

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.

▶ To cite this version:

Hervé Tissot-Dupont, Frederique Gouriet, Leopold Oliver, Matthieu Jamme, Jean-Paul Casalta, et al.. High-dose trimethoprim-sulfamethoxazole and clindamycin for Staphylococcus aureus endocarditis. International Journal of Antimicrobial Agents, 2019, 54 (2), pp.143-148. 10.1016/j.ijantimicag.2019.06.006. hal-02465226

HAL Id: hal-02465226 https://amu.hal.science/hal-02465226

Submitted on 25 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

Hervé Tissot-Dupont, MD, PhD¹[§]; Frédérique Gouriet, MD, PhD¹[§]; Leopold Oliver, MD³[§]; Matthieu Jamme, MD⁴; Jean-Paul Casalta, MD¹; Marie-Thérèse Jimeno, MD⁵; Florent Arregle, MD²; Cécile Lavoute, PhD²; Sandrine Hubert, MD²; Mary Philip, MD²; Hélène Martel, MD², Alberto Riberi, MD⁶; Gilbert Habib, MD, PhD²; 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

Keywords: Endocarditis, *Staphylococcus aureus*, oral route, trimethoprim-sulfamethoxazole, clindamycin, mortality

Words count: 2444

Running title: S. aureus endocarditis oral treatment

Funding

This work was supported by the French State, managed by the "Agence Nationale pour la Recherche" including the "Programme d'Investissement d'Avenir" under the reference Méditerranée Infection 10-IAHU-03

Conflicts of Interest: none

Ethical Committee: 2019-004.

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

- 1 ABSTRACT
- 2

3 **Objective:** The mortality rate from *Staphylococcus aureus* endocarditis remains as high as 4 20-30% despite better medical and surgical treatment. This study evaluates the efficiency and 5 tolerance of a combination of trimethoprim-sulfamethoxazole and clindamycin (T&C) +/-6 rifampicin and gentamicin, with rapid switch to oral T&C. 7 Methods: Before-after intervention study to compare the outcome of 170 control patients 8 before the introduction of the T&C protocol (2001 to 2011) to 171 patients in the T&C group 9 (2012 to 2016). All patients diagnosed as S. aureus-infective endocarditis, and referred to our 10 center between 2001 and 2016 were included. Between 2001 and 2011, the patients were 11 given a standardized antibiotic treatment: oxacillin or vancomycin, for 6 weeks, plus 12 gentamicin for 5 days. Since February 2012, the antibiotic protocol includes high dose of 13 T&C (intravenously, switched to oral at day 7). Rifampicin and gentamicin can be added (if 14 blood culture positive after 48 hours or cardiac abscess). 15 **Results:** The two groups were slightly different. In intention to treat, the global mortality rate 16 was lower in the T&C group (19.3% vs 30% - p=0.024), as well as the in-hospital mortality 17 (9.9% vs 18.2% - p=0.03), and the 30-days mortality (7.1% vs 14.2% - p=0.05). The mean 18 duration of hospital stay alive was significantly shorter in the T&C group (30 vs 39 days -19 p=0.005) 20 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 andthe mortality rate.

- 23
- 24
- 25 Abstract: 249 words

26 Introduction

27 Despite better medical and surgical treatment, the hospital mortality rate from 28 infective endocarditis (IE) is still as high as 20-50% [1–3] depending on the study. 29 Staphylococcus aureus is now the most common cause of IE, around 26% of the cases [4] and 30 Health care-associated IE is more frequent than community-acquired and intravenous drug 31 user associated infection [5]. Patients with S. aureus IE present more aggressive forms [3] 32 associated with higher rates of stroke, systemic embolization and persistent bacteremia [5]. S. 33 aureus is an important prognostic factor in IE [6] usually with a high mortality rate of about 34 13-28% [1,2]. Managing patients with IE is a real challenge. The introduction of a 35 standardized multidisciplinary team approach has reduced the mortality rate from 28% to 13% 36 in-hospital mortality in an Italian team [7] and from 18.5% to less than 10% in one year 37 mortality in our team [8]. However, in our center, early mortality (< 90-days) rate had risen 38 from 9% in 2000-2006 to 12% in 2006-2008 and to 15% in 2009-2012 [9]. Preliminary works 39 have tried to explain this rise of mortality by both a lower coordination with surgery 40 following a change of the head of the cardiac surgery department [10], and an increasing 41 proportion of S. aureus IE (from 11 to 19% in 10 years). This infection was the most severe, 42 with a mortality rate of 20.4% at 90-day, mainly due to septic shocks [9], particularly in 43 sepsis-induced multiple organ dysfunction syndrome in S. aureus prosthetic valve IE. 44 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 45 46 trimethoprim-sulfamethoxazole (TMP-SMZ) with clindamycin for anti-toxin activity [11], 47 intravenously with a rapid oral switch at day 7. A preliminary study published in March 2013 48 presented promising results [9] with a significant drop of mortality from 15% between 2009 49 and 2011 to 8% in 2012 with T&C. Since October 2013, in view of the persistence of early 50 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.

58

59 Material and methods:

60 *Patients*

61 We conducted a prospective a study from 2001-2017. Missing data were 62 retrospectively recorded. Our study population is defined as all patients referred to our center 63 between December 2001 and January 2017, and who have been diagnosed with definitive S. 64 aureus IE, according to the modified Duke criteria [13], and after 2015 to ESC guidelines 65 [14]. We collected data on clinical features and epidemiological data. The patients were 66 managed by our multidisciplinary team including cardiologist, microbiologist, cardiac 67 surgeon, radiologist, neurologist and anesthetist. Patient follow-up includes clinical exam, 68 weight, routine blood test, blood culture after 24 and 48h hours of treatment, 69 electrocardiograms, echocardiography (1 per week TTE or TOE), PET/CT (since 2011), body 70 scanner (+/- arteriography) and evaluation of antibiotic side effect. 71 We studied overall mortality during hospital stay, within 30 days and 90 days, and causes of 72 death within 30 days and 90 days. The analysis was undertaken in intention to treat and on 73 treatment.

74

75 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.

83 Starting on the 1st of February 2012, the antibiotic protocol T&C combined a high 84 dose of TMP-SMZ (960 mg/4800 mg per day in six daily discontinuous intravenous 85 injections, maximal dose adapted to weight and renal function), and clindamycin (1800 86 mg/day in three discontinuous injections) for a period of seven days. The treatment was 87 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 88 89 were still positive after 48h or in the presence of a cardiac abscess at TTE, a combination of 90 rifampicin intravenously (1800 mg/day) and gentamicin intravenously (180 mg/day) for seven 91 days was added to the protocol. Patients who had previously received antibiotic treatment for 92 more than 5 days were not included in the T&C group because the efficacy of T&C could not 93 be evaluated, but received the same management of those included in our study. All S. aureus 94 strains isolated from blood cultures in the T&C were susceptible to TMP-SMZ and 95 clindamycin.

96

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.

6

101

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.

108 **Results**

109

111

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

110 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

114 frequent in the T&C group. The clinical features were almost comparable, except for fever

115 (78.4% vs 89.4%; p=0.007), heart murmur (38% vs 50%; p=0.029) and mycotic aneurism

116 (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

118 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 $176.8 \pm 32.4 \mu$ mol/l;

120 p=0.048). After multivariate analysis including all above mentioned variables, only fever

121 (p=0.04) and vegetation (p=0.003) have revealed to be independently significantly different.

- 122 *Outcome in the T&C group compared to control group:*
- 123 The average length of hospital stay for patients who did not die during hospitalization 124 was significantly shorter in the T&C group than in the control group, in intention to treat

125 (29.8 \pm 3.8 days vs 39.0 \pm 5.2 days – p=0.005) and on treatment (26.4 \pm 3.8 days vs 36.9 \pm 4.8 126 days - p=0.0007) (Table 2).

127	After a median follow up of 166 days following the diagnosis and the treatment of IE,
128	the outcome of the T&C group was associated with a 2-fold lower global mortality rate in
129	intention to treat (19.3% vs 30% p=0.024 ; OR=0.56 [0.34-0.92]), with a 2-fold lower in-
130	hospital mortality rate in intention to treat (9.9% vs 18.2% p=0.03 ; OR=0.49 [0.26-0.93]),
131	and on treatment (10.1% vs 14.7% p=0.036; OR=0.46 [0.23-0.92]). The mortality rate at day
132	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]),
133	and on treatment (7.4% vs 15.3% p=0.05; OR=0.44 [0.20-0.99]) (Table 2). However, the
134	mortality rate at day 90 was not significantly different among the two groups in intention to
135	treat (16.4% vs 21.2%; p=0.32) and on treatment (15.0% vs 20.5%; p=0.32) (Table 2).
136	The analysis of the causes of in-hospital death showed that sepsis or multi-organ
137	failure was almost twice more often associated with the control group (8.2%) than with the
138	T&C group (4.7%), although the trend is not statistically significant (Table 2). In the T&C
139	group, septic failure was observed in 8 patients, of whom only 4 had rifampicin and
140	gentamicin (4 patients were treated before 2013). The T&C protocol was stopped prematurely
141	in two cases because of acute renal failure and in one case because of microbiological failure
142	with an antibiotic switch by daptomycin and linezolid (without success and finally the patient
143	underwent a cardiac transplantation). In one case the patient died after S. aureus IE relapse.
144	The analysis of mortality within 30 days showed that severe sepsis/multi-organ failure
145	was also 2 times more often associated with the control group (5.9%) than with the T&C
146	group (3.0%) although the trend is also not statistically significant (Table 2).
147	Compliance to antibiotic protocols:

8

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).

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

175

176

Discussion

177 Over a 5 years period of management of S. aureus, IE mortality rate of patients treated 178 with T&C was comparable to other published cohorts. The mortality rates were twice lower in 179 T&C group than among controls, as overall, 30-days, and in-hospital mortality rates, as well 180 in intention to treat as on treatment. Among the causes of death, severe sepsis and multi-organ 181 failure was twice less frequent in the T&C group compared to the control group (although not 182 significant). In the subgroup treated by T&C and rifampicin / gentamicin according to a 183 microbiologic failure, we note only one death due to septic cause at 171 days in a patient with 184 S. aureus IE relapse. Using T&C with a rapid switch to oral prescription allowing a 185 significant reduction (10 days) of hospital stay duration.

186

187 TMP-SMZ is particularly effective on S. aureus, regardless of its sensitivity or 188 resistance to methicillin [15][·][16], with a very low resistance rate in our center [9]. This 189 treatment has been used for over 30 years at low standard dose with excellent oral 190 bioavailability.(>90%) [17]. It has also proven effective and tolerable at higher doses in 191 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 192 193 mortality in the treatment of Methicillin resistant (MRSA) S. aureus bacteremia [19]. 194 Markowitz *et al* reported the possible inferiority of low dose TMP-SMZ to vancomycin for 195 methicillin-susceptible S. aureus bacteremia : in right side IE the cure rate was 64% (7/11) for 196 TMP-SMZ versus 92% (11/12) for vancomycin (p=0.095) [20]. In a randomized controlled 197 trial including 252 patients, Paul et al. concluded that TMP-SMZ did not achieve non-198 inferiority to vancomycin in the treatment of severe MRSA infections [21]. The difference 199 was particularly marked in patients with bacteremia. Clindamycin has an excellent tissue 200 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.

206 Four to six weeks of intravenous antibiotic are currently recommended for S. aureus 207 IE treatment [14] and most of the patients remain hospitalized during this period. Oral 208 antibiotic therapy for treatment of IE is not well established [25,26]. Oral therapy was 209 reported in right-sided in S. aureus IE [26] [27], using oral ciprofloxacin plus rifampicin 210 [28,29], oral penicillin in a child [26], oral fucidic acid and linezolid, oral fucidic acid and 211 rifampicin [27]. Recently, rapid oral shift in patients with left side IE in stable condition, was 212 reported was non inferior to intravenous antibiotic treatment [25]. Rapid oral shift of 213 antibiotic regimen in IE reduce the risk of catheter-related infection, the cost and the duration 214 of hospital stay [27]. The tolerance of T&C was acceptable, with no major difference 215 underlined concerning the development of an acute renal failure. In our study, there has been 216 an adjustment of the doses of TMP-SMZ in a significant number of cases (33.9%). Dosage in 217 plasma should allow a better management [30]. The treatment has even been prematurely 218 interrupted in 19.3% of the case (of which 1/3 for acute renal failure and 1/3 for septic 219 failure), which is comparable to the reference treatment, with linezolid and daptomycin 220 [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

12

226 (2.9%) at day 90. Patients in T&C group had less frequently a vegetation (110 patients versus

227 139 patients p=0.0004). This may suggest patients with less severe infections. In the T&C

228 group 39 patients with persistent bacteremia and septic failure were treated with gentamicin

- and rifampicin this may contribute to the effectiveness of our treatment.
- 230 Conclusions
- 231 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.
- 235

236 Declarations

- 237 **Funding**: Supported by the French State, managed by the "Agence Nationale pour la
- 238 Recherche" including the "Programme d'Investissement d'Avenir" under the reference
- 239 Méditerranée Infection 10-IAHU-03
- 240 Competing Interests: None
- 241 Ethical Approval: Ethical Committee approval number: 2019-004

242 **References**

- 243 [1] Abdallah L, Habib G, Remadi J-P, Salaun E, Casalta J-P, Tribouilloy C. Comparison of
- 244 prognoses of *Staphylococcus aureus* left-sided prosthetic endocarditis and prosthetic
- endocarditis caused by other pathogens. Arch Cardiovasc Dis 2016;109:542–9.
- doi:10.1016/j.acvd.2016.02.010.
- [2] Lauridsen TK, Bruun LE, Rasmussen RV, Arpi M, Risum N, Moser C, et al. Linezolid
- as rescue treatment for left-sided infective endocarditis: an observational, retrospective,
- 249 multicenter study. Eur J Clin Microbiol Infect Dis 2012;31:2567–74.
- doi:10.1007/s10096-012-1597-7.
- [3] Fernández Guerrero ML, González López JJ, Goyenechea A, Fraile J, de Górgolas M.
- 252 Endocarditis caused by *Staphylococcus aureus*: A reappraisal of the epidemiologic,
- 253 clinical, and pathologic manifestations with analysis of factors determining outcome.

254 Medicine (Baltimore) 2009;88:1–22. doi:10.1097/MD.0b013e318194da65.

- [4] Selton-Suty C, Célard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, et al.
- 256 Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-
- based survey. Clin Infect Dis Off Publ Infect Dis Soc Am 2012;54:1230–9.
- doi:10.1093/cid/cis199.
- [5] Fowler VG, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, et al.
- 260 Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA
- 261 2005;293:3012–21. doi:10.1001/jama.293.24.3012.
- 262 [6] Miro JM, Anguera I, Cabell CH, Chen AY, Stafford JA, Corey GR, et al.
- 263 Staphylococcus aureus native valve infective endocarditis: report of 566 episodes from
- the International Collaboration on Endocarditis Merged Database. Clin Infect Dis Off
- 265 Publ Infect Dis Soc Am 2005;41:507–14. doi:10.1086/431979.

- 266 [7] Chirillo F, Scotton P, Rocco F, Rigoli R, Borsatto F, Pedrocco A, et al. Impact of a
- 267 multidisciplinary management strategy on the outcome of patients with native valve
- 268 infective endocarditis. Am J Cardiol 2013;112:1171–6.
- doi:10.1016/j.amjcard.2013.05.060.
- [8] Botelho-Nevers E, Thuny F, Casalta J, Richet H, Gouriet F, Collart F, et al. Dramatic
- reduction in infective endocarditis-related mortality with a management-based approach.
- Arch Intern Med 2009;169:1290–8. doi:10.1001/archinternmed.2009.192.
- 273 [9] Casalta J-P, Zaratzian C, Hubert S, Thuny F, Gouriet F, Habib G, et al. Treatment of
- 274 *Staphylococcus aureus* endocarditis with high doses of trimethoprim/sulfamethoxazole
- and clindamycin, Preliminary report. Int J Antimicrob Agents 2013;42:190–1.
- doi:10.1016/j.ijantimicag.2013.05.002.
- [10] Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective
- endocarditis: challenges and perspectives. Lancet Lond Engl 2012;379:965–75.
- doi:10.1016/S0140-6736(11)60755-1.
- [11] Dumitrescu O, Boisset S, Badiou C, Bes M, Benito Y, Reverdy M-E, et al. Effect of
- 281 Antibiotics on *Staphylococcus aureus* Producing Panton-Valentine Leukocidin.
- 282 Antimicrob Agents Chemother 2007;51:1515–9. doi:10.1128/AAC.01201-06.
- 283 [12] Hsu M-S, Huang Y-T, Hsu H-S, Liao C-H. Sequential time to positivity of blood
- 284 cultures can be a predictor of prognosis of patients with persistent *Staphylococcus*
- 285 *aureus* bacteraemia. Clin Microbiol Infect 2014;20:892–8. doi:10.1111/1469-
- 286 0691.12608.
- [13] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed Modifications
- to the Duke Criteria for the Diagnosis of Infective Endocarditis. Clin Infect Dis
- 289 2000;30:633–8. doi:10.1086/313753.

- [14] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015
- 291 ESC Guidelines for the management of infective endocarditis: The Task Force for the
- 292 Management of Infective Endocarditis of the European Society of Cardiology (ESC).
- 293 Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the
- European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–128.
- doi:10.1093/eurheartj/ehv319.
- [15] Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al.
- 297 Methicillin-Resistant *Staphylococcus aureus* Disease in Three Communities. N Engl J
- 298 Med 2005;352:1436–44. doi:10.1056/NEJMoa043252.
- [16] Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health
- 300 care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA
- 301 2003;290:2976–84. doi:10.1001/jama.290.22.2976.
- 302 [17] VanEperen AS, Segreti J. Empirical therapy in Methicillin-resistant *Staphylococcus*
- 303 *aureus* infections: An Up-To-Date approach. J Infect Chemother Off J Jpn Soc

304 Chemother 2016;22:351–9. doi:10.1016/j.jiac.2016.02.012.

- 305 [18] Stein A, Bataille JF, Drancourt M, Curvale G, Argenson JN, Groulier P, et al.
- 306 Ambulatory Treatment of Multidrug-ResistantStaphylococcus-Infected Orthopedic
- 307 Implants with High-Dose Oral Co-trimoxazole (Trimethoprim-Sulfamethoxazole).
- 308 Antimicrob Agents Chemother 1998;42:3086–91.
- 309 [19] Goldberg E, Paul M, Talker O, Samra Z, Raskin M, Hazzan R, et al. Co-trimoxazole
- 310 versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus*
- bacteraemia: a retrospective cohort study. J Antimicrob Chemother 2010;65:1779–83.
- doi:10.1093/jac/dkq179.

- 313 [20] Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared
 314 with vancomycin for the treatment of *Staphylococcus aureus* infection. Ann Intern Med
 315 1992;117:390–8.
- 316 [21] Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, et al.
- 317 Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by
- 318 meticillin resistant *Staphylococcus aureus*: randomised controlled trial. BMJ

319 2015;350:h2219.

- 320 [22] Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on
- 321 the prevention, diagnosis, and treatment of infective endocarditis (new version 2009):
- 322 The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of
- 323 the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369–413.
- doi:10.1093/eurheartj/ehp285.
- 325 [23] Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al.
- 326 Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by
- 327 Staphylococcus aureus. N Engl J Med 2006;355:653–65. doi:10.1056/NEJMoa053783.
- 328 [24] Tattevin P, Boutoille D, Vitrat V, Van Grunderbeeck N, Revest M, Dupont M, et al.
- 329 Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a
- multicentre observational study. J Antimicrob Chemother 2014;69:2010–3.
- doi:10.1093/jac/dku085.
- 332 [25] Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial Oral
- versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med 2018.
- doi:10.1056/NEJMoa1808312.
- [26] Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the
- treatment of infective endocarditis: a systematic review. BMC Infect Dis 2014;14:140.
- doi:10.1186/1471-2334-14-140.

338	[27]	Iversen K, Høst N, Bruun NE, Elming H, Pump B, Christensen JJ, et al. Partial oral
339		treatment of endocarditis. Am Heart J 2013;165:116-22. doi:10.1016/j.ahj.2012.11.006.
340	[28]	Tebas P, Martinez Ruiz R, Roman F, Mendaza P, Rodriguez Diaz JC, Daza R, et al.
341		Early resistance to rifampin and ciprofloxacin in the treatment of right-sided
342		Staphylococcus aureus endocarditis. J Infect Dis 1991;163:204-5.
343	[29]	Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral
344		antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users:
345		prospective randomized comparison with parenteral therapy. Am J Med 1996;101:68-
346		76.
347	[30]	Muhammed Ameen S, Rolain J-M, Le Poullain M-N, Roux V, Raoult D, Drancourt M.
348		Serum concentration of co-trimoxazole during a high-dosage regimen. J Antimicrob

349 Chemother 2014;69:757–60. doi:10.1093/jac/dkt400.

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 Control group		n OP
	I & C group	Control group	p OK
	N=171	N=170	
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)
	(IIUII-CACIUSIVC)

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

45 (26.3%)	48 (28.2%)	0.72
110 (64.3%)	139 (81.8%)	0.0004 0.79 [0.69-0.90]
36 (21.1%)	27 (15.9%)	0.26
9 (5.3%)	8 (4.7%)	1
48 (28.1%)	49 (28.8%)	0.90
23 (13.5%)	34 (20.0%)	0.11
55 [20-75]	60 [20-70]	0.69
uns)		
11.9 [2.1-28]	11.5 [2.9-32]	0.5
146 [3-523]	168 [2-455]	0.15
138 [9-898]	174 [30-933]	0.048
7(4.1%)	10(5.9%)	0.046
6(3.5%)	12(7.06%)	0.15
	10 (5.9%)	
	45 (26.3%) 110 (64.3%) 36 (21.1%) 9 (5.3%) 48 (28.1%) 23 (13.5%) 55 [20-75] ms) 11.9 [2.1-28] 146 [3-523] 138 [9-898] 7(4.1%) 6(3.5%)	45 (26.3%) 48 (28.2%) 110 (64.3%) 139 (81.8%) 36 (21.1%) 27 (15.9%) 9 (5.3%) 8 (4.7%) 48 (28.1%) 49 (28.8%) 23 (13.5%) 34 (20.0%) 55 [20-75] 60 [20-70] ms) 11.5 [2.9-32] 146 [3-523] 168 [2-455] 138 [9-898] 174 [30-933] 7(4.1%) 10(5.9%) 6(3.5%) 12(7.06%) 10 (5.9%) 10 (5.9%)

*including pacemaker, defibrillator and dialysis catheter ** temperature > 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	р		Control Group	T&C group	р	
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	22	9 (36.0) 2	5 (35.7)	1	

	** M	ortality	until	1	ast	kı	nown	follow-up
	*patients not died during the	e hospitalization						
One y	ear mortality	45/170	34/171	0.16		32/126	24/138	0.3
Globa	l mortality**	51 / 170 (30.0)	33 / 171 (19.3)	0.024		37 / 126 (29.4)	28 / 138 (20.3)	0.11
	Other causes	21 (60.0)	19 (70.4)			16 (64.0)	15 (75.0)	
	Sepsis / multi organ failure	14 (40.0)	8 (29.6)	0.43		9 (36.0)	5 (25.0)	0.52
Death	at day 90	35 / 165 (21.2)	27 / 165 (16.4)	0.32		25 / 122 (20.5)	20 / 132 (15.0)	0.32
	Other causes	14 (58.3)	7 (58.3)			13 (68.4)	7 (70.0)	
	Sepsis / multi organ failure	10 (41.7)	5 (41.7)	1		6 (31.6)	3 (30.0)	1
Death	at day 30	24 / 169 (14.2)	12 / 169 (7.1)	0.05		19 / 125 (15.3)	10 / 136 (7.4)	0.05
	Other causes	17 (54.8)	9 (52.9)			16 (64.0)	9 (64.3)	

Fable 3: Protocol modifications	in the Tri	imethoprim-Sul	lfamethoxazole &	k 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

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