Panton-Valentine leukocidin osteomyelitis in children: a growing threat

Panton-Valentine leukocidin-producing* Staphylococcus aureus *osteomyelitis is associated with multiple complications including multiple abscesses, deep vein thrombosis and fulminant sepsis. This article reviews the literature concerning this emerging threat which is currently under-recognized.

Osteomyelitis is a common paediatric infection encountered in orthopaedics. *Staphylococcus aureus* remains the commonest causative pathogen, encountered in 70–90% of cases (Bocchini et al, 2006). *S. aureus* produces a number of toxins including the Panton-Valentine leukocidin toxin, first described in 1932. In the UK, approximately 1–5% of clinical isolates of *S. aureus* produce Panton-Valentine leukocidin toxin, with production in both meticillin-susceptible *S. aureus* and meticillin-resistant *S. aureus* (Holmes et al, 2005). Within orthopaedics, Panton-Valentine leukocidin-producing *S. aureus* has been associated with severe osteomyelitis and complications, e.g. pulmonary infections, that can be fatal (Rafai et al, 2013; Shallcross et al, 2013).

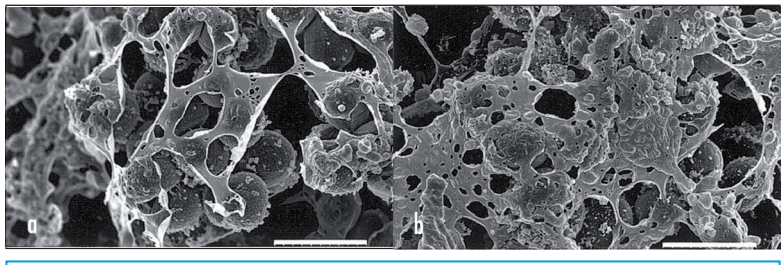
This article reviews the literature concerning Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis which is likely under-recognized as a result of a lack of awareness and infrequent diagnostic testing.

Structure of Panton-Valentine leukocidin and leukocytotoxicity

Panton-Valentine leukocidin is a bi-component cytotoxin produced by certain strains of *S. aureus*. The detection of Panton-Valentine leukocidin-producing *S. aureus* is either by polymerase chain reaction detection of the gene or by toxin assays. Most *S. aureus* that possess the pvl gene produce toxic concentrations of Panton-Valentine leukocidin in vitro (90%) (Badiou et al, 2010).

Panton-Valentine leukocidin belongs to a family of synergo hymenotropic (assemble to form pores) proteins that are leukocytotoxic. Panton-Valentine leukocidin protein subunits assemble in white cell membranes (particularly monocytes and macrophages) to form a central pore through which cell contents can leak (Szmigielski et al, 1999; Kaneko and Kamio, 2004). The resulting apoptosis and necrosis (*Figure 1*) is able to compromise the immune response of the infected micro-environment and facilitate the spread of bacteria (Genestier et al, 2005). The assembled Panton-Valentine leukocidin protein can also act as a super-antigen and therefore trigger a massive immune response (Deresinski, 2005).

Figure 1. Ultrastructural analysis of necrosis of human polymorphonuclear leukocytes infected with (a) Panton Valentine leukocidin-negative meticillin-resistant* Staphylococcus aureus *(bar = 1.67 μm) and (b) Panton Valentine leukocidin-positive meticillin-resistant* S. aureus *(bar= 1.48 μm). Scanning electron microscopy. From Voyich et al (2006).



Mr Hassaan Q Sheikh *is Specialty Registrar and* **Mr Adeel Aqil** *is Specialty Registrar in the Department of Trauma and Orthopaedics,* **Dr Andrew Kirby** *is Consultant Microbiologist in the Department of Microbiology and* **Mr Fahad S Hossain** *is Specialty Senior Registrar in the Department of Trauma and Orthopaedics, Leeds General Infirmary, Leeds LS1 3EX*

Correspondence to: Mr HQ Sheikh (hqsheikh@doctors.org.uk)

Epidemiology of Panton-Valentine leukocidin osteomyelitis

In developed countries, the incidence of paediatric osteomyelitis is between 1.9 and 13/100 000 and the commonest causative organism is *S. aureus* (Dartnell et al, 2012). Owing to a paucity of evidence, the true incidence of Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis is not known. According to the Health Protection Agency in the UK, the overall incidence of Panton-Valentine leukocidin-producing *S. aureus* infections remains low but with evidence of annual increase, possibly as a result of increased awareness and more samples referred for testing (Health Protection Agency, 2008).

In the UK, the Panton-Valentine leukocidin toxin is secreted by 1–2% of all *S. aureus* isolates and around 5% of isolates from established skin and soft tissue infection (Holmes et al, 2005). The majority of these isolates cause skin and superficial soft tissue infections and far fewer musculoskeletal infections (Shallcross et al, 2013).

The prevalence of Panton-Valentine leukocidin-producing *S. aureus* in osteomyelitis in the UK is not known. In the USA, Panton-Valentine leukocidin-producing *S. aureus* accounts for up to two-thirds of *S. aureus*-related paediatric osteomyelitis (Bocchini et al, 2006; Sdougkos

et al, 2007). It is attributed to the USA-300 clone – the most common meticillin-resistant *S. aureus* clone in the USA. The majority of the current literature on Panton-Valentine leukocidin-producing *S. aureus* originates from the USA, giving the impression that Panton-Valentine leukocidin-producing *S. aureus* is associated with the reported severe disease associated with USA-300 meticillin-resistant *S. aureus*. It is therefore difficult to separate the effects of meticillin-resistant *S. aureus* and those truly caused by the presence of the pvl gene. Within the UK and Europe, the USA-300 strain is infrequently reported, and over half of Panton-Valentine leukocidin-producing *S. aureus* strains are meticillin-susceptible *S. aureus* (Holmes et al, 2005).

In a large Australian series of 478 patients, Panton-Valentine leukocidin-producing *S. aureus* was more common in meticillin-resistant *S. aureus* than meticillin-susceptible *S. aureus* (54% *vs* 40%) infections (Tong et al, 2010). Tong et al (2010) concluded that Panton-Valentine leukocidin-producing *S. aureus* causes clinically distinct infections to Panton-Valentine leukocidin-negative strains and emphasized that Panton-Valentine leukocidin-producing *S. aureus* is present in meticillin-susceptible *S. aureus* but under-recognized. In the context of paediatric osteomyelitis, the Panton-Valentine leukocidin strain has been reported in 9–21% of meticillin-susceptible *S. aureus* infections whereas 87–100% of meticillin-resistant *S. aureus*-related infection had Panton-Valentine leukocidin toxin confirmed (Martinez-Aguilar et al, 2004; Bocchini et al, 2006). Interestingly these studies also reported that Panton-Valentine leukocidin-producing *S. aureus* disease was associated with community-acquired infection in younger age groups presenting with overwhelming sepsis.

Panton-Valentine leukocidin in osteomyelitis

Clinical presentation

A meta-analysis suggested that Panton-Valentine leukocidin-producing *S. aureus* is a more common cause of skin and soft tissue infections than deeper musculoskeletal infections (Shallcross et al, 2013). However, children with Panton-Valentine leukocidin-producing *S. aureus* musculoskeletal infection may be at an increased risk of morbidity. The presenting symptoms of Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis are generally similar to Panton-Valentine leukocidin-negative cases, but disease progression is reported to be more aggressive and rapid with severe presentations, e.g. severe sepsis, more severe pain, a greater inability to weight bear and/or swelling of the affected limb (Mitchell et al, 2007). The location of osteomyelitis is similar, with over 60% of infections affecting the femur, tibia or fibula in both Panton-Valentine leukocidin-positive and -negative disease (Bocchini et al, 2006).

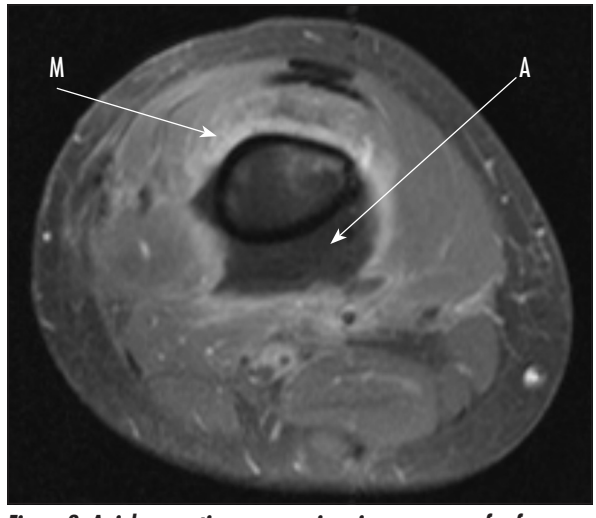


Figure 2. Axial magnetic resonance imaging sequence of a femur infected with Panton-Valentine leukocidin-producing* Staphylococcus aureus *osteomyelitis. Note the large subperiosteal abscess (A) and extensive high signal in the surrounding muscles indicating myositis (M).

Clinical severity

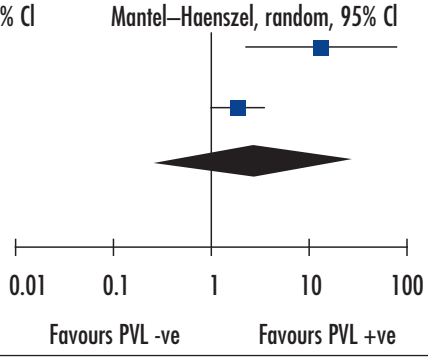
Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis can be multifocal with multiple bones involved. Patients are also more likely to present with large subperiosteal abscesses (risk ratio 3.90, *P*=0.25, *Figures 2* and *3*), multiple bony abscesses (*Figure 4*) and associ-

***Figure 3. Forest plot: risk ratios of subperiosteal abscess. CI = confidence interval; PVL = Panton-Valentine leukocidin-producing* Staphylococcus aureus.**

	PVL +ve		PVL -ve			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	Mantel–Haenszel, random, 95% CI	Mantel–Haenszel, random, 95% CI
Dohin et al (2007)	11	14	1	17	42.1%	13.36 (1.96, 91.20)	
Bocchini et al (2006)	34	45	9	19	57.9%	1.60 (0,97, 2.64)	
Total (95% CI)		59		36	100.0%	3.90 (0.39, 39.16)	
Total events	45		10				

Heterogeneity: Tau^2= 2.33; chi2= 5.53, degrees of freedom=1 (*P*=0.02); I^2=82%

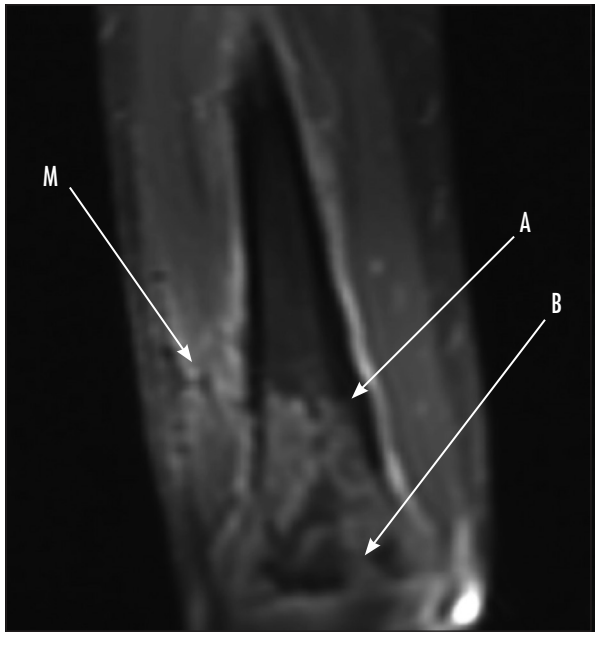
Test for overall effect: Z= 1.16 (*P*=0.25)



ated myositis and/or pyomyositis (risk ratio 3.22, *P*=0.18, *Figure 5*) diagnosed on magnetic resonance imaging scan. Comparatively, Panton-Valentine leukocidin-negative osteomyelitis usually occurs with a single focus of infection without peri-focal involvement (Bocchini et al, 2006; Dohin et al, 2007; Ceroni et al, 2012).

Studies have reported that Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis cases have a more severe disease course. In their series of 59 children with *S. aureus* musculoskeletal infections (81% osteomyelitis), Martinez-Aguilar et al (2004) reported that Panton-Valentine leukocidin-*S. aureus* was significantly associated with longer febrile days and more complications (10 *vs* 0 complications). Similarly Bocchini et al (2006) and Sdougkos et al (2007) have reported in *S. aureus* osteomyelitis that those with Panton-Valentine leukocidin-producing *S. aureus* had higher levels of biochemical inflammatory markers at presentation and at their peaks and take longer to normalize. Bocchini et al (2006) reported that blood cultures were more likely to be positive for *S. aureus* (67.2% *vs* 19.2%) in 89 children and these children were more likely to require intensive care unit admission. These children are also likely to have a longer illness course, with more febrile days and a longer inpatient stay (Dohin et al, 2007). Diagnostic ambiguity is therefore less likely in Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis compared to Panton-Valentine leukocidin-negative cases, owing to a more severe clinical presentation with much higher levels of inflammatory markers and positive blood cultures. Such a clinical picture should prompt the clinician to consider assessing for Panton-Valentine leukocidin-producing *S. aureus*-associated complications, e.g. deep vein thrombosis and multifocal infection.

Figure 4. Coronal magnetic resonance imaging sequence of a femur infected with Panton-Valentine leukocidin-producing* Staphylococcus aureus *osteomyelitis. Subperiosteal abscess (A), bony abscess (B) and myositis (M).



Osteomyelitis caused by Panton-Valentine leukocidin-producing *S. aureus* can result in systemic complications including overwhelming sepsis and septic shock (Mitchell et al, 2007). Complications also reported include multifocal infections including infective endocarditis, cerebral infarcts, deep vein thromboses and rhabdomyolysis with acute kidney injury requiring renal replacement therapy. Multi-organ dysfunction leading to mortality has been reported in adults (Rafai et al, 2013). A rare reported local complication is spontaneous tibio-talar fusion 2 months after Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis of the distal tibial diaphysis (Ceroni et al, 2012). The authors suggested that the pathophysiology of the auto-arthrodesis is linked to higher levels of metallo-proteinases and collagen degrading enzymes that are found in the massive immune response following septic arthritis by Panton-Valentine leukocidin-producing *S. aureus*. Long-term sequelae are therefore common following Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis and require a longer duration of follow up compared to Panton-Valentine leukocidin-negative osteomyelitis (Dohin et al, 2007).

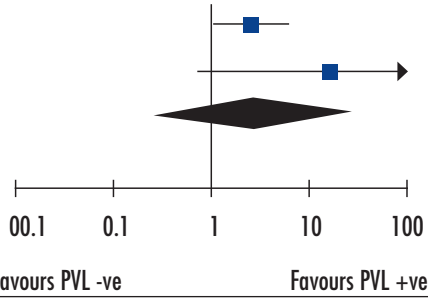
Pulmonary infection is an important systemic complication of Panton-Valentine leukocidin-producing *S.*

***Figure 5. Forest plot: risk ratios of myositis and/or pyomyositis. CI = confidence interval; PVL = Panton-Valentine leukocidin-producing* Staphylococcus aureus.**

	PVL +ve		PVL -ve			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	Mantel–Haenszel, random, 95% CI	Mantel–Haenszel, random, 95% CI
Bocchini et al (2006)	28	45	6	19	74.2%	1.97 (0.98, 3.97)	
Dohin et al (2007)	5	14	0	17	25.8%	13.20 (0,79, 219.87)	
Total (95% CI)		59		36	100.0%	3.22 (0.58, 17.92)	
Total events	33		6				

Hetergeneity: Tau^2= 0.91; chi^2= 1.83, degrees of freedom=1 (*P*=0.18); I^2=45%

Test for overall effect: Z= 1.34 (*P*=0.18)



aureus osteomyelitis. Broadly speaking, pulmonary infection in osteomyelitis has been shown to be related to deep vein thrombosis, probably through septic emboli (Gonzalez et al, 2006; Vander Have et al, 2009). Indicators of pulmonary involvement in Panton-Valentine leukocidin-producing *S. aureus* infection include haemoptysis, abnormal chest radiograph, multilobar involvement and leukopenia (Gonzalez et al, 2005; Mitchell et al, 2007). Pulmonary infection with Panton-Valentine leukocidin-producing *S. aureus* is a very poor predictor of outcome, with a reported mortality of 75.8% (Khanafer et al, 2013).

Venous thromboembolism

Deep vein thrombosis is more commonly seen in patients with Panton-Valentine leukocidin-positive *S. aureus* infection than with Panton-Valentine leukocidin-negative *S. aureus* infection (risk ratio=8.07, *P*=0.04) (*Figure 6*). Primary venous thromboembolism in children is rare. Annual incidence is 0.06–0.07/10 000 compared to 2–7/10 000 in adults (Lachambre et al, 2005). However, the incidence in association with acute osteomyelitis is increasing and is present in around 9% of paediatric cases with osteomyelitis (Bouchoucha et al, 2010). Such patients with deep vein thrombosis (*Figure 7*) are more likely to be infected with meticillin-resistant *S. aureus* (Gonzalez et al, 2006).

Gonzalez et al (2006) reported nine cases of deep vein thrombosis associated with acute haematogenous osteomyelitis, seven of which (78%) were caused by Panton-Valentine leukocidin meticillin-resistant *S. aureus*. Similarly Dohin et al (2007) found that three of their 14 paediatric Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis cases developed a deep vein thrombosis compared to none of their 17 patients with Panton-Valentine leukocidin-negative osteomyelitis (21% *vs* 0%, *P*=0.08). These findings have been echoed in other studies which have shown a strong association between paediatric Panton-Valentine leukocidin-producing *S. aureus* musculoskeletal infections and the risk of developing deep vein thrombosis (Martinez-Aguilar et al, 2004; Obando et al, 2011). It should be borne in mind, however, that the true incidence in the context of Panton-Valentine leukocidin osteomyelitis is likely much higher than reported as previous studies have not routinely investigated for this complication. Although the exact pathophysiology of this is not well understood, it may be linked to the greater systemic response found in Panton-Valentine leukocidin osteomyelitis in relation to a massive local inflammatory response since deep vein thromboses are invariably found adjacent or proximal to the site of osteomyelitis (Gonzalez et al, 2006).

Patients with osteomyelitis and deep vein thrombosis are likely to have a much greater systemic response to their illness with more prominent local signs, a higher temperature, longer duration of pyrexia, higher erythrocyte sedimentation rate, higher C-reactive protein levels and a positive blood culture. Surgery is also more likely to be required for abscess drainage in these patients (Hollmig et al, 2007; Bouchoucha et al, 2010).

Figure 7. Axial magnetic resonance imaging sequence of a femur infected with Panton-Valentine leukocidin-producing* Staphylococcus aureus *osteomyelitis showing multiple complications including deep vein thrombosis (D) in the femoral vein.

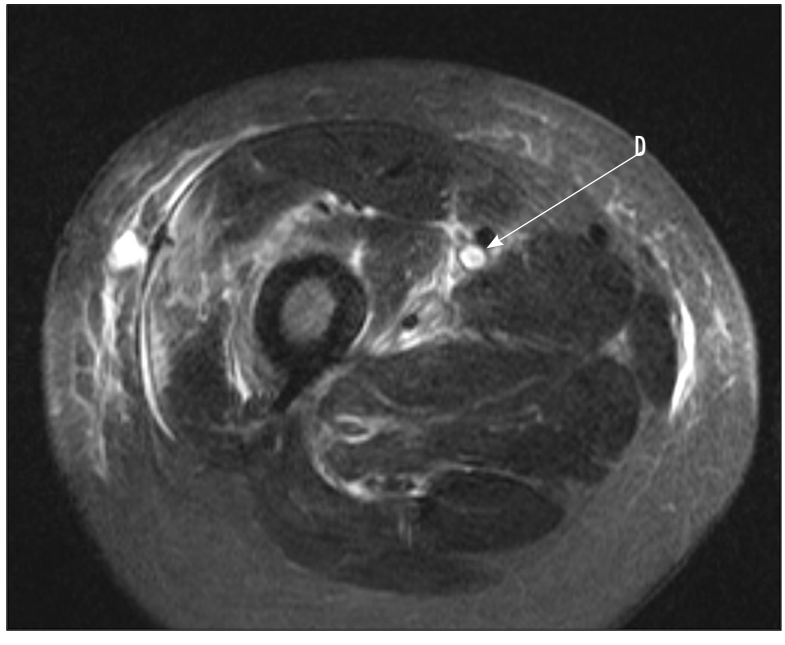
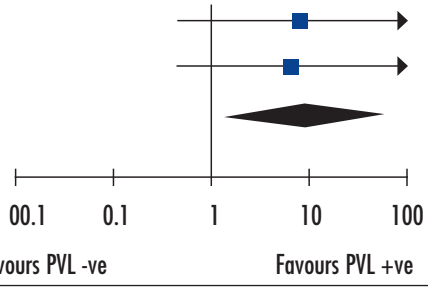


***Figure 6. Forest plot: risk ratios of deep vein thrombosis. CI = confidence interval; PVL = Panton-Valentine leukocidin-producing* Staphylococcus aureus.**

	PVL +ve		PVL -ve			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	Mantel–Haenszel, random, 95% CI	Mantel–Haenszel, random, 95% CI
Dohin et al (2007)	3	14	0	17	49.4%	8.40 (0.47, 150.07)	
Bocchini et al (2006)	5	33	0	23	50.6%	7.76 (0,45, 133.90)	
Total (95% CI)		47		40	100.0%	8.07 (1.06, 61.21)	
Total events	8		0				

Hetergeneity: Tau^2= 0.00; chi^2= 0.00, degrees of freedom=1 (*P*=0.97); I^2=0%

Test for overall effect: Z= 2.02 (*P*=0.04)



Investigations

While Panton-Valentine leukocidin-negative osteomyelitis has a comparatively more insidious onset, Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis tends to present with features of sepsis and higher inflammatory markers (Dohin et al, 2007). Blood cultures are frequently positive for *S. aureus* in Panton-Valentine leukocidin-producing *S. aureus* disease and stay positive for longer than Panton-Valentine leukocidin-negative disease (Martinez-Aguilar et al, 2004). This may reflect an intravascular source of some of these infections, such as infected deep vein thromboses. The current recommendation from the British Society for Children's Orthopaedic Surgery (2013) is to delay starting antibiotics until specimens of suspicious tissue are obtained, apart from in the very unwell child where antibiotic treatment should start immediately. Deep tissue samples or synovial fluid (in septic joints) will isolate organisms in up to 80% of cases.

The clinical utility of Panton-Valentine leukocidin testing is uncertain, as disease severity should prompt investigations for complications of osteomyelitis. Public Health England currently do not specifically request that *S. aureus* isolates from osteomyelitis cases are sent for Panton-Valentine leukocidin testing. They do suggest necrotizing skin or pulmonary infections, and those with recurrent abscesses or where an outbreak is suspected are considered for Panton-Valentine leukocidin testing. Conventional bacterial culture does not differentiate between Panton-Valentine leukocidin-positive and Panton-Valentine leukocidin-negative *S. aureus*. Diagnosis can be made by detection of the pvl gene using polymerase chain reaction analysis of bacterial DNA (Bocchini et al, 2006). Newer techniques allowing rapid detection include enzyme-linked immunosorbent assay and immunochromatographic tests for the Panton-Valentine leukocidin toxin (Badiou et al, 2010).

Given Panton-Valentine leukocidin testing is often a reference test, or may not be completed according to national guidelines, it will often be the case that Panton-Valentine leukocidin status is not known. The evidence suggests that those with severe presentations of osteomyelitis should be considered as possibly being Panton-Valentine leukocidin positive and investigated as such.

Early plain radiographic findings may be subtle or absent and therefore other imaging modalities such as magnetic resonance imaging are invaluable in establishing the focus or foci of infection and any local complications, including incidental findings of deep vein thrombosis. As the abscesses may recur, repeat magnetic resonance imaging is indicated if the clinical picture does not improve despite drainage of pus and appropriate antibiotic therapy. Pulmonary complications can include emboli, which are not infrequently septic, so chest imaging needs to be targeted to the clinical presentation. Gonzalez et al (2005) reported that in a series of 113 children with invasive *S. aureus* infections, abnormal chest X-ray findings were present in 51 of 80 patients with Panton-Valentine leukocidin-producing *S. aureus* and in a multivariate analysis the presence of Panton-Valentine leukocidin-producing *S. aureus* was significantly associated with secondary pneumonia in children with an abnormal chest X-ray.

The role of routine investigation for deep vein thrombosis in children with osteomyelitis is not yet established. Hollmig et al (2007) recommended that all children with osteomyelitis should have diagnostic venous imaging performed to assess for deep vein thrombosis. Gonzalez et al (2006) suggested using duplex Doppler ultrasound venography to assess for deep vein thrombosis, although this may be unreliable as surrounding myositis and oedema may alter venous blood flow. Multiple treatment options for deep vein thrombosis in children with osteomyelitis are described including low molecular weight heparin, intravenous heparin and intra-caval filters for severe cases (Gonzalez et al, 2006), but the ideal treatment is not yet established.

Management

Surgical debridement and washout remains an important aspect of management in most reported Panton-Valentine leukocidin-producing *S. aureus* bone infections to gain local control of infection and multiple procedures may be necessary (Bocchini et al, 2006; Dohin et al, 2007; Ceroni et al, 2012). This is in contrast to guidelines by the British Society for Children's Orthopaedic Surgery (2013) which states that antibiotic therapy is sufficient and surgery does not confer any additional benefits in most cases. The aim of drainage is not only to halt the local infective process, but also to remove the 'glutinous pus' that makes local delivery of antibiotics difficult (Mitchell et al, 2007). As the pus is thick and difficult to drain arthroscopically, an open approach may be preferable if joint washouts are necessary. Dohin et al (2007) and Bocchini et al (2006) both reported that patients with Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis were more likely to require surgical exploration and drainage. The former reported that 71% of these patients required surgical procedures, often multiple (range 1–5), while only 17% of non-Panton-Valentine leukocidin osteomyelitis patients required a single surgical procedure.

Surgical techniques beyond simple drainage and debridement have been described. The use of a well-vascularized interpositional muscular flap such as that from the gastrocnemius in cases of tibial infection has been advocated to allow adequate soft tissue coverage following extensive bone and soft tissue debridement. The use of muscle interposition flaps to cover debrided bony defects has previously been used in chronic osteomyelitis (Smith et al, 2006) but has also proven useful in

treating acute Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis.

Targeted antibiotic therapy is the key to successful treatment following drainage of any associated abscess. Currently, there is a paucity of literature comparing the effectiveness of antibiotic regimens for Panton-Valentine leukocidin osteomyelitis. As the majority of cases of osteomyelitis are caused by meticillin-susceptible *S. aureus*, flucloxacillin is a common empirical first-line antibiotic used in most institutions. However, significant numbers of bone infections are caused by meticillin-resistant *S. aureus* and this only becomes evident after appropriate blood or tissue culture results are available. In such instances, antibiotics with activity against meticillin-resistant *S. aureus* such as vancomycin are started. Panton-Valentine leukocidin-producing *S. aureus* is linked to both meticillin-resistant *S. aureus* and meticillin-susceptible *S. aureus*, however, so first-line antibiotics may not necessarily have significant action against the micro-organism.

In vitro clindamycin, rifampicin, linezolid and fusidic acid all decrease Panton-Valentine leukocidin production (Dumitrescu et al, 2008). In sub-inhibitory concentrations, flucloxacillin increases Panton-Valentine leukocidin production by 250% in vitro (Dumitrescu et al, 2008), but there are no clinical studies demonstrating this in vivo. In-vitro studies also show that combination therapy of flucloxacillin and clindamycin or rifampicin or linezolid all inhibited Panton-Valentine leukocidin production. There are isolated case reports of using other antibiotics such as daptomycin effectively (Erturan et al, 2012).

Current practice in England is based around guidance from the British Society for Children's Orthopaedic Surgery (2013) and antibiotics with anti-toxin effects are recommended. For proven Panton-Valentine leukocidin-producing *S. aureus* infection clindamycin is used as first-line therapy with the addition of vancomycin in meticillin- and clindamycin-resistant cases. Linezolid is also useful in cases where these antibiotics do not show clinical improvement. Ultimately, however, the most effective antibiotic regimen depends upon the sensitivity of the cultured micro-organism and oral antibiotics usually have to be continued on a long-term basis until clinical and biochemical markers of the infection normalize. Panton-Valentine leukocidin-producing *S. aureus*-positive patients are likely to have recurrent abscesses and/or recurrence of bone infection and therefore require a longer follow up. Another important reason to follow up is presence of associated deep vein thrombosis. The ideal duration of follow up after discharge from hospital is not established, although one study reported that thrombus resolved after a mean of 11 weeks (Hollmig et al, 2007). In the authors' experience with this condition, serial magnetic resonance imaging scans are invaluable in assessing disease progression and identifying late complications, e.g. recurrent abscess.

Conclusions

Panton-Valentine leukocidin-producing *S. aureus* can cause severe osteomyelitis that presents with sepsis, may require longer inpatient care and has more short- and long-term sequelae than non-Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis. Clinical associations of Panton-Valentine leukocidin osteomyelitis include subperiosteal abscesses, myositis or pyomyositis, deep vein thrombosis and fulminant pulmonary sepsis.

At presentation, because of the severe clinical picture, there is normally minimal diagnostic ambiguity that a patient with Panton-Valentine leukocidin-producing *S. aureus* osteomyelitis has an aggressive infective process. Expediting confirmation of diagnosis and sensitivities will ensure early use of appropriate antibiotics.

If there is clinical suspicion of Panton-Valentine leukocidin-producing *S. aureus* (effectively in patients with severe osteomyelitis), empirical antibiotic treatment should be administered early with magnetic resonance imaging of the affected site(s). Effective treatment requires drainage of associated abscesses. As the abscesses or foci of infection may be multiple and/or serial, serial magnetic resonance imaging scans are invaluable. Magnetic resonance imaging has the added advantage of identifying local extension of infection and deep vein thromboses.

The ideal antibiotic regimen will vary with local prevalence of strains and sensitivities. There is a current effort to develop an anti-Panton-Valentine leukocidin toxin with limited success in vitro (Libert et al, 2009), but this approach may prove beneficial in combating this emerging threat as more sophisticated treatments become available.

Literature on Panton-Valentine leukocidin-producing *S. aureus* musculoskeletal infections consists mostly of retrospective cohort studies and case series. Prospective epidemiological, diagnostic and therapeutic studies relating to Panton-Valentine leukocidin-producing *S. aureus* in osteomyelitis are needed in the UK population. Awareness of Panton-Valentine leukocidin-producing *S.*

KEY POINTS

- Panton-Valentine leukocidin-producing *Staphylococcus aureus* can cause an aggressive osteomyelitis.
- This condition is commonly associated with deep vein thrombosis.
- It may also be complicated by subperiosteal abscesses, myositis and/or pyomyositis.
- Early and repeat magnetic resonance imaging are invaluable in diagnosis and surveillance.
- Treatment and complications frequently require surgical intervention.

aureus bone infections and its related sequelae is of paramount importance among clinicians treating acute osteomyelitis in children. **BJHM**

Figure 1 *is reproduced from Voyich et al (2006) by kind permission of Oxford University Press.*

The freeware software application Review Manager (RevMan) Version 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen) was used to create the forest plots in Figures 3, 5 *and* 6.

Conflict of interest: none.

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