Methicillin resistance is not a predictor of severity in community-acquired *Staphylococcus aureus* necrotizing pneumonia—results of a prospective observational study

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Abstract

Staphylococcal necrotizing pneumonia (NP) is a severe disease associated with Panton–Valentine leucocidin (PVL). NP was initially described for methicillin-susceptible *Staphylococcus aureus* (MSSA) infection, but cases associated with methicillin-resistant *S. aureus* (MRSA) infection have increased concomitantly with the incidence of community-acquired MRSA worldwide. The role of methicillin resistance in the severity of NP remains controversial. The characteristics and outcomes of 133 patients with PVL-positive *S. aureus* community-acquired pneumonia (CAP) were compared according to methicillin resistance. Data from patients hospitalized for PVL-positive *S. aureus* CAP in France from 1986 to 2010 were reported to the National Reference Centre for Staphylococci and were included in the study. The primary end point was mortality. Multivariate logistic modelling and the Cox regression were used for subsequent analyses. We analysed 29 cases of PVL-MRSA and 104 cases of PVL-MSSA pneumonia. Airway haemorrhages were more frequently associated with PVL-MSSA pneumonia. However, no differences in the initial severity or the management were found between these two types of pneumonia. The rate of lethality was 39% regardless of methicillin resistance. By Cox regression analysis, methicillin resistance was not found to be a significant independent predictor of mortality at 7 or 30 days (p 0.65 and p 0.71, respectively). Our study demonstrates that methicillin resistance is not associated with the severity of staphylococcal necrotizing pneumonia.

Key words: Community-acquired pneumonia, methicillin resistance, Panton–Valentine leucocidin, *Staphylococcus aureus*
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Introduction

Necrotizing pneumonia (NP) due to infection with *Staphylococcus aureus* was described in a study by Gillet *et al.* [1] in 2002, and numerous cases have since been reported worldwide [2–5]. The disease is characterized by rapidly progressing and extensive bilateral pneumonia. The overall mortality rate ranges from 30% to 75% [1,2] and death occurs rapidly with a median survival time between 4 and 10 days [1,2]. Erythroderma, airway bleeding and leukopenia are predictive of mortality [6,7]. NP is associated with the production of Panton–Valentine leucocidin (PVL), an otherwise infrequently encountered virulence factor produced by *S. aureus*. Initially, cases of NP were primarily due to PVL-positive, methicillin-susceptible *S. aureus* (PVL-MSSA) [8]. However, since 2000, NP caused by PVL-positive, community-acquired (CA) methicillin-resistant *S. aureus* (PVL-MRSA) has been reported worldwide [9–12].

The prevalence of CA-MRSA varies considerably by country [11] and has increased over time. In the first series of NP cases published in 2002, only one out of 16 cases was

due to PVL-MRSA [1], whereas PVL-MRSA accounted for 12% of a series of 50 cases collected from 2002 to 2005 [6]. Community-acquired MRSA pneumonia (mostly caused by PVL-MRSA) is reportedly a severe disease, as an American study from the Centers for Disease Control and Prevention found fatality rates as high as 60% [13]. Therefore, focus has recently shifted to the MRSA strains that cause community-acquired pneumonia (CAP) and, specifically, to whether the resistance profile of CA-MRSA increases the severity [10,12,14–16]. This question remains unresolved, as there have been no prospective studies that have compared the characteristics and outcomes of PVL-MRSA and PVL-MSSA NP cases.

From 1986 to 2010, 161 cases of CAP caused by PVL-positive *S. aureus* were collected in France. In this study, we compared the characteristics and outcomes for 104 cases of PVL-MSSA with 29 cases of PVL-MRSA.

Patients and Methods

Since 1986, case reports of CAP caused by strains of *S. aureus* have been collected by the French National Reference Centre for Staphylococci (Lyon, France) [1]. For cases with isolates harbouring the PVL genes, a standardized data form was completed.

Definitions

Community-acquired pneumonia was defined by symptoms of a lower respiratory tract infection (cough, expectoration and chest pain), by pulmonary infiltrates on chest radiographs that were not attributable to other causes and by the lack of the following healthcare risk factors: recent hospitalization, dialysis or residence in a long-term care facility. *Staphylococcus aureus* CAP was defined by isolation of *S. aureus* within 48 h of hospital admission. Isolations were performed using one of the following procedures: (i) puncture of a pleural effusion or lung abscess; (ii) culture from bronchoalveolar lavage fluid (10^4 CFU/mL), Wimberley brushing (10^3 CFU/mL) or protected tracheal aspiration (10^3 CFU/mL); or (iii) blood culture revealing *S. aureus* as the only relevant pathogen.

Microbiological studies

Staphylococcus aureus isolates were tested for toxin genes and antimicrobial susceptibility by the French National Reference Centre for Staphylococci. Genes encoding PVL were detected using PCR-based methods [17]. Isolates were tested for susceptibility by broth microdilution using the interpretive criteria of the CLSI [18]. In addition, the *mec*A gene, which codes for methicillin resistance, was detected by PCR for each isolate [19].

Study design and population

This study was a nested case–control study of a prospective cohort of patients hospitalized for *S. aureus* CAP. Only cases caused by PVL-positive strains were included. A case was defined as a patient with PVL-MRSA CAP, and a control was a patient with PVL-MSSA CAP.

Each of the 161 cases included were examined for temporal changes. Analyses comparing PVL-MRSA and PVL-MSSA were thereafter restricted to those 133 cases with complete data.

Data collection

The following information was collected: demographic data, medical history, signs and symptoms of infection, disease course, radiological and laboratory results from the first 48 h of hospitalization, and the time at which antimicrobial agents active against *S. aureus* were used. The possible outcomes were life or death at discharge. Severity was rated using the Paediatric Risk of Mortality score (PRISM) for patients less than 18 years old, and the Simplified Acute Physiology Score II (SAPS II) for adult patients. A patient with a severity score above the 75th centile or admitted to the intensive-care unit (ICU) was classified as severe.

Statistical analysis

Annual data were clustered into three periods for which MSSA cases were equally distributed. Increasing trends for the time of observed incidence of reported cases of PVL-positive CA-MRSA NP were examined using a chi-square test (for linear trends) and Poisson regression analysis.

The clinical and biological features were compared using the Pearson's chi-square test or Fisher's exact test (for categorical variables) and the Student's *t* test or the Mann–Whitney *U* test (for continuous variables).

To identify risk factors associated with PVL-MRSA, multivariate logistic regression was performed using a threshold of 0.20 for inclusion into the model. The model's goodness of fit was assessed with the Hosmer–Lemeshow test.

Survival probability was estimated using the Kaplan–Meier method. The baseline was defined as the day of admission and patients who survived were followed up upon discharge. If patients died within 24 h of admission, the observation period was rounded to 0.5 days. The differences in 7-day and 30-day cumulative survival distributions of survivors and non-survivors were assessed by log-rank tests. Potential factors associated with survival were examined by a Cox proportional hazards regression analysis. Proportional hazard

assumptions and the interactions between prognostic factors and time were tested.

For all tests performed, a two-tailed p value <0.05 was considered statistically significant. Analyses were performed with SPSS 17.0 software (SPPS Inc., Chicago, IL, USA).

Results

In all, 161 cases of PVL-positive *S. aureus* CAP were identified; 124 of these cases were PVL-MSSA (77%) and 37 were PVL-MRSA (23%). Each of these cases was considered for the trend analysis of the proportion of MRSA, but 28 cases were excluded from further analysis because of missing data.

Incidence of reported cases

The number of patients with PVL-positive CA-MRSA CAP increased from five cases (10.9%) before 2004 to 14 cases (25.5%) between 2005 and 2007, and reached 18 cases (30%) after 2008 (p 0.024).

Demographic conditions and medical history

In total, 104 PVL-MSSA cases and 29 PVL-MRSA cases were analysed (Table 1). The median age of CA-MSSA patients was 22 years, and that of CA-MRSA patients was 22.5 years (p 0.717). Most patients had no underlying conditions (88.5% or 75.9% for PVL-MSSA and PVL-MRSA cases, respectively, p 0.129). The symptoms that occurred before hospitalization were similar, as the percentages of patients with preceding influenza-like symptoms were 59.8% and 65.5% (p 0.669) in PVL-MSSA and PVL-MRSA cases, respectively, and those with pre-existing skin and soft-tissue infections were 26.9% and 10.3% (p 0.082). There was no clear seasonal trend but 33.8% of all cases occurred during January and February. Potential links with an influenza A outbreak were not tested in this study.

Clinical, radiological and biological data

Patients with PVL-MSSA necrotizing pneumonia were significantly more likely to have multiple sites of *S. aureus* infection at the time of admission (25.2% versus 6.9%, p 0.039). Airway haemorrhage tended to be more typically associated with PVL-MSSA (44.2% versus 24.1%; p 0.056). There were no additional statistical differences in clinical or biological data. The radiological findings at the time of admission indicated equally severe disease.

Multivariate analysis

The multivariate analysis identified airway haemorrhage as the only factor negatively associated with PVL-MRSA CAP (adjusted OR 0.32; p 0.028).

Management

Admission to the ICU occurred in 82 PVL-MSSA cases (79.6%) and 20 PVL-MRSA cases (69.0%). There were no differences in the severity scores. Of all cases, 64% required mechanical ventilation (66.3% for PVL-MSSA and 55.2% for PVL-MRSA cases, p 0.797). Of these, 85.5% of PVL-MSSA and 87.5% of PVL-MRSA received inotrope support (p 0.527). Appropriate empirical antibiotic therapy, which consisted of at least one antibiotic that is active *in vitro* on the particular *S. aureus* strain, was initiated during the first 24 h of hospitalization in 86% of all cases (87.8% of CA-MSSA and 79.2% of CA-MRSA, p 0.324). Drug dosage and combination therapy were not recorded.

Antibiotics with antitoxinic properties (i.e. linezolid, clindamycin or rifampicin) were used in 33 patients of 98 (33.7%) but these particular data were missing in 32 cases. In most cases, these treatments were used as a second-line therapy, after the first 24 hours. Polyvalent intravenous immunoglobulins were employed twice and both patients survived.

Survival analysis

There were no differences in mortality between PVL-MSSA and PVL-MRSA cases (39.4% versus 37.9%, respectively; p 0.884). For the deceased patient, median survival times were 1.0 day and 0.5 day for PVL-MSSA and PVL-MRSA cases, respectively (p 0.234). The duration of hospitalization (24 days for PVL-MSSA versus 24 days for PVL-MRSA; p 0.403) and ICU stay (17 days for PVL-MSSA versus 16 days for PVL-MRSA; p 0.985) for survivors were similar.

There were no differences in the cumulative survival rates by log-rank test (p 0.877 and p 0.892 for 7-day and 30-day survival, respectively) (Fig. 1). Cox univariate analysis confirmed that methicillin resistance was not a significant predictor of mortality at 7 days or at 30 days (hazard ratio (HR) 1.29 p 0.656 and HR 1.19 p 0.711, respectively). On univariate analysis, airway bleeding was strongly associated with a fatal outcome (HR 3.75 p <0.001 and HR 3.68 p <0.001 for 7-day and 30-day mortality, respectively). Mortality reached 65% in cases with haemoptysis versus 23% in those without (p <0.001). Leucocyte counts were negatively correlated with mortality, as mortality occurred in 75% of cases with leukopenia (<3000 leucocytes/mL), in 26% of cases with leucocyte counts between 3000/mL and 10 000/mL and in 8% of cases with leucocyte counts >10 000/mL. The use of an antitoxinic treatment was associated with a better outcome (mortality rate 6.1% versus 52.3%, p <0.001): association with a skin and soft-tissue infection was associated with decreased mortality (mortality rate of 16%; p 0.006). The model was adjusted on severity (as defined above) and presence of *mec*A gene. Cox multivariate analysis showed that

TABLE 1. Characteristics and outcome of community-acquired, Panton–Valentine-positive, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* necrotizing pneumonia in a French cohort of 133 patients from 1986 to 2010

Characteristic	CA-MSSA (*n* = 104)	CA-MRSA (*n* = 29)	Univariate OR (95% CI)	p-value[a]
Demographics				
Age (years)	22 (4.5–43.7)	22.5 (0.7–46.5)	0.99 (0.98–1.01)	0.717
Male gender	64 (61.5)	17 (58.6)	1.29 (0.49–2.61)	0.831
Comorbid condition				
No underlying disease[b]	92 (88.5)	22 (75.9)	2.51 (0.82–7.64)	0.111
Personal or familial history of skin and soft-tissue infection[c]	18 (24.0)	4 (18.2)	0.70 (0.21–2.35)	0.773
Symptoms before hospitalization				
Time from onset of symptoms to hospital admission (days)	3.0 (2.00–5.00)	3.5 (2.25–5.75)	1.01 (0.90–1.13)	0.847
Influenza-like syndrome	61 (59.8)	19 (65.5)	1.27 (0.54–3.02)	0.669
Skin and soft-tissue infection[d]	28 (26.9)	3 (10.3)	0.31 (0.09–1.12)	0.082
Clinical symptoms during the first 24 h of hospitalization[e]				
Fever >39°C or temperature <36°C	83 (79.8)	21 (72.4)	0.66 (0.26–1.71)	0.447
Airway haemorrhage[f]	46 (44.2)	7 (24.1)	0.40 (0.16–1.02)	0.056
Additional focus of staphylococcal infection[g]	26 (25.2)	2 (6.9)	0.22 (0.05–0.99)	0.039
Radiological findings during the first 24 h of hospitalization[h]				
Pleural effusion	16 (55.2)	13 (44.8)	1.09 (0.47–2.50)	0.836
Multilobar consolidation	67 (65.7)	15 (51.7)	0.56 (0.24–1.29)	0.195
Biological findings during the first 48 h of hospitalization				
Lowest leucocyte count (10^9/L)	5.5 (1.4–14.6)	4.7 (1.2–11.8)	1.00 (0.99–1.01)	0.586
Categorical leuxcocyte count				
<3000 leucocytes/mL	38 (36.9)	13 (44.8)		0.580
3000–10 000 leucocytes/mL	26 (25.2)	8 (27.6)		
>10 000 leucocytes/mL	39 (37.9)	8 (27.6)		
Lowest platelet count (10^9/L)	171 (92–275)	164 74–275)	1.00 (0.99–1.01)	0.767
ICU admission[e,i]	82 (79.6)	20 (69.0)	0.57 (0.23–1.43)	0.315
Severity markers				
PRISM score (*n*/*N*)	18 (12–35) 18/32	11 (5–31) 6/9	0.95 (0.89–1.02)	0.217
SAPS II score (*n*/*N*)	57 (27–78) 44/50	64 (39–89) 11/11	0.99 (0.97–1.01)	0.436
Pa_{O_2}/Fi_{O_2} ratio (*n*/*N*)	70 (50–105) 49/82	67 (50–99) 10/20	1.00 (0.99–1.01)	0.968
Therapy				
Mechanical ventilation	69 (66.3)	16 (55.2)	0.62 (0.27–1.44)	0.282
Duration of mechanical ventilation (days)	2.0 (1.0–14.0)	3.5 (1.0–11.7)		0.797
Inotrope support	59 (56.7)	14 (48.3)	0.71 (0.31–1.62)	0.527
Appropriate antibiotic therapy in the first 24 h of hospitalization[j]	86 (87.8)	19 (79.2)	0.53 (0.17–1.68)	0.324
Outcome				
Complications[k]	85 (81.7)	23 (79.3)	0.86 (0.31–2.39)	0.790
ARDS	48 (46.2)	10 (34.5)	0.61 (0.26–1.45)	0.296
Mortality	41 (39.4)	11 (37.9)	1.06 (0.46–2.48)	0.884
Time to death (days)	1.0 (0.5–3.7)	0.5 (0.5–3.0)		0.234
Duration of survivor hospitalization (days)	24 (17–41)	24 (14–32)		0.403

OR, odds ratio; ICU, intensive care unit; PRISM, Paediatric Risk of Mortality; SAPS II, Simplified Acute Physiology Score II; ARDS, acute respiratory distress syndrome; CA-MRSA, community-acquired, methicillin-resistant *Staphylococcus aureus*; CA-MSSA, community-acquired, methicillin-susceptible *Staphylococcus aureus;* SSTI, skin and soft-tissue infection.

Data represent the number (%) of patients for categorical variables and the median (interquartile range) for continuous variables.

[a]Fisher's exact test for categorical variables, except for categorical leucocytes (Pearson's chi-square test); Kruskal–Wallis test for continuous variables.

[b]Underlying diseases included diabetes mellitus (four cases of CA-MSSA and three cases of CA-MRSA), chronic respiratory insufficiency (two cases and one case, respectively), corticosteroid use (four cases and four cases, respectively) and immunosuppressive therapy (five cases and three cases, respectively).

[c]Data were available for 90 patients and included those with a personal history of SSTI (10 cases of CA-MSSA and one case of CA-MRSA) and familial history of SSTI (eight cases and three cases, respectively).

[d]SSTIs included cutaneous abscesses in 11 cases of CA-MSSA infection, furuncles in nine cases of CA-MSSA and two cases of CA-MRSA and both superficial SSTI and cutaneous abscess in eight cases and one case, respectively.

[e]Data were collected for 119 patients, because one patient died before admission.

[f]Airway haemorrhages included lower airway haemorrhage in three cases, upper airway haemorrhage in 33 cases and both lower and upper airway haemorrhage in nine cases. All seven CA-MRSA cases involved upper airway haemorrhage.

[g]Other types of infection included pyomyositis, arthritis, spondylodiscitis, uveitis and sinusitis.

[h]Data were collected for 118 patients due to rapid patient death after admission.

[i]Upon hospitalization, ICU admission occurred in 57 cases of CA-MSSA and 18 cases of CA-MRSA, and secondary ICU admission occurred in 25 cases and two cases, respectively.

[j]Data were collected for 111 patients due to rapid patient death after admission and before antibiotic administration.

[k]Complications included septic shock, pyothorax, pneumothorax, empyema, septic myocarditis, pericarditis, osteomyelitis, epidural abscess, hepatic abscess, renal abscess, septic thrombophlebitis, septic retinitis and bronchiectasis.

airway haemorrhage, leukopenia and absence of antitoxinic treatment were risk factors for 30-day mortality (Table 2).

Discussion

Staphylococcal NP was individualized for both MSSA and MRSA in 2002 and was associated with the production of PVL [1]. NP represents only a small fraction of staphylococcal CAP, and some confusion has attended efforts to distinguish between methicillin resistance and other severity-associated factors, especially in studies focusing on MRSA CAP. In a retrospective review of staphylococcal, PVL-positive CAP, Vardakas *et al.* [20] found 71 articles that reported data from 107 cases between 1985 and 2008, and most of these cases were individual case reports. Our study reports

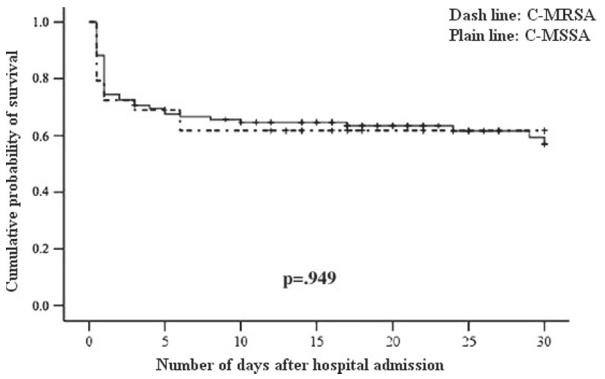

FIG. 1. Kaplan–Meier survival curves after 30 days for patients with community-acquired, Panton–Valentine-positive, *Staphylococcus aureus* necrotizing pneumonia according to methicillin susceptibility.

TABLE 2. Cox regression analysis of factors associated with 30 days mortality in community-acquired, Panton–Valentine leukocidin-positive *Staphylococcus aureus* necrotizing pneumonia[a]

Variable	p-value	Multivariate adjusted hazard ratio (95% CI)
Airway haemorrhage	0.004	2.96 (1.41–6.25)
Leucocyte count (10^9/L)[b]	0.001	0.32 (0.17–0.61)
Antitoxinic treatment	0.002	0.11 (0.03–0.49)

[a]The model was adjusted on severity and presence of the *mec*A gene.
[b]In this model, natural logarithms of leucocyte counts were used.

the results of a prospective surveillance study of 133 PVL-positive staphylococcal necrotizing CAP cases that occurred in France between 1986 and 2010.

In this study, we found no differences between PVL-MRSA and PVL-MSSA CAP in terms of severity or outcome. Multivariate analysis revealed that airway haemorrhage, which was strongly associated with lethality in previous studies, was more likely to be associated with PVL-MSSA pneumonia than PVL-MRSA pneumonia. No other factor was associated with methicillin susceptibility, which indicated that MSSA and MRSA NP were clinically and biologically indistinguishable.

In vitro theoretically appropriate empirical antibiotic therapy was initiated during the first 24 h of hospitalization in 87.8% of PVL-MSSA cases and 79.2% of PVL-MRSA cases (p 0.324), and there were no differences in ICU admission, mechanical ventilation or inotrope support between the groups. Hence, differences in the initial management of the infection could not have interfered with severity.

Our choice to restrict the case definition to PVL-associated strains allowed a more accurate comparison of CA-MSSA and CA-MRSA. In the literature, the only variables significantly associated with CA-MRSA infection were risk factors for the acquisition of CA-MRSA carriage, such as crowding, skin-to-skin contact and a lack of personal cleanliness and hygiene [21,22]. Experimental studies have suggested that CA-MRSA (particularly the USA300 lineages) is especially virulent, as a result of the successful combination of the full arginine catabolic mobile elementACME element and an SCC*mec* element [23]. Conversely, others studies have tended to emphasize the role of PVL in the virulence of CA-MRSA [15,16]. In the present study, we ought to neutralize the effect of PVL by selecting only cases of PVL-positive NP. We cannot rule out the possibility that PVL-MRSA and PVL-MSSA of our series harbour different isoforms of PVL as described previously [24] or different expression levels of PVL and other virulence factors [25] even though PVL concentrations *in vivo* might not be different between PVL-MRSA and PVL-MSSA, as observed for human abscesses [26]. However, given the lack of differences in outcome of the two series, we are confident in the conclusion that resistance to methicillin per se does not impact virulence of PVL-positive strains, at least in the context of French epidemiology where PVL-MRSA mostly belong to the ST80 lineage [27]. Indeed this is not always the case as other studies revealed that certain SCC*mec* elements, especially those present in hospital-acquired MRSA, can affect the overall virulence by modulating core-genome encoded virulence factors [28].

This analysis of 133 cases has confirmed the overall severity of *S. aureus* necrotizing CAP. Cases of NP occurred largely in young people; the median age was 22 years, which was only slightly higher than had been previously reported [1,29]. Although lower than initially reported, lethality remained high (39%) considering the patients' youth and lack of underlying conditions. Initial presentation with airway bleeding and leukopenia were associated with a fatal outcome and appear to be specifically related to this disease. As previously described, we observed a trend for *S. aureus* NP to occur during winter seasons, probably because of the recognized link between *S. aureus* pneumonia and viral respiratory infections, especially influenza [30]. Nevertheless, the number of cases with a definite viral diagnosis was too low to permit any conclusions.

In our study, 86% of patients received antibiotics considered as appropriate during the first 24 h of hospitalization. However, mortality remained high, which suggested that this treatment was not optimal. Clinical data suggest that the inhibition of bacterial toxin production can improve the outcome of infection [31,32]. As we have demonstrated the persistence of high mortality despite theoretically appropriate antibiotics, this study suggests that considerations about

the management of staphylococcal NP should not be based solely on antibiotic susceptibility. Several important staphylococcal toxins, including PVL, are over-expressed in the presence of β-lactams, but their expression can be blocked by the combined use of a toxin-suppressing agent (e.g. clindamycin, linezolid or rifampin) with antibiotics that target the cell wall [33,34]. In addition, intravenous immunoglobulins can neutralize the lytic effect of PVL on polymorphonuclear cells *in vitro* [35]. The use of antitoxinic treatment was independently associated with a better outcome in our study. However, there were important variations between patients, especially in the time of introduction, which limits the interpretation of this result. Nevertheless, the potential benefits of such treatments that target toxin production have been recently emphasized in a retrospective study [36] and may be a promising method to improve the outcome of both MRSA and MSSA NP.

The present investigation had certain limitations. First, case reporting to the Reference Centre was unsolicited and may not have reflected accurate data on the epidemiology and severity of this disease, as severe cases in previously healthy young people and those caused by methicillin-resistant strains are more likely to have been reported. Hence, our result does not reflect the evolution of the true incidence of PVL-MRSA in France but only the trend for cases reported to the Reference Centre. A second limitation concerns the clinical data collection. The analysis of trends over time included 161 cases for which microbiological and demographic data were available, but 28 cases (20 PVL-MSSA and 8 PVL-MRSA) were excluded from further analyses because they lacked at least one important data point. However, comparisons between the 28 excluded cases and the 133 analysed cases revealed no differences in mortality or in the percentage of MRSA. Third, as the data were collected over an extended time period, there may have been significant changes in the epidemiology or in the general knowledge of the disease over time that could have influenced our results. Nevertheless, beside the increase in observed PVL-MRSA frequencies during the study period, no significant changes concerning other data were observed over time.

In conclusion, this report emphasizes that *S. aureus* NP remains an extremely severe disease regardless of methicillin resistance. We found no reliable demographic or clinical factor that could distinguish patients with CA-MRSA pneumonia from those with CA-MSSA pneumonia. We also report that CA-MRSA is an increasing cause of severe CAP in France, which supports the use of anti-MRSA antibiotics for severe pneumonia when clinical and biological features suggest staphylococcal NP.

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Transparency Declaration

None of the authors have to declare conflict of interest.

Key points

The absence of a relationship between disease severity and methicillin resistance in *Staphylococcus aureus* necrotizing pneumonia was demonstrated as well as the persistence of high mortality, despite the significant body of knowledge on this disease.

References

1. Gillet Y, Issartel B, Vanhems P *et al.* Association between *Staphylococcus aureus* strains carrying gene for Panton–Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002; 359: 753–759.
2. Francis JS, Doherty MC, Lopatin U *et al.* Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton–Valentine leukocidin genes. *Clin Infect Dis* 2005; 40: 100–107.
3. Hageman JC, Uyeki TM, Francis JS *et al.* Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003–04 influenza season. *Emerg Infect Dis* 2006; 12: 894–899.
4. Klein E, Smith DL, Laxminarayan R. Community-associated methicillin-resistant *Staphylococcus aureus* in outpatients, United States, 1999–2006. *Emerg Infect Dis* 2009; 15: 1925–1930.
5. Naimi TS, LeDell KH, Como-Sabetti K *et al.* Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003; 290: 2976–2984.
6. Gillet Y, Etienne J, Lina G, Vandenesch F. Association of necrotizing pneumonia with Panton–Valentine leukocidin-producing *Staphylococcus aureus*, regardless of methicillin resistance. *Clin Infect Dis* 2008; 47: 985–986.
7. Kallen AJ, Brunkard J, Moore Z *et al. Staphylococcus aureus* community-acquired pneumonia during the 2006 to 2007 influenza season. *Ann Emerg Med* 2009; 53: 358–365.
8. Lina G, Piemont Y, Godail-Gamot F *et al.* Involvement of Panton–Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis* 1999; 29: 1128–1132.
9. Tristan A, Ferry T, Durand G *et al.* Virulence determinants in community and hospital methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2007; 65 (Suppl 2): 105–109.
10. Diep BA, Chan L, Tattevin P *et al.* Polymorphonuclear leukocytes mediate *Staphylococcus aureus* Panton–Valentine leukocidin-induced

lung inflammation and injury. *Proc Natl Acad Sci USA* 2010; 107: 5587–5592.
11. Tristan A, Bes M, Meugnier H *et al.* Global distribution of Panton–Valentine leukocidin-positive methicillin-resistant *Staphylococcus aureus*, 2006. *Emerg Infect Dis* 2007; 13: 594–600.
12. Vandenesch F, Couzon F, Boisset S *et al.* The Panton–Valentine leukocidin is a virulence factor in a murine model of necrotizing pneumonia. *J Infect Dis* 2010; 201: 967–969; author reply 9–70.
13. CDC. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza – Louisiana and Georgia, December 2006–January 2007. *MMWR Morb Mortal Wkly Rep* 2007; 56: 325–329.
14. Cremieux AC, Dumitrescu O, Lina G *et al.* Panton–Valentine leukocidin enhances the severity of community-associated methicillin-resistant *Staphylococcus aureus* rabbit osteomyelitis. *PLoS ONE* 2009; 4: e7204.
15. Diep BA, Palazzolo-Ballance AM, Tattevin P *et al.* Contribution of Panton–Valentine leukocidin in community-associated methicillin-resistant *Staphylococcus aureus* pathogenesis. *PLoS ONE* 2008; 3: e3198.
16. Labandeira-Rey M, Couzon F, Boisset S *et al. Staphylococcus aureus* Panton–Valentine leukocidin causes necrotizing pneumonia. *Science* 2007; 315: 1130–1133.
17. Jarraud S, Mougel C, Thioulouse J *et al.* Relationships between *Staphylococcus aureus* genetic background, virulence factors, agr groups (alleles), and human disease. *Infect Immun* 2002; 70: 631–641.
18. CLS I. Performance standards for antimicrobial susceptibility testing. 14th informationnal supplement M100-S14. National Committee for Clinical Laboratory. 2004; Wayne, PA.
19. Murakami K, Minamide W, Wada K, Nakamura E, Teraoka H, Watanabe S. Identification of methicillin-resistant strains of staphylococci by polymerase chain reaction. *J Clin Microbiol* 1991; 29: 2240–2244.
20. Vardakas KZ, Matthaiou DK, Falagas ME. Comparison of community-acquired pneumonia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* producing the Panton–Valentine leukocidin. *Int J Tuberc Lung Dis* 2009; 13: 1476–1485.
21. CDC. Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities – Georgia, California, and Texas, 2001–2003. *MMWR Morb Mortal Wkly Rep* 2003; 52: 992–996.
22. Miller LG, Quan C, Shay A *et al.* A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis* 2007; 44: 483–492.
23. Diep BA, Stone GG, Basuino L *et al.* The arginine catabolic mobile element and staphylococcal chromosomal cassette mec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 2008; 197: 1523–1530.
24. O'Hara FP, Guex N, Word JM *et al.* A geographic variant of the *Staphylococcus aureus* Panton–Valentine leukocidin toxin and the origin of community-associated methicillin-resistant *S. aureus* USA300. *J Infect Dis* 2008; 197: 187–194.
25. Li M, Cheung GY, Hu J *et al.* Comparative analysis of virulence and toxin expression of global community-associated methicillin-resistant *Staphylococcus aureus* strains. *J Infect Dis* 2010; 202: 1866–1876.
26. Badiou C, Dumitrescu O, George N *et al.* Rapid detection of *Staphylococcus aureus* Panton–Valentine leukocidin in clinical specimens by enzyme-linked immunosorbent assay and immunochromatographic tests. *J Clin Microbiol* 2010; 48: 1384–1390.
27. Dauwalder O, Lina G, Durand G *et al.* Epidemiology of invasive methicillin-resistant *Staphylococcus aureus* clones collected in France in 2006 and 2007. *J Clin Microbiol* 2008; 46: 3454–3458.
28. Kaito C, Saito Y, Nagano G *et al.* Transcription and translation products of the cytolysin gene psm-mec on the mobile genetic element SCCmec regulate *Staphylococcus aureus* virulence. *PLoS Pathog* 2011; 7: e1001267.
29. Gillet Y, Vanhems P, Lina G *et al.* Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton–Valentine leukocidin. *Clin Infect Dis* 2007; 45: 315–321.
30. Centers for Disease Control and Prevention (CDC). Severe coinfection with seasonal influenza A (H3N2) virus and *Staphylococcus aureus* – Maryland, February–March 2012. *MMWR Morb Mortal Wkly Rep* 2012; 61: 289–291.
31. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired MRSA pneumonia. *Chest* 2010; 138: 130–136.
32. Rouzic N, Janvier F, Libert N *et al.* Prompt and successful toxin-targeting treatment of three patients with necrotizing pneumonia due to *Staphylococcus aureus* strains carrying the Panton–Valentine leukocidin genes. *J Clin Microbiol* 2010; 48: 1952–1955.
33. Dumitrescu O, Badiou C, Bes M *et al.* Effect of antibiotics, alone and in combination, on Panton–Valentine leukocidin production by a *Staphylococcus aureus* reference strain. *Clin Microbiol Infect* 2008; 14: 384–388.
34. Dumitrescu O, Boisset S, Bes M *et al.* Effect of antibiotics on *Staphylococcus aureus* producing Panton–Valentine leukocidin. *Antimicrob Agents Chemother* 2007; 51: 1515–1519.
35. Gauduchon V, Cozon G, Vandenesch F *et al.* Neutralization of *Staphylococcus aureus* Panton–Valentine leukocidin by intravenous immunoglobulin *in vitro*. *J Infect Dis* 2004; 189: 346–353.
36. Li HT, Zhang TT, Huang J, Zhou YQ, Zhu JX, Wu BQ. Factors associated with the outcome of life-threatening necrotizing pneumonia due to community-acquired *Staphylococcus aureus* in adult and adolescent patients. *Respiration* 2011; 81: 448–460.