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High-dose trimethoprim-sulfamethoxazole and clindamycin for *Staphylococcus aureus* endocarditis

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ABSTRACT

Objective: The mortality rate for *Staphylococcus aureus* endocarditis remains as high as 20–30% despite improvements in medical and surgical treatment. This study evaluated the efficiency and tolerance of a combination of intravenous trimethoprim-sulfamethoxazole and clindamycin (T&C) +/- rifampicin and gentamicin, with a rapid switch to oral administration of T&C.
Methods: This before–after intervention study compared the outcomes of 170 control patients before introduction of the T&C protocol (2001–2011) with the outcomes of 171 patients in the T&C group (2012–2016). All patients diagnosed with *S. aureus* infective endocarditis and referred to the study centre between 2001 and 2016 were included. Between 2001 and 2011, the patients received a standardized antibiotic treatment: oxacillin or vancomycin for 6 weeks, plus gentamicin for 5 days. Since February 2012, the antibiotic protocol has included a high dose of T&C (intravenous, switched to oral administration on day 7). Rifampicin and gentamicin are also given in cases of cardiac abscess or persistent bacteraemia.
Results: The two groups were slightly different. On intention-to-treat analysis, global mortality (19% vs 30%, P=0.024), in-hospital mortality (10% vs 18%, P=0.03) and 30-day mortality (7% vs 14%, P=0.05) were lower in the T&C group. The mean duration of hospital stay was significantly shorter in the T&C group (30 vs 39 days; P=0.005).
Conclusions: The management of *S. aureus* infective endocarditis using a rapid shift to oral administration of T&C reduced the length of hospital stay and the mortality rate.

1. Introduction

Despite improvements in medical and surgical treatment, the hospital mortality rate from infective endocarditis (IE) remains as high as 20–30% [1–3]. *Staphylococcus aureus* is now the most common cause of IE, accounting for approximately 26% of cases [4], and healthcare-associated IE is more common than community-acquired and intravenous-drug-user-associated IE [5]. Patients with *S. aureus* IE present more aggressive forms [3] associated with higher rates of stroke, systemic embolization and persistent bacteraemia [5]. *S. aureus* is an important prognostic factor in IE [6], usually with a high mortality rate of approximately 13–28% [1,2]. Managing patients with IE is a real challenge. The introduction of a standardized multi-disciplinary team approach reduced the in-hospital mortality rate from 28% to 13% in an Italian study [7], and reduced the 1-year mortality rate from 19% to <10% in the authors' team [8]. However, at the study centre, the early mortality (<90 days) rate increased from 9% in 2000–2006 to 12% in 2006–2008 and 15% in 2009–2012 [9]. Preliminary works suggested that this increase in mortality could be due to less contact with surgery following a change in the head of the cardiac surgery department [10], and an increasing proportion of *S. aureus* IE (from 11% to 19% in 10 years). *S. aureus* IE had a mortality rate of 20% at 90 days,

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mainly due to septic shock [9], particularly in sepsis-induced multiple organ dysfunction syndrome in *S. aureus* prosthetic valve IE.

In order to improve the septic control of *S. aureus* IE and to reduce the mortality rate at the study centre, the decision was made to modify the antibiotic protocol to a high intravenous dose of trimethoprim-sulfamethoxazole (TMP-SMZ) with clindamycin (T&C) for anti-toxin activity [11], with a rapid switch to oral administration of TMP-SMZ on day 7. A preliminary study published in March 2013 presented promising results [9] with a significant decrease in mortality from 15% between 2009 and 2011 to 8% in 2012 with T&C. Since October 2013, given the persistence of early deaths due to sepsis (cardiac abscess or persistence of positive blood culture), and according to the literature which confirms the persistence of *S. aureus* bacteraemia as a predictor of poor outcome [12], rifampicin and gentamicin were given with T&C in cases of cardiac abscess and persistent bacteraemia.

This study investigated the outcome of a high dose of intravenous T&C +/- rifampicin and gentamicin with a rapid switch to oral therapy in comparison with conventional treatment. This was not a randomized trial because the new protocol was chosen to handle the increased mortality at the study centre.

2. Materials and methods

2.1. Patients

A prospective study was conducted from 2001 to 2017. Missing data were recorded retrospectively. The study population consisted of all patients referred to the study centre between December 2001 and January 2017 who were diagnosed with definitive *S. aureus* IE, according to the modified Duke criteria [13] and (after 2015) the European Society of Cardiology guidelines [14]. Data on clinical features and epidemiological data were collected. The patients were managed by a multi-disciplinary team including cardiologist, microbiologist, cardiac surgeon, radiologist, neurologist and anaesthetist. Patient follow-up included clinical examination, weight, routine blood test, blood culture after 24 and 48 h of treatment, electrocardiograms, echocardiography (one transoesophageal echocardiogram per week), positron emission tomography/computed tomography (since 2011), body scan (+/- arteriography) and evaluation of antibiotic side effects.

Overall mortality during hospital stay, 30-day mortality, 90-day mortality, and causes of death within 30 and 90 days were studied. The analysis was undertaken using intention-to-treat and on-treatment protocols.

2.2. Therapeutic protocols

Starting on 1 December 2001, all patients with IE due to *S. aureus* received a standardized antibiotic treatment [8]: oxacillin 12 g/day intravenously for 6 weeks for meticillin-susceptible *S. aureu* (MSSA), or vancomycin 30 mg/kg/day intravenously (discontinuous) for 6 weeks for meticillin-resistant *S. aureus* (MRSA). This antibiotic therapy was combined with one daily injection of gentamicin 3 mg/kg for 5 days. In cases of renal dysfunction, the doses of aminoglycoside, vancomycin and oxacillin were adjusted according to antibiotic serum levels.

Starting on 1 February 2012, a high dose of TMP-SMZ (960 mg/4800 mg per day in six daily discontinuous intravenous injections, maximal dose adapted for weight and renal function) was administered with clindamycin (1800 mg/day in three discontinuous injections) for a period of 7 days. On day 7, treatment was switched to oral TMP-SMZ 160 mg/800 mg (six tablets per day for a 5-week period, also adapted for weight and renal function) [14] without clindamycin. In cases where blood cultures were still positive after 48 h or cases with a cardiac abscess, a combination of intravenous rifampicin (1800 mg/day) and gentamicin (180 mg/day) was added to the protocol for 7 days. Patients who had previously received antibiotic treatment for more than 5 days were not included in the T&C group because the efficacy of T&C could not be evaluated, but these patients received the same management as those included in the study. All *S. aureus* strains isolated from blood cultures in the T&C group were susceptible to TMP-SMZ and clindamycin.

The T&C group was compared with the control group (oxacillin and gentamicin or vancomycin and gentamicin). The primary endpoint was mortality (global mortality, 30-day mortality, 90-day mortality). Length of hospital stay, causes of death within 30 and 90 days, and emergence of acute renal insufficiency were also studied.

2.3. Statistical analysis

Data were initially collected from patient records using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and analyses were performed using R Version 3.2.3. Continuous variables for individuals were expressed as mean ± confidence interval (CI), and were compared using Student's *t*-test. Categorical variables were expressed as a percentage and were compared using Fisher's *t*-test. A multi-variate analysis was performed on the significant variables using a logit linear regression.

3. Results

3.1. Patient characteristics in the T&C group compared with the control group

In total, 341 patients were included in this study: 171 in the T&C group and 170 in the control group (Table 1). The two groups were almost comparable on univariate analysis, except for age (64.4 ± 17.3 vs 59.4 ± 16.8 years, P=0.007) and elevated blood pressure (36% vs 25%, P=0.034) which were significantly higher or more common in the T&C group. The clinical features were almost comparable, except for fever (78% vs 89%, P=0.007), heart murmur (38% vs 50%, P=0.029) and mycotic aneurism (2% vs 7%, P=0.043). In terms of echocardiographic features, the two groups were comparable except for the presence of vegetation (64% vs 82%, P<0.001). The two groups were comparable for leukocytosis count and C-reactive protein level, but not for serum creatinine level (138.2 ± 17.3 vs 176.8 ± 32.4 µmol/L, P=0.048). On multi-variate analysis including all of the abovementioned variables, only fever (P=0.04) and vegetation (P=0.003) remained significant.

3.2. Outcome in the T&C group compared with the control group

The average length of hospital stay for patients who did not die during hospitalization was significantly shorter in the T&C group than in the control group on intention-to-treat (29.8 ± 3.8 days vs 39.0 ± 5.2 days, P=0.005) and on-treatment (26.4 ± 3.8 days vs 36.9 ± 4.8 days, P=0.0007) analysis (Table 2).

After a median follow-up of 166 days following the diagnosis and treatment of IE, the T&C group was associated with a two-fold lower global mortality rate on intention-to-treat analysis [19% vs 30%, P=0.024, odds ratio (OR)=0.56, 95% CI 0.34–0.92], and a two-fold lower in-hospital mortality rate on intention-to-treat (10% vs 18%, P=0.03, OR=0.49, 95% CI 0.26–0.93) and on-treatment (10% vs 15%, P=0.036, OR=0.46, 95% CI 0.23–0.92) analysis compared with the control group. The 30-day mortality rate was two-fold lower on intention-to-treat (7% vs 14%, P=0.05, OR=0.46, 95% CI 0.22–0.96) and on-treatment (7% vs 15%, P=0.05, OR=0.44, 95% CI

Table 1
Comparison of patient characteristics in the trimethoprim-sulfamethoxazole and clindamycin (T&C) group with the control group using univariate analysis

	T&C group *n*=171	Control group *n*=170	*P*	OR
Comorbidities				
Mean age in years (range)	64.4 (13–94)	59.4 (19–102)	0.007	
Male	115 (67.3%)	125 (73.5%)	0.23	
Prior IE	16 (9.4%)	13 (7.6%)	0.70	
Intravenous drug use	22 (12.9%)	26 (15.3%)	0.54	
HIV	3 (1.8%)	6 (3.5%)	0.34	
Diabetes	38 (22.2%)	30 (17.6%)	0.34	
Coronary artery disease	22 (12.9%)	18 (10.6%)	0.50	
Chronic lung injury	15 (9.1%)	18 (10.6%)	0.61	
Chronic renal failure	23 (13.5%)	27 (15.9%)	0.54	
Dialysis	7 (4.1%)	8 (4.7%)	0.80	
Elevated blood pressure	61 (35.7%)	42 (24.7%)	0.034	1.4 (1.03–2.1)
Alcohol	18 (8.8%)	11 (6.5%)	0.54	
Myocardial infarction	20 (11.7%)	18 (10.6%)	0.86	
Autoimmune disease	10 (5.8%)	6 (3.5%)	0.44	
History of cancer	18 (10.5%)	23 (13.5%)	0.41	
Leukaemia/lymphoma	5 (2.9%)	7 (4.1%)	0.41	
Charlson Comorbidity Index	3 (0–10)	3 (1–5)	0.27	
IE characteristics (non-exclusive)				
Native valve IE	97 (56.7%)	96 (56.5%)	1	
Valvular prosthesis IE	43 (25.1%)	34 (20.0%)	0.3	
Cardiac-device-related IE[a]	48 (28.1%)	48 (28.2%)	1	
Bicuspid valve	6 (3.5%)	8 (4.7%)	0.59	
MRSA	21 (12.3%)	19 (11.2%)	0.87	
Clinical features				
Fever[b]	134 (78.4%)	152 (89.4%)	0.007	0.88 (0.80–0.96)
Acute heart failure	38 (22.2%)	43 (25.3%)	0.53	
Cardiogenic shock	13 (7.6%)	7 (4.1%)	0.25	
Septic shock	24 (14.0%)	12 (7.1%)	0.051	
Heart murmur	65 (38.0%)	85 (50%)	0.029	0.76 (0.60–0.97)
Embolism	81 (47.4%)	94 (55.3%)	0.16	
Major cerebral bleeding	14 (8.2%)	21 (12.4%)	0.22	
Spondylodiscitis	19 (11.1%)	9 (5.3%)	0.074	
Mycotic aneurism	4 (2.3%)	12 (7.1%)	0.043	0.33 (0.11–1.00)
Echocardiographic features				
Aortic IE	57 (33.3%)	57 (33.5%)	1	
Mitral IE	51 (29.8%)	62 (36.5%)	0.13	
Tricuspid IE	37 (21.6%)	30 (17.6%)	0.41	
Cardiac-device-related IE	45 (26.3%)	48 (28.2%)	0.72	
Vegetation	110 (64.3%)	139 (81.8%)	0.0004	0.79 (0.69–0.90)
Annular abscess	36 (21.1%)	27 (15.9%)	0.26	
Pseudo aneurysm	9 (5.3%)	8 (4.7%)	1	
Severe valvular insufficiency	48 (28.1%)	49 (28.8%)	0.90	
Valvular perforation	23 (13.5%)	34 (20.0%)	0.11	
Left ventricle ejection fraction	55 (20–75)	60 (20–70)	0.69	
Biological features (mean)				
Leukocytosis (Giga/L)	11.9 (2.1–28)	11.5 (2.9–32)	0.5	
C-reactive protein (mg/L)	146 (3–523)	168 (2–455)	0.15	
Serum creatinine (µmol/L)	138 (9–898)	174 (30–933)	0.048	
Follow-up				
Relapse	7 (4.1%)	10 (5.9%)	0.046	
Recurrences	6 (3.5%)	12 (7.06%)	0.15	
Persistent bacteraemia		10 (5.9%)		

IE, infective endocarditis; HIV, human immunodeficiency virus; MRSA, meticillin-resistant *Staphylococcus aureus*; OR, odds ratio.
[a] Including pacemaker, defibrillator and dialysis catheter.
[b] Temperature ≥38°C on admission.

0.20–0.99) analysis in the T&C group compared with the control group (Table 2). However, the 90-day mortality rate was not significantly different between the two groups on intention-to-treat (16% vs 21%, *P*=0.32) or on-treatment (15% vs 21%, *P*=0.32) analysis (Table 2).

Analysis of the causes of in-hospital death showed that sepsis and multi-organ failure were almost twice as common in the control group (8%) compared with the T&C group (5%), although the trend was not significant (Table 2). In the T&C group, septic failure was observed in eight patients, of whom only four received rifampicin and gentamicin (four patients were treated before 2013). The T&C protocol was stopped prematurely in two patients because of acute renal failure, and in one patient because of microbiological failure resulting in a switch to daptomycin and linezolid (without success; the patient ultimately underwent a cardiac transplantation). One patient died after *S. aureus* IE relapse.

Analysis of 30-day mortality showed that severe sepsis/multi-organ failure was twice as common in the control group (6%) compared with the T&C group (3%), although the trend was not significant (Table 2).

Table 2
Comparison of patient outcomes in the T&C group and the control group: intention-to-treat and on-treatment analysis

Outcome	Intention-to-treat analysis			On-treatment analysis		
	Control group *n*=170 (%)	T&C group *n*=171(%)	*P*	Control group *n*=126	T&C group *n*=138 (%)	*P*
Septic failure	14 (8.2)	10 (5.8)	0.41	6 (3.5)	3 (2.2)	0.02
Surgery	114 (67.1)	89 (52.1)	0.006	73 (57.9)	73 (52.9)	0.46
Relapses	22 (12.9)	13 (7.6)	0.11	13 (7.6)	8 (5.8)	0.6
Mean hospital stay (days)	34.1 ± 4.5	29.6 ± 3.9	0.14	32.2 ± 4.4	26.6 ± 4.1	0.06
Mean hospital stay alive (days)[a]	39.0 ± 5.2	29.8 ± 3.8	0.005	36.9 ± 4.8	26.4 ± 3.8	0.0007
In-hospital death	31/170 (18.2)	17/ 171 (9.9)	0.03	25/126 (14.7)	14/138 (10.1)	0.036
Sepsis/multi-organ failure	14 (45.2)	8 (47.1)	1	9 (36.0)	5 (35.7)	1
Other causes	17 (54.8)	9 (52.9)		16 (64.0)	9 (64.3)	
Death at day 30	24/169 (14.2)	12/169 (7.1)	0.05	19/125 (15.3)	10/136 (7.4)	0.05
Sepsis/multi-organ failure	10 (41.7)	5 (41.7)	1	6 (31.6)	3 (30.0)	1
Other causes	14 (58.3)	7 (58.3)		13 (68.4)	7 (70.0)	
Death at day 90	35/165 (21.2)	27/165 (16.4)	0.32	25/122 (20.5)	20/132 (15.0)	0.32
Sepsis/multi-organ failure	14 (40.0)	8 (29.6)	0.43	9 (36.0)	5 (25.0)	0.52
Other causes	21 (60.0)	19 (70.4)		16 (64.0)	15 (75.0)	
Global mortality[b]	51/170 (30.0)	33/171 (19.3)	0.024	37/126 (29.4)	28/138 (20.3)	0.11
One-year mortality	45/170	34/171	0.16	32/126	24/138	0.3

[a] Patients who did not die during hospitalization.
[b] Mortality until last known follow-up.

Table 3
Protocol modifications in the trimethoprim-sulfamethoxazole and clindamycin (T&C) group

T&C group	*n*=171
T&C as first-line treatment	69 (40.3 %)
Dose adaptation	58 (33.9%)
Persistant bacteraemia	39 (28%)
T&C as second-line treatment	102 (59.6%)
First-line treatment <5 days	
Cloxacillin-gentamicin	43 (25.1%)
Vancomycin-gentamicin	33 (19.3%)
Other (including T&C)	95 (55.6%)
Interruption of T&C	33 (19.3%)
Followed by second- or third-line treatment	
Cloxacillin	21 (63.6 %)
Vancomycin	3 (9.1 %)
Other antibiotics	9 (27.3 %)
Causes of interruption	33/171
Acute renal failure due to T&C	9 (5.3 %)
Septic failure	10 (5.8 %)
Adverse skin reaction	7 (4.1 %)
Digestive intolerance	1 (0.6 %)
Other	5 (2.9 %)
Medical decision	6 (3.5 %)
Clostridium difficile diarrhoea	0

Table 4
Protocol modifications in the control group

Control group	*n*=170
Dose adaptation	142
Renal adaptation	17 (10%)
First-line treatment	
Cloxacillin-gentamicin	80 (47%)
Vancomycin-gentamicin	58 (34%)
Cloxacillin-gentamicin or vancomycin as second-line treatment <5 days	32 (18%)
Interruption	27 (16%)
Causes of interruption	27/170
Acute renal failure	1
Septic failure	
Adverse skin reaction	4
Other adverse effect	10
Haematological toxicity	1
Medical decision	0
Other associated micro-organism	10

3.3. Compliance with antibiotic protocols

Compliance with antibiotic protocols did not differ significantly between the two groups: 33/171 (19%) antibiotic modifications in the T&C group and 44/170 (26%) in the control group (P=0.16) (Tables 3 and 4).

In 10 of 171 (6%) patients, T&C was stopped because of microbiological failure: four patients received T&C plus rifampicin and gentamicin and six patients received T&C alone. T&C was stopped because of acute renal failure in nine (5%) cases and because of adverse skin reactions in seven (4%) cases. Among the 138 patients treated with T&C, 39 (28%) patients required rifampicin and gentamicin, and 99 (72%) patients received T&C alone (Table 3). In this group, three patients died during hospitalization, two died within 30 days, seven died within 90 days, seven died within 1 year and seven died after 1 year.

In the control group, treatment was stopped prematurely in 27 cases. Treatment was stopped because of acute renal failure in one case, microbiological failure in 10 cases, adverse skin reactions in four cases, other side effects in 10 cases, and haematological toxicity in two cases (Table 4). In this group, six patients died during hospitalization, seven died within 90 days and 14 died after 1 year.

The doses of TMP-SMZ had to be adjusted according to renal insufficiency in 58 (34%) patients in the T&C group and in 17 (10%) patients in the control group. The doses were also adjusted for cytolytic hepatitis in eight patients in the T&C group. Treatment was stopped prematurely in 33 (19%) patients in the T&C group and in 27 (16%) patients in the control group.

3.4. Relapses and recurrence observed in the T&C group

A relapse was defined as a new episode of IE caused by the same bacteria as the initial case, after completion of treatment, based on blood or valve cultures. The occurrence of relapses was not significantly different between the two groups: seven of 171 (4%) patients in the T&C group and 10 of 170 (6%) patients in the control group (P=0.46). However, early relapse (<30 days vs >90 days) was significantly more common in the control group (nine early and one late) than in the T&C group (one early and six late) (P=0.004).

Six of 171 (4%) recurrences of IE involved another micro-organism (two *Enterococcus faecalis* and three *Streptococcus* spp.) in the T&C group, compared with 12 of 170 (7%) recurrences in the

control group (P=0.15). These cases cannot be considered as treatment failures.

4. Discussion

Over a 5-year period, the IE mortality rate of patients treated with T&C was comparable to other published cohorts. The mortality rates in the T&C group were half those in the control group (overall, 30-day mortality and in-hospital mortality) on intention-to-treat and on-treatment analysis. Among the causes of death, severe sepsis and multi-organ failure were twice as common in the control group compared with the T&C group, although the difference was not significant. In the subgroup treated by T&C and rifampicin/gentamicin, one death occurred due to sepsis at 171 days in a patient with *S. aureus* IE relapse. Using intravenous T&C with a rapid switch to oral administration led to a significant reduction (10 days) in the length of hospital stay.

TMP-SMZ is particularly effective against *S. aureus*, regardless of its susceptibility or resistance to meticillin [15,16], with a very low resistance rate at the study centre [9]. This treatment has been used for over 30 years at a low standard dose with excellent oral bioavailability (>90%) [17]. It has also proven to be effective and tolerable at higher doses in orthopaedic implant infections [18]. In an observational study, Goldberg et al. reported similar outcomes for TMP-SMZ and vancomycin, with no significant difference in outcome and mortality in the treatment of MRSA bacteraemia [19]. Markowitz et al. reported the possible inferiority of low-dose TMP-SMZ compared with vancomycin for MSSA bacteraemia: in right-sided IE, the cure rate was 64% (7/11) for TMP-SMZ and 92% (11/12) for vancomycin (P=0.095) [20]. In a randomized controlled trial including 252 patients, Paul et al. concluded that TMP-SMZ did not achieve non-inferiority to vancomycin in the treatment of severe MRSA infection [21]. The difference was particularly marked in patients with bacteraemia. Clindamycin has excellent tissue diffusion, is bacteriostatic on *S. aureus*, and is the most downregulating agent for *S. aureus* toxin secretion [11]. However, the usefulness of clindamycin in *S. aureus* toxins is still debated. Vancomycin remains the reference treatment for IE due to MRSA [22]. New therapeutic solutions such as daptomycin [23], ceftazolin [24] and linezolid [2] have not produced better results. Contrary to drugs introduced to the market recently, T&C is considerably cheaper.

Four to six weeks of intravenous antibiotic are currently recommended for the treatment of *S. aureus* IE [14], and most patients remain hospitalized during this period. Oral antibiotic therapy for treatment of IE is not well established [25,26]. Oral therapy has been reported in right-sided *S. aureus* IE [26,27] using oral ciprofloxacin plus rifampicin [28,29], oral penicillin in a child [26], oral fucidic acid and linezolid, and oral fucidic acid and rifampicin [27]. Recently, a rapid switch to oral administration in patients with left-sided IE in a stable condition was reported to have similar results as intravenous antibiotic treatment [25]. A rapid switch to oral administration of antibiotics in IE reduces the risk of catheter-related infection, the cost and the length of hospital stay [27]. The tolerance of T&C was acceptable, with no major difference concerning the development of acute renal failure. In the present study, the dose of TMP-SMZ was adjusted in a significant number of cases (34%). Dosage in plasma should allow better management [30]. The treatment was interrupted prematurely in 19% of cases (one-third due to acute renal failure and one-third due to septic failure), which is comparable with the reference treatment with linezolid and daptomycin [2,23].

This study has some limitations: it was not a clinical trial, the study institution is a referral centre, and the experience may not be reproduced in other settings, particularly in patients with MRSA who represented only 10% of the study population. Two (1.1%) patients were lost to follow-up in the T&C group compared with one (0.5%) patient in the control group at day 30; corresponding figures for day 90 were six (3.5%) patients and five (2.9%) patients. Patients in the T&C group had vegetations less often than patients in the control group (110 vs 139 patients, P=0.0004). This may suggest that patients in the T&C group had less severe infections. In the T&C group, 39 patients with persistent bacteraemia and septic failure were treated with gentamicin and rifampicin; this may have contributed to the effectiveness of treatment.

5. Conclusions

The management of *S. aureus* IE, using a rapid switch to oral administration of T&C, reduced the length of hospital stay, mortality rate and sepsis-induced multiple organ dysfunction syndrome. This treatment is a safe alternative for *S. aureus* IE.

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Competing interests

None declared.

Ethical approval

Ethical Committee approval number: 2019-004.

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