



Re-evaluating Antibiotic Therapy Duration for Infective Endocarditis: The POET-II Trial

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INFECTIVE ENDOCARDITIS (IE) remains an uncommon but highly morbid disease, and left-sided IE, involving the aortic or mitral valve (native or prosthetic), accounts for most cases encountered in clinical practice.¹ The most common pathogens responsible for left-sided IE are *Staphylococcus aureus*, *Enterococcus faecalis*, and *Streptococcus* species, accounting for ~70% of all IE cases.² While logically the duration of an antibiotic therapy regimen should be the time it takes for complete eradication of the causative pathogen, there are no reliable markers for bacterial clearance in IE.² Consequently, based on historical observations from the 1950s, when lower doses of antibiotic monotherapy were used, the mainstay treatment for IE has long been prolonged intravenous antibiotic therapy (typically up to 6 weeks), a recommendation endorsed for decades by both the American Heart Association (AHA) and the European Society of Cardiology (ESC).^{3,4} Shorter antibiotic regimens confer advantages, such as fewer side effects and healthcare-related infections and a lower risk of antimicrobial resistance, and therefore how long to continue antibiotics, the most consequential decision that clinicians make in treating this life-threatening infection, has rested on consensus statements rather than randomised clinical trial evidence for nearly 70 years.

THE POET TRIAL

The original POET trial pushed towards a shorter, more individualised antibiotic course in IE in 2018.⁵ This trial was a randomised, noninferiority, multicentre study in which it was shown that clinically stable patients with left-sided IE could be safely switched from intravenous to oral step-down antibiotics once they completed 10 or more days of intravenous treatment,

and (a) met a defined set of clinical and biochemical stabilisation (afebrile for 48 hours or more; normalising C-reactive protein/white blood cells); (b) ruled out surgical/abscess complications via transoesophageal echocardiogram within 48 hours; and (c) demonstrated adequate oral drug absorption and outpatient adherence (the POET criteria). The primary composite endpoint of all-cause mortality, unplanned cardiac surgery, embolic events,

or relapse of bacteraemia occurred in 12% in the intravenously treated group, and in 9% in the orally treated group (95% CI: -3.4–9.6%) in 6 months after randomisation, showing that changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment.⁵ Five-year follow up of this trial extended these reassurances, and this body of evidence helped inform the incorporation of oral step-down therapy into the 2023 ESC guidelines for the management of IE.^{3,6} However, in the absence of randomised data specific to IE addressing whether the total duration of antibiotic therapy could be tailored to an individual patient's clinical response rather than fixed at a predetermined number of weeks, both the 2015 AHA scientific statement and the 2023 ESC guidelines continue to recommend up to 6 weeks of therapy for most left-sided IE cases.^{3,4,6} In fact, the persistence is still visible in the newest released scientific statement by the AHA, where the writing group again recommended a native valve antibiotic duration of 4 weeks, and a prosthetic valve duration of 6 weeks.¹

“Around half of the patients seen in clinics with left-sided IE could be eligible for tailored, reduced-duration therapy”

THE POET-II TRIAL

Results from the POET-II randomised clinical trial were recently presented at the ESC Congress 2026 and simultaneously published.² The study was a prospective, investigator-initiated, international, open-label RCT conducted at 13 centres in Denmark, Sweden, and the USA, and was superiority designed for its primary efficacy endpoint and noninferiority designed for its primary safety endpoint.^{2,7} Investigators enrolled adult patients with left-sided IE, either of the native or prosthetic valves, caused by *S. aureus*, *E. faecalis*, or *Streptococcus* species, who had already received a minimum of 2–4 weeks of antibiotic therapy and met the POET stabilisation criteria. Those with previous IE caused by the same microorganism within 6 months before randomisation, and those with known or presumed immunodeficiency, were excluded. A total of 508 patients





underwent 1:1 randomisation to discontinue antibiotics immediately (tailored-therapy group: n=255) or to continue standard treatment for a total duration of 4–6 weeks (standard-therapy group: n=253). The primary efficacy endpoint was the number of days alive without antibiotic treatment for IE or bacteraemia within 6 months, tested for superiority. The primary safety endpoint was a composite of all-cause mortality, unplanned cardiac surgery, or symptomatic embolic events within 6 months, tested for inferiority with a prespecified margin of 7.5 percentage points. Relapse of bacteraemia or IE with the primary pathogen was a key secondary endpoint. Investigators hypothesised that a response-tailored treatment strategy, built on the POET criteria for clinical stabilisation already validated in the original POET trial, would result in 2–3 fewer weeks of intravenous or oral step-down antibiotic treatment than the standard duration of therapy without compromising safety, thereby directly addressing this gap in clinical literature regarding the duration of antibiotic regimen in IE.

SHORTER ANTIBIOTIC REGIMEN DEEMED NONINFERIOR

The mean age of patients was 70 years, with nearly 25% being women, and 26% with prosthetic-valve IE. *Streptococcus* species was the most common bacterial pathogen in participants (57%), followed by *S. aureus* (24%), and *E. faecalis* (19%). The median duration of antibiotic therapy was 26 days (interquartile range [IQR]: 18–30 days) in the tailored-therapy group versus 41 days (IQR: 28–42 days) in the standard-therapy group (absolute difference: 15 days). The primary efficacy endpoint (days alive without antibiotic treatment) was 183 days (IQR: 181–183 days) in the tailored-therapy group versus 169 days (IQR: 166–171 days) in the standard-therapy group, a Hodges-Lehmann estimated between-group difference of 13 days (95% CI: 12–13 days; $p < 0.001$ for superiority). The primary safety endpoint occurred in 21 patients (8%) in the tailored-therapy group compared with 27 patients (11%) in the standard-therapy group (95% CI: -7.7–2.7; $p < 0.001$ for noninferiority), confirming noninferiority in favour of the shorter treatment regimen. Relapse of bacteraemia or IE with the primary pathogen, however, occurred more often in the tailored-therapy group than in the standard-

therapy group (3% versus 5%, respectively; $p=0.004$). The investigators concluded that a response-tailored antibiotic strategy resulted in a longer duration of time alive without antibiotic therapy, and met the criterion for noninferiority with respect to safety, but was associated with a higher incidence of relapse.²

CHALLENGING THE NORMS OF ANTIBIOTIC THERAPY

At the ESC Congress 2026, it was estimated that around half of the patients seen in clinics with left-sided IE could be eligible for tailored, reduced duration therapy, and the clinical trial was framed as a direct challenge to a treatment dogma that had gone essentially untested since it was first articulated in the 1950s. In that sense, the headline results of POET-II, that clinicians can safely shave roughly a third off the total duration of antibiotic courses for a substantial proportion of patients is truly practice changing and practice relevant. However, the shift from fixed-duration regimens towards personalised, response-guided decisions should only occur in select patients and in centres with clinical expertise in managing IE care, owing to the resource-intensive nature of the

POET stabilisation criteria, which require serial biochemical, imaging, and clinical assessments. An important caveat that practitioners need to keep in mind is that a subgroup analysis of the trial showed that the benefits of tailored therapy were only seen among patients with *Streptococcus* or *S. aureus* infections, while outcomes were better with standard therapy among those with *E. faecalis* infections. Importantly, the excess of relapses in the tailored arm warrants caution for careful patient selection, although the majority of the relapses in the trial were managed successfully with re-initiation of antibiotics and were classified as uncomplicated.

CONCLUSION

Overall, the POET-II trial is a well-conducted, adequately powered, and timely randomised clinical trial that will likely occupy a position analogous to that of the original POET clinical trial with respect to oral step-down therapy. In the interim, the trial asks clinicians to carefully evaluate antibiotic therapy in patients with IE based on the individual patient's clinical response, rather than a fixed, calendar-based endpoint.

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