effusions, including cases with empyema, were seen in 33 (34%) patients. Computed tomography and lung biopsy showed evidence of necrotising pneumonia in 51 (77%) out of 66 patients.

All but two patients, for whom data was available, received antibiotics within hours after admission; 14 patients had also received antibiotics prior to admission. Appropriate antibiotics were administered in 37 (47%) out of 79 patients. Modifications in the antibiotic regimen were necessary for 42 (62%) out of 68 patients, reflecting changes for inappropriate therapy and treatment failures. No differences were seen in antibiotic administration for patients who died and patients who survived, except for aminoglycosides in patients who died (p<0.001).

The majority of patients required ICU care (78 (76.5%) out of 102 patients). Inotropic support for circulatory failure was necessary for 49 (65%) patients and mechanical ventilation for respiratory support was necessary for 55 (67%) patients. Other adjunctive therapies included extracorporeal membrane oxygenation, corticosteroids, activated protein C, *i.v.* immunoglobulin, surgical drainage of pleural effusion or empyemas and heparin.

Multi-organ failure developed in 35 (44%) patients and acute respiratory distress syndrome in 19 (23.5%) patients. Other complications included pneumothorax and pneumatoceles, deep venous thrombosis, acidosis, disseminated intravascular

TABLE 1	Comparison of characteristics and interventions between patients with methicillin-resistant *Staphylococcus aureus* (MRSA) community-acquired pneumonia (CAP) who died and survived		
Variable	**Died**	**Survived**	**p-value**
Subjects n	49	61	
Demographic			
Age yrs	26±22.9	24.1±18.3	0.64
Male sex	27/49 (55.1)	37/60 (61.7)	0.49
History			
Smoking	6/43 (14)	4/52 (7.7)	0.34
Alcohol	2/43 (4.7)	4/52 (7.7)	0.69
Drug abuse	2/44 (4.5)	6/56 (10.7)	0.46
Diabetes	3/46 (6.5)	2/55 (3.6)	0.66
Respiratory disease	1/46 (2.2)	6/55 (10.9)	0.12
Heart disease	5/46 (10.9)	2/55 (3.6)	0.24
Cancer	2/46 (4.3)	0/55 (0)	0.21
Immunosuppression	1/46 (2.2)	4/55 (7.3)	0.37
Liver disease	1/46 (2.2)	1/55 (1.8)	1.00
Risk factors for MRSA	12/44 (27.3)	20/53 (37.7)	0.28
Previous antibiotics	1/44 (2.3)	4/53 (7.5)	0.37
Previous MRSA infection/colonisation	2/44 (4.5)	2/53 (3.8)	1.00
Relatives with MRSA	5/44 (11.4)	6/53 (11.3)	1.00
Contact sports	2/44 (4.5)	2/53 (3.8)	1.00
Reason of hospitalisation			
CAP	36/43 (83.7)	32/51 (61.7)	0.22
Shock	1/43 (2.3)	4/51 (7.8)	
Bone-joint infection	1/43 (2.3)	3/51 (5.9)	
SSTI	0/43 (0)	2/51 (3.9)	
Other[#]	5/43 (11.6)	10/51 (19.6)	
Clinical characteristics			
Secondary CAP	5/49 (10.2)	18/61 (29.5)	**0.013**
Antibiotics before admission	7/49 (14.3)	7/61 (11.5)	0.66
Duration of symptoms prior to hospitalisation days	4.4±3.4	5.3±2.7	0.19
Influenza like symptoms	22/39 (56.4)	15/52 (28.8)	**0.008**
Fever	33/40 (82.5)	44/47 (93.6)	0.18
Cough	27/43 (62.8)	27/50 (54)	0.39
Chest pain	4/40 (10)	13/48 (27.1)	**0.043**
Gastrointestinal symptoms	9/42 (21.4)	7/48 (14.6)	0.40
Rash	10/43 (23.3)	4/50 (8)	**0.04**
Confusion/lethargy	6/37 (16.2)	4/42 (9.5)	0.50
Shock	31/37 (83.8)	18/38 (47.4)	**0.001**
Tachypnoea	28/30 (93.3)	28/31 (90.3)	1.00
Airway haemorrhage	14/38 (36.8)	8/39 (20.5)	0.11
Severe CAP	47/47 (100)	38/52 (73.1)	**<0.001**
Radiographical findings			
Unilobar infiltrates	10/42 (21.4)	13/50 (26)	0. 43
Multilobar infiltrates	32/42 (78.6)	37/50 (74)	0. 43
Pleural effusion	9/44 (20.5)	24/52 (46.2)	**0.008**
Necrotising pneumonia	28/33 (84.8)	23/33 (69.7)	0.14
Laboratory findings			
Proven influenza	10/33 (30.3)	6/42 (14.3)	0.09
Leukopenia	19/24 (79.2)	7/34 (20.6)	**<0.001**
Thrombocytopenia	11/13 (84.6)	10/18 (55.6)	0.13
Bacteremia	31/41 (75.6)	41/52 (78.8)	0.71

TABLE 1	Continued		
Variable	**Died**	**Survived**	**p-value**
Interventions			
Admission to ICU	47/48 (97.9)	31/54 (57.4)	**<0.001**
Mechanical ventilation	34/38 (89.5)	21/44 (47.7)	**<0.001**
Glycopeptides/linezolid before culture	16/39 (41)	17/46 (37)	0.70
Appropriate empiric therapy	16/33 (48.5)	21/46 (45.7)	0.80
Treatment changes	13/25 (52)	29/43 (67.4)	0.21
Adjunctive therapy[¶]	21/38 (55.3)	19/27 (70.4)	0.22
ECMO	3/38 (7.9)	9/27 (33.3)	**0.02**
Activated protein C	4/38 (10.5)	3/27 (11.1)	1.00
IVIG	2/38 (5.3)	4/27 (14.8)	0.22
Drainage/surgery	8/38 (21.1)	4/27 (14.8)	0.75
Complications			
ARDS	15/36 (41.7)	4/45 (8.9)	**0.001**
DVT	0/36 (0)	4/44 (9.1)	0.12
Pneumocele/pneumothorax	5/36 (13.9)	5/44 (11.4)	0.75
Acidosis	5/36 (13.9)	1/44 (2.3)	0.09
DIC	6/36 (16.7)	1/44 (2.3)	**0.042**
Multi-organ failure	25/36 (69.4)	10/44 (22.7)	**<0.001**
Outcomes			
Duration of hospitalisation days	8.3±11.7	38.1±25	**<0.001**
Duration of ICU stay days	6.8±9.7	18.9±13.6	**0.003**

Data are presented as mean±SD or n/N available (%), unless otherwise stated. SSTI: skin and soft tissue infection; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; IVIG: intravenous immunoglobulins; ARDS: acute respiratory distress syndrome; DVT: deep vain thrombosis; DIC: disseminated intravascular coagulation. [#]: including DVT, meningitis, endocarditis, gastroenteritis, fever and noncutaneous abscesses; [¶]: including heparin, corticosteroids, haemofiltration, transfusions and surgical procedures. The bold entries refer to values of statistical significance.

coagulation, digital necrosis, abscess formation, Waterhouse–Friederichsen syndrome, secondary hospital infections, cerebral infarcts due to septic emboli, and cardiac arrhythmias or arrest.

Data on outcomes were available for 110 patients. Table 2 summarises the included patients according to age and outcome. Pneumonia improved in 61 patients; 49 (44.5%) died. The median time from symptom onset to death and from hospital admission to death was 8 (3–47) and 3 (1–51) days, respectively. The median duration of hospitalisation for all patients was 10 (1–108) days; the corresponding ICU figure was 3.5 (1–42) days.

The univariate analysis showed that multi-organ failure (p<0.001), leukopenia (p<0.001), admission to ICU (p<0.001), mechanical ventilation (p<0.001), use of aminoglycosides after culture results (p<0.001), shock (p=0.001), acute respiratory distress syndrome (p=0.001), influenza like symptoms (p=0.008), disseminated intravascular coagulation (p=0.042) and rash (p=0.04) were the factors associated with death. However, secondary CAP (p=0.013), pleural effusion (p=0.008), chest pain (p=0.043) and extracorporeal membrane oxygenation (p=0.02) were associated with survival. A subset analysis that included only articles published from 2005 and onwards resulted in similar outcomes with a few differences. In this analysis, chest pain

TABLE 2	Distribution of patients with methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia according to age and outcome		
Age group	Died	Survived	p-value
0–2 yrs	8/49 (16.3)	11/60 (18.3)	
3–16 yrs	16/49 (32.7)	15/60 (25)	
17–35 yrs	11/49 (22.4)	14/60 (23.3)	0.38
35–65 yrs	10/49 (20.4)	19/60 (31.7)	
>65 yrs	4/49 (8.2)	1/60 (1.7)	

Data are presented as n/N available (%), unless otherwise stated.

(p=0.144) and rash (p=0.111) were not associated with death, while thrombocytopenia was (p=0.043).

Data on toxin carriage was available mainly for PVL (76 strains), while data for other toxins were rarely reported. Data for PFGE typing were available for 37 strains. USA 300 was the commoner pattern identified (26 out of 37 strains) followed by the Queensland clone (nine out of 37). All strains for which PFGE type was available were PVL positive. 35 strains contained the SCC*mec* type IV and four strains contained the SCC*mec* type V. Data regarding other molecular typing technique classification were not reported regularly. The majority of the isolated strains were only resistant to oxacillin or methicillin; resistance to macrolides and fluoroquinolones was also reported, while resistance to clindamycin, trimethoprime-sulfamethoxazole and fusidic acid was rare. None of these strains were resistant to linezolid and vancomycin.

Case series of MRSA CAP

Seven case series have been published [105–111]. The characteristics and outcomes of patients reported in these case series are shown in table 3. A total of 98 patients with MRSA CAP were included in these series. Of these, 52% of patients were male and 31% (for whom data was available) had risk factors for CA-MRSA. Influenza like symptoms was present in 57% of patients; influenza infection was documented by culture or serology in 38%. Radiographic or autopsy findings of necrotising pneumonia were reported for 61% of patients. All patients who did not die in the emergency department or during transfer to another hospital were admitted to the hospital, of which 85% required ICU treatment. The duration of hospitalisation varied between studies but, in general, the median length of stay was prolonged (>13 days). Finally, overall mortality was 39%; data regarding mortality attributable to MRSA CAP was not available.

The largest cohort included 51 patients with primary staphylococcal CAP [105]. This cohort included unsolicited case reports submitted to the CDC and requested case reports from infectious disease specialists participating in an Infectious Disease Society of America (IDSA) Emerging Infections Network survey. Identification of *S. aureus* was performed with the Staphaurex latex agglutination test, catalase and coagulase production. All available isolates underwent PFGE typing; toxin production was verified by PCR assays. 47 patients had positive cultures for *S. aureus* (isolated from respiratory secretions (60%), blood (38%), pleural fluid (23%) and lung tissue (9%)) while four additional patients had a positive *S. aureus* immunohistochemistry result at autopsy and pathology; 37 of these isolates were MRSA. Out of the 17 MRSA strains available for further analysis 16 were PVL positive and belonged to the USA 300 PFGE type. The remaining isolate was a PVL negative USA100 strain, a pattern that is most commonly found in hospital acquired infections.

The characteristics of patients with MRSA CAP were not reported separately. However, it was reported that appropriate empiric therapy was instituted in 43% of MRSA patients and 100% of MSSA patients. An interesting finding of this study was that empiric antibiotic therapy was initiated sooner in patients who died than those who survived (median 2 *versus* 5 days). In addition, median length of stay was shorter for influenza positive than influenza negative patients (16 *versus* 8.5 days). Leukopenia was associated with death in multivariate analysis. KALLEN *et al.* [105] emphasised that the limitations of their study were its retrospective design, the possibility of reporting only more severe cases, the isolation of *S. aureus* mainly from sputum specimens that increased the probability to include patients simply colonised with *S. aureus* and the difficulty in collecting data regarding a preceding or concomitant influenza infection.

The remaining descriptive case series included only a small number of patients each (from five to 12 patients) [106–111]. Therefore, strong conclusions could not be made from the individual studies. Figure 2 summarises the annual published reports of MRSA CAP.

DISCUSSION

Studies regarding MRSA CAP are lacking. The limited available data shows that MRSA should not be considered a frequent cause of CAP. Its estimated incidence was 0.51–0.64 cases per 100,000, while the incidence of CAP was 266.8 per 100,000 population in 1991 and 198 cases per 100,000 population in 2004–2005 [119, 120]. However, studies suggest that the incidence of MRSA CAP may be rising, especially in cases complicated with pleural effusion [114–116]. The most worrying findings come from one study that shows a prevalence of 8.9% among hospitalised patients with culture positive CAP [33]. Should these findings be verified in other studies, modifications to the guidelines for treatment of CAP should be considered to incorporate coverage of MRSA in the empirical regimen, at least for those requiring hospitalisation [121].

The published data also suggest that MRSA CAP is a severe disease. Mortality in the individual case series [105–111] was 20–60%, while mortality in case reports [34–104] was 44.5%. The estimated overall mortality in patients with CAP is 5–9%; the corresponding figure in patients with severe CAP was 9–27% [122]. In addition, the majority of patients with MRSA CAP in these reports required ICU treatment. Further evidence supporting the notion of severe disease is provided by the short period from symptom onset or diagnosis of pneumonia to death. However, since most of the published studies are case reports or small case series, and series reporting severe disease are more likely to be published, this finding may not reflect the true burden of the disease.

TABLE 3	Case series with methicillin-resistant *Staphylococcus aureus* (MRSA) community-acquired pneumonia (CAP) patients published after 1985

	First author [ref.]							Total
	KALLEN [105]	**CASTALDO [106]**	**Centers for Disease Control [107]**	**HAGEMAN [108]**	**JANVIER [109]**	**GONZALEZ [110]**	**LEROY [111]**	
MRSA	37/51 (73)	7/7 (100)	10/10 (100)	15/17 (88)	5/5 (100)	12/14 (86)	12/14 (86)	98/118 (83)
Age yrs	16 (<1–81)	14.2 (0.8–16)	17.5 (0.3–48)	21 (0.25–62)	NA	13 (10–15)	NA	NA
Male sex	21/51 (41)	5/7 (71)	5/10 (50)	8/17 (47)	NA	12/14 (86)	NA	51/99 (52)
Comorbidities	27/48 (56)	0/7 (0)	1/10 (10)	5/17 (29)	NA	2/14 (14)	NA	35/96 (36)
MRSA risk factors	13/31 (42)	NA	4/10 (40)	4/17 (24)	NA	1/14 (7)	NA	22/72 (31)
Influenza like symptoms	22/47 (47)	NA	10/10 (100)	17/17 (100)	NA	1/14 (7)	NA	50/88 (57)
Proven influenza infection	11/33 (33)	NA	6/10 (60)	12/17 (71)	0/5 (0)	1/14 (7)	NA	30/79 (38)
Necrotising pneumonia	NA	7/7 (100)	7/10 (70)	4/16 (25)	5/5 (100)	NA	NA	23/38 (61)
PVL production	16/17 (94)	NA	10/10 (100)	11/13 (85)	5/5 (100)	14/14 (100)	NA	56/59 (95)
Resistance to antibiotics[#]	ERM 93 LEV 50	NA	ERM 100 CLN 20 LEV 20	ERM 100 CLN 91 LEV 55	NA	ERM 100	NA	NA
Hospitalisation nm	43/51 (84)[¶]	7/7 (100)	10/10 (100)	16/17 (94)[¶]	5/5 (100)	14/14 (100)	14/14 (100)	109/118 (92)[¶]
ICU treatment	34/43 (74)	7/7 (100)	NA	13/16 (81)	NA	14/14 (100)	NA	68/80 (85)
Appropriate empirical therapy	26/51 (51)	NA	NA	12/15 (80)	NA	NA	2/10 (20)	40/76 (53)
Length of stay days	16 (2–19)	30 (5–53)	NA	13 (1–108)	24 (5–42)	24.5 (1–120)	NA	NA
Death	24/47 (51)	3/7 (43)	6/10 (60)	5/17 (29)[+]	1/5 (20)	3/14 (21)	3/14 (21)	45/114 (39)
Symptom onset to death days	4 (1–33)	30 (5–51)	3.5 (2–25)	7 (3–73)	NA	5 (2–7)	NA	NA

Data are presented as n/total patients (%) or median (range). The data for resistance to antibiotics is presented as per cent. PVL: Panton–Valentine leukocidin; ICU: intensive care unit; NA: not available/applicable; ERM: erythromycin; LEV: levofloxacin; CLN: clindamycin. [#]: strains were sensitive to linezolid, vancomycin, rifampin and gentamycin; [¶]: the remaining patients died in the emergency department or during transfer to another hospital; [+]: four out of five deceased patients had MRSA pneumonia.

The main characteristic of the patients reported in the literature was the severity of pneumonia. The aetiology of severe CAP is diverse. Therefore, the severity of pneumonia cannot be associated with MRSA. However, a combination of severe CAP and younger age could be a clue pointing towards MRSA (or *S. aureus*) infection. Finally, although present in only 32.5% of patients in our study, physicians should seek to identify risk factors for MRSA infections. These, in addition to the recommendations of IDSA of preceding influenza infection and chest radiographs with cavitary lesions without risk factors for aspiration, should prompt physicians to suspect MRSA as the causative organism of pneumonia.
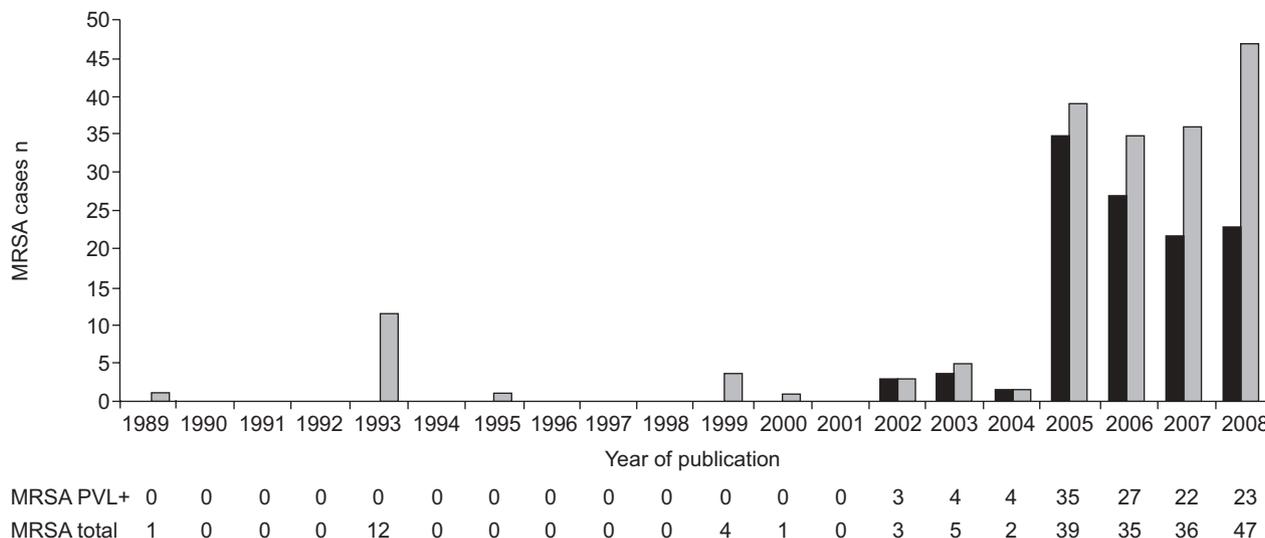

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
MRSA PVL+	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4	4	35	27	22	23
MRSA total	1	0	0	0	12	0	0	0	0	0	4	1	0	3	5	2	39	35	36	47

FIGURE 2. Summary of the annual published reports of methicillin-resistant *S. aureus* (MRSA) cases between 1989 and 2008. ▪: MRSA total; ▪: MRSA Panton–Valentine leukocidin (PVL) positive.

Few patients received an appropriate initial antibiotic denoting that physicians do not consider MRSA as a frequent cause of CAP. The low incidence of MRSA CAP in two studies reporting the incidence of MRSA infections may support this view [31, 32]. Although published guidelines support the use of vancomycin or linezolid in cases of severe CAP to extend antibiotic coverage [121], physicians do not seem to adhere to these guidelines since in the majority of cases these antibiotics were administered only if MRSA was isolated or a similar case was recently encountered in the same hospital. Nevertheless, appropriate antibiotic coverage was not associated with improved outcomes in these cases. Appropriate initial antibiotic therapy and early antibiotic administration, as soon as 4 h following admission, have been associated with better outcomes in patients with CAP [123, 124]. In our study, data regarding timing of antibiotic administration was not available. Furthermore, patients were hospitalised 4–5 days following initiation of symptoms, a fact that probably limits the value of appropriate therapy. In addition, the majority of included patients had severe CAP; it is debatable whether antibiotics or adjunctive therapies have a greater impact on infection outcomes in such cases [125]. Another issue that should be emphasised is that the current study is probably underpowered to show the real value of appropriate therapy. And last but not least, physicians should consider the role of toxin production and regulation (mainly PVL in this study) on outcomes of staphylococcal infections.

The issue of appropriate *versus* optimal treatment in cases of MRSA CAP has not been studied. Vancomycin and linezolid are currently considered the most appropriate treatment options for MRSA pneumonia [121]. Linezolid has been shown to be more effective than vancomycin in retrospective analyses of HAP [126], but a meta-analysis did not confirm the results [127]. In addition, linezolid was associated with less toxin release [128]. CA-MRSA is currently susceptible to fluoroquinolones, clindamycin, trimethoprime-sulfamethoxazole, rifampin and possibly macrolides. The effectiveness of newer antimicrobial agents, such as tigecycline, ceftobiprole and newer lipoglycopeptides, has not been evaluated in MRSA CAP. Comparative trials regarding treatment options of MRSA CAP are not available.

An interesting finding was that influenza like symptoms were frequently present and started shortly before the diagnosis of CAP. None of the patients reported the biphasic illness classically described for CAP following influenza infection. This, in addition to the low sensitivity of the available influenza tests and the relatively infrequent use of these tests by physicians, may lead to a dual implication: MRSA CAP has either similar symptoms with influenza (at least at the beginning), or the two infections develop simultaneously. Finally, MRSA CAP can be considered as a complication of influenza.

The role of PVL in the outcome of MRSA CAP could not be determined in this study because data was not available for patients with PVL negative strains. Although the role of PVL in the development and outcome of staphylococcal disease is debatable in humans, a recent murine model suggested that PVL plays a major role in the development and outcome of pneumonia [129]. This study also showed that the virulence of PVL positive strains is enhanced by the presence of other toxins, especially staphylococcal protein A. Furthermore, the presence of PVL genes up-regulated several genes encoding proteins, known as microbial surface components recognising adhesive matrix molecules, which lead to enhanced tissue adherence and colonisation, thus contributing to the virulence of PVL positive strains.

In conclusion, the limited available evidence shows that MRSA CAP seems to be an infrequent infection. However, there is data suggesting an increase in the incidence of MRSA infections over the last few years. The majority of published cases involved severe disease and were associated with significant mortality. Physicians should consider MRSA more frequently among the possible pathogens in patients with severe CAP. Additional population based studies are needed to identify the true burden of MRSA CAP and the role of antibiotics and other adjunctive therapies.

STATEMENT OF INTEREST
None declared.

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