



HAL
open science

Clindamycin combination treatment for the treatment of bone and joint infections caused by clindamycin-susceptible, erythromycin-resistant *Staphylococcus* spp.

Agathe Bonnaire, Véronique Vernet-Garnier, Delphine Lebrun, Odile Bajolet, Morgane Bonnet, Maxime Hentzien, Xavier Ohl, Saidou Diallo, Firouzé Bani-Sadr

► **To cite this version:**

Agathe Bonnaire, Véronique Vernet-Garnier, Delphine Lebrun, Odile Bajolet, Morgane Bonnet, et al.. Clindamycin combination treatment for the treatment of bone and joint infections caused by clindamycin-susceptible, erythromycin-resistant *Staphylococcus* spp.. *Diagnostic Microbiology and Infectious Disease*, 2021, 99 (1), pp.115225. <10.1016/j.diagmicrobio.2020.115225>. <hal-03048566>

HAL Id: hal-03048566

<https://hal.science/hal-03048566v1>

Submitted on 24 Oct 2022

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 CC BY-NC 4.0 - Attribution - Non-commercial use - International License

1 **Clindamycin combination treatment for the treatment of bone and joint infections**
2 **caused by Clindamycin-Susceptible, Erythromycin-Resistant *Staphylococcus* spp**

3
4
5 Agathe BONNAIRE¹, Véronique VERNET-GARNIER², Delphine LEBRUN³, Odile
6 BAJOLET⁴, Morgane BONNET⁵, Maxime HENTZIEN¹, Xavier OHL⁶, Saidou DIALLO⁶,
7 Firouzé BANI-SADR¹

8
9 ¹ Department of Internal Medicine and Infectious Diseases, Reims Teaching Hospitals,
10 Reims, France

11 ² Department of Bacteriology, Reims Teaching Hospitals, Reims, France

12 ³ Department of Internal Medicine and Infectious Diseases, Manchester Hospital, Charleville-
13 Mezieres, France

14 ⁴ Department of Hygiene, Reims Teaching Hospitals, Reims, France

15 ⁵ Department of Pharmacy, Reims Teaching Hospitals, Reims, France

16 ⁶ Department of Orthopedic Surgery, Reims Teaching Hospitals, Reims, France

17

18 **Corresponding author:**

19 Prof. Firouzé BANI-SADR
20 Department of Internal Medicine, Infectious Diseases, and Clinical Immunology
21 CHU Robert Debré
22 Avenue du Général Koenig
23 51092 Reims, France
24 Telephone number: (+33) 3 26 78 71 89
25 Fax number: (+33) 3 26 78 40 90
26 E-mail address: fbanisadr@chu-reims.fr
27

28 **Running title:** Clindamycin – combination antibiotherapy for bone and joint infections
29 caused by clindamycin-susceptible, erythromycin-resistant *Staphylococcus*

30

31 **Keywords:** bone infection, *Staphylococcus* spp, clindamycin-combination antibiotherapy,
32 clindamycin-susceptible, erythromycin-resistant *Staphylococcus*, clindamycin-rifampicin

33

34 **Total number of words: 2675**

35

36

37

38 **Abstract**

39

40 The objective of this study was to evaluate the clinical outcomes and safety of clindamycin-
41 combination antibiotherapy for the treatment of erythromycin-resistant, lincosamide-
42 susceptible bone and joint infections caused by *Staphylococcus* spp.

43 Between January 2010 and September 2018, 46 patients with *Staphylococcus* spp
44 erythromycin-resistant, lincosamide-susceptible bone and joint infections were treated with
45 clindamycin combination antibiotherapy for 6 to 12 weeks. The type of infection was
46 prosthetic in 20 cases (43.5%), osteosynthetic device in 15 cases (32.6%), chronic
47 osteomyelitis in 7 cases (15.2%), and arthritis in 4 cases (8.7%). The cure rate was 67.4% by
48 intention-to-treat, and 84.6% per-protocol, with a median follow-up of 398 days (range 86-
49 843). Only 2 relapses (5.1%) were observed in patients with chronic osteomyelitis; an
50 acquired resistance to lincosamides developed in one case.

51 Clindamycin combination therapy appears to be effective for the treatment of bone and joint
52 infection caused by erythromycin-resistant, lincosamide-susceptible *Staphylococcus* spp.

53

54 **Introduction**

55

56 Clindamycin has been widely used to treat osteoarticular infections due to *Staphylococcus* spp
57 since 1966 [1]. It presents numerous advantages, including high bone penetration with
58 sustained activity against biofilm formation and bacterial adherence; almost complete
59 absorption after oral administration, yielding serum concentrations comparable to those
60 achieved with intravenous administration; no need to adapt to renal clearance; and few drug-
61 drug interactions, enabling rapid ambulatory treatment and lower costs [1–3]. However, the
62 guidelines of the French infectious diseases society for osteoarticular infections on materials
63 (prostheses, implants, osteosynthesis) explicitly state that clindamycin combination treatment
64 is not recommended in case of susceptibility to lincosamide but resistance to erythromycin
65 [4]. Indeed, most of the *Staphylococcus* strains that are lincosamide-susceptible and
66 erythromycin-resistant have the phenotype of *in vitro* inducible macrolide-lincosamide-
67 streptogramin B resistance (iMLSB) due to the presence of erythromycin ribosomal
68 methylase (*erm*) genes [1,5]. These strains display *in vitro* resistance to 14- and 15-
69 membered macrolides, which are inducer antibiotics. Although clindamycin is not an inducer,
70 exposure of iMLSB *Staphylococcus* to this antibiotic may result in constitutive resistance and
71 MLSB cross resistance [1]. Furthermore, resistance to lincosamides develops much more
72 slowly in erythromycin-susceptible isolates of *Staphylococcus aureus* (*S. aureus*) than in
73 erythromycin-resistant isolates [6]. The combination of resistance to erythromycin with
74 susceptibility to lincosamide can also, albeit more rarely, be due to efflux pumps that remove
75 macrolides but not clindamycin from *Staphylococcus* spp [1]. Several cases have reported
76 discordant efficacy of clindamycin monotherapy for lincosamide -susceptible, erythromycin-
77 resistant *Staphylococcus*, with emergence of MLSB constitutive resistance in some cases [7–
78 9]. It should be stressed that the guidelines of the Infectious Diseases Society of America
79 (IDSA) recommend monotherapy with clindamycin only for indefinite chronic oral

80 antimicrobial suppression for prosthetic joint infection by *Staphylococcus*; no restriction is
81 proposed in case of erythromycin resistance [10]. Of note, both French and American
82 recommendations are based on a low level of evidence [4,10].

83 Against this background, the objective of the current study was to evaluate the clinical
84 outcomes and safety of clindamycin combination antibiotic therapy for the treatment of
85 *Staphylococcus* spp erythromycin-resistant and lincosamide-susceptible bone and joint
86 infections.

87

88 MATERIALS AND METHODS

89

90 This retrospective cohort study was performed from January 2010 to September 2018 in the
91 University Hospital of Reims, France. Using the medical files from the bacteriology
92 laboratory, we retrospectively screened for adult patients with monomicrobial *Staphylococcus*
93 spp erythromycin-resistant, lincosamide-susceptible bone and joint infections who received
94 oral administration of clindamycin-combination antibiotherapy. Patients with diabetic foot
95 infection were excluded. At least three samples were collected intra-operatively.

96 Bone, prosthesis or internal fixation device infection was diagnosed by the presence of at least
97 one of the following: productive fistula, visible intraoperative purulence, growth of the same
98 organism in at least one or more cultures for *S. aureus* and two or more cultures for
99 staphylococci other than *S. aureus* from intraoperative tissue or sonication fluid.

100 *Staphylococcus* spp was identified using Vitek-2 cards (bioMerieux, Marcy l'Etoile, France)
101 until 2012, and thereafter with the MALDI-TOF method (MALDI Biotyper, Bruker, Marne la
102 Vallee, France). Susceptibility results were only determined according to the
103 recommendations of the French Society for Microbiology (SFM) and the European
104 Committee on Antimicrobial Susceptibility Testing (CA-SFM/EUCAST) breakpoints

105 available at <https://www.sfm-microbiologie.org/2019/05/06/casfm-eucast-2019-v2/>. The D-
106 test used to detect iMLSb was performed but results were not specified.

107 In patients with an internal fixation device, the device was retained in case of stable implant
108 and adequate surgical debridement and soft-tissue coverage. The device was removed if the
109 bone was healed, and exchanged if the bone needed further stabilization. In our center,
110 piperacillin/tazobactam plus vancomycin was the first-line antibiotic treatment before
111 bacteriological documentation until 2018 and piperacillin/tazobactam plus daptomycin since
112 2018.

113 Fluoroquinolone- rifampicin combination is the first-line treatment of choice in our center in
114 case of documentation of *Staphylococcus* isolate susceptible to both fluoroquinolone and
115 rifampicin. In patients with erythromycin-resistant, lincosamide-susceptible *Staphylococcus*
116 isolate, clindamycin combination treatment is given only in case of resistance to other oral
117 antibiotics or known intolerance, and to enable administration of oral antibiotics. This
118 combination is given orally after obtaining the bacteriological results and after validation at
119 our weekly multidisciplinary consultation meeting (3 to 7 days after surgery). Blood tests,
120 including full blood cell count, creatinine, alanine aminotransferase and aspartate
121 aminotransferase were controlled every week during the first month, then every two weeks
122 until the end of antibiotic treatment.

123 All patient records were discussed at the weekly multidisciplinary consultation meeting on
124 osteoarticular infection at Reims university hospital. Demographics, comorbidities,
125 clinicopathological, microbiological, and laboratory data were extracted retrospectively from
126 the Reims Hospital Patient Information System.

127 The primary outcome was defined as the remission of symptoms and the absence of failure
128 during follow-up (one year). Therefore, the following events were recorded: relapse and
129 reinfection. Relapse was defined as a new infection caused by the same bacterial species as

130 the initial case. Reinfection was defined as a new infection caused by a bacteria different to
131 that responsible for the initial case.

132

133 **Results**

134 Between January 2010 and September 2018, a total of 641 patients presented erythromycin-
135 resistant *Staphylococcus* spp bone and joint infections. Of these, 595 (93%) were not included
136 in the analysis, for the following reasons: (1) resistance to lincosamides was present in 256
137 cases (40%); (2) the infection was not monomicrobial in 96 cases (15%); (3) 241 patients
138 were not treated with clindamycin-based antibiotherapy (37.5%); (4) 2 (0.5%) patients had
139 diabetic foot. The remaining 46 patients, who were treated with clindamycin combination
140 antibiotherapy, were included in the final analysis. Their characteristics and outcomes are
141 presented in Table 1. Most were men (56.5%) and the median age was 60 (IQR 51-76) years.
142 The median Charlson comorbidity index was 3 (IQR 1-4). Underlying co-morbid conditions
143 included obesity (body mass index > 30 kg/m²) (19.6%), diabetes mellitus (19.6%), chronic
144 renal failure (15.2%) and occlusive peripheral arterial disease (2.2%). Twelve patients
145 (26.1%) had previous bone and joint infections.

146 The type of infection was prosthesis infection in 20 cases (43.5%), osteosynthetic device
147 infection in 15 cases (32.6%), chronic osteomyelitis in 7 cases (15.2%), and arthritis in 4
148 cases (8.7%). Among the 20 cases with prosthesis infection, removal of the prosthesis was not
149 performed in 3 cases (in 2 patients, co-morbidity was too severe to tolerate invasive surgery
150 and in one patient, the prosthesis infection was diagnosed coincidentally during re-
151 intervention for hip prosthesis). Among the 15 cases with osteosynthetic device infection,
152 device removal and 1-stage exchange was performed in 3 cases, device removal in 9 cases
153 and debridement with lavage alone in 3 cases. Among the 7 patients with chronic
154 osteomyelitis, 3 were treated exclusively with antibiotherapy. Among the 40 patients (87%)

155 who underwent surgery, 8 had received previous antibiotherapy for a median of 9 days (IQR
156 3-13) before surgery.

157 At the time of diagnosis of infection, 6 patients (13%) were febrile, 6 patients (13%) had sinus
158 tract and 30 patients (65.2%) presented with local signs of inflammation. Median leukocyte
159 count and C-reactive protein were 10.1G/L (IQR 7.0 -12.3) and 51.3mg/L (IQR 11.8 -121.5),
160 respectively. The median number of intra-operative samples that were positive for
161 *Staphylococcus* spp was 2 (IQR 1 - 4).

162 *S. aureus* was the most frequently isolated pathogen, implicated in 31 patients (67.4%),
163 followed by *Staphylococcus epidermidis* (n=12; 26.1%), by *Staphylococcus haemolyticus*
164 (n=2; 4.4%) and *Staphylococcus lugdunensis* (n=1; 2.2%). Resistance to methicillin was
165 present in one patient with *Staphylococcus aureus* infection and in 4 patients with
166 *Staphylococcus epidermidis* infection. Two patients had hematogenous infection.

167 Clindamycin was given at doses of 600 mg three times daily in association with rifampicin
168 600mg twice daily in 37 cases (80.4%), with fusidic acid in 4 cases (8.7%), with
169 fluoroquinolone in 4 cases (8.7%) and cotrimoxazole in 1 case (1.5%). For patients with BMI
170 > 35 kg/m² (n=3), clindamycin was given at a dose of 600 mg four times daily. The duration
171 of antibiotic therapy was 6 weeks in patients with internal fixation device infection and
172 arthritis, and 12 weeks in those with prosthesis infection and chronic osteomyelitis.

173 The median duration of follow-up was 398 days (IQR 86-843). All patients had at least one
174 year of follow-up except for 7 patients (15.2%) who died during the first year of follow-up.
175 Five of these deaths occurred during the antibiotic treatment. Only one of these was related to
176 the failure to control the bone and joint infection: a patient with hip prosthesis infection and 2-
177 stage exchange revision presented toxidermia on day 7 of clindamycin-rifampicin treatment.
178 He then received intravenous oxacillin plus fusidic acid. Death occurred suddenly one month
179 later, in a context of spacer infection. No bacteriologic documentation was available.

180 The 2 other deaths occurred after antibiotic treatment, and were not related to the bone and
181 joint infection. Their last follow-up was at 230 and 297 days after antibiotic therapy.

182 Four patients (8.7%) discontinued clindamycin due to side effects. Three patients treated with
183 clindamycin plus rifampicin discontinued clindamycin due to toxidermia in 3 cases at days 7,
184 21 and 26. One patient treated with clindamycin plus fusidic acid, discontinued clindamycin
185 at days 16 due to gastrointestinal toxicity.

186 Seven patients had re-infection (n=5) or relapse (n=2) after a median of 52 (42-128) days. The
187 two patients with relapse both had chronic osteomyelitis due to *S. aureus* and were both
188 treated with a combination of clindamycin - fusidic acid. The relapse occurred after
189 discontinuation of antibiotic therapy. *S. aureus* with acquired resistance to lincosamides in
190 addition to *Citrobacter koseri* were isolated in one case. *Staphylococcus aureus* without
191 acquired resistance to lincosamides and *E. cloacae* were isolated in the second case.

192 Among the intention-to-treat population of 46 patients, the success rate was 67.4%. Among
193 the 39 patients who completed antibiotic treatment, the success rate was 84.6%; 4 patients had
194 re infection (10.2%), and 2 patients a relapse (5.1%); with acquired resistance to lincosamides
195 in one out of the 2 cases with relapse. The outcome according to the different antibiotic
196 regimens and according to implant removal are presented in Table 2. Among the 14 patients
197 with prosthesis removal who were treated with clindamycin plus rifampicin, the intention to
198 treat success rate was 71.4%, and the per-protocol success rate was 92.8%. Among the 12
199 patients with fixation device removal who were treated with clindamycin plus rifampicin, the
200 success rate was 85.7% by both intention to treat and per-protocol analysis.

201

202

203 Discussion

204 To the best of our knowledge, this is the first study to evaluate clindamycin combination
205 antibiotics for the treatment of erythromycin-resistant and lincosamide-susceptible bone and
206 joint infections due to *Staphylococcus* spp in a significant number of patients. In this study of
207 46 patients, the cure rate with the clindamycin combination antibiotic therapy was 67.4% by
208 intention-to-treat, and 84.6% per-protocol. Moreover, only 2 relapses (4.3%) were observed;
209 and acquired resistance to lincosamides developed in only one case.

210 Clindamycin combination antibiotic therapy for bone and joint infections has been evaluated
211 in several studies [11–14]. However, patients with erythromycin-resistant strains were
212 excluded in one study, and in the others, the status of erythromycin susceptibility or the
213 outcomes according to erythromycin susceptibility were not given [11–14]. In a study of 61
214 patients with osteoarticular infections (prosthetic infections and chronic osteitis in 50.8% and
215 36.1% of cases, respectively), among the causative micro-organisms, namely *Staphylococcus*
216 spp (72.2%) and *Streptococcus* spp (15.3%), only 9.6% of strains were erythromycin-resistant
217 and lincosamide-susceptible. Clindamycin was associated with either ofloxacin, rifampicin, or
218 teicoplanin in 88.5% of cases. After excluding 5 patients whose death was not related to
219 antibiotherapy and one patient for erythroderma, complete cure was obtained in 91.1% at 18
220 months. The authors did not specify outcomes according to erythromycin-resistance, or
221 whether resistance to lincosamides was observed in failure patients [11]. In a study of 20
222 patients with staphylococcal osteoarticular infection (6 arthroplasty infections, 4 other implant
223 infections, 7 native arthritis, and 3 osteomyelitis), all were successfully treated with a
224 clindamycin-rifampicin combination after a mean follow-up of 2.6 years (range 1.0-6.1 years)
225 [13]. In a study of 10 patients with acute post-surgical infection of joint arthroplasty treated
226 with a clindamycin-rifampicin combination, the cure rate was 70% after 2 years of follow-up
227 [14]. In these 2 studies, the status of erythromycin-resistance was not given by the authors. In

228 a study of 53 patients treated for erythromycin-susceptible *Staphylococcus* strain bone and
229 joint infections, 92% were considered cured after a median duration of follow-up of 30
230 months (range, 24 to 53 months); only one relapse was observed [12]. In our study, most
231 patients (n= 37; 80.4%) were also treated with a clindamycin-rifampicin combination, with a
232 median follow-up of 275 (65-1305) days; no relapse and four reinfections were observed in
233 these patients.

234 Due to the bacteriostatic nature of clindamycin, the choice of the second agent of the
235 antibiotic combination probably plays an important role in the success rate of the treatment,
236 particularly in the prevention of emerging resistance [13,15]. Rifampicin has excellent anti-
237 staphylococcal activity, high bone penetration with sustained activity against biofilm bacteria
238 and can eradicate adherent and stationary-phase staphylococci [13,16]. Although a dramatic
239 decrease in clindamycin concentrations has been observed when associated with rifampicin,
240 the cure rate observed with this combination in our study, as well as data reported in the
241 literature are comparable to other rifampicin-based combinations [17–20]. Furthermore, target
242 concentrations for clindamycin have never been defined and the addition of rifampicin to
243 clindamycin significantly increased bactericidal activity *in vitro* against both coagulase-
244 negative and coagulase-positive staphylococci [21–23]. In addition, a combination of
245 clindamycin-rifampicin for 10 weeks is recommended for the treatment of hidradenitis
246 suppurativa [24].

247 Fusidic acid, like rifampicin, has good penetration into infected bone and good anti-
248 staphylococcal activity. In combination with other agents, it is one of treatment options
249 recommended by the French infectious diseases society for bone and joint infection caused by
250 staphylococci and for osteoarticular infections on materials [4,16]. Reports on the efficacy of
251 a clindamycin-fusidic acid combination are scarce. Seven patients successfully treated with
252 this combination have been reported [11]. In our study, 2 out of 4 patients who received this

253 combination had a relapse. Both of them had chronic osteomyelitis due to *S. aureus* with a
254 previous history of repeated surgical interventions (4 in one case and 8 in the second case).

255 A combination of clindamycin- trimethoprim-sulfamethoxazole was given in only one patient
256 in our study. Of note, this association with high-dose trimethoprim-sulfamethoxazole was
257 evaluated in a prospective study of 171 patients with *S. aureus* endocarditis, although
258 erythromycin susceptibility was not indicated. The mortality was comparable to other
259 published cohorts [25].

260 Tolerance could be the main limitation of clindamycin combination antibiotic regimens, in
261 particular due to clindamycin-related cutaneous and digestive adverse events [11,26]. In our
262 study, 3 patients (6.5%) had to discontinue clindamycin treatment for toxidermia, and one
263 patient for digestive adverse events. In line with other studies, no occurrence of *C. difficile*
264 infection was observed in our study [11–13].

265 Our study suffers from some limitations that deserve to be acknowledged. It is a single-centre,
266 and retrospective study. Furthermore, patients had different types of bone and joint infection
267 and received different antibiotic combinations comprising clindamycin. Finally, both the
268 French Society for Microbiology and the European Committee on Antimicrobial
269 Susceptibility Testing recommend that staphylococci resistant to erythromycin but susceptible
270 to clindamycin be tested for inducible MLSb resistance (D-zone test) [27,28]. According to
271 EUCAST, iMLSb isolates should be reported as resistant by adding this comment:
272 “Clindamycin may still be used for short-term therapy of less serious skin and soft tissue
273 infections as constitutive resistance is unlikely to develop during such therapy” [27].
274 According to the SFM, these isolates should be reported as sensitive, with a warning that rare
275 clinical failures have been reported by selection of cMLSb-related clindamycin resistance
276 [28]. Unfortunately, the D-zone test was performed but unspecified in our study and

277 consequently, the rate of patients with iMLSb strains is unknown. iMLSb isolates were
278 reported as sensitive to clindamycin without a warning indicating potential clinical failure.

279

280 **Conclusion**

281 Although not recommended as a primary treatment option for bone and joint infection caused
282 by erythromycin-resistant *Staphylococcus* spp, clindamycin combination antibiotic therapy
283 appeared to be effective in our study. In patients treated with a clindamycin-rifampicin
284 combination, no relapse and no emergence of resistance was observed. However, further,
285 larger studies are required to confirm these findings.

286

287

288

289 Acknowledgements

290 We thank Fiona Ecartot, PhD (EA3920, University Hospital Besancon, France) for editorial
291 assistance.

292

293 Conflicts of interest: None**294 Author's contributions:**

295 All authors cared for the patients. FBS, VVG and SD were responsible for the overall
296 supervision of the study. AB and FBS wrote the first manuscript draft. All authors critically
297 reviewed the manuscript and gave final approval. FBS was responsible for the overall
298 supervision of the study.

299

300 Compliance with ethical standards**301 Ethical standards**

302 Only parameters collected in routine clinical practice for which patients give their informed
303 consent on admission to the hospital were retrospectively analyzed. Approval by an ethics
304 committee was not required in accordance with French legislation.

305

306 **References**

- 307 1 Woods CR. **Macrolide-Inducible Resistance to Clindamycin and the D-Test: *Pediatr***
308 ***Infect Dis J* 2009; 28:1115–1118.**
- 309 2 Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, *et al.* **Population**
310 **pharmacokinetics of clindamycin orally and intravenously administered in patients**
311 **with osteomyelitis: Clindamycin population pharmacokinetics in osteomyelitis**
312 **patients. *Br J Clin Pharmacol* 2012; 74:971–977.**
- 313 3 Schilcher K, Andreoni F, Dengler Haunreiter V, Seidl K, Hasse B, Zinkernagel AS.
314 **Modulation of *Staphylococcus aureus* Biofilm Matrix by Subinhibitory**
315 **Concentrations of Clindamycin. *Antimicrob Agents Chemother* 2016; 60:5957–5967.**
- 316 4 Société de Pathologie Infectieuse de Langue Française (SPILF), Collège des
317 Universitaires de Maladies Infectieuses et Tropicales (CMIT), Groupe de Pathologie
318 Infectieuse Pédiatrique (GPIP), Société Française d'Anesthésie et de Réanimation
319 (SFAR), Société Française de Chirurgie Orthopédique et Traumatologique (SOFOT),
320 Société Française d'Hygiène Hospitalière (SFHH), *et al.* **[Recommendations for clinical**
321 **practice. Osteo-articular infection therapy according to materials used (prosthesis,**
322 **implants, osteosynthesis)]. *Med Mal Infect* 2009; 39:745–774.**
- 323 5 Leclercq R. **Mechanisms of Resistance to Macrolides and Lincosamides: Nature of**
324 **the Resistance Elements and Their Clinical Implications. *Clin Infect Dis* 2002;**
325 **34:482–492.**
- 326 6 Panagea S, Perry JD, Gould FK. **Should clindamycin be used as treatment of patients**
327 **with infections caused by erythromycin-resistant staphylococci? *J Antimicrob***
328 ***Chemother* 1999; 44:581–582.**
- 329 7 Rao GG. **Should clindamycin be used in treatment of patients with infections caused**
330 **by erythromycin-resistant staphylococci? *J Antimicrob Chemother* 2000; 45:715–715.**
- 331 8 Siberry GK, Tekle T, Carroll K, Dick J. **Failure of Clindamycin Treatment of**
332 **Methicillin-Resistant *Staphylococcus aureus* Expressing Inducible Clindamycin**
333 **Resistance In Vitro. *Clin Infect Dis* 2003; 37:1257–1260.**
- 334 9 Drinkovic D. **Clindamycin treatment of *Staphylococcus aureus* expressing inducible**
335 **clindamycin resistance. *J Antimicrob Chemother* 2001; 48:315–316.**
- 336 10 Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, *et al.*
337 **Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice**
338 **Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013; 56:e1–**
339 **e25.**
- 340 11 El Samad Y, Havet E, Bentayeb H, Olory B, Canarelli B, Lardanchet J-F, *et al.*
341 **Traitement des infections ostéoarticulaires par clindamycine chez l'adulte. *Médecine***
342 ***Mal Infect* 2008; 38:465–470.**
- 343 12 Zeller V, Dzeing-Ella A, Kitzis M-D, Ziza J-M, Mamoudy P, Desplaces N. **Continuous**
344 **Clindamycin Infusion, an Innovative Approach to Treating Bone and Joint**
345 **Infections. *Antimicrob Agents Chemother* 2010; 54:88–92.**

- 346 13 Czekaj J, Dinh A, Moldovan A, Vaudaux P, Gras G, Hoffmeyer P, *et al.* **Efficacy of a**
347 **combined oral clindamycin–rifampicin regimen for therapy of staphylococcal**
348 **osteoarticular infections.** *Scand J Infect Dis* 2011; **43**:962–967.
- 349 14 Soriano A, García S, Bori G, Almela M, Gallart X, Macule F, *et al.* **Treatment of acute**
350 **post-surgical infection of joint arthroplasty.** *Clin Microbiol Infect* 2006; **12**:930–933.
- 351 15 Smith K, Perez A, Ramage G, Gemmell CG, Lang S. **Comparison of biofilm-associated**
352 **cell survival following in vitro exposure of meticillin-resistant Staphylococcus aureus**
353 **biofilms to the antibiotics clindamycin, daptomycin, linezolid, tigecycline and**
354 **vancomycin.** *Int J Antimicrob Agents* 2009; **33**:374–378.
- 355 16 Kim B-N, Kim ES, Oh M-D. **Oral antibiotic treatment of staphylococcal bone and**
356 **joint infections in adults.** *J Antimicrob Chemother* 2014; **69**:309–322.
- 357 17 Nguyen S, Pasquet A, Legout L, Beltrand E, Dubreuil L, Migaud H, *et al.* **Efficacy and**
358 **tolerance of rifampicin–linezolid compared with rifampicin–cotrimoxazole**
359 **combinations in prolonged oral therapy for bone and joint infections.** *Clin Microbiol*
360 *Infect* 2009; **15**:1163–1169.
- 361 18 Aboltins CA, Page MA, Buising KL, Jenney AWJ, Daffy JR, Choong PFM, *et al.*
362 **Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis**
363 **retention and oral rifampicin and fusidic acid.** *Clin Microbiol Infect* 2007; **13**:586–
364 591.
- 365 19 Lora-Tamayo J, Euba G, Cobo J, Horcajada JP, Soriano A, Sandoval E, *et al.* **Short-**
366 **versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic**
367 **joint infection managed with implant retention: a randomised clinical trial.** *Int J*
368 *Antimicrob Agents* 2016; **48**:310–316.
- 369 20 Euba G, Murillo O, Fernandez-Sabe N, Mascaro J, Cabo J, Perez A, *et al.* **Long-Term**
370 **Follow-Up Trial of Oral Rifampin-Cotrimoxazole Combination versus Intravenous**
371 **Cloxacillin in Treatment of Chronic Staphylococcal Osteomyelitis.** *Antimicrob Agents*
372 *Chemother* 2009; **53**:2672–2676.
- 373 21 Béraud G, Le Moal G, Sury S, Venisse N. **Clindamycin and rifampicin: No bull’s eye**
374 **without a target.** *J Infect* 2016; **72**:120–121.
- 375 22 Hackbarth CJ, Chambers HF, Sande MA. **Serum bactericidal activity of rifampin in**
376 **combination with other antimicrobial agents against Staphylococcus aureus.**
377 *Antimicrob Agents Chemother* 1986; **29**:611–613.
- 378 23 Arditi M, Yogev R. **In vitro interaction between rifampin and clindamycin against**
379 **pathogenic coagulase-negative staphylococci.** *Antimicrob Agents Chemother* 1989;
380 **33**:245–247.
- 381 24 Albrecht J, Baine PA, Ladizinski B, Jemec GB, Bigby M. **Long-term clinical safety of**
382 **clindamycin and rifampicin combination for the treatment of hidradenitis**
383 **suppurativa. A Critically Appraised Topic.** *Br J Dermatol* 2019; **180**:749–755.

- 384 25 Tissot-Dupont H, Gouriet F, Oliver L, Jamme M, Casalta J-P, Jimeno M-T, *et al.* **High-**
385 **dose trimethoprim-sulfamethoxazole and clindamycin for Staphylococcus aureus**
386 **endocarditis.** *Int J Antimicrob Agents* 2019; **54**:143–148.
- 387 26 Yang Y, Chen S, Yang F, Zhang L, Alterovitz G, Zhu H, *et al.* **HLA-B*51:01 is strongly**
388 **associated with clindamycin-related cutaneous adverse drug reactions.**
389 *Pharmacogenomics J* 2017; **17**:501–505.
- 390 27 EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint
391 tables for interpretation of MICs and zone diameters. Version 9.0, 2019.
392 <http://www.eucast.org>.
- 393 28 SOCIETE FRANCAISE DE MICROBIOLOGIE. Comité de l'antibiogramme de la
394 Société Française de Microbiologie- Recommandations 2019 V.2.0 Mai.
- 395
- 396

397 **Table 1 Characteristics and outcome data of 46 patients with bone and joint infection**
 398 **caused by erythromycin-resistant, clindamycin-susceptible *Staphylococcus* spp**
 399

	Total N=46
Age (years)	60 (51-76)
Male sex	26 (56.5)
Body mass index (kg/m ²)	27 (24-29)
Diabetes	9 (19.6)
Chronic renal failure	7 (15.2%)
Occlusive peripheral arterial disease	1 (2.2%)
Charlson score	3 (1-4)
Previous osteoarticular infection	12 (26.1)
Prosthesis infection	20 (43.5)
Removal of prosthetic device and 1-stage exchange	11
Removal of prosthetic device and 2-stage exchange	2
Debridement/lavage alone (no removal of prosthesis)	4
No surgical intervention	3
Infection of a fixation device	15 (32.6)
Internal fixation device	13
External fixation device	2
Removal of osteosynthesis device	9
Removal of osteosynthesis device and 1-stage exchange	3
Debridement/lavage alone (no device removal)	3
Chronic osteomyelitis	7 (15.2)
Debridement/lavage	4
Antibiotherapy alone	3
Arthritis	4 (8.5)
Number of intra-operative samples positive for <i>Staphylococcus</i> spp	2 (1- 4)
<i>Staphylococcus aureus</i>	31 (67.4)

<i>Staphylococcus epidermidis</i>	12 (26.1)
<i>Staphylococcus haemolyticus</i>	2 (4.4)
<i>Staphylococcus lugdunensis</i>	1 (2.2)
Median duration of follow-up (days)	398 (86-843)
Follow-up less than one year	7 (15.2)
Early discontinuation of clindamycin for intolerance	4 (8.7)
Re infection with a different strain	4 (8.7)
Relapse with the same bacterial species	2 (4.4)
Relapse with no identified strain in a patient with clindamycin discontinuation at day 7	1 (2.2)
Outcome	
Cured by intention to treat	31 (67.4)
Cured per protocol	33 (84.6)

400 Results are expressed as median (Q1-Q3) or n (%).

401

402

403
404
405
406
407

Table 2: Characteristics and outcome data of 46 patients with bone and joint infection caused by erythromycin-resistant, clindamycin-susceptible *Staphylococcus* spp according to the antibiotic regimen and to implant removal

	Clindamycin-rifampicin N=37	Clindamycin-fluoroquinolone N=4	Clindamycin- fusidic acid N=4	Clindamycin- cotrimoxazole N=1
Prosthesis infection (n=20)	N=17	N=3		
Follow-up less than one year	N=5	N=1		
Early discontinuation of clindamycin for intolerance	N=3	N=0		
Re infection with a different strain	N=1	N=0		
Relapse with the same bacterial species	N= 0	N=0		
Relapse with no identified strain	N=1	N=0		
Outcome				
Cured by intention to treat	64.7%	66.6%		
Cured per protocol	84.6%	66.6%		
Outcome in patients with prosthesis removal	N=14			
Cured by intention to treat	71.4%			
Cured per protocol	92.8%			
Infection of a fixation device N= 15	N=14	N=1		
Follow-up less than one year	N=1	N=0		
Early discontinuation of clindamycin for intolerance	N=0	N=0		
Re infection with a different strain	N=1	N=0		
Relapse with the same bacterial species	N=0	N=0		
Outcome				
Cured by intention to treat	85.7%	100%		

Cured per protocol	85.7%	100%		
Outcome in patients with device removal n=12	N=12			
Cured by intention to treat	83.3%			
Cured per protocol	83.3%			
Chronic osteomyelitis N=11	N=6	N=0	N=4	N=1
Follow-up less than one year	N=0		N=0	N=0
Early discontinuation of clindamycin for intolerance	N=0		N=1	N=0
Re infection with a different strain	N=1		N=1	N=0
Relapse with the same bacterial species	N=0		N=2	N=0
Outcome				
Cured by intention to treat	83.3%		25.0%	100%
Cured per protocol	83.3%		25.0%	100%