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**Staphylococcus aureus colonization and infection:  
optimizing MRSA decolonization and addressing challenges  
in S. aureus bacteremia management**

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**Citation**

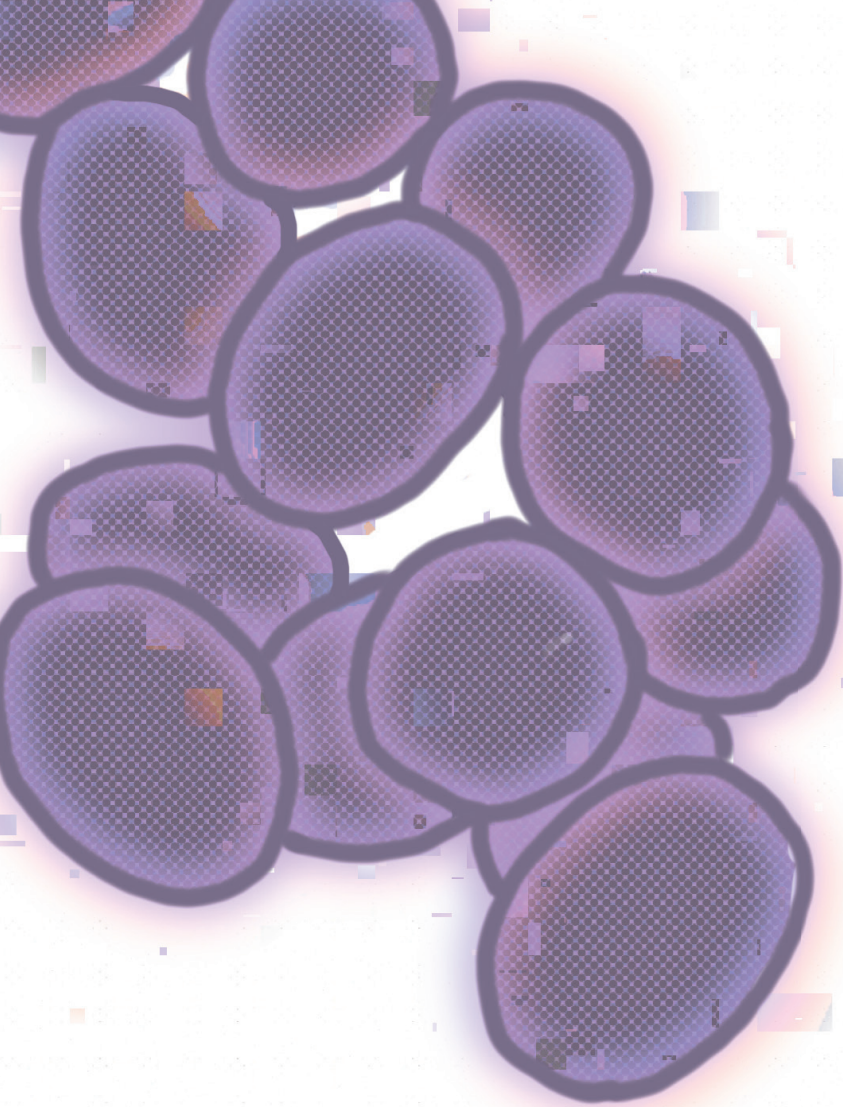
Westgeest, A. C. (2024, September 19). *Staphylococcus aureus colonization and infection: optimizing MRSA decolonization and addressing challenges in S. aureus bacteremia management*. Retrieved from <https://hdl.handle.net/1887/4092834>

Version: Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).



# Chapter 7

## Acute kidney injury in *Staphylococcus aureus* bacteremia

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Eur J Clin Microbiol Infect Dis. 2022 Mar;41(3):431-437.

## Abstract

Acute kidney injury (AKI) is a frequent complication in patients with *Staphylococcus aureus* bacteremia (SAB), with a significant impact on patient management and outcome. This study aimed to provide insight in the proportion of patients with SAB that develop AKI, the risk factors for developing AKI in this population, and its reversibility. In this retrospective, multicenter cohort study, adult patients with SAB were eligible for inclusion. Patient characteristics, clinical variables, and laboratory results were retrieved from the electronic patient files. Primary outcome was development of AKI, defined as 1.5 times baseline creatinine. Secondary outcomes were reversibility of AKI and risk factors for AKI. A total of 315 patients with SAB were included, of whom 115/315 (37%) developed acute kidney injury. In 68/115 (59%), the AKI was reversible. If kidney function recovered, this occurred within 7 days in 56/68 (82%) of patients. In multivariable logistic regression analyses, independent risk factors for AKI were as follows: complicated SAB, use of diuretics, and hemodynamic instability. Development of AKI was associated with 30-day mortality (OR 3.9; CI 2.2–6.9;  $p < 0.01$ ). Acute kidney injury is a frequent complication in patients with *Staphylococcus aureus* bacteremia. Considering the irreversibility in a relevant proportion of patients, future research into the underlying pathophysiology and potential interventions is warranted.

## Introduction

*Staphylococcus aureus* is a major cause of bloodstream infections and is associated with high morbidity and mortality rates [1, 2]. Acute kidney injury (AKI) is a frequent complication in patients with *Staphylococcus aureus* bacteremia (SAB), with a significant impact on patient management and outcome [3, 4]. The etiology of AKI in SAB is diverse, including prerenal, toxic/drug-related, immune-mediated, tubulointerstitial nephritis (TIN), acute tubular necrosis (ATN), and postrenal pathophysiology. Despite the fact that acute kidney injury in patients with SAB is common, little is known about the proportion of patients with SAB that develop AKI, the risk factors for developing AKI in these patients, and its reversibility. The SAB patient population is heterogeneous, and the disease course varies greatly, from transient bacteremia in uncomplicated SAB to widespread infection and metastatic disease in complicated SAB [5]. Although likely on theoretical grounds, it is unknown whether the incidence, etiology, and outcome of AKI differ between complicated and uncomplicated SAB [6].

The aim of this study was to investigate the incidence of AKI in SAB, its reversibility, the risk factors for the development of AKI, and differences in disease course

between complicated and uncomplicated SAB. Additional knowledge of AKI in SAB may provide clinicians tools to predict risk of AKI in individual patients and support diagnostic and therapeutic management. Eventually, it could lead to initiation of intervention studies aimed at prevention or treatment of AKI in patients with SAB.

## Methods

### Study population

This multicenter retrospective cohort study was performed in one academic and two large teaching hospitals in the Netherlands. Patients that were diagnosed with SAB in the period January 2013 to December 2017 were eligible for inclusion. Data on this study cohort have been published previously [7]. All consecutive adult patients ( $\geq 18$  years) with  $\geq 1$  blood culture positive for *S. aureus* were eligible for inclusion. Patients were excluded if (a) *S. aureus* was detected simultaneously with other pathogens (polymicrobial culture), (b) patients were already on renal dialysis before admission, (c) and AKI occurred prior to the episode of SAB. In patients with multiple episodes of SAB, only the first episode was included. Both patients with community acquired SAB and patients who developed SAB during hospitalization for another indication (hospital acquired SAB) were eligible for inclusion.

### Data collection

Blood samples were inoculated in both anaerobic and aerobic bottles and incubated in the BACTEC FX continuous monitoring system (Becton Dickinson BV, Breda, The Netherlands). The clinical data were obtained through review of the electronic patient files. The following data were collected: demographic data, medical history, chronic medication, antibiotic therapy administered for treatment of the SAB episode, vital parameters, and the presence of complicated versus uncomplicated SAB. Baseline serum creatinine ( $\mu\text{mol/L}$ ), i.e., the most recent known serum creatinine before the presentation with SAB, creatinine at presentation, and maximum creatinine during admission were retrieved from the electronic laboratory system. Furthermore, the time to maximum serum creatinine and the time from maximum creatinine to recovery of creatinine were retrieved.

### Definitions

Acute kidney injury was defined as 1.5 times baseline creatinine. Recovery of kidney function was defined as creatinine returning to below 1.5 times baseline creatinine during follow-up. The absence of recovery of renal function  $< 1.5$  times baseline creatinine during follow-up was considered non-reversible AKI. Hemodynamic

instability was defined as a mean arterial pressure (MAP) < 65 mmHg or systolic blood pressure < 90 mmHg or need of inotropic or vasopressor agents [8]. Chronic kidney disease was defined as an eGFR < 60 ml/min/1.73 m<sup>2</sup>. Uncomplicated SAB was defined as an episode of bacteremia with  $\geq 1$  blood culture with *Staphylococcus aureus*, without evidence of endocarditis/ metastatic infection, and without positive cultures after 48 h of adequate therapy and that was treated for a maximum of 2 weeks, and no relapse occurred, and the patient survived > 72 h after presentation. All situations that did not meet the criteria for uncomplicated SAB were considered complicated SAB. Infective endocarditis was defined by the modified Duke's criteria [9]. Metastatic infection was defined as a clinical and/or radiographical examination and/ or culture concordant with vertebral osteomyelitis, epidural abscess, deep tissue abscess (e.g., psoas) septic pulmonary or cerebral emboli, arthritis, or meningitis.

### Statistical analysis

Data were presented as percentages or proportions for categorical variables and as medians plus interquartile range (IQR) for continuous variables. The overall development of AKI and the recovery of AKI were presented as a rate, with 95% confidence interval (95%CI), and were stratified for complicated and uncomplicated SAB. Cox regression analysis was performed to assess time to development and time to recovery of AKI. Recovery of AKI in patients still alive at day 30 was presented as a rate. Univariate analysis was performed by calculating odds ratio's (with 95%CI) and using Fisher's exact tests to identify clinical factors associated with AKI. To assess the correlation of different variables and outcome, a multivariable regression analysis was performed including the variables with  $p < 0.20$  from univariate analysis. Subgroup analyses of prevalence of AKI and reversibility were also performed on patients with hemodynamic instability at presentation and patients with preexistent chronic kidney disease.

### Ethical approval

Ethical approval was granted by the institutional ethical review committee of the Leiden University Medical Center.

### Results

In total, 339 patients with SAB were reviewed. Because of prior chronic (long-term) hemodialysis or development of AKI prior to SAB, respectively 14 and 10 patients were excluded, leaving 315 patients eligible for inclusion in this study. The patient characteristics are summarized in Table 1. In 181/315 (58%) of patients, the SAB

episode met the criteria for complicated SAB. All of the cultured *S. aureus* isolates were methicillin-sensitive (MSSA). Overall 30-day mortality was 21% (67/315).

Table 1. Patient characteristics

	<b>N=315 (100%)</b>
Male sex	213 (67)
Age	68 (57-78)
<b>Comorbidities</b>	
Diabetes	81 (26)
Heart failure	63 (20)
Hypertension	135 (43)
Vascular disease	105 (33)
Chronic kidney disease	53 (17)
<b>Medication</b>	
ACE-i/ARB	103 (33)
Diuretic	101 (32)
<b>Clinical parameters</b>	
Mean arterial pressure	89 (22)
Temperature (°C)	38.5 (37.8-39.1)
Pulse rate (beats/min)	97 (33)
<b>Laboratory parameters</b>	
CRP (mg/L)	148 (68-278)
Leukocytes (x10 <sup>9</sup> /L)	12.9 (8.6-16.6)
Creatinine (μmol/L)	88 (66-138)
<b>Diagnosis</b>	
Uncomplicated SAB	134 (42)
Complicated SAB	182 (58)
<b>Treatment</b>	
Flucloxacillin	271 (86)
Cephalosporin	21 (7)
Glycopeptide (vancomycin)	10 (3)
Carbapenem	1 (1)
Other	5 (2)
<b>Outcome</b>	
Intensive care	66 (21)
30-day mortality	67 (21)

Legend: Values are count (%) for categorical variables and median (IQR) for continuous variables Chronic kidney disease was defined as an eGFR < 60 ml/min/1,73 m<sup>2</sup>. Clinical and laboratory parameters are at presentation. Treatment implies the antibiotics prescribed after the first positive blood culture. ACE-i angiotensin-converting-enzyme inhibitors, ARB angiotensin II receptor blockers. Uncomplicated SAB was defined as an episode of bacteremia with  $\geq 1$  blood culture with *S. aureus*, without evidence of endocarditis/metastatic infection, and without positive cultures after 48 h of adequate therapy and that was treated for a maximum of 2 weeks, and no relapse occurred, and the patient survived > 72 h after presentation. All situations that did not meet the criteria for uncomplicated SAB were considered complicated SAB.

### Incidence and severity of AKI

Acute kidney injury developed in 115/315 (37%; 95%CI 31–42%) of all patients. In the majority of patients, the maximum creatinine was between 1.5 and 2.5 times baseline (Table 2). In patients with complicated SAB, AKI was found more frequently (83/181; 46%) compared to patients with uncomplicated SAB (32/134; 24%;  $p = < 0.01$ ; OR = 2.70; 95%CI 1.65–4.42). Figure 1a depicts the time from first positive blood culture to maximum creatinine in days, in the 115 patients with AKI. In 45/115 (39%) patients, the maximum creatinine was reached on the day of first blood culture sampling. The median time from first positive blood culture to AKI was 3 days (IQR = 0–11 days). Development of AKI during SAB was associated with 30-day mortality (OR 3.9; 95%CI 2.2–6.9;  $p < 0.01$ ). In the patients with non-reversible AKI, 27/47 (57%) died within 30 days after blood culture sampling.

### Reversibility

Recovery of renal function to < 1.5 times baseline creatinine occurred in 68/115 (59%; 95%CI 49–68%) of patients. There was a small numerical difference in reversibility between complicated and uncomplicated SAB (respectively 60% versus 56%,  $p = 0.83$ ). The proportion of recovery of AKI was higher in the category of patients with a maximum creatinine of < 2.5 times baseline creatine compared to the more severe kidney injuries (respectively 68% vs 44%,  $p = 0.02$ ). In patients with reversible AKI, the median time to recovery was two days (IQR = 1–4 days). In 56/68 (82%; 95%CI 73–92%), the recovery occurred within 7 days (Fig. 1b). Among the patients with persistent renal impairment after 7 days, only 12/59 (20%; 95%CI 11–32%) recovered eventually, after temporary renal replacement therapy in five of them. There was no statistically significant difference in reversibility of AKI between patients who presented with AKI and patient who developed AKI during admission (respectively 64% vs 56%,  $p = 0.45$ ). In the selection of patients still alive at day 30, the recovery rate within 30 days after SAB onset was 52/71 (72%).

## Risk factors for AKI

In the univariate analyses, age > 60 years, complicated SAB, chronic kidney disease, cardiovascular disease, the use of diuretics or ACE-i/ARB, hemodynamic instability, temperature > 38.5 °C, and CRP > 150 mg/L, all at baseline, were associated with development of AKI (Table 3). In the multivariable logistic regression analysis, independent risk factors for AKI were complicated SAB, use of diuretics and hemodynamic instability (Table 3).

Table 2. Gradations of acute kidney injuries

		Total incidence <sup>a</sup>	Recovery of AKI <sup>b</sup>
<i>Maximum creatinine</i>	<b>1.5x - 2.5x baseline</b>	74 (64)	51 (68)
	<b>2.5x - 3.5x baseline</b>	17 (15)	10 (59)
	<b>&gt; 3.5x baseline</b>	8 (7)	2 (25)
	<b>Renal replacement therapy</b>	16 (14)	6 (38)

Legend: Total of 115 patients with acute kidney injury (AKI) divided in categories of severity of renal impairment. Values are count (%). <sup>a</sup>Percentages are of column (total group of patients with AKI). <sup>b</sup>Percentages are of row (group of patients in this category of AKI). Recovery of AKI was defined as creatinine drop below 1.5 times baseline creatinine again. Renal replacement therapy was either continuous venovenous hemofiltration (CVVH) or dialysis.

## Subgroup analyses

In the subgroup of patients presenting with hemodynamic instability (n = 35), 26/35 (74%) developed AKI. In 12/26 (46%) patients, AKI was reversible. In the subgroup of patients with chronic kidney insufficiency (n = 53), 31/53 (59%) developed AKI. In 16/31 (52%), AKI was reversible.

Figure 1. a) Time from blood culture sampling to maximum creatinine in days.

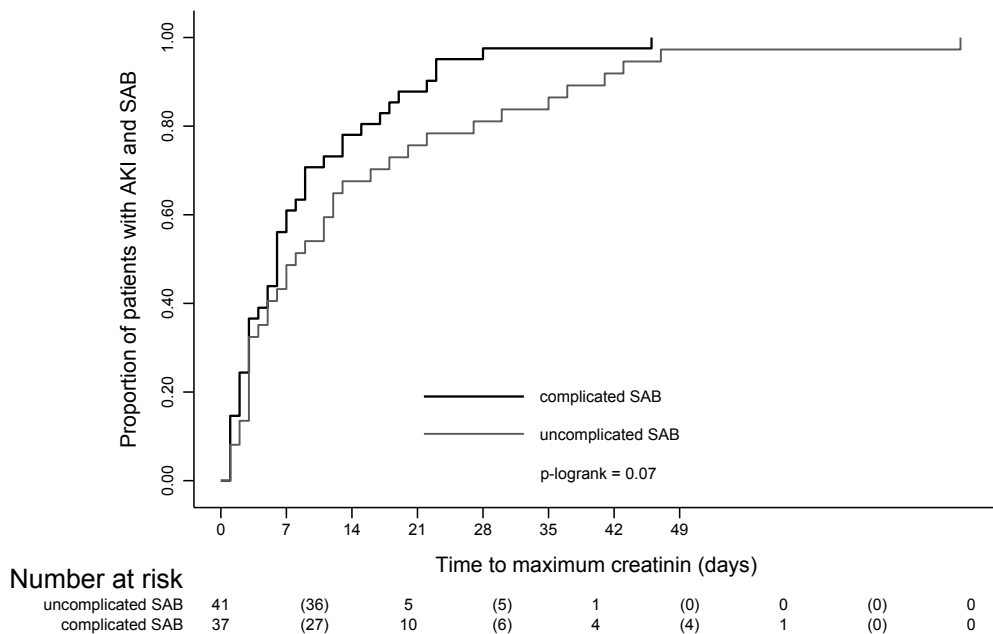
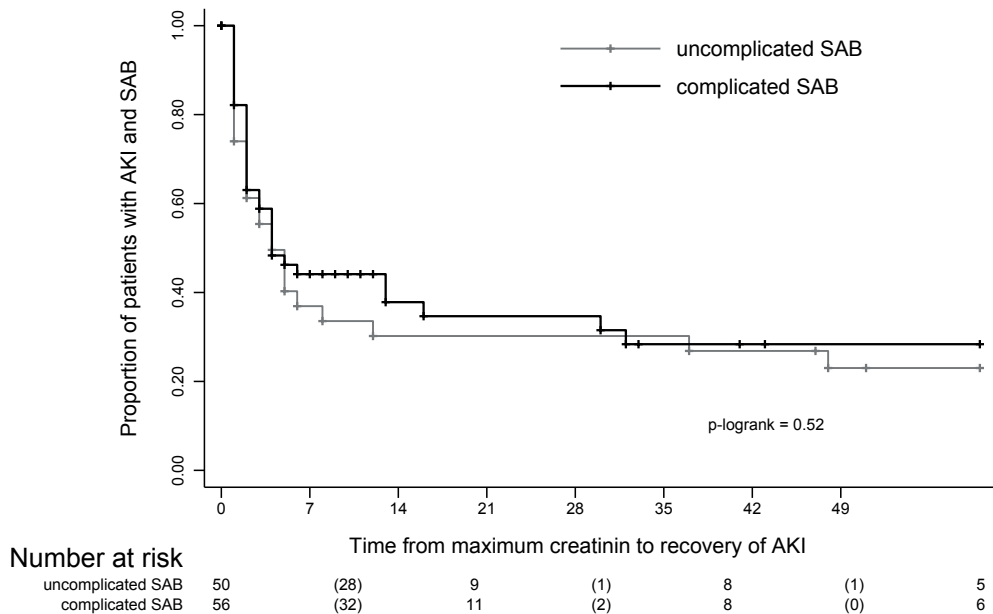


Figure 1. b) Time from maximum creatinine to recovery of creatinine in days.



Legend: a Cox regression of all patients with acute kidney injury. Recovery of kidney function was defined as return of creatinine  $< 1.5 \times$  baseline creatinine. Both: Uncomplicated SAB was defined as an episode of bacteraemia with  $\geq 1$  blood culture with *Staphylococcus aureus*, without evidence of endocarditis/metastatic infection, and without positive cultures after 48 h of adequate therapy and that was treated for a maximum of 2 weeks, and no relapse occurred, and the patient survived  $> 72$  h after presentation. All situations that did not meet the criteria for uncomplicated SAB were considered complicated SAB

Table 3. Factors associated with development of AKI in SAB

Variable	OR (95%CI)	p-value	B	OR (95%CI)	p-value
<i>Patient characteristics</i>					
Age $>60$ y	1.91 (1.1-3.2)	0.01	0.29	1.33 (0.67-2.63)	0.41
Male sex	0.69 (0.4-1.1)	0.13	-0.50	0.61 (0.33-1.12)	0.11
Complicated SAB	2.73 (1.7-4.5)	$<0.01$	1.23	3.42 (1.84-6.36)	$<0.01$
<i>Medical history</i>					
Chronic kidney disease	2.19 (1.3-3.6)	$<0.01$	0.39	1.06 (0.49-2.30)	0.24
Diabetes	1.45 (0.9-2.4)	0.23			
Cardiovascular disease	2.31 (1.4-3.7)	$<0.01$	0.06	1.06 (0.49-2.30)	0.87
Malignancy	0.97 (0.6-1.7)	1.00			
<i>Medication</i>					
Use of ACE-i/ARB	1.89 (1.2-3.1)	0.02	-0.31	0.73 (0.35-1.54)	0.41
Use of diuretic agent	3.07 (1.9-5.0)	$<0.01$	0.70	2.01 (0.99-4.06)	0.05
<i>Clinical and laboratory parameters at presentation</i>					
Hemodynamic instability	6.20 (2.8-13.8)	$<0.01$	1.97	7.17 (2.51-20.48)	$<0.01$
Temperature $> 38.5^{\circ}\text{C}$	0.59 (0.4-0.9)	0.03	-0.28	0.76 (0.42-1.37)	0.36
Leukocyte count $> 15 \times 10^9/\text{L}$	1.54 (0.9-2.5)	0.08	0.32	1.37 (0.73-2.57)	0.32
CRP $> 150\text{mg/L}$	1.63 (1.0-2.6)	0.04	0.26	1.30 (0.70-2.39)	0.41

Legend: Univariate and multivariable analysis of risk factors for acute kidney injury in patients with *S. aureus* bacteremia. OR odds ratio, B regression coefficients. Chronic kidney disease was defined as an eGFR  $< 60$  ml/min/1,73 m<sup>2</sup>. Cardiovascular disease consists of hypertension, vascular disease, and/or heart failure. Hemodynamic instability was defined as a mean arterial pressure (MAP)  $< 65$  mmHg or systolic blood pressure  $< 90$  mmHg or need of inotropic or vasopressor agents. ACE-i angiotensin-convertingenzyme inhibitors, ARB angiotensin II receptor blockers, CRP C-reactive protein.

## Discussion

The main finding of our study is the high overall incidence of AKI in patients with SAB (37%), particularly in patients with complicated disease. This high incidence, combined with the limited reversibility, illustrates the significance of this complication.

We found that AKI in SAB develops early in most patients. In a high proportion (39%) of patients developing AKI the creatinine level peaked at the day of first positive blood culture. Furthermore, the median time to peak creatinine was 3 days after first positive blood culture. These findings are similar with those reported by Holmes et al. [3]. The slightly higher incidence of AKI in the study by Holmes may be explained by a different definition of AKI. They included low urine output in their definition, whereas our definition was based on serum creatinine alone. Other research on AKI in SAB is limited to studies that were primarily aimed at comparing treatment outcome of different antibiotic therapies. In these studies, the incidence of nephrotoxicity was highly variable, ranging from 2 to 33% [10-14].

Acute kidney injury was reversible in the majority of patients (59%), but a significant proportion of patients suffered from irreversible renal impairment. In patients with reversible AKI, recovery occurred within 7 days after onset in the majority of patients (82%). Persistent kidney injury beyond this time point is prognostically unfavorable. In patients with persistent AKI at T = 7 days, recovery was observed in only 20%. The high proportion of non-reversible AKI in our study may partially be explained by disease severity. The association between disease severity and both the prevalence and the reversibility of AKI has been demonstrated for sepsis-associated kidney injury in general [15,16]. Several risk factors for the development of AKI were identified in our study. Apart from diagnosis of complicated SAB, the use of diuretics as well as hemodynamic instability at time of admission remained independent risk factors for AKI in multivariable analysis. Together with the time course of renal insufficiency showing early onset and quick recovery, this finding suggests that hemodynamic deterioration early in the disease plays an important role in the development of AKI.

However, the results of our study do not yield definite answers regarding pathophysiology. Toxicity of antibiotics, i.e., nafcillin and aminoglycosides, has been suggested in the literature to be important in development of AKI, although this assumption was not confirmed by kidney biopsies [10-14, 17, 18]. In the current study, the vast majority (86%) of patients was treated with flucloxacillin according to the Dutch guideline, limiting the comparison of different antibiotic therapies on AKI development [19, 20]. However, based on the median time to AKI of 3 days, toxicity caused by antibiotic therapy does not seem to have been a major cause of AKI. For example, TIN on antibiotic therapy is unlikely if the onset is < 5 days after start of antibiotic therapy [21]. Secondly, TIN is unlikely to recover within 1 week.

This is relevant, as falsely attributing AKI to beta-lactams may deter a patient from optimal antibiotic treatment.

The current lack of non-invasive diagnostic tools to differentiate between the divergent etiologies of AKI in SAB leads to misdiagnoses that cannot be refuted. Insight in the etiology of AKI in SAB and the probability of different causal mechanisms has important diagnostic and therapeutic consequences and warrants prospective studies, focusing on etiology. Urine biomarkers could possibly be of additional value herein, but still need future research.

An association between occurrence of AKI and 30-day mortality in patients with SAB was previously reported and confirmed in this study [22]. Although causality cannot be determined based on either study, AKI is likely to affect patient outcome on theoretical grounds. Patients with AKI— in general—are at increased future risk of chronic kidney disease and death [23]. The high burden of morbidity and mortality stresses the importance of further studies on AKI in SAB.

An important limitation of our study is the fact that the cause of AKI was rarely proven histologically, limiting insights in the etiology of SAB in our population. The lack of biopsy-confirmed etiologic diagnoses in both our study and previously mentioned studies is a reflection of daily practice, as renal biopsies are rarely performed [10–14, 17, 18]. A second limitation of this study is the retrospective design. Variables that were not measured—such as aminoglycoside therapy— may be associated with the development of AKI in SAB.

In conclusion, this study shows that AKI is common in patients with SAB. The risk factors found, and the swift reversibility in most patients, suggest that a major cause for AKI is hemodynamic in nature. This knowledge may provide insights that support diagnostic and therapeutic management of patients with SAB. Future prospective intervention studies are warranted to evaluate the underlying pathophysiology and potential interventions.

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