Effect of Aminoglycoside and β-Lactam Combination Therapy versus β-Lactam Monotherapy on the Emergence of Antimicrobial Resistance: A Meta-analysis of Randomized, Controlled Trials

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Background. The addition of an aminoglycoside to a β-lactam therapy regimen has been suggested to have a beneficial effect in delaying or preventing the development of antimicrobial resistance. We studied the effect of aminoglycoside/β-lactam combination therapy versus β-lactam monotherapy on the emergence of resistance.

Methods. We performed a meta-analysis of randomized, controlled trials (RCTs) that compared aminoglycoside/β-lactam combination therapy with β-lactam monotherapy and that reported data regarding the emergence of resistance (primary outcome) and/or development of superinfection, treatment failure, treatment failure attributable to emergence of resistance, treatment failure attributable to superinfection, all-cause mortality during treatment, and mortality due to infection. Data for this meta-analysis were identified from the PubMed database, Current Contents database, Cochrane central register of controlled trials, and references in relevant articles.

Results. A total of 8 RCTs were included in the analysis. β-Lactam monotherapy was not associated with a greater emergence of resistance than was the aminoglycoside/β-lactam combination (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.56–1.47). Actually, β-lactam monotherapy was associated with fewer superinfections (OR, 0.62; 95% CI, 0.42–0.93) and fewer treatment failures (OR, 0.62; 95% CI, 0.38–1.01). Rates of treatment failure attributable to emergence of resistance (OR, 3.09; 95% CI, 0.75–12.82), treatment failure attributable to superinfection (OR, 0.60; 95% CI, 0.33–1.10), all-cause mortality during treatment (OR, 0.70; 95% CI, 0.40–1.25), and mortality due to infection (OR, 0.74; 95% CI, 0.46–1.21) did not differ significantly between the 2 regimens.

Conclusions. Compared with β-lactam monotherapy, the aminoglycoside/β-lactam combination was not associated with a beneficial effect on the development of antimicrobial resistance among initially antimicrobial-susceptible isolates.

Combination antimicrobial therapy has been tried for the management of a variety of infectious diseases, primarily because drugs with different mechanisms of action may act synergistically (i.e., a >4-fold decrease in the MIC of each drug when tested together against a pathogen in vitro). Combination therapy may also allow the use of smaller doses of each of the combined drugs. The initial successful example of clinical use of combinations of antimicrobial agents was the treatment of infections due to Mycobacterium tuberculosis, for which combination therapy decreased the rate of development of resistance to rifampin [1]. Later, the same approach was used for the management of prosthetic valve endocarditis due to Staphylococcus species [2].

The rationale of using aminoglycoside/β-lactam combinations to delay or prevent the emergence of antimicrobial resistance was developed from data from animal studies in the early and mid-1980s [3–5]. Since then, the practice of using aminoglycoside/β-lactam combination therapy has become very popular for the management of infectious diseases in various conditions and patient populations. However, recent data have questioned the postulated beneficial effect of the
We tried to evaluate whether the addition of an aminoglycoside to a β-lactam therapy regimen has an effect on the development of antimicrobial resistance among hospitalized, nonneutropenic patients with serious infections. Thus, we performed a meta-analysis of the available randomized, controlled trials (RCTs) that examined the use of β-lactam monotherapy versus aminoglycoside/β-lactam combination therapy and presented data regarding the emergence of antimicrobial-resistant organisms during treatment or during the follow-up period.

METHODS

Data sources. Relevant studies for our meta-analysis were identified from searches of the PubMed database, Current Contents database, Cochrane central register of controlled trials, and references from articles, including review papers. Search terms included “monotherapy,” “combination therapy,” “resistance,” “susceptibility,” “synergy,” “β-lactam,” “aminoglycoside,” “clinical trial,” and “randomized controlled trial.”

Study selection. Two independent reviewers performed literature searches and examined the identified relevant studies for further evaluation of data on effectiveness and toxicity. A study was considered eligible if (1) it was an RCT, (2) it compared β-lactam monotherapy with the combination of an aminoglycoside with a β-lactam for the treatment of infection in hospitalized patients, (3) it examined the development of emergence of resistance (i.e., a change to a more-resistant phenotype) of bacterial isolates, (4) it studied the effectiveness of therapy and the mortality rate, (5) it was performed with adult patients, (6) it was written in the English language, and (7) it...
was published after 1 January 1980. Both studies with blinded designs and those with unblinded designs were included in the analysis. Experimental trials and studies focusing on pharmacokinetic and/or pharmacodynamic parameters were excluded. In addition, studies that focused on patients with neutropenia or patients with cystic fibrosis were excluded.

**Data extraction.** The following data were extracted from each study: year of publication, clinical setting, patient population, number of patients, antimicrobial agents and doses used, mortality, and clinical and microbiological outcomes. Data were extracted by 2 independent reviewers. Any disagreement between the 2 reviewers was resolved by consensus in meetings that involved all authors.

**Outcomes.** The primary outcome of the analysis was emergence of antimicrobial resistance—that is, the proportion of patients in whom bacterial isolates became resistant to the drug(s) administered to them, during treatment or during the follow-up study period. An organism was considered to have developed resistance only if it was clear from the study that it was reisolated and its susceptibility had changed to a more-resistant phenotype (i.e., from initially susceptible to intermediate or to resistant, or from initially intermediate to resistant). Secondary outcomes of the analysis were development of superinfection (i.e., isolation of a pathogen thought to be responsible for an infection that was of a different species from the initially isolated pathogen), treatment failure (no response to treatment, no clinical improvement, clinical deterioration, or death from infection), treatment failure attributable to emergence of resistance, treatment failure attributable to superinfection, all-cause mortality during treatment, and mortality due to infection.

**Data analysis and statistical methods.** Statistical analyses were performed using Meta-analyst software (Joseph Lau; Tufts University School of Medicine, Boston, MA). The heterogeneity between studies was assessed by using a $\chi^2$ test; a $P$ value of $<.10$ was used to note statistical significance in the analysis of heterogeneity [7]. Publication bias was assessed by the funnel plot method using Egger’s test [8]. Pooled ORs and 95% CIs for all primary and secondary outcomes were calculated by use of both the Mantel-Haenszel fixed-effects and the Der-Simonian-Laird random-effects models [9, 10]. For all analyses, results from the fixed-effects model are presented only when
there was no heterogeneity between studies; otherwise, results from the random-effects model are presented. The reported results of outcomes of the analyzed studies were weighted by the inverse of their variance with the fixed-effects model.

**RESULTS**

**Study selection.** We identified 65 relevant studies that compared outcomes for patients receiving β-lactam monotherapy with outcomes for those receiving an aminoglycoside/β-lactam combination. Thirty-six evaluable studies were published during 1980–1989 [11–46], and 29 studies were published from 1990 through October 2004 [47–75]. Thirteen studies were excluded from further analysis for various reasons: 7 studies were excluded because they examined perioperative anti-infective prophylaxis [16, 19, 27, 55, 58, 68], 3 were excluded because they were performed with immunocompromised patients [22, 69, 73], 1 was excluded because patients were stratified and received combination therapy or monotherapy according to the severity of disease [75], 1 was excluded because it was a comparative but not randomized trial [46], and 1 was excluded because the studied aminoglycoside was administered endotracheally [43].

Of the remaining 52 studies, 42 were excluded after careful review of the reported data because they did not present specific data regarding the emergence of resistance to the study antibiotics. Two more studies were excluded because it was not clearly stated whether the antimicrobial-resistant isolates were of the same species as the initial pathogens (i.e., there was emergence of resistance) or whether they were resistant isolates of different species (i.e., superinfection occurred) [54, 56]. Subsequently, 8 RCTs were evaluable for further analysis of data regarding the primary or secondary outcomes of our meta-analysis (tables 1 and 2) [12, 21, 30, 33, 61, 62, 67, 74].

**Emergence of resistance.** Analysis of data from 8 RCTs that were included in our study showed no difference in the emergence of antimicrobial resistance between β-lactam monotherapy and aminoglycoside/β-lactam combination therapy (OR, 0.90; 95% CI, 0.56–1.47). A subset analysis of 2 RCTs that used the same β-lactam in both trial arms did not show different results (OR, 0.66, 95% CI, 0.30–1.42). Figure 1 shows the individual study and pooled ORs, as well as their 95% CIs, for emergence of antimicrobial resistance during β-lactam monotherapy, compared with aminoglycoside/β-lactam combination therapy.

Five RCTs reported data regarding development of resistance in different microbial species. The respective noted rates of emergence of resistance for the main pathogens in the monotherapy and the combination therapy group were as follows: *Pseudomonas aeruginosa*, 8 (20.5%) of 39 isolates versus 10 (20.8%) of 48 isolates (P = .97); *Pseudomonas* species, 10 (16.4%) of 61 isolates versus 10 (14.9%) of 67 isolates (P = .82); *Klebsiella* species, 0 (0%) of 22 isolates versus 1 (3.8%) of 26 isolates (P = 1); *Proteus* species, 1 (6.3%) of 16 isolates versus 0 (0%) of 17 isolates (P = .48); *Acinetobacter* species, 0 (0%) of 11 isolates versus 1 (4.6%) of 22 isolates (P = 1); and *Staphylococcus aureus*, 2 (5.4%) of 37 isolates versus 7 (13.7%) of 51 isolates (P = .29).

**Development of superinfection.** Seven RCTs reported data regarding superinfections during the study period in each study group. The results of the analysis of superinfections for the main pathogens in the mono-therapy and the combination therapy group were as follows: Seventeen RCTs reported data regarding development of superinfection.

### Table 2. Reported data on mortality and treatment failure from the randomized, controlled trials included in the analysis.

<table>
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**NOTE.** Data are no. of patients with finding or result/no. of clinically evaluable patients. Combo arm, aminoglycoside/β-lactam combination therapy arm; mono arm, β-lactam monotherapy arm; ND, data not reported.
monotherapy, compared with the aminoglycoside/β-lactam combination (OR, 0.52; 95% CI, 0.28–0.97).

**Treatment failure.** Treatment failure in each treatment arm was reported in all 8 RCTs that were included in our study. Treatment failure was less common in the β-lactam monotherapy arm than in the aminoglycoside/β-lactam combination arm, as shown in figure 3A (OR, 0.62; 95% CI, 0.38–1.01).

Additional analysis of data regarding treatment failure was performed in 5 studies that presented information about treatment failure attributable to emergence of resistance, as well as in 5 studies that presented information about treatment failure attributable to superinfection. No statistically significant difference was found regarding either treatment failure due to emergence of resistance (OR, 3.09; 95% CI, 0.75–12.82; figure 3B) or treatment failure due to superinfection (OR, 0.60; 95% CI, 0.33–1.10; figure 3C).

**Mortality.** All-cause mortality during treatment was reported in 3 RCTs, whereas mortality attributable to infection was presented in 6 RCTs. No difference between β-lactam monotherapy and aminoglycoside/β-lactam combination therapy was found for either all-cause mortality (OR, 0.70; 95% CI, 0.40–1.25; figure 4A) or mortality due to infection (OR, 0.74; 95% CI, 0.46–1.21; figure 4B).

**DISCUSSION**

The results of several observational prospective and retrospective studies with different designs that examined risk factors

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**Figure 1.** Emergence of antimicrobial resistance in randomized controlled trials comparing β-lactam monotherapy with aminoglycoside/β-lactam combination therapy. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of antimicrobial resistance between the 2 regimens; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies. GA Study Group, German and Austrian Imipenem/Cilastin Study Group.

**Figure 2.** Development of superinfections in randomized, controlled trials comparing β-lactam monotherapy with aminoglycoside/β-lactam combination therapy. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in development of superinfections between the 2 regimens; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies.
Figure 3. Treatment failure due to any reason (A), due to emergence of resistance (B), or due to superinfections (C) in randomized, controlled trials comparing β-lactam monotherapy with aminoglycoside/β-lactam combination therapy. The size of each square denotes the proportion of information given by each trial. Vertical line, “no difference” point in development of superinfections between the 2 regimens; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies. GA Study Group, German and Austrian Imipenem/Cilastin Study Group.

and outcomes related to the emergence of antimicrobial resistance have not been consistent. For example, 3 studies that examined the emergence of antimicrobial resistance in initially antimicrobial-susceptible Enterobacter clinical isolates reported different results. Chow et al. [76] (in a prospective, noninterventional study) and Lee et al. [77] (in a retrospective study) reported that emergence of resistance to the administered β-lactam therapy did not occur less frequently among patients receiving aminoglycoside/β-lactam combination therapy than among patients receiving β-lactam monotherapy. On the other hand, in a retrospective study, Kaye et al. [78] reported a lower rate of emergence of antimicrobial resistance with the use of aminoglycoside/β-lactam combination therapy, compared with β-lactam monotherapy, although this finding was not statistically significant. Furthermore, 2 studies that examined the emergence of resistance (among other outcomes) in patients with pneumonia who received combination antimicrobial therapy or monotherapy also reported conflicting results. In a large retrospective study, Kosmidis et al. [79] reported that a lower rate of emergence of resistance was noted among patients with nosocomial pneumonia and among patients in the intensive care unit (ICU) who were receiving various antibiotic combinations (including β-lactams and aminoglycosides), compared with those who were receiving monotherapy. In contrast, in a more recent, large, prospective study, Alvarez-Lerma et al. [80] did not find any protective role for combination antimicrobial therapy against the emergence of resistance in ICU patients with pneumonia.

In an attempt to clarify the controversial issue of the comparative effect of aminoglycoside/β-lactam combination therapy versus β-lactam monotherapy on the emergence of antimicrobial resistance, we used data from RCTs that offer the most methodologically rigorous evidence. Previous meta-analyses have studied various outcomes in neutropenic patients and in immunocompetent patients with sepsis who received aminoglycoside/β-lactam combination therapy [6, 81, 82]. However, these studies mainly examined effectiveness and safety outcomes without focusing on the emergence of resistance. The results from our meta-analysis regarding effectiveness and mortality are in accordance with
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Figure 4. All-cause mortality (A) and mortality attributable to infection (B) in randomized, controlled trials comparing β-lactam monotherapy with aminoglycoside/β-lactam combination therapy. The size of each square denotes the proportion of information given by each trial. Vertical line, “no difference” point in development of superinfections between the 2 regimens; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies. GA Study Group, German and Austrian Imipenem/Cilastin Study Group.

the results from these studies; aminoglycoside/β-lactam combination therapy is associated with more clinical failures, but no difference in mortality rates has been found between the 2 regimens.

Our study has several limitations that should be taken into account when interpreting the results. The most important limitation is that most of the RCTs tested a different β-lactam in the compared treatment arms. Therefore, one may claim that development of resistance was influenced by the different β-lactams in the compared study arms, thus confounding the effect of aminoglycosides on this outcome, as well as other outcomes. However, the results of the analysis of data on the emergence of resistance from 2 studies in which the same β-lactam was administered in both study groups showed similar results with those of the full set of the studied RCTs.

Another limitation of our study is that the available RCTs comparing β-lactam monotherapy versus aminoglycoside/β-

lactam combination therapy focused primarily on effectiveness, toxicity, and mortality outcomes. These RCTs were not designed specifically to study the emergence of antimicrobial resistance and did not include the emergence of antimicrobial resistance as one of the primary outcomes of the analysis. Subsequently, the methodology to study this outcome was not the same in the included RCTs. Specifically, there was considerable variation between RCTs regarding length of the follow-up period and the frequency of follow-up microbiological tests throughout the study period.

Furthermore, although the outcomes in patients receiving β-lactam monotherapy or aminoglycoside/β-lactam combination therapy were compared in >60 studies, only 8 studies fulfilled the criteria for inclusion in our analysis. One may also criticize the fact that all of these studies were published >10 years ago. It should be emphasized that resistance is a continuously evolving phenomenon, and this fact makes the interpretation of results from RCTs performed with a 15- or 20-year time difference difficult. In fact, our data seem to indicate that a lower rate of emergence of antimicrobial resistance was noted in the monotherapy arm in studies performed after 1989.

Another noteworthy limitation of our study is the fact that genetic and/or molecular typing of the initial bacterial isolates and those isolates of the same species that were isolated again during the study and found to have developed resistance was not performed in any of the evaluable RCTs. Thus, we cannot make a definite statement that the isolation of an antimicrobial-resistant microorganism represents, in all cases, emergence of resistance in the same organism and not another isolate (different clone) of the same microbial species. In 2 prospective studies that examined risk factors for development of resistance in Enterobacter bacteremia [76] and Pseudomonas infection [83], molecular typing and PFGE revealed that isolates with altered susceptibility were clones of the initial isolate in 64% and 100% of cases, respectively.

Despite these limitations, we believe that our study adds useful information to the literature regarding the effect of aminoglycoside/β-lactam combination therapy versus β-lactam monotherapy on the emergence of antimicrobial resistance. The data do not support a beneficial effect of aminoglycoside/β-lactam combination therapy, compared with β-lactam monotherapy, with regard to this outcome. In fact, the data from several studies do not provide evidence to support the widespread belief among clinicians that aminoglycoside/β-lactam combinations lead to better outcomes than does β-lactam monotherapy in various populations and settings. All recent meta-analyses of RCTs that examined various outcomes, including effectiveness and toxicity, favor the use of β-lactam monotherapy instead of aminoglycoside/β-lactam combination therapy. Furno et al. [81] and Paul et al. [82] provided evidence against the safety and efficacy of the aminoglycoside/β-lactam...
combination (compared with β-lactam monotherapy) in febrile neutropenic patients. Paul et al. [6] arrived at the same conclusion for nonneutropenic, immunocompetent patients with sepsis. In addition, Saltar et al. [84] also reported that there was no benefit for aminoglycoside/β-lactam combination therapy, compared with β-lactam monotherapy, in a meta-analysis of observational studies and RCTs that involved patients with bacteremia due to gram-negative pathogens. It should be noted that the aminoglycoside/β-lactam combination may have some value in specific subsets of patients with infections, such as those with *Pseudomonas* bacteremia and those with septic shock due to *Klebsiella* bacteremia [84, 85].

In conclusion, a meta-analysis of data of relevant RCTs did not show any protective effect on the emergence of antimicrobial resistance for aminoglycoside/β-lactam combination therapy, compared with β-lactam monotherapy. Several laboratory and clinical studies have showed that emergence of resistance to β-lactams with various mechanisms may occur during treatment with this class of antimicrobial agents. However, our data do not provide support for the belief that the addition of an aminoglycoside to a β-lactam treatment regimen is a likely solution to this problem.

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