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1 **Clinical Microbiology and Infection – Narrative Review**

2 **Aminoglycosides for infective endocarditis: time to say goodbye?**

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19

20 **Key-words:** Aminoglycoside, endocarditis, gentamicin, acute kidney failure, synergism

21

22 **Abstract**

23 **BACKGROUND:** Based on experimental studies showing synergism with β -lactams and glycopeptides,
24 aminoglycosides have long been considered essential in the treatment of infective endocarditis (IE).
25 However, their use is associated with a high risk of renal failure, especially in elderly patients.

26 **OBJECTIVES:** The aim of this narrative review was to summarize the evidence to support reducing or
27 even avoiding the use of aminoglycosides for the treatment of IE. We also analysed data supporting
28 the use of aminoglycosides in specific subgroup of IE patients.

29 **SOURCES:** PubMed database was searched up to July 2019 to identify relevant studies.

30 **CONTENTS:** Recent European Guidelines reduced the use of aminoglycosides in IE, no longer
31 recommended in *Staphylococcus aureus* native-valve IE, and shortened to 2 weeks for IE related to
32 *Enterococcus faecalis* and streptococci with penicillin MIC > 0.125 $\mu\text{g}/\text{mL}$. In addition, alternative
33 regimen without aminoglycosides (ampicillin or amoxicillin plus ceftriaxone) is proposed for *E.*
34 *faecalis*. Observational studies suggested that gentamicin would not be necessary in the case of
35 staphylococcal prosthetic-valve IE as long as rifampicin is maintained. Recent clinical studies showed
36 that for streptococcal IE, gentamicin could be restricted to isolates with penicillin MIC > 0.5 $\mu\text{g}/\text{mL}$.
37 For the empirical and definitive treatment of *E. faecalis* IE, amoxicillin or ampicillin plus ceftriaxone
38 may be considered, irrespective of high-level of aminoglycoside resistance.

39 **IMPLICATIONS:** In a scenario of progressive increase in the age and frailty of IE patients, the use of
40 aminoglycosides can be reduced or avoided in ~90% cases. This should result in reduced incidence of
41 renal failure, an important prognostic factor in IE.

42

43 **Introduction**

44 Infective endocarditis (IE) is a severe disease associated with a ~20% in-hospital mortality and a
45 frequent necessity of cardiac surgery [1, 2]. Optimizing antibiotic regimen is of paramount
46 importance to reduce not only mortality but also valvular damages [3]. Historically, aminoglycosides
47 (AG) were considered as a cornerstone for treatment in IE caused by streptococci, enterococci and
48 staphylococci (altogether responsible for >80% of all IE [4]), mostly because of *in vitro* and *in vivo*
49 data demonstrating synergism with β -lactam or glycopeptide antibiotics [5-8]. However, their use is
50 associated with a high risk of kidney failure, a major prognostic factor in IE [9-12]. Aminoglycoside-
51 induced cochleotoxicity may also have severe consequences [13].

52 In recent years, the median age of IE patients has increased, as did the number of comorbidities [14].
53 About one-third of *Enterococcus faecalis* and *Staphylococcus aureus* IE patients suffer from chronic
54 renal failure [11, 15]. Furthermore, 30-50% of them experience acute kidney dysfunction because of
55 IE-induced glomerulonephritis, septic shock, antibiotic nephrotoxicity, acute heart failure, use of
56 iodinated contrast material and complications of cardiac surgery [11, 15]. Most studies consistently
57 reported that kidney failure at admission was associated with worse outcome during IE. Prospective
58 cohort studies identified that creatinin serum >2 mg/dL, or reduced creatinine clearance at
59 admission were associated with increased mortality [9, 16]. More debated is the prognostic impact
60 of acute kidney failure during treatment of IE. An older retrospective study identified that one-third
61 of patients developed acute renal failure (serum creatinine ≥ 2 mg/dL), associated with a 5-fold
62 increase in mortality [17]. Furthermore, after cardiac surgery for active IE, acute kidney injury (AKI) is
63 also associated with the use of AG [12].

64 Efforts to refine and reduce AG use during IE are of critical importance in order to avoid side effects.
65 Clinical studies demonstrated that indications and duration of AG could be reduced [10, 11, 18, 19].
66 This narrative review investigated whether AG could be avoided or reduced in IE treatment regimen.

67

68 **Strategy for data search**

69 Data were obtained from articles published in English and indexed in PubMed up to July 2019. We
70 also searched the reference lists of retrieved papers.

71

72 **Why were aminoglycosides considered so important in the treatment of IE?**

73 Initially, guidelines recommended at least two weeks of AG for all IE, and four to six weeks for *E.*
74 *faecalis* IE [20, 21]. These statements were mostly influenced by *in vitro* and *in vivo* studies
75 demonstrating synergism between β -lactams or glycopeptides, and AG [7, 8].

76 *In vitro*, several studies reported a frequent tolerance ($\frac{3}{4}$ of clinical isolates) of *E. faecalis* towards
77 penicillin, defined by: *i*) less than a 3-log reduction of bacterial survival in the presence of penicillin
78 and *ii*) higher MBC:MIC ratios [22, 23]. *In vivo*, animals infected with a tolerant *E. faecalis* strain have
79 lower rates of vegetation sterilization, as compared to non-tolerant *E. faecalis* (25% vs. 90% sterility,
80 respectively) when treated with penicillin G [23]. In the early 50's, it was shown that this tolerance
81 could be reduced and even abolished with the adjunction of AG to penicillin [24]. *In vivo*, several
82 groups reported that penicillin-AG regimens were associated with faster reduction of bacterial
83 counts in vegetation, and valve sterilisation rates, in rabbit endocarditis [7, 25]. However,
84 discrepancies were observed in the late 90's: Even if low frequency (<40%) of valve sterility was
85 obtained with a 28 day-course of high-dose penicillin in rabbits IE, 100% valve sterilization rates were
86 obtained with high-dose ampicillin for 21 days, without AG [26, 27]. These conflicting data suggest
87 the influence of model variability, and level of *E. faecalis* tolerance, a phenotype that has been
88 shown not to be constant in this species [22]. Furthermore, data obtained with penicillin G may not
89 be extrapolated to other penicillins, such as ampicillin or amoxicillin. Amoxicillin MIC for
90 *Enterococcus* spp. is about 4 times lower than that of penicillin [28]. Furthermore, time-kill
91 experiments on 15 strains of *E. faecalis* found that amoxicillin was more bactericidal than ampicillin
92 or penicillin, alone and in combination with tobramycin [29].

93 For streptococci, the tolerant phenotype is possible, though rare: in the Netherlands (1986-88), only
94 11% of 135 randomly selected streptococci responsible for IE were tolerant to penicillin, as defined
95 by a survival rate $\geq 0.15\%$ after 24 hours of exposure [28].

96 In line with *in vitro* and *in vivo* data, uncontrolled clinical studies also advocated for penicillin-AG
97 combination for *E. faecalis* IE. Clinical use of penicillin gave disappointing results, as compared to
98 non-*E. faecalis* IE, and streptomycin-containing regimen were more effective in early observational
99 studies [30]. Conversely, for penicillin-susceptible oral streptococci, single-drug regimen with
100 intravenous penicillin G yielded high cure rates ($>95\%$) suggesting that adding AG would not provide
101 any benefit [31].

102 Lastly, *Staphylococcus* spp. IE experimental studies demonstrated decades ago synergism between
103 penicillinase-resistant penicillin or vancomycin, and AG, *in vitro* and *in vivo* [32, 33].

104 Despite this huge amount of experimental data demonstrating synergism between AG and β -lactam
105 agents, clinical studies performed afterwards may allow to reduce indications of AG for IE.

106

107 **Moving to a clinical rationale: 2015 European and American guidelines**

108 These guidelines stated that AG use should be reduced or avoided in three settings: *E. faecalis* and
109 streptococci IE, and *S. aureus* native valve IE [5, 6].

110 For wild-type *E. faecalis* IE, two observational studies suggested that a 2-week AG regimen was
111 associated with similar outcome (mortality, relapse) with less frequent acute kidney injury, as
112 compared to historical cohorts using 4-6 weeks of AG [10, 34]. Specifically, a prospective Swedish
113 study of 93 *E. faecalis* IE episodes [29% on prosthetic valves (PV)], reported a median duration of AG
114 of 15 days (from no AG to >49 days) with a 81% cure rate and a 3% risk of relapse, that was
115 comparable to previous experience with 24-42 days of AG [34]. More recently, a Danish before/after
116 study compared the outcome of 41 left-sided *E. faecalis* IE treated between 2002 and 2007
117 (gentamicin median duration, 28 [18-42] days) and 43 episodes between 2007 and 2011 (gentamicin

118 median duration, 14 [7-15] days) [10]. Relapse and mortality rates were comparable in both groups,
119 and median estimated Glomerular Filtration Rate at discharge was higher in the second period.
120 Another emerging strategy to avoid AG for the treatment of *E. faecalis* IE relies on the synergy of
121 ampicillin or amoxicillin with third-generation cephalosporins (cefotaxime or ceftriaxone) [35], a
122 combination that can be used irrespective of high-level aminoglycoside resistance (HLAR). *In vitro*,
123 the addition of 4 µg/mL of cefotaxime reduced amoxicillin MIC of 48 out of 50 *E. faecalis* strains [35].
124 This synergy is likely due to the saturation of different penicillin-binding proteins (PBPs) by
125 amoxicillin (PBP4 and 5) and cefotaxime (PBP2 and 3), all these PBPs being constitutively expressed
126 in *E. faecalis*. A Spanish multicenter cohort study compared 159 *E. faecalis* IE treated with the
127 ampicillin-ceftriaxone combination and 87 cases treated with ampicillin-gentamicin combination
128 [11]. In 51 (32%) *E. faecalis* IE treated with ampicillin-ceftriaxone, the causal strains exhibited HLAR.
129 Mortality and relapse rates were comparable, but adverse events leading to treatment alteration
130 were more frequent in the ampicillin-gentamicin group (25%), than in the ampicillin-ceftriaxone
131 group (1%) [11]. More recently, a retrospective study of 85 *E. faecalis* IE treated with ampicillin-
132 gentamicin (n=67), or ampicillin-ceftriaxone (n=18) reported similar clinical outcomes, but patients
133 who received ampicillin-gentamicin had a greater increase in serum creatinine at end of therapy [36].
134 For *S. aureus* native valve IE, several prospective studies found no benefits of adding AG [18, 37, 38].
135 These studies mostly included right-sided IE among intravenous drug users and compared the use of
136 penicillinase-resistant penicillin alone and in combination with AG. None observed any clinical
137 benefits or any impact on bacteriologic failures or relapses. A meta-analysis also demonstrated that
138 adjunction of AG in the treatment of *S. aureus* native valve IE increased nephrotoxicity [39].
139 For streptococci, international guidelines acknowledge the importance of defining treatment based
140 on penicillin MIC. In case of penicillin MIC > 0.125 mg/L, both guidelines recommend at least 2 weeks
141 of AG-penicillin combination despite a lack of comparative data (see below) (**Table 1**) [5, 6].

142

143 **AG-free regimen for all IE?**

144 AG-free regimen could be considered for *E. faecalis* IE, which account for ~10% of all IE [40, 41]. HLAR
145 phenotype is observed in up to 38% of the cases [10, 40, 41], and may be emerging: the prospective
146 Spanish cohort study reported an increase of HLAR from 20% (1997-2001) to 50% (2007-2011) in *E.*
147 *faecalis* isolates responsible for IE [19]. Ampicillin or amoxicillin plus third-generation cephalosporin
148 regimen could be used empirically as a first-line treatment, before antibiotic susceptibility testing.
149 Second, patients with *E. faecalis* IE are older than patients with non-*E. faecalis* IE, with more
150 comorbidities, hence at higher risk of AKI [40]. At diagnosis, 18-29% of patients have chronic kidney
151 dysfunction [10, 11]. Ampicillin-ceftriaxone combination may be considered as a kidney function-
152 sparing regimen for these patients. However, a recent randomized controlled trial demonstrated that
153 a switch to oral treatment after 10 days of intravenous antibiotics in patients with left-sided IE
154 caused by staphylococci, streptococci, or enterococci, was non-inferior to a complete IV antibiotic
155 course [42]. It means that after a 2-week ampicillin-gentamicin regimen, patients may be switched to
156 oral treatment to reach 4-6 weeks of antibiotics. Conversely, ampicillin-ceftriaxone regimen has only
157 been assessed with both drugs during 4 to 6 weeks, and cohort studies suggested that treatment
158 duration should not be shorter than 6 weeks [43]. This prolonged parenteral treatment may be
159 associated with IV-line related side effects and ecological consequences on gut microbiota. To
160 identify an effective single-drug regimen for the complete course of *E. faecalis* IE treatment is more
161 challenging [44]. No comparative study ever demonstrated the benefits of adding AG or third-
162 generation cephalosporins to penicillin in this setting. The wide-spread belief that combination
163 therapy is mandatory for *E. faecalis* IE only stems from *in vitro*, and experimental animal studies, as
164 well as initial clinical studies with penicillin G which gave disappointing results (as compared to
165 streptococci IE) [7, 24, 25, 30]. However, this provocative but seducing approach requires additional
166 clinical data [44].

167 Regarding IE caused by streptococci with intermediate susceptibility to penicillin (penicillin MIC 0.25-
168 2 mg/L), guidelines recommend using AG for 2 to 6 weeks (**Table 1**) [5, 6]. This statement can be
169 challenged for several reasons. First, no prospective comparative study ever assessed the benefits of

170 adding AG in this setting. A recent retrospective French study including 414 patients with
171 streptococcal IE (mostly oral and *Streptococcus gallolyticus*) observed that streptococcal IE with
172 amoxicillin MIC between 0.25 and 2 mg/L had higher mortality rates, as compared to those with
173 lower MIC, but combination with AG was not associated with better outcome [45]. Focusing on
174 patients infected with streptococcal isolates with amoxicillin MIC of 0.125-0.5 mg/L, addition of AG
175 was not associated with survival (**Table 2**). On the microbiological point of view, even if penicillin MIC
176 of 0.25-2 mg/L is similar to penicillin MICs for *E. faecalis*, bacterial tolerance to penicillin is
177 uncommon in streptococci (10-20%), as compared to enterococci (75%) [28]. Furthermore,
178 streptococci with high penicillin MIC are rarely associated with IE: of 76 streptococcal isolates
179 responsible for IE in the 1980's, only one had ampicillin MIC >0.5 mg/L [46]. This phenotype may be
180 on the rise: a French study of streptococcal IE diagnosed between 2012 and 2017 found that 27% of
181 isolates had amoxicillin MIC between 0.25 and 2 mg/L, and 1% had MIC >2 mg/L [45]. Nevertheless,
182 150-200 mg/kg intravenous amoxicillin lead to high plasma concentrations: A retrospective study in
183 critically ill patients without IE demonstrated that continuous infusion of amoxicillin allowed plasma
184 concentration of at least 30 mg/L in most patients with normal kidney function [47]. Among 7 IE
185 patients receiving intravenous amoxicillin 12 g/d by continuous infusion, mean plasma concentration
186 was 18.5 mg/L [48], i.e. ~50-times the MIC for isolates with amoxicillin MIC of 0.5 mg/L.

187 This suggests that AG are not necessary for streptococcal IE with intermediate susceptibility for
188 amoxicillin (MIC, 0.25-0.5 mg/L), hence restricting the indication of AG for streptococcal IE with
189 amoxicillin MIC >0.5 mg/L.

190 For the management of IE caused by β -haemolytic streptococci, we recommend not adding AG to
191 antibiotic regimens for the following reasons: *i)* β -haemolytic streptococci are usually fully
192 susceptible to β -lactams, *ii)* they do not exhibit tolerance to penicillin and *iii)* no robust clinical data
193 support the use of AG in this setting [49].

194 Lastly, treatment of staphylococcal PVIE is not well established and experts follow guidelines in only
195 50-60% of the cases [50]. Currently proposed AG duration in this setting is 2 weeks, partly based on a

196 retrospective study of 10 *S. epidermidis* PVIE, with a lower mortality among patients who received
197 gentamicin (2/6, 33%), as compared to those who did not (3/4, 75%) [51]. A rabbit endocarditis
198 model found that in case of *S. epidermidis* IE, the combination of vancomycin, rifampicin and
199 gentamicin was associated with the highest rate of valve sterility, as compared to dual or single-drug
200 regimen [52]. More recent data suggest that the use of AG for staphylococci PVIE should be reduced
201 or even discontinued. A Spanish retrospective study of 94 *S. aureus* PVIE treated with β -lactam (or
202 vancomycin) plus rifampicin compared patients who received 2-week gentamicin regimen, and those
203 who did not [53]. Both groups were comparable in terms of severity (heart failure, perivalvular
204 abscess, surgical indication), and baseline characteristics. In-hospital and one-year mortality were
205 similar. Interestingly, these data are line with an older publication reporting that cure rates of *S.*
206 *epidermidis* PVIE were increased by the use of combination therapy but was comparable between
207 vancomycin-rifampicin-AG and vancomycin-rifampicin regimen [54]. Thus, one can consider that the
208 important factor associated with clinical success is rather the use of combination therapy than using
209 AG, *per se*. However, two studies reported the emergence of rifampicin resistance when rifampicin
210 was introduced at the beginning of IE treatment (when blood cultures are still positive). A
211 prospective study observed that rifampicin resistance developed in 37% of methicillin-resistant
212 coagulase-negative staphylococci PVIE treated with vancomycin plus rifampicin, as compared to 0%
213 in patients receiving vancomycin-rifampicin-gentamicin [55]. In native valve *S. aureus* IE, this
214 complication can be seen in up to 56% of the cases (9/16) [56].

215 We therefore propose to individualize AG duration for staphylococci PVIE: AG may be used in
216 absence of renal failure until valve surgery is performed (leading to a massive inoculum reduction)
217 for a maximum of 1 week or until blood cultures are negative, before being replaced by rifampicin.

218 Lastly, other groups proposed AG-free regimen for the treatment of *S. aureus* PVIE based on the
219 combination of high-dose daptomycin plus another molecule (fosfomicin, cloxacillin, cefazolin or
220 rifampicin, among others) [6, 57].

221

222 **4-Is there any situation in which there is insufficient evidence to avoid or reduce the use of**
223 **aminoglycosides?**

224 Several studies assessed 2-week antibiotic courses of dual treatment with β -lactam antibiotic and AG
225 for non-complicated left-sided native valve IE caused by fully-susceptible streptococci. First
226 uncontrolled studies reported high cure rates using intramuscular penicillin associated with
227 streptomycin [58, 59]. Other studies evaluated the association of ceftriaxone and netilmicin or
228 gentamicin used as short daily IV infusion, with favourable outcomes [60, 61]. The only controlled
229 study compared ceftriaxone and gentamicin for two weeks, and ceftriaxone alone for four weeks
230 [61], with clinical cure in 96% of patients in both arms.

231 Regarding *Bartonella* spp. IE, a retrospective study of 101 patients found that patients who received
232 AG during at least 14 days were more likely to recover [62], and gentamicin was the only bactericidal
233 antibiotic against *Bartonella* spp. on murine macrophage-like cells and in broth culture [63, 64].
234 However, *Bartonella* spp. IE may be cured with AG-sparing regimen (NHF, unpublished data).

235 Lastly, European guidelines recommend AG with ampicillin plus antistaphylococcal penicillin for the
236 empirical treatment of severe acute IE [6]. Conversely, the management of subacute non-severe
237 blood culture-negative IE (up to 10% of all IE cases) is poorly defined [5, 6]. Some experts
238 recommend AG with ampicillin or amoxicillin, considering that negative blood cultures rule out *S.*
239 *aureus* IE, but this may not apply to patients who received antibiotics active on staphylococci prior to
240 blood cultures sampling. Ampicillin-ceftriaxone could be an alternative empirical treatment for
241 subacute IE, since it covers streptococci, *E. faecalis*, HACEK, and has activity against *Bartonella*.
242 Another strategy would be to use amoxicillin as a single-drug regimen in this setting, as proposed by
243 some experts.

244

245 **Conclusions and implications for future research**

246 The constant epidemiological changes of IE, with ageing and frail populations, with comorbidities
247 forces a paradigm shift in the antimicrobial treatment, moving from *in vitro/in vivo* experimental

248 data to clinical rationale. This leads to a significant reduction of the use of AG in IE. This narrative
249 review suggests that we could go further for *staphylococcal* PVIE, *E. faecalis* and streptococci IE, and
250 empirical treatment of subacute IE or blood culture-negative IE, implying that AG use could be
251 reduced or avoided in ~90% of IE cases [4, 65].

252 Treatment of IE is long (2-6 weeks), and the severity of IE may lead to underestimate side-effects of
253 antibiotic treatments. However, given the high risk of nephrotoxicity with AG, and the strong impact
254 of renal failure on outcome, reduced use of AG would most likely be beneficial. Although we
255 identified several situations when AG may be avoided during IE treatment, most data come from
256 experimental, or observational clinical studies. Randomized clinical trial comparing AG-sparing
257 regimen, to standard regimen, would be most welcome, although these are challenging due to the
258 low incidence of IE, and limited funding opportunities. In our opinion, the two main priorities for
259 such trials in the forthcoming years would be: i) amoxicillin/ampicillin associated with a 2 week-
260 course of gentamicin, or with ceftriaxone/cefotaxime, for *E. faecalis* IE; ii) antistaphylococcal agent
261 associated with rifampicin, with or without gentamicin, for staphylococcal PVIE.

262

263 **Transparency declaration**

264 **Conflict of interest:** JLM has received consulting fees (scientific advisor for ceftolozane-
265 tazobactam, Merck Sharp and Dohme and scientific advisor from BioAster) and
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270

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TABLES

Table 1. Duration (in weeks) of aminoglycoside treatment for the most frequent aetiologies of infective endocarditis

	European guideline (ESC 2015)	American guidelines (AHA 2015)	Proposal (this review)
<i>Staphylococcus spp.</i>			
Native valve	0	0	0
Prosthetic valve	2	2	< 1 (until BC are negative or surgery) followed by rifampicin initiation
<i>Streptococcus spp.*</i>			
Native valve			
MIC** ≤ 0.125 mg/L	0	0	0
MIC 0.250–2 mg/l	2	2	2 (only for amoxicillin MIC > 0.5 mg/L)
Prosthetic valve			
MIC ≤ 0.125 mg/L	0	2 (optional)	0
MIC 0.250–2 mg/l	2	6	2 (only for amoxicillin MIC > 0.5 mg/L)
<i>Enterococcus faecalis</i>			
Amoxicillin-gentamicin	2 - 6	4- 6	2
Ampicillin or amoxicillin-ceftriaxone	0	0	0

NOTE. *two-week β-lactam-AG regimen is not depicted here. ** penicillin MIC.
BC: blood cultures, MIC : minimal inhibitory concentration

Table 2. Factors associated with in-hospital mortality among 110 streptococci infective endocarditis with amoxicillin MIC > 0.125 and ≤ 0.5 mg/L who survived at least 72 hours after antibiotic initiation. This analyse was performed on a previously published cohort study [43].

Characteristics	Dead (n=28)	Alive (n=82)	p-value	OR
Males, n (%)	18 (64)	57 (69)	0.64	
Median age (yrs) [range]	76.8 [67.8-79.6]	74.4 [58.1-83.7]	0.78	
Intensive care unit, n (%)	14 (50)	18 (22)	0.007	3.5 [1.29-9.66]
Renal insufficiency, n (%)	10 (36)	21 (26)	0.33	
Diabetes, n (%)	6 (21)	11 (13)	0.36	
IE on prosthetic device, n (%)	10 (36)	30 (36)	0.99	
Embolism, n (%)	12 (43)	31 (38)	0.65	
Amoxicillin MIC (mg/L) [range]	0.25 [0.22-0.36]	0.25 [0.25-0.5]	0.82	
AG > 48 hours, n (%)	16 (57)	52 (63)	0.65	

NOTE. We compared the relation between unfavourable outcome defined as in-hospital mortality at least 72 hours after antibiotic initiation and potential predictors. Results were expressed as the median (range) for continuous variables and N (%) for categorical variables. Statistical analysis was done with R software. All tests were two-tailed and p values less than 0.05 were considered significant.