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Staphylococcus aureus positive skin infections and international travel

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Hautinfektionen durch *Staphylococcus aureus* in der Reisemedizin

Zusammenfassung. *Staphylococcus aureus* kann häufig als Ursache eitriger Hautinfektionen bei Rückkehrern aus den Tropen und Subtropen isoliert werden. In dieser Übersichtsarbeit wird der aktuelle Wissenstand zu reiseassoziierten, *S. aureus* positiven Hautinfektionen referiert, wobei neuere Erkenntnisse sowohl zu Pathogenitätsfaktoren als auch zu angeborenen Immunmechanismen besondere Berücksichtigung finden. Neben der Bedeutung einer Methicillinresistenz und des Panton-Valentine Leukozidin bei der Entstehung dieser Infektionen wird die Rolle antimikrobieller Peptide bei deren Abwehr dargestellt. Widersprüchliche Beobachtungen zu einer möglichen Bedeutung internationaler Reise- und Migrationsbewegungen für die weltweite Zunahme von ambulant erworbenen Infektionen mit Methicillin-resistenten *S. aureus*-Stämmen werden zusammengefasst. Bislang noch ungeklärte Fragestellungen und damit der weitere Forschungsbedarf auf diesem Gebiet werden ebenfalls aufgezeigt.

Summary. *Staphylococcus aureus* is a frequent cause of purulent skin infections in travellers returning from the tropics and subtropics. This review gives an account of the current knowledge on travel-related, *S. aureus* positive skin infections with a focus on recent findings on both bacterial pathogenicity and mechanisms of innate defence. In particular, the potential role of community-acquired methicillin-resistance, Panton-Valentine leukocidin as well as antimicrobial peptides in the evolution of this type of infection are discussed. Moreover, conflicting findings for a possible association of travel and migration with the global emergence of community-acquired methicillin-resistant *S. aureus* infections are summarised. This review highlights areas of uncertainty that require further investigation.

Key words: Pyoderma, travel medicine, staphylococcal skin infections, methicillin-resistant *Staphyloccocus aureus*, community-acquired infections, panton-valentine leukocidin, emerging communicable diseases, epidemiology, review.

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Introduction

Eleven percent of all travellers to developing countries report the onset of skin problems during or shortly after travelling, making these the third most frequently reported illness in this context [1]. Bacterial infections account for up to 21% of these diseases, predominantly caused by ubiquitous pathogens like *Staphylococcus aureus* [1, 2]. Classically, microtraumata leading to superficial skin injury, such as arthropod bites, have been proposed to explain the increased risk of *S. aureus* positive skin infections in travellers [1]. However, a substantial number of reports of community acquired methicillin resistant (CA-MRSA) [3–9] as well as Panton-Valentine leukocidin (PVL) positive *S. aureus* [9–11] in travel related skin infections point towards an important role of pathogenic factors in the evolution of disease. Moreover, our knowledge on innate defence mechanisms of the human skin, in particular the concept of antimicrobial peptides (AMP), has been vastly growing and is likely to explain differences in the propensity of individuals towards this infection [12]. The purpose of this review is to give an account of the current knowledge of travel related, *S. aureus* positive skin infections in the context of CA-MRSA, PVL and AMP. At the same time, areas of uncertainty that require further investigation are identified.

Review

Epidemiology, microbiology and clinical presentation

Pyoderma is the most common clinical presentation of *S. aureus* positive skin infections and accounts for 8–18% of all skin diseases in returning travellers [1, 2, 13]. Characteristically, pyoderma is a purulent skin infection that affects superficial layers of the skin. Its presentation can be further categorized as abscess, furuncle, carbuncle, folliculitis, impetigo or ecthyma. The clinical course of *S. aureus* positive pyoderma varies widely from mild self-limiting superficial infections to deep-seated recurrent and multiple abscesses that require incision and systemic antibiotic therapy [9]. Besides *S. aureus*, group A streptococci (GAS) are frequently isolated from pyoderma, in particular from impetigo and ecthyma, whereas *S. aureus* is the leading cause of abscesses, furuncles, carbuncles and folliculitis. Interestingly, mixed infections of GAS and *S. aureus* are observed in a substantial proportion of pyoderma cases. Cellulitis summarizes soft tissue infections that affect the connective tissue of deeper, subcutaneous skin layers and is thus distinct from pyoderma. Erysipelas is the

most common and more superficial variant of cellulitis and has been found to account for 13% of dermatoses in returning travellers [1]. Group A streptococci are by far the most frequent pathogens causing such infections followed by *S. aureus* and other less frequently encountered bacteria.

Risk factors for S. aureus positive skin infections in travellers

Apart from cases that can be attributed to a major trauma, determinants of an apparently increased risk of skin infections in travellers are largely unknown. Rather intuitive explanations have been suggested including a higher risk of microtraumata and a change in skin colonization which in turn could be a consequence of reduced hygienic standards and increased sweating. While systematic research in this area is virtually absent, certain observations support the hypothesis that arthropod bites are likely a risk factor for pyoderma and that microtraumata play a role in the early evolution of disease: 29–63% of returnees suffering from bacterial skin infections report insect bites at the beginning of the disease [1, 2, 10] and an ecological study conducted in Great Britain found an association between the incidence of impetigo and insect bites [14]. One can speculate that either the bite itself or subsequent scratching with or without distribution of pathogens from colonized reservoirs such as the nares contribute to the evolution of clinical apparent infection. Most likely, it is a combination of both. However, neither case control nor prospective cohort studies have been presented to support the significance of any of theses factors. Future studies are required to quantify the strength of their association with bacterial skin infections as well as their mutually independent contribution to an increased risk in the exposed. In particular the role of a colonization of the nares with *S. aureus*, a known risk factor for pyoderma in the general population [15, 16], and its interplay with microtraumata, bacterial pathogenicity and protective mechanisms of the skin remains to be explored as a risk factor for *S. aureus* skin infections in travellers.

Methicillin resistance of S. aureus and travelling

The emergence of methicillin-resistant *S. aureus* (MRSA) in community acquired infections (CA-MRSA) has generated increasing interest in the evolution of this pathogen and its potential as a cause of human disease. Skin infections account for more than 75% of MRSA positive infections in the community [6, 17]. Compared to its hospital-associated variant (HA-MRSA), CA-MRSA strains exhibit less frequently an extended resistance against antibiotics [17]. A distinct evolution of this pathogen is further suggested by the clinical appearance and the epidemiological characteristics of CA-MRSA infections, which are much more similar to infections caused by methicillin-sensitive *S. aureus* (MSSA) than to those caused by HA-MRSA [18]. An association of travelling and migration with the isolation of CA-MRSA from skin lesions has been reported in a substantial number of case reports, case series and cross-sectional observations [3–9]. Virtually nothing is known about the asymptomatic colonization of individuals with MRSA in this context. Considering an increasingly mobile population, asymptomatic carriers as well as travellers and migrants suffering from overt disease could contribute towards the global spread and emergence of this pathogen. This hypothesis is contrasted by the findings of a recent study that analyzed genetic polymorphisms in a global collection of MRSA isolates and ultimately challenged the general perception that the geographical spread over long distances has played a major role in the emergence of this pathogen [19]. Prospective studies of asymptomatic *S. aureus* carriage in travellers, expatriates and migrants could help to further clarify this controversy.

PVL positive S. aureus infection of the skin in travellers

Panton-Valentine leukocidin (PVL) is a staphylococcal pore-forming exotoxin that causes tissue necrosis and leukocyte destruction. Both the development of recurrent deep seated lesions and the potential of human-to-human transmission has been associated with PVL, an increasingly recognized pathogenicity factor in both methicillin-sensitive [16] and methicillin-resistant *S. aureus*. In MRSA, PVL is frequently found in community acquired infections [17, 20], but regional variations of this association hamper its general use as a marker for CA-MRSA [8]. The few available case reports suggest that PVL has the same clinical significance in the context of international travel as described in the general population. Both deep seated, recurrent pyoderma and person-to-person spread have been reported in travellers [9–11] and non-travellers [16]. However, epidemiologic studies on the prevalence of PVL in travel-related MSSA *and* MRSA infections of the skin are missing.

Antimicrobial peptides (AMP)

Recent insights into innate defence mechanisms of human skin, in particular the concept of antimicrobial peptides and proteins (AMP), have the potential to substantially contribute to our understanding of the interaction of the host with *S. aureus*. Some of these evolutionary highly conserved, naturally occurring antibiotics like RNase 7 are expressed constitutively and can be found at high levels in the upper layers of healthy epidermis [12]. Others like the human beta defensins (HBD) 2 and 3 require induction to be present in relevant concentrations [12]. A wide range of antimicrobial peptides and proteins have been identified, of which human beta defensin 3 (HBD-3) and RNase 7 exhibit highest activity against *S. aureus in vitro* [12] and thus appear to be of particular relevance in pyoderma. In a recently published case control study we showed that constitutive expression of RNase 7 is associated with *S. aureus* positive pyoderma in travellers returning from the subtropics and tropics [21, 22]. Our findings indicated that a 30% lower level of mRNA coding for RNase 7 corresponds to an approximate twofold increase in risk of disease. The results of this study highlight the importance of constitutively expressed AMP as part of the skin's first line of defence against bacterial infections and offer a possible explanation for inter-individual differences in susceptibility to *S. aureus* positive pyoderma.

Summary and outlook

S. aureus infections of the skin frequently affect travellers to the tropics and subtropics. Little is known about risk factors for this disease. Case series and cross sectional studies suggest an association of MRSA and PVL positive infections with complicated disease in returnees. Prospective studies are warranted to further clarify the importance of pathogenic factors in the evolution of travel related disease as well as the role

of international travel and migration in the world-wide emergence of these pathogens. Moreover, epidemiological and immunological studies in travellers reduce the risk of observing confounded associations that may arise from observations in individuals with concurrent disease. In conclusion, research in travellers has great potential to improve our understanding of the evolution and dynamics of *S. aureus* colonization, transmission and infection in the general population.

Conflict of interest

The author declares no conflict of interest.

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