Mechanisms of disease

Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients

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Summary

Background Between 1986 and 1998, eight cases of community-acquired pneumonia due to *Staphylococcus aureus* strains carrying the gene for the Panton-Valentine leukocidin (PVL) were recorded in France, six of which were fatal. We aimed to assess the clinical features of these eight cases, and those of other cases identified prospectively, and to compare them with the characteristics of patients with pneumonia caused by PVL-negative strains.

Methods We compared eight retrospective and eight prospective cases of PVL-positive *S aureus* pneumonia with 36 cases of PVL-negative *S aureus* pneumonia. For all patients, we recorded age, length of hospital stay, risk factors for infection, signs and symptoms, laboratory findings, antibiotic treatment, and serial radiological findings.

Findings Median age was 14·8 years (IQR 5·4–24·0) for the PVL-positive patients and 70·1 years (59·2–81·4) for the others (p=0·001). Influenza-like illness had occurred during the 2 days before admission in 12 of the 16 PVL-positive patients, but in only three of 33 PVL-negative patients (p<0·0001). PVL-positive infections were more often marked by: temperature greater than 39°C (p=0·01), heart rate above 140 beats per min (p=0·02), haemoptysis (p=0·005), onset of pleural effusion during hospital stay (p=0·004), and leucopenia (p=0·001). The survival rate 48 h after admission was 63% for the PVL-positive patients and 94% for PVL-negative individuals (p=0·007). Histopathological examination of lungs at necropsy from three cases of necrotising pneumonia associated with PVL-positive *S aureus* showed extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive haemorrhagic necrosis of interalveolar septa.

Interpretation PVL-producing *S aureus* strains cause rapidly progressive, haemorrhagic, necrotising pneumonia, mainly in otherwise healthy children and young adults. The pneumonia is often preceded by influenza-like symptoms and has a high lethality rate.

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Introduction

Staphylococus aureus is responsible for about 2% of cases of community-acquired pneumonia[1] and at least 10% of cases of nosocomial pneumonia.[1,2] Most patients with *S aureus* pneumonia are elderly and have serious underlying disorders such as cardiovascular disease, malignant disease, chronic pulmonary disease, and diabetes mellitus.[3–5] The lethality rate ranges from 30% to 80%.[3,4]

Panton-Valentine LEUKOCIDIN (PVL) is an extracellular product of *S aureus*. PVL was detected in fewer than 5% of *S aureus* isolates in a general hospital.[6] We have found it to be associated with primary skin infections such as furunculosis, and severe necrotising pneumonia.[7] In 1998, a review of *S aureus* infections reported to the French Reference Centre for Staphylococcal Toxaemia (Lyon, France) between 1986 and 1998 revealed eight cases of severe community-acquired pneumonia caused by *S aureus* strains carrying the PVL gene, six of which were fatal.[7] The patients were all immunocompetent children or young adults. All had a preceding influenza-like syndrome before developing pneumonia, and the six deaths occurred shortly after diagnosis. Necropsy showed diffuse necrotising haemorrhagic pneumonia. We investigated the clinical features and the prognosis of this illness, and compared them with those of *S aureus* pneumonia caused by PVL-negative strains.

Methods

Patients

Since 1985, *S aureus* strains have been sent to the French Reference Centre for Staphylococcal Toxaemia for various purposes, such as the detection of toxin production in *S aureus* toxin-associated diseases or severe staphylococcal suppurative infections. From this collection, a subset of 172 *S aureus* isolates, representative of all staphylococcal infections, was chosen in 1998 to assess the importance of PVL in various clinical syndromes.[7] 27 *S aureus* strains were associated with community-acquired pneumonia and the PVL gene was detected in 22 cases. There was sufficient clinical and biological information to make a firm diagnosis of necrotising pneumonia in eight children with PVL-positive *S aureus*. No information was collected for the five cases of pneumonia from which PVL-negative *S aureus* was cultured.

After reviewing the eight initial cases of pneumonia caused by PVL-positive *S aureus*, we started a prospective surveillance programme to identify further patients. 76 hospitals in France, including all university hospitals, were invited to describe the clinical features of all new cases of community-acquired *S aureus* pneumonia from Jan 1, 1999, to Dec 31, 1999, using a standardised data collection form. The reporting physicians were unaware of whether the relevant *S aureus* strain contained the PVL genetic locus or not. Eight new cases of pneumonia due to *S aureus* bearing the PVL locus and 36 cases of PVL-negative *S aureus* pneumonia were notified during the prospective study period.

GLOSSARY

LEUKOCIDIN

Group of bacterial toxins that kill leucocytes by creating pores in the cell membrane; as well as *S aureus* Panton-Valentine leukocidin, the group includes *Pasteurella haemolytica* leukotoxin, *Actinobacillus actimycetemcomitans* leukotoxin, *Listeria monocytogenes* listeriolysin, *Escherichia coli* haemolysin, and *Fusobacterium necrophorum* leukotoxin.

PORE-FORMING TOXIN

These toxins work by inducing holes in the plasma membrane of eukaryotic cells, thus breaking the permeability barrier that keeps macromolecules and small solutes selectively within the cell. This class of protein is amphipathic, with one part interacting with the hydrophilic cavity filled with water, and the other interacting with the lipid chains or the non-polar segments of integral membrane proteins of eukaryotic cells. The consequences of cell permeation are the release of cytokines, activation of intracellular proteases, sometimes the induction of apoptosis, and ultimately cell death.

SUPERANTIGENS

A variety of molecules that share the ability to activate large populations of T lymphocytes through co-ligation between major histocompatibility complex (MHC) class II molecules on antigen-presenting cells and the variable portion of the T-cell antigen receptor β chain; the pattern of Vβ activation is specific for each of these superantigens. They include staphylococcal enterotoxins and toxic-shock-syndrome toxin.

SYNERGOHYMENOTROPIC TOXINS

Bicomponent toxins that act by cooperation of two components designated S and F (synergy), and which are directed (tropism) against cell membranes (hymen). They include *S aureus* Panton-Valentine leukocidin, γ haemolysin, and other toxins such as LukE-LukD.

The following data were recorded for each patient: age, length of hospital stay, hospital ward, risk factors for infection, signs and symptoms, laboratory findings, antibiotic treatment, and serial radiological findings.

Procedures

Pneumonia was defined by signs and symptoms of lower-respiratory-tract infection (cough, expectoration, chest pain, &c) and pulmonary infiltrates on the chest radiograph that were not attributable to other causes. Cases of pneumonia caused by *S aureus* were defined by the signs and symptoms above in the presence of isolation of *S aureus* as the only pathogen by at least one of the following procedures: puncture of a pleural effusion or lung abscess; culture of bronchoalveolar lavage fluid ($\geq 10^4$ colony-forming units [CFU]/mL), Wimberley brushing specimen ($\geq 10^3$ CFU/mL), or protected tracheal aspirate ($\geq 10^3$ CFU/mL); or blood culture yielding the same *S aureus* strain as that found in tracheal secretions.

S aureus isolates were forwarded to the French Reference Centre for Staphylococcal Toxaemia and tested for toxin production. Genetic sequences encoding SUPERANTIGENS (enterotoxins A–E, G–I, and toxic shock syndrome toxin) and PVL were detected by PCR-based methods.[7,8] The *mecA* gene, coding for meticillin resistance, was also detected by PCR as described by Murakami and colleagues.[9] Pulsed-field gel electrophoresis patterns were obtained with the *Sma*I restriction enzyme and a contour-clamped homogeneous electric field system with CHEF DR-II apparatus (Biorad, Hercules, CA, USA).[10] Histopathological findings were reviewed in the Department of Pathology of the Necker-Enfants Malades Hospital (Paris, France).

Statistical analysis

The characteristics of PVL-positive and PVL-negative cases were compared by means of the χ^2 test or Fisher's exact test for categorical variables, Student's *t* test after logarithmic transformation if necessary, or the Mann-Whitney *U* test for continuous variables. Progression to death was calculated by the Kaplan-Meier method, with admission as time 0 and censoring at discharge or death. Survival distributions were compared by use of the log-rank test. p values of <0·05 were regarded as denoting significant differences. Analyses were done with SPSS software, version 10.0 (SPSS Inc, Chicago, IL, USA).

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	PVL-positive retrospective cases (n=8)	PVL-positive prospective cases (n=8)	PVL-positive pooled cases (n=16)	PVL-negative cases (n=36)	p*
Demographics					
Median (IQR) age (years)	14·5 (4·1–15·1)	17·7 (5·4–32·1)	14·8 (5·4–24·0)	70·1 (59·2–81·4)	0·001
Number of men	4	4	8	21	0·57
Number with underlying disorders†					
0	8	8	16	11	
1	0	0	0	8	
>1	0	0	0	12	0·0001
Clinical features before admission					
Median (IQR) duration of symptoms (days)	3·0 (2·2–4·7)	3·5 (1·5–6·2)	3·0 (2·2–4·7)	4·0 (2·0–10·0)	0·40
Influenza-like syndrome‡	5	7	12	3/33	<0·0001
Diarrhoea	3	2	5	2/33	0·03
Furuncles	2	1	3	0	0·02
Skin rash	1	1	2	0	0·1
Clinical features at admission					
Temperature >39°C	7	6	13	14/34	0·01
Hypotension	6	7	13	18/34	0·054
Respiratory rate >30 breaths per min	5	7	12	18/34	0·2
Cyanosis	5	5	10	22/34	0·87
Heart rate >140 beats per min	4	5	9	7/35	0·02
Cough	4	4	8	22/32	0·2
Haemoptysis	6	0	6	1/33	0·005
Altered mental status§	4	2	6	21/29	0·03
Purulent expectoration	0	3	3	30/34	0·0001

PVL=Panton-Valentine leukocidin. *Based on comparison between pooled PVL-positive cases and PVL-negative cases. †Diabetes mellitus in 13 patients, lung diseases in 12, smoking in 11, alcoholism in eight, haematological disease in five, immunosuppression in five. ‡Fever and cough with coryza or pharyngitis. §At least one of: lethargy, coma or stupor, disorientation.

Table 1: **Baseline characteristics and clinical features of 52 patients with community-acquired *Staphylococcus aureus* pneumonia**

	PVL-positive retrospective cases (n=8)	PVL-positive prospective cases (n=8)	PVL-positive pooled cases (n=16)	PVL-negative (n=36)	p*
Radiographic pattern					
On admission					
Unilobar alveolar infiltrate	1	3	4	11/32	0·51
Multilobar alveolar infiltrate	6	4	10	17/33	0·46
Unilateral interstitial infiltrate	0	3	3	7/22	1·0
Bilateral interstitial infiltrate	1	1	2	11/34	0·18
Pleural effusion	1	5	6	8/32	0·5
Onset during hospital stay					
Bilateral interstitial infiltrate	2	5	7	3/30	0·02
Pleural effusion†	3/7	1/3	4/10	0/24	0·004
Biological findings					
Median (IQR) peak leucocyte count ($\times 10^9$/L)	7·9 (4·8–32·6)	7·6 (1·3–23·0)	7·9 (2·5–24·3)	14·8 (11·6–20·0)	0·71
Median (IQR) days after admission	0·0 (0·0–8·0)	2·0 (0·0–6·0)	2 (0·0–7·5)	1·0 (0·0–7·0)	0·91
Median trough leucocyte count ($\times 10^9$/L)	2·2 (0·7–4·6)	1·4 (0·4–7·5)	1·85 (0·6–6·4)	7·4 (4·9–9·9)	0·001
Median (IQR) days after admission	0·0 (0·0–1·0)	1·0 (0·2–7·0)	1·0 (0·0–1·0)	4·5 (0·7–8·0)	0·1
Median (IQR) trough platelet count ($\times 10^9$/L)	18 (4·5–234)	101 (44–327)	70 (4–325)	157 (88–230)	0·61
Median (IQR) days after admission	0·5 (0·0–3·5)	0·5 (0·0–2·0)	0·5 (0·0–2·2)	3·0 (1·0–6·0)	0·05
Median (IQR) PaO_2/FiO_2§	53·0 (NA)	27·0 (NA)	41·0 (NA)	150·0 (75–220)	0·009
Median (IQR) days after admission	1·0 (NA)	0·0 (NA)	0·5 (0·0–1·7)	1·0 (0·0–3·0)	0·35

PaO_2/FiO_2=ratio of partial pressure of oxygen in arterial blood to fractional concentration of oxygen in inspired gas. NA=not available. *Based on comparison between pooled PVL-positive cases and PVL-negative cases. †Denominator is number of patients without pleural effusion at admission. ‡Data available for 3, 1, 4 (3+1), and 19 patients per group, respectively.

Table 2: **Radiological and biological findings in 52 patients with community-acquired *Staphylococcus aureus* pneumonia**

Results

Preliminary analyses showed that the patients in the prospective study differed from the retrospective cases only in their lower rate of haemoptysis (p=0·007). We therefore pooled all PVL-positive cases for subsequent analysis.

Table 1 shows the baseline characteristics of the cases of necrotising pneumonia due to PVL-positive *S aureus* compared with those caused by PVL-negative *S aureus*. PVL-positive patients were younger than the others, but the median interval between symptom onset and admission was not significantly different. Significantly more PVL-positive patients than PVL-negative patients had a preceding influenza-like syndrome (table 1). None of the PVL-positive patients had risk factors for infection, whereas eight of the PVL-negative cases had one risk factor, and 12 had more than one.

At admission, the PVL-positive patients differed from the others by the frequency of haemoptysis and purulent expectoration (table 1). High fever (>39°C) was more frequent in PVL-positive cases. Hypotension, tachycardia, tachypnoea, and cyanosis occurred at similar frequencies in both groups, but nine of 16 PVL-positive patients had vital sign abnormalities (heart rate >140 beats per min, respiratory rate >30 breaths per min, or hypotension),[11] compared with only five of 36 PVL-negative patients (p=0·005).

Initial radiological features were similar in both groups, usually consisting of multilobar alveolar infiltrates (table 2). Pleural effusion was present at admission in six PVL-positive and eight PVL-negative patients. No cases of pyopneumothorax occurred. Subsequently, seven PVL-positive patients developed rapidly progressive diffuse bilateral infiltrates consistent with acute respiratory distress syndrome, compared with three PVL-negative cases. Four PVL-positive patients and no PVL-negative cases developed pleural effusion during their hospital stay (table 2).

The only noteworthy haematological finding was the trough leucocyte count, which was lower in PVL-positive patients than in PVL-negative patients. The peak leucocyte count was higher in PVL-negative patients, but the difference was not significant (table 2).

The *S aureus* isolates from the PVL-positive patients and PVL-negative patients did not differ with regard to the frequency of production of superantigenic toxins (11/16 *vs* 32/36, p=0·11; data not shown). No superantigenic toxins at all were detected in five of the PVL-positive strains or in five of the 36 PVL-negative strains. Meticillin resistance was detected in a single PVL-positive isolate and in 11 PVL-negative isolates. Most of the PVL-positive isolates did not belong to the same clone, as shown by pulsed-field gel electrophoresis (figure 1). However, strains from case 1 (from Lyon) and case 12 (from Paris) were highly related, with only a single band difference between the two pulsotypes.

Two patients with PVL-positive infections died immediately after admission, before mechanical ventilation or antibiotic administration. 12 PVL-positive patients and 21 PVL-negative patients required mechanical ventilation (p=0·25). Eight PVL-positive patients and 12 PVL-negative patients were intubated within 24 h of hospital admission.

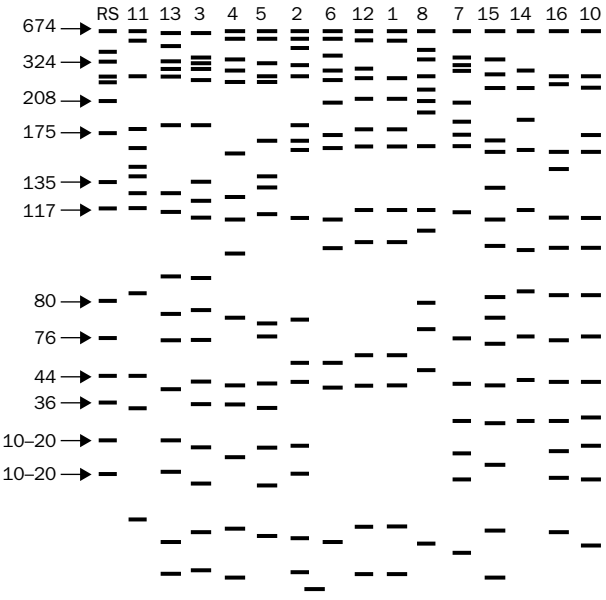
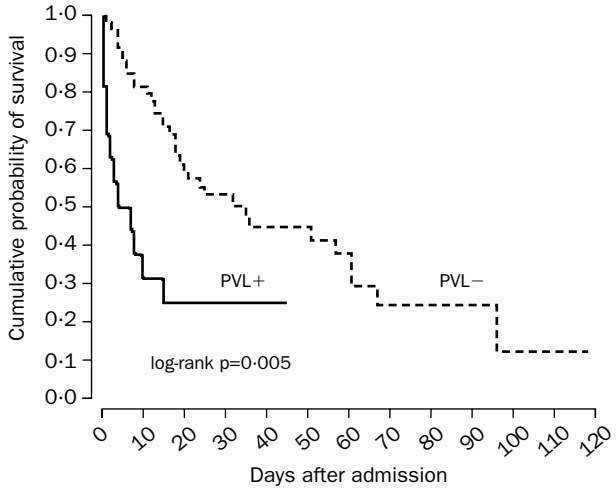


Figure 1: **Schematic representation of pulsed-field gel electrophoresis patterns of PVL-positive isolates**

Each strain number corresponds to one patient except for RS, which corresponds to the PVL-negative reference strain (NCTC 8325). One of the PVL-positive isolates (from case 9) could not be processed despite repeated attempts and is not included in the present figure. Fragment size (kb) is indicated on the left of the figure.



Numbers at risk

PVL+	13	5	2	0							
PVL−	36	26	14	6	4	4	3	2	2	1	1	0

Figure 2: **Survival of patients with *Staphylococcus aureus* pneumonia according to PVL genotype**

31 of the 36 patients infected by PVL-negative *S aureus* and 14 of the 16 PVL-positive patients received empirical antibiotic therapy (p=1·0), usually within the first 24 h after admission to hospital (p=0·40). This empirical treatment was active on the isolated *S aureus* in 13 PVL-positive patients and in 21 PVL-negative patients (p=0·49).

The mean follow-up period was 9·7 days (SD 12·0) in the PVL-positive patients (10·5 days [15·9] for the retrospective patients and 8·9 days [7·4] for the prospective patients, p=0·44), and 24·5 days (25·4) in the PVL-negative patients (p=0·03). The crude lethality rate was 75% (12 patients) in the PVL-positive group (six of eight retrospective and six of eight prospective patients), and 47% (17 patients) in patients with pneumonia caused by PVL-negative *S aureus* (p=0·11). Ten PVL-positive patients who died rapidly developed acute respiratory distress syndrome characterised by deterioration in pulmonary function with refractory hypoxaemia (median ratio of partial pressure of oxygen in arterial blood to fractional concentration of oxygen in inspired gas [PaO_2/FiO_2]=41) accompanied by multiorgan system failure despite aggressive therapy.

The survival rate 48 h after admission was 62·5% in the PVL-positive group and 94% in the PVL-negative group; median survival was 4 days in PVL-positive patients and 25 days in PVL-negative patients (figure 2). Among the patients who died, the interval between admission and death was 4·3 days (SD 4·8) in the PVL-positive group and 11·0 days (6·9) in the PVL-negative group (p=0·007). When the analysis was restricted to patients with no underlying diseases (16 PVL-positive and 11 PVL-negative individuals), the lethality rate was 75% (n=12) in the PVL-positive group and 36% (n=4) in the PVL-negative group (p=0·05).

Necropsies were done on three PVL-positive patients. Macroscopically, the tracheal and bronchial mucosae were massively ulcerated, with a grey-white necrotic appearance. The main bronchi contained abundant haemorrhagic sputum. The lungs were diffusely enlarged and solidified, with a congestive haemorrhagic appearance. Microscopically, ulcerations of the respiratory epithelium, which was coated by numerous colonies of gram-positive cocci (figure 3), extended from the larynx to the lobar bronchi. The bases of the ulcers were composed of necrotic tissue devoid of inflammatory cells. The lung parenchyma contained massive alveolar haemorrhage with necrosis of the interalveolar septa and large clusters of gram-positive cocci. Acute alveolitis with

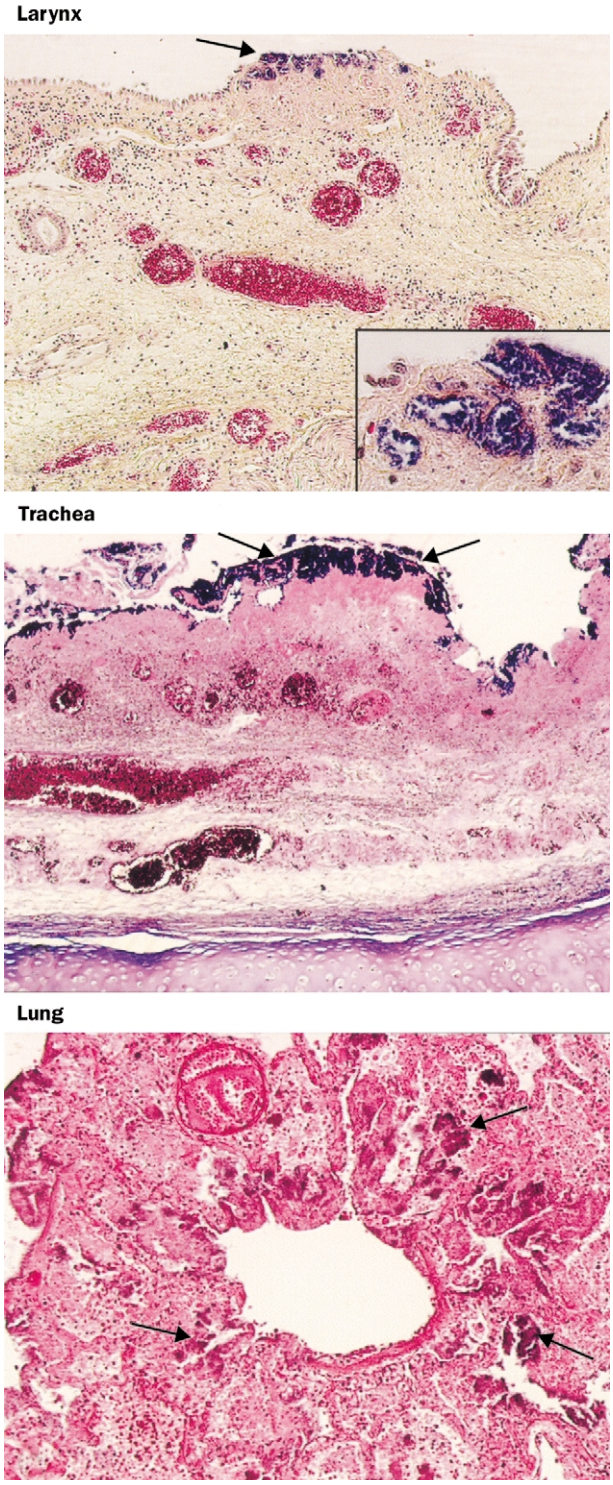


Figure 3: ***Staphylococcus aureus* infiltration of the whole respiratory tract in a patient with PVL-positive *S aureus* pneumonia**

Larynx: small clusters of gram-positive cocci (arrow) are seen on the surface of the laryngeal mucosa. Beyond them, note the zone of mucosal necrosis and haemorrhage. Trachea: the tracheal mucosa is extensively necrotised and haemorrhagic and is coated by clusters of cocci (arrows).
Lung: the lung parenchyma is massively haemorrhagic. The alveoli are filled with erythrocytes and clusters of cocci (arrows).

polymorphonuclear cell infiltration was not seen. The bronchial tree showed massive necrosis of the respiratory epithelium and numerous haemorrhagic foci were present in the lamina propria. There was no parietal infiltration by polymorphonuclear cells or bronchial suppuration.

Discussion

Pneumonia caused by PVL-positive *S aureus* seems to be a specific disease entity with a poor prognosis. It occurs in otherwise healthy children and young adults and is preceded by an influenza-like syndrome. It is characterised by fever, haemoptysis, and leucopenia, and rapidly progresses to acute respiratory distress syndrome. The lethality rate is high. Because of the necrotic histopathological appearance of the lungs, we designate this illness "*S aureus* necrotising pneumonia". The disease is apparently not caused by the spread of a single clone of *S aureus*, as shown by pulsed-field gel electrophoresis (figure 1).

Age influences the survival of patients with pneumonia, and we were unable to age-match cases of PVL-positive and PVL-negative *S aureus* pneumonia. However, we saw strong colinearity between age and the number of underlying disorders (Spearman's correlation coefficient r=0·51, p<0·0001), suggesting that our comparison of survival rates among patients with no underlying disorders would partly control for age. Retrospective and prospective cases were pooled in the PVL-positive group, whereas all data in the PVL-negative group were collected prospectively. We investigated possible time-related memory or information bias by studying the relation between time since recruitment and clinical features. No interaction was significant (except for haemoptysis), suggesting that information concerning PVL-positive individuals was not biased by faulty recall (data not shown). Additionally, the mean follow-up period and the mortality rate were not significantly different between retrospective and prospective PVL-positive individuals.

The biological and clinical peculiarities of *S aureus* necrotising pneumonia could be directly due to PVL rather than superantigenic toxins. We compared the clinical features listed in table 1 for strains of PVL-positive *S aureus* with and without additional superantigen loci, and obtained exactly the same characteristics for both groups (data not shown). Together with the observation that five of 16 PVL-positive strains did not produce any superantigen, this finding could rule out a primary role for superantigenic toxin in the pathogenesis of the disease.

PVL, together with γ haemolysin and other leukocidins such as LukE–LukD, belongs to the family of bicomponent SYNERGOHYMENOTROPIC TOXINS.[12,13] All of the toxins of this family contain two synergistically acting proteins designated S and F. PVL is encoded by two contiguous and cotranscribed genes, *lukF-PV* and *lukS-PV*,[14] carried on a bacteriophage. Different PVL-positive strains of *S aureus* have been shown to carry different phages.[15–17] At least one of the PVL-carrying phages (ϕSLT) can be liberated and is capable of infecting PVL-negative *S aureus* strains, which then acquire PVL expression.[17] Leukocidins act as activators of human neutrophils before creating lytic pores sensitive to monovalent cations.[18] The active PORE-FORMING TOXIN is assembled from two components, which are separately secreted by the bacteria as water-soluble molecules rich in β-sheet structure.[19] As for the γ haemolysins, attack on the cellular membrane begins with the recognition of a specific receptor by one of the soluble molecules (LukS). Polymorphonuclear leucocytes and monocytes can bind tens of thousands of LukS molecules specifically at high affinity.[20] Incorporation of the second component, LukM, and oligomerisation leads to formation of a β-barrel molecular complex perpendicular to the plane of the membrane, creating a pore rather similar to that made by α haemolysin.[21] Purified PVL induces a pronounced release of histamine from human basophilic granulocytes, and of enzymes such as β glucuronidase and lysozyme, chemotactic components such as leukotriene B4 and interleukin 8, and oxygen metabolites from human neutrophilic granulocytes.[22] It induces severe inflammatory lesions when injected intradermally in rabbits, leading to capillary dilation, chemotaxis, polymorphonuclear infiltration, polymorphonuclear karyorrhexis, and skin necrosis.[6,23]

An essential step in the establishment of infection is attachment of the staphylococci. Viral culture was not attempted in the present cases, but an initial viral lung infection could have led to desquamation of ciliated and secretory cells, permitting bacterial adhesion to basal epithelial cells, as has been shown for *Streptococcus pneumoniae* adhesion after infection of mice by influenza virus.[24] Influenza is commonly complicated by *S aureus* pulmonary infection.[25] Moreover, in-vitro studies showed that *S aureus* adhered mainly to poorly differentiated airway epithelial cells, thus confirming its tropism for injured and remodelled airway epithelium.[26] The possibility that our PVL-positive strains that caused necrotising pneumonia harbour specific adhesins for the respiratory epithelium is currently under investigation.

The steps following adhesion are multiplication of the bacteria and toxin secretion. In the three patients who died and on whom we did necropsies, there was a high density of gram-positive cocci adhering to the epithelium, extending from the larynx to the lobar bronchi. This finding suggests that the pathogenesis of the necrotising pneumonia was due not only to toxin production but also to in-situ multiplication of the bacteria.

PVL could be a direct cause of the leucopenia seen in our patients with *S aureus* necrotising pneumonia because of its leucocytotoxic action.[27] Its proinflammatory effects and its potent lytic activity towards attracted granulocytes seen in vitro could participate in the creation of the massive haemorrhage and necrosis in the lung parenchyma and the extensive necrotic ulceration of the tracheobronchial mucosa seen in the PVL-positive group. These aspects mimic the skin necrosis seen when purified PVL is injected intradermally in rabbits.[6,23]

Purulent expectoration is rare in paediatric pneumonia,[28] by contrast with adult pneumonia, and was significantly more frequent in the PVL-negative group (p=0·0001). This difference could be due to the greater age of these patients and possibly to the infiltration of alveolar spaces and interalveolar septa by polymorphonuclear cells—a typical feature of classic *S aureus* pneumonia.[29] No inflammatory cells were seen in the bronchial and parenchymal lesions of PVL-positive *S aureus* necrotising pneumonia, perhaps because of the cytotoxic properties of PVL.

S aureus necrotising pneumonia does not correspond to the staphylococcal pleuropneumonia that was common in children in developed countries from the early 1950s to the mid-1960s. About 75% of cases of staphylococcal pleuropneumonia were seen in infants younger than 1 year; additionally, haemorrhagic sputum was absent and leucopenia uncommon.[28] As in *S aureus* necrotising pneumonia, radiography usually showed extensive bilateral pneumonia, often associated with pleural effusion; pneumothorax or pyopneumothorax was seen in more than 40% of patients (none of our patients had

pneumothorax) and pneumatoceles in 85% (no cases of pneumatocele were seen in our PVL-positive group). Additionally, the mortality rate was about 10% in staphylococcal pleuropneumonia, compared with 75% in our study. Since the late 1960s, staphylococcal pleuropneumonia has been unusual in developed countries.[28]

Individual cases of fatal *S aureus* pneumonia with clinical features similar to those of our PVL-positive group have been reported,[30–33] but the presence of PVL was usually not investigated. Some of these reported cases were associated with focal skin infection (as in three patients in our PVL-positive group, table 1), suggesting a haematogenous spread of *S aureus* to the lungs;[32] other reports suggested airborne transmission, as in most of our patients.[30,31] Since the present study, 13 other cases of necrotising pneumonia have been recognised in our laboratory (one from Germany and 12 from France). In 1999, four paediatric deaths from community-acquired meticillin-resistant *S aureus* infection were reported in the USA;[34] three patients developed rapid respiratory failure and the clinical data correspond to those of *S aureus* necrotising pneumonia. The corresponding strains were analysed in our laboratory and were found to carry the PVL locus (data not shown). Only one of the 16 PVL-positive isolates in our study was resistant to meticillin. In the wake of the 1918 influenza epidemic in Camp Jackson, SC, USA, a similar fulminating clinical course was reported for 385 soldiers who died, and *S aureus* was isolated from 153 post-mortem lung cultures.[35] That the severity of these cases of pneumonia was caused by PVL-producing strains is a tempting hypothesis that remains to be explored.

Our 36 cases of PVL-negative pneumonia resemble non-specific *S aureus* pneumonia,[1] which occurs in older adults (age 60 years or older), is generally severe, and is frequently superimposed on underlying diseases.[3,4] The mortality rate is always high, despite the availability of effective antibiotics.[3]

In conclusion, PVL-positive strains of *S aureus* can complicate influenza-like illness in otherwise healthy children and young adults, with rapid progression to severe pneumonia with haemoptysis and leucopenia. Although the comparison of the disease manifestations after infection with PVL-positive or PVL-negative *S aureus* is complicated by the difference in age of the typical patients, we note that the younger and previously healthier group are more at risk of death than their elderly and infirm counterparts.

Contributors

J Etienne, F Vandenesch, D Floret, and Y Piémont were responsible for the conception and overall coordination of the study and for drafting of the paper. Y Gillet, B Issartel, G Lina, and M Bes did the data collection, data assessments, collation, and interpretation. P Vanhems provided statistical input to the design, data analysis, interpretation, and writing of the paper. J-C Fournet and N Brousse collected and described the pathological data. All investigators revised the report and agreed to its final form.

Conflict of interest statement

None declared.

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Clinical picture

Fahr's disease

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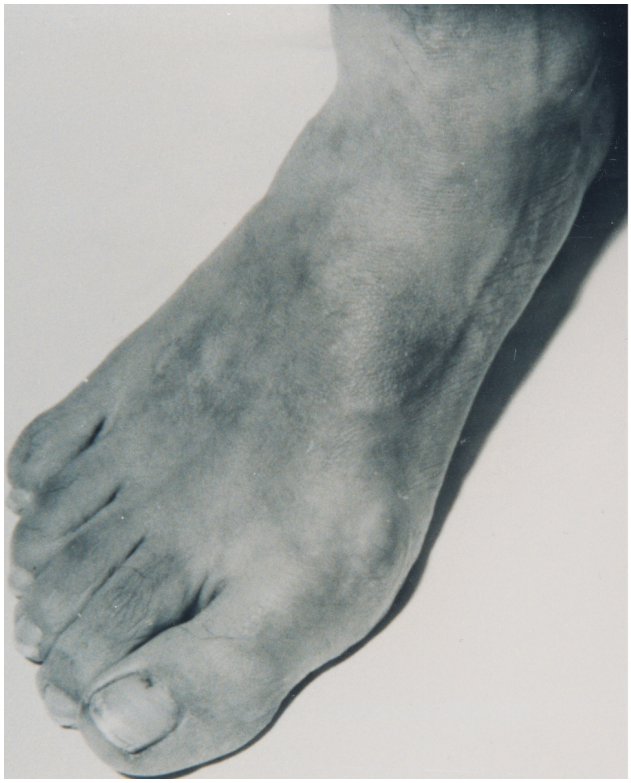

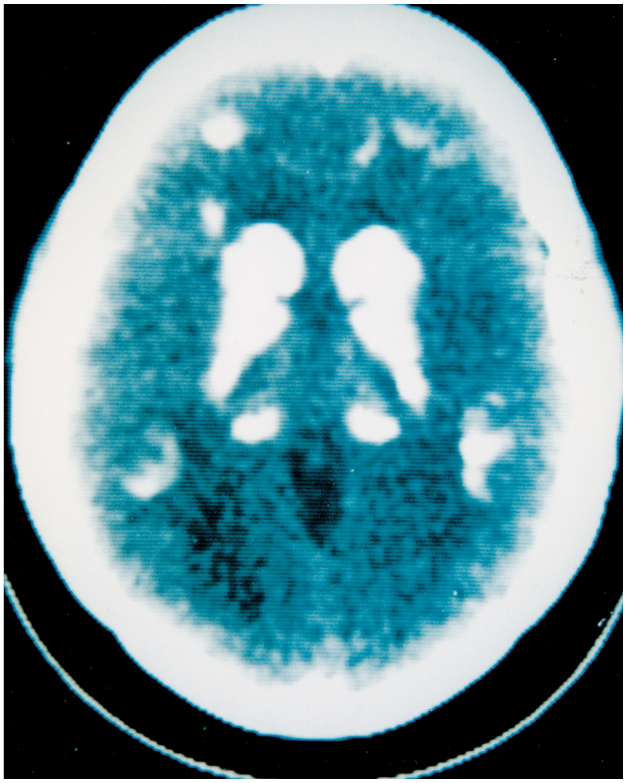

A 35-year-old white man was admitted with generalised tonic-clonic seizures. He had short stature, plethoric facies, shortened metatarsals (figure, left) and metacarpals. Blood tests showed hypocalcaemia, hypomagnesaemia, hyperphosphataemia, high serum parathyroid hormone, and normal serum creatinine, the combination of which suggested pseudohypoparathyroidism type I. Cerebral computed tomography showed symmetrical dense calcifications in the subcortical white matter of the frontal and parietal lobes and in the basal ganglia (figure, right).

Fahr's disease is a neurodegenerative syndrome that is associated with symmetric, intracerebral calcifications in the basal ganglia and adjacent parenchyma, and with neuropsychological, cognitive and movement disorders. It can be idiopathic or associated with endocrinopathy, frequently with parathyroid disorders.

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