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THE CUTTING EDGE: RESEARCH UPDATE

Assessment of the feasibility of a partial oral regimen for antibiotic therapy of endocarditis

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Background

Infective endocarditis (IE) is a relatively uncommon although severe disease, with an incidence ranging from 3 to 7 per 100,000 person-years. It is still characterized by high morbidity and mortality (in-hospital mortality 15–45%). According to the latest versions of the European Society of Cardiology (ESC) and the American Heart Association (AHA) guidelines, the antimicrobial therapy for patients with IE consists in prolonged (up to 6 weeks) intravenous (IV) therapy, targeted on microbiological findings [1, 2]. For these reasons, the majority of patients with IE have a prolonged in-hospital length of stay to complete the antibiotic infusion program. There are some situations in which optimal IV antibiotic therapy is not feasible or advisable. Moreover, the long hospitalization can lead to increased risk of adverse events as well as an early discharge can determine a better quality of life for the patient [3]. Oral anti-bacterial therapy could be an effective alternative.

Only a few studies on this topic exist in literature and, at the moment, there is not sufficient evidence that oral administration can safely replace IV therapy in patients with IE [4].

Summary

Iversen et al. performed a randomized controlled trial to evaluate the non-inferiority of partial oral antibiotic regimens for IE compared to usual IV regimens [5].

This was a nationwide investigator-initiated, multicenter, randomized, unblinded, non-inferiority trial conducted at cardiac centers treating patients with infectious endocarditis in Denmark. Eligible patients were adults, at least 18 years old, clinically stable, receiving IV antibiotic treatment for endocarditis on the left side of the heart (native or prosthetic valves). Inclusion criteria were: fulfilling the modified Duke criteria; having blood cultures positive for streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus* or coagulase-negative staphylococci; having carried out at least 10 days of appropriate IV antibiotic therapy (at least 7 days after valve surgery, if performed); body temperature < 38 °C since at least 2 days; C-reactive protein dropped to less than 25% of peak value or < 20 mg/L and white blood cell count $< 15 \times 10^9$/L during antibiotic treatment; no signs of abscess formation revealed by echocardiography; and transthoracic or transesophageal echocardiography (TTE, TEE) performed within 48 h of randomization. Exclusion criteria comprised body mass index > 40; concomitant infections requiring IV antibiotic therapy; inability to give informed consent to participation; suspicion of reduced absorption of oral treatment due to abdominal disorder; and reduced compliance. Participants were randomized in a 1:1 ratio to continue IV antibiotic treatment or to shift to orally administered antibiotic treatment. Patients assigned to receive IV treatment remained hospitalized until therapy was completed, while patients randomized to oral treatment were discharged, if possible, and seen 2–3 times per week in outpatient clinics. Within 1–3 days before the completion of the treatment TEE was performed to confirm response. IV antibiotic treatment was administered in accordance with guidelines of the European Society of Cardiology, with modifications endorsed by the Danish Society of Cardiology, and the trial investigators developed oral antibiotic treatment regimens as part of the trial. Oral regimens comprised two antibiotics from different drug classes with different antimicrobial mechanisms and different metabolization processes. All patients were seen at 1 week and at 1, 3 and 6 months after the regimen completion. The primary

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outcome was a composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events or relapse of bacteremia with the primary pathogen from randomization through 6 months after antibiotic treatment was completed. A non-inferiority margin of 10% for the difference in primary outcome was chosen (under the assumption of a 10% event rate). From July 15, 2011, to August 30, 2017, 1954 patients were screened for inclusion; 400 patients (20%) were enrolled; 199 patients were randomly assigned to continue intravenous treatment, and 201 shifted to oral treatment. The two groups resulted to have similar characteristics except for the C-reactive protein level at the moment of randomization that was slightly but significantly higher in the intravenously treated group. The median time from the diagnosis of endocarditis to randomization was 17 days. In the orally treated group, 160 patients (80%) were partially or completely treated as outpatients. After randomization, the median length of hospitalization was 19 days in the intravenously treated group and 3 days in the orally treated group ($P < 0.001$). Four patients crossed over from the orally treated group to the intravenously treated group, while no patients crossed over from the intravenously treated group to the orally treated group. The primary outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group. The between-group difference was 3.1% points (95% CI 3.4–9.6; $P = 0.40$) in favor of oral treatment, meeting the non-inferiority criterion. In a sensitivity analysis in which the four patients who were switched from oral to intravenous therapy were considered to have had treatment failure, the criterion for non-inferiority was still met.

Strengths of the study

- The topic addressed in the paper is of particular interest and can positively affect daily clinical practice.
- The study design is adequate to address the topic.

Weaknesses of the study

- The fact that only 20% of the screened population was randomized could affect the external validity of the study and the generalizability of the findings.

Question marks

- In the study, only 20% of the screened patients were randomized. It could be interesting if the authors could deep the reasons that led to such a low percentage of randomization to understand if the study results exportable on these bases.

Sponsorship

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Clinical bottom line

This study suggests the safety of an established regimen of oral antibiotic therapy in a well-defined group of stable patients with endocarditis of the valves of the left heart after an initial IV regimen for at least 10 days. This therapy strategy could be considered for similar patients. More studies are necessary to enlarge this evidence and consent the applicability of this kind of approach in the usual clinical practice to a wider population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statements All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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