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Panton-Valentine Leucocidin (PVL) *Staphylococcus aureus* a position statement from the International Society of Chemotherapy

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Introduction

Panton Valentine Leucocidin (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* (PVLPSA) varies globally and suffers from a selective reporting bias towards community associated MRSA (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 offer a position statement on the important aspects of PVL in *S. aureus* epidemiology, antimicrobial treatment, and decolonisation, and aims to highlight future areas for collaboration and research.

1) What is Panton-Valentine Leucocidin (PVL)?

PVL belongs to a family of synergo-hymenotropic toxins which consist 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 PVLPSA [1].

The main PVL cellular targets are polymorphonuclear leukocytes, monocytes and macrophages. PVL binds to complement receptors on the membranes 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 in neutrophils and is an important virulence factor in necrotizing infections [2]. In PVLPSA pneumonia the risk of

death has been reported to be higher than with non-PVL-producing *S. aureus* (PVLNSA) [3]. PVL has also been identified in *S. haemolyticus* and *S. simulans* [2].

Outbreaks of PVLPSA 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 is conflicting data regarding the role of PVL in the pathogenesis of CA-MRSA infection. PVL+ve MSSA, which produce a similar clinical presentation as PVL+ve MRSA, is thought to be a potential reservoir for the emergence of PVL+ve CA-MRSA [8, 9].

2) Overview of the global prevalence of PVL in *S. aureus*

Globally, the reported incidence of PVLPSA 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 an 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 PVLPSA and PVLNSA that are methicillin resistant varies. Some studies have shown the prevalence of PVLPSA 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 PVLPSA were methicillin sensitive and approximately one third of PVLNSA were methicillin resistant [12]. Conversely, in other studies, when compared to PVLNSA, a greater proportion of PVLPSA were methicillin resistant [13, 14].

A strong epidemiologic association has been found in the USA between SSTIs and the PVLPSA USA300 MRSA strain. For example, in a large study in 2004, 78% of *S. aureus* from SSTI were MRSA, among which 98% were USA300 with nearly all of them PVL+ve [15]. In another study in the USA, of 1,055 *S. aureus* causing various infections, 36% were PVL+ve, there was a high level of methicillin resistance (78% of all isolates), a higher level of PVLPSA amongst MRSA than amongst MSSA (48% vs 11.5%), and a higher level of methicillin resistance among PVLPSA isolates than among PVLNSA isolates (89.1% vs 53.5%). The differences were even more pronounced amongst isolates causing SSTI [13]. The prevalence of PVL+ve MRSA isolates from SSTIs in China has been reported to be as high as 19% [16]. A longitudinal study investigated the transmission of *S. aureus* between mothers and their newborns showed high prevalence of USA300-related *S. aureus* among MRSA isolates with 56.7% of all *S. aureus* carried PVL encoding genes [17]. Detection of nasopharyngeal PVLPSA colonization in 0.22% of patients without SSTI admitted to a UK hospital implies that PVLPSA carriage can be asymptomatic, in a country with a low prevalence of CA-MRSA infections [18].

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

3) Overview of main clinical presentations associated with PVLPSA

Recurrent SSTIs are the hallmark clinical syndrome of PVLPSA. For example in a large USA study performed in 2004, 78% of *S. aureus* from SSTI were MRSA, of which 98% were due to the PVL-positive USA300 clone [15]. In a Chinese study the prevalence of PVL+ve 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, PVLPSA are less frequently isolated in abscesses, cellulitis and finger pulp infections [19].

PVLPSA SSTI often has distinctive features when compared to PVLNSA SSTIs : 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 [20].

The clinical spectrum of PVLPSA however is much broader than just SSTIs, ranging from asymptomatic nasopharyngeal colonization [18] to fatal necrotizing pneumonia [3]. As with other coagulase-positive staphylococci, nasal carriage is a risk factor for PVLPSA infections [21].

PVLPSA can be isolated in the majority of patients with community-acquired necrotizing pneumonia, among whom mortality ranges from 40 to 60% [19]. PVLPSA pneumonia usually occurs in children and young adults, without comorbidities, and tends to be preceded by an influenza-like prodrome [3]. The pneumonia is characterized by the rapid onset of fever and hemoptysis. This rapidly progresses to acute respiratory distress syndrome (ARDS) and septic shock, often requiring mechanical ventilation and circulatory support. Leucopaenia is common. Radiology shows rapidly progressive multilobar consolidation, pleural effusions with cavitory infiltrates.

PVLPSA 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 high frequency of complications leading to longer stays in intensive care units and a more frequent need for surgical treatment [22].

4) PVL on the move

Although defence mechanisms against phage infections in *S. aureus* have been described, including three restriction modification systems [23] and clustered regularly interspaced short palindromic repeats (CRISPR) loci [24], the PVL-associated genes, *lukS-PV* and *lukF-PV*, have been identified in many *S. aureus* genetic backgrounds including clonal complex (CC)1, CC5, CC6, CC8, CC22, CC30, CC45, CC59, ST772, CC75, CC80, CC88, CC93, CC121, CC152, ST154, CC398, ST1349, CC942 and ST2563 [25-34]

lukS-PV and *lukF-PV*, are located on several temperate Siphoviridae phages including ϕ Sa2958, ϕ Sa2MW, ϕ PVL, ϕ 108PVL, ϕ SLT, ϕ 7247PVL, ϕ Sa119, ϕ TCH60 and ϕ Sa2USA [25, 26, 35]. This family of double-stranded DNA viruses shares a long noncontractile tail and capsid with an isometric or an elongated shape [35]. The PVL-associated phages belong to group 1 (isometric head type), group 2 (elongated head type) or group 3 of Sfi21-like cosite Siphoviridae [35,36]. More variation in the phages carrying the PVL-associated genes is found in MSSA than in MRSA [26]. Phages in *S. aureus* can be induced as a consequence of antibiotic treatment with tobramycin, ciprofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), imipenem or trimethoprim [37-39], 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+ phages [26, 40]. 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 [41]. Genetic analyses of the *S. aureus* host is required if it is crucial, for example, to distinguish between a highly transmissible PVLPSA strain and a PVL+ phage that is spreading among *S. aureus*.

5) Antibiotics and their effect on PVL production

It has been known for some time, when incorporated into culture media at sub minimal inhibitory concentrations (sub-MIC) antibiotics are capable of modifying the metabolic processes of bacteria [42]. The antibiotic can induce modulation of virulence factors which may lead to either aggravation or attenuation of an 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 clindamycin, linezolid and fusidic acid inhibit PVL production, vancomycin has little or no effect, and sub-inhibitory concentrations of oxacillin and other β -lactams enhance PVL production [43 ,44]. Antibiotics binding to penicillin binding protein 1 (PBP1) increases PVL expression by modulating *sarA* and *rot*, which are essential mediators of the inductor effect of β -lactams on PVL expression [44].

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 [45], which provides a plausible explanation why linezolid may be ideal for the management of aggressive or invasive PVLPSA infections. This action of clindamycin is not clearly understood [46].

As bacterial exposure to sub-MIC of antibiotics under clinical conditions is plausible, particularly within biofilms and necrotic tissues, one can argue β -lactam antibiotics should be avoided in PVLPSA 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 PVLSPA infections it is prudent to give antibiotics at the highest safest dose at regular intervals to avoid a drop in concentration to sub-MIC

levels and ideally choose a combination of antibiotics which included those that inhibit PVL production .

5A) Antimicrobial treatment strategies for SSTI associated with PVLPSA

The most appropriate management of SSTIs with purulent collection is represented by the surgical drainage of the purulent collection/ abscess. In the case of uncomplicated SSTI 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 patients who received TMP/SMX (1920 mg twice daily, for 7 days) had a higher cure rate than those who received a placebo. Additionally there were fewer subsequent surgical drainage procedures, new skin infections, and infections among household members in the TMP/SMX group than in the placebo group [47].

To our knowledge there are no published clinical data to support treating non necrotic PVLPSA infections with anti-PVLPSA antibiotics. Consequently unless there is a high prevalence of methicillin resistance standard therapy with adequate doses of anti-staphylococcal 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. Choice of antibiotics (table 1) will depend on local epidemiology and national guidelines. In severe infections with features of toxic shock, necrotising 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 [48, 49].

5B) Antimicrobial treatment strategies for bone and joint infections (BJI) associated with PVLPSA

In bone and joint infections (BJI), 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 PVLPSA 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 due to the risk of selecting resistant isolates with a high inoculum.

The pattern of antimicrobial susceptibilities of the etiological agent has to be considered for the selection of the most appropriate antibiotic treatment. If the infection is caused by PVLPSA-MSSA, the highest possible dose of flucloxacillin (or equivalent semisynthetic β -lactamase-resistant penicillin) with clindamycin could be combined. For suspected or proven PVL+ve MRSA, several antimicrobial regimens could be administered (Table 1). The combination of linezolid and vancomycin is not recommended because of potential antagonistic effect [50]. The new agent tedizolid may prove useful for PVLPSA BJI infections, 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.

5C) Antimicrobial treatment strategies for pneumonia associated with PVLPSA

In cases of suspected or confirmed PVLPSA pneumonia, in addition to physiological support, it is crucial to commence appropriate antimicrobial therapy (often combinations) without delay. Initial 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 PVLPSA pneumonia, it is recommended inhibitors of toxin production such as clindamycin, linezolid, or rifampicin is included in the regimen. Combinations of vancomycin with clindamycin or rifampicin, or rifampicin with linezolid or clindamycin have demonstrated success [51-53]. Early in the disease period adjuvant therapy with IVIG can be considered, for toxin neutralisation [54] although the evidence is still limited. Intensive care support is often required and extracorporeal membrane oxygenation (ECMO) may be considered early during therapy [55]. To our knowledge there are no reports demonstrating a clinical benefit of corticosteroids in PVLPSA pneumonia.

6) Eradication of MRSA/MSSA 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 health care facilities. In Denmark eradication always involve 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 necrotising 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 [56-58].

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 PVLPSA carriers. Perl *et al* [59] and Bode *et al* [60] showed intranasal application of mupirocin in carriers [54] or in combination with chlorhexidine body wash [60] significantly decreased the rate of nosocomial *S. aureus* infections. Clinical evidence on methods for *S. aureus* eradication from the mouth is lacking. Because environmental surfaces serve as reservoirs, the implementation of cleaning is recommended as part of regimens to eradicate body colonization. Studies evaluating the use of systemic antibiotics in eradicating *S. aureus*

produced conflicting data with emergence of antimicrobial resistance and toxicities being reported. Therefore treatment with systemic antibiotics for decolonisation is limited to particular circumstances [61-63].

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 and colonisation of extra nasal 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 [64], a factor that needs to be considered before implementing widespread use of eradication therapies.

Although the optimal decolonization therapy for PVLPSA is not known, it is likely to be similar to those used for MRSA decolonisation. Recommendations regarding decolonisation for PVLPSA vary by geographical region and are generally adapted from MRSA eradication regimens. In the USA, where PVL+ve 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 PVLPSA disease is relatively rare [65, 66]. Although practiced in some countries, limited data support performing initial eradication in all household members [58]. In eradication failure, particularly where no cause was identified, it is generally not reasonable to perform more than five standard decolonization attempts. In such cases treatment of underlying conditions (skin disease or change of devices) should be optimized and simultaneous treatment of the index patient and household contacts is recommended. Extended decolonization regimens over three months with intranasal mupirocin on five consecutive days each month and antimicrobial baths two to three times per week have been proposed [67]. Further studies are required to support this approach. Systemic antibiotics may be considered [47, 61-63].

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

7) PVLPSA infections 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 [68]. Cefai *et al*, reported isolation of an MRSA with an identical phage type from the nose of a health care worker, his partner and their pet dog [69]. While another report demonstrated recurrence of the MRSA infection of a couple only stopped once their pet dog was no longer an MRSA carrier [70]. Transmission of MRSA between humans and horses has also been suspected in veterinary settings [71].

It is widely recognized, because of the close contact with humans, companion animals tend to share the same lineages identified in humans. Consequently, pets may become reservoirs of PVLPSA in regions with high PVL prevalence in the human *S. aureus* population. Three

studies have reported a likely role of the household pet in human PVL+ve MRSA carriage and infection. In two studies, the patient's cure and decolonization required treatment of all "family members" (including the pet) with ciprofloxacin and rifampin [68, 72]. However, a recent case report on the dynamics of household transmission of MRSA USA300 by whole genome sequencing failed to implicate the pet in human MRSA outcomes [73].

According to European Union guidelines [74], companion animals for which clinical infection with MRSA is suspected or confirmed should be monitored and quarantine considered. It has been recommended MRSA-infected pets should be restricted from human contact until clinical cure [75]. As for healthy pet carriers, there is currently insufficient evidence to recommend routine decolonization. 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 decolonization should be considered if there is a specific plan for the pet's decolonization or short-term removal from the household while the humans are being treated [75]. To our knowledge PVL has not been identified in a bona fide livestock associated strains. Studies of CC398 strains have pointed to distinct groups: a livestock clade (PVL negative) and a human clade (can be PVL+ve). PVL+ve CC398-MRSA belonging to the human clade has been identified, particularly in China and surrounding countries [76].

8) Outbreak management in hospitals/ barracks/ prisons etc.

8A) Managing PVLPSA clusters in hospitals

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

Most of the reported PVLPSA hospital clusters are MRSA involving pediatric or neonatal intensive care units [77-80]. 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 PVLPSA infections or colonisation including, ST80 (European community MRSA clone), ST22, ST772 (Bengal Bay MRSA) and ST30 (Southwest Pacific or Oceanic clone). A multicenter study from France showed 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 PVLPSA prevalence among SSTIs was high, only a few of the PVLPSA-colonized patients subsequently showed signs of an infection [80].

The PVLPSA transmission routes within hospital clusters are not completely understood. In most clusters, HCWs were found to be colonized or infected with the cluster strain [77, 79].

Very few environmental investigations detected the respective strains, leaving the transmission route unknown [77]. However, application of bacterial whole-genome sequencing in real time has been shown to help in identifying carriage by a HCW as a potential source of an ongoing MRSA outbreak and directly inform infection-control interventions [81]. Transmission is normally limited to close physical contact. Therefore, targeted decolonization of colonized patients and staff is important. Nonetheless, escalating general hygiene measures such as contact isolation and improved hand hygiene compliance and cleaning the environment are the most successful interventions.

8 B. 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 colonized 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 [82-84] and close contact sports, e.g., wrestling, rugby, or judo. Many PVLSPA patients however may have no identifiable risk factors.

8C) Managing household outbreaks of PVLPSA.

Household (or family) outbreaks of PVLPSA 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 PVLPSA isolates are more likely to generate SSTIs among household contacts compared to PVLNSA isolates. A summary of PVLPSA outbreak management in hospitals, community settings and among households is presented in Table 2.

9) The role of cleaning and decontamination for controlling PVLPSA in healthcare and community settings

People colonised or infected with PVLPSA 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 [40]. PVLPSA will persist for months, even in dry environmental niche, and therefore need to be removed by cleaning or disinfecting.

Community institutions facing particular risk from PVLPSA 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 colonization of companion animals may represent an additional source for human colonisation, however data remain scarce in this field (please see section 7) . Members of staff at healthcare facilities treating people with PVLPSA carriage or infection are themselves at risk [85-88].

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, 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 PVLPSA transmission. Automated decontamination devices dispelling hydrogen peroxide (H₂O₂) and UVC micro biocidal light, although costly, may be employed in the terminal cleaning of vacated single rooms, but not communal areas [89]. Comprehensive environmental cleaning is essential for controlling PVLPSA in healthcare and other environments.

10) Chlorhexidine resistance in *S. 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 which efflux chlorhexidine in exchange for protons. Such efflux pumps are primarily encoded by *qacA/B* genes which are present on large conjugative plasmids carrying multiple determinants of resistance to antibiotics and other biocides [90, 91]. This raises a concern of potential cross-resistance between chlorhexidine and antibiotics as well as inter-strain and inter-species horizontal transmission of multidrug resistance plasmids. Nonetheless, the clinical significance of *qacA/B* carriage itself remains unclear. While 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 [91, 92]. Recently, *qacA/B* carriage has also been reported in PVL+ve MSSA from osteomyelitis and necrotising pneumonia [92]. While there are no reports of *qacA/B* carriage in PVL+ve MRSA, this trend may well change as the prevalence of hospital-associated PVLPSA strains increases.

In *S. aureus*, mutations of the promoter region of *norA* have been implicated in potential cross-resistance of chlorhexidine and fluoroquinolones [93, 94]. Randomised controlled trials to measure the effect of chlorhexidine-based strategies *versus* use of alternative antiseptics, but more importantly universal *versus* targeted decolonisation strategies, will elucidate the effect of intensive use of chlorhexidine on emergence of resistance to antimicrobials and antiseptics in MRSA, MSSA and CoNS.

11) Decolonisation agents for PVLPSA (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 povidone-iodine and octenidine were superior to polyhexanide, chlorhexidine and triclosan (in decreasing order of efficacy) for immediate MRSA decolonisation [95] (Table 3).

For nasal decolonisation mupirocin remains the drug of choice in hospital settings. It should be remembered though sustained use can lead to resistance and decolonisation failure.

Genetic determinants for resistance to mupirocin have been reported in PVLPSA. Therefore alternative regimens have been sought widely, although the superiority of these approaches in terms of MRSA eradication and long-term impact on emergence of resistance has not been demonstrated (table 3).

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 PVLPSA, and optimal strategies for the treatment, decolonization, prevention, and environmental control of PVLPSA in the community and in the health care setting.

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Table 1: Examples, pros, cons and potential indications for antimicrobials used in the treatment of PLVPSA

Drug*	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.	Prolong use of these agents necessitate folic 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 beta-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)
Rifampin	Anti-MRSA and PVL activity, anti-biofilm activity/Resistance selection if used alone, drug-drug interactions, liver toxicity	Should only be used in combination therapy (fluoroquinolones for MSSA or a glycopeptide or 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, anti-biofilm 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 MRSA)
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**	Anti-MRSA, anti-PVL activity, good bone penetration, oral formulation, once daily/High cost	Treatment of outpatients

*In general please follow local guidance and antimicrobial susceptibilities. Anti MRSA agents can also be used for MSSA if indicated. For uncomplicated SSTI combination treatment is seldom required.

** There is limited clinical experience with this drug to date for complicated SSTIs and BJI.

Table 2 Overview of PVLPSA outbreak management in hospitals, community settings and households

Location of outbreaks	Hospitals	Community institutions	Household
Outbreak control strategies	<p>Increased environmental cleaning, hand hygiene compliance along with either single room isolation or cohorting of affected patients, were first line precautions [77, 79]. 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 PVLPSA respiratory infections. The number of staff present should be limited to avoid unnecessary exposures. Additionally intra or inter hospital 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.</p> <p>Excessive waiting times in departments should be minimized. 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 decolonization were additional measures [77]. Active screening proved effective when it included all patients at risk, all involved HCWs and patient family members, and colonized HCWs were excluded from the working environment pending successful decolonization [79]. Lee et al. implemented universal decolonization in order to curtail transmission of PVLPSA [78]. However, one should keep in mind that not all antiseptic substances and concentrations are suitable for pediatric patients.</p> <p>Staff with proven PVLPSA 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 five-day decolonization regimen for staff with proven PVLPSA infections commencing after all skin lesions are dry, and at least 48 hours prior to return to work. Weekly follow-up screens following topical decolonization are advised by the PHE [65, 66]. 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 PVLPSA SSTI is not recommended unless active skin lesions or dermatological conditions are present. Staff exposed to respiratory secretions, e.g., intubation in PVLPSA necrotising pneumonias without appropriate PPE such as surgical face masks and eye protection, should be screened three to seven days after exposure and monitored for symptoms subsequently.</p>	<p>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 minimized. Hand hygiene should be emphasized with frequent and thorough cleaning with soap and water or alcohol based sanitizer. Personal items which 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 [82, 84]. In athletes, strategies to minimize skin breaks, including prevention of turf burns [82], could also be considered. Individuals with active lesions may be advised to avoid use of shared sports equipment [84]. 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.</p> <p>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. Decolonization 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 PVLPSA eradication, should be implemented on an individualised risk based approach, taking into consideration the severity of the infection in the outbreak, vulnerability of contacts in the setting, degree and nature of contact and risk of ongoing transmission despite general hygiene measures.</p>	<p>Management of family outbreaks requires screening of the whole household (nose, groin and any skin lesions) for PVLPSA. The general principles of <i>S. aureus</i> control need to be employed [62]. 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.</p> <p>Evidence for prevention is limited specifically for PVLPSA. 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 laundry of towels, bed linen, and clothing using a hot wash (60°C) are recommended where possible [85,86]. The household should be cleaned regularly with vacuuming and dusting [58]. Household pets have occasionally been implicated in persisting PVLPSA (please refer to topic 7 and 8 of this manuscript)</p> <p>Infected householders should be advised to avoid communal and recreational settings until lesions are healed if they cannot be adequately contained by a dressing.</p> <p>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.</p> <p>Limited data support performing initial eradication in all household members, however this can be offered. Quarterly decolonization has been proposed in refractory or recurrent PVLPSA colonization and infections among families [67]. Further studies are required to support these suggestions and proposals.</p>

Table 3: Alternative agents proposed for skin and nasal decolonisation

Proposed use	Agent	Decolonisation rates relative to placebo or gold standard agents	Resistance mechanisms in <i>S. aureus</i>	Adverse effects identified
Skin decolonisation	Polyhexadine ⁹⁶	Clinical trial of a single decolonisation course with polyhexadine was not more efficacious than the placebo in eradication of MRSA.	None identified	None in most studies
	Octenidine ⁹⁷	Placebo-controlled efficacy comparable to chlorhexidine, but the 2 agents not yet compared in RCT	None identified	Inconsistent data across studies
	Tea tree oil ⁹⁸	Eradication rates comparable to chlorhexidine-based treatments (small trial)	Not investigated	Further studies required; concern for gyencomastia in boys
	Sodium hypochlorite ⁹⁹	More efficacious than chlorhexidine in eradication. Currently recommended by the Infectious Diseases Society of America for prevention of recurrence of MRSA-related skin infections.	None identified	Dry skin
	Hexachlorophene ¹⁰⁰	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 ^{91, 101}	Not more efficacious than placebo or non-antimicrobial soaps	Multiple mechanisms identified	Rare
	SHRO ¹⁰²	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) ¹⁰³	Less efficacious than mupirocin	Multiple mechanisms identified	High prevalence of contact dermatitis
	Tea tree oil ⁹⁸	Less efficacious than mupirocin	Not investigated	Further studies required
	SHRO ¹⁰²	No comparator studies been done with mupirocin.	Not known	Rare
	Pleuromutulins ¹⁰⁴	More potent than mupirocin <i>in vitro</i> but the 2 agents not yet compared in RCT	Multiple mechanisms identified	Contact dermatitis
	Lauric acid ¹⁰⁵	More efficacious than mupirocin in a preclinical model, but the 2 agents not yet compared in RCT	Not investigated	Not assessed in clinical studies
	Lytic phage ^{106, 107}	More efficacious than mupirocin in a preclinical model, but the 2 agents not yet compared in 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