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REVIEW ARTICLE

A Narrative Review on the Role of *Staphylococcus aureus* Bacteriuria in *S. aureus* Bacteremia

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Staphylococcus aureus bacteriuria (SABU) can occur in patients with *S. aureus* bacteremia (SAB). However, little is known on the (molecular) pathomechanisms of the renal passage of *S. aureus*. This review discusses the epidemiology and pathogenesis of SABU in patients with SAB and identifies knowledge gaps. The literature search was restricted to the English language. The prevalence of SABU in patients with SAB is 7.8%–39% depending on the study design. The main risk factor for SABU is urinary tract catheterization. SABU in SAB patients is associated with increased mortality. Given present evidence, hematogenous seeding—as seen in animal models—and the development of micro-abscesses best describe the translocation of *S. aureus* from blood to urine. Virulence factors that might be involved are adhesion factors, sortase A, and coagulase, among others. Other potential routes of bacterial translocation (eg, transcytosis, paracytosis, translocation via "Trojan horses") were identified as knowledge gaps.

Keywords. *Staphylococcus aureus*; bacteremia; bacteriuria; pathogenesis; renal abscess.

Staphylococcus aureus urinary tract infections (UTIs) are rare (0.5%–1%) [1]. The detection of *S. aureus* from urine samples can be associated with asymptomatic colonization or points toward *S. aureus* bacteremia (SAB) resulting from hematogenous seeding [2–4].

The objectives of this review are to describe (1) the epidemiology of subsequent *S. aureus* bacteriuria (SABU) in patients with SAB, (2) the renal pathogenesis of bacterial translocation from blood to urine, and (3) potential virulence factors and (4) to identify knowledge gaps. After a broad literature search, we identified only in vitro models and epidemiological studies but no controlled clinical trials. Hence, we concluded that a narrative review is an appropriate format to address these objectives.

METHODS

The literature search (original articles, reviews indexed in PubMed) was limited to the English language but no restriction to publication date was applied. Using the search term "*S aureus* AND bacteriuria AND bacteremia," we identified 43 records, of which 3 Spanish records were removed. The resulting 40 articles were screened, resulting in 26 eligible publications that were included in the qualitative synthesis. For *S. aureus*–associated risk factors, we consecutively used "*S aureus* AND kidney infection" (screened 385 records, assessed 9 full-text articles), "*S aureus* AND kidney abscess" (screened 225 records, assessed 9 additional full-text articles), "*S aureus* AND renal abscess" (screened 244, no additional publication), and "*S aureus* AND pyelonephritis" (screened 214, 2 additional full-text articles). References of identified studies were screened for additional sources.

Definition, of SABU

The definition of SABU varies broadly. Some eligible studies did not clarify if SABU is defined as any growth in urine culture or only above a minimum count of colony-forming units (CFU). Many microbiology laboratories consider bacteriuria only above a minimum CFU, although a low concentration of *S. aureus* in urine samples may also be clinically relevant [5]. We define SABU as "the detection of *S. aureus* in a urine sample in any concentration (CFU/mL), independent of co-detected pathogens" [6].

Ethical Considerations

Ethical approval was obtained from the institutional review board (IRB, Ethikkommission der Westfälischen Wilhelmsuniversität Münster, 2020-615-f-S). The IRB granted a waiver to obtain written informed consent from patients.

EPIDEMIOLOGY

In SAB patients, concomitant SABU was present in 7.8%–39% [3, 4, 7–13] (Table 1). The pooled prevalence of concomitant SABU in all SAB cases from eligible studies is 13%. We conducted a retrospective study (2012–2019) at the University

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Hospital Münster, Germany, among hospitalized patients with SABU and observed that 26.9% had concurrent or subsequent SAB [6]. Rates in other studies (Table 2) range from 6.9% to 17.2% [15–21]. These numbers should be taken with caution, as a general definition of SABU and universal methodology to screen for SAB are lacking. For instance, in 1 study, all patients with SABU had blood cultures sampled [6], whereas others tested patients only for bacteremia when signs and symptoms of systemic infection (fever, leukocytosis, elevated C-reactive protein levels) were present [10].

Methodology/technical issues also impede understanding of the true burden of SABU in SAB: for instance, gram-negative bacteria might overgrow *S. aureus* in urine culture, leading to low detection rates. Our own unpublished observation revealed that about one-third (n = 11/35) of SABU with a mixed infection of gram-negative bacteria might have gone unnoticed because selective agar for gram-positive bacteria was not used but rather universal Columbia blood agar and MacConkey agar (selective agar for gram-negative bacteria).

The detection of *S. aureus* in urine seems to be more common in patients without previous or ongoing exposure to antimicrobials. In our own unpublished observations, 12 of 50 SAB patients who provided urine samples had concomitant SABU. The blood and urine samples from these 12 patients were obtained before the commencement of an effective *S. aureus* antimicrobial treatment. Only 1 of the 12 patients had other antimicrobial treatment (piperacillin/tazobactam) one day before blood and urine culture sampling. Cefazolin or flucloxacillin intravenously for the treatment of methicillin-susceptible *S. aureus* and vancomycin, linezolid, or daptomycin

Table 1. Characteristics and Findings of Reviewed Studies for the Prevalence of *Staphylococcus aureus* Bacteriuria in Patients With *S. aureus* Bacteria

Location	Design	Duration	Patient Population[a]	Inclusion Criteria	Exclusion Criteria	Patients With SAB, No.	Patients With SABU, No. (%)	Reference
Iceland	Retrospective cohort study	2003–2008	Age ≥18 y, different hospitals	Urine culture submitted <24 h of the index blood culture	Diagnosis of *S. aureus* UTI	152	16 (16)	[9]
Chicago, Illinois, USA	Case-control study	2002–2006	Age ≥18 y, community hospital	Urine culture submitted <72 h of the index blood culture	None	289	57 (19.7)	[13]
Seoul, Korea	Retrospective cohort study	2006–2007	Age ≥18 y, tertiary care hospital	Urine culture submitted <48 h of the index blood culture	Patients with indwelling urinary catheters	128	25 (19.5)	[12]
Utrecht, Netherlands	Retrospective cohort study	2001–2006	Tertiary care hospital	Urine sample obtained for culture on the day of the positive blood culture result	Diagnosis of *S. aureus* UTI	153 (study group 1)	12 (7.8)	[7]
Christchurch, New Zealand	Retrospective cohort study	2000–2003	Age ≥18 y, tertiary care hospital	Urine culture submitted <24 h of the index blood culture	Bacteremia deemed to represent contamination	378	37 (9.8)	[8]
Berlin, Germany	Retrospective cohort study	2014–2017	Age ≥18 y, 3 tertiary care hospitals	Urine culture submitted <48 h of the index blood culture	None	202	78 (39)	[3]
Minnesota, USA	Retrospective cohort study	1972–1976	Minneapolis Veterans Administration Hospital	≥2 positive blood cultures or *S. aureus* with the same antimicrobial susceptibility was recovered from another site; urine culture with >10^5 CFU/mL *S. aureus* in pure culture <48 h of the index blood culture	None	59	16 (27.1)	[4]
Pittsburgh, Pennsylvania, USA	Retrospective cohort study	2010–2013	Age ≥18 y	*S. aureus* from at least 1 blood culture, urine culture submitted <48 h of the index blood culture, SABU ≥10^5 CFU/mL	No urine culture performed, *S. aureus* <10^5 CFU/mL	179	36 (20.1)	[14]
Ohio, USA	Retrospective cohort study	2004–2007	Community hospital	Urine culture submitted <7 d days of the index blood culture	Inadequate/incomplete treatment for SAB	118	28 (23.7)	[11]
Nice and Paris, France	Prospective observational study	Nice: 2006–2008, Paris: 2008	Age ≥18 y, university hospital and tertiary care hospital	Evident SIRS, consultation of an infectious diseases specialist	A polymicrobial bloodstream infection, death before evaluation	104 (68 had concomitant urine cultures submitted)	23 (33.8)	[10]

Abbreviations: CFU, colony-forming units; SAB, *Staphylococcus aureus* bacteremia; SABU, *Staphylococcus aureus* bacteriuria; SIRS, systemic inflammatory response syndrome; USA, United States; UTI, urinary tract infection.

[a]All patients were admitted.

Table 2. Characteristics and Findings of Reviewed Studies on the Prevalence of *Staphylococcus aureus* Bacteria in Patients With *S. aureus* Bacteriuria

Location	Design	Duration	Patient Population	Inclusion Criteria	Exclusion Criteria	Patients With SABU, No.	Patients With SAB, No. (%)	Criteria for SAB	Reference
Houston, Texas, USA	Retrospective cohort study	2008–2010	Veterans Affairs Medical Center	1 episode of SABU (ie, any growth of *S. aureus* from urine) per patient	Patients with invasive SAB 2 d before SABU patients with invasive SAB due to an *S. aureus* isolate with a different methicillin susceptibility profile to the urinary isolates	326	56 (17.2)	SAB within 12 mo of SABU	[2]
Denmark	Retrospective cohort study	Unknown	Most patients were elderly men	Unknown	Unknown	132	11 (8.3)	Unknown	[15]
Minneapolis, Minnesota USA	Retrospective cohort study	1972–1976	Inpatients/outpatients (97% male)	SABU ≥ 10^5 CFU/mL	NA	123	16 (13)	None	[16]
Pennsylvania, USA	Prospective, observational study	Unknown	Male patients from long-term care Veterans Affairs facility	≥1 urine culture positive for *S. aureus*	NA	102	13 (12.7)	SAB 2 d before to 4 d after the initial positive urine culture	[17]
Israel	Retrospective cohort study	2003–2006	Hospitalized patients aged ≥18 y at a tertiary care hospital	≥10^5 CFU/mL MSSA from midstream urine or ≥10^2 CFU/mL from a single urethral catheterized urine or ≥10^5 CFU/mL with no more than 2 species of microorganisms in a patient with a permanent urinary catheter	Patients with MRSA bacteriuria	106	13 (12)	SAB within 24 h to SABU	[18]
Camden, New Jersey, USA	Retrospective cohort study	1 y	Hospitalized patients	SABU (not further defined)	Concurrent SAB in the week preceding or 72 h after the first urine culture yielding *S. aureus*	45	5 (11.1)	See exclusion criteria	[19]
Calgary Health Zone, Canada	Retrospective cohort study	2010–2013	Inpatients/outpatients ≥18 y	*S. aureus* 10^6–10^7 CFU/mL or >10^7 CFU/mL with no more than 1 other organism present *S. aureus* from nonroutine urine cultures (eg, suprapubic aspiration) was reported as positive if the *S. aureus* was >10^4 CFU/mL with no more than 1 other organism present	Concurrent periurethral flora, defined as organisms <10^7 CFU/mL in the presence of a uropathogen ≥10^7 CFU/mL urine cultures within 3 mo of each other and the same *S. aureus* antibiogram	2540 cultures from 2054 patients	175 (6.9)	Documented SAB within 3 mo of SABU	[20]

Abbreviations: CFU, colony-forming units; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not applicable; SAB, *Staphylococcus aureus* bacteremia; SABU, *Staphylococcus aureus* bacteriuria; USA, United States.

for the treatment of methicillin-resistant *S. aureus* were considered effective antimicrobial therapies [6, 22].

RISK FACTORS AND CLINICAL IMPLICATIONS

The main predisposing factor for SABU is urinary tract catheterization (63%–82%), followed by obstruction of the urinary tract, invasive procedures, or recent hospitalization—especially in elderly men [7, 8, 12, 13, 15, 16, 23]. Concurrent skin and mucosal colonization with *S. aureus* in patients with SABU is high, suggesting higher rates of contamination during sampling (66%–75%) [17, 24]. "False positive" SAB as a result of nonsterile venipuncture is possible but unlikely. To assess the hematogenous route as a cause of SABU, it may be necessary to exclude urinary tract catheterization in future studies. Karakonstantis et al published a detailed review and meta-analysis on the clinical significance of concomitant bacteriuria in patients with SAB. Their study revealed that SABU was significantly associated with endocarditis (odds ratio [OR], 1.8 [95% confidence interval {CI}, 1.16–2.79]) [25] when excluding patients with *S. aureus* UTIs. However, the definition of UTI that led to inclusion/exclusion in the meta-analysis was inconsistent. It comprised recorded UTI diagnosis from the patient's file including the assumption that patients with endocarditis or bone-joint disease would not have been labeled as having a UTI. The study group also performed a pooled analysis found that SABU was significantly associated with bone/joint infection (OR, 2.39 [95% CI, 1.11–5.14]) and septic embolism in the spleen, kidneys, or central nervous system (OR, 2.81 [95% CI, 1.33–5.9]) [25].

Risk factors for elevated mortality of SAB in general are broadly studied (eg, nondialysis-dependent chronic kidney disease, cerebrovascular disease in men, moderate to severe liver disease) [1, 3, 8, 26, 27]. Karakonstantis et al showed that SABU is associated with increased mortality in patients with SAB in a meta-analysis [25], which has also been observed at 3 different tertiary care hospitals in a study by Kramer et al [3]. A few studies observed increased clinical complications (septic shock [11], intensive care unit admission [8, 9]) in SAB patients with concomitant SABU.

In conclusion, the observation that SABU is associated with increased morbidity and mortality in SAB should have a caveat as the few studies done so far differed markedly in the study design and are therefore only comparable with caution (Table 1) [25].

PATHOGEN DETECTION IN THE URINE DURING INVASIVE DISEASE

Concomitant detection of specific pathogens in patients with invasive infection is not unique for *S. aureus* but has also been rarely reported for *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or *Candida* species [28–30].

Nguyen et al observed that 2 of 33 patients with invasive pneumococcal infection also had pneumococcosuria, leading to death [28]. Pneumococcosuria was frequently not accompanied by systemic infection and resolved whether or not the patient received antibiotics.

The proportion of candiduria in patients with candidemia might be even larger: 3 of the 6 patients with candiduria had concomitant candidemia. None of them had evidence of a genitourinary infection [29].

In an immunocompetent child, *S. pyogenes* caused an invasive disease with septic embolism to the kidney and consecutive detection in the urine [30]. These examples illustrate that some bacteria can be detected in the urine in the course of systemic infections. As it appears that the translocation from blood to urine is more common in *S. aureus* than in other pathogens, *S. aureus* might be used as a model organism to study principles in the pathogenesis to break the barriers between the blood and urine in vivo.

PATHOGENESIS

SABU may be the primary outcome of ascending UTI with potentially secondary SAB. In contrast, SABU may also be secondary to bacteremia with or without a known focus (other than the urinary tract).

While the concept of ascending UTI is well established, the translocation of *S. aureus* from the bloodstream to the urinary tract is poorly understood [4], and there is only 1 recent animal study [31]. Two pathways are discussed on how *S. aureus* invades the urinary tract secondary to SAB: parenchymal (micro) abscesses and transcytosis. Here, we provide the current evidence for both pathways, which are illustrated in Figure 1.

Abscess Formation

Traditionally, *S. aureus* is considered to invade the kidney via the hematogenous route, causing symptomatic suppurative tubulointerstitial nephritis with microscopic renal abscesses in the cortex. The cortical location is supposed to be associated with the rarity of pyuria due to the poor access to the tubular system [32]. In 1978, Lee et al carried out autopsies in 33 patients with detected SAB (27 with SABU and 6 without SABU). Renal abscesses could be found in 6 patients; 2 of them presented initially with SABU [4]. Due to the small numbers of patients investigated, it is not possible to establish a correlation between renal abscesses and SABU. In addition, the true frequency of renal abscesses in the course of bacteremia in humans remains unknown and needs to be studied in larger cohorts.

A mouse model from 1956 showed that intravenous *S. aureus* injection leads to bacterial deposition in the kidney, and the number was linearly related to the injected bacterial dose [33]. The peak bacterial concentrations (CFU/g of tissue) in the

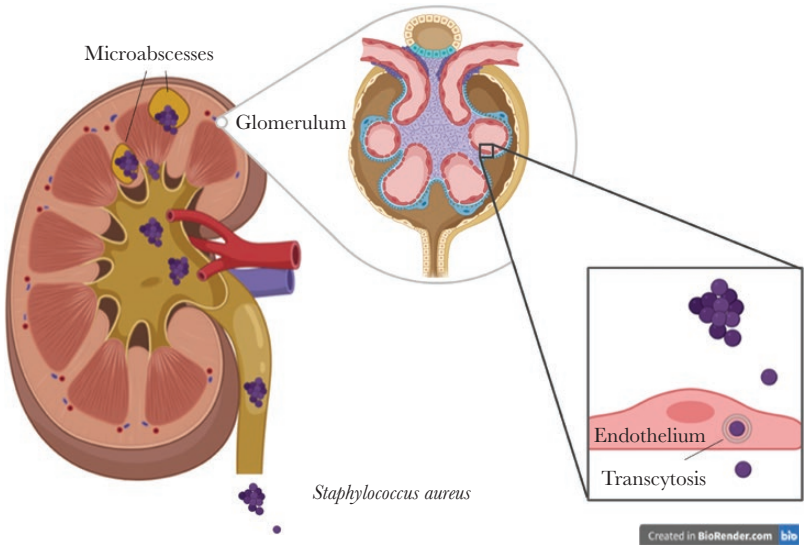

Figure 1. Translocation of *Staphylococcus aureus* from blood to urine.

kidney of a mouse model was reached at day 4 postinjection (p.i.) with *S. aureus* [34].

In a more recent study, mice were infected (via caudal vein injection) with 3 different doses of *S. aureus* strain Newman followed by magnetic resonance imaging at days 1, 3, and 7 p.i. Renal abscesses were observed in 60% of the mice (n = 6) receiving the highest *S. aureus* load (10^7 CFU) at day 1 p.i. and in 80% of the mice at day 3 p.i. [35]. A rat model for hematogenous pyelonephritis describes the detection of bacteriuria before the development of leukocyturia following inoculation of *S. aureus* in the caudal vein [31]. Nesbit et al made a similar observation in patients with hematogenous pyelonephritis [32]. Tancheva et al highlighted the importance of venous stasis (1) for an increase of microbial concentration in renal vessels and (2) to maintain and boost the inflammatory process due to an increase in renal pressure and therefore reduction of tissue resistance [31]. In this mechanistic theory, the reduced resistance is supposed to facilitate *S. aureus* passing cell barriers and translocating to urine.

In addition to these histopathological observations, abscess formation should be seen as a form of microbial translocation across cell barriers, where molecular factors certainly play a role. In infective endocarditis, *S. aureus* interacts with the endothelium and secretes toxins and proteases, eventually causing tissue destruction [36, 37]. In the kidneys it might be similar, leading to abscess formation in the renal parenchyma. Potential virulence factors are discussed below.

Suppurative tubulointerstitial nephritis must be discriminated from postinfectious glomerulonephritis (PIGN), which is the current definition of renal changes originally devised as Löhlein nephritis [38, 39]. PIGN is an immunologic disease characterized by hypercellular glomerular infiltrated by neutrophils and monocytes. This leads to the proliferation of endothelial and mesangial cells with immune complex deposits in the mesangium and glomerular basement membrane after the acute phase of infection [38]. A few studies observed the occurrence of glomerulonephritis in the acute phase of *S. aureus* endocarditis. This might occur along with tubulointerstitial nephritis or due to a nonimmune activation of the alternative complement pathway as shown by O'Connor et al in patients with *S. aureus* endocarditis [39–41].

Transcytosis

Staphylococcus aureus uptake into nonprofessional phagocytes has been demonstrated for many different cell types. Invasion is mediated via fibronectin bridging between host-α5β1 integrins and the staphylococcal surface proteins FnBPA and FnBPB. This binding triggers intracellular signaling that finally leads to cytoskeletal rearrangements and uptake of the bacteria [42]. It has also been shown that renal (mouse) cells can ingest *S. aureus* [43]. Therefore, it could be hypothesized that the route of *S. aureus* from blood to urine is via transcytosis through endothelial cells, mesangium intraglomerular cells, and eventually podocytes.

VIRULENCE FACTORS

Staphylococcus aureus is known to harbor numerous different virulence factors, partly with redundant functions. Table 3 summarizes the effectors that are associated with renal pathogenicity in animal models and might influence the renal passage of *S. aureus* from blood to urine. *Staphylococcus aureus* binds host cells through different bacterial adhesins to extracellular matrix proteins (eg, fibronectin, fibrinogen/fibrin, von Willebrand factor). This attachment might also be the first step in the uptake of

Table 3. Virulence Factors Associated With *Staphylococcus aureus*–Specific Renal Pathomechanisms

Effector	Function	Design	Reference
Sortase A and sortase A anchored surface proteins	Formation of abscess lesions and persistence of bacteria in host tissues	Murine infection model	[44]
Coagulase	Proposed cessation of the capillary flow followed by bacterial growth in the capillaries; coagulative necrosis of the tubules	In vivo animal studies (rabbit model)	[45]
		In vivo animal studies (guinea pigs, mice)	[46]
Staphylokinase	Activation of plasminogen (antivirulence properties)	Murine infection model	[47]
Urease	Promoting bacterial fitness in the low-pH, urea-rich kidney	Murine infection model	[48]
Superantigens	Increased virulence (lethal sepsis, infective endocarditis, kidney infections) in MRSA strain MW2 (especially staphylococcal enterotoxin C)	In vivo animal studies (rabbit model)	[49]
Staphylococcal enterotoxin B	Proposed induction of renal proximal tubule epithelial cells leading to dysregulation of the vascular tone	Cell cultures	[50]
Adhesion factors, ie, FnBPs, Eap, clumping factor A and B, or protein A	Binding to extracellular matrix proteins (eg, fibronectin, fibrinogen/fibrin, von Willebrand factor), this attachment might also be the first step in the uptake from the blood into the tissue via a transcellular or paracellular route (see Knowledge Gaps)	Animal infection models, cell cultures	[36, 51, 52]
α-hemolysin	Dispensable for renal abscess lesions	Murine infection model	[53]
Siderophore production	Renal abscess formation	Murine infection model	[54]
Surface polysaccharide (poly-*N*-acetylglucosamine)	Renal abscess formation	Murine infection model	[55]
Extracellular complement-binding protein and extracellular fibrinogen-binding protein	Impairment of complement activation followed by a decrease in renal abscess formation	Murine infection model	[56]
Eukaryotic-like serine/threonine-kinase	Renal abscess formation	Murine infection model	[57]

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

bacteria from the blood into the tissue, via a transcellular or paracellular route (see "Knowledge Gaps" below).

KNOWLEDGE GAPS

While there are some data on the epidemiology and risk factors of SABU in patients with SAB, the pathogenesis is only vaguely understood.

Apart from microabscesses and transcytosis, 2 other possible routes from blood to urine could play a role in the renal passage of *S. aureus* [58]:

1. Paracellular crossing (paracytosis): *S. aureus* can translocate across polarized airway epithelial cell monolayers via paracellular junctions. In this process, protein A of *S. aureus* stimulates the RhoA/ROCK/MLC cascade, leading to contraction of the cytoskeleton. Induction of TNF and EGFR signaling and activation of epithelial proteolytic activity lead to cleavage of the membrane-spanning junction proteins occludin and E-cadherin, which facilitates staphylococcal transmigration through the cell-cell junctions. [59] *Staphylococcus aureus* α-toxin is also believed to be associated with the formation of paracellular gaps between airway epithelial cells as well as human epithelial colorectal cells [59, 60]. In line with these observations, it can also be speculated that *S. aureus* can enter the urine from the blood via the paracellular route.
2. Trojan horse: It has been known for some years that *S. aureus* can persist in leukocytes and macrophages. It was hypothesized that a "Trojan horse" mechanism could be responsible for the metastasis of *S. aureus* to distant sites [61, 62]. In this context, it was suggested that *S. aureus* can also leave the blood vessel inside professional phagocytes [36, 63]. It could therefore be that bacteria within neutrophils gain access to the urinary tract.

To understand the pathogenesis of secondary SABU in patients with SAB, the "disease triangle" consisting of the pathogen, the host, and the environment could be a helpful tool for a systematic approach [64]. Table 4 provides a summary of knowledge gaps and how they could be addressed in future studies.

CONCLUSIONS

A high proportion of patients with SAB develop SABU (7.8%–39%), and SABU is associated with increased mortality in SAB patients. The pathomechanisms of secondary SABU are poorly understood. Possible routes of translocation from blood to urine might include tissue destruction and abscess formation, transcytosis, or paracytosis, along with Trojan horses. A combination of different pathways is likely. Some *S. aureus* virulence factors (eg, adhesion factors, coagulase) are likely to play a central role. Further studies are needed to determine the clinical management of SABU in patients with SAB in terms of diagnostics and therapy regimens.

Table 4. Knowledge Gaps

Disease Triangle	Knowledge Gap	Research Strategy
The pathogen	Which virulence factors and *Staphylococcus aureus* clonal lineages are associated with SABU in patients with SAB?	Whole-genome sequencing and genome-wide association studies in the identification of loci that are associated with SABU in a case (SABU + SAB) control (SAB) study. Use of virulence factor mutants (in vitro and in vivo studies).
	Does the mechanism of immune evasion (eg, intracellular survival, interaction with signaling pathways) play a role?	Cell cultures, animal models
	Does *S. aureus* directly influence the dysregulation of vascular tone in septic disease, ie, via RPTEC?	In vitro studies
	Where does *S. aureus* accumulate in the kidney?	Imaging of animal models [35]; animal infection model with bioluminescent *S. aureus*
The environment	Do nutrients, drugs, and artificial compounds favor or impede the translocation of *S. aureus* from blood to urine?	Controlled animal models, ie, parenteral iron administration, which aggravated pyelonephritis development in rats [65]
	Should therapy regimes be altered dependent on the detection of *S. aureus* in urine culture?	Controlled clinical trials
The host	Which surface antigens favor the seeding in renal parenchyma cells?	In vitro studies, animal models, knock-out mutants
	Which immune mechanism (Th1/Th2 ratio, complement) plays a role in the translocation of *S. aureus* from the bloodstream to urine?	In vitro studies, animal models, knockout mutants, ie, complement anaphylatoxin C5a receptors [66] or staphylococcal lipoproteins [67]
	Can *S. aureus* be found in neutrophils in urine sediments?	Patient studies and animal studies
	Which comorbidities are confounders of increased mortality due to SABU and to what extent can SABU alone explain increased mortality?	Prospective studies with weighing comorbidities (ie, Charlson weighted index of comorbidity [68])
	What is the impact of *S. aureus* mucosal colonization on the rate of SABU?	Patient studies
	What is the frequency of renal (micro) abscesses in humans with SAB? Is renal imaging prudent in the management of SAB?	Patient studies
	Should diagnostics be routinely optimized to detect SABU in SAB and vice versa?	Patient studies

Abbreviations: RPTEC, renal proximal tubule epithelial cells; SAB, *Staphylococcus aureus* bacteremia; SABU, *Staphylococcus aureus* bacteriuria.

Notes

Author contributions. Conceptualization: F. Schuler and F. Schaumburg. Methodology: F. Schuler. Validation: F. Schuler and F. Schaumburg. Formal analysis: F. Schuler. Investigation: F. Schuler. Resources: F. Schuler. Data curation: F. Schuler. Original draft preparation: F. Schuler. Review and editing: S. N., P. J. B., F. Schaumburg. Visualization: F. Schaumburg. Supervision: F. Schaumburg. Project administration: F. Schuler. All authors have read and agreed to the published version of the manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest.

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