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1 **Title:** A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream
2 infections and infective endocarditis

3

4 **Running Title:** Treatment for *E. faecalis* infections

5

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31

32 **Keywords:** *Enterococcus faecalis*, infective endocarditis, antimicrobials

33

34 **Summary:** The purpose of this review to highlight available treatment options, their limitations,
35 and provide direction for future investigative efforts to aid in the treatment of severe *E. faecalis*
36 infections, namely infective endocarditis.

37 **ABSTRACT**

38 Enterococci, one of the most common causes of hospital-associated infections, are responsible
39 for substantial morbidity and mortality. *Enterococcus faecalis*, the more common and virulent
40 species, cause serious high-inoculum infections, namely infective endocarditis, that are
41 associated with cardiac surgery and mortality rates that remained unchanged for the last 30 years.
42 The best cure for these infections are observed with combination antibiotic therapy; however,
43 optimal treatment has not been fully elucidated. It is the purpose of this review to highlight
44 treatment options, their limitations, and provide direction for future investigative efforts to aid in
45 the treatment of these severe infections. While ampicillin plus ceftriaxone has emerged as a
46 preferred treatment option, mortality rates continue to be high, and from a safety standpoint,
47 ceftriaxone, unlike other cephalosporins, promotes colonization with vancomycin resistant-
48 enterococci due to high biliary concentrations. More research is needed to improve patient
49 outcomes from this high mortality disease.

50 INTRODUCTION

51 Severe enterococcal infections including infective endocarditis (IE), are associated with mortality
52 rates as high as 20-40% and have remained unchanged for the last three decades despite
53 advances in antimicrobial therapy.[1] Although *Enterococcus faecalis* and *Enterococcus faecium*
54 are the two most clinically relevant species, *E. faecalis* accounts for approximately 97% of all IE
55 cases predominantly impacting the elderly and patients with comorbidities.[2] *E. faecalis*, unlike
56 *E. faecium*, is less frequently multidrug resistant.[2] However, lack of bactericidal activity of beta-
57 lactams[3], and ability to form biofilm at higher rates than *E. faecium* (87-95% vs. 16-29%,
58 respectively)[4, 5], makes treatment of *E. faecalis* infections particularly challenging, and may
59 contribute to the unchanging mortality rates. Consequently, combination antimicrobial therapy is
60 required for deep-seated *E. faecalis* infections, and with over 50% of isolates expressing
61 aminoglycoside resistance, treatment options are becoming limited.[6] It is the purpose of this
62 review to highlight available treatment options, their limitations, and provide direction for
63 investigation of future novel combination therapies including ampicillin plus non-ceftriaxone beta-
64 lactams and daptomycin combination therapy, to further aid in the treatment of *E. faecalis* IE.

65

66 METHODS

67 Studies were identified by conducting PubMed, and EMBASE searches using the following
68 keywords in one or more combinations with '*Enterococcus faecalis*': infective, endocarditis,
69 bacteremia, bloodstream, infection, treatment, guideline, antibiotic, combination, synergy,
70 resistant, biofilm, clinical, diagnosis, epidemiology, in vitro, in vivo, simulated endocardial
71 vegetation, experimental, and beta-lactamase. Manual searches of reference lists of relevant
72 articles found from initial searches were also conducted. No limitation was placed on publication
73 time period. Studies were selected based on authors' (MB and MKL) judgment of relevance to
74 topic.

75

76 **ORIGIN OF COMBINATION THERAPY**

77 For serious *E. faecalis* infections, such as IE, bactericidal agents often as combination therapy
78 are preferred.[2] Beta-lactam antibiotics lack bactericidal activity against enterococci when used
79 as monotherapy, making treatment of systemic infections particularly challenging.[3] Although *E.*
80 *faecalis* are often susceptible to ampicillin, treatment failure of 60%, and lack of bactericidal
81 activity of cell-wall active agents (i.e. penicillin G, ampicillin, vancomycin) prompted efforts to
82 identify combination therapies that would yield a bactericidal effect in severe infections.[1-3]
83 Originally, penicillin or ampicillin was combined with gentamicin or streptomycin to facilitate intra-
84 cellular uptake of aminoglycosides.[3] The recognition of in vitro bactericidal synergism between
85 beta-lactams and aminoglycosides was supported by observational clinical data and led to
86 improvements in IE cure rates up to 75%.[3] However, rising high-level aminoglycoside resistance
87 (HLAR), which may range to up to 63%[1, 6, 7] prompted the need for alternative therapy.
88 Subsequently, dual beta-lactam combination therapy emerged as a viable, safe treatment option
89 for severe infections with *E. faecalis*.

90

91 **DUAL BETA-LACTAM THERAPY**

92 *In Vitro and Experimental Animal Data*

93 In 1995, Mainardi and colleagues were the first to report synergy between amoxicillin and
94 cefotaxime in *E. faecalis*. [8] The results showed that the MIC for amoxicillin decreased
95 substantially in the presence of cefotaxime, as did the MIC of cefotaxime in the presence of
96 amoxicillin. The proposed mechanism of synergy is that partial saturation of essential penicillin
97 binding proteins (PBPs) 4 and 5 by amoxicillin, coupled with complete saturation of non-essential
98 PBPs 2 and 3 by cefotaxime leads to a bactericidal effect.[8] Taken together, the combination of
99 cefotaxime and amoxicillin exploits the optimal inactivation of PBPs 2, 3, 4 and 5, thereby
100 producing synergism on *E. faecalis*. Presumably the marked impairment in cell wall synthesis is
101 the basis for this effect.

102

103 In 1999, Gavalda and colleagues further explored beta-lactam combinations by evaluating the
104 activity of ampicillin plus ceftriaxone (AC) against *E. faecalis* strains with HLAR.[9] They confirmed
105 Mainardi's synergistic findings, and observed up to a fourfold reduction in ampicillin MIC in the
106 presence of ceftriaxone. Furthermore, rabbits treated with AC in HLAR *E. faecalis* endocarditis
107 had lower bacterial vegetation counts than rabbits treated with ampicillin alone.[9] In 2003,
108 Gavalda et al. evaluated the utility of AC versus ampicillin plus gentamicin (AG) against *E. faecalis*
109 with or without HLAR in rabbits with catheter-induced endocarditis.[10] They determined that the
110 two combinations were comparable in efficacy, and further concluded that AC may be an
111 alternative to AG particularly in special populations, such as patients with renal insufficiency
112 (Table 1).[10]

113

114 *Human Data*

115 Clinical data have since evaluated the combination of AC against HLAR and non-HLAR *E. faecalis*
116 IE.[6, 11, 12] In 2007, Gavalda et al. assessed the efficacy and safety of AC in 21 patients with
117 HLAR, and 22 patients with non-HLAR *E. faecalis* IE in a multicenter, open-label clinical trial.[6]
118 In this observational study of enterococcal IE, it was concluded that in addition to AC being a safe
119 and effective treatment option for HLAR IE, it is a reasonable alternative for patents at risk for
120 nephrotoxicity infected with non-HLAR organisms.[6] Subsequently, Fernandez-Hidalgo and
121 colleagues conducted a large, non-randomized, multicenter, cohort study comparing the safety
122 and efficacy of AC and AG in 246 episodes (159 subjects in AC group; 87 subjects in AG group)
123 of IE caused by *E. faecalis*.[11] The authors concluded that the two combinations were equally
124 effective as there was no difference in mortality while on antimicrobial treatment and during the
125 3-month follow-up, relapse, or treatment failures requiring alternate therapy. However, patients
126 treated with AG had significantly higher rates of adverse events (i.e. renal impairment) requiring
127 therapy withdrawal.[11] These findings coincide with a retrospective study of prospectively

128 collected data that evaluated 69 episodes of IE caused by *E. faecalis* (30 subjects in AG group;
129 39 subjects in AC group).[12] Similar to Fernandez-Hidalgo and colleagues, the authors did not
130 observe a difference in in-hospital mortality or 1-year mortality between AG and AC groups, and
131 found that patients on AG had higher rates of treatment-induced renal failure than patients
132 receiving AC. Interestingly, the authors captured epidemiologic data that demonstrates a
133 significant increase in IE caused by HLAR-producing *E. faecalis* over the course of 14 years,
134 along with an increase in AC therapy, although the small sample size limits definite conclusions
135 (Table 1).[12]

136

137 *Clinical trials are limited in IE*

138 As a result of these two clinical studies [6, 11], the 2015 national IE guidelines have been updated
139 to recommend double beta-lactam therapy (i.e. AC) as a treatment option for HLAR infections,
140 and a reasonable alternative to aminoglycosides for non-HLAR *E. faecalis* infections (Class IIa;
141 Level of Evidence B recommendation).[2] Of note, isolates with gentamicin resistance may be
142 susceptible to streptomycin, and vice versa, although monitoring for streptomycin concentrations
143 is often difficult and inefficient for clinicians since it is not available within most hospitals. The
144 guideline recognizes that the AC regimen has several limitations – notably 1) all data were
145 retrospectively collected without randomization, 2) treatment recommendations were center-
146 dependent; therefore, unmeasured confounding factors as well as treatment and indication bias
147 impacting these results cannot be ruled out and 3) gentamicin dosing and therapeutic drug
148 monitoring were not consistent across all centers, and higher levels may have contributed to the
149 observed increase in renal impairment.[11, 12] While data supporting the use of AC has
150 limitations, it is important to note that studies recommending AG treatment are observational and
151 have similar limitations.[2, 3]

152

153 As it currently stands, data providing support for optimal drug, dose and duration for the currently
154 available treatment options remain controversial. A recent study investigated optimal gentamicin
155 treatment duration in 84 patients with non-HLAR *E. faecalis* IE by comparing two groups: patients
156 admitted prior to the Danish 2007 guideline modification versus patients admitted after guideline
157 modification that recommended reducing gentamicin treatment duration from 4-6 weeks to 2
158 weeks.[13] Forty-one patients received gentamicin for a median of 28 days (IQR, 18-42), and 43
159 patients received a median of 14 days (IQR, 7-15). There was no difference between groups for
160 the primary outcome of 1-year event-free survival (27 [66%] vs. 29 [69%], $p = 0.75$) measured
161 from the end of treatment. No differences in complications, relapse, in-hospital mortality, baseline
162 renal function, and 14-day renal function were observed between groups. However, patients
163 receiving 14-day treatment with gentamicin therapy experienced a significantly lower reduction in
164 renal function at discharge compared to those receiving the full course, as measured by estimated
165 glomerular filtration rate (median -11 versus -1mL/min, $p = 0.009$).[13] They concluded that
166 patients may be adequately treated with two weeks of gentamicin, thereby avoiding renal
167 impairment that is associated with long duration of aminoglycoside therapy.[13] However, this
168 study was limited by a small sample size, and insufficient power, thereby leaving the optimal
169 duration of therapy unclear.

170

171 Interestingly, other studies demonstrate that toxicity resulting in gentamicin discontinuation
172 occurred after approximately two weeks of treatment.[11, 12] Although Fernández-Hidalgo did not
173 directly evaluate a shorter gentamicin treatment duration, the authors describe outcomes of
174 gentamicin treatment failure due to adverse events, namely renal dysfunction. For the 25% of
175 patients that failed AG therapy, the median duration of therapy with gentamicin was 14 days (IQR,
176 12–20 days).[11] Furthermore, ten patients did not receive combination therapy after stopping
177 gentamicin and completed their treatment course with ampicillin monotherapy.[11] Pericas et al.
178 reported that 43% of patients in the AG group had to discontinue treatment due to toxicity; thirteen

179 patients were switched to AC therapy after a median of 18 days (range, 5-30 days; IQR, 15-24.5
180 days).[12] Overall these data indicate that gentamicin toxicity is associated with longer treatment
181 durations, and a two-week treatment course may be reasonable.

182

183 **CONCERN FOR DEVELOPMENT OF RESISTANCE**

184 Enterococcal resistance to beta-lactams is primarily acquired by overproduction of PBP5, and by
185 amino acid substitutions that result in altered binding site and reduced beta-lactam interaction
186 with PBP5.[14] Additionally, rare isolates of *E. faecalis* produce beta-lactamase enzymes, which
187 in theory could compromise beta-lactam therapy against enterococcal endocarditis, and further
188 limit the available treatment options.[3, 15] While the impact of enterococcal beta-lactamase in
189 low-inoculum infections is difficult to detect, the impact in high-inoculum infections, such as
190 endocarditis, has not been fully elucidated. Data suggest that although most beta-lactamase
191 enzymes are inducible, enterococcal beta-lactamase is produced constitutively, and at
192 substantially lower amounts.[3, 15] Furthermore, the enzyme remains membrane-bound, making
193 detection of phenotypic resistance difficult unless high-inocula are used.[3, 15]

194

195 **CEFTRIAXONE SAFETY AND ADVERSE EVENTS CONCERNS**

196 Currently, AC combination therapy is the only tested option for the treatment of IE and bacteremia
197 due to HLAR *E. faecalis* with supportive clinical data. While seemingly safe as compared to AG,
198 safety risk associated with ceftriaxone use should not be negated. In addition to being an
199 independent risk-factor for *Clostridium difficile* infections[16] numerous clinical and observational
200 studies implicate ceftriaxone as a major risk factor for occurrence of vancomycin resistant *E.*
201 *faecium* (VRE) infection, including bacteremia.[17, 18] This is in addition to a wealth of animal
202 studies that have linked ceftriaxone use to promotion of gastrointestinal (GI) colonization by
203 VRE.[19, 20] It is suggested that the high biliary excretion of ceftriaxone, with levels that exceed
204 GI concentrations of 5,000 µg/ml, promote overgrowth of ampicillin- and vancomycin-resistant *E.*

205 *faecium*, whose MIC for ceftriaxone typically exceeds 10,000 µg/ml.[20] This ability of ceftriaxone
206 to “select” for drug-resistant enterococci poses not only a risk to individual patients, but also
207 threatens public health by contributing to developing of resistance in multiple organisms in the
208 hospital environment. Consequently, studies investigating alternative treatment options,
209 particularly novel beta-lactam combinations, are crucial to expand the therapeutic armamentarium
210 against these organisms.

211

212 **OTHER COMBINATION THERAPIES AND FUTURE RESEARCH POTENTIAL**

213 *Novel Dual Beta-Lactam Combinations*

214 Unlike ceftriaxone, other cephalosporin antibiotics, such as cefepime [19] and ceftaroline [21] do
215 not appear to promote VRE colonization. When cefepime, cefotetan, ceftriaxone and ceftazidime
216 were studied in the GI tract of mice, it was noted that cefepime was the least likely of the four to
217 cause VRE colonization (no difference in colonization compared to 0.9% sodium chloride), while
218 ceftriaxone and cefotetan reached the highest levels of colonization.[19] This is presumably a
219 result of minimal biliary excretion of cefepime and ceftaroline, and lack of antianaerobic effect of
220 cefepime. The combination of ampicillin plus ceftaroline demonstrated efficacy similar to AC in
221 several in vitro pharmacodynamics studies.[22, 23] A recent in vitro study evaluated high-
222 inoculum *E. faecalis* against ampicillin in combination with ceftaroline, cefepime, and ceftriaxone
223 in an in vitro pharmacodynamic model simulating human concentration-time profiles.[22] The data
224 indicated that AC activity was similar to ampicillin plus ceftaroline, and ampicillin plus cefepime.
225 Although ceftaroline and cefepime are not associated with VRE colonization, their utilization
226 necessitates careful evaluation for safety and development of resistance. Dual beta-lactam
227 therapy warrants further investigation, not only for efficacy, but also for the development of
228 resistance and optimal dosing.

229

230 *Daptomycin plus Beta-Lactam Therapy*

231 Daptomycin, a lipopeptide antibiotic with activity against Gram-positive bacteria, is of interest in
232 treating enterococcal infections due to its activity against *E. faecalis* and *E. faecium*, including
233 VRE. Recent data has indicated that the combination of daptomycin with beta-lactam antibiotics
234 has synergistic effects.[24, 25] Daptomycin activity can be potentiated due to beta-lactam-
235 mediated shifts in surface charge of enterococci, causing increased uptake of the drug. While
236 daptomycin combination therapy is more often observed in patients with resistant strains of *E.*
237 *faecium*, case reports of successful utilization of daptomycin combination therapy in patients with
238 severe *E. faecalis* infections have been published.[24, 26]

239
240 Sierra-Hoffman et al. report using daptomycin (6mg/kg Q48h) in combination with ampicillin (1g
241 Q6h) for the treatment of mitral valve IE in an 89-year-old female with stage 4 chronic kidney
242 disease.[26] The patient was not a surgical candidate, and received 6 weeks of treatment.
243 Subsequent surveillance blood cultures 2 weeks after cessation of therapy remained negative,
244 and patient remained alive without signs or symptoms of IE at her 1-year follow up.[26] Although
245 this case report used a 6mg/kg/day dose, several in vitro, in vivo and clinical outcome studies
246 suggest higher doses (10-12mg/kg/day) are associated with better patient outcomes, particularly
247 in severe infections [27-29]. This suggests that synergistic combinations may be daptomycin
248 dose-sparing. Further studies exploring dosing for synergistic combinations of daptomycin and
249 beta-lactams are warranted.

250
251 Daptomycin (8 mg/kg/day) plus ceftaroline was successfully used in a case report of a 63-year-
252 old male with recurrent aortic valve endocarditis caused by HLAR *E. faecalis*.[24] Therapy was
253 initiated after patient failed 6 weeks of AC therapy as evidenced by recurrent signs and symptoms
254 of IE, and doubling in vegetation size from 5mm to 10mm. This combination was selected due to
255 unpublished observations of synergy against several bacteremia-causing enterococci.[24] A
256 fourfold reduction in daptomycin MIC, as well as increased daptomycin binding to the

257 enterococcal cell membrane in the presence of ceftaroline was observed.[24] Smith and
258 colleagues evaluated several beta-lactams in combination with daptomycin.[25] Similar to
259 Sakoulas et al., the authors found that ceftaroline demonstrated the greatest daptomycin MIC
260 reduction (average 19.1+/-17.6 –fold [baseline daptomycin MIC/ daptomycin combination MIC]),
261 followed by (in decreasing order) cefepime, ceftriaxone, ampicillin, ertapenem, ceftazidime and
262 cefotaxime.[25] Time-kill studies demonstrated synergy with daptomycin in combination with
263 ceftaroline, ampicillin, ertapenem, ceftriaxone, and cefepime. Inconsistent synergy was noted with
264 daptomycin and cefotaxime. No synergy was observed with daptomycin in combination with
265 ceftazidime, possibly due to differences between PBP binding profiles of beta-lactam antibiotics.[25]

266

267 *Fosfomycin Combinations*

268 Fosfomycin demonstrated synergy in combination with daptomycin in in vitro studies.[30]
269 However, a follow-up in vivo aortic valve endocarditis study in rats infected with HLAR, beta-
270 lactamase producing strain of *E. faecalis* demonstrated no difference between the number of
271 valves sterilized by daptomycin-alone versus daptomycin plus fosfomycin when administered as
272 a continuous infusion through the left internal jugular vein.[31] More recent in vitro data
273 demonstrated synergy with fosfomycin in combination with ceftriaxone[32], rifampin, tigecycline,
274 and teicoplanin (unavailable in the US), and antagonism with ampicillin.[33] Teicoplanin is
275 particularly interesting for further investigation as previous in vitro data demonstrate advantage
276 over vancomycin against *E. faecalis*. [34] Despite in vitro synergy, current fosfomycin use is limited
277 to uncomplicated UTIs and should not be used to treat severe infections due to limited systemic
278 absorption when administered orally.[35] Intravenous formulations of fosfomycin are currently
279 unavailable in the US, but may have future utility. A recent study of in vitro and in vivo (guinea pig
280 model) use of intraperitoneal fosfomycin demonstrated promising activity against both planktonic
281 and biofilm-forming *E. faecalis* when fosfomycin was used in combination with gentamicin, and
282 daptomycin [36] demonstrating a need for further investigation.

283

284 *Miscellaneous Combinations*

285 Several other in vitro and in vivo studies have been conducted evaluating combination
286 therapy.[37-40] Synergistic combinations and their respective study designs are summarized in
287 Table 2. Of particular interest, Arias et al. evaluated a beta-lactamase stable cephalosporin,
288 ceftobiprole (currently unavailable in the US), and observed efficacy against bla+ and VanB-
289 resistant strains of *E. faecalis* in addition to synergy when used in combination with
290 aminoglycosides.[37] Overall, ceftobiprole demonstrates high affinity for enterococcal PBPs, and
291 requires further exploration in human subjects.

292

293 **CONCLUSION**

294 Although aminoglycoside-containing regimens have been the standard of enterococcal IE
295 treatment, the rise in resistance and availability of less nephrotoxic agents have led to novel
296 treatment options.[2] Double beta-lactam therapies have emerged as a novel strategy in the
297 treatment of serious high-inoculum enterococcal infections due of their favorable side effect
298 profiles, and tolerability during long-term use. Currently, AC is the only combination beta-lactam
299 therapy supported by clinical data for the treatment of IE and bacteremia due to HLAR
300 enterococci. However, AC combination is not without risk (i.e. resistance, VRE colonization).
301 Therefore, there is a critical need to investigate novel drug combinations, and explore dosing
302 strategies that optimize dose and overall exposure needed to improve efficacy and suppress the
303 emergence of resistance.

304 **Disclaimer**

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307

308 **Potential Conflict of Interest**

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