Aminoglycoside/β-lactam combinations in clinical practice

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Randomized controlled trials failed to show an advantage of the addition of aminoglycosides to broad-spectrum β-lactams. In the present issue of the Journal of Antimicrobial Chemotherapy, an analysis of a large series of bacteraemic patients from Denmark, treated either with a narrow-spectrum β-lactam or with a combination of a β-lactam and an aminoglycoside, shows comparable outcomes in the two groups. In locations where broad-spectrum β-lactams are in common use, the addition of an aminoglycoside does not improve efficacy and adds side effects. In countries where the resistance is low enough to use ‘old’ β-lactams, and there is an unwillingness to use broad-spectrum β-lactams, evidence for the efficacy of combination treatment and for its role in keeping the resistance at a low level is wanting.

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The time-honoured practice of adding an aminoglycoside drug to a β-lactam antibiotic is not supported by evidence. Two systematic reviews and meta-analyses of randomized controlled trials addressing neutropenic patients1 and patients with sepsis2 failed to show a benefit in mortality or in treatment success for patients given combination therapy. The rate of side effects was increased by the addition of an aminoglycoside,1,2 whereas the percentage of infections caused by resistant microorganisms was not lowered.1–3

In the present issue of the Journal of Antimicrobial Chemotherapy, Freundlich et al.4 compared outcomes for patients treated with an appropriate β-lactam alone versus patients treated with an aminoglycoside in combination with a β-lactam, one of which provided appropriate coverage for the culprit pathogen. No differences were noted with regard to 30 and 180 day all-cause mortality and nephrotoxicity. The authors carefully discuss the limitations of the non-interventional retrospective study design. Data on sepsis presentation are lacking. Also we have no insight into the implicit considerations that led clinicians to choose combination or monotherapy, a shortcoming common to all observational studies. Nonetheless, several pertinent topics regarding combination therapy are addressed in this study and can be compared with the evidence available from randomized controlled trials.

The first issue is to address whether synergism between β-lactam drugs and aminoglycosides observed in vitro confers a clinical advantage. The two systematic reviews1,2 (and an unpublished update of ref. 1) included 34 studies (total of 4607 patients) in which a single β-lactam was compared with the combination of the same β-lactam and an aminoglycoside. The relative risk (RR) for mortality was 0.91 [95% confidence interval (95% CI) 0.73–1.15]; RR smaller than 1 favouring monotherapy. For treatment failure, the RR favoured combination treatment, with borderline statistical significance (RR 1.19, 95% CI 1.05–1.36). However, the definition of failure included a change in the initial antibiotic regimen. Most studies were not blinded, and thus the small excess of failures for monotherapy reflects the addition of an aminoglycoside and not a clinical event. All side effects, especially nephrotoxicity, were increased by the addition of an aminoglycoside. The synergism between β-lactam antibiotics and aminoglycosides observed in vitro could not be demonstrated in clinical trials.

Ninety-five randomized controlled trials (including 12 240 patients) compared a broad-spectrum β-lactam with a combination of a narrow-spectrum β-lactam and an aminoglycoside.1,2 Mortality was lower in the monotherapy arm, with borderline statistical significance, RR 0.87 (95% CI 0.75–1.01), as was treatment failure, RR 0.80 (95% CI 0.73–0.86). Side effects and nephrotoxicity were lower in the monotherapy arm. Infections assessed in these trials included mainly febrile neutropenia and abdominal and respiratory tract infections.

The only subgroup of Gram-negative pathogens for which the question of combination therapy is still open is Pseudomonas aeruginosa.5 Conclusive evidence is lacking, but we believe that a single antipseudomonal β-lactam drug is as efficient as combination treatment.6

The second issue is to address whether combination therapy is useful in order to broaden the empirical spectrum of coverage. In the Danish cohort, for example, aminoglycosides covered
99% of Gram-negative bacteria. However, this means single aminoglycoside coverage for patients with bacteria resistant to the empirically used β-lactam. In the Freundlich et al. study, adjusted mortality in the subgroup of patients given only an aminoglycoside as appropriate empirical treatment (525 patients, 54% of the aminoglycosides cohort) was similar to that of patients given an appropriate β-lactam (RR 0.92, 95% CI 0.65–1.30). Most patients in the aminoglycoside cohort had a urinary tract infection. Similar data are available from randomized controlled trials. Thirty-seven trials compared single aminoglycoside treatment with other antibiotics.7 The large majority of these trials assessed patients with urinary tract infections. Efficacy outcomes were similar, but bacteriological failure was more frequent with aminoglycosides. Single aminoglycoside therapy is safe for urinary tract infections, but there are insufficient data to recommend its use in other types of infections.

Finally, it is debatable whether combination therapy can prevent resistance development. For the individual patient, the answer is no.1–3 As for hospitals, treatment of septic patients with a narrow-spectrum β-lactam (mostly ampicillin or mecillinam) with the addition of an aminoglycoside is part of the ‘package’ that probably kept resistance in Scandinavian countries at very low levels, although we cannot know whether it had an important or a negligible contribution.

There are two questions that we could address to policy makers in Denmark. The first one is whether they should switch from the combination of a narrow-spectrum β-lactam and aminoglycoside to monotherapy with a broader spectrum β-lactam, given that research evidence shows an advantage to monotherapy with a broad-spectrum β-lactam. We can guess that their answer would be that it is part of a policy that keeps resistance at a minimum and provides effective treatment for present and future patients and that such an advantage should not be forfeited for the benefit of broad-spectrum antibiotics. The results of the study of Freundlich et al.4 raise another question, i.e. whether a single ‘narrow-spectrum’ β-lactam is as effective as its combination with an aminoglycoside, given that Freundlich et al.4 were unable to show a benefit for the combination therapy. There are not enough randomized controlled trials to answer this question.

In conclusion, in locations where penicillins with anti-Gram-negative activity combined with a β-lactamase inhibitor, or third-generation cephalosporins, or carbapenems are in common use, the addition of an aminoglycoside does not improve efficacy and adds side effects. In countries where the resistance is low enough to use ‘old’ β-lactams, and there is unwilling to use broad-spectrum β-lactams, evidence for the efficacy (or lack of) of combination treatment is wanting. A large pragmatic study in Scandinavian countries comparing monotherapy with ‘old’ β-lactams with a combination of β-lactam/aminoglycosides would be of huge interest.

### Transparency declarations

None to declare.

### References