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Hot Topic

Panton–Valentine leukocidin-positive *Staphylococcus aureus*: a position statement from the International Society of Chemotherapy

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1. Introduction

Panton–Valentine leukocidin (PVL), a pore-forming cytotoxic secreted toxin, has been associated with severe *Staphylococcus aureus* pneumonia and prototypical skin lesions. The reported incidence and prevalence of PVL-positive *S. aureus* (PVLP-SA) varies globally and suffers from a selective reporting bias towards community-associated methicillin-resistant *S. aureus* (CA-MRSA). Recent studies, however, have identified PVL-positive methicillin-susceptible *S. aureus* (MSSA) more frequently than previously expected. In this review, a group of experts from four continents affiliated with the International Society of Chemotherapy (ISC) offer a position statement on the important aspects of PVL in *S. aureus* epidemiology, antimicrobial treatment and decolonisation, and aim to highlight future areas for collaboration and research.

2. What is Panton–Valentine leukocidin?

PVL belongs to a family of synergohymenotropic toxins that consists of two non-associated components acting synergistically on cell membranes. The toxin is encoded by the *lukS-PV* and *lukF-PV* bacteriophage-transmitted genes whose detection is used in epidemiological studies to detect and determine the prevalence of PVLP-SA [1].

The main PVL cellular targets are polymorphonuclear leukocytes, monocytes and macrophages. PVL binds to complement receptors on the membrane of these cells and induces membrane channel formation leading to cell destruction. The toxin also induces the release of pro-inflammatory cytokines and nuclear factor-kappa B (NF-κB) in neutrophils and is an important virulence factor in necrotizing infections [2]. In PVLP-SA pneumonia, the risk of death has been reported to be higher than with non-PVL-producing *S. aureus* (PVLN-SA) [3]. PVL has also been identified in *Staphylococcus haemolyticus* and *Staphylococcus simulans* [2].

Outbreaks of PVLP-SA were initially reported in MSSA in the mid twentieth century [4]. In the 1990s, PVL was reported in the 'newly' emerging CA-MRSA [5,6], with ST8/USA300 becoming the predominant PVL-producing clone in the USA, ST80 in Europe, ST59-V in Asia, ST30 in the Asia Pacific, and ST93-IV in Australia [7]. However, not all CA-MRSA produce PVL. Furthermore, the toxin is not exclusive in the success of some CA-MRSA clones and consequently there are conflicting data regarding the role of PVL in the pathogenesis of CA-MRSA infections. *PVL-positive* MSSA, which produce a similar clinical presentation as *PVL-positive* MRSA, is thought to be a potential reservoir for the emergence of *PVL-positive* CA-MRSA [8,9].

3. Overview of the global prevalence of Panton–Valentine leukocidin in *Staphylococcus aureus*

Globally, the reported incidence of PVLP-SA is variable and its presence is strongly attributed to strain types/lineages. Unlike local and national reference centres, diagnostic microbiology laboratories do not routinely test for PVL. When testing is performed it is often based on a clinician, microbiologist or infectious diseases specialist request and tends to favour MRSA, in particular CA-MRSA, and isolates from severe *S. aureus* infections. In most places, PVL testing on MSSA is not routinely performed. Consequently, the reported prevalence of PVL is largely inaccurate and/or underrepresented.

The proportion of PVLP-SA and PVLN-SA that are methicillin-resistant varies. Some studies have shown that the prevalence of PVLP-SA is the same for MSSA and MRSA, and the prevalence of PVL-positive CA-MRSA is the same as PVL-negative CA-MRSA [10,11]. However, in other studies all PVLP-SA were methicillin-sensitive and approximately one-third of PVLN-SA were methicillin-resistant [12]. Conversely, in other studies, when compared with PVLN-SA, a greater proportion of PVLP-SA were methicillin-resistant [13,14].

A strong epidemiological association has been found in the USA between skin and soft-tissue infections (SSTIs) and the PVLP-SA USA300 MRSA strain. For example, in a large study in 2004, 78% of

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S. aureus from SSTIs were MRSA, among which 98% were USA300 with nearly all of them were PVL-positive [15]. In another study in the USA, of 1055 *S. aureus* causing various infections, 36% were PVL-positive, there was a high level of methicillin resistance (78% of all isolates), a higher level of PVLP-SA amongst MRSA than amongst MSSA (48% vs. 11.5%), and a higher level of methicillin resistance among PVLP-SA isolates than among PVLN-SA isolates (89.1% vs. 53.5%). The differences were even more pronounced amongst isolates causing SSTI [13]. The prevalence of PVL-positive MRSA isolates from SSTIs in China has been reported to be as high as 19% [16]. A longitudinal study investigating the transmission of *S. aureus* between mothers and their newborns showed a high prevalence of USA300-related *S. aureus* among MRSA isolates and 56.7% of all *S. aureus* carried PVL-encoding genes [17]. Detection of nasopharyngeal PVLP-SA colonisation in 0.22% of patients without SSTI admitted to a London hospital in the UK, a country with a low prevalence of CA-MRSA infections, implies that PVLP-SA carriage can be asymptomatic [18].

Overall, robust global epidemiological data on PVLP-SA are lacking. Driven by the availability of laboratory facilities and selective testing, international collaborative studies are warranted to determine the true incidence and dynamics of PVLP-SA.

4. Overview of main clinical presentations associated with Panton–Valentine leukocidin-positive *Staphylococcus aureus*

Recurrent SSTIs are the hallmark clinical syndrome of PVLP-SA. For example, in a large US study performed in 2004, 78% of *S. aureus* from SSTI were MRSA, of which 98% were the PVL-positive USA300 clone [15]. In a Chinese study, the prevalence of PVL-positive MRSA isolates from SSTIs was reported to be as high as 19% [16]. Although in furunculosis up to 93% of *S. aureus* strains are PVL-positive, PVLP-SA are less frequently isolated in abscesses, cellulitis and finger pulp infections [5].

PVLP-SA SSTI often has distinctive features compared with PVLN-SA SSTI: (i) often no portal of entry is identified, hence the classification as 'primary' skin infection; however, disruption of the skin barrier (e.g. chronic skin disease, scabies, minimal trauma, insect bites, shaving) can facilitate the infection; (ii) lesions tend rapidly to become extensive; (iii) the risk of transmission within households, or to other close contacts, is particularly high; and (iv) recurrence is frequent [19].

The clinical spectrum of PVLP-SA, however, is much broader than just SSTIs, ranging from asymptomatic nasopharyngeal colonisation [18] to fatal necrotizing pneumonia [3]. As with other coagulase-positive staphylococci, nasal carriage is a risk factor for PVLP-SA infection [20].

PVLP-SA can be isolated in the majority of patients with community-acquired necrotizing pneumonia, among whom mortality ranges from 40% to 60% [5]. PVLP-SA pneumonia usually occurs in children and young adults, without co-morbidities, and tends to be preceded by an influenza-like prodrome [3]. The pneumonia is characterised by the rapid onset of fever and haemoptysis. This rapidly progresses to acute respiratory distress syndrome (ARDS) and septic shock, often requiring mechanical ventilation and circulatory support. Leukopenia is common. Radiology shows rapidly progressive multilobar consolidation, pleural effusions with cavitary infiltrates.

PVLP-SA are also associated with severe musculoskeletal infections, particularly in children. The main characteristics of the infection include long-term fever, high levels of inflammatory markers and a high frequency of complications leading to longer stays in the intensive care unit (ICU) and a more frequent need for surgical treatment [21].

5. Panton–Valentine leukocidin on the move

Although defence mechanisms against phage infection in *S. aureus* have been described, including three restriction–modification systems [22] and clustered regularly interspaced short palindromic repeats (CRISPR) loci [23], the PVL-associated genes *lukS-PV* and *lukF-PV* have been identified in many *S. aureus* genetic backgrounds, including clonal complex 1 (CC1), CC5, CC6, CC8, CC22, CC30, CC45, CC59, ST772, CC75, CC80, CC88, CC93, CC121, CC152, ST154, CC398, ST1349, CC942 and ST2563 [8,9,24–31].

lukS-PV and *lukF-PV* are located on several temperate Siphoviridae phages including φSa2958, φSa2MW, φPVL, φ108PVL, φSLT, φ7247PVL, φSa119, φTCH60 and φSa2USA [24,25,32]. This family of double-stranded DNA viruses shares a long non-contractile tail and capsid with an isometric or an elongated shape [32]. The PVL-associated phages belong to group 1 (isometric head type), group 2 (elongated head type) or group 3 of Sfi21-like cos-site Siphoviridae [32,33]. More variation in the phages carrying the PVL-associated genes is found in MSSA than in MRSA [25]. Phages in *S. aureus* can be induced as a consequence of antibiotic treatment with tobramycin, ciprofloxacin, trimethoprim/sulfamethoxazole (SXT), imipenem or trimethoprim [34–36], which in turn may facilitate the transmission of PVL-carrying phages among the *S. aureus* population.

Several PCR-based typing systems have been developed to identify the different PVL-positive phages [25,37]. However, these systems are not on their own very useful for outbreak control and epidemiological use. A study found extremely small variation among CC80 outbreak or non-outbreak isolates hence the phage type may only reflect the CC background [38]. Genetic analysis of the *S. aureus* host is required if it is crucial, for example, to distinguish between a highly transmissible PVLP-SA strain and a PVL-positive phage that is spreading among *S. aureus*.

6. Antibiotics and their effect on Panton–Valentine leukocidin production

It has been known for some time that antibiotics, when incorporated into culture medium at sub-minimum inhibitory concentrations (sub-MICs), are capable of modifying the metabolic processes of bacteria [39]. The antibiotic can induce modulation of virulence factors that may lead to either aggravation or attenuation of infection.

As some of the products of virulence-associated genes can be measured, it is possible to rank individual antibiotics in order of their effect upon toxin production. In vitro findings suggest that clindamycin, linezolid and fusidic acid inhibit PVL production, vancomycin has little or no effect, and subinhibitory concentrations of oxacillin and other β-lactams enhance PVL production [40,41]. Antibiotics binding to penicillin-binding protein 1 (PBP1) increase PVL expression by modulating *sarA* and *rot*, which are essential mediators of the inductor effect of β-lactams on PVL expression [41].

Clindamycin and linezolid are inhibitors of protein synthesis and are therefore likely to inhibit the synthesis of *S. aureus* structural proteins and enzymes. Exposure to linezolid even at sub-MIC levels has been shown to reduce *spa* gene expression, increasing the susceptibility of *S. aureus* to phagocytosis by human neutrophils [42], which provides a plausible explanation why linezolid may be ideal for the management of aggressive or invasive PVLP-SA infections. This action of clindamycin is not clearly understood [43].

As bacterial exposure to sub-MICs of antibiotics under clinical conditions is plausible, particularly within biofilms and necrotic tissues, one can argue that β-lactam antibiotics should be avoided in PVLP-SA infections. However, the in vivo clinical significance of PVL production enhancement using β-lactam antibiotics is unknown. Therefore, unless there are features of severe infection with

necrosis, patients should be commenced on β-lactam antibiotics, at least at the empirical stage of therapy. In severe PVLP-SA infections it is prudent to give antibiotics at the highest safest dose at regular intervals in order to avoid a drop in concentration to sub-MIC levels, and ideally to choose a combination of antibiotics which includes those that inhibit PVL production.

6.1. *Antimicrobial treatment strategies for skin and soft-tissue infections associated with Panton–Valentine leukocidin-positive Staphylococcus aureus*

The most appropriate management of SSTIs with purulent collection is represented by surgical drainage of the purulent collection/abscess. In the case of uncomplicated SSTIs there may be no need for the use of systemic antibiotics. Localised lesions without systemic features may be managed with topical antimicrobial therapy. However, a recent trial involving >1200 patients with a drained cutaneous abscess (majority due to USA300 CA-MRSA) demonstrated that patients who received SXT (1920 mg twice daily for 7 days) had a higher cure rate than those who received a placebo. In addition, there were fewer subsequent surgical drainage procedures, new skin infections, and infections among household members in the SXT group than in the placebo group [44].

To our knowledge, there are no published clinical data to support treating non-necrotic PVLP-SA infections with anti-PVLP-SA antibiotics. Consequently, unless there is a high prevalence of methicillin resistance, standard therapy with adequate doses of antistaphylococcal β-lactams should be the primary choice. In times of rising antimicrobial resistance and greater need for antibiotic stewardship, this approach should be the aim in clinical practice. Apart from in severe necrotic cases, combination therapy is seldom required. The choice of antibiotics (Table 1) will depend on local epidemiology and national guidelines. In severe infections with features of toxic shock, necrotizing fasciitis or purpura fulminans there may be a theoretical case for using two or three agents with or without intravenous immunoglobulin (IVIg). Emergency surgical debridement may also be necessary [45,46].

6.2. *Antimicrobial treatment strategies for bone and joint infections (BJIs) associated with Panton–Valentine leukocidin-positive Staphylococcus aureus*

In BJIs, concentrations below the MIC may occur because of poor antibiotic penetration, especially in the presence of necrosis associated with PVL. Hence, an effective antimicrobial treatment for PVLP-SA-associated BJI should include antibiotics inhibiting protein synthesis. This would be particularly important when using β-lactams or vancomycin in necrotic tissues. The use of linezolid alone for BJIs could be effective, but it is limited by its potential toxicity in prolonged therapy (4–6 weeks), which is often necessary. The use of rifampicin alone is strongly not recommended owing to the risk of selecting resistant isolates with a high inoculum.

The pattern of antimicrobial susceptibility of the aetiological agent has to be considered for selection of the most appropriate antibiotic treatment. If the infection is caused by PVL-positive MSSA, the highest possible dose of flucloxacillin (or equivalent semisynthetic β-lactamase-resistant penicillin) combined with clindamycin could be used. For suspected or proven PVL-positive MRSA, several antimicrobial regimens could be administered (Table 1). The combination of linezolid and vancomycin is not recommended because of a potential antagonistic effect [47]. The new agent tedizolid may prove useful for PVLP-SA BJIs, but data to support its use are still lacking. Once again, national and local guidelines should be followed. Off-label use of antimicrobials with favourable pharmacological and microbiological characteristics (e.g. good bone penetration and optimal activity against MRSA), such as daptomycin and linezolid, is frequently necessary.

6.3. *Antimicrobial treatment strategies for pneumonia associated with Panton–Valentine leukocidin-positive Staphylococcus aureus*

In cases of suspected or confirmed PVLP-SA pneumonia, in addition to physiological support it is crucial to commence appropriate antimicrobial therapy (often combinations) without delay. Initial

Table 1
Examples, pros and cons, and potential indications for antimicrobials used in the treatment of Panton–Valentine leukocidin-positive *Staphylococcus aureus*.

Antimicrobial agent [a]	Pros/cons	Clinical use
Antistaphylococcal β-lactam (e.g. oxacillin, flucloxacillin)	Good tolerability profile/No PVL activity, no MRSA activity	Use at highest possible dose, in combination when treating complicated necrotic infection or BJI
Trimethoprim/sulfamethoxazole	Good bioavailability and can be used as oral switch, effective against MSSA and MRSA when sensitive	Prolonged use of these agents necessitate folinic acid supplements. Consider combination therapy with rifampicin
Vancomycin	Anti-MRSA/Slow bactericidal activity, i.v. only, renal toxicity	Consider use in combination therapy (clindamycin or rifampicin). Antistaphylococcal β-lactam is preferable in MSSA
Moxifloxacin, levofloxacin	Good bone penetration, oral formulation/No PVL activity, limited tolerability (e.g. elderly), not ideal for MRSA, concern for development of resistance on therapy	Consider use in combination therapy, e.g. with rifampicin
Doxycycline	Good tolerability profile effective against MSSA and MRSA when sensitive	Can be used in combination with other agents (e.g. rifampicin)
Rifampicin	Anti-MRSA and PVL activity, antibiofilm activity/Resistance selection if used alone, drug–drug interactions, liver toxicity	Should only be used in combination therapy (fluoroquinolones for MSSA or a glycopeptide, daptomycin or fusidic acid for MRSA)
Clindamycin	Anti-PVL activity and MRSA when sensitive	Use in combination treatment (e.g. β-lactam for MSSA or a glycopeptide or daptomycin for MRSA)
Daptomycin	Anti-MRSA, rapid bactericidal, antibiofilm activity, good tolerability profile, once daily/Only i.v., high dose required (>8 mg/kg)	Use in combination therapy (clindamycin for MSSA or rifampicin for MSSA)
Tigecycline	Anti-MRSA/Only i.v.	Use in polymicrobial infections
Linezolid	Anti-MRSA, anti-PVL activity, good bone penetration, oral formulation/Drug–drug interactions, toxicity for prolonged treatment	Treatment of outpatients. Early oral switch
Tedizolid [b]	Anti-MRSA, anti-PVL activity, good bone penetration, oral formulation, once daily/High cost	Treatment of outpatients

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; SSTI, skin and soft-tissue infection; BJI, bone and joint infection; i.v., intravenous.
[a] In general, please follow local guidance and antimicrobial susceptibilities. Anti-MRSA agents can also be used for MSSA if indicated. For uncomplicated SSTIs, combination treatment is seldom required.
[b] There is limited clinical experience with this drug to date for complicated SSTIs and BJIs.

empirical coverage against *S. aureus* should be initiated, for example, when *S. aureus* pneumonia is suspected or during influenza season, followed by targeted therapy when culture results are available.

In cases of fulminant PVLP-SA pneumonia, it is recommended that inhibitors of toxin production, such as clindamycin, linezolid or rifampicin, is are included in the regimen. Combinations of vancomycin with clindamycin or rifampicin, or rifampicin with linezolid or clindamycin, have demonstrated success [48–50]. Early in the disease period, adjuvant therapy with IVIg can be considered for toxin neutralisation [51], although the evidence is still limited. Intensive care support is often required, and extracorporeal membrane oxygenation (ECMO) may be considered early during therapy [52]. To our knowledge there are no reports demonstrating a clinical benefit of corticosteroids in PVLP-SA pneumonia.

7. Eradication of methicillin-resistant and -susceptible *Staphylococcus aureus* and recurrent colonisation (why, what are the risk factors, what should we do?)

Decolonisation is part of a process to completely remove or eradicate bacterial colonisation (eradication) or to reduce its bioburden (bioburden reduction).

In countries with a 'search and destroy' policy, the detection (search) of MRSA is followed by the eradication (destroy) protocol. The goal of 'search and destroy' is to reduce the chance of introducing and spreading MRSA into healthcare facilities. In Denmark, eradication always involves treating all household members. In other countries, treatment of household members is dependent on the individual situation, i.e. repeated infections in more than one household member, a case of necrotizing pneumonia, or where contacts are in a high-risk group for transmission (e.g. healthcare workers). Although various periods of long-term follow-up are used in different countries, declaring successful eradication usually requires multiple negative culture sets at different time points [53–55].

Bioburden reduction, as opposed to eradication, is the goal of decolonisation therapy in certain cases, e.g. prior to an operative procedure, recurrent SSTI, and decreasing the risk of transmission to others.

Various agents and strategies have been used to eradicate *S. aureus* colonisation, however the optimal schedule has yet to been defined. Most studies are not focused on known PVLP-SA carriers. Perl et al [56] and Bode et al [57] showed that intranasal application of mupirocin in carriers [51] or in combination with chlorhexidine body wash [57] significantly decreased the rate of nosocomial *S. aureus* infection. Clinical evidence on methods for *S. aureus* eradication from the mouth is lacking. Because environmental surfaces serve as reservoirs, implementation of cleaning is recommended as part of regimens to eradicate body colonisation. Studies evaluating the use of systemic antibiotics in eradicating *S. aureus* produced conflicting data, with the emergence of antimicrobial resistance and toxicities being reported. Therefore, treatment with systemic antibiotics for decolonisation is limited to particular circumstances [58–60].

Failure of eradication or re-colonisation can occur even after multiple decolonisation attempts. This has been associated with non-compliance with the decolonisation regimen, active wounds, presence of devices, chronic pulmonary diseases, colonisation of extranasal sites (e.g. throat, gastrointestinal tract) or re-colonisation from a close contact. In addition, resistance to agents used for topical decolonisation has been associated with persistent *S. aureus* carriage [61], a factor that needs to be considered before implementing widespread use of eradication therapies.

Although the optimal decolonisation therapy for PVLP-SA is not known, it is likely to be similar to those used for MRSA decolonisation. Recommendations regarding decolonisation for PVLP-SA vary by geographical region and are generally adapted from MRSA eradication regimens. In the USA, where PVL-positive MRSA is relatively common, eradication therapy is only considered once other hygiene measures have failed. In contrast, a more aggressive approach of eradication for cases and contacts (after a risk assessment) is taken in England and Scotland where PVLP-SA disease is relatively rare [62,63]. Although practiced in some countries, limited data support performing initial eradication in all household members [55]. In eradication failure, particularly where no cause is identified, it is generally not reasonable to perform more than five standard decolonisation attempts. In such cases, treatment of underlying conditions (skin disease or change of devices) should be optimised, and simultaneous treatment of the index patient and household contacts is recommended. Extended decolonisation regimens over 3 months with intranasal mupirocin on five consecutive days each month and antimicrobial baths two to three times per week have been proposed [64]. Further studies are required to support this approach. Systemic antibiotics may be considered [44,58–60].

Further research will better inform clinical and public health measures to control PVLP-SA. In the era of increasing antibiotic resistance, future research is also urgently required on non-antibiotic strategies in the eradication of PVLP-SA and other *S. aureus*, e.g. application of ultraviolet (UV) light, SurgihoneyRO™, probiotics and others.

8. Panton–Valentine leukocidin-positive *Staphylococcus aureus* infection in pets and zoonotic cross-infections: what can be done?

Although dogs and cats are not natural reservoirs for *S. aureus*, they can become colonised. For example, MRSA colonisation frequently occurs while living in close contact with human MRSA carriers [65]. Cefai et al reported isolation of an MRSA with an identical phage type from the nose of a healthcare worker, his partner and their pet dog [66]. Whilst another report demonstrated that recurrence of the MRSA infection of a couple only stopped once their pet dog was no longer an MRSA carrier [67]. Transmission of MRSA between humans and horses has also been suspected in veterinary settings [68].

It is widely recognised, because of the close contact with humans, that companion animals tend to share the same lineages identified in humans. Consequently, pets may become reservoirs of PVLP-SA in regions with a high PVL prevalence in the human *S. aureus* population. Three studies have reported a likely role of the household pet in human PVL-positive MRSA carriage and infection. In two studies, the patient's cure and decolonisation required treatment of all 'family members' (including the pet) with ciprofloxacin and rifampicin [65,69]. However, a recent case report on the dynamics of household transmission of MRSA USA300 by whole-genome sequencing (WGS) failed to implicate the pet in human MRSA outcomes [70].

According to European Union guidelines [71], companion animals for which clinical infection with MRSA is suspected or confirmed should be monitored and quarantine considered. It has been recommended that MRSA-infected pets should be restricted from human contact until clinical cure [72]. As for healthy pet carriers, there is currently insufficient evidence to recommend routine decolonisation. Rigorous hygiene measures should be taken, where possible combined with temporary isolation to ease cleaning and disinfection. Testing pets of MRSA-positive owners who failed decolonisation should be considered if there is a specific plan for the pet's decolonisation or short-term removal from the household while the humans are being treated [72]. To our knowledge, PVL has not been identified in a bona fide livestock-associated strain.

Studies of CC398 strains have pointed to distinct groups: a livestock clade (PVL-negative) and a human clade (can be PVL-positive). PVL-positive CC398-MRSA belonging to the human clade has been identified, particularly in China and surrounding countries [73].

9. Outbreak management in hospitals/barracks/prisons etc.

9.1. Managing Panton–Valentine leukocidin-positive Staphylococcus aureus clusters in hospitals

Clusters of PVLP-SA infections or colonisation are rare (or not reported) in hospitals. However, hospital patients often suffer from co-morbidities rendering them prone to serious infection. In regions with a single predominant strain type of PVLP-SA, defining a cluster is difficult. Table 2 gives an overview on possible strategies one should consider when facing a PVLP-SA cluster in a hospital.

Most of the reported PVLP-SA hospital clusters are MRSA involving paediatric or neonatal ICUs [74–76,81]. However, in this setting MSSA would often be regarded as part of the normal flora and would not be tested for PVL. Alongside ST8 (USA300), there are reports of other PVL-positive MRSA clones causing clusters of PVLP-SA infections or colonisation, including ST80 (European community MRSA clone), ST22, ST772 (Bengal Bay MRSA) and ST30 (South-west Pacific or Oceanic clone). A multicentre study from France showed that lineages varied by geographical origin, suggesting multiple independent clusters. Some patients suffered from necrotizing pneumonia or sepsis, but most clinical isolates were from SSTIs. Even though the prevalence of PVLP-SA among SSTIs was high, only a few of the PVLP-SA-colonised patients subsequently showed signs of an infection [81].

The PVLP-SA transmission routes within hospital clusters are not completely understood. In most clusters, healthcare workers were found to be colonised or infected with the cluster strain [74,75]. Very few environmental investigations detected the respective strains, leaving the transmission route unknown [74]. However, application of bacterial WGS in real time has been shown to help in identifying carriage by a healthcare worker as a potential source of an ongoing MRSA outbreak and directly inform infection control interventions [82]. Transmission is normally limited to close physical contact. Therefore, targeted decolonisation of colonised patients and staff is important. None the less, escalating general hygiene measures such as contact isolation as well as improved hand hygiene compliance and cleaning the environment are the most successful interventions.

Table 2
Overview of Panton–Valentine leukocidin-positive *Staphylococcus aureus* (PVLP-SA) outbreak management in hospitals, community settings and households.

Hospitals	Community institutions	Households
Increased environmental cleaning, hand-hygiene compliance along with either single-room isolation or cohorting of affected patients, were first-line precautions [74,75]. Personal protective equipment (PPE) with contact precautions should be employed. Surgical masks and eye protection should be worn during aerosol-generating procedures (e.g. nebulisers, intubation, airway suctioning) in patients with PVLP-SA respiratory infections. The number of staff present should be limited to avoid unnecessary exposures. In addition, intrahospital or interhospital transport of affected patients should be limited. Exposed sites of colonisation, such as wounds and ulcers, should be covered with an occlusive dressing before leaving the ward. Excessive waiting times in departments should be minimised. Surfaces exposed to the patient or potentially contaminated secretions should be wiped down after use, with frequent scheduled cleaning. On discharge, terminal environmental cleaning should be performed. Active screening followed by decolonisation were additional measures [74]. Active screening proved effective when it included all patients at risk, all involved HCWs and patient family members, and colonised HCWs were excluded from the working environment pending successful decolonisation [75]. Lee et al implemented universal decolonisation in order to curtail transmission of PVLP-SA [76]. However, one should keep in mind that not all antiseptic substances and concentrations are suitable for paediatric patients. Staff with proven PVLP-SA infection should be treated with appropriate antibiotics and should not return to work until infection has been eradicated. In the UK, Public Health England (PHE) recommends a topical 5-day decolonisation regimen for staff with proven PVLP-SA infection, commencing after all skin lesions are dry, and at least 48 h prior to return to work. Weekly follow-up screens following topical decolonisation are advised by PHE [62,63]. If the staff remains a carrier despite two courses of decolonisation treatment, the staff should be able to continue work provided they cease working as soon as possible if infected skin lesions recur. Routine screening of HCWs who have had contact with PVLP-SA SSTIs is not recommended unless active skin lesions or dermatological conditions are present. Staff exposed to respiratory secretions, e.g. intubation in PVLP-SA necrotizing pneumonia without appropriate PPE such as surgical face masks and eye protection, should be screened 3–7 days after exposure and monitored for symptoms subsequently	Principles for preventing and controlling the spread of infection in the community setting centre on early suspicion of infection with rapid diagnosis, appropriate treatment and hygiene measures. Risk factors for transmission should be minimised. Hand hygiene should be emphasised, with frequent and thorough cleaning with soap and water or alcohol-based sanitiser. Personal items that may become contaminated (e.g. towels, clothing, bedding, bars of soap, razors) should not be shared. Clothing should be laundered in hot water and dried thoroughly [77,78]. In athletes, strategies to minimise skin breaks, including prevention of turf burns [77], could also be considered. Individuals with active lesions may be advised to avoid the use of shared sports equipment [78]. Environmental sanitation should be performed with scheduled cleaning of frequently touched surfaces. Users of shared equipment, e.g. exercise machines, should use clothing or towels to act as a barrier between surfaces of equipment and bare skin. Draining wounds should be kept covered with clean, dry dressings. Patients with open wounds should avoid recreational or communal activities involving skin-to-skin contact until wounds are fully healed. Individual decolonisation therapy may be offered once the acute infection has resolved. Decolonisation efforts in large community settings are of unclear benefit. However, exclusion of staff or members of a closed community, as well as screening confirmation of PVLP-SA eradication, should be implemented on an individualised risk-based approach, taking into consideration the severity of the infection in the outbreak, the vulnerability of contacts in the setting, the degree and nature of contact and the risk of ongoing transmission despite general hygiene measures	Management of family outbreaks requires screening of the whole household (nose, groin and any skin lesions) for PVLP-SA. The general principles of *S. aureus* control need to be employed [59]. Successful eradication requires rigorous attention to infection prevention principles within the family. These include initial management with early suspicion of infection, rapid diagnosis and appropriate treatment. Infected lesions must be covered with clean, dry dressings, which are changed as soon as discharge seeps to the surface. Evidence for prevention is limited specifically for PVLP-SA. Once confirmed, personal hygiene and good skin care (particularly those with eczema) should be encouraged. Use of separate towels, not sharing personal items such as razors, toothbrushes and face cloths, and ensuring laundering of towels, bed linen and clothing using a hot wash (60 °C) are recommended where possible [79,80]. The household should be cleaned regularly with vacuuming and dusting [55]. Household pets have occasionally been implicated in persisting PVLP-SA (refer to Sections 8 and 9 of this manuscript). Infected householders should be advised to avoid communal and recreational settings until lesions are healed if they cannot be adequately contained by a dressing. Those who work in occupations where they might pose a risk of infection to others, such as HCWs, carers in nurseries, residential or care homes or similar, or food handlers, should be excluded from work until the lesions have healed. Limited data support performing initial eradication in all household members, however this can be offered. Quarterly decolonisation has been proposed in refractory or recurrent PVLP-SA colonisation and infections among families [64]. Further studies are required to support these suggestions and proposals.

HCW, healthcare workers; SSTI, skin and soft-tissue infection.

9.2. Outbreak management associated with community institutions

Community outbreaks have been reported in multiple settings (Table 2) and commonly occur in situations where risk factors for *S. aureus* transmission are present. Risk factors include: closed crowded communities where frequent skin-to-skin contact occurs with others who are colonised or infected; the presence of compromised skin integrity such as lacerations, abrasions or tattoos; sharing of contaminated items or equipment that have not been cleaned or laundered between users; and lack of cleanliness. Such settings include athletic gyms used by sports teams, military barracks, correctional facilities amongst prison inmates and guards [77,78,83] and close-contact sports, e.g. wrestling, rugby or judo. Many PVLP-SA patients, however, may have no identifiable risk factors.

9.3. *Managing household outbreaks of Panton–Valentine leukocidin-positive Staphylococcus aureus*

Household (or family) outbreaks of PVLP-SA have been reported. Outbreaks usually become evident when one or more family member presents to their general practitioner or hospital with recurrent SSTIs. In general, PVLP-SA isolates are more likely to generate SSTIs among household contacts compared with PVLN-SA isolates. A summary of PVLP-SA outbreak management in hospitals, community settings and among households is presented in Table 2.

10. The role of cleaning and decontamination for controlling Panton–Valentine leukocidin-positive *Staphylococcus aureus* in healthcare and community settings

People colonised or infected with PVLP-SA contaminate the items that they touch and shed the organism into the air. Onward transmission to additional surfaces will be facilitated by dust via air currents and by hand contamination [37]. PVLP-SA will persist for months, even in a dry environmental niche, and therefore needs to be removed by cleaning or disinfecting.

Community institutions facing particular risk from PVLP-SA transmission include private homes, nursing and residential homes, military barracks, prisons, hostels for students and homeless, orphanages, youth correctional facilities, sports centres and swimming pools. Schools, youth clubs, nurseries, brothels, shopping centres, public transport, cinemas and theatres may also have environmental contamination. Persistent colonisation of companion animals may represent an additional source for human colonisation, however data remain scarce in this field (see Section 8). Members of staff at healthcare facilities treating people with PVLP-SA carriage or infection are themselves at risk [79,80,84,85].

Similar control methods apply to the majority of these institutions. Personal protection starts with hand hygiene, followed by cleaning and decontamination of the environment, including frequent hand-touch sites in wards, kitchens, toilets, bathrooms, and changing and treatment rooms. Cleaning practices should first focus on physical removal of dirt and debris using detergent-based methods. Disinfectants may be applied to high-risk sites provided the agent chosen is effective against *S. aureus*. Floors and other surfaces would also benefit from disinfection in isolation rooms and multi-bedded areas, particularly if there is evidence of ongoing PVLP-SA transmission. Automated decontamination devices dispelling hydrogen peroxide (H_2O_2) and UV-C microbicidal light, although costly, may be employed in the terminal cleaning of vacated single rooms, but not communal areas [86]. Comprehensive environmental cleaning is essential for controlling PVLP-SA in healthcare and other environments.

11. Chlorhexidine resistance in *Staphylococcus aureus*

The intensive use of chlorhexidine has been associated with reduced susceptibility in healthcare-associated *S. aureus* and coagulase-negative staphylococci (CoNS). The resistance mechanism widely implicated is the expression of transmembrane pumps that efflux chlorhexidine in exchange for protons. Such efflux pumps are primarily encoded by *qacA/B* genes that are present on large conjugative plasmids carrying multiple determinants of resistance to antibiotics and other biocides [87,88]. This raises a concern of potential cross-resistance between chlorhexidine and antibiotics as well as interstrain and interspecies horizontal transmission of multidrug resistance plasmids. None the less, the clinical significance of *qacA/B* carriage itself remains unclear. Whilst many studies report minimal *qacA/B* carriage in MRSA over sustained periods of time in intensive care settings, others continue to report high *qacA/B* carriage and reduced susceptibility to chlorhexidine in *S. aureus* and CoNS [88,89]. Recently, *qacA/B* carriage has also been reported in PVL-positive MSSA from osteomyelitis and necrotizing pneumonia [89]. Whilst there are no reports of *qacA/B* carriage in PVL-positive MRSA, this trend may well change as the prevalence of hospital-associated PVLP-SA strains increases.

In *S. aureus*, mutations in the promoter region of *norA* have been implicated in potential cross-resistance to chlorhexidine and fluoroquinolones [90,91]. Randomised controlled trials to measure the effect of chlorhexidine-based strategies versus the use of alternative antiseptics, but more importantly universal versus targeted decolonisation strategies, will elucidate the effect of intensive use of chlorhexidine on the emergence of resistance to antimicrobials and antiseptics in MRSA, MSSA and CoNS.

12. Decolonisation agents for Panton–Valentine leukocidin-positive *Staphylococcus aureus* (alternatives to chlorhexidine and mupirocin)

To our knowledge, no decolonising agent has shown definite superior efficacy to chlorhexidine. However, an in vitro comparison has shown that povidone-iodine and octenidine were superior to polyhexanide, chlorhexidine and triclosan (in decreasing order of efficacy) for immediate MRSA decolonisation [92] (Table 3).

Mupirocin remains the drug of choice for nasal decolonisation in hospital settings. It should be remembered though that sustained use can lead to resistance and decolonisation failure. Genetic determinants for resistance to mupirocin have been reported in PVLP-SA. Therefore, alternative regimens have been sought widely, although the superiority of these approaches in terms of MRSA eradication and long-term impact on the emergence of resistance has not been demonstrated (Table 3).

13. Conclusion

PVL, a staphylococcal toxin known for 80 years and more intensively studied for the last 20 years, remains an enigma. Why is the bacteriophage-encoded PVL frequently present among CA-MRSA strains while it is rare among many MSSA strains? Clearly it offers certain strains an evolutionary advantage. Further research is needed to understand fully the dynamics of PVL-bearing bacteriophage transmission among *S. aureus* strains, the global epidemiology of PVLP-SA, and optimal strategies for the treatment, decolonisation, prevention and environmental control of PVLP-SA in the community and in healthcare settings.

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Table 3
Alternative agents proposed for skin and nasal decolonisation of *Staphylococcus aureus*.

Proposed use	Agent	Decolonisation rates relative to placebo or gold-standard agents	Resistance mechanisms in *S. aureus*	Adverse effects identified
Skin decolonisation	Polyhexanide [93]	Clinical trial of a single decolonisation course with polyhexanide was not more efficacious than the placebo in eradication of MRSA	None identified	None in most studies
	Octenidine [94]	Placebo-controlled efficacy comparable with chlorhexidine, but the two agents not yet compared in a RCT	None identified	Inconsistent data across studies
	Tea tree oil [95]	Eradication rates comparable with chlorhexidine-based treatments (small trial)	Not investigated	Further studies required; concern for gyaencomastia in boys
	Sodium hypochlorite [96]	More efficacious than chlorhexidine in eradication. Currently recommended by the IDSA for prevention of recurrence of MRSA-related skin infections	None identified	Dry skin
	Hexachlorophene [97]	Narrow-spectrum agents such as the Gram-positive-specific hexachlorophene may be useful for targeted decolonisation approaches. Not more efficacious than placebo	Not investigated	Systemic absorption leading to neurotoxicity
	Triclosan [88,98]	Not more efficacious that placebo or non-antimicrobial soaps	Multiple mechanisms identified	Rare
	SurgihoneyRO™ [99]	Excellent activity against Gram-positive organisms, including MRSA, as well as Gram-negatives, however there are no RCTs to determine superiority to mupirocin or other agents	Not known	Rare
Nasal decolonisation	Bacitracin (±gramicidin, polymyxin B) [100]	Less efficacious than mupirocin	Multiple mechanisms identified	High prevalence of contact dermatitis
	Tea tree oil [95]	Less efficacious than mupirocin	Not investigated	Further studies required
	SurgihoneyRO™ [99]	No comparator studies done with mupirocin	Not known	Rare
	Pleuromutilins [101]	More potent than mupirocin in vitro, but the two agents not yet compared in a RCT	Multiple mechanisms identified	Contact dermatitis
	Lauric acid [102]	More efficacious than mupirocin in a preclinical model, but the two agents not yet compared in a RCT	Not investigated	Not assessed in clinical studies
	Lytic phage [103,104]	More efficacious than mupirocin in a preclinical model, but the two agents not yet compared in a RCT. The breadth of action across clinical isolates of genus-specific approaches such as obligate lytic phage is yet to be demonstrated	Low potential	Not assessed in clinical studies

MRSA, methicillin-resistant *S. aureus*; RCT, randomised controlled trial; IDSA, Infectious Diseases Society of America.

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