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

Hervé Tissot-Dupont, Frederique Gouriet, Leopold Oliver, Matthieu Jamme, Jean-Paul Casalta, Marie-Therese Jimeno, Florent Arregle, Cecile Lavoute, Sandrine Hubert, Mary Philip, et al.

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Hervé Tissot-Dupont, MD, PhD[1§]; Frédérique Gouriet, MD, PhD[1§]; Leopold Oliver, MD[3§]; Matthieu Jamme, MD[4]; Jean-Paul Casalta, MD[1]; Marie-Thérèse Jimeno, MD[5]; Florent Arregle, MD[2]; Cécile Lavoute, PhD[2]; Sandrine Hubert, MD[2]; Mary Philip, MD[2]; Hélène Martel, MD[2,] Alberto Riberi, MD[6]; Gilbert Habib, MD, PhD[2]; Didier Raoult, MD, PhD[1*]

[1] Aix Marseille Univ., IRD, AP-HM, MEPHI, IHU Méditerranée Infection, 19-21 Boulevard Jean Moulin 13005 Marseille, France

[2] Service de Cardiologie, Hôpital de la Timone, 264 rue St Pierre, 13385 Marseille cedex 5, France

[3] USIC - SOS endocardites Fédération de cardiologie, CHU Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France

[4] Urgences Néphrologiques et Transplantation Rénale, CHU Tenon, APHP, 4 rue de la Chine 75020 Paris, France

[5] Service d'Information Médicale, Hôpital de la Timone, 264 rue St Pierre, 13385 Marseille cedex 5, France

[6] Service de Chirurgie Cardiaque, Hôpital de la Timone, 264 rue St Pierre, 13385 Marseille cedex 5, France

[§]: The three first authors have equally participated to this work

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Corresponding author: **Didier RAOULT**

Tel +33 4 13 73 20 51

Fax + 33 4 13 73 20 52

Email: didier.raoult@gmail.com

Alternate corresponding author: **Hervé TISSOT-DUPONT**

Tel +33 4 13 73 20 51

Fax +33 4 13 73 20 52

Email: herve.tissot-dupont@mediterranee-infection.com

ABSTRACT

Objective: The mortality rate from *Staphylococcus aureus* endocarditis remains as high as 20-30% despite better medical and surgical treatment. This study evaluates the efficiency and tolerance of a combination of trimethoprim-sulfamethoxazole and clindamycin (T&C) +/- rifampicin and gentamicin, with rapid switch to oral T&C.

Methods: Before-after intervention study to compare the outcome of 170 control patients before the introduction of the T&C protocol (2001 to 2011) to 171 patients in the T&C group (2012 to 2016). All patients diagnosed as *S. aureus*-infective endocarditis, and referred to our center between 2001 and 2016 were included. Between 2001 and 2011, the patients were given a standardized antibiotic treatment: oxacillin or vancomycin, for 6 weeks, plus gentamicin for 5 days. Since February 2012, the antibiotic protocol includes high dose of T&C (intravenously, switched to oral at day 7). Rifampicin and gentamicin can be added (if blood culture positive after 48 hours or cardiac abscess).

Results: The two groups were slightly different. In intention to treat, the global mortality rate was lower in the T&C group (19.3% vs 30% - p=0.024), as well as the in-hospital mortality (9.9% vs 18.2% - p=0.03), and the 30-days mortality (7.1% vs 14.2% - p=0.05). The mean duration of hospital stay alive was significantly shorter in the T&C group (30 vs 39 days - p=0.005)

Conclusions: The management of *S. aureus* IE in our multidisciplinary team, using a rapid shift to oral antibiotic with T&C, shows promising results reducing length of hospital stay and the mortality rate.

Abstract: 249 words

Introduction

Despite better medical and surgical treatment, the hospital mortality rate from infective endocarditis (IE) is still as high as 20-50% [1–3] depending on the study. *Staphylococcus aureus* is now the most common cause of IE, around 26% of the cases [4] and Health care–associated IE is more frequent than community-acquired and intravenous drug user associated infection [5]. Patients with *S. aureus* IE present more aggressive forms [3] associated with higher rates of stroke, systemic embolization and persistent bacteremia [5]. *S. aureus* is an important prognostic factor in IE [6] usually with a high mortality rate of about 13-28% [1,2]. Managing patients with IE is a real challenge. The introduction of a standardized multidisciplinary team approach has reduced the mortality rate from 28% to 13% in- hospital mortality in an Italian team [7] and from 18.5% to less than 10% in one year mortality in our team [8]. However, in our center, early mortality (< 90-days) rate had risen from 9% in 2000-2006 to 12% in 2006-2008 and to 15% in 2009-2012 [9]. Preliminary works have tried to explain this rise of mortality by both a lower coordination with surgery following a change of the head of the cardiac surgery department [10], and an increasing proportion of *S. aureus* IE (from 11 to 19% in 10 years). This infection was the most severe, with a mortality rate of 20.4% at 90-day, mainly due to septic shocks [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 in our center, we decided to modify the antibiotic protocol (T&C), combining a high dose of trimethoprim-sulfamethoxazole (TMP-SMZ) with clindamycin for anti-toxin activity [11], intravenously with a rapid oral switch at day 7. A preliminary study published in March 2013 presented promising results [9] with a significant drop of mortality from 15% between 2009 and 2011 to 8% in 2012 with T&C. Since October 2013, in view of the persistence of early deaths due to sepsis (cardiac abscess or persistence of positive blood culture), and according

to the literature that confirms the persistence of *S. aureus* bacteremia as a predictor of poor outcome [12] rifampicin and gentamicin were associated with T&C in case of cardiac abscess and persistent bacteremia.

We report our experience of a high dose of T&C +/- rifampicin and gentamicin with rapid switch to oral therapy. In comparison with the conventional treatment. This is not a randomized trial because the new protocol was decided to handle the increased mortality in our center.

Material and methods:

Patients

We conducted a prospective a study from 2001-2017. Missing data were retrospectively recorded. Our study population is defined as all patients referred to our center between December 2001 and January 2017, and who have been diagnosed with definitive *S. aureus* IE, according to the modified Duke criteria [13], and after 2015 to ESC guidelines [14]. We collected data on clinical features and epidemiological data. The patients were managed by our multidisciplinary team including cardiologist, microbiologist, cardiac surgeon, radiologist, neurologist and anesthetist. Patient follow-up includes clinical exam, weight, routine blood test, blood culture after 24 and 48h hours of treatment, electrocardiograms, echocardiography (1 per week TTE or TOE), PET/CT (since 2011), body scanner (+/- arteriography) and evaluation of antibiotic side effect.

We studied overall mortality during hospital stay, within 30 days and 90 days, and causes of death within 30 days and 90 days. The analysis was undertaken in intention to treat and on treatment.

Therapeutic Protocols

Starting on the 1st of December 2001, all patients with an IE due to *S. aureus* were given a standardized antibiotic treatment [8]: oxacillin 12 g/day intravenously during six weeks for methicillin sensible *S. aureus,* or vancomycin 30 mg/kg/day intravenously (discontinuous) during six weeks for MRSA. This antibiotic-therapy was combined with one daily injection of 3 mg/kg of gentamicin for five days. In case of renal dysfunction, the doses of aminoglycoside, vancomycin and oxacillin were adjusted according to the antibiotics serum levels.

Starting on the 1st of February 2012, the antibiotic protocol T&C combined a high dose of TMP-SMZ (960 mg/4800 mg per day in six daily discontinuous intravenous injections, maximal dose adapted to weight and renal function), and clindamycin (1800 mg/day in three discontinuous injections) for a period of seven days. The treatment was switched at day 7 to oral TMP-SMZ 160/800 only (six tablets a day for a five weeks period, also adapted to weight and renal function) [14] without clindamycin . When blood cultures were still positive after 48h or in the presence of a cardiac abscess at TTE, a combination of rifampicin intravenously (1800 mg/day) and gentamicin intravenously (180 mg/day) for seven days was added to the protocol. 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 received the same management of those included in our study. All *S. aureus* strains isolated from blood cultures in the T&C were susceptible to TMP-SMZ and clindamycin.

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

Statistical Analysis

The data were initially collected from the patient's records on an Excel table. The analyses were performed using R Software (version 3.2.3). Continuous variables for individuals were expressed as mean ± confidence interval, and were compared using student's t-test. Categorical variables were expressed as a percentage and were compared using Fisher's t-test. A multivariate analysis was performed on the significant variables, using a logit linear regression.

Results

Patient's characteristics in the T&C group compared to the control group

A total of 341 patients were included in this study: 171 patients in the T&C group and 170 patients in the control group (table 1). After univariate analysis, the two groups were almost comparable, except for age (64.4 ± 17.3 vs. 59.4 ± 16.8 years old; p=0.007), and elevated blood pressure (35.7% vs 24.7%; p=0.034), which were significantly higher or more frequent in the T&C group. The clinical features were almost comparable, except for fever (78.4% vs 89.4%; p=0.007), heart murmur (38% vs 50%; p=0.029) and mycotic aneurism (2.3% vs 7.1%; p=0.043). For echocardiography features, the two groups were comparable expect for the presence of vegetation (64.3% vs 81.8%; p<0.001). For biological features, the T&C group and the control group were comparable for leukocytosis count and protein C reactive level, but not for serum creatinine level (138.2 ±17.3 vs 176.8 ± 32.4 µmol/l; p=0.048). After multivariate analysis including all above mentioned variables, only fever (p=0.04) and vegetation (p=0.003) have revealed to be independently significantly different.

Outcome in the T&C group compared to 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, in 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) (Table 2).

After a median follow up of 166 days following the diagnosis and the treatment of IE, the outcome of the T&C group was associated with a 2-fold lower global mortality rate in intention to treat (19.3% vs 30% p=0.024 ; OR=0.56 [0.34-0.92]), with a 2-fold lower in-hospital mortality rate in intention to treat (9.9% vs 18.2% p=0.03 ; OR=0.49 [0.26-0.93]), and on treatment (10.1% vs 14.7% p=0.036 ; OR=0.46 [0.23-0.92]). The mortality rate at day 30 was also 2 time lower in intention to treat (7.1% vs 14.2% p=0.05 ; OR=0.46 [0.22-0,96]), and on treatment (7.4% vs 15.3% p=0.05 ; OR=0.44 [0.20-0.99]) (Table 2). However, the mortality rate at day 90 was not significantly different among the two groups in intention to treat (16.4% vs 21.2%; p=0.32) and on treatment (15.0% vs 20.5%; p=0.32) (Table 2).

The analysis of the causes of in-hospital death showed that sepsis or multi-organ failure was almost twice more often associated with the control group (8.2%) than with the T&C group (4.7%), although the trend is not statistically significant (Table 2). In the T&C group, septic failure was observed in 8 patients, of whom only 4 had rifampicin and gentamicin (4 patients were treated before 2013). The T&C protocol was stopped prematurely in two cases because of acute renal failure and in one case because of microbiological failure with an antibiotic switch by daptomycin and linezolid (without success and finally the patient underwent a cardiac transplantation). In one case the patient died after *S. aureus* IE relapse.

The analysis of mortality within 30 days showed that severe sepsis/multi-organ failure was also 2 times more often associated with the control group (5.9%) than with the T&C group (3.0%) although the trend is also not statistically significant (Table 2).

Compliance to antibiotic protocols:

148 Compliance to the antibiotic protocols was not statistically different between the two
149 groups: 33/171 (19.3%) antibiotic modifications in the T&C group versus 44/170 (25.9%) in
150 the control group (p=0.16) (Table 3, 4).
151 In 10 of 171 patients (5.8%), T&C was stopped because of a microbiologic failure: 4
152 received T&C rifampicin and gentamicin and 6 received only T&C. In 9 cases (5.3%) T&C
153 was stopped because of acute renal failure, in 7 cases (4.1%) because of skin adverse
154 reactions. Among the 138 patients treated with T&C, 39 (28.26%) required rifampicin and
155 gentamicin, and 99 patients had only T&C (Table3). In this group, 3 patients died during
156 hospitalization, 2 within 30 days, 7 within 90 days, 7 within 1 year and 7 after 1 year.
157 In the control group, treatment was stopped prematurely in 27 cases (acute renal
158 failure (n=1), microbiological (n=10), skin adverse effect (n=4), other side effects (n=10),
159 hematologic toxicity (n=2) (table 4). In this group, 6 patients died during hospitalization, 7
160 within 90 days and 14 after 1 year.
161 The doses of TMP-SMZ had to be adjusted according to renal insufficiency in 58
162 patients (33.9%) and in 17 patients in the control group (10%). The doses were also adjusted
163 for cytolytic hepatitis in 8 patients in the T&C group. T&C treatment was stopped
164 prematurely in 33 patients (19.3%) and in 27 patients in the control group (16%).
165 *Relapses and recurrence observed in the T&C group*
166 We defined a relapse as a new episode of endocarditis caused by the same bacteria as
167 in the initial case, after completion of treatment, based on blood or valve cultures. The
168 occurrence of relapses, observed in 7/171 (4.1%) patients in the T&C group was not
169 significantly different from 10/170 (5.9%) patients in the control group (p=0.46). However,
170 the early relapses (< 30 days vs > 90 days) were significantly more frequent in the control
171 group (9 early – 1 late) than in the T&C group (1 early – 6 late) (p=0.004).

We observed 6/171 (3.51%) IE recurrences with another micro-organism (2 *E. faecalis*, 3 *Streptococcus* sp.) in the T&C group, and 12/170 (7.06%) in the control group (p=0.15). They cannot be considered as treatment failures.

Discussion

Over a 5 years period of management of *S. aureus*, IE mortality rate of patients treated with T&C was comparable to other published cohorts. The mortality rates were twice lower in T&C group than among controls, as overall, 30-days, and in-hospital mortality rates, as well in intention to treat as on treatment. Among the causes of death, severe sepsis and multi-organ failure was twice less frequent in the T&C group compared to the control group (although not significant). In the subgroup treated by T&C and rifampicin / gentamicin according to a microbiologic failure, we note only one death due to septic cause at 171 days in a patient with *S. aureus* IE relapse. Using T&C with a rapid switch to oral prescription allowing a significant reduction (10 days) of hospital stay duration.

TMP-SMZ is particularly effective on *S. aureus*, regardless of its sensitivity or resistance to methicillin [15],[16], with a very low resistance rate in our center [9]. This treatment has been used for over 30 years at low standard dose with excellent oral bioavailability.(>90%) [17]. It has also proven effective and tolerable at higher doses in orthopedic implant infections [18]. In an observational study, Goldberg *et al*. reported similar outcomes for TMP-SMZ and vancomycin, no significant difference between outcome and mortality in the treatment of Methicillin resistant (MRSA) *S. aureus* bacteremia [19]. Markowitz *et al* reported the possible inferiority of low dose TMP-SMZ to vancomycin for methicillin-susceptible *S. aureus* bacteremia : in right side IE the cure rate was 64% (7/11) for TMP-SMZ versus 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 infections [21]. The difference was particularly marked in patients with bacteremia. Clindamycin has an excellent tissue diffusion, is bacteriostatic on *S. aureus*, and is the most down regulating agent for *S. aureus*

toxin secretion [11]. However the usefulness of clindamycin in *S. aureus* infections toxins is still debated. Vancomycin remains the reference treatment of IE due to MRSA [22]. New therapeutic solutions such as daptomycin [23], ceftazolin [24], or linezolid [2] have not produced better results. Contrary to the molecules recently introduced on the market, T&C are considerably cheaper and efficient.

Four to six weeks of intravenous antibiotic are currently recommended for *S. aureus* IE treatment [14] and most of the patients remain hospitalized during this period. Oral antibiotic therapy for treatment of IE is not well established [25,26]. Oral therapy was reported in right-sided in *S. aureus* IE [26] [27], using oral ciprofloxacin plus rifampicin [28,29], oral penicillin in a child [26], oral fucidic acid and linezolid, oral fucidic acid and rifampicin [27]. Recently, rapid oral shift in patients with left side IE in stable condition, was reported was non inferior to intravenous antibiotic treatment [25]. Rapid oral shift of antibiotic regimen in IE reduce the risk of catheter-related infection, the cost and the duration of hospital stay [27]. The tolerance of T&C was acceptable, with no major difference underlined concerning the development of an acute renal failure. In our study, there has been an adjustment of the doses of TMP-SMZ in a significant number of cases (33.9%). Dosage in plasma should allow a better management [30]. The treatment has even been prematurely interrupted in 19.3% of the case (of which 1/3 for acute renal failure and 1/3 for septic failure), which is comparable to the reference treatment, with linezolid and daptomycin [2,23].

Our study has some limitations: this is not a clinical trial, we are a reference center and our experience may not be reproduced in other settings, particularly in patients with MRSA, who represent only 10% of our study population. It is a non-randomized study in a monocentric study in a reference center. The number of patients lost to follow-up in the T&C group was 2 (1.1 %) versus 1 (0.5%) in the control group at day 30 and 6 (3.5%) versus 5

(2.9%) at day 90. Patients in T&C group had less frequently a vegetation (110 patients versus 139 patients p=0.0004). This may suggest patients with less severe infections. In the T&C group 39 patients with persistent bacteremia and septic failure were treated with gentamicin and rifampicin this may contribute to the effectiveness of our treatment.

Conclusions

The management of *S. aureus* IE in our multidisciplinary team, using a rapid oral antibiotic shift with TMP-SMZ, shows promising results, reduces the length of hospital stay, the mortality rate and sepsis-induced multiple organ dysfunction syndrome. This treatment is a safe alternative treatment in *S. aureus* IE.

Declarations

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

MRSA: methicillin resistant *Staphylococcus aureus*

	T&C group N=171	**Control group** N=170	**p**	**OR**
COMORBIDITIES				
Mean Age (years) [range]	64.4 [13-94]	59.4 [19-102]	0.007	
Sex 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	

Leukemia / 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*	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**	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 (means)			
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 creatinin (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 bacteremia		10 (5.9%)	

*including pacemaker, defibrillator and dialysis catheter ** temperature $\geq$ 38°C on admission

Table 2: Comparison of patients' outcome in the T&C group vs the control group, as Intention to Treat and On Treatment

	Intention to Treat			**On Treatment**		
	Control Group	**T&C Group**	**p**	**Control Group**	**T&C group**	**p**
OUTCOME	N=170 (%)	N=171(%)		N= 126	N=138 (%)	
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) *	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**	***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***

*patients not died during the hospitalization

** Mortality until last known follow-up

Table 3: Protocol modifications in the Trimethoprim-Sulfamethoxazole & Clindamycin (T&C) group

Trimethoprim-Sulfamethoxazole & clindamycin group	**N=171**
T&C as first line treatment	**69 (40.3 %)**
Dose adaptation	**58 (33.9%)**
Persistant bacteriemia	**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 C&C)	95 (55.6%)
Interruption of T&C:	**33 (19.3%)**
Followed by a second or a 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 %)
Skin adverse effect	7 (4.1 %)
Digestive intolerance	1 (0.6 %)
Other	5 (2.9 %)
Medical decision	6 (3.5 %)
Clostridium difficile diarrhea	0

Table 4: Protocol modifications in the control group

Control group	**N=170**
	142
Dose adaptation	
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	
Skin adverse effect	4
Other adverse effect	10
Hematologic toxicity	1
Medical decision	0
Others associated micro-organism	10