Factors Associated with the Outcome of Life-Threatening Necrotizing Pneumonia due to Community-Acquired *Staphylococcus aureus* in Adult and Adolescent Patients

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Key Words

Staphylococcus aureus · Panton-Valentine leukocidin · Pneumonia, adult, adolescent

Abstract

Background: Although community-acquired *Staphylococcus aureus* pneumonia with highly virulent Panton-Valentine leukocidin (PVL)-positive strains, a severe disease with significant lethality, is rare, especially in adult and adolescent patients, recent reports highlight that these infections are on the rise. **Objectives:** To describe the demographic and clinical features of reported cases of life-threatening community-acquired *S. aureus* pneumonia with usually PVL-positive strains in adult and adolescent patients, to evaluate the variables related to death, and to select a more appropriate antimicrobial treatment for this potentially deadly disease. **Methods:** We summarized all of the 92 reported cases and our case. The effect of 5 variables on mortality was measured using logistic regression. **Results:** *S. aureus* community-acquired pneumonia (CAP) with usually PVL-positive strains is a severe disease with significant lethality, i.e. 42.9%; a short duration of the time from the onset of symptoms to death, i.e. 5.5 ± 10.1 days, and prolonged hospital admissions, i.e. 33.2 ± 29.5 days. Seventy-three cases have been tested for the gene for PVL, and 71 strains have been found to carry the

PVL gene. Logistic regression analysis showed that leucopenia ($p = 0.002$), influenza-like symptoms or laboratory-confirmed influenza ($p = 0.011$), and hemoptysis ($p = 0.024$) were the factors associated with death. Antibiotic therapies inhibiting toxin production were associated with an improved outcome in these cases ($p = 0.007$). **Conclusions:** Physicians should pay special attention to those patients who acquired severe CAP during influenza season and have flu-like symptoms, hemoptysis, and leucopenia, and they should consider *S. aureus* more frequently among the possible pathogens of severe CAP. Empiric therapy for severe CAP with this distinct clinical picture should include coverage for *S. aureus*. Targeted treatment with antimicrobials inhibiting toxin production appears to be a more appropriate selection.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains producing cytotoxin Panton-Valentine leukocidin (PVL) are associated with an increased risk of severe soft tissue infections as well as with serious community-acquired pneumonia (CAP) [1–4]. Currently, special attention is being paid to methicillin-resistant strains of *S. aureus*. However, some strains of community-acquired

methicillin-susceptible *S. aureus* (CA-MSSA) could harbor the PVL toxin, which is of particular concern as infections with these organisms have resulted in increased levels of morbidity and mortality [5]. PVL, which is usually produced by less than 5% of *S. aureus* strains [6], is now known to be a dimer of 2 proteins, i.e. S and F [1, 7]. We have obtained recombinant staphylococcal F and S components of PVL (rPVL) by gene engineering: the genes for lukS-PV and lukF-PV were successfully cloned into plasmid pET22b (+) and expressed in *Escherichia coli* [8]; Hoechst 33342 fluorescence staining, transmission electron microscopy examination, and flow cytometry indicated that rPVL-treated samples decreased human alveolar macrophage viability, leading to apoptosis at low concentrations and necrosis at high concentrations. In addition, rPVL-treated cells released increased amounts of IL-10 and decreased amounts of TNF- α under apoptosis-inducing concentrations. The results suggested that rPVL could induce the disordered release of anti-inflammatory and proinflammatory cytokines by human alveolar macrophages and play a negative role in human alveolar macrophage function, which may be one of the important mechanisms underlying the high mortality of infection with PVL-positive *S. aureus* [9]. A recent murine model suggested that PVL plays a major role in the development and outcome of pneumonia [10]. PVL also causes tissue necrosis and leukocyte destruction by creating lytic pores in the cell membranes of neutrophils and inducing the release of neutrophil chemotactic factors [11]. The presence of PVL genes upregulates 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. The inflammatory response in the lung associated with PVL is thought to be the mediator of tissue necrosis, accounting for the clinical and radiographic presentation of patients with PVL-positive community-acquired MRSA (CA-MRSA) pneumonia [12].

S. aureus CAP is a potentially lethal necrotizing infection that is now raising considerable concern. Recently, there have been increasing numbers of case reports of PVL-positive *S. aureus* CAP in developed countries, including the USA, France, Sweden, Italy, Canada, and the UK, and some review articles have been published [13–18]. However, those cases were reported predominantly in North America and Europe, while few cases were reported in Asia, especially in developing countries. Series describing patients with *S. aureus* CAP included only a small number of MRSA cases [14, 19, 20]. Most analyses

were descriptive [13, 21]. Although 2 articles analyzed factors associated with death using the mean of univariate analysis, variables were mostly related to classic severity factors such as multiorgan failure [15, 18]. In addition, case series involved not only adult and adolescent patients but also pediatric patients [15, 18].

We describe 1 case of severe MRSA CAP carrying the PVL genes with a favorable outcome in China (unpublished data). Here, we summarize our case and all of the other 91 reported cases in adult and adolescent patients. The effects of a low white blood cell (WBC) count, influenza (influenza-like symptoms or laboratory-confirmed influenza), skin and soft tissue infection, hemoptysis, and antibiotic therapy (specifically inhibiting exotoxin production) on mortality were analyzed using logistic regression. Because reports of *S. aureus* CAP are rare in adults [22] and mainly occur in children and young adults [19], and because PVL-positive *S. aureus* has been correlated with a linear decline in age [23, 24], the purpose of this report is to familiarize clinicians with severe *S. aureus* CAP in nonpediatric patients in order to create awareness of the clinical characteristics of this important community-acquired respiratory infection, especially the variables related to death, and to select a more appropriate antimicrobial treatment for this potentially life-threatening disease. To the best of our knowledge, analysis of the effect of antibiotic therapy specifically inhibiting exotoxin production on the mortality of *S. aureus* CAP has not been reported.

Material and Methods

Study Strategy

We systematically searched the PubMed database from January 1995 to December 2009 using the free text words ‘community-acquired pneumonia’, ‘community-onset pneumonia’, ‘*S. aureus*’, ‘staphylococcal’, ‘methicillin-resistant’, ‘methicillin-susceptible’, ‘pneumonia’, ‘MRSA’, and ‘MSSA’, in combination with ‘case report’ or ‘case series’, limiting our search to ‘English’. A manual search of citations from relevant original studies and review articles was also performed. We corresponded with authors if original data were not available in their articles. For inclusion into this analysis, the publications had to be about *S. aureus* CAP in adult and adolescent patients (age ≥ 14 years). Case reports on pediatric patients or studies evaluating animal models were excluded from the study. This study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University.

Data Extraction and Statistical Analysis

For each study, information was collected concerning the characteristics of the subjects (clinical, microbiological, and outcome data). Two investigators extracted data independently, dis-

cussed disagreements, and reached a consensus on all items. The severity of *S. aureus* CAP was based either on the need for intensive care unit (ICU) treatment or the opinion of the authors of each article. Analysis of *S. aureus* CAP was stratified by antimicrobial resistance profiles. The cases of *S. aureus* CAP were subdivided into patients with MRSA and patients with MSSA. χ^2 tests were used for categorical variables and Student's *t* test for continuous variables was used for calculating differences between the 2 groups. Logistic regression was used to measure the effect of a low WBC count, influenza (influenza-like symptoms or laboratory-confirmed influenza), skin and soft tissue infection, hemoptysis, and antibiotic therapy (specifically inhibiting exotoxin production) on mortality. SPSS 13 software (SPSS, Inc., Chicago, Ill., USA) was utilized for the inputting, tabulation, and statistical analysis. $p < 0.05$ was considered statistically significant.

Results

Ninety-two cases of severe *S. aureus* CAP were reported in 70 articles during the period from 1995 to 2009 from North America (35 cases, 38.0%) [2, 25–42], Europe (40 cases, 43.5%) [1, 7, 43–74], Asia (11 cases, 12.0%) [75–82], and Australia (6 cases, 6.5%) [83–88] (table 1). Data on outcomes were available for 91 patients. The demographic and clinical characteristics of these patients are shown in table 2, and the outcomes of the patients are shown in table 3.

Demographics and Clinical Manifestations

The median age of the 91 patients (the age of 1 case was not available) was 35.1 ± 18.0 years (range 14–89). Thirty-eight (41.8%) of the 91 patients (the gender of 1 case was not available) were female. Twenty-six (26/90, 28.9%) had underlying diseases including diabetes, hypertension, and hepatitis B. Eleven (12.4%, 11/89) of the patients were current or previous smokers, and 10 (11.2%) were drug abusers or had HIV or AIDS. None of the other patients had any relevant medical history. Therefore, *S. aureus* CAP affects mainly previously healthy individuals. It has been reported that its incidence is also rising among patients infected with HIV at a rate 18 times higher than that in the general population [89]. All patients had ≥ 1 of the following symptoms at the time they sought medical care: fever, cough, myalgias, sore throat, headache, shortness of breath, or hemoptysis. Fever was the most common clinical finding reported, occurring in 90.9% (50/55) of patients. Cough, shortness of breath, and hemoptysis was reported in 62.5% (50/80), 67.9% (55/81), and 35.4% (29/82) of the case patients, respectively. Prior flu-like illnesses were present in 51 (68%) of 75 cases, and 10 (13.3%) of 75 patients had laboratory-confirmed influ-

enza. Forty (48.2%) of 83 patients had documented skin and soft tissue infection.

Laboratory findings were not reported consistently in these case reports. Leukopenia was reported in 23 (37.1%) of 62 patients, while C-reactive protein (CRP) with a median value of 242.8 ± 126.2 mg/l was reported in 19 (20.7%) of 92 patients. Liver and kidney function tests as well as arterial oxygen saturation or blood gas analyses were reported by only a few cases. Echocardiograms were reported in 20 patients and revealed no cardiac vegetations, which excludes the possibility of a persistent endovascular source of infection. Radiologic information on the initial evaluation was available for 78 patients: 17 cases (21.8%) had unilobar infiltrates, 61 (78.2%) had multilobar infiltrates, and 17 (21.8%) had pleural effusion. *S. aureus* was isolated from multiple sources including sputum (57/79, 72.3%), blood (55/73, 75.3%), bronchoalveolar lavage fluid (BALF) (16/75, 21.3%) and pleural fluid (4/72, 6%) with no other previously identified bacterial pathogen from a sterile site, except for 1 case [78] in which cultures of the drainage fluid on day 32 revealed MRSA and *Pseudomonas aeruginosa* instead of only *S. aureus* in the blood culture on the day of admission. As shown in the case series, pleural fluid cultures may have low diagnostic yields, partly due to prior antibiotic use [90]. In this case series, MRSA tended to be less resistant to antimicrobial agents than hospital-acquired MRSA strains. The majority of the isolated strains were only resistant to oxacillin or methicillin; resistance to clindamycin, macrolides, and fluoroquinolones was rarely reported. None of these strains was resistant to linezolid or vancomycin. In CA-MRSA isolates *mec*, which is the gene coding for methicillin resistance, is usually contained in the type IV or V variant of the genetic element staphylococcal chromosomal cassette (SCC)*mec*, which is smaller and probably more mobile than the other SCC*mec* elements [91]. In this case series, 20 (80%) and 5 (20%) MRSA isolates available from 25 patients had SCC*mec* types IV and V, respectively. The gene for PVL occurred in 71 (97.3%) of 73 patients, while in Japan the predominant CA-MRSA clones were PVL negative [76].

Treatment and Outcome

Information on empiric antimicrobial therapy (i.e. before *S. aureus* culture results were known) available for 78 patients included cephalosporin (38/78, 48.7%), respiratory fluoroquinolone (i.e. levofloxacin, gatifloxacin, or moxifloxacin) (24/78, 30.8%), piperacillin/tazobactam or ticarcillin/clavulanate (23/78, 29.5%), and imipenem/cilastatin or meropenem (7/78, 9.0%). Information on

Table 1. Review of life-threatening *S. aureus* CAP in adult and adolescent patients

Study reference	Year	Country	Sex		Patients n	Age years	PVL gene	Outcome	Time to death
			M	F					
Dicpinigaitis et al. [39]	1995	USA	1	0	1	40	NA	died	9 days
Miyashita et al. [78]	2002	Japan	1	0	1	17	+	survived	
Dufour et al. [1]	2002	France	2	0	2 ^a	67	+	died	NA
						17	+	died	NA
Van der Flier et al. [43]	2003	The Netherlands	0	1	1	15	+	died	3 days
Boussaud et al. [7]	2003	France	3	0	3	67	+	died	1 day
						38	+	died	2 h
						25	+	survived	
Nimmo et al. [86]	2003	Australia	1	0	1	23	NA	survived	
Klein et al. [48]	2003	UK	0	1	1	30	+	survived	
Peleg et al. [85]	2004	Australia	1	0	1	21	+	died	2 days
Miklasevics et al. [58]	2004	Latvia	1	0	1	46	+	survived	
Hsu et al. [81]	2004	Singapore	0	1	1	18	+	died	20 days
Al-Tawfiq et al. [80]	2005	Saudi Arabia	1	0	1	37	NA	survived	
Francis et al. [2]	2005	USA	1	3	4	31	+	survived	
						52	+	died	2 days
						20	+	survived	
						33	+	survived	
Frazee et al. [28]	2005	USA	1	0	1	31	+	died	38 h
Alonso-Tarrés et al. [50]	2005	Spain	1	0	1	28	+	survived	
Gonzalez et al. [31]	2005	USA	1	0	1 ^a	14	+	died	5 days
Micek et al. [12]	2005	USA	3	1	4	45	+	survived	
						40	+	survived	
						34	+	survived	
						40	+	survived	
Kravitz et al. [36]	2005	USA	1	0	1	21	+	died	1 day
Torell et al. [61]	2005	Sweden	0	1	1	24	+	survived	
Peleg et al. [87]	2005	Australia	0	1	1 ^a	34	+	survived	
Kuhn et al. [64]	2005	Germany	0	1	1	39	NA	survived	
Tordecillas et al. [73]	2005	Spain	1	0	1	27	+	survived	
Chua et al. [77]	2006	Singapore	1	1	2	83	NA	died	2 days
						71	NA	died	10 days
Garnier et al. [46]	2006	France	0	1	1	59	+	died	1 day
Jones et al. [37]	2006	USA	1	2	3	35	+	died	1 day
						NA	+	survived	
Obed et al. [54]	2006	Germany	0	1	1	14	+	survived	
						55	+	died	8 days
Gerogianni et al. [49]	2006	Greece	1	0	1	42	+	survived	
Söderquist et al. [47]	2006	Sweden	1	0	1	49	+	survived	
Enayet et al. [27]	2006	USA	0	1	1	27	+	survived	
Laiher et al. [67]	2006	Switzerland	1	0	1	64	+	survived	
Hyvernath et al. [71]	2006	France	1	1	2	41	+	died	20 h
						22	+	died	4 h
Salliot et al. [74]	2006	France	1	1	2	19	+	survived	
						26	+	survived	
Swaminathan et al. [88]	2006	Australia	1	0	1	14	+	survived	
Hampson et al. [56]	2006	UK	1	0	1	14	+	survived	
Michalopoulos et al. [57]	2006	Greece	1	0	1	64	NA	survived	
Agwu et al. [25]	2007	USA	0	1	1	14	+	died	NA
Vayalumkal et al. [26]	2007	Canada	1	0	1	48	+	died	3 days
Risson et al. [84]	2007	Australia	0	1	1	23	+	died	17 h
Pogue et al. [30]	2007	USA	1	0	1 ^a	14	+	died	6 h
Monaco et al. [51]	2007	Italy	0	1	1	37	+	survived	

Table 1 (continued)

Study reference	Year	Country	Sex		Patients n	Age years	PVL gene	Outcome	Time to death
			M	F					
Magira et al. [52]	2007	Greece	0	1	1	61	+	died	3 days
Balis et al. [53]	2007	Greece	1	1	2	17	+	survived	
						37	+	died	2 h
Adam et al. [33]	2007	Canada	1	0	1	17	+	died	5 days
Tronci et al. [55]	2007	Italy	1	0	1	16	+	survived	
Hsu et al. [79]	2007	Singapore	1	0	1	52	NA	NA	
Castaldo et al. [40]	2007	USA	3	1	4 ^a	15	NA	survived	
						14	NA	died	51 days
						14	NA	died	30 days
						14	NA	died	5 days
Quadri et al. [60]	2007	UK	0	1	1	28	+	died	2 days
Rotas et al. [38]	2007	USA	0	1	1	21	NA	survived	
Honarpour et al. [42]	2007	USA	0	1	1	48	+	died	NA
Schefold et al. [66]	2007	Germany	1	0	1	51	+	survived	
Chetchotisakd et al. [82]	2007	Thailand	1	0	1	38	+	died	2 days
Hasan et al. [32]	2008	USA	3	0	3	49	NA	survived	
						18	NA	survived	
						27	NA	survived	
Baldwin et al. [59]	2008	UK	0	1	1	62	+	survived	
Tomita et al. [76]	2008	Japan	2	0	2	89	–	died	NA
						15	–	survived	
Valentini et al. [44]	2008	Italy	1	0	1	15	+	survived	
Tong et al. [83]	2008	Australia	0	1	1	56	+	died	10 days
Jung et al. [45]	2008	Germany	0	1	1	23	+	survived	
Martino et al. [29]	2008	USA	0	1	1	39	NA	survived	
Lee et al. [75]	2008	Singapore	1	0	1	41	NA	survived	
Roberts et al. [41]	2008	USA	0	1	1	30	+	died	<1 day
Dickson et al. [34]	2008	USA	0	1	1	63	NA	died	3 days
Beilouny et al. [65]	2008	France	0	1	1	47	+	died	21 h
Mushtaq et al. [69]	2008	UK	1	0	1	14	+	died	<24 h
Ditzen et al. [61]	2008	Germany	0	1	1	24	+	survived	
van Nieuwkoop et al. [72]	2008	Dutch	1	0	1	30	+	died	NA
Ebert et al. [35]	2009	USA	0	1	1	29	+	survived	
Stefani et al. [63]	2009	Italy	1	0	1	25	+	survived	
Turtle et al. [62]	2009	UK	0	1	1	80	+	survived	
Libert et al. [68]	2009	France	NA		1	37	+	survived	
Hidron et al. [21]	2009	USA	1	1	2	45	+	survived	
						36	+	survived	
Li et al. (our case)	2009	China	1	0	1	45	+	survived	

^a Only cases of *S. aureus* CAP in adult and adolescent patients were included. NA = Not available.

targeted antimicrobial therapy (i.e. after *S. aureus* culture results were known) was provided for 70 patients and consisted of vancomycin (45/70, 64.3%), clindamycin (22/70, 31.4%), linezolid (17/70, 24.3%), and teicoplanin (2/70, 2.9%). Among the 45 cases of targeted therapy with vancomycin, 9 (20.0%) cases were switched to linezolid due to a lack of response to treatment with vancomycin. Most patients (72/78, 92.3%) received multiple anti-

crobial agents. Information on antimicrobial agents that specifically inhibit exotoxin production was available for 36 cases (36/76, 47.4%); 32 patients survived (32/48, 66.7%) and 4 patients died (4/28, 14.3%).

As is reported elsewhere [15], most patients were admitted to the ICU and required intubation (table 3). Forty-three percent (37/86) were cases of shock or ARDS (table 2). In the 39 (42.9%) patients who died, the median

Table 2. Demographic and clinical characteristics of cases of life-threatening *S. aureus* CAP

Characteristic	Patients
Median age (range), years	35.1 ± 18.0 (14–89)
Sex, male	53/91 (58.2)
Underlying disease ^a	26/90 (28.9)
Skin and soft tissue infection	40/83 (48.2)
Evidence of influenza infection	51/75 (68.0)
Laboratory-confirmed influenza	10/75 (13.3)
Influenza-like illness	41/75 (54.7)
Clinical symptoms	
Cough	50/80 (62.5)
Shortness of breath	55/81 (67.9)
Hemoptysis	29/82 (35.4)
Clinical signs	
Temperature >38°C	50/55 (90.9)
Hypotension (systolic blood pressure <90 mm Hg)	17/51 (33.3)
Shock or ARDS	37/86 (43.0)
Elevated leukocyte count ($\geq 10.0 \times 10^9/l$)	26/62 (41.9)
Median WBC count, $\times 10^9/l$	10.6 ± 10.0
Leukopenia ($<4 \times 10^9/l$)	23/62 (37.1)
Median value, $\times 10^9/l$	1.5 ± 0.8
Chest radiography examination	
Unilobar infiltrates	17/78 (21.8)
Multilobar infiltrates	61/78 (78.2)
Pleural effusion	17/78 (21.8)
Staphylococcal cassette chromosome	
mec IV	23/28 (82.1)
mec V	5/28 (17.9)

Data were not available for all patients. Data are presented as number of patients/number of patients for whom data were available, unless otherwise indicated. Figures in parentheses are percentages. ARDS = Acute respiratory distress syndrome.

^a One each of diabetes, hypertension, liver cirrhosis, COPD, stroke, and renal or liver transplantation. Not all patients had these variables recorded, hence, the denominator is less than the total pool.

period from the onset of respiratory symptoms to death was 5.5 ± 10.1 days. Their median age was 37.6 ± 21.3 years (range 14–89), and only 7 (17.9%) had an underlying illness. Although 15 patients with MRSA CAP who had received an appropriate treatment of vancomycin or teicoplanin and 8 patients with MSSA CAP who had been treated with antistaphylococcal antibiotics died, only 4 (10.3%) cases had been treated by antibiotics inhibiting PVL. Most died within 1 week of the onset of symptoms. Among the 52 (57.1%) patients who survived, the median number of hospital days was 33.2 ± 29.5 (table 3).

Table 3. Outcomes of life-threatening *S. aureus* CAP

Outcome	Patients
Hospitalization	87/88 (98.9)
Admitted to the ICU	56/80 (70.0)
Required intubation	52/80 (65.0)
Recovered	52/91 (57.2)
Length of stay, days	33.2 ± 29.5
Died	39/91 (42.9)
Mean age, years	37.6 ± 21.3
Time from onset of symptoms to death, days	5.5 ± 10.1
Underlying disease ^a	7/39 (17.9)
Antibiotic therapies with inhibiting PVL	4/39 (10.3)

Data were not available for all patients. Data are presented as number of patients/number of patients for whom data were available, unless otherwise indicated. Figures in parentheses are percentages.

^a One each of diabetes, hypertension, liver cirrhosis, COPD, stroke, and renal or liver transplantation.

Factors Associated with Outcome

Data on 5 variables, i.e. leucopenia, influenza-like symptoms or laboratory-confirmed influenza, hemoptysis, skin and soft tissue infection, and targeted antimicrobial therapy inhibiting PVL production and clinical outcomes were collected. Logistic regression analysis showed that leucopenia ($p = 0.002$), influenza-like symptoms or laboratory-confirmed influenza ($p = 0.011$), and hemoptysis ($p = 0.024$) were the factors associated with death. On the other hand, antibiotic therapies inhibiting toxin production (clindamycin or linezolid) ($p = 0.007$) were associated with improved outcomes in these cases. In this analysis, skin and soft tissue infection ($p = 0.530$) was not associated with death.

Characteristics and Outcomes of Case Patients by *S. aureus* Susceptibility

The demographic characteristics, clinical characteristics, and outcomes of patients with MRSA and MSSA CAP are shown in table 4. There were no statistical differences in age, gender, underlying disease, skin and soft tissue infection, evidence of influenza infection, clinical symptoms and signs, WBC count, CRP, or chest radiography examination between the 2 groups. As expected, due to the difference in antimicrobial resistance profiles, antibiotic therapies with inhibiting PVL such as clindamycin and linezolid were more frequently used in patients with MRSA CAP compared with MSSA CAP ($p < 0.05$). Information on outcomes was available for 71 pa-

Table 4. Comparison of characteristics between patients with MRSA and MSSA CAP

Characteristic	Patients with MRSA CAP	Patients with MSSA CAP	p value
Median age, years	36.0 ± 19.1 (n = 71)	31.8 ± 13.4 (n = 20)	0.3601
Sex, male	42/72 (58.3)	11/19 (57.9)	0.9725
Underlying disease ^a	21/72 (29.2)	5/18 (27.8)	0.9074
Skin and soft tissue infection	30/64 (46.9)	10/19 (52.3)	0.6592
Evidence of influenza infection	34/50 (68.0)	9/18 (50.0)	0.1422
Clinical symptoms			
Cough	41/63 (65.1)	9/17 (52.9)	0.3589
Shortness of breath	41/64 (64.1)	14/17 (82.4)	0.1510
Hemoptysis	20/65 (30.8)	9/17 (52.9)	0.0887
Clinical signs			
Temperature >38°C	38/40 (95.0)	12/15 (80.0)	0.0848
Hypotension	13/36 (36.1)	4/15 (26.7)	0.5145
(systolic blood pressure <90 mm Hg)			
Shock or ARDS	27/68 (39.7)	9/18 (50.0)	0.4312
Elevated leukocyte count ($\geq 10.0 \times 10^9/l$)	20/44 (45.5)	6/18 (33.3)	0.3800
Median leukocyte count, $\times 10^9/l$	11.0 ± 9.8 (n = 44)	9.7 ± 10.7 (n = 18)	0.6460
Leukopenia ($<4.0 \times 10^9/l$)	14/44 (31.8)	9/18 (50.0)	0.1785
CRP	200.8 ± 112.9 (n = 9)	280.7 ± 131.0 (n = 10)	0.1749
Chest radiography examination			
Unilobar infiltrates	13/59 (22.0)	4/19 (21.1)	0.9282
Multilobar infiltrates	46/59 (78.0)	15/19 (78.9)	0.9282
Pleural effusion	12/59 (20.3)	5/19 (26.3)	0.5831
Antibiotic therapies with inhibiting PVL	32/60 (53.3)	4/17 (23.5)	0.0297
Recovered	42/71 (59.2)	10/20 (50.0)	0.4649
Length of stay, days	32.0 ± 31.2 (n = 31)	38.6 ± 21.6 (n = 7)	0.6036
Died	29/71 (40.8)	10/20 (50.0)	0.4649
Mean age, years (range)	39.3 ± 23.7 (n = 29)	32.6 ± 11.8 (n = 10)	0.3992
Time from onset of symptoms to death, days	6.1 ± 11.0 (n = 26)	3.2 ± 6.8 (n = 8)	0.4883

Data regarding these characteristics and outcomes were not available for all patients. Data are presented as means ± SD or as number of patients/number of patients for whom data were available. Figures in parentheses are percentages.

^a One each of diabetes, hypertension, liver cirrhosis, COPD, stroke, and renal or liver transplantation.

tients with MRSA and 20 patients with MSSA CAP. There was no statistical difference in mortality between the 2 groups ($p = 0.46$). The median time from the onset of symptoms to death was 6.1 ± 11.0 and 3.2 ± 6.8 days ($p = 0.49$) in patients with CA-MRSA or MSSA CAP, respectively. The mean length of stay (32.0 ± 31.2 vs. 38.6 ± 21.6 days) was also similar between patients with MRSA and MSSA CAP.

Discussion

Our case series suggests that *S. aureus* organisms usually harboring the genes encoding PVL have been associated with a severe course and poor prognosis in patients

with pneumonia. Admission for pneumonia is associated with an increased mortality even in relatively young patients [92, 93], the estimated overall mortality in patients with CAP is 5–9%; the corresponding figure in patients with severe CAP is 9–27% [94]. In accordance with other reports in which mortality in the individual case series was 20–60%, while mortality in case reports was 44.5% [94], mortality in our *S. aureus* CAP case series was 42.9%; this value is slightly lower than that in the study by Gillet et al. [14] which reported and overall mortality of 56%. The majority of patients (70.0%) with *S. aureus* CAP in our case series required ICU treatment, and about 43% of cases had shock or ARDS. In addition, most of the persons received aggressive treatment, with 65% of patients receiving mechanical ventilation. Further evidence

supporting the notion of severe disease is provided by the short period from the onset of symptoms or diagnosis of pneumonia to death, with only 5.5 ± 10.1 days in our cases series. Among the cases which survived in our case series, there were patients who had prolonged hospital admissions with a median of 33.2 ± 29.5 days.

Although CAP caused by *S. aureus* in nonpediatric patients is uncommon, early recognition is important because of the high mortality rate associated with it [95]. Clinicians, therefore, should be concerned regarding the variables related to the severity and fatal outcome of *S. aureus* CAP. In other studies [14, 15, 18], the need for inotrope support, the onset of acute respiratory distress syndrome, a low $\text{PaO}_2:\text{FiO}_2$ ratio, high severity scores, multiorgan failure, admission to the ICU, mechanical ventilation, shock, and disseminated intravascular coagulation were found to be associated with a fatal outcome by univariate analysis, but these characteristics were generally found in studies of severe infectious respiratory diseases. In contrast, hemoptysis, which is uncommon in adults and adolescents with severe pneumonia, occurred very frequently in our series and was associated with a fatal outcome ($p = 0.024$). Thus, hemoptysis appears to be both a major diagnostic sign of necrotizing pneumonia and an important predictor of a fatal outcome [14]. The logistic regression analysis in our case series also showed that leucopenia ($p = 0.002$) was the factor associated with a fatal outcome, which is similar to the results described by Gillet et al. [14]. Although the median WBC count was slightly high [$(10.6 \pm 10.0) \times 10^9/\text{l}$], 37.1% of case patients in the series had a low ($<4.0 \times 10^9/\text{l}$) WBC count for which the median value was $(1.5 \pm 0.8) \times 10^9/\text{l}$, and 42% had a high ($>10.0 \times 10^9/\text{l}$) leukocyte count. In addition, the relation between the leukocyte count and the risk of death appeared to be linear; the death rate was 12.9% when the leukocyte count was $>10.0 \times 10^9/\text{l}$, 25% when the leukocyte count was normal ($4.0 \times 10^9/\text{l}$ to $9.9 \times 10^9/\text{l}$), and 73.9% when the leukocyte count was $<4.0 \times 10^9/\text{l}$. This suggests that leukopenia is a specific feature of severe staphylococcal necrotizing pneumonia and that it is statistically associated with a fatal outcome. This is in agreement with in vitro data showing that PVL induces both apoptosis and necrosis in human leukocytes [96].

With regard to influenza, influenza-like symptoms or laboratory-confirmed influenza was found in our case series to be associated with mortality ($p = 0.011$), which was in accordance with other studies [14, 15, 18]. Previous flu-like infections are known to facilitate the onset of bacterial pneumonia, both by impairing local defenses and

by enhancing bacterial adhesion to damaged epithelia [97], and lung involvement tends to be global and diffuse. It is worth noting, however, that laboratory-confirmed viral infections were only reported in 10 cases. A study [50] reported 1 case of MRSA CAP with a favorable outcome associated with the absence of flu-like illness. It is thought that the absence of a prior flu-like infection probably precluded massive infestation and may explain the absence of absolute neutropenia and satisfactory evolution in this case. These findings suggest that pneumonia due to PVL-producing *S. aureus* may have a better prognosis when absolute leukopenia and prior flu-like illness are absent.

Any history of preceding skin or soft tissue infection should further raise suspicion, as many patients, i.e. 48.2%, in our case series presenting with *S. aureus* CAP had a documented recent history of skin and soft tissue infection. *S. aureus* CAP is usually associated with soft tissue superficial infections [98]; mild injuries usually precede community-acquired *S. aureus* infections and are the portal of entry for invasion [31, 99]. In our analysis, however, skin and soft tissue infections did not reach statistical significance ($p = 0.530$), suggesting that skin and soft tissue infection was not associated with death, which was different from the findings of other studies [14, 15].

The optimal therapy for *S. aureus* CAP, especially for MRSA CAP, remains to be determined. The recently released Infectious Disease Society of America/American Thoracic Society CAP guidelines for adults recommend vancomycin or linezolid for CA-MRSA, though the most effective therapy has not yet been defined [100]. Vancomycin has been considered the gold standard for the treatment of MRSA infections; however, clinical failures have also been reported in the presence of in vitro susceptibility with increasing minimum inhibitory concentrations for vancomycin [101, 102]. Patients may fail to adequately respond to vancomycin, whereas the addition of antimicrobial therapies that inhibit toxin production such as clindamycin and linezolid may be life saving. It is important to note that the initial choice in most published series was intravenous vancomycin but, as shown in this case series, in about 20% of the cases targeted therapy with vancomycin was switched to linezolid due to a lack of response to treatment with vancomycin which, however, resulted in improved outcomes with 8 cases (8/10, 80.0%) surviving. Our patient was also initially treated with vancomycin and was then switched to linezolid because of continued fevers. However, it is important to note that most of cases in the series received van-

comycin 1,000 mg every 12 h, but no measurements of vancomycin plasma levels were performed. Our logistic regression was first performed using antibiotic therapies inhibiting toxin production (clindamycin or linezolid) as the independent variable, and it was found that this was associated with survival ($p = 0.007$). In the case series, 32 cases of MRSA and 4 cases of MSSA CAP were treated with antibiotic therapies inhibiting PVL and 88.9% received a better prognosis. The use of a protein synthesis inhibitor, such as linezolid or clindamycin, may be especially beneficial in the setting of a PVL-mediated staphylococcal infection, and clinical data at least partially support such an approach [103]. Wunderink et al. [104] also found that, compared with vancomycin, linezolid treatment of MRSA-infected patients was associated with improved survival. Three of 4 patients with necrotizing pneumonia clinically failing vancomycin therapy responded to a change to linezolid and rifampicin [12]. However, linezolid is not a first-line option for the current management of CAP due to MSSA. It remains to be ascertained in randomized controlled trials whether this antibiotic could prove effective for such fatal infections for which bactericidal compounds are currently recommended [105]. We think, therefore, that physicians should consider the role of toxin production and regulation in the outcomes of staphylococcal infections. Linezolid may provide improved outcomes compared with vancomycin in patients with MRSA pneumonia which, therefore, means it may be the optimal treatment in cases of MRSA CAP; however, validation in a prospective trial is currently lacking. Additional population-based studies are needed to determine whether a difference truly exists. However, there are theoretical reasons to believe that agents such as linezolid or clindamycin may have an additional benefit because they are associated with less toxin release [106] and attain good concentrations in the lung parenchyma [107, 108]. Both clindamycin and linezolid markedly suppress PVL production as staphylococci approach the stationary phase, and there may be no PVL detectable 12 h after starting treatment [109]. Clindamycin has been used successfully to treat *S. aureus* pneumonia, but concern over the possibility of inducible clindamycin resistance has discouraged its use as the sole agent for the empiric treatment of severe pneumonia that may be due to community-associated *S. aureus* [110]. Although the optimal duration of antibiotic therapy remains unknown, an extended duration of antibiotic therapy has been prescribed on the basis of the presence of cavitory infiltrates and the duration of symptoms [27]. Other toxin-neutralizing strategies have been described, such as treatment

with intravenous immunoglobulin, although no randomized controlled trials have been performed to assess the role of immunoglobulin therapy in this setting. This therapy was used in several patients with PVL-associated pneumonia in our case series [25, 26, 64].

This case series also illustrated that life-threatening MSSA and MRSA with usually PVL-positive strains, regardless of the *S. aureus* antibiotic susceptibilities, are both associated with severe necrotizing pneumonia. No differences were found in the final outcome of patients with MRSA and MSSA CAP. Patients with MRSA CAP did not have higher rates of mortality than did patients with MSSA CAP even though patients with MRSA CAP did not receive empirical glycopeptide therapy, which was in accordance with the study of Vardakas et al. [18]. Several attempts have been made to investigate whether MRSA strains are more virulent than MSSA or vice versa. The mortality of community-acquired *S. aureus* bacteremia was similar in patients with MSSA or MRSA strains [111]. The genes encoding the exotoxin PVL are typically present in CA-MSSA [19] with about 2–5% of PVL-positive MSSA strains. The SCCmec element may have been transferred to an MSSA genetic background. It is possible that SCCmec IV was inserted into a CA-MSSA isolate, thereby converting it into a CA-MRSA strain [112]. The presence of PVL has been considered a genetic marker for CA-MRSA [113].

Certain limitations of this study need to be addressed. First, 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 be representative of the full spectrum of this disease and may not reflect the true burden of the disease. Furthermore, due to the fact that this is a retrospective study, information was not available for all patients, creating the possibility of information bias in history collection. We limited our search to English language databases (although we did include non-English articles if identified) so the possibility of some studies in other languages does exist. The number of cases of life-threatening MSSA CAP involved in the study may be too small to show the difference in some clinical presentations and outcomes in comparison with MRSA CAP. Another issue that should be emphasized is that although some of the reported patients had laboratory-confirmed influenza as the cause of a preceding illness, those diagnoses, based solely on clinical symptoms, may have been caused by other viral respiratory pathogens.

In conclusion, although the present evidence shows that *S. aureus* is an infrequent cause of CAP, there is data

suggesting an increase in the incidence of *S. aureus* infections over the past several years. As for reported cases in adults and adolescents, patients with MRSA CAP have the same demographic characteristics, clinical characteristics, and outcomes, except for the use of antibiotic therapies with inhibiting PVL, as patients with MSSA CAP. Because *S. aureus* CAP is a severe disease with significant lethality, community-acquired *S. aureus* must now be borne in mind as a possible cause of life-threatening CAP. Physicians need to be highly aware that both CA-MRSA and MSSA can cause rapidly progressive necrotizing pneumonia and should pay special attention to those patients who acquired severe CAP during influenza season, with flu-like symptoms, hemoptysis, and leucopenia, independent of the methicillin resistance phenotype. Testing for the presence of toxins such as PVL may need to be incorporated into diagnostic panels to help stratify patients' risk of a more invasive disease. Empiric therapy for

severe CAP with this distinct clinical picture as described above should include coverage for *S. aureus* as soon as possible, without waiting for the bacteriological results. Targeted treatment with antimicrobials inhibiting toxin production (linezolid or clindamycin) appears to be the more appropriate selection.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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