Tropical pyomyositis (TP) is a life-threatening bacterial infection of the skeletal muscle that occurs particularly among children, young adults and those with immunocompromised conditions. The appropriate diagnosis and treatment are often delayed due to its non-specific signs, leading to fatal consequences. *Staphylococcus aureus*, especially methicillin-susceptible *S. aureus*, is responsible for most TP cases. However, other bacteria (i.e. streptococci, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp., *Candida* spp., *Mycobacterium* spp.) have been reported. This narrative review provides an update on the epidemiology and clinical course of TP. A special focus is laid on the role of toxins (i.e. Panton-Valentine Leucocidin and α-toxin) in the pathogenesis of TP and their implication for the clinical management of infection.

**keywords** tropical pyomyositis, *Staphylococcus aureus*, epidemiology, clinical course, pathogenesis, review

**Sustainable Development Goals (SDGs):** SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)
major bacterial toxins, which can have a direct impact on the management of infection. The aim of this narrative review is to provide a concise update on the clinical and microbiological aspects of this (not fully recognised as such) ‘neglected tropical disease’ [17].

After the initial literature search (term: ‘pyomyositis’), we were unable to identify controlled trials for instance on the treatment or diagnostics of TP. Due to the lack of a critical mass of high-quality studies, a narrative review was deemed more appropriate for our aim than a systematic review.

Epidemiology

The disease can occur in all age groups but is more common in children (2–5 years) and young adults (20–45 years), with a male-to-female ratio of 1.5:1 [2,18]. It is increasingly recognised among patients with immunocompromised conditions (e.g. HIV infection, malnutrition, diabetes mellitus, malignancy, rheumatologic conditions, intravenous drug abuse) [2,19-21]. Some case reports point to an increased risk in patients receiving monoclonal antibodies such as certolizumab [22], tocilizumab [23] and infliximab [24,25]. Although the incidence of TP is still unclear in the tropics, it is an important cause of morbidity [26,27], including longer hospital stays (>10 days) [13,20]. The disease represents approximately 1% of all hospital admissions in the Amazonian region of Brazil or Peru [7,14]. Furthermore, it accounted for 4% (Gabon) to 27% (Benin) of *S. aureus* infections in Africa [28,29]. Very few prospective monocentre studies with only limited case numbers that systematically assessed the clinical course and outcome of TP are available [12,16], and to the best of our knowledge, no prospective multicentre studies have been carried out, or are currently ongoing. However, limited data on mortality [7,8] suggest that it ranges between 0 (14-day mortality, sub-Saharan Africa [30]), 2.4% (in-hospital mortality, Brazil [7]) and 10% (in-hospital mortality, Northern India [8]). A meta-analysis revealed a clear association of the *S. aureus* Pan-Valentine leucocidin (PVL) with severe SSTI (e.g. pyomyositis) [31]. While PVL is rare in *S. aureus* from colonisation and infection in Europe (3%), high rates are reported from Africa (45%–74%) [30,32].

Molecular pathogenic mechanisms

*S. aureus* secretes more than 40 known exotoxins which can be classified into three groups: superantigens,
cystotoxic enzymes and cytotoxins [33]. The lytic function of cytotoxins is receptor-mediated. Although numerous cytotoxins are involved in the pathogenesis of SSTI, the molecular action of α-toxin (Hla) and PVL in disease are best elucidated. Hla is a cytolytic heptameric β-barrel pore-forming toxin that targets membranes of erythrocytes, leucocytes, endothelial and epithelial cells through the binding to ADAM10 (a disintegrin metalloproteinase domain-containing protein 10) [34,35]. PLEKHA7 (pleckstrin homology domain-containing family A member 7) and other functional proteins are involved in ADAM10 clustering and promote cell death by the formation of stable pores [36]. This leads to intracellular ion dysregulation and finally to cell death. Sublytic concentrations of Hla cause an inflammatory response of the cells [33]. In addition, Hla activates ADAM10 to degrade E-cadherin (epithelial-cadherin), which in turn leads to the loss of epithelial barrier function [37,38]. The disruption of these barriers is an important step for tissue invasion of S. aureus, which is not only associated with SSTI.

PVL is a pore-forming protein toxin consisting of the lukF-PV and lukS-PV subunits. The binding of these subunits to their cellular targets (lukF-PV → CD45 and lukS-PV → C5a receptor) is required to lyse the host cells (i.e. granulocytes, monocytes, macrophages) or to activate the inflamasome [39-41]. In S. aureus-infected tissues, recruited granulocytes are rapidly killed by secreted PVL. The release of neutrophil proteases most likely culminates in severe tissue damage [42]. Although the role of PVL in S. aureus disease was controversial in the past, there is now strong molecular and epidemiological evidence on the critical role of PVL in (tropical) SSTI, in particular pyositis [31]. A recent genome-wide association study on S. aureus from Cambodia using isolates from pyositis and asymptomatic nasal colonisation revealed that only the presence of PVL (and no other S. aureus toxin) was strongly associated with disease (OR> 55). This observation indicates that pyositis is ‘critically dependent’ on PVL, an observation similar to other toxin-related diseases (e.g. tetanus, diphtheria) [43]. The factors that favour the high prevalence of PVL-positive isolates in the tropics are currently unclear. Potential explanations are the environment (e.g. warm/humid climate, high concentration of PVL-carrying phages in surface waters), the pathogen (acquisition of mobile genetic elements that facilitate the spread, similar to sasX) or the human host. Indeed, one missense mutation of the human C5a receptor I (N279K of the third extracellular domain), the target of the lukS-PV component, was associated with the nasopharyngeal colonisation of PVL-positive S. aureus in a remote African Pygmy population [44] and might explain why PVL-positive S. aureus are widespread among Africans compared to Caucasians.

Diagnosis

A high degree of clinical suspicion, especially in high-risk patients or those with previous (blunt) trauma, is necessary to detect cases especially in the early stages of the disease. In settings with limited resources, the diagnosis of TP is based on clinical presentation and ultrasound [45]. Although MRI is the imaging gold standard, ultrasound demonstrating muscle enlargement, changes in echogenicity due to inflammation and abscess formation are increasingly recognised as appropriate imaging tools [7,46]. There are no specific laboratory tests, but C-reactive protein, leucocyte counts and erythrocyte sedimentation rates (which can also be performed in resource-poor settings) can be helpful [12]. It is recommended that blood culture (aerobic and anaerobic) and pus from intra-muscular abscesses are taken for microbiological analysis, including species identification and antimicrobial susceptibility testing [47].

Clinical management

TP evolves in three stages: the invasive, supplicative and late stage [2,18]. The invasive stage (phlegmonous inflammation, no pus) is managed solely with antibiotics. In addition, incision and drainage are key in the management of supplicative and late-stage pyomyositis (i.e. drainage of purulent material). In the late stage with the potential for bacterial dissemination, supportive, even intensive care management may be needed to prevent death [48]. Although S. aureus is the major pathogen in TP, timely empirical therapy should cover Enterobacterales and non-fermenters particularly in patients with immunocompromising conditions or open trauma [47,48]. Thus, broad-spectrum antibiotics are the drugs of primary choice with subsequent review based on species identification and antimicrobial susceptibility testing [48]. For empirical therapy, ampicillin/sulbactam, or carbapenems appear to be appropriate [48]. Targeted therapies should include penicillin and clindamycin for β-haemolytic Streptococcus spp., anti-staphylococcal penicillins (e.g. nafcillin, oxacillin) or ceftazolin for methicillin-susceptible S. aureus, and glycopeptides or linezolid for methicillin-resistant S. aureus [47,48]. The optimal duration of the definitive antimicrobial therapy is not clear but should be several weeks (2–9 weeks) [12,47,49].

However, this treatment scheme is dependent on availability. Since TP is a clearly toxin-dependent entity,
adjunctive protein synthesis inhibitors (PSI) might be beneficial to inhibit bacterial toxin production. Macrolides, lincosamides, rifampicin or oxazolidinone can reduce the production of both PVL and Hla in vivo [50]. There is no good clinical evidence that favours any PSI; However, clindamycin appears to be the most promising to be tested in future clinical studies (e.g. CASSETTE trial) [51]. Intravenous immunoglobulins (IVIG) could be beneficial to neutralise bacterial toxins in severe infection. IVIG have been applied to patients with pyomyositis and toxic shock syndrome (TSS) as underlying condition [11], but the additional value is controversial. For other toxin-mediated SSTI, the adjunctive use of IVIG was associated with reduced organ failure and mortality [18]. However, there is no clear evidence on the beneficial use of IVIG in TP.

Knowledge gaps and outlook

Epidemiology

TP is not recognised as a stand-alone entity of global concern, and our knowledge of the incidence, risk factors and the spectrum of causative agents in different settings (epidemiologic understanding is based on case reports and small case series) remains poor. However, health and demographic surveillance systems (HDSSs) are in place in many African countries (e.g. Mozambique, Mali, Ethiopia, Kenya, Sierra Leone and South Africa) [52]. This infrastructure might be used to integrate ancillary cohort studies to address knowledge gaps of TP (incidence, risk factors, bacterial spectrum, antimicrobial susceptibility).

Molecular pathogenesis

There is now good evidence that PVL is the relevant toxin for TP. However, the factors responsible for the high prevalence of PVL-positive S. aureus across sub-Saharan Africa, but low prevalence in temperate regions are still unclear. Future studies should therefore address potential factors for the dissemination of PVL-positive S. aureus. They include adaptive and clonal characteristics of the bacterium (e.g. frequent uptake of PVL-carrying phages from the environment, factors that facilitate the spread of certain clones) and the host (e.g. humoral and cellular immune response to PVL, polymorphisms of the cellular targets in African vs. Caucasians).

Future clinical studies

Most of our knowledge about TP is based on individual case reports and very few, mostly retrospective and monocentre case series. There is a need for prospective, multicentre studies to address two main points: validate current diagnostic strategies in centres which are fully equipped both with respect to imaging and bacteriological diagnostic tools, and to determine treatment strategies to safeguard appropriate regional empirical treatment regimen tailored to the needs of resource-limited settings.

Microbiological laboratories and reference centres

With bacteriological identification and characterisation being key to diagnose and treat TP successfully, it is evident that access to appropriate bacteriological facilities is essential. However, this remains challenging in many resource-poor settings to date. Nevertheless, the need to develop human competencies and laboratory capacity has been catalysed with strategies to tackle antimicrobial resistance (AMR) with a ‘One-Health’ approach in Africa, mainly through the activities of the African Centres for Disease Control (African CDC, http://www.africacdc.org), the African Society for Laboratory Medicine (ASLM, https://aslm.org), and laboratory support initiatives by WHO (https://www.who.int/antimicrobial-resistance/en/) and the Fleming Fund (https://www.flemingfund.org/) in low- and middle-income countries.

Networks and training

As with any other condition which is in principle treatable if recognised early, awareness is key. To this end, opportunities to create awareness amongst healthcare providers for this potentially lethal condition should be used wherever possible. The African Sepsis Alliance (https://www.africansepsisalliance.org), for example, or regional scientific networks such as the ‘West African Network for Antimalarial Drugs’ (http://www.waneacam.org/) in West and the ‘Central African Clinical Research network’ (http://www.cantam.org/) should be mobilised to raise awareness as well as funding mechanisms should be exploited to finance studies aimed at optimising TP management.

Conclusion

TP is known for its challenging and non-specific clinical presentation among patients in tropical and temperate regions. There is strong evidence that PVL is the key toxin in TP. The additional value of a toxin-directed therapy (e.g. protein synthesis inhibitors, intravenous immunoglobulins) has to be tested in future clinical trials.
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