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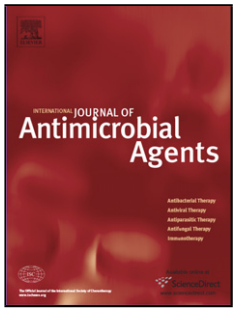

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Pragmatic management of Panton–Valentine leukocidin-associated staphylococcal diseases

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ABSTRACT

Panton–Valentine leukocidin (PVL)-producing *Staphylococcus aureus* is associated with a broad spectrum of diseases, ranging from common uncomplicated soft tissue infections to severe diseases such as complicated soft tissue infections, extensive bone and joint infections, and necrotizing pneumonia. Specialised management of infection based on the presence of PVL may not be required for mild infections, whereas it could be lifesaving in other settings. Moreover, most severe PVL diseases are recently identified entities and a ‘gold standard’ treatment from comparatives studies of different therapeutic options is lacking. Thus, recommendations are based on expert opinions, which are elaborated based on theory, in vitro data and analogies with other toxin-mediated diseases. In this review, we consider the potential need for specialised PVL-based management and, if required, which tools should be used to achieve optimal management.

1. Introduction

Panton–Valentine leukocidin (PVL) is a bicomponent, pore-forming toxin produced by several strains of *Staphylococcus aureus*. PVL was initially associated with necrotic and recurrent skin and soft-tissue infections (SSTIs). Its role in more severe disease, such as PVL-associated staphylococcal necrotizing pneumonia, was not described until the beginning of the 21st century [1–3]. PVL is also a predictive marker for the severity of bone and joint infections (BJIs) [4], deep-seated abscesses and complicated SSTIs (cSSTIs) [5,6]. The concomitant emergence of severe infections due to PVL-producing *S. aureus* and community-acquired meticillin-resistant *S. aureus* (CA-MRSA) initially led to a certain degree of confusion and controversy. The PVL gene, whose product has known necrotic and pro-inflammatory properties, was present in most of the described clones of CA-MRSA [7], yet PVL was not considered a key virulence factor by several authors, who instead focused mainly on meticillin resistance [8]. Nevertheless, various clinical studies and animal models of BJIs and necrotizing pneumonia have confirmed the role of PVL, and it is now accepted that PVL is associated with the severity of disease, independent of meticillin resistance [9,10].

When considering clinical management of PVL-associated infections, it is important to assess the broad spectrum of diseases, ranging from common uncomplicated SSTIs to rare but life-threatening entities such as necrotizing pneumonia [1,2,4–6,11]. Hence, specific management based on the presence of PVL may not be required for mild infections, whereas it could be life-saving for more severe disease. Moreover, although recommendations for the management of PVL-associated disease and/or for CA-MRSA infections have been published by public health

authorities in several countries [12–14], most of these diseases are recently identified entities and a ‘gold standard’ treatment based on comparatives studies of different therapeutic options is lacking. Thus, recommendations are based on expert opinion, which are based on theory, in vitro data and analogies with other toxin-mediated diseases.

In this review, we evaluate the potential need for specific PVL-based management for each disease and, if required, which tools should be used to achieve optimal management.

2. When is Panton–Valentine leukocidin-based management needed?

It is difficult to determine whether PVL-based management is needed because of the lack of comparative studies. Nevertheless, we can assess whether alternatives should be considered when standard management is insufficient or when PVL leads to specific disease defined by a significant difference in symptoms or severity from those induced by non-toxic strains. Thus, the first step should be the clinical identification of PVL-associated infection, followed by identification of the PVL-producing strain, especially because PVL remains rare in the general population in most Western European countries.

3. Diagnosis of Panton–Valentine leukocidin-associated disease

3.1. Clinical suspicion

In areas with a low-to-moderate incidence of PVL-secreting bacteria, PVL infection should be diagnosed on an individual clinical basis and confirmed by laboratory tests, except during outbreaks of PVL-positive *S. aureus* infection. Most of the cases occur in young immunocompetent patients without underlying disease or other conditions favouring staphylococcal infection. Risk factors for acquisition are the same as those for CA-MRSA in the USA. These include compromised skin integrity; all situations of skin-to-skin contact, including contact sports (e.g. wrestling, judo, rugby, and American and Australian football); and sharing of contaminated items (towels) [12,15,16]. Living in close and crowded communities is also a risk factor; outbreaks have occurred in prisons, military camps and colleges [12]. Nevertheless, all of these risk factors are for SSTIs, whereas no risk factors have been identified for more severe disease, including necrotizing pneumonia and BJIs. Close contact with persons who have purulent skin infections prior to the development of infection may indicate the presence of PVL-producing bacteria.

Clinical symptoms are usually characterised by their severity and the presence of necrosis, abscesses and tissue destruction, and are marked by local and general inflammatory symptoms. Lesions are always painful and general reactions such as fever and asthenia are frequent, even when the infection is localised. In severe deep-seated infections, leukoneutropenia may be observed [1,17]. The discordance between high levels of biological inflammation markers (C-reactive protein or procalcitonin) and a normal or low leukocyte count is highly suggestive of PVL bacteria [4].

Primary skin infection of the hair follicle is the most frequent PVL-associated disease [11,18] and usually presents as large skin abscesses, boils or furuncles with large erythema, without an inoculation wound. The sores are often multiple, which may occur through self-inoculation [19]. Necrosis ranging from local to necrotizing fasciitis has been observed, and secondary deep-seated localisations appear to be frequent. Deep abscesses may be localised in subcutaneous tissue, muscle or in various organs such as the kidneys, lungs or bones, and they are often complicated by deep venous thrombosis.

PVL-associated infection should be considered as the cause of BJI in severe cases presenting with high fever, painful lesions and signs of sepsis [4,20]. Multiple sites of infection at admission and aggravation, despite appropriate antibiotics, that lead to local extension (subperiosteal abscesses and/or soft tissue extensions) and metastatic abscesses may indicate infection by PVL bacteria.

Severe diseases such as septic shock or purpura fulminans may be indistinguishable from other bacterial infections [21], and PVL may only be suspected if there is a context of preceding furunculosis in the patient or his close contacts and if bacteriological cultures grow *S. aureus* [22–26].

Staphylococcal necrotizing pneumonia should be evoked before severe extensive pneumonia; it is usually multilobar and preceded by an influenza-like syndrome [1]. Prompt progression to septic shock with acute respiratory distress syndrome (ARDS), initial leukopenia and signs of airway haemorrhage are highly suggestive of

infection with PVL bacteria and are strongly associated with lethality [27]. Therefore, specific, aggressive management should be instigated as soon as the diagnosis is suspected, even before confirmation of PVL.

3.2. Microbiological diagnosis

To date, detection of PVL-producing *S. aureus* strains is mainly performed with homemade polymerase chain reaction (PCR) on DNA from bacterial colonies. From the 13 sets of primers that have been described, 8 sets target genes in the non-polymorphic region [2,28–33]. The manufactured molecular kits for detecting PVL genes include the GenoType® *Staphylococcus* test (Biocentric) and the DNA microarray *S. aureus* (ARLE). The problem with molecular methods is that they do not reflect PVL production. PVL production can be detected with experimental latex agglutination assays, enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic tests [34,35]. These two last tests can even be performed directly on clinical specimens.

4. Therapeutic tools for Panton–Valentine leukocidin-associated infections

To determine specific treatments for PVL-associated infections, it is necessary to postulate that PVL is directly or indirectly (pro-inflammatory response) responsible for the lesions and tissue damage that leads to clinical symptoms. Hence, the main goal of treatment should be not only to eradicate the PVL-producing *S. aureus* but also to diminish the effects of PVL by (i) removing PVL from the patient, (ii) inhibiting PVL production by *S. aureus* and (iii) blocking the toxic effects of PVL after its production.

PVL removal can only be achieved by complete drainage, surgical or spontaneous, of all PVL-containing suppuration [36]. Therefore, one of the key rules for management of PVL-associated disease should be to perform surgical drainage whenever possible and as soon as possible.

Inhibition of PVL production may be promptly achieved with all antistaphylococcal antibiotics, but only if the drug concentration is far above the minimum inhibitory concentration (MIC) at the site of infection. This may be very difficult in PVL-associated infections because intense necrosis leads to a very low concentration of antibiotics in the pus. Dumitrescu et al. [37,38] have shown experimentally in vitro and in experimental infection of animals that if the concentration of β-lactams and, to a lesser extent, vancomycin is below the MIC, PVL secretion may be enhanced, which may aggravate symptoms. Hence, a treatment targeting PVL should include molecules able to reduce bacterial protein synthesis of PVL, even at suboptimal concentrations. Clindamycin, linezolid and rifampicin have been shown to be able to achieve this goal [38] and these antitoxic effects persist even when these molecules are associated with β-lactams or vancomycin [37].

Neutralisation of the PVL effect in vivo requires specific antibodies. It is proven that deep infection with a PVL-positive *S. aureus* induces the production of significant amount of neutralising antibodies [39]. Moreover, Gauduchon et al. [40] demonstrated that polyvalent human intravenous immunoglobulin (IVIg) may inhibit the cytotoxicity of PVL from *S. aureus* on polymorphonuclear cells in a concentration-dependent manner. This inhibition starts at a concentration above 2 mg/L and is

complete at 10 mg/L. These concentrations are easily achieved using a high-dose regimen of IVIg (2 g/kg/day) in humans. The inhibitory effect of IVIg was tested in various batches of commercially available preparations of IVIg and was confirmed in all cases (personal data). There is no clinical study on the in vivo efficacy of IVIg, but several case reports have shown dramatic improvement in severe PVL-associated infections after the use of IVIg [41–43].

5. Indications

Indications and therapeutic options for the different types of PVL-associated diseases are summarised in Table 1.

5.1. Uncomplicated skin and soft-tissue infection

SSTIs are the most frequent PVL-associated diseases, but in uncomplicated cases PVL-specific management is probably not required because studies have not demonstrates a link between PVL and worse outcome [44]. In most cases, SSTIs result in collection of pus; in such situations surgical drainage is recommended. In a large series of 422 uncomplicated SSTIs, Moran et al. [45] found that outcomes were usually favourable (in >90% of cases), even if antibiotics were inappropriate (i.e. β-lactams for MRSA), as long drainage was performed. Most of the published guidelines do not recommend the use of systemic antibiotics in the case of cutaneous abscesses or boils [12,13,45,46] and there are no data suggesting that the presence of PVL may modify these guidelines. Nevertheless, antibiotics are recommended both by the UK Health Protection Agency (HPA) and the Infectious Disease Society of America (IDSA) in particular conditions [12,13]. The HPA

considers antibiotics if the diameter of the abscess is >5 cm, in cases of associated cellulitis and in cases of severe extensive disease with systemic symptoms. In the latter case, the patient should be immediately referred to a hospital [12]. The recommendations of the IDSA are the same, but some additional indications are included in the recommendation for antibiotic treatment [13]:

- associated co-morbidities or immunosuppression;
- extreme age;
- abscesses in difficult to drain areas (e.g. face, hands and genitalia);
- associated septic phlebitis; and
- lack of response to incision and drainage (A-III).

Because of the emergence of CA-MRSA, empirical therapy should be adapted based on the bacteriological culture [16,47] of any cutaneous exudates, or blood cultures in the case of systemic symptoms. The choice of molecule, if indicated, is based on the incidence of CA-MRSA in the community. In areas with low-to-moderate incidence, antistaphylococcal β-lactams (flucloxacillin) remain the first choice, but when available the combination of amoxicillin and clavulanic acid may be better because of increased coverage of β-haemolytic streptococci, especially in case of associated cellulitis [46,48]. In high-incidence areas, such as North America, CA-MRSA should be systematically covered in the case of a purulent lesion. For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin (A-II); trimethoprim/sulfamethoxazole (TMP/SMX) (A-II); a tetracycline (doxycycline or minocycline) (A-II); and linezolid (A-II). If coverage of both β-haemolytic streptococci and CA-MRSA is desired, options include the following:

clindamycin alone (A-II); TMP/SMX (A-II); a tetracycline in combination with a β-lactam (e.g. amoxicillin) (A-II); or linezolid alone (A-II) [12–14]. There are no studies supporting significant differences between these molecules or a recommendation for using specific treatments for antitoxic activity, even in cases of documented PVL-associated infection.

5.2. Severe skin and soft-tissue infections

The severity of SSTIs associated with PVL could be due to local extension, metastatic localisations, or association with septic or toxic shock syndrome. Severe local extensions lead to necrosis of cutaneous and deep subcutaneous tissue and are clinically undistinguishable from streptococcal necrotizing fasciitis before bacteriological documentation. Moreover, monomicrobial or polymicrobial necrotizing skin infections containing PVL-producing *S. aureus* may exist. In this case, the role of PVL may be less important, and PVL-targeted management is probably not required. Because of its rarity, the optimal management of monomicrobial staphylococcal necrotizing fasciitis is unknown and there are no data supporting major differences in the management versus streptococcal cases, except for the adaptation of antibiotics. Hence, penicillin and ampicillin, which are the first-choice β-lactams for streptococcal infections [46], should be switched to penicillinase-resistant semisynthetic penicillin in meticillin-susceptible *S. aureus* (MSSA) cases. If MRSA is found or strongly suspected because of local epidemiology, therapeutic options recommended by the IDSA and HPA include intravenous (i.v.) vancomycin (A-I), oral or i.v. linezolid (A-I), i.v. daptomycin (A-I), i.v. telavancin (A-I) or i.v. clindamycin (A-III). As with uncomplicated SSTIs, there are no data regarding significant differences between outcomes when patients are treated with these molecules. Nevertheless, the

usefulness of treatment with antitoxins has been demonstrated for streptococcal necrotizing fasciitis, especially with clindamycin [49–52]. Even if no comparable data for *S. aureus* necrotizing fasciitis exist, we believe that such treatment should be considered systematically for severe SSTIs. If clindamycin is used, clinicians must be aware of the possible discrepancy between clinical efficacy and susceptibility testing, which is due to inducible resistance when the strain is not susceptible to erythromycin. In such cases, a D-zone test procedure is warranted [53]. Some experts recommend bactericidal activity in the case of intravascular infection, which is a common feature in severe SSTIs, and none of the antitoxic treatments have shown such activity. Thus, considering the risk of inducible resistance and the need for bactericidal activity, we recommend a combination of clindamycin and β-lactam for MSSA or vancomycin for MRSA. Linezolid alone is approved for the treatment of cSSTIs but, to our knowledge, there is no study regarding its effects on necrotizing fasciitis.

Apart from standard antibiotic treatment, most of the recommendations for streptococcal necrotizing fasciitis can be considered useful for PVL-associated infections. The IDSA's guidelines recommend surgical intervention as the primary therapeutic modality. Aggressive surgical debridement is indicated when antibiotics fail and the SSTI worsens, despite treatment, to severe sepsis or septic shock and in cases of skin necrosis with easy dissection along the fascia during a limited surgical exploration. Considering the role of PVL in necrosis and the difficulty in achieving active concentrations of antibiotics in necrotic tissues, it is reasonable to apply these recommendations to staphylococcal necrotizing SSTIs.

The use of clindamycin is recommended for streptococcal necrotizing fasciitis based on in vitro studies demonstrating both toxin suppression and modulation of cytokine [i.e. tumour necrosis factor (TNF)] production in animal studies, which demonstrate the superior efficacy of clindamycin versus penicillin [51]. In addition, observational studies have demonstrated that clindamycin has greater efficacy than β-lactam antibiotics [49,50,52]. Clindamycin may protect against *S. aureus* infection in undocumented cases and its antitoxin properties may be useful against PVL-associated disease [37].

The usefulness of IVIg for the treatment of necrotizing fasciitis remains controversial, despite evidence that the toxin plays a role in shock, organ failure and tissue necrosis and that variable amounts of neutralising antibodies are observed after treatment with IVIg. There are no studies on the effects of IVIg against staphylococcal necrotizing fasciitis and few data for streptococcal necrotizing fasciitis. One observational study demonstrated better outcomes for streptococcal necrotizing fasciitis in the IVIg group versus historical controls, but the IVIg patients were also more likely to have benefited from a surgical procedure and to have been treated with clindamycin [54,55]. A second placebo-controlled study showed reduced mortality in the IVIg group but failed to demonstrate a statistically significant difference owing to the small number of patients enrolled in the study [56]. Therefore, even if the in vitro data are promising, there is not enough evidence to recommend routine use of IVIg in severe PVL-associated SSTIs. Nevertheless, in cases when optimal therapy has failed, including surgical drainage, appropriate antibiotics with at least one antitoxin molecule and optimal management of septic shock, IVIg should be considered as a therapeutic option.

5.3. Complicated skin and soft-tissue infections

The most common complications of SSTIs are deep abscesses associated with deep vein thrombosis, which are caused by PVL-positive strains. The management of these complications depends on the number, size and location of the abscesses. As in any purulent collection, antibiotics alone are often insufficient and, therefore, surgical drainage is the primary therapeutic option. There are no data on treatment with antitoxin antibiotics. In cases of multiple abscesses that are not surgically accessible and that are progressing despite appropriate antibiotics, two published cases report a dramatic improvement after treatment with IVIg [42,57].

Considering the risk of developing deep venous thrombosis, prophylaxis is usually recommended, and curative treatment should be considered for acquired thrombosis. Nevertheless, the haemorrhagic risk should be taken into account in case of pulmonary localisation because severe airway haemorrhages are common in PVL-associated necrotizing pneumonia [1,27].

5.4. Bone and joint infections

Staphylococcus aureus is the most common cause of BJI. The potential need for a specific management plan for PVL-associated BJIs is illustrated in the description of these infections: standard care (i.e. use of antistaphylococcal drugs approved for BJIs) resulted in treatment failure, as indicated by extension of the lesions in 85% of cases that were treated with active antibiotics. The extension is usually local, with abscess formation in the infected bones and local soft tissues and secondary

bacterial metastasis in various organs. In 71% of cases additional surgery is required after the initial procedure (drainage for arthritis or puncture for osteomyelitis), with a median of three procedures per patient. This unfavourable outcome is observed in areas where MRSA is dominant [20] and in Europe, where the majority of cases are due to MSSA [4]. Unfortunately, comparisons were made with historical controls and no comparative studies for different therapeutic options have been reported. Therefore, no definite conclusions can be made regarding the optimal therapy for PVL-associated BJIs. However, the use of clindamycin or linezolid as the first-line regimen appears to be rational, because both drugs are approved for treatment of BJIs and have antitoxin properties. Because clindamycin is only bacteriostatic, there are some limitations for its use alone, and considering the high incidence of sepsis in the published series of PVL-associated BJIs we recommend combining clindamycin with i.v. cloxacillin (or equivalent semisynthetic β-lactamase-resistant penicillin) when the incidence of CA-MRSA is low in the community. For suspected (in a high-incidence area) or proven PVL MRSA, clindamycin could be combined with vancomycin (despite the poor bone penetration associated with that drug) [58] or daptomycin [13], which is approved for treatment of BJIs in the US and off-label in Europe. Alternative regimens for the treatment of MRSA are linezolid alone, a combination of TMP/SMX plus rifampicin or vancomycin plus rifampicin. Like clindamycin and linezolid, rifampicin has shown interesting antitoxin properties against PVL in vitro, but there is some concern about its use as a first-line regimen owing to the risk of selecting resistant isolates with high inoculum. There are limited data about the use of linezolid alone, which appears to be effective, but may be limited by its toxicity, especially in the bone marrow. Weekly monitoring of complete blood counts is recommended if therapy exceeds 2 weeks, and an ophthalmological

examination should be performed 1 month after initiation of therapy because optic neuritis may occur after prolonged treatment, which is usually required for BJIs.

Like in other PVL-associated diseases, the frequency of abscesses is important. Drainage of any bone or subperiosteal abscess, surgical debridement and any associated soft-tissue abscesses is the most common therapy and should be performed whenever feasible [4,12,13,20]. Because bone abscesses are quite rare in non-PVL staphylococcal BJIs and therefore may not be immediately suspected, even in cases with unfavourable outcome we suggest performing magnetic resonance imaging (MRI) and gadolinium imaging during the week following initiation of therapy whenever a PVL-associated BJI is documented. MRI should be repeated unless a favourable outcome is achieved.

5.5. Necrotizing pneumonia

Staphylococcal necrotizing pneumonia is by far the most severe presentation of PVL-associated infections and therefore requires special management. Although lethality has diminished since the initial description in 2002, overall mortality remains high (42.9–56%) [1,17,27,59,60] and the median survival is only 4 days. Approximately one-half of deaths occur before PVL identification, and in some cases even before bacterial documentation. Necrotizing pneumonia is a rare disease and there are no comparative studies evaluating its management. Nevertheless, guidelines for specific management are necessary considering the severity and the fact that standard antibiotic regimens have no impact on mortality. Hence, in the 51 cases we studied, the percentage of patients who received antibiotics that were active against their

staphylococcal strain was the same for survivors and non-survivors (76.2% vs. 76.9%, respectively) [27].

Unfortunately, surgical drainage of the infected lesions is almost never feasible during the early stages of necrotizing pneumonia. In most cases there is global necrosis of the bronchial and alveolar epithelium with diffuse alveolar damage, and surgical debridement is not possible. Delimited lung abscesses may appear secondarily if the patient survives and should be drained if the clinical situation has not improved, but in most severe cases there is no individualised collection. Drainage of pleural effusion should be performed whenever significant effusion is present, but this has little influence on the evolution of lung infection.

Most necrotizing pneumonia causes symptoms that are consistent with severe sepsis or septic shock at admission or during the first hours following admission. Therefore, we recommend systematically referring patients with suspected necrotizing pneumonia to the Intensive Care Unit. Aggressive non-specific management is required, following the guidelines of the Surviving Sepsis Campaign [61], and artificial ventilation is needed in up to 60% of cases. Progression to ARDS is common and respiratory support should follow the standard recommendation for ARDS [62]. There are no published data regarding adjunctive treatment of sepsis with activated protein C, which is associated with a high frequency of severe airway haemorrhage in necrotizing pneumonia; in our opinion, this fact contraindicates this treatment.

There is no comparative study for antibiotics in necrotizing pneumonia. The IDSA, which focuses on MRSA and not on the severity of disease, recommends

vancomycin, i.v. linezolid or i.v. clindamycin, whereas the HPA recommends a combination of clindamycin plus linezolid [12,13]. As in severe SSTI, there is some concern regarding the use of only bacteriostatic molecules for such a severe condition, but a recent retrospective review of necrotizing pneumonia has shown that using therapies that inhibit toxin production is associated with better outcomes and with a significant impact on mortality [59]. Therefore, we consider that initial antibiotic therapy should combine at least one molecule with antitoxin effects with a bactericidal antibiotic. Some recommend avoiding β-lactams in cases of suspected PVL-associated disease, arguing that β-lactams at suboptimal concentration enhance PVL production in vitro [12,60]. We do not fully agree with this point of view because it is shown that, under the same experimental conditions, the overproduction of PVL induced by β-lactams is completely reversed when clindamycin or linezolid is added, which results in inhibition comparable with using clindamycin or linezolid alone [37].

Moreover, it is important to consider that, at the time of treatment, the bacteria has often not been identified and the possibility of severe necrotizing pneumonia due to other bacteria, such as *Streptococcus pyogenes* or *Streptococcus pneumoniae*, cannot be excluded. Hence, we believed that a third-generation cephalosporin should be added to the initial antibiotic regimen to achieve full coverage for *S. pyogenes* and penicillin-resistant pneumococci. The choice to systematically cover MRSA is evident in high-incidence areas, but considering the severity and the risk of prompt degradation before full susceptibility testing, coverage of MRSA should be considered during the first-line regimen, even in low-incidence areas. Taking into account all these points, our recommendations for the first line of antibiotic treatment

for suspected necrotizing pneumonia would be to combine a third-generation cephalosporin with vancomycin and clindamycin or linezolid at the highest acceptable doses through an i.v. route. Treatment should be adapted after susceptibility testing and should always be combined with a bactericidal antibiotic (cloxacillin for MSSA or vancomycin for MRSA) and molecules that can inhibit toxin production. As an alternative, linezolid could be used alone for the treatment of MRSA infection because the concentration of linezolid in the epithelial lining of the lung fluid is at higher levels than its concentration in plasma [63]. Nevertheless, the comparison between linezolid and vancomycin was performed with nosocomial MRSA ventilator-associated pneumonia, and no study on community-acquired pneumonia has been performed [64,65]. Adding rifampicin to the treatment regimen has been proposed to optimise diffusion in necrotic lung tissue and to achieve optimal clearance of intracellular staphylococci [41], but its limitations in cases of high inoculum may restrict it to a second-round therapy after the initial sepsis has cleared.

Although recommended by UK health authorities, IVIg has never been studied in necrotizing pneumonia, and evidence for efficacy or optimal dosage is lacking. In fact, the use of IVIg is only supported by in vitro data and a few promising case reports [41,43]. Comparison with other severe staphylococcal toxin-mediated diseases is tempting but is not appropriate because PVL does not have superantigenic activity, and although shock is often present, only a small number of patients have toxic shock syndrome. Therefore, it is difficult to recommend systematic use of IVIg. Because of the low frequency of the disease, it will probably take years or even decades before a well-designed placebo-controlled study is performed. On the other hand, necrotizing pneumonia is a frightening disease with a

high mortality rate, in which insufficient use of antibiotics is proven, and therefore it may be unethical to not use such a promising therapy. Moreover, rapid progression of the disease does not allow a lot of time to make the decision. The choice remains difficult, but learning more about factors associated with severity may help. All of the largest necrotizing pneumonia studies have emphasised the role of initial leukopenia and airway haemorrhages as independent factors associated with mortality [17,27,59]. A leukocyte count $<3 \times 10^9$/L increases by 8-fold the odds of death, with an overall mortality of >80%. Airway bleeding is also associated with poor outcome, with a lethality of 80%. Hence, we could propose the systematic use of a high dose of IVIg (2 g/kg in one dose or 1 g/kg/day during two consecutive days) as soon as *Staphylococcus* is identified or whenever lethality-associated factors (i.e. leukopenia $<3 \times 10^9$/L and/or airway haemorrhage) are present. Moreover, when symptoms of toxic shock syndrome are present, especially skin eruption (even if the eruption is probably due to other toxins), IVIg should be used, even if the effect of IVIg on staphylococcal toxic shock syndrome is not fully proven [66,67].

6. Conclusion

Establishing guidelines for the management of PVL-associated diseases is challenging because of the diversity of diseases and because of the lack of knowledge regarding treatment outcomes. Nevertheless, we propose a pragmatic approach based on clinical reports and experimental studies. Our recommendation can be summarised in five key points.

- The presence of PVL should be suspected on an individual clinical basis, independent of meticillin resistance, and every effort should be made to obtain laboratory confirmation.
- Standard management should be used when there are not indicators of the presence of PVL bacteria, such as in uncomplicated SSTIs.
- In cases where antibiotics with proven antitoxin activity (clindamycin, linezolid and rifampicin) are approved, as in complicated SSTI and BJI, they should be used as the first line of defence and should be combined with bactericidal antibiotics in the most severe cases.
- Surgical drainage of purulent collection is recommended when possible.
- In cases of severe life-threatening disease, antitoxic antibiotics and adjunctive treatment such as polyvalent IVIg should be considered systematically because there is not enough time for evidence-based medicine in many cases. Decision-making could be helped in such situations by the knowledge of severity-associated factors.

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Competing interests

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Table 1

Treatment guidelines for Panton–Valentine leukocidin (PVL) *Staphylococcus aureus* infections

Type of infection	Surgical drainage	Microbiological analysis	Antibiotics	Antitoxic antibiotics	IVIg
Skin and soft-tissue infections					
Uncomplicated	Yes	No	No	No	No
Moderate infection (abscess diameter >5 cm; cellulitis, deep infection; systemic symptoms; co-morbidity; extreme age)	Yes	Yes, for antimicrobial resistance	MSSA: AMX/CLA, clindamycin, TMP/SMX, tetracycline, linezolid MRSA: vancomycin, daptomycin, telavancin, linezolid	No	No
Severe or complicated infection (cutaneous necrosis; deep subcutaneous necrosis; deep abscesses; deep venous	Yes	Yes, for antimicrobial resistance and PVL status	MSSA: AMX/CLA, TMP/SMX, tetracycline, linezolid	Yes, clindamycin, linezolid [a]	Yes, in cases when optimal therapy has failed or toxic shock syndrome is present

thrombosis; septic shock)			MRSA: vancomycin, daptomycin, telavancin, linezolid		
Bone and joint infections	Yes	Yes, for antimicrobial resistance and PVL status	MSSA: cloxacillin MRSA: vancomycin, daptomycin, TMP/SMX	Yes, clindamycin, rifampicin, linezolid [a]	No
Necrotizing pneumonia	Not feasible	Yes, for antimicrobial resistance and PVL status	Initial: 3GC plus vancomycin MSSA: cloxacillin MRSA: vancomycin, linezolid	Yes, clindamycin, linezolid [a] Yes, clindamycin, linezolid [a], rifampicin	Yes, when leukopenia $<3 \times 10^9$/L and/or airway haemorrhage

IVIg, intravenous immunoglobulin; MSSA, meticillin-susceptible *Staphylococcus aureus*; AMX/CLA, amoxicillin/clavulanic acid; TMP/SMX, trimethoprim/sulfamethoxazole; MRSA, meticillin-resistant *S. aureus*; 3GC, third-generation cephalosporin.

[a] Linezolid could be used alone for bone and joint infections and skin and soft-tissues infections. No studies for community-acquired pneumonia. The combination of vancomycin and linezolid is not be recommended because of potential antagonism.