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Commentary

Which trial do we need? Aminopenicillin-gentamicin versus aminopenicillin-ceftriaxone for Enterococcus faecalis endocarditis

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We read with great interest the editorial note entitled, ‘Which randomized controlled trial do we need?’ [1]. Infective endocarditis (IE) is a rare and difficult-to-treat disease carrying in-hospital and five-year mortality rates of around 20% and 40%, respectively [2]. Among the main bacteria responsible for IE are enterococci, which disproportionately affect elderly and/or frail patients, inducing even higher risks of adverse events (heart failure, neurological impairment and infectious complications) and mortality [3].

Over recent decades, major advances in the management of IE have come from the fields of cardiac surgery, imaging and microbiology. However, the antibiotic regimens recommended in current European and North American guidelines continue to be based on *in vitro* and experimental data, observational clinical studies and very few randomized trials [4,5]. Thus, the level of evidence on the best antibiotic regimens remains low, especially when it comes to enterococcal IE.

Enterococci originate in the digestive tract and are increasingly associated with IE (i.e., approximately 10% in most contemporary cohorts). These bacteria are associated with high tolerances to antibiotic-induced killing, and an increased risk of treatment failure or relapse [3,6]. Within enterococcal IE, more than 90% is due to *E. faecalis* [3]. To ensure bactericidal effect, the treatment of *E. faecalis* IE (EFIE) has long been restricted to the combination of a cell-wall active agent, i.e., aminopenicillin, and aminoglycosides, with gentamicin, in the absence of high-level aminoglycoside resistance (HLAR). These recommendations have been particularly difficult to apply, due to the toxicity of aminoglycosides in elderly patients or those with comorbidities. Indeed, aminoglycosides are associated with cochlea-vestibular toxicity and nephrotoxicity, which increases with treatment duration [7]. The occurrence of acute kidney failure in IE is an independent predictor of one-year mortality and chronic renal failure, and hearing loss induced by aminoglycosides impairs the quality of life [8]. Hence, aminoglycosides are often discontinued before the end of treatment. In this sense, Swedish and Danish researchers have demonstrated in observational studies that gentamicin can be given q.d. instead of b.i.d. or t.i.d. and that the total duration of aminoglycoside administration can be safely reduced to two weeks without increasing the risk of treatment failure or relapse [9,10]. Alternatively, another EFIE treatment is the double-beta-lactam combination of a third-generation cephalosporin (ceftriaxone or cefotaxime) plus an amino-penicillin, which has been found to be

synergistic and bactericidal [4]. Several observational studies reported not only similar outcomes using this regimen in comparison to ampicillin-gentamicin in the treatment of enterococcal IE, but also a reduced risk of renal failure [11,12]. Current endocarditis guidelines consider the two regimens equivalent in terms of efficacy in non-HLAR EFIE, but the gold standard remains the combination of amino-penicillin and gentamicin, with amino-penicillin and ceftriaxone placed as the first-line alternative [3,4]. In cases of HLAR EFIE, the double beta-lactam combination is the treatment of choice.

Although the combination of aminopenicillin and third-generation cephalosporin does not induce renal toxicity, it is not without its downsides. Firstly, it should be pursued throughout the six-week treatment course, even for native valve enterococcal IE. Furthermore, the risk of relapse may be increased, as suggested by a recent study, where the incidence at one year was lower with a sequential regimen (initial amoxicillin plus gentamicin followed by amoxicillin plus ceftriaxone) than with amoxicillin plus ceftriaxone [6]. In addition, the broad antibacterial spectrum of ceftriaxone may increase the risk of alterations to gut microbiota, with the emergence of multidrug-resistant bacteria or the occurrence of *Clostridioides difficile* infections.

Comparisons of efficacy and safety between these two combinations have never been assessed in a randomized controlled trial (RCT)[13]. No definitive conclusions on the optimal treatment combination can be drawn from historical comparisons, neither in terms of clinical response, microbiological eradication, nor safety. Only a head-to-head comparison through a rigorous RCT can determine the optimal treatment regimen in terms of efficacy and tolerability. Conducting such a trial faces obvious challenges. First, IE has a low annual incidence, estimated at around 30 cases per one million inhabitants. Moreover, EFIE is less common than staphylococcal or streptococcal endocarditis, which may limit the number of eligible patients. For example, a Spanish multicentre trial took eight years to enrol 43 patients [11]. Beyond clinical efficacy, an analysis of safety would require a larger sample size in order to address this issue appropriately. Consequently, conducting a large RCT of this rare disease would need a multinational approach, making it expensive, with no support expected from industry. A large consortium of experts from Denmark, France, Greece, Italy, the Netherlands, Spain and Sweden did design a large RCT of this kind. It was selected and approved by the European

Union's Seventh Framework Programme (FP7) in 2011, but the lack of available funding prevented it from starting. Finally, further attempts to fund it also failed, illustrating the challenges of large-scale academy-initiated RCTs when the only source of funding available is public monies. Only a large-scale international trial, promoted by experts in the field of EFIE in each participating country, can allow us to overcome these difficulties. Under these conditions, this RCT will only ever be financed by public funding, as the anti-infective agents recommended for EFIE are available as generic drugs. The design of this RCT, including PICO (population, intervention, comparison and outcomes) queries, is detailed below (Figure 1). The trial would cover adult patients suffering from non-HLAR EFIE (P), comparing the combination of aminopenicillin-ceftriaxone (I), and the combination of aminopenicillin-gentamicin (C), through a rigorous evaluation of efficacy and safety (O). The main objective would be to demonstrate that the combination of aminopenicillin (200 mg/kg/day i.v., 4 to 6 weeks) and ceftriaxone (4g/day i.v. in 2 doses, 4 to 6 weeks) is not inferior to aminopenicillin (200 mg/kg/day i.v., 4 to 6 weeks) and gentamicin (3 mg/kg/day i.v. in 1 dose, first 2 weeks) in terms of cure and bacterial eradication. The duration of beta-lactam treatment would be restricted to four weeks in non-complicated EFIE and prolonged to six weeks in complicated EFIE. Complicated IE is defined by the presence of prosthetic valve and/or paravalvular complications and/or cardiac failure and/or metastatic infectious or embolic events and/or symptoms of illness for longer than three months. The primary outcome would be defined by the occurrence of failure at the test-of-cure visit in each arm, both in an intent-to-treat and in a per-protocol analysis. Failure would include death and microbiological or clinical failure. The secondary objectives would be: (i) to demonstrate that aminopenicillin-ceftriaxone is better tolerated, with a lower incidence of drug-related adverse events, especially renal and cochleo-vestibular toxicities; (ii) to compare the proportions of relapse with each regimen during a 12-month follow-up after the end of treatment; (iii) to assess whether aminopenicillin-ceftriaxone use is associated with a higher risk of multidrug-resistant bacteria emergence in the digestive microbiota through systematic centralized studies of faecal flora performed at baseline, at the end of treatment, and at the test-of-cure. The trial would include adults fulfilling the following criteria: (i) definite endocarditis according to the Duke-Li classification, (ii) at least one positive blood culture yielding *E. faecalis* [14], (iii) *E. faecalis*

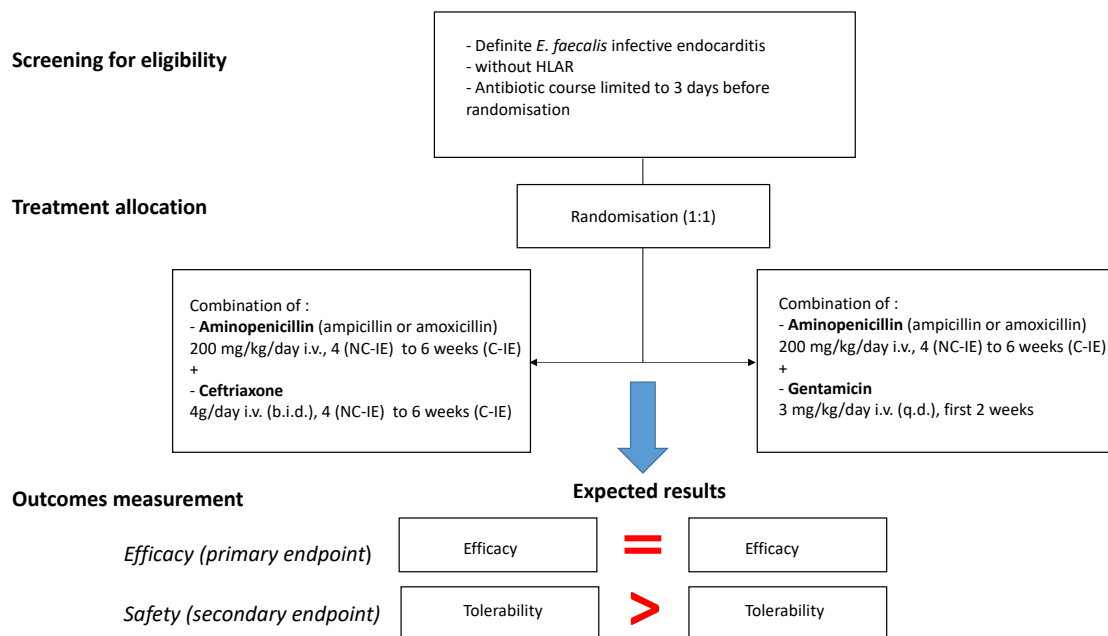
without HLAR; (iv) no allergy to beta-lactams, and (v) a limited duration of aminopenicillin, ceftriaxone or gentamicin received before randomization (≤ 3 days).

This long-awaited RCT could address the striking lack of international standardization in EFIE antibiotic treatment and optimize patient care. New opportunities for large-scale academy-driven RCTs are urgently required in the field of endocarditis. It is time for action; it is time to conduct this RCT.

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Figure 1. Flowchart of the trial.



HLAR: high level of aminoglycoside resistance

NC-IE: non-complicated endocarditis defined by native valve, no paravalvular complications, no cardiac failure, no metastatic infectious or embolic events, and symptoms of illness < 3 months

C-IE: complicated endocarditis defined by prosthetic valve and/or paravalvular complications and/or cardiac failure and/or metastatic infectious or embolic events and/or symptoms of illness > 3 months.

q.d.: once a day; b.i.d.: twice a day