Letters to the Editor

Sir, Dr Parienti reminds us, in his comments1 on the DAUFIN trial,2 that simpler is not always better, even if the adherence rate was better with once-daily regimens than with twice-daily regimens according to a recent meta-analysis3 (but the effect was only modest and more pronounced at the time of treatment initiation). Treatment interruptions are a risk factor for non-nucleotide reverse transcriptase inhibitor (NNRTI) resistance development, but no difference has been shown when nevirapine was administered once or twice a day.4

More early virological failures with resistance to efavirenz have been observed with didanosine/lamivudine/efavirenz once a day compared with zidovudine/lamivudine + efavirenz twice a day,5 but the adherence rate was not different between treatment arms; therefore, the resistance mutations are probably more associated with the NRTI background choice.

Despite a non-optimal adherence rate with the once-daily regimen in the DAUFIN trial, the high virological failure rate remains unexplained, and the same virological failures have been observed in a study by Lapadula et al.,6 which evaluated the tenofovir, emtricitabine and nevirapine combination, but with a twice-a-day nevirapine administration.

Finally, if we agree that simpler is not always better, on the other hand, it is not worse. According to clinical trials, as well as real life, most of the patients on antiretroviral treatment remain in virological success while more and more combinations are administered once daily.

Transparency declarations

C. A. has received consulting fees from Gilead and GlaxoSmithKline and lecture fees from Bristol-Myers Squibb, GlaxoSmithKline and Merck. All other authors: none to declare.

References


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Keywords: sepsis, infective endocarditis, antibiotic combinations, guidelines

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Sir,

We read with great interest the recently published review ‘Aminoglycoside drugs in clinical practice: an evidence-based approach’.1 We welcome the authors’ intention to present an evidence-based approach to aminoglycoside use, which they do in the form of a systematic review of the literature, followed by a meta-analysis.

We would like to raise several points:

(i) The authors have stated that ‘Resistant bacteria have renewed our interest in the aminoglycoside drugs’. While this is partly true, we would argue that interest has never diminished as these drugs are widely used, regarded as being effective as monotherapy and in combination, and are being increasingly seen as a treatment and surgical prophylactic alternative to many β-lactam antibiotics, which, rightly or wrongly, are perceived as more potent initiators of Clostridium difficile colitis.

(ii) The authors state that there is interest in aminoglycoside use for Gram-negative infections that are resistant to ‘more efficacious and less toxic drugs’. We would question which drugs are more efficacious and of course if the organisms are resistant to these agents, efficacy would be unlikely.

(iii) Later, the reader’s attention is drawn to Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella spp. (because they are resistant to the above-mentioned drugs), with the statement that ‘The alternatives are usually aminoglycosides, colistin and (potentially) tigecycline’, with a suggestion for comparative clinical trials. As far as we know, Acinetobacter spp. are inherently resistant to aminoglycosides.2

(iv) Regarding infective endocarditis, the authors recommend that ‘Practitioners would be well advised to use published guidelines, but within their limits, to take into account the fact that combination treatment is not supported by evidence’. The authors point out that trials with small numbers of patients were in favour of monotherapy (without aminoglycosides), but they ‘did not reach statistical significance’. Lack of evidence is not an argument against a practice. Such recommendations made by the working groups of scientific
societies and prominent experts\(^3\) should not be dismissed out of hand, as these recommendations, while perhaps not having the full weight of evidence, are supported by much clinical experience. It would be a brave clinician who deviates from internationally agreed guidelines that aim to provide the optimum care for the patient within a framework of ‘best practice’. In addition, medicolegal investigations tend to take a dim view of those who deviate from guidelines and policies. Infective endocarditis and sepsis still remain with significant mortality. The rate of treatment failure is even higher when different factors of microbial virulence (formation of biofilm, quorum sensing and destructive enzymes) or antimicrobial resistance (methicillin-resistant \textit{Staphylococcus aureus} and vancomycin-resistant enterococci) are implicated\(^4\) and, therefore, this is another argument pro aminoglycosides.

(v) Similarly, the authors argue against combination therapy with aminoglycosides for Gram-negative infections, stating that combinations do not improve efficacy and add side effects. However, in severe systemic infections, aminoglycosides in combination are a widely used and reliable therapeutic intervention, especially for empirical treatment of sepsis, systemic inflammatory response syndrome and septic shock. Combinations are used to achieve a rapid synergistic bactericidal effect, to broaden the spectrum of activity and to prevent emergence of resistance.\(^5\) In our own practice, we use aminoglycoside combinations except when the main antibiotic is a carbapenem. Recently, Spanish authors\(^6\) have found a lower mortality rate with aminoglycosides (9\%) in comparison with carbapenems (24.4\%) and quinolones (12.5\%) in the treatment of \textit{Enterobacter} bacteraemia. What we should ask is why the superiority of antibiotic combinations for infective endocarditis and sepsis, already proved \textit{in vitro} and in animal experiments,\(^5\) has not been confirmed in the studies cited by the authors. The reasons might be due to pharmacokinetics, severity of infection and co-morbidity.

(vi) A final comment is whether meta-analysis is the best method to draw evidence-based conclusions. How can such a variety of trials involving diverse settings, different patient populations, different antibiotics and dosage regimens, different timings of the appropriate therapy and different microorganisms with their virulence factors and specific mechanisms of resistance, and performed over a long period of time (25–30 years) be assessed and provide meaningful comparative conclusions?\(^7\)

These are just a few issues we wanted to share in the hope that it would stimulate scientific discussion and be helpful both for the investigators and the patients. We congratulate the authors on their comprehensive review, as well as for their continuous work on antibiotic stewardship in severe infections.

**Transparency declarations**

None to declare.

**References**


**Journal of Antimicrobial Chemotherapy**

doi:10.1093/jac/dkp091

Advance Access publication 14 March 2009

**Aminoglycoside drugs in clinical practice: an evidence-based approach—authors’ response**

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Sir,

We thank Keuleyan and Kirillov\(^1\) for their comments and beg to differ with most of them. The question of the advantages and disadvantages of aminoglycosides compared with other drugs is discussed in our review.\(^2\) Based on observational studies, we believe that treatment with an aminoglycoside is less effective than \(\beta\)-lactam treatment in septic patients with Gram-negative infections in sites other than those in the urinary tract. Randomized controlled trials on aminoglycosides as single treatment (for infections other than the urinary tract) are few and included a small number of septic patients.