EXPERT REVIEWS

Pathogenesis of *Staphylococcus aureus* necrotizing pneumonia: the role of PVL and an influenza coinfection

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Only recently necrotizing pneumonia was defined as a specific disease entity that is caused by a Panton-Valentine leukocidin (PVL)-producing *Staphylococcus aureus* strain and is frequently preceded by an influenza infection. Necrotizing pneumonia is characterized by a sudden onset and rapid worsening of symptoms, leukopenia, airway hemorrhages, severe respiratory failure and a high mortality rate. Despite clear epidemiological data, the function of PVL in necrotizing pneumonia has been controversially discussed due to conflicting results from different disease models. Furthermore, there are many proposed mechanisms how a viral infection could facilitate and interact with a bacterial superinfection. In this review, we summarize current data from 43 clinical cases and results from various infection models on necrotizing pneumonia. We discuss the contribution of *S. aureus* PVL and a preceding influenza infection and present a concept of the pathogenesis of necrotizing pneumonia.

Keywords: bacterial superinfection • influenza • lung alveolar destruction • necrotizing pneumonia • *Staphylococcus aureus* PVL

Staphylococcus aureus necrotizing pneumonia is described as a highly lethal infection that mainly affects healthy children and young adults and is associated with *S. aureus* strains producing the pore-forming toxin Panton-Valentine leukocidin (PVL). PVL is composed of two subunits, the LukS-PV and the LukF-PV proteins encoded by the *pvl* genes that have been integrated into the chromosome of methicillin-sensitive (MSSA) or -resistant *Staphylococcus aureus* (MRSA) [1]. Current clinical knowledge of necrotizing pneumonia is mainly based on a series of worldwide case reports. In general, previously healthy children or young adults initially present with influenza-like symptoms that rapidly worsen to respiratory failure and septic shock. If therapy is not started early, mortality rates are very high. Post-mortem examinations of the lung usually reveal hemorrhagic necrosis and destructions of wide lung areas [2]. PVL-associated necrotizing pneumonia can be distinguished from other forms of *S. aureus*-caused pneumonias, which are much more frequent. PVL-negative strains generally induce a 'classical' *S. aureus* pneumonia, which is less fulminant, occurs in older adults (age ≥60 years), is frequently superimposed on underlying diseases and has lower mortality rates [2,3]. *S. aureus* is estimated to cause 1–10% of community-acquired pneumonias and 20–50% of nosocomial pneumonias [4].

In the last decades, there was a dramatic increase in the infection rate with community-associated methicillin-resistant *S. aureus* strains (CA-MRSA) that carry the genes for PVL. Particularly, the MRSA strain USA300 has widely spread in North America and also in some areas of Europe [5]. In Europe, there is a much higher genetic diversity among the CA-MRSA strains, but the predominant clone is the European ST80 [6]. These CA-MRSA strains often cause a more severe disease such as deep skin infections. In the USA, the high prevalence of PVL-positive CA-MRSA is

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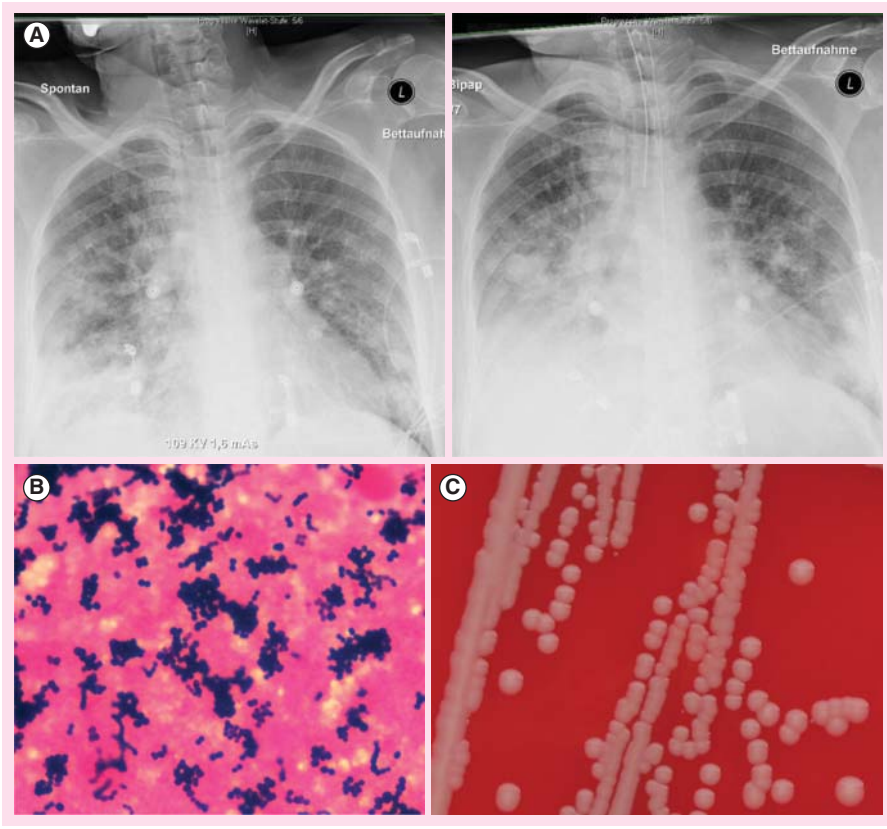

Figure 1. Clinical case of necrotizing pneumonia from a 58-year-old woman.
(A) Radiographs show severe bilateral infiltrations upon submission that rapidly increased in the following hours. **(B)** Tracheal secretion with massive infiltration of immune cells and overgrowth with staphylococci. **(C)** Panton-Valentine leukocidin (PVL)-positive *Staphylococcus aureus* strain that was recovered from tracheal secretion and blood cultures showed hardly any hemolysis on agar plates.

mostly responsible for necrotizing infections, whereas in Europe the majority of cases of necrotizing pneumonia are caused by PVL-positive methicillin-susceptible *S. aureus* strains that are as virulent as the PVL-positive CA-MRSA clones [3,7].

Although a clear epidemiological association between PVL-positive *S. aureus* strains and necrotizing pneumonia has been shown [2,3,8], some authors doubt the role of PVL in disease development, as there are conflicting results particularly from different murine infection models. They suggest that the presence of the PVL genes is not a major virulence factor and that PVL is only a marker of other more relevant virulence factors [9–11].

The scope of this article is to review current data from 43 clinical cases and results from various infection models on necrotizing pneumonia. We discuss the contribution of *S. aureus* PVL and a preceding influenza infection and present a concept of the pathogenesis of necrotizing pneumonia.

A clinical case of necrotizing pneumonia & description of the typical symptoms and treatments

Only recently, a clinical case of necrotizing pneumonia occurred at our University Hospital in Münster: A 54-year-old woman with a medical history of hypertension and coronary artery disease presented to her primary-care physician with nausea, emesis, fever and cough since 8 days. Suspecting a respiratory tract infection, she received antimicrobial treatment with amoxicillin. Her condition rapidly worsened in the course of 2 days and she was admitted to the University Hospital in critical condition. On admission to the intensive care unit, the patient was hypotensive (blood pressure 90/40 mm Hg with a frequency of 125/min), obtunded and in respiratory distress (p/F-index ~1.1 [MK3]). Laboratory investigation found arterial lactate levels of 3 mmol/l, severe hyperglycemia at 744 mg/dl with metabolic acidosis, renal failure and a marked elevation of inflammatory markers (CRP 53, PCT 33, leucocytes 7.45 [MK4]). Radiography of the chest showed large bilateral pneumonic infiltrations (Figure 1A). A diagnosis of septic shock with moderate ARDS secondary to suspected pneumonia was made. Tracheal secretions and blood cultures were taken for microbiological testing. Antimicrobial therapy was started with piperacillin/tazobactam and ciprofloxacin. Due to deteriorating respiratory function despite non-invasive ventilation, the patient had to be sedated and mechanically ventilated after tracheal intubation (Figure 1A). First microscopic analysis of the tracheal secretion revealed a huge accumulation of immune cells and massive overgrowth with staphylococci (Figure 1B). Tracheal secretions and blood cultures yielded a PVL-positive MSSA strain, showing hardly any hemolysis on agar plate (Figure 1C). Therefore, the antibiotic therapy was changed to flucloxacillin, meropenem and clindamycin. Additionally, the tracheal secretion was tested positive for influenza A. Due to the progressive deterioration of respiratory function into severe ARDS (p/F-index >0.9, respiratory acidosis with $paCO_2$ >90 mm Hg), extracorporal membrane oxygenation was started on the second day of therapy. During this phase of the disease, a marked leukopenia of 2560/ml and thrombopenia of 21000/ml was observed. Despite aggressive measures, the patient did not improve and died of multiple organ failure secondary to septic shock after 10 days in the intensive care unit.

This patient showed many symptoms typically associated with necrotizing pneumonia. Initial symptoms often mimic an influenza infection, with dyspnea, cough, fever, muscle pains and unspecific symptoms, like nausea and vomiting (Table 1). After several days, the situation suddenly worsens and patients become critically ill. In many cases of influenza and PVL-positive *S. aureus* coinfection, like in the patient described

Table 1. Forty three clinical reports of necrotizing pneumonia with or without a preceding influenza infection.

Viral coinfection	Number of cases	Number of cases with confirmed PVL-positive *Staphylococcus aureus*	Survival rate
Total number of cases	43	37 (86%)	20 (46.5%)
Confirmed viral coinfection (influenza A and B, respiratory syncytical virus, human metapneumovirus, parainfluenza type 1 and 3)	12 (2 of these patients showed unspecific symptoms as well)	9	7 (58.3%)
Suspected viral coinfection (fever, dry cough)	16 (7 of these patients showed unspecific symptoms as well)	16	6 (37.5%)
Only unspecific symptoms (nausea, vomiting, diarrhea, fatigue)	3	2	1 (33.3%)
Viral coinfection not reported	12	10	6 (50%)

The cases with the references [59–92] were analyzed for a viral coinfection. The mortality rates are given for each group. The mean age was 24.7 ± 21.5 years.
PVL: Panton-Valentine leukocidin.

above, low leukocyte counts can be found that appear to be linear predictors of lethal outcome [3,12]. Leukopenia could be directly caused by the cytotoxic action of PVL while we cannot rule out the participation of influenza and systemic inflammatory response syndrome. Hemoptysis or airway hemorrhages at this stage of disease have been defined as further negative prognostic criteria, as they most likely reflect the degree of lung damage [3]. Mortality rates of necrotizing pneumonia are usually high and vary between 40 and 60% [2]. In the 43 reviewed cases, 23 of the patients died (53.5%) (Table 1). Cure of the infection has been reported particularly when therapy was started early before the patients enter into a lung-destructive or septic stage [13]. The best treatment of this specific disease entity has not been clearly defined [14]. Anti-staphylococcal therapy is mostly performed with compounds, such as vancomycin, linezolid or flucloxacillin, in combination with clindamycin or rifampicin that are known to decrease production of staphylococcal exotoxins. A beneficial and toxin suppressing effect has been reported for linezolid, as well [15,16]. As the disease is supposed to be mainly toxin-mediated, an additional approach is targeted at toxin production with anti-toxin antibodies, for example, via intravenous immunoglobulin containing anti-PVL antibodies. Yet, clinical data are still required to prove and guide this therapy [14,17,18].

From the first described cases to a specific disease entity

The association of *S. aureus* with fatal pneumonia during influenza seasons is not a new phenomenon [19]. *S. aureus* superinfections probably accounted for a big part of the mortality in the influenza pandemic, such as the 1918–1919 'Spanish flu' pandemic or the 1957–1958 'Asian influenza' pandemic, when *S. aureus* was the commonest bacterial respiratory pathogen [20,21]. Already in 1919, clinicians reported that patients suffering from coinfections associated with *S. aureus* were 'extremely prostrated almost from the onset of their symptoms' and that 'the course of the disease is extremely rapid'. Furthermore, characteristic symptoms that could be indicative of necrotizing pneumonia were described, for example, leukopenia, diffuse and confluent bronchopneumonia involving wide areas of the lung in x-ray analysis, hemoptysis and massive accumulation of cocci in the sputum [12]. In the following decades, important *S. aureus* virulence factors, including hemolysins and leukocidins, were analyzed and associated with disease developments. The *S. aureus* exotoxin PVL is named by Wright [22] in 1936 on Sir Philip Noel Panton and Francis Valentine, who in 1932 described its involvement in severe soft tissue infections [23]. It became more and more clear that from the numerous *S. aureus* bi-component toxins that consist of type S and F proteins PVL was the most potent inducer of inflammation and dermonecrosis [24]. In 1999, Lina *et al.* screened a collection of clinical *S. aureus* isolates for PVL genes and found that PVL was not only associated with deep skin infections but also with severe forms of primary community-acquired pneumonia with hemorrhagic and necrotic features. From this epidemiological study, they drew the conclusion that PVL is a possible virulence factor associated with necrotic lesions and they also mentioned that 'typical patients had a predisposing viral infection' [8]. Three years later, in 2002, Gillet *et al.* described the characteristics of necrotizing pneumonia on eight retrospective and eight prospective clinical cases. Necrotizing pneumonia was defined as a separate disease entity caused by PVL-producing *S. aureus* strains and being distinct from pneumonia of PVL-negative strains. Because of the necrotic histopathologic appearance of the lungs, the illness was named '*S. aureus* necrotizing pneumonia' [2]. In 2007, a much larger clinical study with 50 cases of necrotizing pneumonia followed analyzing disease courses, typical symptoms and risk factors predictive for lethal outcome. From this study, the authors conclude that airway bleeding and leukopenia are associated with fatal outcome [3]. In subsequent years, additional clinical reports on single cases and therapeutic approaches were

published that reinforce the severe clinical courses and high mortality rates. The clinical reports of *S. aureus* necrotizing pneumonia that were found in PubMed in English language are summarized in Table 1.

The role of PVL in necrotizing pneumonia

Despite the epidemiological data, some authors doubt the pathogenic role of PVL and suggest the presence of PVL genes to be only a marker of other more virulent determinants [9,10]. The underlying reasons are contradictory results from various infection models on necrotizing diseases. Using different species for their models, some groups could demonstrate a pathogenic function of PVL [25,26], whereas other groups failed to detect an effect of PVL, but proposed other factors, such as α-hemolysin, phenol-soluble modulins, enterotoxins like toxin X and protein A, as responsible agents [9,11,27–29].

These discrepancies can be partly explained by the strong cell- and species-specificity of PVL. PVL exerts pro-inflammatory and cytotoxic effects on neutrophils, monocytes and macrophages. Incubation of the cells with only low doses of PVL (0.04–0.4 μg/ml; 1–10 nM) results in inflammasome activation and induces a huge IL-1β release within minutes [30,31]. Cell activation is followed by rapid cell death induction (within 20 min) that is mainly caused by pore-formation and largely lacks apoptotic features. These inflammatory and cytotoxic effects are not only strongly cell-specific and restricted to cells derived from the granulocyte precursor line, but also very species-specific [32,33]. Cells originating from humans and rabbits are highly sensitive toward PVL, whereas cells isolated from various mice strains or monkeys are largely resistant toward PVL, even when PVL is applied at 1000-fold higher doses. This strong target cell- and species-specificity can be explained by the binding mechanism of LukS-PV to the C5a complement receptors that has been identified only recently [34]. Other staphylococcal virulence factors, for example, the phenol-soluble modulins, do not exhibit this species-specificity, but act on cells from different species equally [32]. Consequently, murine or even simian models are not always adequate to investigate *S. aureus* virulence for humans. Particularly to study the role of PVL, more complex models based on cells from human origin or from sensitive organisms, like rabbits, are required [25,35].

The detrimental effect of PVL on lung tissue cannot be directly explained, as the strong pro-inflammatory and cytotoxic actions of PVL are apparently restricted to granulocytes, monocytes and macrophages, whereas PVL has no effect on lung cells, such as epithelial and endothelial cells [32,35]. These findings point to an indirect impact of PVL on tissue integrity via rapid destruction of granulocytes. Neutrophil granulocytes are the first cells recruited to inflammatory sites and form the earliest line of defense against invading microorganisms such as influenza and *S. aureus*. They contain serine proteases and other aggressive compounds stored in large quantities in granules that are intended to help degrade engulfed microorganisms inside phagolysosomes [36,37]. In case of an infection with a PVL-producing *S. aureus* strain, PVL-induced cell death is rapid and largely lacks apoptotic features [32]. As necrosis is an uncontrolled way of cell death, the potent antimicrobial molecules spill within the host tissue and cause tissue damage. The involvement of granulocytes in tissue damage was already shown in a rabbit model of necrotizing pneumonia, as neutropenic rabbits did not develop severe lung damage upon installation of PVL in the lungs [25]. Only recently, this mechanism could be reproduced in a murine model, where PVL-treated human neutrophils induced severe tissue damage when infiltrated in the lungs of mice [35]. Consequently, a massive and uncontrolled death of neutrophils with release of aggressive enzymes is a very unfavorable situation for the organism that needs to be confined. The serum contains various compounds, for example, α1-antitrypsin, that rapidly inactivate neutrophil proteases. Although the surfactant in the lung contains some protease inhibitors [38], the protective activity is apparently not sufficient in the alveolar spaces. Therefore, proteases released by uncontrolled dying neutrophils can cause disruption of the sensitive alveolar tissue structures resulting in necrotizing pneumonia.

The role of a preceding virus infection in necrotizing pneumonia

The major epidemiological studies on the causative factors for necrotizing pneumonia revealed that a preceding influenza infection is a very common feature [2,3,8]. This association was further supported by individual case reports. From the 43 reviewed cases in 12 patients, an influenza infection could be confirmed and 16 patients featured typical symptoms of influenza (Table 1). As the symptoms of a virus infection are not always clear and obvious and can be also unspecific, this represents a high rate of documented or suspected viral coinfections. It was also remarkable that in 12 clinical cases, as well as in our described case, unspecific symptoms, including nausea, vomiting, diarrhea or bowl inflammation, have been reported (Table 1). These symptoms are rarely described in a 'classical' *S. aureus* pneumonia, but have been more commonly found in influenza infections, for example, during the swine influenza (H1N1) pandemic that began in 2009 [39]. It remains unclear, if there is a direct effect of viral infections on the gastrointestinal system, or if influenza predisposes to increased frequency of bacterial bowl inflammation, such as appendicitis.

Viral factors that contribute to the outcome of severe pneumonia are particularly changes and dynamics in influenza virus protein expression varying between different strains. Strain-specific sequence variations of virulence factors, such as the non-structural proteins NS-1 and PB1-F2, are responsible for differences in cellular responses. The latter protein is not expressed by each influenza virus strain, but is often connected with pneumonia [40]. In context of the onset of severe secondary pneumonia cellular mechanisms including the induction of apoptosis upon influenza virus infection regulated by NS-1, PB1-F2 and the ion-channel protein M2 are discussed [41,42]. Furthermore, influenza viruses are able to manipulate

apoptotic and immunomodulatory cellular mechanisms and to take advantage of apoptosis to support their replication [40]. Especially influenza virus-induced tissue damage is considered as major cause to pave the way for infection with bacterial pathogens [41,42].

To evaluate the impact of a preceding influenza infection in *S. aureus* pneumonia, different coinfection models have been performed that propose a number of mechanisms of pathogen–pathogen and host–pathogen interactions. There is some evidence that influenza virus and bacteria promote the infection process of each other, for example, viral infection enhances bacterial binding and invasion of lung cells [43] and some *S. aureus* strains secrete proteases that cleave and activate virus hemagglutinin and in this way enhance influenza virus replication, infectivity and pathogenicity [44,45]. Regarding host defense, it was demonstrated that pulmonary virus infections can impair the immune system and promote secondary pulmonary infections. An important mechanism is that pulmonary IFN-I produced by T cells during an influenza infection disrupt defense against bacteria, for example, by inhibiting clearance of alveolar macrophages and by impairing the natural killer cell responses [46,47]. The multiple interactions between pathogens and host can be very strain specific and probably differ between epidemics and geographical regions, which needs to be considered particularly for vaccine developments [41,42].

Another critical pathogenic factor can be the exacerbated pulmonary inflammatory situation in the lung during bacterial superinfection of influenza [48]. It is well known that influenza virus is a strong pro-inflammatory stimulus in the lung. The cytokine release induced by an influenza infection causes influx of immune cells, including neutrophils, monocytes and macrophages, to lung tissue [49,50]. Although cytokine responses are essential during immune responses to influenza pneumonia, an overly aggressive and dysregulated cytokine release, known as a 'cytokine storm', has been associated with influenza-related morbidity and mortality [51,52]. If a lung that is massively infiltrated with immune cells is superinfected by a PVL-producing *S. aureus* strain, lysis of recruited immune cells by PVL can be expected at a large scale resulting in necrotizing pneumonia (Figure 2).

Expert commentary & concept of the pathogenesis for necrotizing pneumonia

Necrotizing pneumonia was defined as a separate disease entity based on the severe clinical symptoms that differ from the 'classical' pneumonia caused by PVL-negative *S. aureus* strains. Main characteristics and typical symptoms of necrotizing pneumonia are a preceding influenza infection, sudden onset and rapid worsening of the symptoms, leukopenia, airway hemorrhages, severe respiratory failure, a high mortality rate and necrotic destruction of wide areas of the lung [2,3]. Despite a large amount of epidemiological data that show a clear association between PVL and the clinical picture of necrotizing pneumonia, the role of PVL in disease development has been doubted, due to negative results from murine or simian experimental models [9,11,27,28]. As the inflammatory and cytotoxic actions of PVL are largely restricted to neutrophils, monocytes and macrophages isolated from humans and rabbits [32], appropriate model systems are required to study the role of PVL in clinical disease development. Rabbit models and experiments based on human cells provide strong evidence that PVL exerts a destructive effect that causes necrotizing pneumonia [25,35].

For experimental, clinical and epidemiological studies, a clear differentiation between PVL-induced necrotizing diseases and other *S. aureus* infections is crucial, as different *S. aureus* virulence factors are involved in disease developments. In a 'classical' *S. aureus* pneumonia, a large set of virulence factors, such as toxins, adhesins, enzymes and immunomodulators have been proposed to contribute to induce an infection [53,54]. By contrast, necrotizing infections are most likely toxin-mediated diseases caused by the cytotoxic action of PVL on immune cells (Figure 2). As PVL is a very potent activator and cytotoxic factor for human neutrophils, monocytes and macrophages, lung destruction can be explained by an indirect effect of dying immune cells on tissue structures. Neutrophils contain large amounts of serine proteases stored in vesicles that are released uncontrolled upon PVL-induced cell death in the surrounding tissue. Particularly in lung tissue this mechanism can cause massive tissue destruction, as there is insufficient activity of protease inhibitors in the alveolar spaces. Consequently, lung tissue is vulnerable to PVL-mediated diseases, whereas PVL and its action are rapidly inactivated within serum via the protease inhibitors and antibodies against PVL. The inactivation of PVL by serum antibodies might also account for the observation that a previous skin and soft-tissue infection is associated with improved prognosis in necrotizing pneumonia [3,55] and that preferentially young patients are affected by PVL-mediated diseases. The mean age in our reviewed cases was 24.7 years, ranging from newborn to 74 years (Table 1). The reason for this might be that young patients are less likely to have developed a protective antibody titer against PVL than older patients [35].

Under the terms of this concept the detrimental effect of PVL is dependent on the number of sensitive immune cells that are affected. In case of a preceding influenza infection, the lung can be strongly infiltrated with activated inflammatory cells [49,50] that contain large amounts of proteases and additional active compounds [56]. As low doses of PVL are already sufficient to cause cell death, a superinfection with a PVL-producing strain can induce massive activation and destruction of infiltrated granulocytes, monocytes and macrophages that discharge their granular content and overrun the neutralizing capacity in the lung resulting in necrotizing pneumonia (Figure 2). An earlier influenza infection is documented or suspected in many cases of necrotizing pneumonia. In several clinical cases, it was reported that different types of viral infections, such as respiratory syncytial virus or parainfluenza virus, precede necrotizing pneumonia.

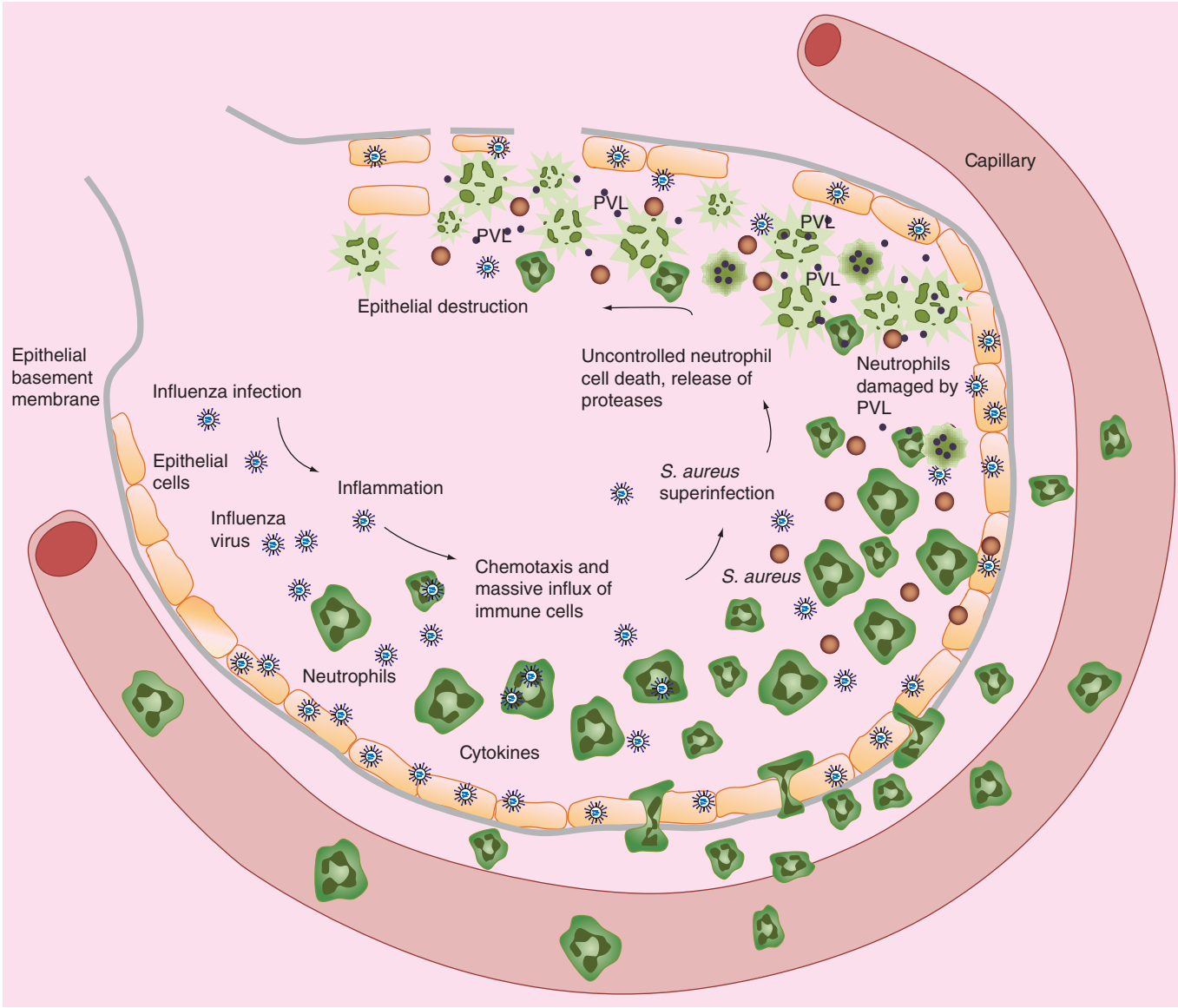

Figure 2. The pathogenesis of necrotizing pneumonia. A viral infection activates lung epithelial cells that release chemokines and induce the influx of immune cells. In case of a superinfection with a PVL-producing *Staphylococcus aureus* strain, PVL rapidly kills the recruited immune cells. Active components such as proteases stored in neutrophils are uncontrolled released in the surrounding lung tissue that can result in massive tissue destruction with the clinical picture of necrotizing pneumonia.
PVL: Panton-Valentine leukocidin.

Sometimes only unspecific symptoms, like nausea or vomiting, are reported that might be indicative of an undetected virus infection (Table 1). These observations support the hypothesis that a virus-induced influx of immune cells rather than a specific virulence factor of influenza virus contributes to necrotizing pneumonia.

Accordingly, necrotizing pneumonia is supposed to be a mainly toxin-mediated disease of the lung. As toxins exert their destructive action quickly and cannot be confined by antimicrobial treatments when released, therapy needs to be started early to prevent severe tissue damage. Therefore, necrotizing pneumonia should be diagnosed, before the disease enters into a septic and lung destructive stage. A young patient that presents with pulmonary or uncharacteristic symptoms, but rapidly worsens and develops dyspnea and leukopenia should be suspected of necrotizing pneumonia. Massive overgrowth of staphylococci in tracheal secretion can quickly support the diagnosis. After samples for microbiological analysis are taken, therapy should be started immediately with an anti-staphylococcal antibiotic in combination with clindamycin to decrease toxin release or even with additional toxin-suppressing agents. If therapy is started early, patients can fully recover without further signs of pulmonary disease [13].

Five-year view

Up to now necrotizing pneumonia is supposed to be a rare disease. Yet, many cases of necrotizing pneumonia might not be correctly diagnosed, as the clinical course proceeds rapidly and is easily misdiagnosed as bacterial sepsis of unknown origin. The reported cases of necrotizing pneumonia are characterized by a severe clinical course often affecting young and otherwise healthy patients. If the correct diagnosis is not made at an early stage, antimicrobial therapy is often inadequate and wide lung areas are already destroyed by the action of toxins. Once this stage of the disease is reached, an effective therapy is almost impossible, accounting for the high mortality rate.

Effective and tested therapeutic agents that specifically act against PVL-mediated diseases are currently not available, but several approaches are under development. In absence of vaccine, polyvalent human immunoglobulin (IVIG) containing antibodies against PVL could be proposed since it inhibits the cytotoxicity of PVL on polymorphonuclear cells *in vitro* [18]. Nevertheless, work from other PVL-related infection models, for example, abscess models, suggests that antibodies to PVL might even contribute to host susceptibility to infection [57]. Furthermore, high levels of antibodies against PVL were not associated with resistance to *S. aureus* skin and soft tissue infection [58]. Consequently, the exact role of PVL antibodies in different types of PVL-related diseases, including necrotizing pneumonia and skin and soft tissue infections, need to be evaluated separately in appropriate model systems.

Only recently, a specific PVL-binding mechanism to human immune cells has been characterized [34], which might open new possibilities for therapeutic strategies. As the binding of PVL to target cell membranes is the critical step for pore formation and cell destruction, intervention at this stage might be very effective to prevent disease development. Nevertheless, these therapies must be started before irreversible destruction of wide lung areas has occurred. The similar susceptibilities of rabbit and human neutrophils to PVL indicate that the rabbit model of necrotizing pneumonia could be used for preclinical development and evaluation of anti-PVL therapeutic approaches. Yet, further clinical trials testing the efficacy of novel anti-PVL therapies (for example, specific monoclonal antibody that neutralizes PVL) in protecting against rapidly progressive necrotizing pneumonia in humans will be required.

In the setting of an influenza pandemic, necrotizing pneumonia might develop into a larger and serious clinical problem. As in the last decades, PVL-positive *S. aureus* clones have widely spread in the USA and other areas of the world, a superinfection with a PVL-expressing *S. aureus* strain in influenza patients might become a frequent situation. Consequently, particularly during influenza seasons an increased rate of necrotizing pneumonia should be expected and considered as possible diagnosis.

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Key issues

- Necrotizing pneumonia is defined as a separate disease entity that is characterized by sudden onset and rapid worsening of the symptoms, leukopenia, airway hemorrhages, severe respiratory failure, a high mortality rate and necrotic destruction of wide areas of the lung.
- Epidemiological studies show a clear association between necrotizing pneumonia and Panton-Valentine leukocidin (PVL)-positive *Staphylococcus aureus* strains. Despite the clear epidemiological data, there are conflicting results on the role of PVL from different disease models that can be partly explained by the strong cell- and species-specificity of PVL.
- PVL is a pore-forming exotoxin that rapidly activates and kills human neutrophils, monocytes and macrophages. The destructive effect of PVL is most likely caused by uncontrolled death of these immune cells that release proteases and other active compounds that are spilled in the surrounding tissue and induce tissue destruction.
- A preceding viral infection is frequently reported and a possible causative factor for necrotizing pneumonia. A number of mechanisms of bacterial–viral interactions have been proposed. In necrotizing pneumonia, a viral-induced influx of immune cells to lung tissue could promote disease development.
- Patients presenting with symptoms of lower respiratory tract infections that rapidly worsen to respiratory failure in combination with leukopenia should be suspected of necrotizing pneumonia. Cure of the infection has been reported particularly when therapy was started early before the patients enter into a lung destructive or septic stage.
- The best treatment of this specific disease entity has not been clearly defined. Therapy should be performed with anti-staphylococcal therapy in combination with clindamycin. Although the mortality rate is high, patients can fully recover without further signs of pulmonary disease.

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