Randomized controlled trials in the Journal of Antimicrobial Chemotherapy

Leonard Leibovici1,2*, Colin Drummond3 and Alan Johnson3

1Department of Medicine E, Rabin Medical Center, Beilinson Campus, 49100 Petah-Tiqva, Israel; 2Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv, Tel Aviv, Israel; 3JAC Editorial Office, Griffin House, 53 Regent Place, Birmingham B1 3NJ, UK

The Journal of Antimicrobial Chemotherapy welcomes submissions of well-reported randomized controlled trials (RCTs) with solid methodology based on the CONSORT statement (http://www.consort-statement.org). The Journal would be especially happy to publish RCTs in the area of antimicrobial chemotherapy if they address significant problems and look at measurable outcomes that matter to patients.

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In the present issue of the JAC, we publish a randomized controlled trial (RCT), showing that a single dose of oral ivermectin relieved pruritus in homeless people, but the effect waned by the fourth week. Although maybe not a momentous discovery, the merits of this article are that it addresses a real problem and that the study population comprised people who need treatment but whose needs are easy to ignore. Particularly noteworthy is that the primary outcome is one that matters to this group of patients and that the intervention is inexpensive and can be easily used in this population. Finally, the methodology, analysis and reporting were solid.

The purpose of this Editorial is to highlight the fact that JAC welcomes submission of articles describing results of RCTs. In common with many medical journals, we aim to publish material (pertaining to antibacterial, antifungal, antiviral or antiparasite chemotherapy) that will advance management of patients or improve our understanding of diseases, their prevention and treatment. The paradigm of evidence-based medicine is gaining wide acceptance, and good quality RCTs (and also systematic reviews)2 are better placed to influence clinical practice than any other research designs, as solid methodology prevents bias and strengthens our confidence in the results. As highlighted previously,3 authors are required to structure their reports according to the CONSORT statement (http://www.consort-statement.org), a minimum set of recommendations for reporting RCTs, and to submit the 22-item CONSORT checklist. Although primarily dealing with the reporting of trials, the CONSORT statement stresses many methodological issues that are important for planning a trial, and some of them were empirically shown to reduce bias. A few important examples are correct calculation of sample size based on the main outcome, adequate randomization and allocation concealment, triple blinding whenever possible and analysis according to intention to treat.

The JAC is particularly interested in studies that have the potential to influence clinical practice. To make a difference, an RCT has to address an unsolved question that matters. For example, the question of whether the addition of a macrolide to a β-lactam drug in community-acquired pneumonia makes a difference has not been addressed even in one RCT,4 although this common practice is under debate.4,5 Equally, there is uncertainty as to whether to add an aminoglycoside to an anti-pseudomonal β-lactam for the treatment of pseudomonal infections, and no RCTs have addressed this question to date.6 The optimal length of antibiotic treatment for many common infections has not been adequately addressed in RCTs. The common practice of antibiotic prophylaxis for recurrent erysipelas was addressed in only two small RCTs7,8 and the data were inconclusive. In contrast, we do not lack antibiotics for the treatment of common skin and soft tissue infections; however, a multitude of trials have dealt with this question because it is an easy path towards regulatory approval. The need for more non-inferiority trials for the treatment of sinusitis or otitis media, the majority of which are non-bacterial infections,9,10 remains a source of controversy.

Ideally, the main outcomes measured in RCTs should be the ones that matter most to patients. In severe infections, these outcomes are death and major complications. However, for most infections, these outcomes are fortunately rare, and to show an improvement, a very large sample size (often not realistic in practice) is required. For this reason, ‘clinical failure’ is often
used instead. Clinical failure is a composite outcome, and we reiterate that the components of this composite outcome should be those that matter to patients. ‘Change in antibiotic treatment’, for example, is sometimes counted as treatment failure, but is of no importance if the patient is well at the end of the episode.

There is a tension between pragmatic and explanatory trials. Pragmatic trials usually recruit patients at presentation, when the pathogen is unknown, and look at clinical outcomes. Their results matter to patients, but are sometimes difficult to interpret without detailed microbiological data. Studies in antimicrobial chemotherapy commonly use many populations for analysis (intention to treat, modified intention to treat, microbiologically modified intention to treat etc.), which potentially allows emphasis to be placed on the analysis that shows a drug at its best. Both pragmatic outcomes (was the clinical outcome of patients improved?) and explanatory ones (was the pathogen eradicated? how well did the drug work against ‘susceptible’ pathogens?) are interesting and should be reported, although reporting of pragmatic outcomes may have a better chance of influencing practice. However, the main analysis, the one we learn from, should be the intent to treat analysis, i.e. where all patients who were randomized are included for analysis of the main outcome in their original study arms.

To sum up, the Journal welcomes submissions of well-designed and well-reported RCTs in the area of antimicrobial chemotherapy, particularly those that address significant problems and assess outcomes that matter to patients.

Transparency declarations

None to declare.

References