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Paediatric musculoskeletal infections with Panton-Valentine leucocidin

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Summary

AIMS OF THE STUDY: Paediatric musculoskeletal infections by Panton-Valentine leucocidin (PVL)-producing *Staphylococcus aureus* constitute a rare, but highly critical event. They are characterised by a rapid course of marked inflammation, worsening under conservative therapy and a high rate of recurrence. This study aimed to illustrate the importance of paediatric PVL-producing *S. aureus* musculoskeletal infections in western Switzerland.

METHODS: Case records, clinical parameters and biological assessments of children with musculoskeletal infections due to PVL-producing *S. aureus* who attended the University Hospitals of Lausanne and Geneva from 2008 to 2016 were studied retrospectively.

RESULTS: Of the nine cases (seven male), four presented with haematogenous acute osteomyelitis, two with septic arthritis, and three with skin and soft tissue infections. Laboratory analysis revealed mean values for white blood cell count of 12,700/mm^3, C-reactive protein (CRP) 171mg/l, erythrocyte sedimentation rate (ESR) 62 mm/h and platelet count 241,000/mm^3. Notably, fever and laboratory values were higher for osteoarticular infections. PVL was produced by methicillin-sensitive *S. aureus* (MSSA) in eight cases and by community-acquired methicillin-resistant *S. aureus* (CA-MRSA) in one case. PVL was identified in blood cultures (six cases), operative samples (seven cases) and an oral swab (one case). Treatment relied on surgical procedures, endorsed by two-agent antimicrobial therapy for up to 9 weeks. Complications included recurrent infections (five cases), pathological fracture (one case) and growth arrest (two cases), as well as an important psychological impact (one case).

CONCLUSION: The results of this study highlight the low prevalence of PVL-producing *S. aureus* musculoskeletal infections in the paediatric population in our region. Nevertheless, given the importance of complications, the recurrence rate and the duration of treatment, clinicians caring for children need to be especially well versed with the peculiarity of this entity. Retrospective case series. Level of evidence: IV

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Introduction

Panton-Valentine leucocidin (PVL) is a cytotoxin produced by any strain of *Staphylococcus aureus* that causes leucocyte destruction and important tissue necrosis. This pathogen is currently responsible for extensive necrotic skin lesions, potentially fatal necrotising pneumonia and severe musculoskeletal infections. PVL may be produced by various *S. aureus* strains, both methicillin-sensitive *S. aureus* (MSSA) and community-acquired methicillin-resistant *S. aureus* (CA-MRSA) [1]. In a European study, the prevalence of PVL-positive community-acquired *S. aureus* amounted to 18.6% and 7.8% of the isolates were MRSA [2]. The correlation between production of PVL and the severity of infection is controversial, since the latter seems most likely to depend on the patient's age. A recent meta-analysis in adults illustrated the lack of coherence between infection by PVL-positive strains and the outcome of pneumonia, musculoskeletal disease or bacteraemia [3]. Nevertheless, the paediatric literature reports severe local necrosis with a pronounced inflammatory response induced by PVL, with consequent short- and long-term complications. As a matter of fact, several studies highlight the peculiarity of PVL-positive musculoskeletal infections in children and demonstrate that affected patients presented more elevated inflammatory parameters and a higher complication rate requiring repeated surgical interventions, intensive care unit admission and a consequently long hospital stay [4–9]. At our two university medical centres, we identified the first case of PVL-positive musculoskeletal infection only in 2008. The purpose of this article was to present a series of nine cases of paediatric musculoskeletal infections due to PVL-producing *S. Aureus*, highlighting their clinical aspects, the results of laboratory studies and the outcome of therapy (both surgical procedures and length of antibiotic treatment), as well as the complications noted.

Patients and methods

After approval from the respective Children's Hospital Ethics Review Committee, we retrospectively collected

the medical charts of all children aged from 0–16 years old admitted in our two university hospitals (CHUV Lausanne and HUG Geneva) between January 2008 and December 2016 for PVL-positive musculoskeletal infections. The criteria established by Morrey were used to estimate children's risk of having a bone or joint infection [10]. Diagnoses of osteoarticular infections were confirmed using imaging techniques (plain radiography, ultrasonography, ^{99m}TC bone scan, computed tomography, magnetic resonance imaging). Children diagnosed as having musculoskeletal infections were further categorised according to the following primary diagnoses: acute haematogenous osteomyelitis, septic arthritis, and skin and soft tissue infections. Demographics such as age, gender and place of origin were recorded for each patient as well as clinical parameters such as onset of symptoms before admission, fever at the time of admission, the fever duration under treatment, and the time elapsed between the onset of symptoms and diagnosis. Biological work-up included white blood cell (WBC) count, left-band shift percentage, platelet count, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

Microbiological methods

Blood cultures were typically used to isolate the microorganisms responsible for musculoskeletal infections. The study's blood culture media used was an automated blood culture system (BD BACTEC FX). Joint fluid, pus from soft tissue abscesses or bone aspirate samples were sent to the laboratory for Gram staining, cell count, and immediate inoculation onto Columbia blood agar (incubated under anaerobic conditions), CDC anaerobe 5% sheep blood agar (incubated under anaerobic conditions), chocolate agar (incubated in a CO_2-enriched atmosphere), and brain-heart broth. These media were incubated for 10 days. The presence of the PVL gene in *S. aureus* strains was assessed with a rapid real time polymerase chain-reaction (PCR) assay in one centre until 2014. The remaining two cases in 2016 were analysed as described previously [11].

Treatment

If a suspect fluid was recovered from joint-fluid aspiration, joint lavage was performed via arthrotomy, or arthroscopy. Surgical exploration for osteomyelitis generally included taking subperiosteal or bone aspirate specimens, and aspiration-curettage of any abscesses. For skin and soft tissue infections, any abscesses were drained. Empirical antibiotic therapy started with an intravenous antibiotic chosen by the attending physician responsible for each patient, after having obtained samples. The antibiotic regimen was thereafter adjusted according to antibiotic sensitivity. The duration of antibiotic treatment and mode of administration were then determined with regard to each patient's age, bacterial characteristics and, above all, their response to the treatment. Collected data about treatment and follow-up included duration of intravenous and oral antibiotic treatment, number of surgical procedures and length of hospital stay. Long-term outcome was evaluated through clinical assessment and radiological follow-up.

Results

The study enrolled nine children admitted for PVL-positive musculoskeletal infection (seven males, two females) during the 9 years considered, with ages ranging from 2 to 15 years old (median 12 years) (table 1). A retrospective analysis of all paediatric bacteriological samples positive for *S. aureus* available in one centre yielded five PVL-positive cases out of 571 samples, resulting in a prevalence of 0.9% in our observation period from 2008 to 2016. Vaccination status was recorded for seven of the nine patients, all of them being vaccinated according to national guidelines. The children studied had haematogenous acute osteomyelitis in four cases, septic arthritis in two and skin and soft tissue infections in the remaining three. The mean admission temperature was 38.7°C (range 37.3–41.0°C), whereas three patients (33%) had a temperature beneath 38°C on admission.

The median WBC count was 12,700/mm^3 (range 6500–22,600) and was considered elevated in five patients (cut-off: 12,000/mm^3). CRP was available for eight patients and was elevated in six, with a median value of 171 mg/l. The ESR was available for seven patients and was elevated in all of them with the mean value of 62 mm/h. Finally, the mean platelet count was 241,000/mm^3.

The pathogen was identified from blood cultures in six patients and in operative samples cultures in seven cases, with five patients having both positive blood cultures and positive operative samples. Bacteriological investigations demonstrated eight cases of MSSA and one case of CA-MRSA.

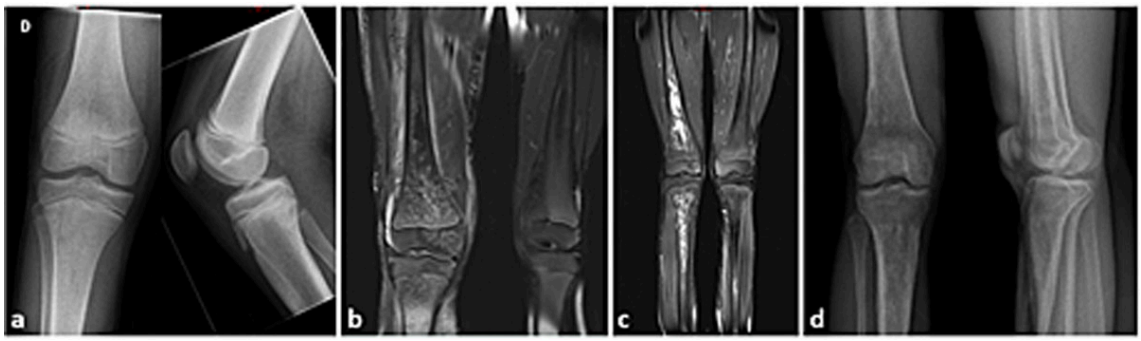
All patients underwent surgical procedures (open surgical drainage/lavage) and the mean number of interventions per patient was three (range one to eight). The site of infection

Table 1: Patient characteristics.
Note the important differences between osteoarticular infections (patients 1–6) and skin and soft tissue infections (patients 7–9).

Patient	Age (years)	Onset (days)	T (°C)	Fever (days)	WBC (K/mm^3)	CRP (mg/l)	ESR (mm/h)	Diagnosis
1	12	10	38.5	6	19.0	200	78	Osteomyelitis (tibia)
2	10	1	40.2	2	17.0	91	43	Osteomyelitis (humerus)
3	12	2	39.8	50	*8.7*	*189*	39	Panosteomyelitis (femur, tibia)
4	13	7	41.0	1	12.5	194	102	Necrotising pandiaphysitis (tibia)
5	10	7	40.0	3	22.6	200	89	Arthritis (hip)
6	15	5	37.3	8	*6.4*	*152*	62	Arthritis (knee)
7	2	2	38.7	3	8.5	9	35	Abscess (foot)
8	2	4	37.7	0	–	–	–	Abscess (gluteal) CA-MRSA
9	12	5	37.6	0	12.9	10	–	Abscess (finger)

CA-MRSA = community-acquired methicillin-resistant *S. aureus;* CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, T = temperature on admission, WBC = white blood cells. *Italics = discordance leucocyte count – CRP*

Figure 1: Clinical course of patient 6.Note the rapid evolution from a normal X-ray on day 1 (a) to persisting defects after 5 years (d), and between magnetic resonance imaging on day 3 (b) and at 10 months (c).



was accessed by bone drilling in cases of osteomyelitis, arthrotomy for arthritis and local incision for skin and soft tissue infection. Surgical treatment was complemented by antibiotherapy, and the antibiotics used are listed in table 2. The duration of intravenous treatment amounted in average to 16 days (range 0–62 days); all but one patient were subsequently treated with oral antibiotics (mean duration 25 days). Intravenous antibiotherapy was stopped for the remaining case after 54 days without switching to oral antibiotics.

Patients sustained various complications (fig. 1) in the form of infection recurrence (five cases), growth arrest with limb length discrepancy (two cases) and pathological fracture (one case) from underlying oncological disease; one patient developed psychological troubles (suicidality) in the course of treatment.

Finally we noted that patients with PVL-positive osteoarticular infections had a higher temperature on admission, and WBC, CRP and ESR were more elevated compared with patients with skin and soft tissue infections.

The following risk factors were identified among the patients with osteoarticular infections: one had a history of acute lymphoid leukaemia and a medical port *in situ*. Two patients had a history of previous trauma, one had furunculosis at the site of infection and one reported a scratch injury from intense itching. One patient performed contact sport. Among the patients with skin and soft tissue infections, only one case of furunculosis was described.

Discussion

Nine cases of musculoskeletal infections due to PVL-producing *S. aureus* were identified during this 9-year study. Six were osteoarticular and three affected skin and soft tissue. Our case series illustrates that the prevalence of PVL-positive musculoskeletal infections is still low in western Switzerland. This study is consistent with the results of investigations conducted by the Paediatric Infectious Disease Group Switzerland, which found only 1.6% of PVL producers in a cohort of 572 MSSA strains [12]. Our observation is in line with other studies reporting a low prevalence of PVL-positive strains [13] and on the predominance of MSSA-PVL in continental Europe [7, 9, 14, 15]. Elsewhere, it is recognised that the proportion of PVL-producing strains is consistently higher in MRSA (74–100%) than MSSA (9–46%) [1], and that the rate of MRSA differs between locations (USA 56–68% MRSA-positive vs Greece 26%). Thus, the overall reported proportion of PVL-producing *S. aureus* depends on the prevalence of MRSA (USA 78% vs Greece 37%) [1].

One must nevertheless keep in mind that our result may be biased by two facts, as previously reported [9]. Firstly, we know neither the number of PVL-positive cases that are treated in primary institutions nor the proportion of *S. aureus* strains referred for PVL testing. We can thus expect that the number of musculoskeletal infections due to PVL-positive *S. aureus* is currently probably underestimated. Secondly, the rate of MRSA in the paediatric population is very low in western Switzerland. Since the prevalence of PVL-producing strains depends on the prevalence of MRSA, this very low prevalence of MRSA might play

Table 2: Management and outcome.
Among all patients, osteoarticular infections stood out by long antibiotic treatment, high complication rate (observation period in years) and long hospital stay due to several relapses.

Patient	Surgery (OP)	Intravenous antibiotics (days)	Oral antibiotics (days)	Complications (years)	Initial HS (days)	Total HS (days)
1	5	CXM, FLU, GEN (54)	–	Sepsis, growth arrest (2)	39	39
2	1	ACA, CLI, FLU (14)	CLI (42)	Fracture, relapse (5)	14	16
3	3	ACA, AMI, FLU, VAN (50)	LEV, RIF (217)	Relapse, suicidality (3)	57	83
4	8	CTX, FLU (62)	CXM (62)	Relapse, sepsis, growth arrest (6)	30	35
5	2	FLU, GEN (18)	CLI (25)	None	27	27
6	4	ACA, CLI, FLU, IMI, VAN (62)	CLI (63)	Relapse (5)	53	74
7	5	ACA, CLI, FLU (7)	CLI (7)	None	17	17
8	1	–	ACA, CLI (10)	None	1	1
9	2	–	FLU (10)	None	8	8

ACA = amoxicillin clavulanic acid; AMI = amikacin; CLI = clindamycin; CTX = ceftriaxone; CXM = cefuroxime; FLU = flucloxacillin; GEN = gentamicin; HS = hospital stay; IMI = imipenem; LEV = levofloxacin; OP = number of operations; RIF = rifampicin; VAN = vancomycin

a role in the distribution of PVL in our region. The majority of European reports, mainly from France and the UK, report on MSSA-PVL. Hence, our results confirm both the low general prevalence of PVL in the paediatric population and the predominance of MSSA-PVL in Europe [7, 9, 14, 15].

PVL is secreted by any *S. aureus* strains as two components that assemble to a pore-forming complex on polymorphonuclear leucocyte membranes [16]. Depending on the concentration, PVL induces either apoptosis or cytolysis with release of inflammatory factors and subsequent tissue inflammation [16]. Generally, destruction of leucocytes leads to the characteristic discordance of a low/normal leucocyte count and high levels of inflammatory parameters (e.g., CRP) [17]. In our series, this discrepancy of low WBC and high CRP level was detected in only two cases on admission (table 1). Interestingly, the discordance arose from osteoarticular infections only, since skin and soft tissue infections presented with a normal white blood cell count in all three patients and merely increased CRP levels. The low number of two out of nine patients with the "typical" initial laboratory findings illustrates the risk of misinterpreting the infection at a first glance.

To our knowledge, no risk factors for PVL-positive infections have been defined so far. However, it is well known that sharing of personal items, particularly in sports clubs and poor hygiene practices, including insufficient disinfection and protection of skin lesions, increase the rate of PVL-related infections [17]. Among other factors that increase the suspicion are non-white ethnicity, preceding injury, contact sport, recent travel and influenza or other respiratory infection [9, 11]. Our results correspond with these, apart from influenza status, which was not tested in our patients given the lack of relevant symptoms of pneumonia. The risk factors listed here overlap with the risk factors for transmission of MSSA and MRSA. Therefore, no PVL-specific risk factors were identified. Controversy persists as to whether nasal carriage of PVL is systematically linked to infection [17, 18]. Since nasopharyngeal swabs was tested in only one of our patients, we cannot comment on this potential coherence.

The rate of complications is recognised to be high with PVL-producing *S. aureus* infections. In our series, we recorded orthopaedic and psychological sequels. Two of them merit particular attention: a pathological fracture, which occurred in the context of an underlying oncological disease following local PVL infection; and suicidality in a patient with a particularly long evolution, requiring 8 weeks of hospitalisation followed by 30 weeks of peroral antibiotic treatment. Interestingly, one of the antimicrobial agents used in the latter case was levofloxacin, a substance known to potentially favour psychological deterioration (*swissmedic* database). Hence, these observations highlight multiple facets of PVL-positive infections: a rapidly evolving disease with the need for urgent invasive treatment and the potential for multiple long-term sequels. However, neither of our cases suffered from pulmonary involvement or thrombosis [3].

Despite the low prevalence of PVL in our area, PVL represents an important component in the cascade of paediatric musculoskeletal infections. The observed rapid deterioration, the high recurrence rate and the long list of complications underline the need for early and targeted treatment. Generally, a combination of an anti-staphylococcal regimen (amoxicillin / clavulanic acid or flucloxacillin) and an anti-toxic agent blocking bacterial protein-synthesis of PVL (clindamycin, linezolid, or gentamicin) is recommended [8, 14, 19]. Antibiotic therapy is essential, yet not exclusive. Inhibition of PVL production requires an anti-staphylococcal agent at a drug concentration that ranges far above the minimal inhibitory concentration at the site of infection [19]. Insufficient dosage of β-lactams and, to a lesser extent, vancomycin have been shown to even enhance PVL secretion, thus aggravating the symptoms [19–21]. Antibiotic treatment is even more challenging in the case of CA-MRSA, where the use of β-lactams is limited. Consequently, standard care limited to antibiotic therapy (even in the case of approved regimens) results in failure of treatment in 85% of cases [19], especially as antibiotic distribution is reduced in necrotic tissue. Therefore, surgery plays a major role in achieving a positive outcome. Early and complete removal of PVL suppuration from the body and debridement of necrotic tissues with surgery is a mandatory goal in treatment [19]. Surgical resection of affected areas is mandatory to stop the circle of encapsulation of bacteria and their toxin. According to the literature, 71% of patients with bone and joint infections require more than one procedure, with a median of three interventions per patient [19], which is consistent with our results. In soft tissue infections, outcomes are particularly dependent on surgical drainage and remain favourable, even in the event of inappropriate antibiotic treatment [19].

Conclusion

Paediatric musculoskeletal infections by Panton-Valentine leucocidin represent a rare, but highly dangerous entity. They are characterised by rapid local extension and aggravation despite antibiotic treatment. A discordance of low/normal leucocyte count and high inflammatory parameters (CRP) may be present at the time of diagnosis. Suspected cases require rapid identification of the toxin and early, comprehensive imaging. Successful treatment relies on surgical interventions with two-agent antimicrobial therapy, and a multidisciplinary approach by health professionals of paediatrics, paediatric surgery, radiology and infectious diseases.

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