Aminoglycoside drugs in clinical practice: an evidence-based approach

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Resistant bacteria have renewed our interest in the aminoglycoside drugs. Evidence on the efficiency of aminoglycosides in their different clinical uses is available from numerous randomized controlled trials and has been accrued and examined in recent systematic reviews and meta-analyses. Their results show that aminoglycosides should not be added to broad-spectrum β-lactams to achieve synergism in treating Gram-negative infections as combination does not improve efficacy and adds side effects. The evidence from randomized trials in humans does not support the use of aminoglycosides in staphylococcal or streptococcal endocarditis, and is lacking for endocarditis caused by enterococci. Aminoglycosides are efficacious and safe as single drugs for the treatment of pyelonephritis and sepsis of a urinary source, but their efficacy might be lower than that of β-lactams in Gram-negative infections of other sources. In patients with no risk factors, aminoglycosides are as safe as β-lactams regarding side effects. They probably induce less resistance. Pragmatic large trials are needed to answer open clinical questions on the use of aminoglycosides.

Keywords: aminoglycosides, synergism, β-lactams, evidence-based medicine

Introduction

The emergence of multiresistant bacteria and the impression that the decline in susceptibility to aminoglycoside drugs is less steep over the years than for other drugs have renewed our interest in the aminoglycosides. Several recent systematic reviews and meta-analyses have examined the evidence for efficiency of aminoglycosides. ‘Evidence’ is used here in the manner of evidence-based medicine, assuming that the best evidence is derived from methodologically correct randomized controlled trials; while data gleaned from other designs (observational studies, in vitro and animal experiments) are less convincing.

There are several instances in which clinicians may consider the use of an aminoglycoside drug:

(i) In combination with a β-lactam drug for treatment of septic patients with Gram-negative infections. The justifications for combination treatment are: synergism and thus increased efficacy; the hope that it will repress the emergence and selection of resistant strains during treatment; and broader coverage (which is relevant for empirical treatment of suspected Gram-negative infections).

(ii) In combination with another drug for specific Gram-positive infections, mainly bacterial endocarditis, to achieve synergy.

(iii) As single-drug treatment for Gram-negative pathogens that are resistant to more efficacious and less toxic drugs.

(iv) As first-line, single-drug treatment for Gram-negative infections (including the use of aminoglycosides together with other drugs to broaden anti-Gram-negative spectrum). The assumptions underlying these uses are: that aminoglycosides are inexpensive and induce less resistance than other drugs; that their efficiency is equal to that of other drugs; and if not, the difference is of no great magnitude, being compensated by the beneficial ecological impact and by the cost difference. This instance should be divided into three. In countries with low resistance and strict policies on antibiotic use (mainly Scandinavian countries), aminoglycosides are used this way1–3. Physicians in low-income countries may elect to use aminoglycosides because of their low cost and convenience of administration.4 Theoretically, countries with a moderate problem of resistance (such as the USA and some European countries) might decide on a policy by which wide-spectrum anti-Gram-negative β-lactam drugs and fluoroquinolones are replaced to a high degree by aminoglycosides.

The counterbalances of efficacy are immediate costs (of the drug, administration and monitoring), side effects and impact on future resistance. Immediate costs differ from place to place. In general, they are lower for aminoglycoside drugs than for other...
intravenous drugs with comparable in vitro spectrum, and we will not discuss them further.

In the present review, we examine the evidence for the efficacy, side effects and ecological impact of the aminoglycosides, according to the different clinical scenarios in which the use of aminoglycoside drugs might be considered.

Aminoglycosides in combination with a β-lactam drug for suspected or proven Gram-negative sepsis

The main question to address under this heading is whether combinations of an aminoglycoside drug and a β-lactam are synergistic in vivo. If synergism confers a measurable benefit to patients, then those given a β-lactam drug should fare worse than comparable patients given the same β-lactam drug plus an aminoglycoside. Two systematic reviews have addressed the question of whether a single β-lactam drug is as efficient as the combination of an aminoglycoside with a β-lactam drug, one in neutropenic patients and one in immunocompetent patients.

For the purposes of this review, we combined the results of 30 studies (references 5 and 6, and an unpublished update of reference 5, total of 4314 patients randomized) in which a single β-lactam drug was compared with a combination of the same β-lactam drug and an aminoglycoside. Mortality was reported in 15 studies and was comparable for the two arms [relative risk (RR) of 0.91, 95% confidence interval (CI) 0.72–1.15, RR < 1 favouring monotherapy] [Figure S1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. For treatment failure, the RR favoured combination treatment (RR 1.12, 95% CI 1.04–1.20) [Figure S2, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. However, in most studies, 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.

Nephrotoxicity, all side effects and side effects that led to discontinuation of treatment were more common in the arm in which an aminoglycoside was added. All these studies but four tested broad-spectrum β-lactams: third-generation cephalosporins, a broad-spectrum penicillin plus a β-lactam inhibitor; or carbapenems. Eighteen studies used amikacin; and the others, gentamicin, netilmicin and tobramycin in equal numbers. No difference in efficacy or toxicity could be shown among drugs. We can safely state that the addition of an aminoglycoside to these antibiotics does not improve efficacy but increases the chance of side effects. The in vitro synergy of β-lactam drugs and aminoglycosides does not translate into a benefit for patients.

A clinical effect for synergy might exist only for specific pathogens (mainly Pseudomonas aeruginosa), that are too rare to influence the results of studies addressing all patients with Gram-negative infections. No randomized trials addressed this issue in patients with P. aeruginosa (or other specific Gram-negative pathogens), and results from randomized controlled trials on mortality in the subgroup of patients with P. aeruginosa infections were rarely reported. In 71 patients with P. aeruginosa infections (reported in nine trials), the RR for mortality was 0.87 (95% CI 0.34–2.24); RR < 1 favouring monotherapy. Among children with cystic fibrosis, eradication of P. aeruginosa at end of therapy was higher with monotherapy compared with combination therapy with an odds ratio of 5.63 (95% CI 2.12–14.94). Safdar et al. found a significant survival advantage of combination therapy for bacteraemia caused by P. aeruginosa in comparative, non-randomized studies. However, when excluding aminoglycoside monotherapy from the monotherapy arm, the RR for mortality was 0.81 (95% CI 0.48–1.35), a statistically non-significant result, but certainly not supporting the use of combination therapy for P. aeruginosa infections.

A second aim in adding an aminoglycoside to a β-lactam drug is to extend empirical coverage. This increment in coverage was not translated into a practical benefit for patients (see above). However, the susceptibility of Gram-negative isolates to the β-lactam drug used in studies comparing a single β-lactam drug with a combination of the same β-lactam drug and an aminoglycoside was ~90% (reported in 10 studies). The research evidence does not help to decide beneath which threshold of susceptibility broadening of the coverage by adding an aminoglycoside to the empirical treatment might translate into a clinical benefit.

A recent Cochrane review showed no advantage for combination treatment compared with a single β-lactam for patients with cystic fibrosis in terms of lung function, symptom scores and bacteriological outcome measures. Seven trials assessing the same β-lactam in both arms addressed this comparison, but the overall methodological rigour of the trials was low.

During treatment, pathogens resistant to the β-lactam drug were isolated with the same frequency from patients given a single β-lactam drug, and from patients given combination treatment. The addition of an aminoglycoside did not suppress the emergence and selection of resistant strains.

A case for combination therapy might be made in locations in which the policy is to avoid the use of broad-spectrum β-lactams, claiming that the combination of a synthetic, anti-Gram-negative penicillin and an aminoglycoside is equivalent to a broad-spectrum β-lactam and might induce less resistant strains. In a large observational study from Denmark, no difference in 1 month mortality was shown between patients with bacteraemia treated with a β-lactam (mainly ampicillin) plus an aminoglycoside, and patients treated with a β-lactam only (mainly ampicillin or cefuroxime).

However, the results from randomized controlled trials show that patients given such combination therapy fare worse than patients given broad-spectrum β-lactam monotherapy of equal coverage. Ninety-five randomized controlled trials (including 12 240 patients) compared a single β-lactam with a combination of a different β-lactam and an aminoglycoside. 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). In patients with Gram-negative bacterial infections and a baseline fatality rate of 5% (e.g. patients with neutropenia), this RR translates into 154 patients needed to be treated to prevent one death; if the fatality rate is ~10%, the number needed to be treated to prevent one death is 77.

Because of restrictive inclusion criteria, results of randomized controlled trials might have limited applicability to critically ill patients; namely those with septic shock and end-organ damage. Two large observational studies in which such restrictions on patient inclusion were not imposed assessed the effect of monotherapy versus combination therapy in bacteraemic patients and
did not demonstrate a survival advantage of combination therapy over monotherapy with a β-lactam drug.1,14

Aminoglycosides in combination with a β-lactam drug for bacterial endocarditis caused by Gram-positive cocci

Four randomized controlled trials addressed this question in patients with Staphylococcus aureus endocarditis, and one in patients with endocarditis caused by viridans streptococci. The point estimates for survival, treatment success and treatment success without surgery were in favour of monotherapy, but did not reach statistical significance. Nephrotoxicity was significantly more common in patients given an aminoglycoside drug. No randomized controlled trial included patients with enterococcal endocarditis.6,12

Aminoglycosides as single-drug treatment for Gram-negative pathogens that are resistant to more efficacious and less toxic drugs

We are witnessing the emergence of Gram-negative pathogens (Acinetobacter baumannii, P. aeruginosa and Klebsiella spp.) that are resistant to drugs perceived to be both efficacious and non-toxic. The alternatives are usually aminoglycosides, colistin and (potentially) tigecycline. There is a dearth of randomized controlled trials on these drugs as single treatment, and no trial that compares them. Whether aminoglycosides are better or worse than colistin or tigecycline is an open question.

Aminoglycosides as first-line, single-drug treatment

Aminoglycosides as monotherapy were compared with other drugs (mainly β-lactams and fluoroquinolones) in 37 trials, of which 26 included only patients with urinary tract infection.13 Only a minority of the included patients had sepsis. Aminoglycosides were equally effective as comparator drugs looking at all-cause mortality (RR 1.11, 95% CI 0.68–1.81, nine trials, 503 patients) and treatment failure (RR 1.10, 95% CI 0.96–1.27, 32 trials, 1890 patients); but were associated with a significantly higher rate of bacteriological failure at end of therapy (RR 1.44, 95% CI 1.21–1.72, 27 trials, 1668 patients). Most studies tested gentamicin, and no significant difference in toxicity or efficacy between aminoglycoside drugs could be shown. Because of the patient mix in these studies, the equivalence of aminoglycosides to other drugs can be purported for patients with urinary tract infections, but hardly for patients with other types of Gram-negative infections. On the basis of a large, prospective, observational study on patients with bacteremia,11 we believe that single treatment with an aminoglycoside is less effective than β-lactam treatment in septic patients with Gram-negative infections from sites other than the urinary tract. A special instance under this heading is that of patients with an intra-abdominal infection in which an aminoglycoside is used as the main anti-Gram-negative agent. Two meta-analyses14,15 found that regimens including an aminoglycoside were less effective in terms of clinical response than regimens including a β-lactam as the anti-Gram-negative agent; but mortality was unaffected. A Cochrane review assessed trials of secondary peritonitis and concluded that regimens including aminoglycosides were as effective as other regimens in terms of clinical response and survival, although the point estimates favoured the comparators and not the aminoglycosides.16

Side effects

Convincing evidence shows that a single daily dose of an aminoglycoside drug is at least as effective, and might cause fewer and milder side effects than multiple daily doses in immunocompetent adult patients (excluding patients with bacterial endocarditis),17,18 children,19,19 neutropenic patients18,20 and patients with cystic fibrosis.21 It is interesting to note that the absolute rate of nephrotoxicity (generally defined as an increase in creatinine concentration of 50% or 25–45 μmol/L over the pretreatment value) in patients given a single daily dose in clinical trials was low, 5.5%,19 and no data were available on severe nephrotoxicity. The duration of treatment in these studies was, in general, 7–10 days. In trials that compared aminoglycosides as monotherapy with β-lactams,13 significantly fewer and milder adverse effects were observed in patients treated with aminoglycosides compared with patients treated with β-lactams (RR 0.46, 95% CI 0.33–0.63), mainly because of the higher percentage of antibiotic-associated diarrhoea with β-lactams. Discontinuation rates because of severe adverse events were similar. On the other hand, a high rate of nephrotoxicity and some cases of irreversible nephrotoxicity and ototoxicity were registered in patients with risk factors for nephro- and ototoxicity.22–24

We can conclude that patients without risk factors for nephrotoxicity to whom aminoglycosides are given for 7–10 days or less are at about the same risk of suffering a severe side effect as patients given a β-lactam drug. In a recent review, Drusano et al.25 suggest ways of deciding on the dose and schedule of administration of aminoglycosides to minimize toxicity and increase efficacy, based mainly on pharmacokinetic and pharmacodynamic considerations.

Linking consumption to future resistance

The question of whether aminoglycosides have a gentler slope for the rise in resistance over time versus consumption can be considered on two levels. The first is the level of the individual patient. Only five trials that compared an aminoglycoside with a β-lactam reported on isolation of resistant bacteria during or shortly after treatment. Bacteria resistant to aminoglycosides were isolated less often from patients treated with aminoglycosides than bacteria resistant to the β-lactam drug in patients treated with the same β-lactam, RR 0.44, 95% CI 0.23–0.83.13

On the second level are ecological studies that look at the association between consumption and change in resistance to aminoglycoside in large units (departments, hospitals, or even counties or countries) over a longer time-scale. The general impression is that the slope in rise of resistance to aminoglycosides might be gentler than for other drugs,26–28 although the quality of the data is far from satisfying.
We have asked whether the consumption of an antibiotic in a specific department influences the chance that a patient with a hospital-acquired bacteraemia will have a pathogen resistant to the same antibiotic (patient-level data, taking into account the antibiotic treatment the patient was given in the last month).29 Departmental consumption of cephalosporins and amikacin in the year previous to acquiring the infection was associated with significantly higher odds of a resistant pathogen, but this was not the case with gentamicin.

In Denmark, for which good-quality data are available, the resistance of *Escherichia coli* blood isolates to gentamicin rose from <1% in 2000 to ~2% in 2006.30 However, the consumption of gentamicin in 1997 constituted only 8% of the total consumption of antibiotics in hospitals (in defined daily doses), and only 3% in 2006.30

The addition of an aminoglycoside to a β-lactam did not prevent the development of resistance to the β-lactam drug.5,6,10 In trials assessing monotherapy versus combination therapy, the rate of breakthrough infections representing infections purportedly resistant to the given regimen, occurred with similar frequency following monotherapy and combination therapy. Surveillance for resistance development and colonization with resistant pathogens were rarely performed in these trials. A systematic review focusing on these outcomes identified eight randomized controlled trials that reported these outcomes.10 Emergence of resistance was not significantly different (odds ratio 0.90, 95% CI 0.56–1.47) for combination versus monotherapy. In these trials, superinfections were actually significantly less frequent with monotherapy (OR 0.62, 95% CI 0.42–0.93), while failure due to superinfections or due to emergence of resistance was not significantly different.

Patients with cystic fibrosis are chronically colonized with Gram-negative bacteria, mainly *P. aeruginosa*, thus forming a special subgroup of patients to assess with regard to emergence and selection of resistance. No consistent advantage to combination therapy could be demonstrated in the Cochrane review assessing people with cystic fibrosis.7 Thus, the evidence does not corroborate the notion that combination therapy prevents or reduces the development of resistance to the β-lactam.

**Implications for practice**

**Combination therapy for Gram-negative infections**

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 for Gram-negative infections and cover a large percentage of the local pathogens, an aminoglycoside should not be added as combination does not improve efficacy and adds side effects.

For locations in which broad-spectrum β-lactams cover significantly less than 90% of Gram-negative isolates, the addition of an aminoglycoside to empirical treatment in order to improve coverage might be considered. To do that we have to take into account: (i) that the efficacy of aminoglycosides as single drugs might be lower than for other drugs; and (ii) the local cross-resistance and the fact that other anti-Gram-negative drugs (e.g. fluoroquinolones)31 might be candidates for this role.

Broad-spectrum β-lactams are probably more effective and less toxic than combinations of narrow-spectrum β-lactams with an aminoglycoside. For countries in which the resistance is low enough to use ‘old’ β-lactams, and that are unwilling to use broad-spectrum β-lactams, evidence from randomized controlled trials for the efficacy (or lack of) of combination treatment is wanting. At least one observational study showed no advantage of combination therapy over an ‘old’ β-lactam drug.

Data on the treatment of *P. aeruginosa* infections with combination therapy are scant and their interpretation is contradictory. We believe that the evidence does not support an advantage to the addition of an aminoglycoside to an anti-pseudomonal β-lactam, and thus in our practice we use monotherapy with an anti-pseudomonal β-lactam for *P. aeruginosa* infections.

**Combination with a β-lactam drug for bacterial endocarditis caused by Gram-positive cocci**

The evidence from randomized trials in humans does not support the use of aminoglycosides in staphylococcal or streptococcal endocarditis, and is lacking for endocarditis caused by enterococci. However, the trials are few and included a small number of patients. Practitioners would be well advised to use published guidelines,32,33 but within their limits, to take into account the fact that combination treatment is not supported by evidence.

**Aminoglycosides as first-line, single-drug treatment**

Aminoglycosides are efficacious and safe for the treatment of pyelonephritis and sepsis of a urinary source. The data from randomized controlled trials are too scarce to draw conclusions on severe Gram-negative infections from other sources of infection, while observational studies show that aminoglycosides might be less efficacious than β-lactam drugs. Use of aminoglycosides as a first-line anti-Gram-negative treatment for severe infections (other than urinary infections) implies a strong belief that their low cost and convenience of administration and a (possible) gentler ecological pressure outweigh the disadvantage (in terms of mortality) to present patients. It is difficult to support such a belief from existing data or models. Better evidence and models might support or defeat such a belief.

**Implications for research**

We believe that further randomized clinical trials comparing a β-lactam drug with the combination of the same β-lactam and an aminoglycoside for suspected or proven Gram-negative infections (other than *P. aeruginosa*) cannot be justified. The ‘conventional’ arm in antibiotic trials in these patients should be a single appropriate β-lactam drug and not combination treatment. Table 1 is a list of randomized clinical trials that should be done to answer clinical questions. They have a few problems in common: the drugs are old and a sponsor will be difficult to find; these are trials to test equivalence, demanding a large sample size; and (but for the last item) they address relatively rare infections, and a large number of centres will have to recruit patients to complete the trials in a reasonable timeframe. To perform these trials (which are needed), and other trials that address antibiotic agents that lack commercial appeal, we need...
a working paradigm for inexpensive, pragmatic, large multicentre trials.

The question of the rise in resistance to aminoglycoside drugs compared with other antibiotics is difficult to address by randomized controlled trials. A good design would be a comparison between two periods with a measurable change in aminoglycoside consumption, looking at consumption and resistance to aminoglycosides (and other drugs) performed and reported according to good standards.34

Changes in the spectrum of activity (new drugs or successful development of inhibitors of enzymes that inactivate aminoglycosides)35 or a better safety profile36 would justify further clinical testing of aminoglycoside drugs.

Transparency declarations

We have no conflict of interests.

Supplementary data

Figures S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


Review


