A narrative review on the role of *Staphylococcus aureus* Bacteriuria in *S. aureus* Bacteremia

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**Key Points**

- The prevalence of *Staphylococcus aureus* bacteriuria in patients with *S. aureus* bacteremia is high (7.8%-39%) and associated with increased morbidity and mortality
- The development of micro-abscesses may allow the translocation of *S. aureus* from blood to urine
Abstract

*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, haematogenous seeding - as seen in animal models - and the development of micro-abscesses best describes the translocation of *S. aureus* from blood to urine. Virulence factors that might be involved are adhesion factors, sortase A and coagulase and among others. Other potential routes of bacterial translocation (e.g. transcytosis, paracytosis, translocation via `Trojan horses`) were identified as knowledge gaps.

**Keywords:** *Staphylococcus aureus*, bacteremia, bacteriuria, pathogenesis, renal abscess
1. Introduction

*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 towards *S. aureus* bacteremia (SAB) resulting from haematogenous seeding \(^2\-^4\).

The objectives of this review are to describe (i) the epidemiology of subsequent SABU in patients with SAB, (ii) the renal pathogenesis of bacterial translocation from blood to urine, (iii) potential virulence factors and (iv) to identify knowledge gaps.

After a coarse 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.

**Patient Consent Statement**

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 a signed written informed consent from patients.

**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 term “*s aureus AND bacteriuria AND bacteremia*”, we identified 43 records, of which three 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 nine full-text articles), “s aureus AND kidney abscess” (screened 225 records, assessed nine additional full-text articles), “s aureus AND renal abscess” (screened 244, no additional publication) and “s aureus AND pyelonephritis” (screened 214, two 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. We define SABU as “the detection of *S. aureus* in a urine sample in any concentration (CFU/mL), independent of co-detected pathogens”.

**Epidemiology**

In SAB patients, concomitant SABU was present in 7.8%-39% (see 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 Hospital Münster, Germany among hospitalized patients with SABU and observed that 26.9% had concurrent or subsequent SAB. Rates in other studies (see
Table 2) range from 6.9%-17.2%\textsuperscript{14-20}. 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 one study, all patients with SABU had blood cultures sampled\textsuperscript{6}, while others tested patients only for bacteremia when signs and symptoms of systemic infection (fever, leucocytosis, elevated CRP levels) were present\textsuperscript{10}.

Methodology/technical issues also impede understanding of the true burden of SABU in SAB: for instance, Gram negative bacteria might overgrow \textit{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 Columbia CAP (selective agar for Gram positive bacteria) was not used but Columbia blood agar and MacConkey agar.

The detection of \textit{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 that provided urine samples had concomitant SABU. The blood and urine samples were obtained from 12 patients before the commencement of an effective \textit{S. aureus} antimicrobial treatment. Only one of the 12 patients had other antimicrobial treatment (piperacillin/tazobactam) before blood and urine culture sampling (one day earlier). Cefazolin or flucloxacillin i.v. for the treatment of methicillin-susceptible \textit{S. aureus} and vancomycin, linezolid, or daptomycin for the treatment of methicillin-resistant \textit{S. aureus} (MRSA) were considered effective antimicrobial therapies\textsuperscript{6,21}.
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. The concurrent skin and mucosal colonization with S. aureus in patients with SABU is high, suggesting higher rates of contamination during sampling (66-75%). “False positive” SAB as a result of non-sterile venipuncture is possible, but unlikely. To assess the haematogenous 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. The study revealed that SABU was significantly associated with endocarditis (OR=1.8, 95%CI: 1.16-2.79) 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 labelled as having a UTI. The study group also performed a pooled analysis of four, respectively two, studies and 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), respectively.

Risk factors for elevated mortality of SAB in general are broadly studied (e.g. for instance, non-dialysis dependent chronic kidney disease, cerebrovascular disease in male, moderate to severe liver disease). Karakonstantis et al. showed that SABU is associated with increased mortality in patients with SAB in a meta-analysis which has also been observed at three different tertiary care hospitals in a study.
by Kramer et al. A few studies observed increased clinical complications (septic shock, ICU admission) 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).

**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 sp.*

Nguyen et al. observed that two of 33 patients with invasive pneumococcal infection also had pneumococcosuria, leading to death. 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: Three out of the six patients with candiduria had concomitant candidemia. None of them had evidence of a genitourinary infection.

In an immunocompetent child, *Streptococcus pyogenes* caused an invasive disease with septic embolism to the kidney and consecutive detection in the urine. 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.
2. Pathogenesis

SABU may be the primary outcome of ascending urinary tract infection 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 urinary tract infection is well established, the translocation of *S. aureus* from the bloodstream to the urinary tract is poorly understood and there is only one recent animal study. Two pathways are discussed on how *S. aureus* invade 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 haematogenous 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. 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 six patients; two of them presented initially with SABU. 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 studies 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 \(^3\). The peak bacterial concentrations (CFU/gram of tissue) in the kidney of a mouse model was reached at day 4 post-injection (p.i.) of \textit{S. aureus} \(^3\). In a more recent study, mice were infected (via caudal vein injection) with three different doses of \textit{S. aureus} strain Newman followed by magnetic resonance imaging measurement at day 1, 3 and day 7 p.i. Renal abscesses were observed in 60% of the mice (n=6) receiving the highest \textit{S. aureus} load \((10^7\text{ CFU})\) at day 1 p.i. and in 80% of the mice at day 3 p.i. \(^3\). A rat model for haematogenous pyelonephritis describes the detection of bacteriuria before the development of leukocyturia following inoculation of \textit{S. aureus} in the caudal vein \(^3\). Nesbit \textit{et al.} made a similar observation in patients with haematogenous pyelonephritis \(^3\). Tancheva \textit{et al.} highlighted the importance of venous stasis (i) for an increase of microbial concentration in renal vessels and (ii) to maintain and boost the inflammatory process due to an increase in renal pressure and therefore reduction of tissue resistance \(^3\). In this mechanistic theory, the reduced resistance is supposed to facilitate \textit{S. aureus} passing cell barriers and translocate 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, \textit{S. aureus} interacts with the endothelium and secretes toxins and proteases eventually causing tissue destruction \(^3\). In the kidneys it might be similar leading to abscess formation in the renal parenchyma. Potential virulence factors are discussed later.

Suppurative tubulointerstitial nephritis must be discriminated from postinfectious glomerulonephritis (PIGN), which is the current definition of renal changes originally devised as Löhlein’s nephritis \(^3\). PIGN is an immunologic disease characterised 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\textsuperscript{37}. A few studies observed the occurrence of glomerulonephritis in the acute phase of \textit{S. aureus} endocarditis. This might occur along with tubulointerstitial nephritis or due to a non-immune activation of the alternative complement pathway as shown by O´Connor et al. in patients with \textit{S. aureus} endocarditis\textsuperscript{38-40}.

\textit{Transcytosis}

\textit{S. aureus} uptake into non-professional phagocytes has been demonstrated for many different cell types. Invasion is mediated via fibronectin bridging between host-\textalpha 5\textbeta 1 integrins and staphylococcal surface proteins, FnBPA and FnBPB. This binding triggers intracellular signaling that finally leads to cytoskeletal rearrangements and uptake of the bacteria\textsuperscript{41}. It has also been shown that renal (mouse) cells can ingest \textit{S. aureus}\textsuperscript{42}. Therefore, it could be hypothesized that the route of \textit{S. aureus} from blood to urine is via transcytosis through endothelial cells, mesangium intraglomerular cells and eventually podocytes.

\textbf{Figure 1:} Translocation of \textit{S. aureus} from blood to urine

\section*{3. Virulence factors}

\textit{S. aureus} is known to harbor numerous different virulence factors, partly with redundant functions. Table 3: Virulence factors associated with \textit{S. aureus}-specific renal pathogenicity in animal models and might influence the renal passage of \textit{S. aureus} from blood to urine. \textit{S. aureus} binds host cells through different bacterial adhesins to
extracellular matrix proteins (e.g. fibronectin, fibrinogen/ fibrin, von Willebrand factor). This attachment might also be the first step in the uptake of bacteria from the blood into the tissue, via a transcellular or paracellular route (see knowledge gaps).

4. Knowledge gaps

While there is 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, two other possible routes from blood to urine could play a role in the renal passage of *S. aureus*.

(i) 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 signalling 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. *S. aureus* alpha-toxin is also believed to be associated with the formation of paracellular gaps between airway epithelial cells as well as human epithelial colorectal cells. In line with these observations, it can also be speculated that *S. aureus* can enter the urine from the blood via the paracellular route.

(ii) 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. In this context, it was suggested that *S. aureus* can also leave the blood vessel inside professional phagocytes. 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. Table 4 provides a summary of knowledge gaps and how they could be addressed in future studies.

*Table 4: Knowledge gaps*

### 5. Conclusions

A high proportion of patients with SAB develop SABU (7.8%-39%) and SABU is associated with increased mortality in SAB-patients. The understanding of the pathomechanisms of secondary SABU is poorly understood. Possible routes of translocation from blood to urine might include (i) tissue destruction and abscess formation, (ii) transcytosis, (iii) paracytosis and/or (iv) along with ‘Trojan horses’. A combination of different pathways is likely. Some *S. aureus* virulence factors (e.g. adhesion factors, coagulase) are likely to play a central role. Further studies are needed to determine the clinical management of SABU in SAB in terms of diagnostics and therapy regimens.
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Conceptualization: Fra. S. and Fri. S.; methodology, Fra. S.; validation: Fra. S. and Fri. S.; formal analysis: Fra. S.; investigation, Fra. S.; resources: Fra. S.; data curation: Fra. S.; writing—original draft preparation: Fra. S.; writing—review and editing: S.N., P.B., Fri. S.; visualization: Fri. S.; supervision: Fri. S.; project administration: Fra. S.; All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest referring to the ICMJE standards.

Abbreviations

CFU colony-forming unit
p.i. post-injection
PIGN postinfectious glomerulonephritis
RPTEC renal proximal tubule epithelial cells
S. aureus Staphylococcus aureus
SAB Staphylococcus aureus bacteremia
SABU Staphylococcus aureus bacteriuria
UTI urinary tract infection
References

1. Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VG. Staphylococcus aureus Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. Clinical Microbiology Reviews. 2015;28(3):603-661.

2. Al Mohajer M, Darouiche RO. Staphylococcus aureus Bacteriuria: Source, Clinical Relevance, and Management. Current infectious disease reports. 2012;14(6):601-606.

3. Kramer TS, Schlosser B, Gruhl D, et al. Staphylococcus aureus Bacteriuria as a Predictor of In-Hospital Mortality in Patients with Staphylococcus aureus Bacteremia. Results of a Retrospective Cohort Study. Journal of clinical medicine. 2020;9(2).

4. Lee BK, Crossley K, Gerding DN. The association between Staphylococcus aureus bacteremia and bacteriuria. The American journal of medicine. 1978;65(2):303-306.

5. Karakonstantis S, Kalemaki D. Evaluation and management of Staphylococcus aureus bacteriuria: an updated review. Infection. 2018;46(3):293-301.

6. Schuler F, Froböse N, Schaumburg F. Prevalence and risk factors for bacteremia in patients with Staphylococcus aureus bacteriuria: a retrospective cohort study. International journal of infectious diseases: 2020.

7. Ekkelenkamp MB, Verhoef J, Bonten MJ. Quantifying the relationship between Staphylococcus aureus bacteremia and S. aureus bacteriuria: a retrospective analysis in a tertiary care hospital. Clinical Infectious Diseases 2007;44(11):1457-1459.

8. Huggan PJ, Murdoch DR, Gallagher K, Chambers ST. Concomitant Staphylococcus aureus bacteriuria is associated with poor clinical outcome in
adults with *S. aureus* bacteraemia. *Journal of Hospital Infection*. 2008;69(4):345-349.

9. Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. Clinical significance of Staphylococcus aureus bacteriuria in a nationwide study of adults with *S. aureus* bacteraemia. *The Journal of infection*. 2012;64(1):41-46.

10. Pulcini C, Matta M, Mondain V, et al. Concomitant *Staphylococcus aureus* bacteriuria is associated with complicated *S. aureus* bacteremia. *The Journal of infection*. 2009;59(4):240-246.

11. Perez-Jorge EV, Burdette SD, Markert RJ, Beam WB. *Staphylococcus aureus* bacteremia (SAB) with associated *S. aureus* bacteriuria (SABU) as a predictor of complications and mortality. *Journal of hospital medicine*. 2010;5(4):208-211.

12. Choi SH, Lee SO, Choi JP, et al. The clinical significance of concurrent *Staphylococcus aureus* bacteriuria in patients with *S. aureus* bacteremia. *The Journal of infection*. 2009;59(1):37-41.

13. Chihara S, Popovich KJ, Weinstein RA, Hota B. *Staphylococcus aureus* bacteriuria as a prognosticator for outcome of *Staphylococcus aureus* bacteremia: a case-control study. *BMC infectious diseases*. 2010;10:225.

14. Demuth PJ, Gerding DN, Crossley K. *Staphylococcus aureus* bacteriuria. *Archives of Internal Medicine* 1979;139(1):78-80.

15. Saidel-Odes L, Riesenberg K, Schlaeffer F, Borer A. Epidemiological and clinical characteristics of methicillin sensitive *Staphylococcus aureus* (MSSA) bacteriuria. *The Journal of infection*. 2009;58(2):119-122.

16. Sheth S, DiNubile MJ. Clinical significance of *Staphylococcus aureus* bacteriuria without concurrent bacteremia. *Clinical Infectious Diseases*. 1997;24(6):1268-1269.

17. Stokes W, Parkins MD, Parfitt ECT, Ruiz JC, Mugford G, Gregson DB. Incidence and Outcomes of *Staphylococcus aureus* Bacteriuria: A Population-based Study. *Clinical Infectious Diseases*. 2019;69(6):963-969.
18. Al Mohajer M, Musher DM, Minard CG, Darouiche RO. Clinical significance of Staphylococcus aureus bacteriuria at a tertiary care hospital. Scandinavian journal of infectious diseases. 2013;45(9):688-695.

19. Muder RR, Brennen C, Rihs JD, et al. Isolation of Staphylococcus aureus from the urinary tract: association of isolation with symptomatic urinary tract infection and subsequent staphylococcal bacteremia. Clinical Infectious Diseases. 2006;42(1):46-50.

20. Arpi M, Renneberg J. The clinical significance of Staphylococcus aureus bacteriuria. The Journal of urology. 1984;132(4):697-700.

21. Holland TL, Arnold C, Fowler VG, Jr. Clinical management of Staphylococcus aureus bacteremia: a review. Journal of the American Medical Association. 2014;312(13):1330-1341.

22. Baraboutis IG, Tsagalou EP, Lepinski JL, et al. Primary Staphylococcus aureus urinary tract infection: the role of undetected hematogenous seeding of the urinary tract. European Journal of Clinical Microbiology and Infectious Diseases. 2010;29(9):1095-1101.

23. Looney AT, Redmond EJ, Davey NM, et al. Methicillin-resistant Staphylococcus aureus as a uropathogen in an Irish setting. Medicine 2017;96(14).

24. Karakonstantis S, Kalemaki D. The clinical significance of concomitant bacteriuria in patients with Staphylococcus aureus bacteremia. A review and meta-analysis. Infectious diseases. 2018;50(9):648-659.

25. Kim YS, Kim J, Cheon S, Sohn KM. Higher Risk for All-cause Mortality of Staphylococcus aureus Bacteremia in Patients with Non-Dialysis Dependent Chronic Kidney Disease. Infection & chemotherapy. 2020;52(1):82-92.

26. Bassetti M, Trecarichi EM, Mesini A, et al. Risk factors and mortality of healthcare-associated and community-acquired Staphylococcus aureus bacteraemia. Clinical Microbiology and Infection. 2012;18(9):862-869.
27. Nguyen VQ, Penn RL. Pneumococcosuria in adults. *Journal of Clinical Microbiology*. 1988;26(6):1085-1087.

28. Sobel JD, Bradshaw SK, Lipka CJ, Kartsonis NA. Caspofungin in the treatment of symptomatic candiduria. *Clinical infectious diseases*. 2007;44(5):e46-49.

29. Jordán I, García MT, García J, Vicente A, Luaces C. [Invasive disease caused by Streptococcus pyogenes. Report of a case with cutaneous and kidney metastasis]. *Anales espanoles de pediatria*. 2000;52(6):577-579.

30. Tancheva S, Valcheva-Kuzmanova SV, Radev RZ, et al. A model of experimental acute hematogenous pyelonephritis in the rat. *Folia medica*. 2011;53(2):63-68.

31. Nesbit RN, Dick VS. Acute staphylococcal infections of the kidney. *The Journal of Urology*. 1940;43(5):623-636.

32. Gorrill RH. The establishment of staphylococcal abscesses in the mouse kidney. *Br J Exp Pathol*. 1958;39(2):203-212.

33. Lee JC, Perez NE, Hopkins CA. Production of toxic shock syndrome toxin 1 in a mouse model of *Staphylococcus aureus* abscess formation. *Reviews of infectious diseases*. 1989;11 Suppl 1:S254-259.

34. Kromrey ML, Göhler A, Friedrich N, et al. Monitoring of abdominal *Staphylococcus aureus* infection using magnetic resonance imaging: a murine animal model for hepatic and renal abscesses. *European Journal of Clinical Microbiology and Infectious Diseases*. 2017;36(2):373-378.

35. Edwards AM, Massey RC. How does *Staphylococcus aureus* escape the bloodstream? *Trends in microbiology*. 2011;19(4):184-190.

36. Schwarz C, Hoerr V, Töre Y, et al. Isolating Crucial Steps in Induction of Infective Endocarditis With Preclinical Modeling of Host Pathogen Interaction. *Frontiers in Microbiology*. 2020;11:1325.

37. Fogo AB, Cohen AH, Colvin RB, Jennette JC, Alpers CE. *Fundamentals of renal pathology*. Springer; 2014.
38. Neugarten J, Baldwin DS. Glomerulonephritis in bacterial endocarditis. *The American Journal of Medicine*. 1984;77(2):297-304.

39. O’Connor D, Weisman M, Fierer J. Activation of the alternate complement pathway in Staph. aureus infective endocarditis and its relationship to thrombocytopenia, coagulation abnormalities, and acute glomerulonephritis. *Clinical and Experimental Immunology*. 1978;34(2):179.

40. Levine DP, Cushing RD, Jui J, Brown WJ. Community-acquired methicillin-resistant *Staphylococcus aureus* endocarditis in the Detroit Medical Center. *Annals of Internal Medicine*. 1982;97(3):330-338.

41. Josse J, Laurent F, Diot A. Staphylococcal Adhesion and Host Cell Invasion: Fibronectin-Binding and Other Mechanisms. *Frontiers in Microbiology*. 2017;8(2433).

42. Alexander EH, Hudson MC. Factors influencing the internalization of *Staphylococcus aureus* and impacts on the course of infections in humans. *Applied microbiology and biotechnology*. 2001;56(3-4):361-366.

43. Doran KS, Banerjee A, Disson O, Lecuit M. Concepts and mechanisms: crossing host barriers. *Cold Spring Harbor Perspectives in Medicine*. 2013;3(7):a010090.

44. Soong G, Martin FJ, Chun J, Cohen TS, Ahn DS, Prince A. *Staphylococcus aureus* protein A mediates invasion across airway epithelial cells through activation of RhoA GTPase signaling and proteolytic activity. *Journal of Biological Chemistry*. 2011;286(41):35891-35898.

45. Kwak YK, Vikström E, Magnusson KE, Vécsey-Semjén B, Colque-Navarro P, Möllby R. The *Staphylococcus aureus* alpha-toxin perturbs the barrier function in Caco-2 epithelial cell monolayers by altering junctional integrity. *Infection and immunity*. 2012;80(5):1670-1680.

46. Thwaites GE, Gant V. Are bloodstream leukocytes Trojan Horses for the metastasis of *Staphylococcus aureus*? *Nature reviews Microbiology*. 2011;9(3):215-222.
47. Zhu H, Jin H, Zhang C, Yuan T. Intestinal methicillin-resistant Staphylococcus aureus causes prosthetic infection via ‘Trojan Horse’ mechanism: Evidence from a rat model. Bone and joint research. 2020;9(4):152-161.

48. Prajsnar TK, Hamilton R, Garcia-Lara J, et al. A privileged intraphagocyte niche is responsible for disseminated infection of Staphylococcus aureus in a zebrafish model. Cellular microbiology. 2012;14(10):1600-1619.

49. Scholthof K-BG. The disease triangle: pathogens, the environment and society. Nature Reviews Microbiology. 2007;5(2):152-156.

50. Manandhar S, Pai G, Gidwani H, et al. Does Staphylococcus aureus Bacteriuria Predict Clinical Outcomes in Patients With Bacteremia?: Analysis of 274 Patients With: Staphylococcus aureus: Blood Stream Infection. Infectious Diseases in Clinical Practice. 2016;24(3):151-154.

51. Cheng AG, Kim HK, Burts ML, Krausz T, Schneewind O, Missiakas DM. Genetic requirements for Staphylococcus aureus abscess formation and persistence in host tissues. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(10):3393-3404.

52. De Navasquez SJTJop, bacteriology. Experimental pyelonephritis in the rabbit produced by staphylococcal infection. The Journal of Pathology and Bacteriology. 1950;62(3):429-436.

53. Smith W, Hale JH, Smith MM. The role of coagulase in staphylococcal infections. British journal of experimental pathology. 1947;28(1):57-67.

54. Kwieciński J, Josefsson E, Mitchell J, et al. Activation of plasminogen by staphylokinase reduces the severity of Staphylococcus aureus systemic infection. The Journal of infectious diseases. 2010;202(7):1041-1049.

55. Zhou C, Bhinderwala F, Lehman MK, et al. Urease is an essential component of the acid response network of Staphylococcus aureus and is required for a persistent murine kidney infection. PLoS pathogens. 2019;15(1):e1007538.
56. Salgado-Pabón W, Breshears L, Spaulding AR, et al. Superantigens are critical for *Staphylococcus aureus* Infective endocarditis, sepsis, and acute kidney injury. *mBio*. 2013;4(4).

57. Ionin B, Hammamieh R, Shupp JW, Das R, Pontzer CH, Jett M. Staphylococcal enterotoxin B causes differential expression of Rnd3 and RhoA in renal proximal tubule epithelial cells while inducing actin stress fiber assembly and apoptosis. *Microbial pathogenesis*. 2008;45(5-6):303-309.

58. Hartleib J, Köhler N, Dickinson RB, et al. Protein A is the von Willebrand factor binding protein on *Staphylococcus aureus*. *Blood*. 2000;96(6):2149-2156.

59. Hussain M, Haggar A, Peters G, et al. More than One Tandem Repeat Domain of the Extracellular Adherence Protein of *Staphylococcus aureus* Is Required for Aggregation, Adherence, and Host Cell Invasion but Not for Leukocyte Activation. *Infection and immunity*. 2008;76(12):5615-5623.

60. Rauch S, DeDent AC, Kim HK, Bubeck Wardenburg J, Missiakas DM, Schneewind O. Abscess formation and alpha-hemolysin induced toxicity in a mouse model of *Staphylococcus aureus* peritoneal infection. *Infection and immunity*. 2012;80(10):3721-3732.

61. Dale SE, Doherty-Kirby A, Lajoie G, Heinrichs DE. Role of siderophore biosynthesis in virulence of *Staphylococcus aureus*: identification and characterization of genes involved in production of a siderophore. *Infection and immunity*. 2004;72(1):29-37.

62. Kropec A, Maira-Litran T, Jefferson KK, et al. Poly-N-acetylglucosamine production in *Staphylococcus aureus* is essential for virulence in murine models of systemic infection. *Infection and immunity*. 2005;73(10):6868-6876.

63. Jongerius I, von Köckritz-Blickwede M, Horsburgh MJ, Ruyken M, Nizet V, Rooijakkers SH. *Staphylococcus aureus* virulence is enhanced by secreted factors that block innate immune defenses. *Journal of innate immunity*. 2012;4(3):301-311.
64. Débarbouillé M, Dramsi S, Dussurget O, et al. Characterization of a serine/threonine kinase involved in virulence of *Staphylococcus aureus*. *Journal of Bacteriology*. 2009;191(13):4070-4081.

65. Anğ O, Güngör M, Aricioğlu F, et al. The effect of parenteral iron administration on the development of *Staphylococcus aureus*-induced experimental pyelonephritis in rats. *International journal of experimental pathology*.. 1990;71(4):507-511.

66. Horst SA, Itzek A, Klos A, Beineke A, Medina E. Differential Contributions of the Complement Anaphylotoxin Receptors C5aR1 and C5aR2 to the Early Innate Immune Response against *Staphylococcus aureus* Infection. *Pathogens*. 2015;4(4):722-738.

67. Bubeck Wardenburg J, Williams WA, Missiakas D. Host defenses against *Staphylococcus aureus* infection require recognition of bacterial lipoproteins. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(37):13831-13836.

68. Lesens O, Methlin C, Hansmann Y, et al. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteremia: a prospective study using the Charlson weighted index of comorbidity. *Infection control and hospital epidemiology* 2003;24(12):890-896.
Table 1: Characteristics and findings of reviewed studies for the prevalence of SABU in patients with SAB

| Location            | Design                 | Duration          | Patient populationa | Inclusion criteria                                                                 | Exclusion criteria       | Patients with SAB | Patient with SABU (%) | Reference |
|---------------------|------------------------|-------------------|---------------------|-------------------------------------------------------------------------------------|--------------------------|-------------------|-----------------------|-----------|
| Iceland             | Retrospective cohort study | 2003-2008        | ≥18 years, different hospitals | urine culture submitted <24h of the index blood culture                           | diagnosis of S. aureus UTI | 152               | 16 (16)               | 9         |
| Chicago, Illinois, USA | Case-control study | 2002-2006        | ≥18 years, community hospital | urine culture submitted <72h of the index blood culture                           | none                      | 289               | 57 (19.7)             | 13        |
| Location       | Study Type          | Year Range | Age Criteria | Culture Details                                                                 | Patients with Indwelling Urinary Catheters | Patients with S. aureus UTI (Study Group 1) |
|---------------|---------------------|------------|--------------|--------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|
| Seoul, Korea  | Retrospective cohort study | 2006-2007  | ≥18 years, tertiary care hospital | urine culture submitted <48h of the index blood culture | 128 (19.5) | 12 (7.8) |
| Utrecht, Netherlands | Retrospective cohort study | 2001-2006 | tertiary care hospital | urine sample obtained for culture on the day of the positive blood culture result | 153 (study group 1) | 7 |
| Christchurch  | Retrospective       | 2000-      | ≥18 years, tertiary care hospital | urine culture deemed bacteremia | 378 | 37 (9.8) |
| Location          | Study Type         | Years     | Age Group   | Source                          | Blood Culture Submitted | Urine Culture Submitted | Contamination Criteria                                      | Cases | Controls | p Value |
|-------------------|--------------------|-----------|-------------|---------------------------------|--------------------------|-------------------------|-------------------------------------------------------------|-------|----------|---------|
| New Zealand       | Retrospective      | 2003      | Tertiary    | Hospital                        | <24h of index blood culture | none                   | To represent contamination                                  |       |          |         |
| Berlin, Germany   | Retrospective      | 2014-2017 | ≥18 years   | 3 tertiary care hospitals       | <48h of index blood culture | none                   | none                                                        | 202   | 78 (39)  |         |
| Minnesota, USA    | Retrospective      | 1972-1976 | ≥ two positive blood cultures or S. aureus with the same | None                           | none                   | None                                                        | 59    | 16 (27.1)|         |
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

| Pittsburgh, Retrospective 2010- | ≥18 years | *S. aureus* no urine culture | 179 | 36 | su |
| Location | Study Type | Year(s) | Setting | Criteria | N | Rate |
|----------|------------|---------|---------|----------|---|------|
| PA, USA  | Cohort study | 2013 | | from at least one blood culture, urine culture submitted <48h of the index blood culture, SABU $\geq 10^5$ cfu/ml performed, S. aureus less than $10^5$ cfu/ml | | (20.1) |
| Ohio, USA | Retrospective cohort study | 2004-2007 | Community hospital | urine culture submitted <7d days of the index blood culture inadequate/incomplete treatment for SAB | 118 | 28 (23.7) |
| Location | Study Type | Criteria | Outcomes | Results |
|----------|------------|----------|----------|---------|
| Nice and Paris, France | Prospective observational study | Nice: ≥18 years, university hospital and tertiary care hospital, Paris: 2008, evident SIRS, consultation of an ID specialist | a polymicrobial bloodstream infection, death before evaluation | 104 (68 had concomitant urine cultures submitted), 23 (33.8)% |

*all patients were admitted*
| Location | Design                     | Duration | Population    | Inclusion Criteria                                                                 | Exclusion Criteria                                                                 | Patients with SABU | Patients with SAB (%) | Criteria for SAB | Reference |
|----------|----------------------------|----------|---------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|----------------------|-------------------|------------|
| Houston, TX, USA | Retrospective cohort study | 2008-2010 | Veterans Affairs Medical Center | one episode of SABU (= any growth of *S. aureus* from urine) per patient | patients with invasive SAB two days before SABU patients with invasive SAB due to | 326                 | 56 (17.2)           | SAB within 12 months of SABU | 2          |
| Country       | Study Type         | Start Year-End Year | Setting       | Growth Medium | Threshold | Total Isolates | Number with \(SABU \geq 10^3\) cfu/ml | NA    | Percentage (NA) | Notes |
|---------------|--------------------|---------------------|---------------|---------------|-----------|----------------|--------------------------------------|-------|-----------------|-------|
| Denmark       | Retrospective cohort study | Unknown             | Most patients were elderly men | Unknown        | Unknown   | 132            | 11 (8.3)                            | Unknown | None            | 20    |
| Minneapolis, MN USA | Retrospective cohort | 1972-1976           | In-/outpatients | SABU \(\geq 10^3\) cfu/ml | NA        | 123            | 16 (13)                             | None   | 14              |       |
| Study Location | Study Design | Sex | Patients | Urine Culture Positive | Treatment Duration | Number | Duration | Notes |
|----------------|--------------|-----|----------|------------------------|-------------------|--------|----------|-------|
| PA, USA        | Prospective, observational study | Male patients from long-term care Veterans Affairs facility | ≥ one urine culture positive for *S. aureus* | NA | 102 | 13 (12.7) | SAB 2 days before to 4 days after the initial positive urine culture |
| Israel         | Retrospective cohort study | ≥ 18 years patients hospitalized at a tertiary care hospital | ≥ 10^6 cfu/ml MSSA from midstream urine or ≥ 10^2 cfu/ml from a single urethral catheterized | patients with MRSA bacteriuria | 106 | 13 (12) | SAB within 24h to SABU |
Camden, NJ, USA  Retrospective cohort study  one year hospitalized patients  SABU (not further defined) concurrent SAB in the week preceding or 72h after the first 45 5 (11.1) see exclusion criteria

| Location          | Study Type          | Duration | Hospitalized Patients | Definition of SABU | Concurrent SAB | N | 5%  |
|-------------------|---------------------|----------|-----------------------|--------------------|----------------|---|-----|
| Camden, NJ, USA   | Retrospective cohort study | one year | hospitalized patients | SABU (not further defined) | concurrent SAB in the week preceding or 72h after the first | 45 | 5 (11.1) |

urine or $ \geq 10^5$ cfu/ml with no more than two species of microorganisms in a patient with a permanent urinary catheter
| Location          | Study Design         | Study Period | Participants | Eligibility Criteria                                                                 | Cultures | Positive Cultures | SAB Documented Within 3 Months of SABU |
|-------------------|----------------------|--------------|--------------|--------------------------------------------------------------------------------------|----------|-------------------|-----------------------------------------|
| Calgary Health Zone, Canada | Retrospective cohort study | 2010-2013 | in-/outpatients ≥18 years | S. aureus 10⁶–10⁷ cfu/ml or >10⁷ cfu/ml with no more than one other organism present | 2540     | 175 (6.9)         | documented SAB within 3 months of SABU |

S. aureus from nonroutine urine cultures (eg. suprapubic concurrent periurethral flora, defined as organisms <10⁷ cfu/ml in the presence of a uropathogen ≥10⁷ cfu/ml |

|                  |                      |              |              | S. aureus 10⁶–10⁷ cfu/ml or >10⁷ cfu/ml with no more than one other organism present |          |                   |                                        |
| aspiration) was reported as positive if the S. aureus was $>10^4$ cfu/ml with no more than one other organism present. | urine cultures within 3 months of each other and the same S. aureus antibiogram |
Table 3: Virulence factors associated with *S. 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      | 51        |
| 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) | 52        |
|                                       |                                                                          | in vivo animal studies (guinea-pigs, mice) | 53        |
| Staphylokinase                        | activation of plasminogen (antivirulence properties)                     | murine infection model      | 54        |
| Urease                                | promoting bacterial fitness in the low-pH, urea-rich kidney              | murine infection model      | 55        |
| Superantigens (SAgs)                  | increased virulence (lethal sepsis, infective endocarditis, kidney infections) in methicillin-resistant *S. aureus* strain MW2 (especially staphylococcal enterotoxin C) | in vivo animal studies (rabbit model) | 56        |
| **Staphylococcal enterotoxin B** | proposed induction of renal proximal tubule epithelial cells (RPTEC) leading to dysregulation of the vascular tone | cell cultures | 57 |
|---------------------------------|-------------------------------------------------------------------------------------------------------------|--------------|----|
| **Adhesion factors, i.e. FnBPs, Eap, Clumping factor A and B, or Protein A** | binding to extracellular matrix proteins (e.g. 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 | 35, 58, 59 |
| **Alpha haemolysin** | dispensable for renal abscess lesions | murine infection model | 60 |
| **Siderophore production** | renal abscess formation | murine infection model | 61 |
| **Surface polysaccharide (Poly-N-acetylglucosamine)** | renal abscess formation | murine infection model | 62 |
| **Extracellular complement-binding protein (Ecb) and extracellular fibrinogen** | impairment of complement activation followed by a decrease in renal abscess formation | murine infection model | 63 |
| binding protein (Efb) | Eukaryotic-like Serine/Threonine-Kinase | renal abscess formation | murine infection model | 64 |
| Disease triangle | Knowledge gap | Research strategy |
|------------------|---------------|-------------------|
| The pathogen     | Which virulence factors and *S. 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. |
|                  | Do the mechanism of immune evasion (e.g. intracellular survival, interaction with signalling pathways) play a role? | Cell cultures, animal models |
|                  | Does *S. aureus* directly influence the dysregulation of vascular tone in septic disease i.e. via RPTEC? | *in vitro* studies |
|                  | Where does *S. aureus* accumulate in the kidney? | Imaging of animal models; animal infection model with bioluminescent *S. aureus* |
| The environment  | Do nutrients, drugs, artificial compound favour or impede the translocation of *S. aureus* from blood to urine? | controlled animal models, i.e. parenteral iron administration, which aggravated pyelonephritis development in rats |
|                  | Should therapy regimes be altered dependent on the | controlled clinical trials |
| The host | Detection of *S. aureus* in urine culture? | *in vitro* studies, animal models, knock-out mutants |
| --- | --- | --- |
| | Which surface antigens favour the seeding in renal parenchyma cells? | *in vitro* studies, animal models, knock-out mutants, i.e. complement anaphylatoxin C5a receptors or staphylococcal lipoproteins |
| | Which immune mechanism (TH1/Th2-ratio, complement) play a role in the translocation of *S. aureus* from the bloodstream to urine? | *in vitro* studies, animal models, knock-out mutants, i.e. complement anaphylatoxin C5a receptors or staphylococcal lipoproteins |
| 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 (i.e. “Charlson weighted index of comorbidity”)
| | What is the impact *S. aureus* of 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 optimised to detect SABU in SAB and vice versa? | Patient studies |
