



HAL
open science

EMID:7362154fb580dd56 Fusidic acid in a Tertiary Hospital: an observational study focusing on prescriptions, tolerance and susceptibility of Staphylococcus & Cutibacterium spp strains from bone samples. Revised Version R2 Fusidic acid, Staphylococcus and Cutibacterium spp (2911 Words)

Juliette Romaru, Anne Limelette, Delphine Lebrun, Morgane Bonnet, Véronique Vernet Garnier, Yohan N'Guyen

► **To cite this version:**

Juliette Romaru, Anne Limelette, Delphine Lebrun, Morgane Bonnet, Véronique Vernet Garnier, et al.. EMID:7362154fb580dd56 Fusidic acid in a Tertiary Hospital: an observational study focusing on prescriptions, tolerance and susceptibility of Staphylococcus & Cutibacterium spp strains from bone samples. Revised Version R2 Fusidic acid, Staphylococcus and Cutibacterium spp (2911 Words). European Journal of Clinical Microbiology and Infectious Diseases, 2022. hal-04648923

HAL Id: hal-04648923

<https://hal.science/hal-04648923>

Submitted on 15 Jul 2024

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.

2
3
4 Original Article

5 EMID:7362154fb580dd56

6
7 Fusidic acid in a Tertiary Hospital: an observational study focusing on
8 prescriptions, tolerance and susceptibility of *Staphylococcus* &
9 *Cutibacterium spp* strains from bone samples. Revised Version R2

10 *Fusidic acid, Staphylococcus and Cutibacterium spp*

11 (2911 Words)

12
13 Juliette Romaru ^{1*}, Anne Limelette ^{2*}, Delphine Lebrun ^{3**}, Morgane Bonnet ^{4**},
14 Véronique Vernet Garnier ², Yohan N'Guyen ¹.

15
16 ¹ Service de Médecine Interne, Maladies Infectieuses et Immunologie Clinique, Hôpital
17 Robert Debré, 51100 Reims, France

18 ² Laboratoire de Bactériologie, Pôle de Biologie, 51100 Reims, France

19 ³ Service d'Orthopédie, Hôpital Maison Blanche, 51100 Reims, France

20 ⁴ Pharmacie Hospitalière, Hôpital Robert Debré, 51100 Reims, France

21 * equally contributed to this work

22 ** equally contributed to this work

23 Corresponding author : Avenue du général Koenig, 51100 Reims, France. Tel

24 (+33)326789422. Fax (+33)326784090 mail: yohan.nguyen@wanadoo.fr.

26 **Abstract: (249 words)**

27 **Purpose :** Adverse drug reactions of broad spectrum fluoroquinolones or rifampicin are not
28 uncommon during Osteomyelitis and orthopaedic implants infections (OOII). Thus, we made
29 an overview (i) of the prescription of Fusidic acid (FA) (ii) of FA susceptibility of
30 *Staphylococcus* spp and *Cutibacterium* spp strains isolated from bone samples.

31 **Methods:**

32 All prescriptions of FA and all bone samples with positive culture for *Staphylococcus* spp or
33 *Cutibacterium* spp (Reims University Hospital June 2017-May 2021) were included. All
34 *Staphylococcus aureus* strains were considered as significant, whereas *Coagulase Negative*
35 *Staphylococcus* and *Cutibacterium* spp strains were not if these strains grew only on one sole
36 sample. Antibiotic susceptibility of *Staphylococcus* spp strains and the susceptibility to FA of
37 *Cutibacterium* spp strains had been determined using disk diffusion methods, as described for
38 *Staphylococcus* spp in CASFM/EUCAST guidelines.

39 **Results:**

40 The mean FA consumption was 0.6 daily defined doses /1000 patient days. FA was prescribed
41 for OOII due to *Staphylococcus* spp and *Cutibacterium* spp in 24 and 2 cases respectively.
42 Among 401 *Staphylococcus* spp strains, there were 254 *S.aureus* (63.3%), 84 methicillin-
43 resistant (20.9%) and 333 FA susceptible (83.0%) strains. *S.aureus* and methicillin-sensitive
44 strains were more likely to be susceptible to FA ($p<0.001$). Among 39 *Cutibacterium* spp
45 strains, FA inhibition zone diameters geometric mean was 28.6mm [24-35mm], suggesting
46 that all these strains could be considered as susceptible to FA.

47 **Conclusion:**

48 These data suggested that FA could be more frequently used in OOII due to *Staphylococcus*
49 spp and *Cutibacterium* spp, subject to the absence of other resistant bacteria.

50 **Keywords:** Osteomyelitis; *Staphylococcus* spp; *Cutibacterium* spp; Fusidic Acid;
51 Orthopaedic implant infection.

52

53

54 **Introduction:**

55 Bacterial resistance to antibiotics is a challenging complication in bone and joint
56 infections as well as in periprosthetic joint infections [1]. Besides inappropriate broad
57 spectrum antibiotics use [2], a prolonged exposure to antibiotics is a key driver of the
58 development of antibiotic resistance [3].

59 Among hospital and healthcare associated infections, osteomyelitis and orthopaedic
60 implants infections (OOII) are associated with the most prolonged antibiotics exposure (i.e
61 from six to twelve weeks) [4,5]. Strategies to reduce antibiotics duration are currently
62 investigated in these kinds of infection, where bacteria in stationary phase did not appear as
63 susceptible to antibiotics as bacteria in exponential phase and probably required longer course
64 of antibiotic treatments [4,6]. Nevertheless, no equivalence study investigating the impact of
65 narrow spectrum antibiotics are being performed in this field, where the use of broad
66 spectrum fluoroquinolones are recommended in the treatment of Gram-negative bacilli as
67 well as staphylococci, which are the most frequently isolated bacteria during OOII [4].
68 Fluoroquinolones are frequently prescribed in association with rifampicin[5,7,8], but adverse
69 drug reactions (ADRs) of fluoroquinolones or rifampicin are not uncommon when prescribed
70 for OOII [9,10]. Moreover, a negative impact of prolonged course of rifampicin (which is the
71 major drug active on sleeping mycobacteria during the six-month treatment of tuberculosis)
72 onto the development of resistance of *Mycobacterium tuberculosis* strains has been discussed
73 elsewhere [11].

74 Fusidic acid (FA) is an oral narrow spectrum (almost exclusively anti-staphylococcal)
75 antibiotic that belongs to the steroids family and exerts its bacteriostatic activity through
76 binding Elongation Factor G necessary for bacterial protein synthesis [12]. Because of its
77 pharmacokinetic properties [13], it is approved for skin and soft tissues as well as bone
78 staphylococcal infections, but despite being well tolerated [13], it remained frequently
79 prescribed only if rifampicin cannot be used among those latter [14,15]. In the present report,
80 to describe the use and the potential use of FA as a narrow spectrum antibiotic in OOII, we
81 made an overview (i) of the prescription and tolerance of FA (ii) of FA susceptibility of
82 *Staphylococcus* spp and *Cutibacterium* spp strains isolated from bone samples taken in our
83 tertiary Hospital.

84 **Material and methods:**

85 *Fusidic acid prescriptions:*

86 All prescriptions of FA referenced in Hospital Pharmacy database of Reims University
87 Hospital (Easily software- Hospices Civils de Lyon) during the period June 1st 2017-May
88 31th 2021 were included. Prescriptions of FA lasting less than two days were excluded from
89 the analysis. Corresponding sociodemographic and clinical data were retrospectively
90 extracted from patient's medical records (Easily software- Hospices Civils de Lyon) by an
91 external reviewer (YNG). Indications and ADRs of FA were defined according to
92 documented bacterial infections and adverse events reported in medical files before and after
93 FA prescription respectively. All ADRs have been reported except those that were more

94 probably due to another antimicrobial treatment, prescribed before or in association with or
95 FA.

96 FA consumption had been calculated by dividing the number of FA daily defined
97 doses (DDD) over the period 2017-2020 by the number of Patient-days (PD) using
98 Consores®-2020, CEPIAS Grand Est. Results of FA consumption in Reims University
99 Hospital during study period are expressed in DDD/1000 PD.

100 *Ethics:*

101 The patients were not required to provide individual consent because of the
102 retrospective and non-interventional nature of this study, in accordance with French
103 legislation. No patient had previously objected to the further use of their medical data. Data
104 confidentiality was preserved throughout this internal study (Reims University Hospital
105 GDPR register number RMR004-03072021), in accordance with the principles of the
106 Declaration of Helsinki. Written consent had been obtained from the two patients, whose
107 cases were reported as supplementary material.

108 *Fusidic acid susceptibility of bacterial strains*

109 All multiple bone samples performed in Reims University Hospital between June 1st
110 2017 and May 31th 2021 with staphylococcal positive culture referenced in Bacteriology
111 Laboratory database (Labo Serveur, Inlog) were included and screened for significant
112 staphylococcal cultures suggestive of infection. Briefly, at least three samples per patient
113 including bone or peri-implant tissues or synovial fluids had been previously taken during
114 surgery of OOII. Patients did not receive antibiotic before sampling only in case of first
115 surgery. When more than one surgical procedures were required (e.g two stage orthopaedic
116 implant exchange), further samples could have been collected while patient received
117 antibiotics. All *Staphylococcus aureus* strains were considered as significant and none were
118 excluded, whereas coagulase-negative staphylococci were not considered as significant and
119 therefore excluded if these strains grew only on one sole sample. Antibiotic susceptibility
120 testing had been routinely performed using disk diffusion method according to each year's
121 CASFM/EUCAST guidelines [16]. Each isolate was not considered as susceptible when it
122 was categorized as "intermediate" and "susceptible, increased exposure", according to these
123 guidelines before and after 2019 respectively. Except FA, Vancomycin and Methicillin, the
124 susceptibility of each included staphylococcal isolate was also extracted for Ofloxacin,
125 Erythromycin plus Lincomycin, Linezolid, Tetracycline, Rifampicin and
126 Trimethoprim/Sulfamethoxazole. A score between 0 and 6 was assigned to each strain
127 according to the remaining number of susceptibilities to these antibiotics.

128 All multiple bone samples performed in Reims University Hospital between June 1st
129 2017 and May 31th 2021 with culture positive for *Cutibacterium spp* (formerly
130 *Propionibacterium spp*) referenced in Bacteriology Laboratory database (Labo Serveur,
131 Inlog) were included and screened for significant *Cutibacterium spp* cultures suggestive of
132 infection. *Cutibacterium spp* strains were not considered as significant and therefore excluded
133 if these strains grew only on one sole sample and if a specific antibiotic treatment was not

134 given to treat these strains. The susceptibility to Fusidic acid has been determined for all
135 included *Cutibacterium spp* strains using disk diffusion methods, as described for
136 *Staphylococcus spp* in CASFM/EUCAST guidelines [16]. The susceptibility of each included
137 *Cutibacterium spp* isolate was also extracted for Amoxicillin, Imipenem, Lincomycin,
138 Levofloxacin or Moxifloxacin, Vancomycin, Rifampicin and Chloramphenicol.

139 *Statistical analysis:*

140 Quantitative variables usually expressed as median + range were compared using the
141 Mann Whitney U-test and qualitative variables expressed as percentages were compared using
142 Pearson's Chi-square test. A *p* value <0.05 was considered as significant. Statistical analyses
143 were performed using Stat view 5.0 software (SAS institute).

144

145 **Results:**

146 *Fusidic acid prescriptions:*

147 The mean FA consumption in Reims University Hospital over the study period was
148 0.6 DDD/1000 PD and 44 patients received FA. Among these 44 patients, 19 (43.1%) were
149 male and median age was 71.5 [36-96] years. Forty one out of 44 patients (93.1%) received
150 exclusively oral FA, two intravenous plus oral FA and one exclusively intravenous FA. FA
151 was prescribed for *Staphylococcus* and *Cutibacterium spp* infections in 42 and 2 cases
152 respectively (Supplementary Table 1).

153 Among the 42 remaining patients receiving FA for staphylococcal infections, FA was
154 prescribed for OOII and skin and soft tissues infection (SSTI) in 24 (57.1%) and 9 (21.4%)
155 cases respectively. The other indications for FA were: mediastinitis in 3 cases, catheter related
156 bloodstream infection in 2 cases, spinal cord stimulation neurostimulator infection, keratitis,
157 peritoneal dialysis associated peritonitis and vascular bypass infection (one case each). FA
158 was prescribed alone for SSTI in 5 cases which all occurred in one nursing home of Reims
159 University Hospital, whereas FA was prescribed in association with another antibiotic in the
160 37 remaining cases. FA was prescribed because of a side effect due to a previous line of
161 antibiotics in 9 cases (21.4%) and FA was also withdrawn in 9 cases (21.4%). Interestingly,
162 FA was withdrawn because of the occurrence of a side effect only in 4 out of these 9 cases
163 (44.4%), the 5 remaining withdrawals corresponding to the need of an intensification of the
164 antimicrobial treatment (secondary infection...). Reported FA side effects were: diarrhoea,
165 vomiting, skin rash, hypocalcaemia and rhabdomyolysis (one case each). One side effect (skin
166 rash) did not lead to FA withdrawal. Rhabdomyolysis was due to a drug-drug interaction with
167 statins. Interestingly, statins were not stopped during FA treatment in 2 cases, without
168 occurrence of rhabdomyolysis.

169 To better assess if FA could be prescribed more frequently especially during OOII, we
170 then investigated FA susceptibility of *Staphylococcus spp* isolates from bone samples in our
171 centre during the same time period.

172 *Fusidic acid susceptibility of Staphylococcus spp isolates from bone samples*

173 Eight hundred and eighty six bone samples collected between June 2017 and May
174 2021 were screened and 401 *Staphylococcus spp* isolates were considered as significant (see
175 methods section above): 254 *S.aureus* (63.3%) and 147 coagulase negative *Staphylococcus*
176 strains (36.7%). Eighty four strains (20.9%) were methicillin-resistant. Among these 401
177 strains, 86 and 315 had been sampled during surgery of osteomyelitis and surgery of
178 orthopaedic implants infections respectively. *S.aureus* and methicillin-resistant strains
179 accounted for 198 (62.8%) and 63 (20.0%) out of the 315 orthopaedic implants infections
180 strains respectively. Three hundred and thirty three out of the 401 strains (83.0%) remained
181 susceptible to FA. We then tested whether FA susceptibility was statistically associated or
182 not with (i) *S.aureus* strains, (ii) methicillin-sensitive strains and (iii) susceptibilities to other
183 anti-staphylococcal antibiotics. *S.aureus* and methicillin-sensitive strains were more likely to
184 be susceptible to FA than coagulase-negative staphylococci and methicillin-resistant strains
185 respectively, $p < 0.001$ (Table 1). Moreover, FA susceptible strains were also more likely to be
186 susceptible to a higher number of antibiotics among Ofloxacin, Erythromycin plus
187 Lincomycin, Linezolid, Tetracycline, Rifampicin and Trimethoprim/Sulfamethoxazole than
188 non-susceptible strains (Table 1). Supplementary data about antibiotic susceptibility pattern of
189 staphylococci is given in Table 2. The lowest susceptibility rate to FA was observed among
190 *Staphylococcus epidermidis* strains. Twenty four out of 25 (96.0%) Methicillin Resistant
191 *S.aureus* (MRSA) strains remained susceptible to FA.

192 The evolution of Fusidic Acid susceptible strains between June 2017 and May 2021 is
193 depicted in figure 1. FA susceptibility of staphylococcal strains remained stable during this
194 time period (all statistical comparisons gave non-significant results), whereas FA
195 consumption remained low.

196 *Fusidic acid susceptibility of Cutibacterium spp isolates from bone samples*

197 As stated above, FA was prescribed and led to treatment success in 2 female patients,
198 one with *Cutibacterium acnes* OOII and one with *Cutibacterium avidum* OOII
199 (Supplementary Table 1). These cases are reported as supplementary material. To better
200 assess if FA could be prescribed more frequently during OOII due to *Cutibacterium spp*, we
201 then investigated the Fusidic acid susceptibility of *Cutibacterium spp* isolates from bone
202 samples in our centre during the same time period.

203 One hundred and forty five bone samples collected between June 2017 and May 2021
204 were screened and 37 supplementary *Cutibacterium acnes* isolates were considered as
205 significant (see methods section above). The susceptibility to Fusidic acid of all these 39
206 strains (38 *Cutibacterium acnes* and 1 *Cutibacterium avidum* strains) was expressed as
207 inhibition zone diameters using disk diffusion methods. Diameter geometric mean was
208 28.6mm, range [24-35mm] (Supplementary figure 2). These data suggested that 100% of
209 *Cutibacterium spp* isolates could be considered as susceptible to FA with diameter ≥ 24 mm, if
210 clinical breakpoints for *Staphylococcus spp* of CASFM/EUCAST guidelines were used [16].
211 All 38 *Cutibacterium acnes* isolates were susceptible to all tested antibiotics (Amoxicillin,
212 Imipenem, Lincomycin, Vancomycin, Rifampicin and Chloramphenicol). Only the

213 *Cutibacterium avidum* strain was non susceptible to Lincomycin. Levofloxacin or
214 Moxifloxacin susceptibilities were routinely tested only among 18 out of the 39 isolates but
215 all tested strains were susceptible.

216

217 **Discussion:**

218 In the present manuscript focusing on the use and the potential use of Fusidic Acid
219 (FA) as a narrow spectrum antibiotic in OOII, we reported that FA was rarely prescribed in
220 our centre even for staphylococcal OOII, whereas *Staphylococcus spp* strains from bone
221 samples were susceptible to FA in more than eighty percent of cases. FA was given almost
222 exclusively orally, because of ADRs due to a previous line of antibiotics in 20% of cases.
223 This latter assertion is in line with the fact that FA susceptible staphylococcal strains were
224 more likely to be susceptible to a higher number of antibiotics (Table 1). Taken together,
225 these data suggested that FA could potentially be more frequently used in OOII due to
226 *Staphylococcus spp* strains, subject to the absence of other resistant bacteria.

227 Firstly, FA seemed to be considered as a well-tolerated second line [14,15] antibiotic
228 regimen, as suggested by a withdrawal rate for ADR of less than 10% (4 out of 42 cases) in
229 our study. Diarrhoea, gastrointestinal discomfort and skin rash have been reported since years
230 [13], but the occurrence of hypocalcaemia as ADR seemed more anecdotal [17]. The main
231 precaution while prescribing FA remained the need to check for potentially detrimental drug-
232 drug interaction especially interaction between FA and statins that could lead to the
233 occurrence of Rhabdomyolysis [18]. One such case was observed in our study, but, in two
234 cases, statins were not stopped (albeit recommended during FA treatment) without occurrence
235 of rhabdomyolysis.

236 Secondly, we could hypothesize from these bacteriological data that FA could be more
237 frequently used during the prolonged treatment of staphylococcal OOII (especially those due
238 to *S.aureus*, table 1 and 2) because of its narrow spectrum, subject to the absence of other
239 resistant bacteria during polymicrobial infection that could occur between 10 and 30% of
240 OOII [4]. It should be used in association with another antibiotic to prevent the development
241 of resistance of staphylococcal strains [19], but not rifampicin, because of unfavourable
242 interaction between these two drugs [20]. Other drugs with narrower spectrum than
243 fluoroquinolones (with whom we did not observe in vivo antagonism in association with FA
244 [21]) should be prioritized. Companion drugs with FA could be Lincomycin, Linezolid,
245 Tetracycline, Trimethoprim/Sulfamethoxazole, Vancomycin or Daptomycin. Siala et al
246 showed a median reduction of bacterial viability (evaluated by resoflurin fluorescence) of 6
247 staphylococcal strains forming biofilm of 27, 45, 41, 19 and 30% when exposed to FA,
248 Daptomycin, Linezolid, Vancomycin and Doxycyclin respectively [22]. Synergies with FA
249 were observed with Vancomycin but especially with Daptomycin and Linezolid [22], whose
250 prescription must be cautious in case of treatment lasting more than four weeks. The
251 association between bacteriostatic antibiotics such as FA, tetracycline or linezolid might
252 probably not be problematic during OOII where surgical treatment allowed reducing bacterial
253 inoculum. The efficacy of each antibiotic combination should be assessed by *in vivo* studies

254 (retrospective matched pair analysis) then in clinical trials as an alternative to
255 fluoroquinolones and rifampicin in the treatment of OOII due to *Staphylococcus* spp strains,
256 but after bacteriological documentation, avoiding an empirical risk of premature failure due to
257 FA resistant strains [23]. Such studies are mandatory steps before investigating an eventual
258 lesser impact of narrow spectrum antibiotic regimen onto the acquisition of other multi-
259 resistant bacterial strains in the human microbiota.

260 Lastly, albeit not routinely tested, FA was reported here as an effective treatment in
261 two cases of *Cutibacterium* spp strains OOII (supplementary material). All these 39 study
262 *Cutibacterium* spp strains isolated from bone samples were tested as susceptible to FA with
263 large zone of inhibition ≥ 24 mm suggesting low Minimum Inhibitory Concentrations, if
264 clinical breakpoints for *Staphylococcus* spp of CASFM/EUCAST guidelines were used [16].
265 This suggested that FA may be an option in treating infections due to *Cutibacterium* sp. More
266 clinic-bacteriological studies are required in this field to confirm the further utility of FA in
267 OOII due to *Cutibacterium* spp strains, which are the most common microorganisms involved
268 in Shoulder prosthesis infection [24,25] and accounted for 15% of total hip arthroplasty
269 infection cases in a Swedish study [26].

270 The main limit of this descriptive monocentric study was the absence of collection of
271 data concerning the other bacteria (e.g *Pseudomonas* spp) that could co-infect bone with
272 *Staphylococcus* spp or *Cutibacterium* spp and limit the possibility of a narrow spectrum
273 antibiotic regimen. Conversely, excluding non-significant *Staphylococcus* spp and/or
274 *Cutibacterium* spp strains could not be considered as a limit, because it allowed to exclude
275 skin contaminants and to focus on strains involved in genuine OOII. We fully acknowledge
276 that one cannot draw definitive conclusion from this retrospective study without standardized
277 clinical results assessing treatment success. That is the reason why further studies are needed,
278 especially for *S.aureus* OOII (Table 2), taking into account FA consumption and resistance
279 rate of *S. aureus* that remains low [27] but also the wide use of broad spectrum
280 fluoroquinolones and rifampicin now in our centre as in others [28].

281 **Conclusion:**

282 Fusidic Acid was rarely prescribed in our centre; whereas *Staphylococcus* spp strains
283 from bone samples remained susceptible to FA in 83.0% of cases. These data suggested that
284 oral narrow spectrum antibiotic with FA could be more frequently used in OOII due to
285 *Staphylococcus* spp, subject to the absence of other resistant bacteria. Further studies are also
286 required to investigate the utility of FA in OOII due to *Cutibacterium* spp strains.

287 **Acknowledgements:** We are indebted to Drs Saidou Diallo and Jean Charles Kleiber for their
288 help while taking care of the patients.

289 **Declarations:**

290 a. **Funding:** None.

291 b. **Conflicts of interest:** The authors report no conflict of interest.

- 292 c. **Availability of data and material (data transparency):** Yes.
- 293 d. **Code availability (software application or custom code):** Not applicable.
- 294 e. **Ethics approval:** Data confidentiality was preserved throughout this internal study (Reims
295 University Hospital GDPR register number RMR004-03072021), in accordance with the
296 principles of the Declaration of Helsinki.
- 297 f. **Authors' contributions :** All authors contributed to the study conception and design.
298 Material preparation, data collection and analysis were performed by JR, AL, DL, MB and
299 YNG. The first draft of the manuscript was written by YNG and all authors commented on
300 previous versions of the manuscript. All authors read and approved the final manuscript.
- 301 g. **Consent to participate:** The patients were not required to provide individual consent
302 because of the retrospective and non-interventional nature of this study, in accordance with
303 French legislation. No patient had previously objected to the further use of their medical data.
- 304 h. **Consent for publication:** Written consent was obtained from the two patients, whose cases
305 had been reported as supplementary material

306 **References:**

- 307 1- Drago L, De Vecchi E, Bortolin M, Zagra L, Romanò CL, Cappelletti L.
308 Epidemiology and Antibiotic Resistance of Late Prosthetic Knee and Hip Infections. *J*
309 *Arthroplasty*. 2017;32(8):2496-2500.
- 310 2- Paharik AE, Schreiber HL 4th, Spaulding CN, Dodson KW, Hultgren SJ. Narrowing
311 the spectrum: the new frontier of precision antimicrobials. *Genome Med*.
312 2017;9(1):110.
- 313 3- Armand-Lefèvre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppé E, et al.
314 Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive
315 care patients. *Antimicrob Agents Chemother*. 2013;57(3):1488-95
- 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
320 (SOFCOT); Société Française d'Hygiène Hospitalière (SFHH) et al. Clinical practice
321 recommendations. Osteoarticular infections on materials (prosthesis, implant,
322 osteosynthesis. *Med Mal Infect*. 2009;39(11):815-63.
- 323 5- Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al.
324 Diagnosis and management of prosthetic joint infection: clinical practice guidelines by
325 the Infectious Diseases Society of America. *Clin Infect Dis*. 2013 Jan;56(1):e1-e25.
- 326 6- Benkabouche M, Racloz G, Spechbach H, Lipsky BA, Gaspoz JM, Uçkay I. Four
327 versus six weeks of antibiotic therapy for osteoarticular infections after implant
328 removal: a randomized trial. *J Antimicrob Chemother*. 2019;74(8):2394-2399.
- 329 7- Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for
330 treatment of orthopedic implant-related staphylococcal infections: a randomized

- 331 controlled trial. Foreign-Body Infection (FBI) Study Group.
332 JAMA.1998;279(19):1537-41.
- 333 8- Bernard A, Kermarrec G, Parize P, Caruba T, Bouvet A, Mainardi JL, et al. Dramatic
334 reduction of clindamycin serum concentration in staphylococcal osteoarticular
335 infection patients treated with the oral clindamycin-rifampicin combination. J Infect.
336 2015;71(2):200-6.
- 337 9- Roblot F, Besnier JM, Giraudeau B, Simonnard N, Jonville-Bera AP, Coipeau P et al.
338 Lack of association between rifampicin plasma concentration and treatment-related
339 side effects in osteoarticular infections. Fundam Clin Pharmacol. 2007;21:363-9.
- 340 10- Vollmer NJ, Rivera CG, Stevens RW, Oravec CP, Mara KC, Suh GA, et al. Safety
341 and Tolerability of Fluoroquinolones in Patients with Staphylococcal Periprosthetic
342 Joint Infections. Clin Infect Dis. 2021;73(5):850-856.
- 343 11- Mendes-Bastos P, Macedo R, Duarte R. Treatment of hidradenitis suppurativa with
344 rifampicin: have we forgotten tuberculosis? Br J Dermatol. 2017;177:e150-e151.
- 345 12- Jones RN, Mendes RE, Sader HS, Castanheira M. In vitro antimicrobial findings for
346 fusidic acid tested against contemporary (2008-2009) gram-positive organisms
347 collected in the United States. Clin Infect Dis. 2011;52 Suppl 7:S477-86
- 348 13- Curbete MM, Salgado HR. A Critical Review of the Properties of Fusidic Acid and
349 Analytical Methods for Its Determination. Crit Rev Anal Chem . 2016;46(4):352-60.
- 350 14- Minassian AM, Osmon DR, Berendt AR. Clinical guidelines in the management of
351 prosthetic joint infection. J Antimicrob Chemother. 2014;69 Suppl 1:i29-35.
- 352 15- Klein S, Nurjadi D, Eigenbrod T, Bode KA. Evaluation of antibiotic resistance to
353 orally administrable antibiotics in staphylococcal bone and joint infections in one of
354 the largest university hospitals in Germany: is there a role for fusidic acid? Int J
355 Antimicrob Agents. 2016;47(2):155-7.
- 356 16- Comité de l'antibiogramme de la Société Française de Microbiologie. European
357 Committee on Antimicrobial Susceptibility Testing. Guidelines 2021 (April).
358 [https://www.sfm-microbiologie.org/wp-](https://www.sfm-microbiologie.org/wp-content/uploads/2021/04/CASFM2021__V1.0.AVRIL_2021.pdf)
359 [content/uploads/2021/04/CASFM2021__V1.0.AVRIL_2021.pdf](https://www.sfm-microbiologie.org/wp-content/uploads/2021/04/CASFM2021__V1.0.AVRIL_2021.pdf). (accessed July 27th)
- 360 17- Biswas M, Owen K, Jones MK. Hypocalcaemia during fusidic acid therapy. J R Soc
361 Med. 2002;95(2):91-3.
- 362 18- Bataillard M, Beyens MN, Mounier G, Vergnon-Miszczycha D, Bagheri H, Cathebras
363 P. Muscle Damage Due to Fusidic Acid-Statin Interaction: Review of 75 Cases From
364 the French Pharmacovigilance Database and Literature Reports. Am J Ther.
365 2019;26(3):e375-e379.
- 366 19- Farrell DJ, Castanheira M, Chopra I. Characterization of global patterns and the
367 genetics of fusidic acid resistance. Clin Infect Dis. 2011;52 Suppl 7:S487-92.
- 368 20- Pushkin R, Iglesias-Ussel MD, Keedy K, MacLauchlin C, Mould DR, Berkowitz R et al.
369 A Randomized Study Evaluating Oral Fusidic Acid (CEM-102) in Combination
370 With Oral Rifampin Compared With Standard-of-Care Antibiotics for Treatment of
371 Prosthetic Joint Infections: A Newly Identified Drug-Drug Interaction. Clin Infect Dis.
372 2016;63(12):1599-1604
- 373 21- Ertek M, Yazgi H, Erol S, Altoparlak U. Demonstration of in vitro antagonism
374 between fusidic acid and quinolones. J Int Med Res. 2002;30(5):525-8.

- 375 22- Siala W, Rodriguez-Villalobos H, Fernandes P, Tulkens PM, Van Bambeke F.
376 Activities of Combinations of Antistaphylococcal Antibiotics with Fusidic Acid
377 against Staphylococcal Biofilms in In Vitro Static and Dynamic Models. *Antimicrob*
378 *Agents Chemother.* 2018;62(7):e00598-18.
- 379 23- Hajikhani B, Goudarzi M, Kakavandi S, Amini S, Zamani S, van Belkum A, et al. The
380 global prevalence of fusidic acid resistance in clinical isolates of *Staphylococcus*
381 *aureus*: a systematic review and meta-analysis. *Antimicrob Resist Infect Control.*
382 2021;10(1):75.
- 383 24- Fink B, Sevelde F. Periprosthetic Joint Infection of Shoulder Arthroplasties:
384 Diagnostic and Treatment Options. *Biomed Res Int.* 2017;2017:4582756.
- 385 25- Boisrenoult P. *Cutibacterium acnes* prosthetic joint infection: Diagnosis and treatment.
386 *Orthop Traumatol Surg Res.* 2018;104(1S):S19-S24.
- 387 26- Hedlundh U, Zacharatos M, Magnusson J, Gottlander M, Karlsson J. Periprosthetic
388 hip infections in a Swedish regional hospital between 2012 and 2018: is there a
389 relationship between *Cutibacterium acnes* infections and uncemented prostheses? *J*
390 *Bone Jt Infect.* 2021;6(6):219-228.
- 391 27- Faber M, Rosdahl V T. Susceptibility to fusidic acid among Danish *Staphylococcus*
392 *aureus* strains and fusidic acid consumption *J Antimicrob Chemother.* 1990;25 Suppl
393 B:7-14.
- 394 28- Bernard L, Arvieux C, Brunschweiler B, Touchais S, Ansart S, Bru JP et al. Antibiotic
395 Therapy for 6 or 12 Weeks for Prosthetic Joint Infection. *N Engl J Med .*
396 2021;384(21):1991-2001.
397
398
399

400 **Tables**

401 **Table 1:** Antimicrobial Susceptibility of *Staphylococcus spp* isolates from bone samples
 402 between June 2017 and May 2021: association between Fusidic acid susceptibility and
 403 *Staphylococcus aureus* species, methicillin-sensitive strains and susceptibilities to other anti-
 404 staphylococcal antibiotics.

	All Staphylococcal Strains (n=401)	Fusidic acid susceptible strains (n=333)	Fusidic acid resistant strains (n=68)	P
<i>S.aureus</i> n(%)	254 (63.3)	248 (74.5)	6 (8.8)	<0.001
Methicillin resistant strains n(%)	84 (20.9)	47 (14.1)	37 (54.4)	<0.001
Remaining number of susceptibilities to antibiotics* Median [range]	6 [0-6]	6 [1-6]	4 [0-6]	<0.001

405 *S.aureus* : *Staphylococcus aureus* species

406 * among those : Ofloxacin, Erythromycin plus Lincomycin, Linezolid, Tetracycline,
 407 rifampicin and Trimethoprim/Sulfamethoxazole.

408 **Table 2:** Antimicrobial Susceptibility pattern of some *Staphylococcus spp* isolates according
 409 to species and methicillin resistance.

	MSSA n=229	MRSA n=25	MSSE n=33	MRSE n=46	MSoCONS n=55	MRoCONS n=13
Ofloxacin susceptibility n(%)	220 (96.0)	7 (28.0)	24 (72.7)	14 (30.4)	55 (100.0)	5 (38.4)
Erythromycin plus Lincomycin susceptibility n(%)	168 (73.3)	14 (56.0)	17 (51.5)	6 (13.0)	43 (78.1)	6 (46.1)
Linezolid susceptibility n(%)	228 (99.5)	25 (100.0)	33 (100.0)	44 (95.6)	55 (100.0)	13 (100.0)
Tetracycline susceptibility n(%)	223 (97.3)	19 (76.0)	24 (72.7)	20 (43.4)	51 (92.7)	9 (69.2)
Rifampicin susceptibility n(%)	224 (97.8)	22 (88.0)	25 (75.7)	31 (67.3)	55 (100.0)	7 (53.8)
Trimethoprim sulfamethoxazole susceptibility n(%)	225 (98.2)	24 (96.0)	23 (69.6)	29 (63.0)	55 (100.0)	9 (69.2)
Vancomycin susceptibility n(%)	229 (100.0)	25 (100.0)	33 (100.0)	46 (100.0)	55 (100.0)	13 (100.0)
FA susceptibility n(%)	224 (97.8)	24 (96.0)	15 (45.4)	15 (32.6)	47 (85.4)	8 (61.5)

410 MSSA : Methicillin susceptible *Staphylococcus aureus* ; MRSA : Methicillin resistant
411 *Staphylococcus aureus* ; MSSE : Methicillin susceptible *Staphylococcus epidermidis* ;
412 MRSE : Methicillin resistant *Staphylococcus epidermidis* ; MSoCONS : Methicillin
413 susceptible other Coagulase Negative staphylococci (*S. lugdunensis* n=16, *S. simulans* n=8,
414 *S. hominis* n=7, *S. caprae* n=6, *S. pettenkofferi* n=4, *S. capitis* n=4, *S. warneri* n=3, *S. cohnii*
415 n=2, *S. schleiferi* n=2, *S. saccharolyticus* n=1, *S. pseudointermedius* n=1, *S. lentus* n=1) ;
416 MRoCONS : Methicillin resistant other Coagulase Negative staphylococci (*S. haemolyticus*
417 n=4 , *S. pettenkofferi* n=4, *S. hominis* n=2, *S. lugdunensis* n=1, *S. caprae* n=1, *S. capitis* n=1);
418 FA : Fusidic Acid.

419

420 **Figures caption**

421 **Figure 1:** Number of Fusidic Acid (FA) susceptible and resistant *Staphylococcus spp* strains
422 and FA consumption between June 2017 and May 2021. * 2017 FA consumption
423 corresponded to the whole year and not only the period June to December. ** 2021 FA
424 consumption not yet available.

425

426