Enterococcus faecalis Infective Endocarditis: Is It Time to Abandon Aminoglycosides?

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(See the Major Article by Fernández-Hidalgo et al on pages 1261–8.)

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Since the first description of enterococcal infective endocarditis (IE) in 1899 and the subsequent availability of antibiotics for the treatment of this life-threatening infection, clinicians have faced important challenges in the management of this disease [1, 2]. Enterococci exhibit intrinsic antibiotic resistance (eg, to cephalosporins, clindamycin), are less susceptible to various antibiotics (eg, β-lactams) that are active against streptococci and staphylococci, and are often tolerant to compounds (penicillin) that normally have a bactericidal effect against other susceptible bacteria. Indeed, the lack of bactericidal activity of penicillin against enterococci was recognized when failure rates using penicillin monotherapy for the treatment of IE caused by enterococci were found to be higher than when caused by staphylococci and streptococci [3]. The lack of efficacy of penicillin for many cases of enterococcal IE sparked interest in possible alternative therapies. Reports of clinical cure in patients with enterococcal IE failing penicillin monotherapy when streptomycin was added to penicillin resulted in seminal experiments in the 1950s that showed that the combination of penicillin plus an aminoglycoside was bactericidal in vitro [4, 5]. This combination was used clinically with success and improved cure rates for enterococcal IE [6]. However, after this regimen became the standard of care, enterococcal strains exhibiting high-level resistance (HLR) to streptomycin (mainly due to ribosomal mutations) and, eventually, gentamicin (due to acquisition of the bifunctional enzyme AAC [6′]-Ie-APH(2′′)-Ia) were described. More recently, the widespread dissemination of antimicrobial resistance determinants in enterococci has further complicated the clinical picture with the emergence and dissemination of strains of Enterococcus faecium with HLR to ampicillin, indicative of the hospital-associated clade of multidrug-resistant E. faecium causing nosocomial infections worldwide [7, 8]. Modern-day clinical isolates belonging to this genetic clade often exhibit resistance to vancomycin (harboring the vanA gene cluster) and HLR to aminoglycosides, in addition to HLR to ampicillin (minimum inhibitory concentration >64 µg/mL), reducing antibiotic choices even further [9, 10].

Despite the high frequency of ampicillin-resistant E. faecium, ampicillin-resistant E. faecalis is strikingly uncommon. The pressing issue in the latter species is the increasing frequency of HLR to all aminoglycosides, as the presence of HLR to aminoglycosides abilishes the synergistic, bactericidal effect of the penicillin-aminoglycoside combination against enterococci. Additionally, toxicity of the aminoglycosides is a limiting factor for their use, even against E. faecalis isolates lacking HLR to aminoglycosides. Indeed, renal injury and ototoxicity are the 2 most feared complications of prolonged aminoglycoside therapy. An article entitled “Deaf or Dead?” published in 1959 dramatically illustrates, albeit with neomycin, the potential risks of using these drugs for E. faecalis IE [11]. Furthermore, the safety of aminoglycosides may be even more of an issue today, as patients who develop enterococcal IE in the modern-day era tend to be older, with a higher number of comorbidities and likely receiving more potentially nephrotoxic agents than in previous decades, increasing the risk of aminoglycoside-related renal dysfunction.

The above-mentioned limitations in the use of aminoglycosides have prompted the study of alternative therapeutic strategies
to obtain bactericidal activity. Using a penicillin-binding protein (PBP) binding assay, Mainardi et al [12] showed that the concomitant presence of amoxicillin and cefotaxime was synergistic in vitro. The basis for the synergistic activity of the β-lactam combination appears to be related to differential saturation of *E. faecalis* PBPs. Indeed, total saturation (100%) of PBP 2 and 3 by cefotaxime (at concentrations <1 µg/mL) plus partial saturation (25%) of the essential PBPs 4 and 5 by amoxicillin (0.06 µg/mL) appears to explain the synergistic effect [12]. A similar combination was able to eradicate *E. faecalis* in experimental in vivo models of IE [13, 14]. These observations were further supported by 2 clinical reports. In one, the combination of ampicillin plus ceftriaxone was able to cure a patient with *E. faecalis* IE who relapsed after treatment with ampicillin plus gentamicin [15]. The second was a multicenter, observational, open-label study that evaluated 43 patients with *E. faecalis* IE (21 with and 22 without HLR to aminoglycosides) treated with the combination of ceftriaxone (2 g every 12 hours) plus ampicillin (2 g every 4 hours) [16]. The clinical cure rates at the end of treatment in the latter study were 71.4% and 72.7% (isolates with and without HLR to aminoglycosides, respectively), with relapse in 5% (2 patients). However, the overall success rate at 3 months was rather low (67.4%). One important caveat of the above-mentioned study is that the overall mortality during treatment was 23.3%, higher than previously reported (between 9% and 18%) [17–22]. Based on those results, the American Heart Association (AHA) included a recommendation for use of the combination of ceftriaxone plus ampicillin as an alternative for the treatment of IE caused by *E. faecalis* isolates that exhibit HLR to both streptomycin and gentamicin [23].

In this issue of *Clinical Infectious Diseases*, Fernandez-Hidalgo et al present a nonrandomized, observational, multicenter study to evaluate the combination of ampicillin plus ceftriaxone in the treatment of *E. faecalis* IE. The main differences from the earlier study of Gavalda et al are that the authors studied more patients and included a control group that received the standard-of-care antimicrobials (combination of ampicillin plus an aminoglycoside), although not all patients received the recommended duration of the aminoglycoside (see below). The main finding of the study was that no differences in mortality or rates of treatment failure/relapse were found between the ampicillin plus gentamicin and the ampicillin plus ceftriaxone groups. However, patients receiving gentamicin had a higher frequency of acute kidney injury and interruption of therapy.

The authors should be congratulated for coordinating this ambitious study and amassing the data from so many institutions. The study provides useful clinical data in a field in which information is scarce and therapeutic alternatives are limited, and gives us greater confidence in using the combination of ampicillin and ceftriaxone in IE when facing strains of *E. faecalis* exhibiting HLR to aminoglycosides. But what about strains lacking HLR? The results of Fernandez-Hidalgo et al confirm that many patients with enterococcal endocarditis do not need an aminoglycoside (indeed, some patients with *E. faecalis* IE, previously estimated as approximately 50%, are cured with penicillin or ampicillin monotherapy) [6]. So, is it time to abandon aminoglycosides and treat all patients with *E. faecalis* IE with ampicillin–ceftriaxone? Although the overall results of the current study are impressive, several caveats need to be taken into consideration when interpreting the data. First, all patients included in the study had symptoms for <2 months, yet the overall relapse rate was 4% in the ampicillin-gentamicin group versus 3% in the ampicillin–ceftriaxone group (P = 0.67). These findings contrast with the results of Wilson et al in a 1984 report of 0% relapse in patients treated with an aminoglycoside-containing regimen when symptoms were present for <3 months [17]. Would 0% be achievable today? Was that result a statistical accident? Failure has been reported even with 4 weeks of therapy and short-term symptoms [18], but how often this occurs in the current era is not known. If 0% is the expected outcome with a complete course of an aminoglycoside-containing regimen, the higher rate of relapse with the gentamicin-containing regimen in the current study might be explained by the fact that, among 87 patients who received the ampicillin-gentamicin combination, only 31 (35.9%) received a full course of gentamicin as recommended in the AHA guidelines (4–6 weeks). Moreover, among the 87 patients in the ampicillin-gentamicin group, information regarding dose scheduling was provided for 80 patients; of those 80 patients, gentamicin was administered 3 times daily (as recommended by the AHA) in only 37 patients, 37 additional patients received a once-daily regimen, and the remaining 6 received gentamicin twice daily. Unfortunately, there is no analysis of outcomes based on dose schedule. Furthermore, adequacy of aminoglycoside dosing was not documented as gentamicin levels were obtained in only 60% of patients and information regarding these levels was not provided. Although a previous study by Olaison et al [18] suggested that clinical outcomes of patients with enterococcal IE treated with 2 weeks of aminoglycoside therapy were similar to those of patients treated for 4–6 weeks (mean duration of symptoms of 21 days), the outcomes of the patients who stopped aminoglycoside therapy in the current study are unclear, as some were switched to the ampicillin–ceftriaxone arm, others received alternative agents (eg, daptomycin), and 10 of 22 did not receive any other combination therapy.

Second, the definition of acute kidney injury chosen by the authors (increase...
in 25% of the serum creatinine) is a potentially misleading way to assess renal dysfunction. As an example, a patient with a basal creatinine of 0.5 mg/dL who experienced an increase in creatinine to 0.63 mg/dL while on therapy had acute kidney injury, by definition, and aminoglycoside therapy may have been withdrawn. The clinical relevance of such changes in creatinine values is questionable and the use of the RIFLE score—which classifies patients with renal dysfunction according to the degree of impairment into patients at risk (R), with injury (I), with failure (F), with sustained loss (L), and with end-stage (E) status in relation to their renal function [24]—would have been more appropriate. It is also unclear if the renal dysfunction resolved after stopping the aminoglycosides, because follow-up was limited. Furthermore, the decision to discontinue the aminoglycoside therapy in the current study was left to the treating physicians, thus introducing potential biases into the study.

Finally, patients within the ampicillin-ceftriaxone group had a higher proportion of healthcare-related IE. Recent data based on genomic information indicate that certain E. faecalis genetic lineages are more prevalent in hospital-associated infections [10]. One could argue that the findings in the study might potentially be explained, at least in part, if there were differences in pathogenicity or persistence of genetic lineages that could be unevenly distributed between groups. Unfortunately, no molecular epidemiology data are provided in the manuscript to allow conclusions regarding the population genetics of the recovered isolates.

Despite these caveats, Fernandez-Hidalgo et al provide important data that support the use of ampicillin plus ceftriaxone for the treatment of IE caused by E. faecalis. The limitations of the study, including the fact that it was a nonrandomized, observational, and nonblinded study, raise important questions that remain unanswered. Foremost, would ampicillin-ceftriaxone be as efficacious as ampicillin-gentamicin/streptomycin in a prospective, randomized study that evaluated patients who actually received the current AHA recommendation of 4–6 weeks of ampicillin plus an aminoglycoside, while documenting aminoglycoside serum concentrations and closely monitoring kidney function with the RIFLE score? An even bigger question is the following: Can the risk-benefit ratio of the 2 regimens be compared? Would a 0% relapse rate using 4 weeks of ampicillin-gentamicin (or, say, 1 patient in 100), if achieved in a properly designed randomized study, be considered sufficiently favorable to warrant the risk of aminoglycoside toxicity, even if mild and reversible, compared to the 3% relapse, if reproduced, reported in the current study with 6 weeks of ampicillin plus ceftriaxone? If not, then we should give strong consideration to a switch to the ampicillin-ceftriaxone regimen. This would then raise another major question: Are there some patients (eg, those with prosthetic valve endocarditis) for whom the risk of relapse, or the risk from potential complications of a relapse, is sufficiently high to warrant using a regimen with greater toxicity, if that regimen were a little better? Other questions also remain unanswered: Are there other regimens that would yield a 0% relapse rate with less toxicity, such as 2 weeks of ampicillin-gentamicin followed by 2–4 weeks of ampicillin-ceftriaxone? Is streptomycin any better than gentamicin? Could agents with in vitro bactericidal activity against enterococci (eg, daptomycin and oritavancin) be used to yield cure rates better than those reported here, for example, daptomycin combined with ampicillin, which might decrease emergence of daptomycin resistance [25] or might be synergistic, as recently shown for the ampicillin-daptomycin combination in E. faecium [26]? What regimen should be used if patients relapse?

This study is certain to stimulate discussion regarding the therapy of enterococcal IE. Until some of the questions above are answered, if they ever are, should clinicians continue to consider the combination of ampicillin plus an aminoglycoside as the standard of care for E. faecalis IE for isolates lacking HLR? The data presented by Fernandez-Hidalgo et al indicate that abandoning the aminoglycoside-based regimen deserves serious consideration. Among the 3 coauthors of this commentary, one likely will continue for now, at least for some patients, to include an aminoglycoside for at least part of the course, followed by ampicillin-ceftriaxone to complete 6 weeks. Another will likely abandon aminoglycosides now. The third is currently undecided, and we suspect that many of our colleagues will face the same dilemma. All 3 of us, however, agree that we would like to see a large, multinational study that addresses as many of the questions posed above as possible. Thus, the current study adds important data to the evolving paradigm of treating enterococcal IE and opens avenues for relevant clinical trials in the future.

Note

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