Incidence, characteristics and outcomes of patients with severe CA-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 100000. We identified 74 articles reporting data on 114 patients. Influenza like symptoms was reported in 41% of patients. Pneumonia improved in 59/109 (54.1%) patients; 49/110 (44.5%) patients died. The duration of hospitalization was 38.1±24.9 and 8.3±11.7, respectively. The duration of ICU stay was 18.9±13.6 and 6.8±9.7 days, respectively. Seventy six strains carried the PVL gene. The univariate analysis showed that multiorgan failure (p<0.001), leucopenia (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

Keywords: pneumonia, S. aureus, resistance
INTRODUCTION

*Staphylococcus aureus* is a common cause of infection of all organs of the human body. 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. Furthermore, *S. aureus* has acquired genes that promote resistance for several classes of antibiotics; the most important to date is the *meca* gene that confers resistance to methicillin (methicillin-resistant *S. aureus*, MRSA) and almost all β-lactams. From the clinical point of view, MRSA has become the primary pathogen of skin and soft tissue infections, but invasive infections also occur. Among them, nosocomial (NP), health-care associated (HCAP) and community acquired pneumonia (CAP) are of major importance due to the morbidity and mortality attributed to them.

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

Although the incidence of MRSA NP/HCAP has been evaluated in several studies, the incidence of MRSA CAP is unknown. *S. aureus* is responsible for 1-10% of CAP cases reported in the literature. Series describing patients with *S. aureus* CAP included only a very small number of MRSA cases. 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” was used. We also searched reference lists of retrieved articles and review papers for relevant studies. A time limit
was set to include only articles written after 1985, when the first reports of community acquired MRSA infections were reported (January 1985 - September 2008).

**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, randomized controlled trials). A language restriction was set for articles published in English, French, German, Italian, Spanish, Greek and Scandinavian languages. 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 group of patients with MRSA pneumonia were not available. Studies evaluating animal models were not eligible for inclusion in this review.

Subsequently, data on demographics, history, risk factors for CA-MRSA (close contact with CA-MRSA colonization or infection, contact sports, recent military service, men having sex with men, intravenous drug use (IVDU), steam bath use, recent antibiotic use before the current infection), severity and course of the disease, antibiotic use or need for intensive care unit treatment and/or outcome of the infection were extracted from the studies. Hospitalization was not an inclusion criterion. Both primary and secondary cases of CAP (hematogenous 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 community-acquired 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 hospitalization, surgery, dialysis, or residence in a long term–care facility <1 year before the onset of illness; and permanent indwelling catheter or percutaneous medical device. In addition, the definition was broadened to include cases in which the genotyping data [pulsed field gel electrophoresis (PFGE), multilocus sequence typing (MLST) or other techniques] provided evidence of a community strain.
CAP was defined as baseline chest radiograph demonstrating new or progressive infiltrates, consolidation with or without effusion, and 4 of the following signs and symptoms: cough, new or worsened purulent sputum production, rales and/or signs of pulmonary consolidation, dyspnea and/or hypoxemia, fever (≥38 °C); respiratory rate ≥20 breaths/minute; systolic hypotension (<90 mmHg); heart rate ≥120 beats/minute; altered mental status; requirement for mechanical ventilation; white blood cell count ≥10,000 cells/mm³ with ≥15% immature neutrophils, or leukopenia (white blood cell count ≤4500 cells/mm³). The severity of CAP was based either on the opinion of the author of each article and the need for intensive care unit 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 analyzed accordingly. Data was analyzed with SPSS 15.0 software (SPSS Inc, Chicago, Illinois, USA). For categorical variables, chi-square test or Fisher’s exact was used. For continuous variables, Student’s t-test was used. For all tests performed, a two-tailed p value less than 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 2602 studies; 1292 of them were published from 1985 and onwards. After screening according to the inclusion criteria 201 articles were retrieved for detailed evaluation. One hundred and fifteen were excluded for reasons depicted in figure 1. Thus 81 studies were included in the systematic review. Three of these reports provided data regarding the incidence of MRSA infections. The remaining studies provided data regarding the characteristics and outcomes of patients with MRSA CAP (71 case reports and 7 case series).
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 CAP (which is also scarce). One of them also commented that “this should be attributed to the lack of routine culture in patients with uncomplicated pneumonia”. 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. Accordingly, an increase in staphylococcal infections, caused primarily by an increase in MRSA infections has been confirmed.

However, we came across studies that reported the incidence of CA-MRSA infections and included also patients with MRSA CAP. Fridkin et al reported that the annual incidence of CA-MRSA infections (based on a population-based surveillance in Baltimore and Atlanta and hospital-laboratory sentinel surveillance of 12 hospitals in Minnesota, all in USA between 2001 and 2002) was 25.7 cases per 100000 in Atlanta and 18.0 per 100000 in Baltimore. In both areas, the incidence was higher among patients younger than 2 years of age than patients older than 2 years. 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 100000 and 0.54 cases per 100000, respectively. Clinical and outcome data regarding patients with MRSA CAP were not available.

Klevens et al also reported that the incidence of CA-MRSA infections (based on population-based surveillance in 9 sites participating in the Active Bacterial Core surveillance from July 2004 through December 2005) was 4.6 cases per 100000. Incidence varied among age groups. The lower incidence was found between 2-17 years (median 0.7/100000 cases), and the higher among age groups 35-64 years (median 6.5/100000 cases) and >65 years (8.9/100000 cases). CAP accounted for 14.0% of CA-MRSA infections for an estimated incidence of 0.64 cases per 100000. Mortality among patients with CA-MRSA infections was 0.5 cases per 100000. 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 that included approximately 2200 patients with culture positive CAP requiring hospitalization reported that MRSA was responsible for 8.9% of all cases and 34.8% of staphylococcal CAP; 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 P. 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; data on outcomes were available for 110 patients. Twenty three patients had CAP secondary to another infection. The demographic, 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. Sixty nine per cent of patients (75/109) were younger than 35 years. Fifty nine percent were males. Risk factors for CA-MRSA colonization were reported for 32 patients.

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

Laboratory findings were not reported consistently in these case reports. Leukopenia was reported in 26 (45%) patients, while thrombocytopenia in 21 (68%). 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 (69/92, 75%) 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 77% (51/66) of patients.

All but 2 patients, for whom data was available, received antibiotics within hours from admission; 14 patients had also received antibiotics prior to admission. Appropriate antibiotics were administered in 47% (37/79) of patients. Modifications in the antibiotic regimen were necessary for 62% (42/68) of 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 (76.5%, 78/102). Inotropic support for circulatory failure was necessary for 49 (65%) patients and mechanical ventilation for respiratory support for 55 (67%) patients. Other adjunctive therapies included extracorporeal membrane oxygenation, corticosteroids, activated protein C, intravenous immunoglobulin, surgical drainage of pleural effusion or empyemas and heparin.

Multiorgan 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 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 summarizes the included patients according to age and outcome. Pneumonia improved in 61 patients; 49 (44.5%) died. The median time from symptoms onset and from admission to the hospital to death was 8 (3-47) and 3 (1-51) days, respectively. The median duration of hospitalization for all patients was 10 (1-108) days; the corresponding ICU figure was 3.5 (1-42) days.
The univariate analysis showed that multiorgan failure (p<0.001), leucopenia (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. On the other hand, 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 (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 (26/37) followed by the Queensland clone (9/37). All strains for which PFGE type was available were PVL positive. Thirty five strains contained the SCSmec type IV and 4 strains the SCCmec type V. Data regarding other molecular typing techniques classification was 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, trimethoprim-sulfamethoxazole and fusidic acid was rare. None of these strains was resistant to linezolid and vancomycin.

Case series of MRSA CAP
Seven case series have been published. 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 this series. Fifty two percent of patients were males and 31% of patients (for whom data was available) had risk factors for CA-MRSA. Influenza-like symptoms were present in 57% of patients; influenza infection was documented by culture or serology in 38% of them. 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; 85% required ICU treatment. The duration of hospitalization varied
between studies, but in general, the median length of stay was prolonged (over 13d). Finally, overall mortality was 42%; data regarding mortality attributable to MRSA CAP was not available.

The largest cohort included 51 patients with primary staphylococcal CAP.112 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 Emerging Infections Network survey. Identification of \textit{S. aureus} was done with the Staphaurex latex agglutination test, catalase and coagulase production. All available isolates underwent pulsed-field gel electrophoresis typing; toxin production was verified by polymerase chain reaction assays. Forty seven patients had positive cultures for \textit{S. aureus} [isolated from respiratory secretions (60% of patients), blood (38%), pleural fluid (23%) and lung tissue (9%)] while 4 additional patients had a positive \textit{S. aureus} immunohistochemistry result at autopsy and pathology; 37 of these were MRSA. Out of the 17 MRSA strains available for further analysis 16 were PVL positive and belonged to the USA 300 pulsed-field gel electrophoresis 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 vs 5 days). In addition, median length of stay was shorter for influenza positive than influenza negative patients (16 vs 8.5 days). Leukopenia was associated with death in multivariate analysis. The authors emphasized that the limitations of their study were its retrospective design, the possibility of reporting only more severe cases, the isolation of \textit{S. aureus} mainly from sputum specimens that increased the probability to include patients simply colonised with \textit{S. aureus} and the difficulty to collect data regarding a preceding or concomitant influenza infection.

The remaining descriptive case series included only a small number of patients each (from 5 to 12 patients).113-118 Therefore, strong conclusions could not be made from
the individual studies. Figure 2 summarizes 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 to 0.64 cases/100000, while the incidence of CAP was 266.8/100000 population in 1991 and 198 cases/100000 population in 2004-2005. However, studies suggest that MRSA CAP incidence may be rising, especially in cases complicated with pleural effusion. The most worrying findings come from one study that shows a prevalence of 8.9% among hospitalized patients with culture positive CAP. 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 hospitalization.

The published data also suggest that MRSA CAP is a severe disease. Mortality in the individual case series was 20 to 60%, while mortality in case reports was 44.5%. The estimated overall mortality in patients with CAP is 5 to 9%; the corresponding figure in patients with severe CAP was 9-27%. 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.

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 this review, 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.
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.\textsuperscript{38,39} Although published guidelines support the use of vancomycin or linezolid in cases of severe CAP to extend antibiotic coverage,\textsuperscript{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 encountered in the same hospital in the near past. 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 hours from admission- have been associated with better outcomes in patients with CAP.\textsuperscript{123,124} In this review 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.\textsuperscript{125} Another issue that should be emphasised is that the current review 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 review) 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.\textsuperscript{121} Linezolid has been shown to be more effective than vancomycin in retrospective analyses of HAP,\textsuperscript{126} but a meta-analysis did not confirm the results.\textsuperscript{127} In addition, linezolid was associated with less toxin release.\textsuperscript{128} CA-MRSA is currently susceptible to fluoroquinolones, clindamycin, trimethoprim-sulfamethoxazole, rifampin and possibly macrolides. The effectiveness of newer antimicrobial agents like 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 soon 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 review 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. 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 recognizing adhesive matrix molecules, which lead to enhanced tissue adherence and colonization, 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.

REFERENCES


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Figure 1. Flow diagram of reviewed studies.

1292 studies identified from Pubmed, Scopus and reviewed articles*

↓ —> 

• 1091 studies were excluded as irrelevant to the review based on their title or abstract ¥

201 studies retrieved for detailed evaluation

↓ —> 

• 63 articles reported patients with MSSA CAP
• 14 studies did not provide data on S. aureus susceptibility
• 13 studies not written in the pre-specified language
• 13 studies on nosocomial MRSA pneumonia
• 12 studies did not provided data regarding patients with MRSA CAP

86 appropriate studies to be included in the review

↓ —> 

• 4 cohorts reporting mainly MSSA CAP patients
• 1 cohort describing the radiologic findings in patients with MRSA sepsis, including patients with CAP

81 articles included in the review

↓ —> 

• 7 case series regarding characteristics and outcomes of patients with MRSA CAP
• 71 case reports regarding characteristics and outcomes of patients with MRSA CAP
• 3 studies regarding incidence of MRSA CAP

* 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, CA-MRSA infections other than CAP
Figure 2. Annual published reports of MRSA cases between 1989 and 2008.
Table 1. Comparison of characteristics and interventions between patients with MRSA CAP who died and survived.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Died (n=49)</th>
<th>Survived (n=61)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Died (n=49)</strong></td>
<td>Survived (n=61)</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
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<tr>
<td>Age, years</td>
<td>26 +/-22.9</td>
<td>24.1 +/-18.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender (male)</td>
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<td>37/60 (61.7)</td>
<td>0.49</td>
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<td><strong>History</strong></td>
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<td>Smoking</td>
<td>6/43 (14)</td>
<td>4/52 (7.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2/43 (4.7)</td>
<td>4/52 (7.7)</td>
<td>0.69</td>
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<tr>
<td>Drug abuse</td>
<td>2/44 (4.5)</td>
<td>6/56 (10.7)</td>
<td>0.46</td>
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<tr>
<td>Diabetes</td>
<td>3/46 (6.5)</td>
<td>2/55 (3.6)</td>
<td>0.66</td>
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<tr>
<td>Respiratory disease</td>
<td>1/46 (2.2)</td>
<td>6/55 (10.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart disease</td>
<td>5/46 (10.9)</td>
<td>2/55 (3.6)</td>
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<td>Cancer</td>
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<td><strong>Risk factors for MRSA</strong></td>
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<td>Previous antibiotics</td>
<td>1/44 (2.3)</td>
<td>4/53 (7.5)</td>
<td>0.37</td>
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<tr>
<td>Previous MRSA</td>
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<td>2/53 (3.8)</td>
<td>1.00</td>
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<td>infection/colonization</td>
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<tr>
<td>Relatives with MRSA</td>
<td>5/44 (11.4)</td>
<td>6/53 (11.3)</td>
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<tr>
<td>Contact sports</td>
<td>2/44 (4.5)</td>
<td>2/53 (3.8)</td>
<td>1.00</td>
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<td><strong>Reason of hospitalization</strong></td>
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<tr>
<td>CAP</td>
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<td>32/51 (61.7)</td>
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<td>Shock</td>
<td>1/43 (2.3)</td>
<td>4/51 (7.8)</td>
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<td>Bone-joint infection</td>
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<td>Other*</td>
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<td>10/51 (19.6)</td>
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<td>18/61 (29.5)</td>
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<td>Antibiotics before admission</td>
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<td>7/61 (11.5)</td>
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<td>Duration of symptoms prior to 4.4 +/-3.4</td>
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<tr>
<td>hospitalization, days</td>
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<tr>
<td>Influenza like symptoms</td>
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<td>15/52 (28.8)</td>
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<td>Fever</td>
<td>33/40 (82.5)</td>
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<td>Chest pain</td>
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<td>13/48 (27.1)</td>
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<td>Gastrointestinal symptoms</td>
<td>9/42 (21.4)</td>
<td>7/48 (14.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Rash</td>
<td>10/43 (23.3)</td>
<td>4/50 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Confusion/lethargy</td>
<td>6/37 (16.2)</td>
<td>4/42 (9.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Shock</td>
<td>31/37 (83.8)</td>
<td>18/38 (47.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tachyplea</td>
<td>28/30 (93.3)</td>
<td>28/31 (90.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Airway hemorrhage</td>
<td>14/38 (36.8)</td>
<td>8/39 (20.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Severe CAP</td>
<td>47/47 (100)</td>
<td>38/52 (73.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Radiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilobar infiltrates</td>
<td>10/42 (21.4)</td>
<td>13/50 (26)</td>
<td>0.43</td>
</tr>
</tbody>
</table>
## Laboratory findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilobar infiltrates</td>
<td>32/42 (78.6)</td>
<td>37/50 (74)</td>
<td>0.43</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>9/44 (20.5)</td>
<td>24/52 (46.2)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
<td>28/33 (84.8)</td>
<td>23/33 (69.7)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

## Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven influenza</td>
<td>10/33 (30.3)</td>
<td>6/42 (14.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>19/24 (79.2)</td>
<td>7/34 (20.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11/13 (84.6)</td>
<td>10/18 (55.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>31/41 (75.6)</td>
<td>41/52 (78.8)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

## Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>15/36 (41.7)</td>
<td>4/45 (8.9)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>DVT</td>
<td>0/36 (0)</td>
<td>4/44 (9.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pneumocele/pneumothorax</td>
<td>5/36 (13.9)</td>
<td>5/44 (11.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Acidosis</td>
<td>5/36 (13.9)</td>
<td>1/44 (2.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>DIC</td>
<td>6/36 (16.7)</td>
<td>1/44 (2.3)</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>25/36 (69.4)</td>
<td>10/44 (22.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization, days</td>
<td>8.3+/−11.7</td>
<td>38.1+/−25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of ICU stay, days</td>
<td>6.8+/−9.7</td>
<td>18.9+/−13.6</td>
<td><strong>0.003</strong></td>
</tr>
</tbody>
</table>

* Other reasons included deep vein thrombosis, meningitis, endocarditis, gastroenteritis, fever and non-cutaneous abscesses
** Other reported therapies included heparin, corticosteroids, hemofiltration, transfusions and surgical procedures.

Abbreviations: ARDS acute respiratory distress syndrome, CAP community-acquired pneumonia, DIC disseminated intravascular coagulation, DVT deep vein thrombosis, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, IVIG intravenous immunoglobulins, MRSA methicillin-resistant *S. aureus* SSTI skin and soft tissue infection,
Table 2. Distribution of patients with MRSA CAP according to age and outcome.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Died</th>
<th>Survived</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>8/49 (16.3)</td>
<td>11/60 (18.3)</td>
<td></td>
</tr>
<tr>
<td>3-16 years</td>
<td>16/49 (32.7)</td>
<td>15/60 (25)</td>
<td></td>
</tr>
<tr>
<td>17-35 years</td>
<td>11/49 (22.4)</td>
<td>14/60 (23.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>35-65 years</td>
<td>10/49 (20.4)</td>
<td>19/60 (31.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>4/49 (8.2)</td>
<td>1/60 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Case series with MRSA CAP patients published after 1985.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA/all patients (%)</td>
<td>37/51 (73)</td>
<td>7/7 (100)</td>
<td>10/10 (100)</td>
<td>15/17 (88)</td>
<td>5/5 (100)</td>
<td>12/14 (86)</td>
<td>12/14 (86)</td>
<td>98/118 (83)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>16 (&lt;1-81)</td>
<td>14.2 (0.8-16)</td>
<td>17.5 (0.3-48)</td>
<td>21 (0,25-62)</td>
<td>NA</td>
<td>13 (10-15)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex, male n/N (%)</td>
<td>21/51 (41)</td>
<td>5/7 (71)</td>
<td>5/10 (50)</td>
<td>8/17 (47)</td>
<td>NA</td>
<td>12/14 (86)</td>
<td>NA</td>
<td>51/99 (52)</td>
</tr>
<tr>
<td>Comorbidities, n/N (%)</td>
<td>27/48 (56)</td>
<td>0/7 (0)</td>
<td>1/10 (10)</td>
<td>5/17 (29)</td>
<td>NA</td>
<td>2/14 (14)</td>
<td>NA</td>
<td>35/96 (36)</td>
</tr>
<tr>
<td>MRSA risk factors, n/N (%)</td>
<td>13/31 (42)</td>
<td>NA</td>
<td>4/10 (40)</td>
<td>4/17 (24)</td>
<td>NA</td>
<td>1/14 (7)</td>
<td>NA</td>
<td>22/72 (31)</td>
</tr>
<tr>
<td>Influenza like symptoms, n/N (%)</td>
<td>22/47 (47)</td>
<td>NA</td>
<td>10/10 (100)</td>
<td>17/17 (100)</td>
<td>NA</td>
<td>1/14 (7)</td>
<td>NA</td>
<td>50/88 (57)</td>
</tr>
<tr>
<td>Proven influenza infection, n/N (%)</td>
<td>11/33 (33)</td>
<td>NA</td>
<td>6/10 (60)</td>
<td>12/17 (71)</td>
<td>0/5 (0)</td>
<td>1/14 (7)</td>
<td>NA</td>
<td>30/79 (38)</td>
</tr>
<tr>
<td>Necrotizing pneumonia, n/N (%)</td>
<td>NA</td>
<td>7/7 (100)</td>
<td>7/10 (70)</td>
<td>4/16 (25)</td>
<td>5/5 (100)</td>
<td>NA</td>
<td>NA</td>
<td>23/38 (61)</td>
</tr>
<tr>
<td>PVL production, n/N (%)</td>
<td>16/17 (94)</td>
<td>NA</td>
<td>10/10 (100)</td>
<td>11/13 (85)</td>
<td>5/5 (100)</td>
<td>14/14 (100)</td>
<td>NA</td>
<td>56/59 (95)</td>
</tr>
<tr>
<td>Resistance to antibiotics (%)</td>
<td>ERM 93%, LEV 50%,</td>
<td>NA</td>
<td>ERM 100%, CLN 20%, LEV 20%,</td>
<td>ERM 100%, CLN 91%, LEV 55%,</td>
<td>NA</td>
<td>ERM 100%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hospitalization, n/N (%)</td>
<td>43/51 (84)</td>
<td>7/7 (100)</td>
<td>10/10 (100)</td>
<td>16/17 (94)*</td>
<td>5/5 (100)</td>
<td>14/14 (100)</td>
<td>14/14 (100)</td>
<td>109/118 (92) *</td>
</tr>
<tr>
<td>ICU treatment, n/N (%)</td>
<td>34/43 (74)</td>
<td>7/7 (100)</td>
<td>NA</td>
<td>13/16 (81)</td>
<td>NA</td>
<td>14/14 (100)</td>
<td>NA</td>
<td>68/80 (85)</td>
</tr>
<tr>
<td>Appropriate empirical therapy, n/N (%)</td>
<td>26/51 (51)</td>
<td>NA</td>
<td>NA</td>
<td>12/15 (80)</td>
<td>NA</td>
<td>NA</td>
<td>2/10 (20)</td>
<td>40/76 (53)</td>
</tr>
<tr>
<td>Length of stay, days, median (range)</td>
<td>16 (2-19)</td>
<td>30 (5-53)</td>
<td>NA</td>
<td>13 (1-108)</td>
<td>24 (5-42)</td>
<td>24.5 (1-120)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Death, n/N (%)</td>
<td>24/47 (51)</td>
<td>3/7 (43)</td>
<td>6/10 (60)</td>
<td>5/17 (29)**</td>
<td>1/5 (20)</td>
<td>3/14 (21)</td>
<td>3/14 (21)</td>
<td>45/114 (39)</td>
</tr>
<tr>
<td>Symptom onset to death, days, median (range)</td>
<td>4 (1-33)</td>
<td>30 (5-51)</td>
<td>3,5 (2-25)</td>
<td>7 (3-73)</td>
<td>NA</td>
<td>5 (2-7)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CDC Centers for Disease Control and Prevention, MRSA methicillin-resistant S. aureus, PVL Panton-Valentine leucocidin, ICU intensive care unit, ERM erythromycin, LEV levofloxacin, CLN clindamycin, NA not available/applicable
* the remaining patients died in the emergency department or during transfer to another hospital
** 4 of 5 deceased patients had MRSA pneumonia
¥ Strains were sensitive to linezolid, vancomycin, rifampin and gentamycin