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BRIEF REPORT

Intravenous to Oral Switch in Complicated *Staphylococcus aureus* Bacteremia Without Endovascular Infection: A Retrospective Single-Center Cohort Study

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In this retrospective cohort study, selected patients with disseminated *Staphylococcus aureus* bacteremia, but without endovascular infection on echocardiography and ^{18}F-FDG-PET/CT, were free of relapse after IV-oral switch. Mortality was low and similar to patients who received prolonged intravenous treatment. IV-oral switch was associated with a shorter length of hospital stay.

Keywords. *Staphylococcus aureus*; bacteremia; treatment; IV-oral switch.

In complicated *Staphylococcus aureus* bacteremia (SAB), guidelines recommend prolonged intravenous (IV) antibiotic therapy for at least 4–6 weeks [1]. Few studies suggest the safety of sequential IV to oral switch in these patients [2, 3]. Also, bone and joint infections, which are common metastatic infections in SAB, can be safely managed with predominant oral treatment [4]. In these patients, early IV-oral switch is associated with shorter hospital stay and fewer complications [4]. Our institute has the policy that patients with SAB with nonendovascular metastatic infectious foci can be treated with oral antibiotics after 14 days of IV treatment. This study determined the outcome and adverse events of this strategy in comparison to prolonged IV treatment.

METHODS

In this retrospective observational study, all adult patients with complicated SAB, defined as the presence of metastatic infections, admitted to our hospital from 2013 until 2020 were eligible for inclusion. Exclusion criteria were endocarditis or other endovascular infections, no *2-[$_{18}$F]fluoro-2-deoxy-D-glucose*–positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) and echocardiography performance, and death within 14 days. The regional ethics committee approved this study and waived the requirement to obtain informed consent (no. 2019–6025). We manually retrieved clinical characteristics of all patients (Table 1) from the electronic medical charts, including outcome 3 months after discontinuation of treatment.

All patients with SAB underwent both echocardiography and ^{18}F-FDG-PET/CT to search for endocarditis or metastatic infection as described elsewhere [5]. Additionally, bedside consultation by an infectious disease specialist was mandatory and source control including surgical drainage was performed, if possible. Flucloxacillin was the preferred initial IV treatment, with cefazolin as an alternative in case of allergy or adverse events. In patients with complicated SAB but without evidence of endovascular infection on echocardiography and ^{18}F-FDG-PET/CT, the institutional guideline recommended IV-oral switch after 2 weeks of IV treatment. The preferred oral regimen was clindamycin 600 mg 3 times/day fixed dose. Antibiotic treatment duration in SAB with metastatic foci was based on the following institutional guidelines: SAB and arthritis as metastatic infection, 4 weeks; vertebral osteomyelitis (without epidural abscesses), 6 weeks; soft tissue or visceral abscesses, 6 weeks; and for pulmonary foci, 6 weeks. Duration of antibiotic treatment could be prolonged based on clinical status. Patients with IV-oral switch were compared with patients without IV-oral switch.

The primary outcome parameter was relapse of infection—that is, a new episode of SAB within 3 months after discontinuation of antibiotic treatment. Secondary outcome parameters were 3-month all-cause mortality, length of hospital stay, and adverse events (Table 1). The presence of liver toxicity or acute kidney injury (AKI) was defined as the decision of the attending physician to switch antibiotic treatment because of elevated liver enzyme concentrations or creatinine concentrations.

SPSS (version 22.0; SPSS, Inc) was used for analyzing data. Unpaired Student's *t* tests were used to compare normally distributed, continuous variables; otherwise, the Mann-Whitney *U* test was used. Categorical variables were compared by use

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Table 1. Baseline Characteristics and Outcome in All Patients With *Staphylococcus aureus* Bacteremia

	Prolonged IV Antibiotic Treatment (n = 45)	IV-Oral Switch (n = 61)	*P*
Male, n (%)	27 (60.0)	44 (72.1)	.193
Mean age, years	61.4	58.9	.926
Charlson comorbidity index	3.8	3.3	.446
Community acquisition, n (%)	19 (42.2)	28 (45.9)	.883
Persistent fever (>72 hours), n (%)	27 (60.0)	24 (39.3)	.043
Persistent positive blood cultures (>48 hours), n (%)	25 (55.6)	14 (22.9)	.001
Signs of infection >48 hours before start of adequate therapy, n (%)	20 (44.4)	26 (42.6)	.832
MRSA, n (%)	2 (4.4)	2 (3.3)	1.000
Metastatic infection, n (%)			
Vertebral osteomyelitis	14 (31.1)	9 (14.8)	.044
Nonvertebral osteomyelitis	7 (15.6)	16 (26.2)	.091
Infected osteosynthesis	3 (6.7)	11 (18.0)	.089
Arthritis	12 (26.7)	11 (18.0)	.291
Prosthetic joint infection	5 (11.1)	7 (11.5)	.954
Splenic abscess	0	2 (3.3)	.224
Soft tissue abscess	25 (55.6)	33 (54.1)	.883
Pulmonary foci	17 (37.8)	12 (19.7)	.039
Total, n	83	101	
Relapse	0	0	
3-Month mortality, n (%)	6 (13.3)	4 (6.6)	.242
Drainage, radiologically or surgically, n (%)	26 (57.8)	31 (50.1)	.666
Hospital admission duration, median (IQR), days	29 (33)	17 (11)	.001
Treatment duration, median (IQR), days	45 (44)	45 (49)	.355
Addition of rifampicin, n (%)	15 (33.3)	16 (26.2)	.643
Adverse events,[a] n (%)	25 (55.6)	30 (49.2)	.516
Phlebitis	16 (35.6)	24 (39.3)	.691
Central venous line–related infection	0	1 (1.6)	1.000
Central venous line–related thrombosis	0	0	
Rash	1 (2.2)	1 (1.6)	1.000
Acute kidney injury	6 (13.3)	2 (3.3)	.069
Nausea/vomiting	1 (2.2)	2 (3.3)	1.000
Clostridiodes difficile infection	2 (4.4)	0	
Increased liver enzymes	3 (6.7)	0	

Abbreviations: IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]In 4 patients, more than 1 adverse event occurred.

of the chi-square test or Fisher's exact test. Differences were considered statistically significant at a 2-sided *P* value of less than .05. With these analyses, the sample size of 106 had limited power to detect differences in relapse rate: 30% power to detect a 2-fold increase from 10% to 20% or 38% power to detect a 3-fold increase from 5% to 15%. The sample size provided adequate power to detect moderate effect sizes in continuous secondary parameters: 72% power to detect a standardized effect size of 0.5. Hence, analyses are primarily descriptive.

RESULTS

A total of 106 patients were included: 45 patients (42.5%) received only IV antibiotics and 61 patients (57.5%) underwent IV-oral switch. Baseline characteristics are shown in Table 1. Patients with prolonged IV antibiotic treatment more often had persistent fever and persistently positive blood cultures.

Median treatment duration in the prolonged IV treatment group was 45 days (interquartile range [IQR], 44; range, 12–356 days) and in the IV-oral switch group was 45 days (IQR, 49; range, 17–149 days) (*P* = .355). IV-oral switch took place after a median of 16 days (IQR, 4; range, 12–19 days) and oral clindamycin was prescribed to 88.5% of patients. Of all patients, 95 (89.6%) received flucloxacillin as first IV antibiotic treatment, of whom 18 patients (17.0%) were switched to cefazolin due to AKI (8; 44.4%), nausea (3; 16.7%), rash (2; 11.1%), phlebitis (1; 5.5%), or other reasons (4; 22.2%). IV-IV antibiotic switch of flucloxacillin to cefazolin occurred more often in the prolonged IV treatment group (28.9% vs 8.2%, respectively; *P* = .011). Three-month follow-up was available in all but 1 surviving patient (99.1%). No relapses were observed (Table 1). Three-month mortality was 13.3% in the prolonged IV group versus 6.6% in the IV-oral switch group (*P* = .242). Median hospital admission duration was 29 days (IQR, 33; range, 9–129 days) in the prolonged IV group and 17 days (IQR, 11; range, 9–67 days) in the IV-oral switch group (*P* = .001).

Twenty-five adverse events were observed in the prolonged IV treatment group: 17 (68.0%) within 2 weeks and 8 (32.0%) after 2 weeks of treatment. Of these 8 late adverse events, 4 were phlebitis and 4 were AKI. In the IV-oral switch group, all 30 adverse events were reported in the first 2 weeks of IV antibiotic treatment. In all patients, phlebitis occurred only in patients who received flucloxacillin via a peripheral IV catheter. Acute kidney injury was only reported in patients who were on IV flucloxacillin and occurred more often in the prolonged IV group (13.3% vs 3.3% in the IV-oral switch group; $P = .069$). Other adverse events are shown in Table 1.

DISCUSSION

This retrospective single-center study showed that IV-oral switch after 14 days of IV treatment was not associated with relapses in a selected group of patients with complicated SAB without signs of endovascular infection on echocardiography and ^{18}F-FDG-PET/CT. The 3-month mortality rate was low in both groups and not statistically different. Importantly, almost 60% of the patients were considered clinically eligible for IV-oral switch. Reasons for continuation of IV antibiotic treatment in the other patients were unknown, but patient characteristics showed that patients with prolonged IV antibiotic treatment included significantly more high-risk populations (Table 1). Moreover, IV-oral switch was associated with a shorter length of hospital stay and no adverse events were reported during oral antibiotic treatment.

To ensure sterilization of the metastatic foci, international guidelines recommend prolonged IV antibiotic treatment for at least 4–6 weeks in patients with complicated SAB [1, 6]. The present study, however, showed that eradication of deep-seated nonendovascular infectious foci complicating SAB is also possible with oral stepdown. The majority of patients with IV-oral switch were treated with clindamycin. The high bioavailability and excellent bone and abscess penetration of clindamycin make it well suited as an oral alternative for the treatment of *S. aureus* infections. Based on in vitro data, clindamycin is classified as a bacteriostatic agent, causing hesitation to use this antibiotic for serious infections. However, the in vitro distinction between bacteriostatic and bactericidal does not translate well to clinical situations. This also applies to gram-positive infections [7] and our study shows that an excellent outcome with a bacteriostatic agent can be obtained in a selected group of patients. There are several studies demonstrating the efficacy of oral stepdown therapy for SAB with other highly bioavailable oral antibiotics such as linezolid or fluoroquinolones with rifampicin [2, 3], which suggests that clindamycin may also be a sound choice, as shown in this study.

No relapses were reported in either group of patients. This contrasts with reported relapse rates of 2–23% [6]. One explanation for our low relapse rate is the extensive diagnostic workup we performed in patients with SAB, including echocardiography and ^{18}F-FDG-PET/CT in case of the presence of risk factors for complicated SAB [5]. Performance of ^{18}F-FDG-PET/CT in patients with SAB is associated with lower mortality and relapse rates [5].

IV-oral switch is one of the goals that antimicrobial stewardship teams focus on, because it reduces costs and length of hospital stay [8]. Correspondingly, in the present study, the median duration of hospital admission was 12 days shorter in patients with IV-oral switch compared with patients with prolonged IV antibiotic treatment. Phlebitis was frequently reported and was probably related to the physicochemical properties of flucloxacillin [9], because it was not observed during treatment with cefazolin. All patients with AKI were treated with flucloxacillin. The etiology of AKI in these patients was probably tubule-interstitial nephritis, as shown in other studies that reported higher rates of nephrotoxicity in patients receiving anti-staphylococcal penicillin compared with cefazolin [10].

A limitation of our study is its retrospective design with a relatively small population sample. Inherent to the retrospective noninterventional design of our study is the risk of bias due to confounding by indication.

Our results provide evidence to the efficacy and safety of IV-oral switch in a specific group of patients with complicated SAB (96.2% methicillin-susceptible *S. aureus* [MSSA]) ie, without endovascular infection and complex deep-seated infections, such as undrained epidural abscesses. An individualized approach in a multidisciplinary setting to define treatment of complicated SAB could lead to a safe IV-oral switch with a reduction in adverse events and length of hospital stay in these patients. Prospective studies should further validate IV-oral switch for the treatment of complicated MSSA bacteremia.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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