Abstract

Objective To compare β lactam monotherapy with β lactam-aminoglycoside combination therapy for severe infections.

Data sources Medline, Embase, Lilacs, Cochrane Library, and conference proceedings, to 2003; references of included studies; contact with all authors. No restrictions, such as language, year of publication, or publication status.

Study selection All randomised trials of β lactam monotherapy compared with β lactam-aminoglycoside combination therapy for patients without neutropenia who fulfilled criteria for sepsis.

Results 64 trials with 7586 patients were included. There was no difference in all cause fatality (relative risk 0.90, 95% confidence interval 0.77 to 1.06). 12 studies compared the same β lactam (1.02, 0.76 to 1.38), and 31 studies compared different β lactams (0.85, 0.69 to 1.05). Clinical failure was more common with combination treatment overall (0.87, 0.78 to 0.97) and among studies comparing different β lactams (0.76, 0.68 to 0.86). There was no advantage to combination therapy among patients with Gram negative infections (1835 patients) or Pseudomonas aeruginosa infections (426 patients). There was no difference in the rate of development of resistance. Nephrotoxicity was significantly more common with combination therapy (0.36, 0.28 to 0.47). Heterogeneity was not significant for these comparisons.

Conclusions In the treatment of sepsis the addition of an aminoglycoside to β lactams should be discouraged. Fatality remains unchanged, while the risk for adverse events is increased.

Introduction

Treatment with a combination of a β lactam and an aminoglycoside is purported to be superior to β lactam alone for sepsis on the basis of potential advantages such as in vitro synergism and prevention of development of resistance.1-7 Textbooks and guidelines advise the combination for specific pathogens, such as Pseudomonas aeruginosa and other Gram negative bacteria, and for infections commonly caused by these pathogens.3 In aiming for optimal antibiotic treatment of severe infections, hospital clinicians tend to use combination therapy despite the lack of direct evidence for its effectiveness. Observational studies show that 56% of patients with septic shock in the intensive care unit are given β lactam-aminoglycoside combination therapy.

We performed a systematic review and meta-analysis of randomised trials comparing β lactam-aminoglycoside combination therapy with β lactam monotherapy for severe infections in patients without neutropenia.

Methods

We searched Medline, Embase, Lilacs, the Cochrane Library (all up to March 2003), conference proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (1995-2002), and citations of included trials (see bmj.com for details).

We included all randomised and quasi-randomised trials that compared any β lactam monotherapy with any β lactam-aminoglycoside combination therapy.
combination of a β-lactam and an aminoglycoside for severe infections. Severe infection was defined as clinical evidence of infection, plus evidence of a systemic response to infection. We excluded studies with a drop-out rate above 30%, unless intention to treat analysis was given for mortality or failure outcomes, and studies with more than 15% of patients with neutropenia, neonates, and preterm babies.

The primary outcome assessed was all cause fatality by the end of study follow up and up to 30 days. Secondary outcomes included treatment failure, defined as death, non-resolving primary infection, any modification to allocated antibiotics, or any therapeutic invasive intervention not defined by protocol; bacteriological failure, defined as persistence of primary pathogen; bacterial and fungal superinfections and colonisation; adverse events; and length of hospital stay. We separated studies that compared the same β-lactam from studies that compared different β-lactams. We performed subgroup analyses for P. aeruginosa infections, any Gram negative infection, bacteraemia, any Gram positive infection, and endocarditis. We did not detect an advantage to combination therapy with any subgroup tested (see bmj.com).

**Development of resistance**—Combination therapy did not lower bacterial superinfection or colonisation rates, which we would have expected if combination therapy prevented the development of resistance. Relative risks tended to favour monotherapy for bacterial superinfections (0.79, 0.59 to 1.06). Rates of fungal superinfection were similar. Twenty six studies reported coverage rates of the allocated treatment, although outcomes were not related to coverage. Among studies with different β-lactams, the monotherapy β lactam provided broader coverage than the combination β lactam in 13 studies, the opposite occurring in two studies. Combined coverage of the β lactam and the aminoglycoside equalled monotherapy in these studies.

**Dropouts and adverse events**—The dropout rate was 12.6% and similar in both study groups (1.01, 0.85 to 1.20, 24 studies, 3631 patients). Few patients (2%) discontinued treatment because of adverse events with no difference between study groups (0.89, 0.52 to 1.52, 15 studies, 3042 patients). Nephrotoxicity was more common with combination therapy in nearly all studies, and the combined relative risk was 0.56 (0.28 to 0.47, fig 2), corresponding to a number needed to harm of 15 (14 to 17) for combination therapy.

**Sensitivity analysis**—Sensitivity analyses were carried out for measures of study quality. All sensitivity comparisons were non-significant. The advantage of monotherapy was more significant in trials that used some type of blinding. The funnel plot for treatment failure generated a nearly symmetrical “funnel distribution” (see bmj.com).

**Discussion**

### Main findings

In this systematic review of all randomised trials we have shown that β-lactam-aminoglycoside combination therapy and β-lactam monotherapy for the treatment of sepsis have similar effects in patients without neutropenia.

Twenty trials compared the same β-lactam. All cause fatality, the most significant and objective outcome, was not reduced by the addition of aminoglycosides. Clinical and bacteriological failure, which may be prone to bias with non-blinded trials and are of much lesser relevance to patients, were not significantly different. However, rates of adverse events increased with the aminoglycoside. Nephrotoxicity was much more common with combination therapy.

Forty four trials compared a broad spectrum, usually novel, β lactam with a “routine” combination regimen. Rates of appropriate antibiotic treatment with combination therapy and monotherapy were significantly superior to combination therapy among studies that compared different β-lactams. The overall comparison favoured monotherapy for clinical failure (0.87, 0.78 to 0.97; 6616 patients; number needed to treat 34, 20 to 147) and for bacteriological failure (0.86, 0.72 to 1.02; 3511 patients).

**Subgroup analysis**—Major effectiveness outcomes were compared within the defined patient subgroups: P. aeruginosa infections, any Gram negative infection, bacteraemia, non-urinary tract infections, Gram positive infections, and endocarditis. We did not detect an advantage to combination therapy with any subgroup tested (see bmj.com).
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How should these findings be interpreted?

It can be debated which design appropriately examines the clinical interpretation of synergism, studies comparing same or different β-lactams. Synergism has been defined as a 2 log₁₀ or greater reduction in bacterial count with the combination versus that with each of the agents alone. In studies comparing the same β-lactam this is directly tested, but the effect of increasing the antibiotic spectrum cannot be separated from a synergistic effect. In studies comparing different β-lactams the spectrum of coverage was similar in both arms. However, synergism can be examined only indirectly. If we assume that the aminoglycoside offers more than its additional coverage, the combination arm should perform as well, or better, than the broader table of data.
spectrum β lactam monotherapy. With the former design we did not detect an advantage to the combination, while with the latter we found an advantage to monotherapy.

Weaknesses of the study
The quality of included studies was poor overall. We did not detect bias induced by any of the measures assessed. We could not obtain data on all cause fatality for 33% of studies. It is unlikely that missing results would shift the results for studies comparing the same β lactam, but it is of concern that studies comparing different β lactams may not detect important harm to patients.

Our assessment of treatment effects for patients with *P. aeruginosa*, Gram negative, and blood infections relies on subgroup analysis. We did not detect an advantage for combination therapy among these patients. Only few patients with documented *P. aeruginosa* infections could be evaluated. The types of infections addressed by included studies suggest that further infections were caused by this pathogen.

**Does further evidence support our findings?**
Suggestions for an advantage for combination treatment for *P. aeruginosa* rely mostly on a prospective observational study. A similar study focusing on Klebsiella bacteraemia found an advantage for combination therapy only among patients with hypotension, while other studies have not found such an advantage.

In a comparison of β lactam monotherapy with β lactam-aminoglycoside combination therapy restricted to patients with neutropenia we found no advantage to combination treatment. Although the approach to the management of patients with and without neutropenia is separated in clinical practice, this similarity supports a biological basis underlying our results.
Early appropriate antibiotic treatment for severe infections decreases mortality.

In vitro studies have shown that the bactericidal activity of a β-lactam may be enhanced by the addition of an aminoglycoside.

Prospective studies have suggested that the combination also has a clinical advantage.

There is no difference in mortality when β-lactam-aminoglycoside combination therapy is compared with β-lactam monotherapy.

Clinical failure and renal toxicity are more common with combination therapy.

β-lactam-aminoglycoside combination therapy does not improve clinical outcomes in patients with severe infections.

Implications for practice
Antibiotic treatment is nearly always instituted empirically and is often continued with no isolate to direct specific treatment. Most trials assessed this scenario and do not support a benefit for combination therapy. Clinicians may still opt for combination empirical treatment to increase the probability of appropriate empirical treatment, which has indeed been shown to improve survival. Current evidence suggests that aminoglycoside monotherapy may be inadequate for infections outside the urinary tract. Thus, for the purpose of enhancing antimicrobial spectrum, aminoglycosides may constitute a poor choice.

Implications for further research
Novel β-lactams should not be compared with older generation β-lactams or penicillins combined with aminoglycosides. The reason for further trials assessing the addition of an aminoglycoside to a β-lactam seems dubious as well.

We included in our review a small subset of trials that assessed the value of addition of an aminoglycoside in Gram positive infections, β-lactam-aminoglycoside combination therapy is well ingrained in existing guidelines and clinical practice with these infections, yet our results do not point to a clinical benefit with combination therapy. With these infections, further studies should assess whether the addition of an aminoglycoside is justified.

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