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Severe infections of Panton-Valentine leukocidin positive *Staphylococcus aureus* in children

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Abstract

Infections caused by Panton-Valentine leukocidin-positive *Staphylococcus aureus* (PVL-SA) mostly present as recurrent skin abscesses and furunculosis. However, life-threatening infections (eg, necrotizing pneumonia, necrotizing fasciitis, and osteomyelitis) caused by PVL-SA have also been reported.

We assessed the clinical phenotype, frequency, clinical implications (surgery, length of treatment in hospitals/intensive care units, and antibiotic treatments), and potential preventability of severe PVL-SA infections in children.

Total, 75 children treated for PVL-SA infections in our in- and outpatient units from 2012 to 2017 were included in this retrospective study.

Ten out of 75 children contracted severe infections (PVL-methicillin resistant *S aureus* n = 4) including necrotizing pneumonia (n = 4), necrotizing fasciitis (n = 2), pyomyositis (n = 2; including 1 patient who also had pneumonia), mastoiditis with cerebellitis (n = 1), preorbital cellulitis (n = 1), and recurrent deep furunculosis in an immunosuppressed patient (n = 1). Specific complications of PVL-SA infections were venous thrombosis (n = 2), sepsis (n = 5), respiratory failure (n = 5), and acute respiratory distress syndrome (n = 3). The median duration of hospital stay was 14 days (range 5–52 days). In 6 out of 10 patients a history suggestive for PVL-SA colonization in the patient or close family members before hospital admission was identified.

PVL-SA causes severe to life-threatening infections requiring lengthy treatments in hospital in a substantial percentage of symptomatic PVL-SA colonized children. More than 50% of severe infections might be prevented by prompt testing for PVL-SA in individuals with a history of abscesses or furunculosis, followed by decolonization measures.

Abbreviations: ARDS = acute respiratory distress syndrome, CA-MRSA = community acquired MRSA, DVT = deep venous thrombosis, ICU = intensive care unit, IMC = intermediate care unit, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin sensitive *Staphylococcus aureus*, PVL = Panton-Valentine leukocidin, PVL-SA = Panton-Valentine leukocidin positive *Staphylococcus aureus*, SA = *Staphylococcus aureus*, SSTI = skin and soft tissue infections, URTI = upper respiratory tract infection.

Keywords: children, infection, intensive care, Panton-Valentine leukocidin

1. Introduction

In recent years, the staphylococcal exotoxin Panton-Valentine leukocidin (PVL) has been recognized for its involvement in recurrent skin and soft tissue infections (SSTI).[1,2] While PVL-negative *Staphylococcus aureus* strains are still the predominant cause for SSTI, PVL-positive *S aureus* strains (PVL-SA) are responsible for a growing number of local epidemic outbreaks and serious illnesses.[3,4] PVL-SA infections are characterized by multiple or recurrent furuncles, abscesses, or periorbital infections.[2,5] Options to prevent recurrent SSTI include a decolonization protocol comprising mupirocin nasal ointment, antiseptic throat rinses, antiseptic washings, change of towels, bed linen, and clothes; and disinfection of potentially contaminated items over a period of 5 days[6]; see also: www.pvl-abszess.de.

Although PVL-SA is primarily known for causing furunculosis, it is also associated with life-threatening infections such as necrotizing pneumonia, necrotizing fasciitis, and osteomyelitis, especially in young, previously healthy patients.[7,8]

The 2-component pore-forming leucocidin is coded by bacteriophage genes *lukS* and *lukF* and can be expressed by both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) strains of *S aureus*.[9] The human-pathogen interaction of PVL-SA remains poorly understood and in vitro studies and murine models often show conflicting results.[10–13] Regional differences in MRSA and MSSA distribution have been reported. Most of the PVL-SA strains in Europe have been identified to be MSSA,[14] while in the US, the main causes of PVL-SA infections are a variety of community-acquired MRSA (CA-MRSA) strains, especially strain USA-300.[15]

In Germany, when *S aureus* is identified in culture, assessment of PVL expression by *lukS/lukF* using polymerase chain reaction (PCR) is not performed routinely. Moreover, knowledge of PVL-SA and its clinical consequences remains insufficient in clinicians treating the patients with PVL-SA infections, leading to a significant diagnostic delay. Many PVL-SA colonized patients suffer from recurrent SSTI and may receive multiple antibiotic treatments and surgeries before diagnosis and decolonization. Some patients even undergo testing for immunodeficiency, before PVL-SA colonization is considered.[16,17]

The aims of this study were to

(1) determine the clinical spectrum and the frequency of severe infections due to PVL-SA, in children treated at an university hospital from 2012 to 2017,

(2) report the length of treatment in affected children at hospitals/ intensive care units (ICU), and

(3) identify the cases in which severe disease and prolonged hospital stay may have been preventable.

2. Methods

We conducted a retrospective case study of children who were treated in our in- and outpatient units (Charité Universitätsmedizin Berlin – Childrens' Hospital) for PVL-SA infections from January 2012 to December 2017. Only patients who had been tested positive for PVL + SA in at least 1 sample (naso-pharyngeal swabs and/or swabs from other location, eg, tracheobronchial secretion or material from SSTI) were included in this study.

Swabs were cultivated on Columbia agar with 5% sheep blood. Species identification and antimicrobial susceptibility testing were performed using a Vitek 2 system, applying EUCAST breakpoints. The detection of PVL *LukS/LukF* was performed using commercially available PCR (eazyplex MRSAplus REF7611; Amplex Biosystems GmbH, Giessen, Germany).

Molecular genetic testing for PVL was not routinely performed by our microbiology division after isolation of *S aureus* but was requested when the clinical course was suggestive for an infection with PVL-SA.

Patient records were retrieved from electronic medical records and archived files. We defined "severe infection" as "intravenous antibiotic treatment" and "admission to an ICU" or "admission to an intermediate care unit (IMC)" or "major emergency surgery" associated with active PVL-SA infection in contrast to mere asymptomatic colonization or minor skin infections. In the identified cases, we collected data on duration of hospital stay in days, antibiotic treatment, surgery, as well as ventilation assistance. Potential prevention options were retrospectively assessed via telephone interviews. We obtained written informed consent to publish diagnostic images from the patient's custodians.

Data processing and statistical analyses: data were processed using Microsoft Excel 2013.

3. Results

A total of 75 children treated for PVL-SA infection were included in the analysis. Sixty-five children suffered from SSTI and/or hordeola with PVL-SA detection in SSTI material or nasopharyngeal swabs.[5] Ten children presented with infections that fulfilled the criteria of a severe infection. Data about these patients are presented in Table 1.

Age of the patients ranged from 1 week to 15 years (mean age 5.5 years). Six patients were boys and 4 were girls. Two patients presented with serious pre-existing conditions: patient 5 with neonatal drug withdrawal and asymptomatic congenital cytomegalovirus infection and patient 9 with status post heart transplantation and subsequent immunosuppressive treatment. MRSA was detected in 4 cases. Clinical manifestations included necrotizing pneumonia (n=4), necrotizing fasciitis (n=2), pyomyositis (n=2), mastoiditis (n=1), preorbital cellulitis (n= 1), and recurrent deep furunculosis in an immunosuppressed patient (n=1). Specific complications of severe PVL-SA infections were venous thrombosis (n=2), sepsis (n=5), cerebellitis (n=1), respiratory failure (n=5), and acute respiratory distress syndrome (ARDS; n=3). The median hospital stay was 14 days (range 5–52 days) and the median ICU/ IMC stay was 10 days (range 0–52 days). All patients survived; 1 patient had residual disability after discharge (patient 6, see below). Primary immunodeficiency (in particular, chronic granulomatous disease) was excluded in all patients with severe infections.

3.1. Necrotizing pneumonia

Four children who had previously been in good general health were diagnosed with necrotizing pneumonia. Four days before his admission, patient 1 had an axillary abscess surgically incised and drained. Patients 3 and 4 had close relatives who had recurrent SSTI. In 3 patients, pneumonia was preceded by 3 to 10 days of symptoms of upper respiratory tract infections (URTI). One patient was diagnosed with influenza A-H5N1 and 1 with human respiratory-syncytial-virus-B. PVL-SA was cultured from blood, pleural exudate, sputum, and bronchial lavage samples. CA-MRSA was detected in 2 patients. Figures 1 and 2 show initial imaging of patient 4 and 6, respectively. Intensive care

Table 1

Pediatric patients with severe PVL-SA infections.

Patient no.:	Gender	Age, mo	Clinical phenotype	Pre-existing conditions	SSTI in patient	SSTI in relatives	Prodromal URTI or co-infection	MRSA	Deep venous thrombosis	Hospital stay, d	ICU/IMC stay, d
1	Male	172	Necrotizing pneumonia Pyomyositis	None	Axillary abscess	None	None	No	Left femoral vein thrombosis	14	13
2	Male	9	Necrotizing fasciitis	Purulent conjunctivitis	None	None	Yes; unspecified	No	None	14	10
3	Male	12	Necrotizing pneumonia	None	None	Yes	Yes; unspecified	Yes	None	51	29
4	Female	14	Necrotizing pneumonia	None	None	Yes	Yes; RSV-B[3]	No	None	18	14
5	Male	0	Necrotizing fasciitis	NDW[4] Congenital CMV[5] Purulent conjunctivitis	Furunculosis Panaritium	None	None	Yes	None	37	37
6	Male	182	Necrotizing pneumonia	None	None	None	Yes; Influenza A	Yes	None	58	58
7	Male	138	Mastoiditis Cerebellitis	None	Furunculosis	Yes	None	Yes	Cerebral sinus vein thrombosis	14	14
8	Female	61	Pyomyositis	None	None	None	None	No	None	8	0
9	Female	100	Furunculosis	s/p Heart-transplantation Immunosuppression	Furunculosis	None	None	No	None	7	7
10	Female	0	Preorbital cellulitis Furunculosis	None	None	None	None	No	None	5	5

CMV = cytomegalovirus, d = days, ICU = intensive care unit, IMC = intermediate care unit, MRSA = methicillin-resistant *Staphylococcus aureus*, NDW = neonatal-drug-withdrawal, RSV = respiratory-syncytial-virus, SSTI = skin and soft tissue infections (before admission), URTI = upper respiratory tract infections (before admission).

treatment included varying regimens of intravenous antibiotics, ventilation assistance (including veno-venous extracorporeal membrane oxygenation, controlled ventilation, noninvasive ventilation, and heated humidified high flow therapy), and therapeutic anticoagulation (see below). Complications observed included sepsis, ARDS, pyomyositis, and deep vein thrombosis (DVT). Patients 1, 3, and 4 were discharged in satisfying general health. After a lengthy rehabilitation due to complications and re-admission, patient 6 had persisting postintensive care syndrome, including reduced lung capacity (Fig. 3) and critical illness polyneuropathy.

3.2. Invasive soft tissue infections

Two patients were diagnosed with necrotizing fasciitis of the thorax. Patient 2, a previously healthy infant, initially presented with symptoms of URTI and purulent conjunctivitis. Within hours after admission, he rapidly developed swelling and redness

of the right thorax. Patient 5 was an in-patient in the neonatal ICU receiving treatment for neonatal drug withdrawal from opioids. Six days after birth, he developed multiple panaritia, purulent conjunctivitis, and purulent pustules of the left axilla. At 4 weeks, he developed rapid swelling and redness of the left thorax (Fig. 4). In both patients, early surgical intervention with necrosectomy and drainage, in combination with broad antibiotic treatment, led to satisfying improvement of the clinical situation. Negative pressure wound therapy was used in patient 2. Both patients were discharged in satisfying general health.

Two patients were diagnosed with pyomyositis. Three days after admission, while still in intensive care, patient 1 (see above)
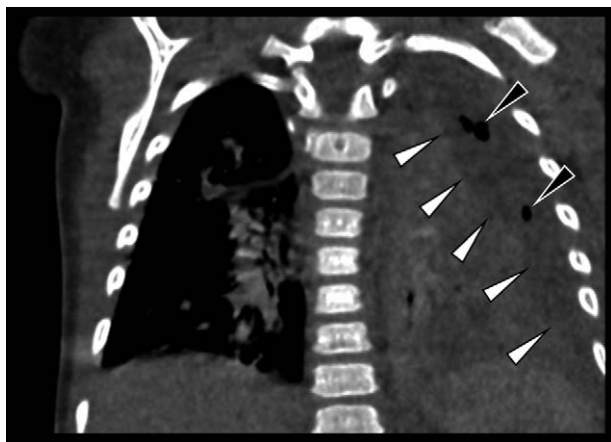

Figure 1. Patient 4 at admission. Coronal CT of the chest. Lobar pneumonia of the left lung. Small arrows: border of pleural empyema with gas inclusions (small black arrows). CT = computed tomography.
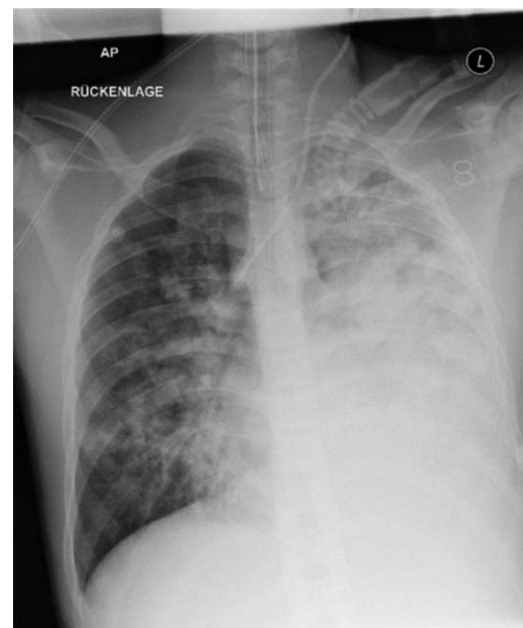

Figure 2. Patient 6 at admission. Anteriorposterior radiograph of the chest at the time of admission. Left lung: Primarily basal lobar pneumonia. Right lung: perihilar infiltration. Intubation tube, central line, and gastric tube in loco typico.
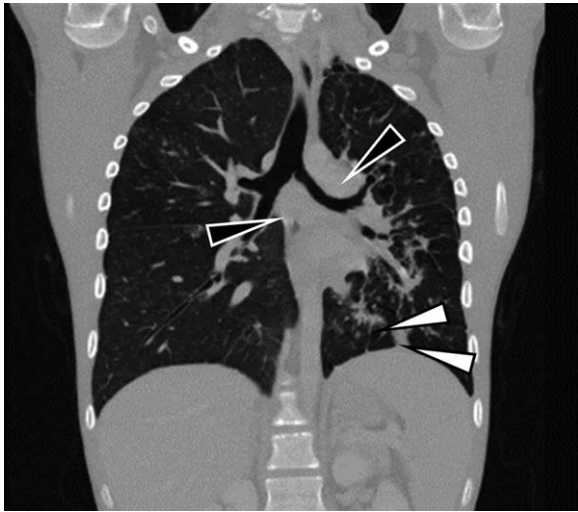
Figure 3. Patient 6 at 4 months after admission. Coronal CT of the torso. Small arrows: epiphrenic residual lesions. Small black arrows: hilar lymph nodes. CT = computed tomography.

developed new swelling and pain on his left leg and a resurgence of fever. Diagnostic imaging showed signs of pyomyositis and fasciitis (Fig. 5). Purulent infections in the left anterior femoral and anterior tibial compartments were surgically drained. The previously healthy patient 8 presented with recurrent fever and painful swelling of the upper arm, which had developed in 2 weeks. Prompt surgical intervention showed a purulent infection of the flexor compartment of the arm. Both patients were discharged in satisfying general health.
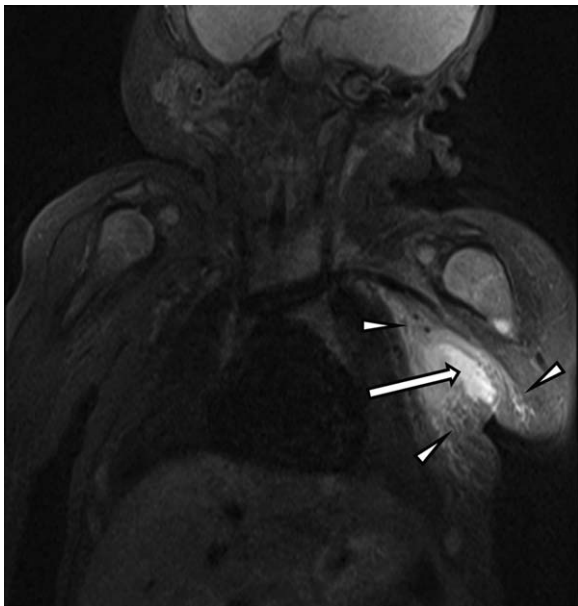

Figure 5. Patient 1 at 3 days after admission. Coronal contrast-enhanced MRI with TIRM sequence of the lower extremities. Indicative of myositis and fasciitis. Large arrow: feathered intramuscular enhancement. Small arrows: subcutaneous enhancement. Small black arrows: fascial enhancement. MRI = magnetic resonance imaging; TIRM = turbo-inversion recovery-magnitude.

3.3. Others

Patient 7 and all family members initially presented with recurring SSTI in our pediatric immunological clinic. PVL-MRSA was detected in nasopharyngeal swabs and decolonization measures were initiated. Four months later, he was re-admitted with mastoiditis and cerebellitis (Fig. 6). Mastoidectomy was performed promptly and intravenous antibiotic treatment was initiated. Patient 9 underwent heart transplantation at the age of one and a half years. At the age of 8, she developed multiple and recurrent abscesses over a period of 1 month while under immunosuppressive therapy. After admission to the pediatric IMC, PVL-SA detection, and 6 days of intravenous antibiotic treatment plus hygienic measures to decolonize the patient and her home, the patient was discharged in satisfying general health. One week after her birth, patient 10 developed massive swelling of the eyelid and purulent secretion with detection of *S aureus*. PVL testing was performed when the patient developed SSTI after discharge from hospital.[17]

Figure 4. Patient 5 at 4 weeks after admission. Coronal MRI with TIRM sequence of the torso. Large arrow: axillary abscess formation. Small arrows: cellulitis. MRI = magnetic resonance imaging; TIRM = turbo-inversion recovery-magnitude.
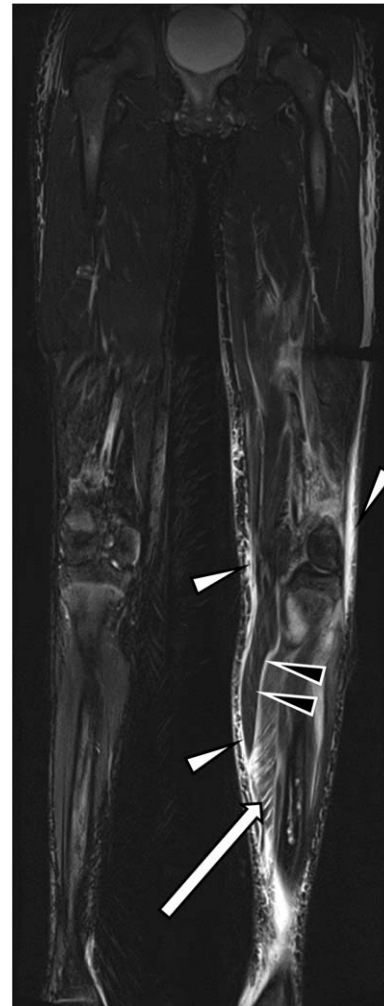
Figure 6. Patient 7 at admission. Coronal contrast-enhanced T1-weighted MRI of the head with fat suppression. Large arrow: abscess-forming, destructive mastoiditis with infiltration into the cerebellum. Small arrows: meningeal enhancement. Small black arrows: cervical lymphadenopathy. MRI = magnetic resonance imaging.
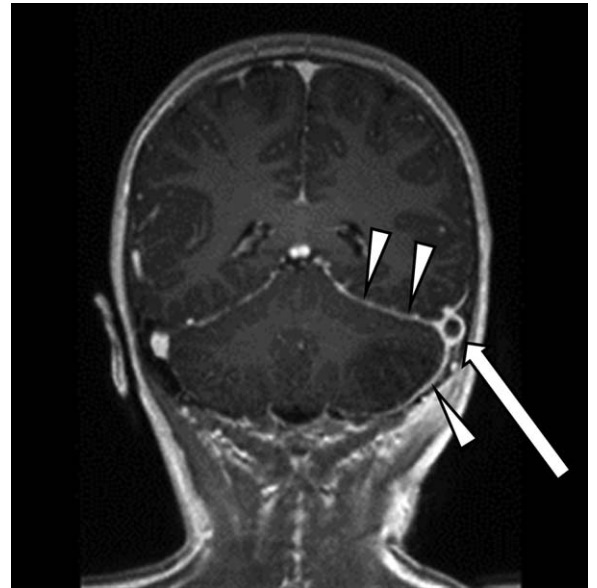

Figure 8. Patient 7 at admission. Coronal contrast-enhanced T1-weighted cranial MRI with fat suppression. Large arrow: thrombosis of sigmoid sinus. Small arrows: meningeal enhancement. MRI = magnetic resonance imaging.

3.4. Deep venous thrombosis

Two patients presented with deep venous thrombosis (DVT) associated with PVL-SA infection of the adjacent tissue. Patient 1 (see above) initially presented with extensive thrombosis of the left communal femoral vein. Despite prompt initiation of therapeutic anticoagulation, the size of the thrombosis initially increased further (Fig. 7). A cranial magnetic resonance imaging of patient 7 (Fig. 8) revealed a thrombosis of the left sigmoid venous sinus and the distal jugular vein, as complication of a mastoiditis and SSTI of the neck. Both patients were treated with low molecular weight heparin, for which high doses were required to reach a therapeutic anti Xa level of 0.5 to 1 IU/mL.
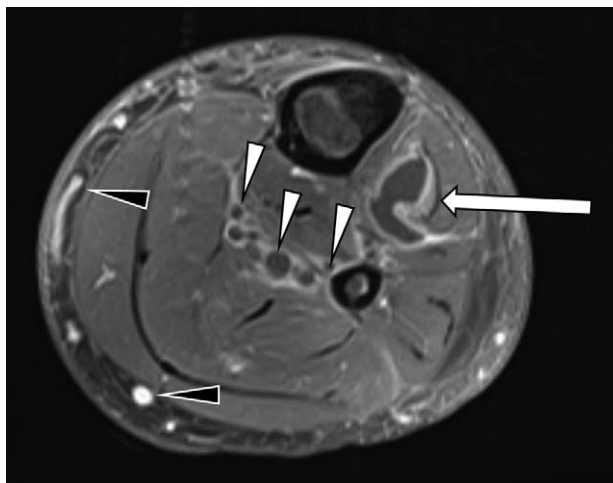
3.5. Preventability

As presented in Figure 9, only in 4 out of 10 patients, history of patients or of household members was not suggestive of PVL-SA colonization before admission, due to severe infections. Three patients had recently suffered from SSTI, 2 from recurrent furunculosis (plus panaritia in 1 patient) and 1 from a single axillary abscess. In 2 patients recurrent SSTI was reported in relatives (in the parents in 1 patient and in a grandparent in another patient), who had not been tested for PVL-SA. The PVL-MRSA colonization of patient 7 and his family was known before he acquired severe mastoiditis. He and his family had been given instructions for decolonization (comprising 5 days of mupirocin nose ointment, throat rinses, antiseptic washings, and change of bed clothing and towels) but did not arrange an appointment for control swabs.

Figure 7. Patient 1 at 3 days after admission. Axial contrast-enhanced T1-weighted MRI with fat suppression of the proximal left lower thigh. Large arrow: abscess formation with circular contrast enhancement in the ventral compartment. Small arrows: thrombosis of deep veins. Small black arrows: subcutaneous veins with contrast. MRI = magnetic resonance imaging.
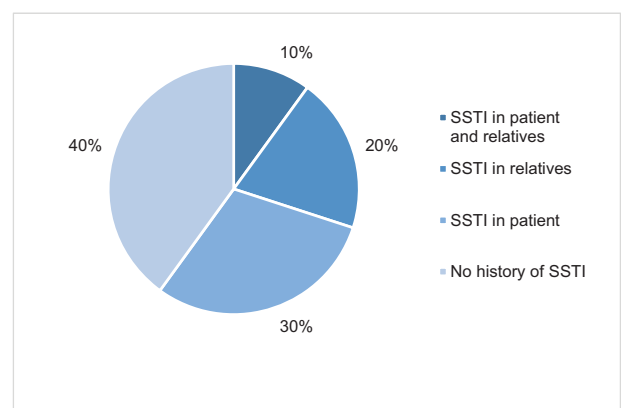

Figure 9. History of SSTI in patients and relatives of our cohort before admission for serious infection (n = 10). SSTI = skin and soft tissue infections.

4. Discussion

The present study outlines the clinical spectrum of severe PVL-SA infections in children. Ten out of 75 children treated for PVL-SA infections at our center developed an infection classified as severe, within 5 years.

The clinical phenotypes described in our study correspond with results from other clinical and epidemiological studies, particularly regarding the phenotypes of formerly healthy affected children and the presence of URTI symptoms before admission for pneumonia.[18] DVT is increasingly being detected in patients with infections caused by PVL-SA.[19] In our cohort, 2 out of 10 patients developed symptomatic DVT. In both patients reported in this study, DVT was associated with extensive SSTI of the tissue surrounding the involved vessels.

It remains unclear whether it is the higher virulence of PVL-SA in general or if pathogen specific mechanisms contribute to thrombus formation in these patients. In an ex vivo model, it was shown that PVL activates platelets via neutrophil secretion products in patients with *S aureus* positive osteomyelitis,[20] potentially contributing to thrombus formation. In a mouse model, early antibiotic treatment significantly reduced cytokine synthesis, thrombin generation, and thrombo-inflammatory response in MRSA infection. These results support our observation that infection control is crucial for thrombus control.[21]

Patient 1 in our study presented with an extensive venous thrombosis of the lower extremity. Although anticoagulation treatment was administrated immediately, the clinical situation worsened. Concomitant symptoms such as fever, pneumonia, and swelling of the surrounding tissue were at first misinterpreted as secondary to venous thromboembolism, leading to delay in causal treatment for staphylococcal infection. Severe PVL-SA associated infections are still rare in children. A high index of suspicion for the association of DVT and PVL-SA infections is warranted for prompt diagnosis and treatment. This approach may improve outcomes and minimize morbidity.

Thrombotic complications in children are rare. However, the serious thrombotic complications observed in our patients and in previous studies[22] mandate the need for investigating whether thromboprophylaxis, for instance, with low molecular heparin, should be routinely administered in children with severe PVL-SA infection. Further studies are required to identify the appropriate recipients of prophylactic anticoagulation in this high-risk patient group.

In 6 out of the 10 presented cases, either the patients themselves or their close contacts experienced symptoms suggestive of PVL-SA infection before admission due to serious infections. Prompt testing for PVL colonization in affected individuals, followed by subsequent decolonization procedures as suggested by Shallcross et al[6] may have prevented severe disease in these patients. However, in 1 case (patient 7), prior decolonization measures (mupirocin nasal ointment, antiseptic throat rinses, antiseptic washings, change of towels, bed linen and clothes, and disinfection of potentially contaminated items over a period of 5 days [6]) had been initiated but had not been successful. Subsequently, an acute life-threatening illness occurred that might have been preventable by control swabs and a second decolonization procedure. Recommended decolonization measures for PVL-SA are frequently difficult to implement. Patients and physicians report low adherence, because the measures are time-consuming and costly, particularly in multi-person house-

holds. Further study to improve the rate of persistent decolonization and the practicability of the decolonization measures is needed.

In our study, only 1 child was immunocompromised. She developed multiple recurring deep furuncles and abscesses, rather than 1 life-threatening infection. In contrast, the 2 teenagers with necrotizing pneumonia had been healthy boys and were active in youth athletics. Both fell ill with life-threatening infections without any warning signs. A recent outbreak analysis of PVL-SA in a German kindergarten showed that even in a close social group, with the same strain of PVL-SA, not all colonized children showed symptoms.[4] It has yet to be determined, which PVL-SA colonized patients

(1) remain asymptomatic,
(2) suffer from recurrent minor SSTI or
(3) develop severe infections.

A recent study by Tromp et al investigated the molecular tropism of the leucocidin to human phagocytes and identified human surface antigen CD45 to be a binding molecule for the PVL-component *LukF*.[23] Determination of whether specific binding properties of PVL mediate different clinical phenotypes or specific host factors are of importance warrants further studies.

The limitations of this study are the small number of patients and the retrospective study design. Furthermore, we were unable to evaluate preventive measures.

In conclusion, increased awareness of PVL-SA-associated disease, together with routine diagnostic testing and knowledge of potential complications and adequate therapeutic strategies are important

(1) to prevent severe infections by early diagnosis and consequent decolonization and
(2) to prevent serious complications such as DVT.

Author contributions

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Visualization: Renate Krüger.
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