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

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

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30

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33

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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/m<sup>2</sup>) (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/m<sup>2</sup> (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

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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

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397 **Table 1 Characteristics and outcome data of 46 patients with bone and joint infection**  
 398 **caused by erythromycin-resistant, clindamycin-susceptible *Staphylococcus* spp**  
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	Total <b>N=46</b>
Age (years)	60 (51-76)
Male sex	26 (56.5)
Body mass index (kg/m <sup>2</sup> )	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)
<b>Outcome</b>	
Cured by intention to treat	31 (67.4)
Cured per protocol	33 (84.6)

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

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**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		
<b>Outcome</b>				
Cured by intention to treat	64.7%	66.6%		
Cured per protocol	84.6%	66.6%		
<b>Outcome in patients with prosthesis removal</b>	<b>N=14</b>			
Cured by intention to treat	71.4%			
Cured per protocol	92.8%			
<b>Infection of a fixation device N= 15</b>	<b>N=14</b>	<b>N=1</b>		
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		
<b>Outcome</b>				
Cured by intention to treat	85.7%	100%		

Cured per protocol	85.7%	100%		
<b>Outcome in patients with device removal n=12</b>	N=12			
Cured by intention to treat	83.3%			
Cured per protocol	83.3%			
<b>Chronic osteomyelitis N=11</b>	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
<b>Outcome</b>				
Cured by intention to treat	83.3%		25.0%	100%
Cured per protocol	83.3%		25.0%	100%