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1 Antibiotic prophylaxis of infective endocarditis in patients with predisposing cardiac
2 conditions: French cardiologists' implementation of current guidelines

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31 Keywords: Infective endocarditis; antibiotic prophylaxis; guideline; compliance

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33

34 **Abstract**

35 **Background:** To prevent infective endocarditis (IE), with the exception of the United
36 Kingdom, antibiotic prophylaxis (AP) is recommended in patients with predisposing cardiac
37 conditions (PCCs) worldwide. To conclude on the relevance of this strategy, how the current
38 guidelines are applied is a crucial point to investigate. The first aim of this study was to assess
39 cardiologists' implementation of the current guidelines. The secondary objective was to
40 identify specific areas where the training and knowledge of French cardiologists could be
41 improved . **Methods:** A national online survey was carried out among the 2228 cardiologist
42 members of the French Society of Cardiology. **Results:** The high risk PCCs for which IE AP
43 is recommended were correctly identified by the vast majority of the respondents so that IE
44 AP is mostly prescribed correctly in such patients. But only 12% identified all the right
45 indications for IE AP according to 13 predefined PCCs (3 at high-risk, 6 at moderate-risk and
46 4 at low-risk of IE) so that some IE AP misuses are recorded, overprescription in particular.
47 Only 47% prescribed the proper amoxicillin schedule and only 15% prescribed the
48 appropriate clindamycin schedule in cases with penicillin allergy. **Conclusion:** This study
49 evidenced relevant areas where the training of cardiologists could be improved such as
50 knowledge of the risk of IE for certain PCCs and some common invasive dental procedures.
51 Cardiologists' knowledge should be improved before any conclusion can be drawn on the
52 relevance of this AP strategy and its influence on IE incidence.

53

54 **Keywords:** Infective endocarditis; antibiotic prophylaxis; guideline; compliance

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56

57 **Introduction**

58 Infective endocarditis (IE) is a rare (< 7 cases per 100,000 persons per year) and severe
59 disease (20% early mortality, 40% at 5 years) [1]. A causal link between IE and the oral
60 cavity has long been assumed, [2] stemming from bacteremia and particularly oral
61 *Streptococcus* resulting from invasive dental procedures [3]. To prevent IE, antibiotic
62 prophylaxis (AP) has been recommended in the United States since 1955 for patients with
63 predisposing cardiac conditions (PCCs) undergoing invasive procedures [4]. The AP
64 prescription strategy is based on the recognition of a PCC that carries a risk of developing IE
65 and a procedure at risk of causing IE bacteremia. Whether AP is a crucial factor for the
66 prevention of IE remains debatable since three case-control studies evidenced an association
67 between dental procedures and streptococcal IE [5-7], whereas three others did not [8-10]. But
68 before any conclusion may be drawn, the primary question, as suggested by several authors, is
69 whether the current guidelines are correctly implemented by the main prescribers of IE AP,
70 i.e., dentists and cardiologists [11, 12].

71 A recent survey among French dentists illustrated their lack of knowledge and
72 implementation of the current guidelines [13]. However, to date no data have been produced
73 for a population of general cardiologists. Only very specific data on pediatric cardiologists or
74 congenital heart disease (CHD) specialists regarding the compliance with the 2007 AHA
75 guidelines [14] are available [15-17]. All of them highlighted the correct identification of
76 PCCs at high risk of IE by the cardiologic populations surveyed but all of them underlined IE
77 AP overprescription for PCCs at moderate risk of IE that no longer require IE AP or for some
78 PCCs with a low risk for IE with no indication for IE AP.

79 The aim of this study was to assess cardiologists' knowledge regarding implementation of the
80 current European Society of Cardiology (ESC) guidelines for IE AP in a wide practitioners'

81 population and **second**, to identify specific areas where the training and knowledge of French
82 cardiologists could be improved.

83 **Methods**

84 **1.1 Study design**

85 An online national survey was carried out among the 2228 cardiologist members of the
86 French Society of Cardiology (FSC) in 2014. The survey was anonymous and was approved
87 by the French data protection agency (agreement no. 169 83 56).

88 **1.2 Data collection**

89 A tailored anonymous questionnaire comprising 40 questions was constructed, mostly based
90 on a previous survey managed by the Association for the Study and Prevention of Infective
91 Endocarditis (AEPEI) in 2012 among French dentists [13].

92 This questionnaire was divided into four parts: 1/ demographic and practice-related
93 characteristics: age, gender, type of practice; 2/ knowledge of patients at high risk of IE:
94 knowledge of the definition of an invasive dental procedure, knowledge of the IE risk of 13
95 predefined IE PCCs (three PCCs with high risk for IE, six PCCs with moderate risk for IE and
96 four with low risk for IE), knowledge of the indication for an AP according to the same 13
97 predefined PCCs; 3/ knowledge of IE AP: knowledge of the indication for IE AP according to
98 13 predefined PCCs for IE and for a patient with a valvular prosthesis according to seven
99 dental procedures, knowledge of the antibiotics recommended for an IE AP, knowledge of the
100 IE AP schedule (dosage, number and time of intake); 4/ applicability of the current
101 guidelines: criteria of choice for an IE AP, changes in the prescription habits of an IE AP.

102 The questionnaire was formatted on the SurveyMonkey software (SurveyMonkey Europe
103 Sarl, Luxembourg). Its validity had been previously ascertained among a limited cohort of 10
104 hospital physicians. Thereafter, a survey link was sent to all members of the FSC and was

105 posted on its website for 2 months. No incentive was given to the responders and a recall was
106 performed a couple of weeks before the closing date.

107 **1.4 Data analysis**

108 Descriptive statistics were performed using Microsoft Excel 2007. Then the data were
109 compared using the chi-square test or the Fisher test. Differences were considered significant
110 if $p < 0.05$.

111 **Results**

112 **2.1 Demographic and practice-related characteristics of the respondents**

113 Two hundred sixty-five cardiologists responded to the survey (crude response rate: 13.4%);
114 nine were excluded because the questionnaire was not fully completed and 13 because the
115 data were unusable. The 243 remaining were included (true response rate: 12.3%). The
116 male/female ratio was 2.2 and practitioners were mainly 35–50 years (38%) and 51–60 years
117 of age (32%) with a hospital-based practice (60%).

118 **2.2 Knowledge of patients at high risk of IE and IE AP**

119 For 61% of the respondents, an invasive dental procedure is defined as a procedure requiring
120 manipulation of the gingival or perforation of the oral mucosa but for only 56% as a
121 procedure inducing significant bacteremia, i.e., the right definition (multiple choice question).

122 Among the 13 different predefined PCCs, the three high-risk conditions for IE (prosthetic
123 cardiac valve, previous IE, unrepaired cyanotic CHD) were correctly identified as PCCs at
124 high risk for IE by at least 92% of the cardiologists (Figure 1). Mitral valve prolapse was
125 correctly identified by 70% of the cardiologists as a PCC at moderate risk for IE; 9% of the
126 respondents considered this condition as a PCC with a high risk of IE. All other PCCs
127 carrying a moderate risk were correctly identified by at least 68% of the cardiologists, except
128 tricuspid valve and functional mitral valve failures by only 49% and 36%, respectively
129 (Figure 2). Regarding the PCCs with a low risk for IE, three of them, arterial hypertension,

130 coronary artery disease and coronary bypass, were correctly identified by at least 94% of the
131 respondents. Regarding most particularly pacemakers and implantable cardioverter
132 defibrillators, only 23% of the cardiologists correctly identified them as PCCs with a low risk
133 for IE, 60% of the respondents considering pacemakers and implantable cardioverter
134 defibrillators as PCCs with a moderate risk for IE.

135 Taken together, only 18% of the cardiologists correctly identified the risk of developing IE
136 for all the 13 predefined PCCs.

137 Of these 13 predefined PCCs, at least 93% of the cardiologists correctly identified the three
138 high-risk conditions for IE requiring an IE AP before an invasive dental procedure (Figure 2).

139 Regarding PCCs with a moderate risk for IE, mitral valve prolapse was correctly identified as
140 not requiring IE AP before an invasive dental procedure by 76% of the cardiologists but 21%
141 of the respondents overprescribed IE AP for this condition. Cardiologists overprescribed IE
142 AP by a large amount for two other PCCs at moderate risk of IE, i.e., 30% for functional
143 mitral valve failure and 29% for bicuspid aortic valve. Arterial hypertension, coronary artery
144 disease and coronary bypass were identified as not requiring IE AP before an invasive dental
145 procedure by at least 95% of the cardiologists. Regarding pacemakers and implantable
146 cardioverter defibrillators, although classified as a PCC with a low risk for IE, 18% of
147 cardiologists overprescribed IE AP before invasive dental procedures.

148 Taken together, only 12% of the cardiologists identified all the right indications for IE AP
149 according to the 13 predefined PCCs,

150 **2.3 Knowledge of the IE AP indication in regard to dental procedures.**

151 Among seven different dental procedures, five required IE AP in high-risk patients. Three of
152 them were correctly identified by at least 89% of the cardiologists (dental extraction, surgical
153 management of soft tissue or bone tissue), but endodontic treatment of vital monoradicular
154 tooth and scaling were less often recognized as warranting IE AP (73% and 65% of the

155 **respondents respectively**) (Figure 3). The two procedures that did not require IE AP
156 (treatment of caries without pulp exposure and prosthetic preparation) were correctly
157 identified by only 65% and 30% of the **respondents respectively**.

158 Taken together, only 25% of the cardiologists correctly identified all seven predefined dental
159 procedures.

160 Regarding invasive dental procedures in a high-risk patient, **cardiologists** correctly prescribed
161 more IE AP for **tooth extraction than for** endodontic treatment of a vital monoradicular tooth
162 and scaling (**89% vs 75% vs 58%**, respectively; $p < 0.001$).

163 An appropriate amoxicillin first-line prescription for IE AP was given by 90% of the
164 respondents but only 47% according to the right schedule: a 2-g single dose 1 h before the
165 invasive dental procedure, the main misapplication being a 3-g dosage of amoxicillin. In case
166 of allergy to penicillin, only 15% prescribed the appropriate second-line drug (clindamycin) at
167 the right dosage (600 mg).

168 **2.4 Applicability of the current guidelines**

169 The IE AP prescription of the vast majority of the respondents (95%) was declared to be
170 based on **ESC** current guidelines [11], whereas the remaining declared basing prescriptions on
171 their own clinical experience. Regarding **these** guidelines, 16% of the cardiologists declared
172 they had not changed their usual IE AP prescription from the previous 2002 guidelines of the
173 French Society of Infectious Diseases (previously applicable guidelines by French
174 cardiologists) [18].

175 **Discussion**

176 To our knowledge, this is the first study specifically devoted to evaluating the self-assessment
177 of **ESC** guidelines for IE prevention in a general cardiologist population. The main results
178 showed that cardiologists were overall well aware of these recommendations. **Importantly, the**
179 **high risk PCCs for which IE AP is recommended in case of invasive procedures, were**

180 correctly identified by the vast majority of the respondents except some seldom CHD mostly
181 managed by cardiologists with a specialist interest. So, it is likely that cardiologists generally
182 prescribed IE AP correctly in such patients. But significant misunderstandings were
183 highlighted in this study. An IE AP overprescription was still recorded for some PCCs at
184 moderate and low risk of IE, whereas some invasive dental procedures at risk of IE
185 bacteremia were not accurately identified, inducing IE AP underprescription. Interestingly,
186 this study provided specific areas where the training of cardiologists could be improved.
187 This survey demonstrated that cardiologists' knowledge of the different IE risk levels
188 according to PCCs varied greatly. The main change introduced by the ESC guidelines
189 (endorsing 2007 AHA guidelines [14]) was the limitation of AP to a population of patients
190 with PCCs putting them at high risk for IE. In the present study, these three PCCs were
191 clearly identified as an indication for IE AP by at least 92% of the respondents, in accordance
192 with other studies [15, 17]. But the good knowledge of PCCs at high risk of IE doesn't
193 necessarily induce an appropriate management of patients at high risk of IE. In a crossover
194 study about patients with prosthetic heart valves, Tubiana et al., highlighted that only
195 approximately half received IE AP when undergoing an invasive dental procedure [7].
196 Moreover, about 25% of such patients received an inappropriate IE AP prescription for a non
197 invasive dental procedure. But whether the IE AP prescription came from cardiologists or
198 from dentists was not recorded in this study.

199 However, in some studies, the residual IE risk of some repaired CHDs appeared variously
200 appreciated by specialized cardiologists such as perimembranous ventricular septal defect
201 with no residual shunt or corrected tetralogy of Fallot with no residual shunt, inducing
202 overprescription of IE AP [15-17]. Surprisingly, some cardiologists were less likely to
203 recommend IE AP for patients at high risk for IE, mainly because some palliated cyanotic
204 CHD cases are classified as being at high risk of IE by some authors [15] and at low risk for

205 IE by others [16], such as Fontan palliation. However, our questionnaire was not intended to
206 investigate such conditions. ESC guidelines appeared potentially ambiguous and need more
207 specifications for certain cyanotic PCCs. Moreover, the responses also appeared ambiguous
208 for PCCs with a moderate risk for IE, which no longer required IE AP for invasive dental
209 procedures. This induced IE AP misuse, sometimes considerable, more than 30%
210 overprescription for organic mitral valve failure or bicuspid aortic valve. Such tendencies
211 were also recorded for rheumatic heart disease with aortic insufficiency or aortic stenosis in a
212 limited cohort of cardiologists [11,18]. For such PCCs with a moderate risk for IE, highly
213 experienced cardiologists were more likely not to prescribe IE AP than their less experienced
214 counterparts [16]. We did not evidence this correlation in our study, possibly because the
215 study reported by Patel et al. was conducted only in pediatric cardiologists less aware of some
216 of these conditions that are more frequent in an adult population. We cannot exclude that
217 some cardiologists had shown reluctance to discontinue IE AP in individuals who are
218 accustomed to receiving IE AP. Recognition of the IE risk of these diseases and the fact that
219 IE AP was unnecessary for invasive dental procedures clearly appear as specific points that
220 could be improved in the cardiologists' training. The PCCs at low risk for IE were clearly
221 identified and did not induced IE AP misuse except for one condition, pacemakers and
222 implantable cardioverter defibrillators. This condition was inappropriately classified as a PCC
223 with a moderate risk for IE by more than 70% of the respondents and was a source of IE AP
224 overprescription by 20% of them. This is clearly another specific point to improve in the
225 cardiologists' training. **These misuses of IE AP was pointed out by the NICE (National**
226 **Institute for health and Clinical Excellence - that recommended complete cessation of IE AP**
227 **whatever the IE risk in UK in 2008), to lead to a greater number of deaths through fatal**
228 **anaphylaxis than a strategy of no AP, to favor antibiotic resistance and not to be cost-effective**
229 **[20]. But no fatal anaphylaxis after oral amoxicillin IE AP has been recorded in France and**

230 worldwide for decades whereas alternative clindamycin AP regimen for patients allergic to
231 penicillin could be a greater source of adverse drug reactions including fatalities [14, 21-22].
232 A strategy of directing AP at patients at high risk of IE is likely to be cost-effective even at
233 low rates of AP clinical effectiveness [23]. The impact of antibiotic resistance associated with
234 IE AP has not been formally assessed but antibiotic resistance is believed to be encouraged
235 when repeated courses of antibiotics at inadequate doses are given and is minimized by
236 infrequent doses of antibiotics at high doses as for IE AP [24].

237 As expected, cardiologists were less accurate in the identification of invasive dental
238 procedures inducing bacteremia than in the identification of PCCs, except tooth extraction
239 and surgical management of soft tissue or bone tissue. It is worrying that approximately 40%
240 of the cardiologists do not prescribe IE AP for scaling in a high-risk patient since it is a very
241 common invasive dental procedure. It is not surprising that more specific dental procedures
242 such as invasive endodontic treatment of vital monoradicular tooth or noninvasive treatment
243 of caries without pulp exposure were correctly identified by a small part of the cardiologists.
244 These mistakes probably reflect the too general definition of an invasive dental procedure in
245 the ESC guidelines: “procedures requiring manipulation of the gingival or the periapical
246 region of the teeth or perforation of the oral mucosa” [11]. Of course cardiologists are not
247 dentists but they are often the first line specialists to whom patients at high risk of IE ask for
248 information about the risk associated with some dental (and not dental) invasive procedures.
249 Thus, it could be important that cardiologists are aware of the most frequent risky dental
250 procedures as those that are not risky. This is also a clear point revealed in this study to
251 improve.

252 Regarding the IE AP prescription, although the vast majority of the cardiologists correctly
253 identified the two recommended antibiotic drugs (amoxicillin and clindamycin in case of
254 allergy to penicillins), only 47% prescribed the right regimen of 2 g of amoxicillin or 600 mg

255 of clindamycin 1 h before the invasive dental procedure. The main misapplication was a 3-g
256 dosage of amoxicillin (instead of 2 g in the current guidelines) accordingly to the 2002
257 guidelines of the French Society of Infectious Diseases [18].

258 The ESC guidelines were globally considered as applicable, clear, well presented and easily
259 accessible by a majority of the respondents. This is of huge importance given that clinicians'
260 compliance to guidelines firstly depends on factors related to their readability [19]. **But these**
261 **factors are not sufficient to induce a good implementation of guidelines. Assessment of the**
262 **cardiologist compliance to the NICE guidelines in UK or in Ireland through questionnaire**
263 **based surveys revealed that if the vast majority was aware, only a small part of them based**
264 **their practice on these guidelines [25, 26]. Most of these cardiologists clearly feel that AP still**
265 **has a role in certain conditions (patients with prosthetic heart valve or patients with prior IE)**
266 **and refer to alternative guidelines in case of invasive dental procedures.**

267 This study has highlighted major differences regarding IE AP between dentists and
268 cardiologists. As expected, PCCs and the related IE risk appear better identified by
269 cardiologists. **A nationwide survey of French dentists' knowledge and implementation of**
270 **current guidelines for antibiotic prophylaxis of infective endocarditis in patients with**
271 **predisposing cardiac conditions showed that** high risk for IE are recognized by both
272 specialties, but dentists clearly identify unrepaired cyanotic CHD less easily [13]. This
273 difference is also recorded in the Anguita et al. study [27], probably due to dentists not having
274 knowledge of this type of heart disease, whose incidence is increasing in the general
275 population because of improved survival. PCCs with low and moderate risk for IE that no
276 longer require IE AP also appear better identified by cardiologists except for pacemakers and
277 implantable cardioverter defibrillators, better identified by dentists [13]. Interestingly, this
278 specific finding is also recorded in the Anguita et al. study [27]. Targeted information on this
279 specific point is needed in training for cardiologists.

280 As expected, dentists identify invasive dental procedures better, whether or not they require
281 IE AP [13]. This could be explained by the exhaustiveness of the guidelines for dentists. The
282 2011 ANSM guidelines endorsed the ESC 2009 guidelines but added a large descriptive
283 section regarding invasive dental procedures [12]. This study underscores that cardiologists
284 have to be better informed about the most frequent invasive dental procedures such as scaling.
285 The misunderstandings we observed led to more declarations of IE AP overprescription from
286 cardiologists for noninvasive dental procedures and more underprescription for invasive
287 dental procedures compared to dentists [13].

288 In this study, the cardiologists had a hospital-based practice more frequently than did the
289 dentists, who worked more often in individual primary-care private practice [13]. This
290 difference may in part explain the discrepancies in the knowledge of the current guidelines
291 **between both specialists, dentists knowing less well their dedicated guidelines [13].** Hospital
292 practitioners are generally more aware of new developments, keep informed on a regular basis
293 by attending conferences more frequently and become more involved in writing or
294 disseminating recommendations to colleagues and students. Moreover, they are more often in
295 charge of patients at risk for IE.

296 This study has a number of unavoidable methodological drawbacks, as do most survey studies
297 examining self-assessment of guideline implementation. Only FSC members, accounting for
298 approximately 32% of the French cardiologist population, were questioned [28]. Despite the
299 low 12.3% true response rate to this online survey, the number of these responses made this
300 study one of the most reliable. Even though only 243 responses were included in this survey,
301 the profile of the respondents is roughly comparable to that of the French cardiologist
302 population according to gender and age distributions [29]. It can also be questioned to what
303 extent questionnaire respondents were those who knew the ESC guidelines best, which may
304 have resulted in an overestimation of guideline implementation. Moreover, it should be

305 underlined that both surveys were conducted at different times after guideline publications.
306 The present cardiologists' survey was conducted 5 years after the 2009 ESC guidelines were
307 published, whereas the dentists' survey was carried out only 1 year after the 2011 ANSM
308 guidelines appeared. This was probably not long enough for a full completion of new
309 guidelines because adoption of new habits always requires time [29].

310 Despite these limitations, this prospective study is the largest and the most detailed survey to
311 date on IE AP in a general cardiologists' population.

312 In conclusion, although IE incidence has not increased in France since the restriction of IE AP
313 [30], the interpretation of this result is confusing given the low level of **complete**
314 implementation of ESC guidelines revealed by this survey. It is crucial to improve compliance
315 with current guidelines by sustaining continuous medical education in the training of French
316 cardiologists, particularly on specific areas revealed by this survey: **regular dedicated sessions**
317 **are organized during international, national and local meetings and guidelines and information**
318 **are easily available on several websites** (www.escardio.org, www.endocardite.org,
319 www.cardio-online.fr, www.fedecardio.org). It also seems necessary to strengthen the
320 dialogue between cardiologists and dentists and organize shared education sessions. Only then
321 can the relevance of such guidelines be properly assessed.

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326

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411 **Figure legends**

412 Figure 1: Identification by cardiologists of infective endocarditis (IE) risk for patients with
413 various cardiac conditions according to the current ESC guidelines. % Values in the
414 histograms underlined the correct rate answer. CHD: cyanotic heart diseases; RHD: rheumatic
415 heart disease; ICD: implantable cardioverter defibrillators; CABG: coronary artery bypass
416 grafting.

417 Figure 2: Identification by cardiologists of indications for infective endocarditis (IE)
418 antibiotic prophylaxis for various cardiac conditions according to the current ESC guidelines.
419 % Values in the histograms underlined the correct rate answer. CHD: cyanotic heart diseases;
420 RHD: rheumatic heart disease; ICD: implantable cardioverter defibrillators; CABG: coronary
421 artery bypass grafting.

422 Figure 3: Identification by cardiologists of dental procedures requiring or not antibiotic
423 prophylaxis for a patient with a valvular prosthesis according to the current ESC guidelines.
424 % Values in the histograms underlined the correct rate answer. CHD ET: endodontic
425 treatment.

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