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Staphylococcus aureus bloodstream infection in patients with atopic dermatitis - or: Think twice before placing a venous catheter into lesional atopic skin

Mathé Philipp Joshua Gebhard, Joost Insa, Peyerl-Hoffmann Gabriele, Schneider Christian, Kern Winfried, Rieg Siegbert

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Title page***Staphylococcus aureus* bloodstream infection in patients with atopic dermatitis - or:
Think twice before placing a venous catheter into lesional atopic skin**

Last name	Forename	ORCID	Department	Institution	e-mail	CRediT Role
Mathé	Philipp Joschua Gebhard	0000-0002-0448-5338	Division of Infectious Diseases, Department of Medicine II	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	philipp.mathe@uni-freiburg.de	2, 12, 13, 14
Joost ⁽¹⁾	Insa	0000-0003-3162-920X	Division of Infectious Diseases, Department of Medicine II	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	Insa.Joost@med.uni-duesseldorf.de	2,5
Peyerl-Hoffmann	Gabriele	000-0002-0670-4848	Division of Infectious Diseases, Department of Medicine II	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	gabriele.peyerl-hoffmann@uniklinik-freiburg.de	2,5,7
Schneider	Christian	0000-0002-8510-9472	Institute for Medical Microbiology and Hygiene	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	christian.schneider@uniklinik-freiburg.de	5,8
Kern	Winfried	0000-0003-2550-358X	Division of Infectious Diseases, Department of Medicine II	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	winfried.kern@uniklinik-freiburg.de	1,3,10,11,14
Rieg	Siegbert	0000-0001-7493-7080	Division of Infectious Diseases, Department of Medicine II	Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany	siegbert.rieg@uniklinik-freiburg.de	1-3,5-7,10-14

⁽¹⁾ Current affiliation: Institute of Medical Microbiology and Hospital Hygiene, Heinrich-Heine-University Düsseldorf, 40225 Düsseldorf, Germany

Short title: *S. aureus* bloodstream infection in AD

Corresponding author: S. Rieg

Short summary of the major findings:

Due to the high rate of colonization, patients with atopic dermatitis are at risk of *S. aureus* bloodstream infection, the most severe manifestation of *S. aureus* infections. Intravascular devices and the skin are the major portals of entry for *S. aureus* in AD. With prompt and adequate diagnostic and therapeutic management, mortality is lower than in Non-AD patients with SAB and severe sequelae can be averted. Important preventive strategies include AD treatment to reduce *S. aureus* colonization and meticulous care of intravascular catheters, which should not be placed in/on lesional atopic skin.

Abbreviations: AD (atopic dermatitis); HIV (human immunodeficiency virus); ID (infectious diseases); IE (infective endocarditis); MSSA (methicillin-susceptible *Staphylococcus aureus*); MRSA (methicillin-resistant *Staphylococcus aureus*); SAB (*Staphylococcus aureus* bloodstream infection); SSTI (skin and soft tissue infection)

To the Editor

Patients with atopic dermatitis (AD) are prone to *Staphylococcus aureus* colonization and suffer from recurrent *S. aureus* infections, which most often manifest as circumscribed superinfection of lesional atopic skin (Leung 2008). In contrast, *S. aureus* bloodstream infection (SAB) is a particularly severe disease with a high risk of complications like deep-seated metastatic foci, endocarditis, septic shock or recurrences and an in-hospital mortality rate of 20-30% (van Hal et al. 2012). Identified risk factors are (among others) healthcare contact with invasive procedures and interventions, diabetes mellitus, HIV infection, and other primary or secondary T cell deficiencies. Moreover, the risk to develop invasive *S. aureus* infections is 4-5 times higher in *S. aureus* carriers compared to non-carriers (Wertheim et al. 2005). Compared to the overall rate of ~20% permanent carriage in the general population, 70-90% of patients with atopic dermatitis are permanently colonized with *S. aureus* in high bacterial density, particularly in lesional atopic skin. (Leung 2008; Totté et al. 2016; Wróbel et al. 2018). Underlying mechanisms are a combination of reduced expression of innate defense antimicrobial peptides, dysbiosis and increased adhesion of *S. aureus* on/within inflammatory lesions (Kim and Leung 2018; Leung 2008; Rieg et al. 2006; Williams and Gallo 2017). Dense colonization with *S. aureus* may render AD patients at risk for developing SAB and perhaps for suffering severe complications due to a high pathogen inoculum. However, systematic studies of the association of SAB and AD are rare. In two epidemiologic reviews, a higher risk for bacteremia in patients with AD could be identified but without specification of pathogens and clinical manifestations (Narla and Silverberg 2018; Oestergaard et al. 2018). Triggered by the clinical observation of SAB in otherwise healthy young patients with AD we sought to characterize the clinical manifestations and outcome of SAB in this specific patient subgroup using data of a prospectively evaluated cohort.

This study is a post hoc analysis of data collected at the University Medical Center Freiburg. Since 2006 blood cultures growing *S. aureus* are reported daily by the microbiology laboratory with the intention that all SAB patients are prospectively evaluated by infectious disease (ID) physicians on the ward. Definitions and collected data of the resulting prospective SAB cohort have been described in detail previously (Rieg et al. 2017). In three consecutive years (2014-2016) 419 SAB patients were prospectively evaluated for the presence of AD: if AD or atopic eczema was reported in the past medical history and/or if clinical findings were consistent with AD or dermatitis as judged by ID physicians, patients were reviewed and evaluated by a dermatological consultant (S.R.), who either approved or discarded the diagnosis of AD on the basis of the diagnostic criteria of Hanifin and Rayka (Hanifin and Rayka 1980). The Institutional Review Board of the University Medical Center Freiburg considered the investigation as evaluation of service within a quality assurance program and waived the need for written informed consent. The study is registered in the German Clinical Trials registry (DRKS00005045). Statistical analysis was performed by using R Studio. P-values < 0.05 were considered to be statistically significant.

Of the 419 included SAB patients, 14 patients (3.3%) were diagnosed with mild or moderate AD. A comparison of epidemiological and clinical characteristics is outlined in **Table 1**. SAB patients with AD were younger with a median age of 56 years (vs. 64 years in Non-AD patients) and had significantly less comorbidities (Charlson comorbidity index 2.7 vs. 5.9, $p=0.001$). SAB in patients with AD was more often hospital-acquired ([defined as onset of SAB >48 hours after hospital admission] 57% vs. 39%, $p=0.23$), the portal of entry was an intravascular catheter in 7 patients (50%) or the skin in 5 patients (36%). Accordingly, in AD patients the identified main foci of infection (i.e. the most severe manifestation in a patient, thereby defining management and treatment duration) were either skin and soft tissue infections or intravascular catheter-related infections in 71% of patients (3 and 7 patients,

respectively), differing significantly from Non-AD patients, in which infective endocarditis (10%), osteoarticular infections or a deep-seated abscess (20%), pneumonia (15%) or unknown foci accounted for the majority of main foci. Overall, the clinical course of SAB was less severe in AD patients with only 14% of patients developing severe sepsis and no cases of septic shock (vs. 31% in Non-AD patients). No case of infective endocarditis was observed. One patient in the AD group died during hospitalization due to his underlying conditions (all-cause in-hospital mortality 7% vs. 20% in Non-AD group). There was no SAB-related death in the AD group, while 52 patients (13%) died as a consequence of SAB during hospitalization in the Non-AD group (Table 1).

We found SAB in AD patients to be hospital-acquired in about 60% of cases. The portals of entry and main foci were almost exclusively intravascular catheters and skin/soft tissue infections. Mortality was lower and complications less frequent compared to SAB in Non-AD patients.

The observed AD rate of 3.3% in our SAB cohort is in the range of the reported AD prevalence of 1-3% at the age of ~60 years (Bozek et al. 2012; Tanei and Hasegawa 2016). However, as we did not systematically investigate all SAB patients with regard to the presence of minor AD manifestations (or having suffered from AD in childhood) and since hospitalisation in AD is often a consequence of *S. aureus* superinfection (which may introduce selection bias), our study does not allow for firm conclusions if and to what extent AD may represent a risk factor for developing SAB., Only a population-based study could clearly delineate the prevalence of SAB in AD . Due to the observed differential pattern of portal of entry and main focus, our study indicates that atopic skin, either directly via superinfection of lesional AD skin, or indirectly via intravascular catheters, plays a major role in the development of SAB in AD patients. As *S. aureus* carriage is a known risk factor for

invasive infections and SAB, and ~90% of SAB isolates are of endogenous origin, the high-level *S. aureus* colonization in AD may be even more so.

Treatment outcome was better in AD patients, which is most likely due to the fact that AD patients were younger, suffered from fewer comorbidities and, as outlined above, portals of entry and main foci were predominant superficial (i.e. uncomplicated). Nevertheless, prompt and adequate diagnostic and therapeutic management (basic principles are outlined in **Table 2**) are indispensable, as severe sequelae undoubtedly may arise of ‘uncomplicated’ SAB if rigorous diagnostic work-up and antibiotic treatment are not secured (Park et al. 2019).

Beside adequate management, prevention is pivotal (**Table 2**). Therefore, intravascular catheters (short- or long-term) should be used only when clearly indicated as high-density *S. aureus* colonization may lead to catheter infection even within 24-48 hours i.e. in peripheral (very) short-term intravascular catheters. If catheters are placed, meticulous care and screening for complications is warranted. Development of fever in patients with AD and indwelling intravascular catheters should trigger prompt sampling of blood cultures. If no other plausible focus of infections can be detected, early catheter removal is mandatory, particularly upon loss of function of the catheter or development of any signs of inflammation/infection at the catheter site.

Larger prospective studies are needed to substantiate the findings of this monocenter cohort study. However, SAB is yet another reason to tackle the vicious circle of *S. aureus* and AD in our patients.

DATA AVAILABILITY

Original data is available on request.

CONFLICT OF INTEREST

The authors state no conflicts of interest.

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None.

AUTHOR CONTRIBUTIONS

Conceptualization: SR, WK; Data Curation: GPH, IJ, SR; Formal Analysis: PM, SR, WK;
Funding Acquisition:; Investigation: CS, IJ, SR; Methodology: SR; Project Administration:
SR; Resources: CS; Software:; Supervision: SR, WK; Validation: SR, WK; Visualization:
PM, SR; Writing - Original Draft Preparation: PM, SR; Writing - Review and Editing: IJ, PM,
SR, WK.

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Table 1: Comparison of epidemiological and clinical characteristics in *S. aureus* bloodstream infection patients with and without AD.

Characteristic	All	AD+	AD-	p-value
	n = 419	n = 14	n = 405	
Age, median (Q ₁ -Q ₃)	64 (53 – 77)	56 (44 – 67)	64 (54 – 77)	0.09 ¹
Female	142 (34%)	6 (43%)	136 (34%)	0.57
Charlson comorbidity index, mean (Q ₁ -Q ₃)	5.8 (3 – 8)	2.7 (1.3 – 4)	5.9 (3 – 9)	0.001 ¹
Mode of acquisition				0.23 ²
Community-acquired	106 (25%)	4 (29%)	102 (n = 403; 25%)	
Community-acquired healthcare-associated	146 (35%)	2 (14%)	144 (n = 403; 36%)	
Hospital-acquired	165 (39%)	8 (57%)	157 (n = 403; 39%)	
MRSA as causative pathogen	26 (6%)	1 (7%)	25 (6%)	0.60
Portal of entry				0.03 ²
Skin lesion incl. surgical wound infection	67 (16%)	5 (36%)	62 (15%)	
Intravascular catheter-related	154 (37%)	7 (50%)	147 (36%)	
Intravascular drug abuse	18 (4%)	0	18 (4%)	
Other (including urogenital tract)	46 (11%)	0	46 (11%)	
Unknown	133 (32%)	2 (14%)	131 (32%)	
Main focus				0.02 ²
SSTI	41 (10%)	3 (21%)	38 (9%)	
Intravascular catheter-related	133 (33%)	7 (50%)	126 (31%)	
Infective endocarditis	39 (9%)	0	39 (10%)	
Pneumonia and other foci	59 (14%)	0	59 (15%)	
Osteoarticular infections, deep tissue/visceral abscesses	84 (20%)	4 (29%)	80 (20%)	
Unknown	62 (15%)	0	62 (15%)	
Clinical characteristics				
Severe sepsis or septic shock	128 (31%)	2 (14%)	126 (31%)	0.24
Secondary foci of hematogenous dissemination	37 (9%)	1 (7%)	36 (9%)	0.79
Mortality and follow-up				
All-cause in-hospital mortality	82 (20%)	1 (7%)	81 (20%)	0.32
SAB-related in-hospital mortality	52 (13%)	0	52 (13%)	0.24
Mortality at day 90 post onset	100 (n = 324; 31%)	1 (n = 10; 10%)	99 (n = 314; 32%)	0.18

Abbreviations: MRSA (methicillin-resistant *Staphylococcus aureus*); SSTI (skin and soft tissue infection); SAB (*Staphylococcus aureus* bloodstream infection)

¹ Mann-Whitney-U-Test was used; ² χ^2 -Test was used; all other Fisher's exact test.

Table 2: Management standards of *S. aureus* bloodstream infection in patients with AD.

Prevention and early detection of <i>S. aureus</i> bloodstream infection Adequate treatment of atopic dermatitis to reduce adherence and high-level colonization of <i>S. aureus</i> on lesional skin Meticulous care of intravascular (peripheral or central) catheters with daily exchange of dressing No placement of intravenous catheters in areas of lesional atopic skin Daily critical review concerning indication of intravascular catheter Early removal of intravascular catheters with direct or indirect signs of infection (loss of function, erythema, warmth, tenderness, secretion) Sampling of blood cultures before initiation of antibiotic treatment
Diagnostic quality-of-care standards in <i>S. aureus</i> bloodstream infection Blood culture sampling every 24-48 hours to demonstrate bloodstream sterilization Thorough clinical examination to evaluate the portal of entry, main focus and (depending on clinical signs and symptoms) sites of metastatic seeding (psoas abscess, joint empyema, vertebral osteomyelitis, endocarditis, intravascular [e.g. pacemaker] or orthopedic devices) If suspicion of deep-seated focus or metastatic seeding complementary imaging (abdominal ultrasound scan, CT or MRI) Transthoracic and/or transesophageal echocardiography to rule out infective endocarditis
Therapeutic quality-of-care standards in <i>S. aureus</i> bloodstream infection Intravenous antibiotic treatment with agents of choice being flucloxacillin or cefazolin in MSSA and vancomycin or daptomycin in MRSA bloodstream infection Adequate treatment duration (2 weeks in uncomplicated SAB [main focus (removable) intravascular catheter or skin/soft tissue infection], 4-6 weeks in complicated SAB [with any deep-seated foci, endocarditis or osteoarticular infection]) Early source/focus control i.e. removal of intravascular catheters, infected foreign devices, debridement/drainage of abscesses

Abbreviations: AD (atopic dermatitis); CT (computer tomography); MRI (magnetic resonance imaging); MSSA (methicillin-sensitive *Staphylococcus aureus*); MRSA (methicillin-resistant *Staphylococcus aureus*); SAB (*Staphylococcus aureus* bloodstream infection)