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# Combination Therapy for Treatment of Infections with Gram-Negative Bacteria

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## INTRODUCTION

Multidrug-resistant Gram-negative organisms (MDRGNs) have emerged as a major threat to hospitalized patients and have been associated with mortality rates ranging from 30 to 70% (30, 33, 89, 102, 153, 177, 203). The abundant and often inappropriate use of broad-spectrum antibiotics contributes to the emergence of MDRGNs (208). A vicious cycle is created as MDRGN infections force us to rely on additional broad-spectrum antibiotics to treat these infections, leading to yet more resistance (208, 241). The emergence and proliferation of these highly resistant Gram-negative organisms are particularly concerning given the limited number of antimicrobial agents that are currently available or in the drug development pipelines of the pharmaceutical industry to combat these organisms (35). A reduction in inappropriate utilization of broad-spectrum antibiotics is clearly important to minimize the emergence of MDRGNs. Every effort needs to be made to carefully select antibiotics, balancing the need for a broad spectrum of empiric coverage of potential microorganisms with the need to preserve available antibiotics for when they are absolutely necessary.

One area where the approach to antibiotic use needs to be readdressed is the use of combination antibiotic therapy, which

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generally consists of a β-lactam and an aminoglycoside or fluoroquinolone, for the treatment of infections with Gram-negative bacteria. There is evidence supporting the initial use of combination therapy for severe infections with Gram-negative bacteria, such as sepsis or ventilator-associated pneumonia (VAP), in the existing environment of MDRGNs because of the broad empiric coverage provided by two antimicrobial agents with different spectra of activity (20, 33, 89, 116, 117, 134, 136, 153, 246). However, when identification and susceptibility testing results are known, an argument can be made that the antibiotic regimen for Gram-negative organisms can be "fine-tuned" and narrowed in many cases (20, 134).

Observational studies show that between 25 and 50% of patients with bacteremia, surgical site infections, or pneumonia and over 50% of patients with septic shock in the intensive care unit (ICU) are administered combination antibiotic therapy (20, 54, 100, 117, 134, 138, 152, 173, 228, 246). The question of whether a combination of a β-lactam and an aminoglycoside or fluoroquinolone confers a benefit in patients beyond broadening the antimicrobial spectrum during the empiric treatment period before culture results are available is unsettled. With the availability of new broad-spectrum and highly bactericidal antibiotics, the need to combine β-lactams with a second agent for the treatment of infections with Gram-negative bacteria should be reassessed. The major objective of this review is to evaluate clinical outcomes, comparing monotherapy versus combination antimicrobial therapy for infections with Gram-negative bacteria. This review primarily focuses on β-lactam and aminoglycoside or fluoroquinolone combination therapy compared with β-lactam monotherapy, but other combinations are briefly discussed.

## THE INTUITIVE APPEAL OF COMBINATION THERAPY

Whether combination antimicrobial therapy is more efficacious than monotherapy for infections with Gram-negative bacteria remains controversial, particularly for infections due to organisms more commonly acquired in hospital settings, such as *Pseudomonas* spp., *Serratia* spp., *Acinetobacter* spp., and *Enterobacter* spp. Traditionally, combination antibiotic therapy for infections with Gram-negative bacteria has included two agents to which an organism demonstrates *in vitro* susceptibility, typically a β-lactam and an aminoglycoside. Although there are theoretical advantages to combination therapy shown by *in vitro* and animal studies, clinical data have been conflicting (90, 120, 200).

The initial use of combination therapy for infections with Gram-negative bacteria is often justified by one of the following three reasons: (i) to broaden the empiric coverage provided by two antimicrobial agents with different spectra of activity (an effort to ensure that the pathogen is adequately covered by at least one of the two components of the regimen), (ii) to exploit the synergy observed *in vitro* between two antibiotic agents compared to one (and hence improve clinical outcomes), or (iii) to prevent or delay the emergence of resistance during antimicrobial therapy (69, 101, 167).

Despite the intuitive appeal of these approaches, strong evidence supporting the use of two antimicrobials to treat infections with Gram-negative bacteria is lacking, and there is evidence that it may even be harmful. The addition of a second antimicrobial agent to treat a Gram-negative organism that is susceptible to a single agent may actually lead to increased antimicrobial resistance, adverse effects, and costs (195, 209). The development of adverse effects such as aminoglycoside-related nephrotoxicity is well documented. Some may argue, however, that definitive combination therapy (as opposed to empiric therapy) may still be warranted for certain subpopulations or circumstances. For example, some have suggested that there is an advantage to the prescription of combination therapy for profoundly neutropenic patients, patients with *Pseudomonas aeruginosa* sepsis, intensive care unit (ICU) patients, patients with VAP, or septic patients with significantly elevated severity-of-illness scores. The evidence supporting or refuting these claims is detailed below.

## ARGUMENTS IN FAVOR OF COMBINATION THERAPY

### Broad Spectrum of Activity

In the age of increasingly resistant Gram-negative infections, the likelihood that empiric antimicrobial therapy will provide adequate coverage for potential pathogens causing an infection is increased with the use of two antimicrobial agents compared to a single agent. Prompt institution of antimicrobial therapy active against the causative pathogen is crucial in the treatment of severely ill patients suspected of having a bacterial infection. The use of at least one antimicrobial agent to which a pathogen is susceptible for empiric therapy leads to lower mortality and improved outcomes in patients with sepsis caused by Gram-negative bacteria, as observed in a number of studies (6, 33, 46, 48, 84, 89, 106, 108, 133, 137, 140, 153, 158, 172, 207, 210). Mortality rates are higher among patients with health care-associated infections when they are initially treated with an empiric antimicrobial agent lacking *in vitro* activity against the infecting pathogen (116, 146, 186). Evidence exists that patients infected with MDR organisms are more likely to experience a delay in the initiation of effective antimicrobial therapy, and some of this risk can be avoided with the addition of a second agent (116, 147).

**Studies demonstrating a benefit with empiric combination therapy.** Kumar et al. conducted a retrospective, propensity-matched cohort study involving 28 ICUs to evaluate the therapeutic benefit of empiric combination therapy (β-lactams in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin) compared with β-lactam monotherapy in 4,662 eligible cases of culture-positive bacterial septic shock (144). Empiric combination therapy was associated with a decreased 28-day mortality (36% versus 29%; $P = 0.0002$) and increases in both mechanical ventilation-free days (median [interquartile range], 10 [0 to 25] versus 17 [0 to 26]; $P = 0.008$) and pressor-free days (23 [0 to 28] versus 25[0 to 28]; $P = 0.007$). Notably, antipseudomonal penicillins, antipseudomonal cephalosporins, and carbapenems failed to exhibit a benefit with the addition of a second agent. This may be due to the broad spectra of activity of these agents against the vast majority of Gram-negative pathogens responsible for septic shock, with minimal incremental benefit from the addition of a second agent. The rationale for inclusion of clindamycin/macrolides alone or in combination with other agents in this study is unclear, as these agents are not routinely prescribed for septic shock, with a notable exception being clindamycin for toxin-mediated shock. In the described study, clindamycin or macrolides were used in approximately 15% of patients either as single agents or as "combination" therapy.

Similarly, a retrospective cohort analysis establishing the relationship between initial inappropriate antimicrobial treatment and the clinical outcomes for *P. aeruginosa* infections showed that

hospital mortality was significantly higher for patients receiving inappropriate initial antimicrobial treatment than for those receiving appropriate therapy (31% versus 18%; $P < 0.02$) (163). Inappropriate therapy was defined as "the absence of Gram-negative antimicrobial agents with *in vitro* activity against *P. aeruginosa*." Inappropriate initial administration occurred more frequently among patients receiving monotherapy (35% versus 21%; $P = 0.01$) (165). The All-Patient Refined Diagnosis-Related Group (APR-DRG) score was used to measure severity of illness. Patients receiving inappropriate initial antimicrobial treatment had statistically greater APR-DRG scores ($P = 0.01$); however, APR-DRG scores were not incorporated into the final models, making it difficult to determine if mortality was attributable to empiric antibiotic choices or to the underlying severity of illness.

Similar results were achieved in other studies, with mortality in excess of 30% and an increased length of hospital stay related to delays in the initiation of appropriate therapy in ICU patients with sepsis caused by Gram-negative bacteria (84, 85, 117, 136, 141, 145, 152, 162). These studies suggest that inappropriate antimicrobial treatment can be reduced with empiric administration of combination therapy. One must recognize, however, that it is difficult to adequately control for illness severity in these studies, and therefore it is difficult to assess the excess attributable mortality due to inadequate empiric antimicrobial therapy. When empiric combination therapy is prescribed, the second agent that is selected should have activity against an organism potentially resistant to the β-lactam agent.

**Use of local antimicrobial epidemiology to inform empiric antibiotic choices.** The selection of empiric combination therapy for presumed infections with Gram-negative bacteria needs to be made after considering local epidemiology and individual patient characteristics. Prior to prescribing antimicrobial therapy, resistance patterns within an institution are important to consider, and close liaison with the microbiology laboratory facilitates the decision-making process (238). Surveillance data and hospital-specific antibiograms inform empiric antibiotic choices. Data from U.S. ICU studies, surveillance studies, the National Nosocomial Surveillance System, and the SENTRY Antimicrobial Surveillance Program have shown that overall susceptibilities within a 10-year period have declined significantly for all drug classes studied, and these trends are likely mirrored in individual institution antibiograms as well (82, 135, 182). Nationally, for example, multidrug resistance of *P. aeruginosa* to three or more antipseudomonal agents rose from 4% in 1993 to 14% in 2002 ($P < 0.001$), and it continues to rise (148, 187).

Increasing Gram-negative resistance complicates the selection of empiric therapy in severe infections. This is highlighted in a study by Lautenbach et al., who found that the time to effective therapy for infections due to extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacilli was approximately six times longer than that for infections caused by non-ESBL-producing strains (medians, 72 h versus 11.5 h) (147). These results are supported by a meta-analysis of 16 studies which found that ESBL production is associated with a delay in effective antimicrobial therapy for patients with Gram-negative bacteremia and a subsequent increased mortality (225).

When resistance to β-lactam therapy is anticipated in patients with sepsis presumed to be caused by Gram-negative bacteria, the addition of an aminoglycoside until antimicrobial susceptibilities are known appears to be justified. It is important to evaluate local antibiograms to determine which aminoglycoside would be most likely to increase the range of coverage against Gram-negative bacteria. However, when the β-lactam agent is sufficiently broad (e.g., carbapenem) and there is no local epidemiologic evidence supporting the likelihood of highly resistant organisms, the benefit of combination therapy, even empirically, is unclear.

**Individualization of empiric therapy based on patient characteristics.** Information on local antimicrobial resistance patterns should be supplemented with patient-specific characteristics to guide empiric treatment choices. Individualization of initial empiric antibiotic therapy is essential, as patients differ with regard to preexisting medical conditions, severity of illness, nature of infection, previous antibiotic and hospital exposure, presence of indwelling catheters, and colonization with antibiotic-resistant organisms (186, 191).

Bhat et al. demonstrated how knowledge of recent receipt of antibiotics and colonizing flora can improve the adequacy of initial empirical therapy (20). Thirty-seven percent of patients receiving piperacillin-tazobactam in the month prior to their current infection were infected with piperacillin-tazobactam-resistant *P. aeruginosa* in the subsequent month. Piperacillin-tazobactam was considered to be appropriate empiric therapy only if during the prior month, the patient had neither received the antibiotic nor had isolation of a piperacillin-tazobactam-resistant organism. In these situations, broadening empiric therapy to a carbapenem or addition of an aminoglycoside improved the likelihood of adequate empiric coverage.

**Deescalation of antimicrobial therapy when susceptibility results are known.** Although ample evidence demonstrates that initial prescription of combination therapy may be beneficial in a septic patient potentially infected with an MDRGN, when identification and susceptibility testing are complete, the antibiotic regimen should be "fine-tuned." Narrowing antimicrobial therapy based on antibiotic susceptibility results and appropriately limiting the duration of therapy are the cornerstones of responsible antimicrobial prescription (238).

## Synergy

A potential benefit of adding a second antimicrobial agent is the synergistic effect of the combination (i.e., more rapid killing of the pathogen) (9, 38, 57, 91, 95, 130). Synergy between two antimicrobial agents is defined as a greater-than-2-log increase in bactericidal activity *in vitro* compared with the bactericidal activity of each agent alone (60, 91, 95, 129, 130). The rate of bacterial killing by a fixed concentration of a single agent or multiple agents in combination can be depicted by a time-kill curve. (Fig. 1) Alternatively, various concentrations of two different agents can be used to evaluate their synergistic effect using the checkerboard technique. (Fig. 2).

**β-Lactam and aminoglycoside synergy in *in vitro* and animal models.** For infections with Gram-negative bacteria, antimicrobial synergy has traditionally been seen with β-lactam–aminoglycoside combinations. The combination of a β-lactam and an aminoglycoside allows for different mechanisms of bacterial killing (8, 66, 98, 237). β-Lactam-mediated disturbance of the cell walls of Gram-negative bacilli facilitates passage of aminoglycosides into the periplasmic space (105, 169).

Synergy was initially studied in enterococcal endocarditis in *in vitro* models (170, 171). These studies demonstrated that penicillin enhanced the uptake of aminoglycosides (170, 171). Other *in*

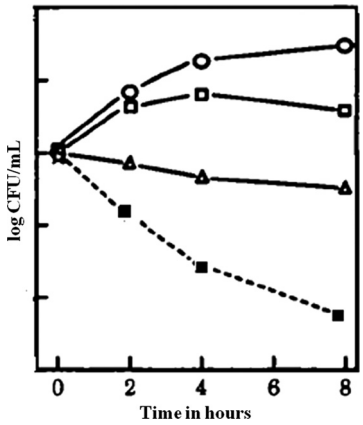


**FIG 1** Time-kill kinetics demonstrating growth of organisms in the settings of no drug (circles), addition of drug A (open squares), addition of drug B (triangles), and addition of both drugs A and B (closed squares).

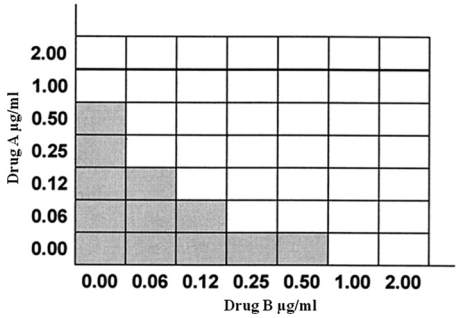


**FIG 2** Synergy of a two-drug combination determined using the checkerboard technique.

*vitro* studies, albeit using small numbers of isolates, have similarly found that treatment with a combination of a β-lactam and an aminoglycoside is superior to treatment with a β-lactam alone (60, 95, 130, 250). Synergy was not observed in an *in vitro* study of *P. aeruginosa* when a dense inoculum of microorganisms was present (62). I*n vitro* synergy appears to be variably present and strain dependent and varies with different β-lactam and aminoglycoside combinations (109). With the use of newer, broader-spectrum β-lactams, it is unclear if the results of these studies would be different if the studies were repeated.

A viridians group streptococcal rabbit endocarditis model was used to determine *in vivo* synergism between penicillin and streptomycin (217). The use of low-dose gentamicin in rabbits experimentally infected with *Staphylococcus aureus* demonstrated more rapid bactericidal activity of *S. aureus* from cardiac vegetations when initial low-dose gentamicin was combined with antistaphylococcal penicillins than when antistaphylococcal penicillins were used alone (216). With combination therapy, the bacteria were eradicated from the cardiac vegetations in half the time required to achieve the same results with penicillin monotherapy. Similar findings were seen in Gram-negative animal models (10, 11, 14, 38). Rabbits with *P. aeruginosa* endocarditis treated with 2 weeks of combination therapy with carbenicillin and gentamicin were significantly more likely to have sterilization of vegetations than rabbits treated with 2 weeks of carbenicillin therapy alone (14).

**β-Lactam and aminoglycoside synergy: clinical evidence.** While synergistic action between β-lactams and aminoglycosides has been shown *in vitro*, clinical evidence to support these data are sparse and conflicting (9, 28, 38, 45, 56, 57, 126, 185). A prospective cohort study of 200 patients with *P. aeruginosa* bacteremia (both neutropenic and nonneutropenic patients) was undertaken to compare *in vitro* susceptibility results with mortality (112). No significant correlation between *in vitro* synergy testing (either time-kill or checkerboard) and clinical outcome was demonstrated. Additionally, results obtained by time-kill curve and checkerboard synergistic testing were not correlated; combination therapy found to be synergistic by one method was not necessarily synergistic by the other method. A similar study conducted by Chandrasekar et al. compared *in vitro* synergy testing with clinical outcomes in 14 nonneutropenic patients infected with *P. aeruginosa* (45). Clinical cure was defined as the resolution of symptoms and signs of infection. The investigators found no clinical evidence of increased likelihood of clinical cure in patients treated with a β-lactam and an aminoglycoside, regardless of *in vitro* testing.

In contrast, in a retrospective study of 444 cases of Gram-negative bacteremia, there was an 80% clinical response rate in patients who received antibiotic therapy that was synergistic against the organism (using the checkerboard technique), compared to a 64% response rate in patients who received nonsynergistic combinations ($P < 0.05$) (24). Synergism *in vitro* was correlated with better clinical responses in patients with neutropenia, shock, and *P. aeruginosa* infections.

In a second retrospective study of profoundly neutropenic patients with Gram-negative bacteremia, a clinical response was observed in 7 of 11 (64%) of patients in whom synergism was present (as defined by the checkerboard technique) compared to 0 of 6 patients when synergism was not present (0%). The authors concluded that synergistic combinations were indicated for profoundly neutropenic patients with Gram-negative bacteremia (57).

There are discrepancies when comparing *in vitro* and *in vivo* studies assessing combination therapy for infections with Gram-negative bacteria. When weighing the unclear benefit of *in vivo* synergy with the potential negative consequences of combination therapy (i.e., nephrotoxicity, ototoxicity, additional monitoring requirements, etc.), the rationale for combination therapy becomes questionable.

**β-Lactam and fluoroquinolone synergy in *in vitro* models.** Although antimicrobial synergy appears to be best established for β-lactam–aminoglycoside combinations, similar data on synergistic activity have emerged for combinations of β-lactams and fluoroquinolones (14, 50, 77, 96, 99, 132, 168, 183, 189, 205, 252, 253). *In vitro* synergy between β-lactams and fluoroquinolones against Gram-negative organisms has ranged from 17% to 82% (96, 119, 168). One study evaluated ciprofloxacin in combination with imipenem versus ciprofloxacin and amikacin against clinical isolates of multidrug-resistant *P. aeruginosa*; 42% (11/26) of strains demonstrated synergy with the combination of ciprofloxacin and imipenem, whereas only 15% (4/26) of isolates demonstrated enhanced killing with the combination of ciprofloxacin and amikacin (94). An *in vitro* study of 12 clinical isolates of *P. aeruginosa* found no difference in the degree of synergy between β-lactam–aminoglycoside and β-lactam–fluoroquinolone com-

binations, with synergy percentages ranging from 58% to 79% (34).

In an *in vitro* study assessing synergy against *Burkholderia cepacia*, ciprofloxacin in combination with imipenem demonstrated synergy against 44% (7/16) of isolates (143). Ciprofloxacin in combination with ceftazidime, aztreonam, or azlocillin produced synergy rates of ≥50% against 108 isolates of *P. aeruginosa* resistant to ciprofloxacin but susceptible to the β-lactam used in the combination in another *in vitro* study using the checkerboard technique. However, in cases where the *P. aeruginosa* isolates were susceptible to both antibiotics, the synergy was <20%; if the isolates were resistant to the β-lactam but susceptible to ciprofloxacin, the synergy rate was <5% (37). Pohlman et al. evaluated ciprofloxacin synergy in combination with aztreonam, ceftazidime, piperacillin-tazobactam, and ticarcillin-clavulanic acid against various Gram-negative organisms (205). They concluded that synergy between ciprofloxacin and β-lactams was sporadic and was not consistent across drug concentrations or sampling times. Existing data do not demonstrate synergistic activity between fluoroquinolones and aminoglycosides. The synergistic potential of β-lactams and fluoroquinolones remains unclear.

**β-Lactam and fluoroquinolone synergy: clinical evidence.** Fluoroquinolones are recognized for excellent tissue penetration into lung, meninges, and bone, and they have minimal nephrotoxicity compared with aminoglycosides (29). Al-Hasan et al. conducted a retrospective cohort study incorporating propensity scores evaluating 28-day mortality in 702 patients with Gram-negative bacteremia receiving a combination of β-lactam and fluoroquinolone or β-lactam monotherapy. Combination therapy was associated with lower 28-day mortality than monotherapy (4.2% versus 8.8%; adjusted hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.20 to 0.98; $P = 0.04$); however, the additional benefit of fluoroquinolones was not evident for critically ill patients (5). The authors believed that increased mortality in severely ill patients, regardless of the use of combination therapy, may have been the result of other patient factors, including multiorgan failure, systemic inflammatory response, and other underlying medical conditions.

A meta-analysis of 8 randomized, controlled trials (RCTs) was conducted, comparing a β-lactam and ciprofloxacin to a β-lactam and aminoglycoside for the treatment of patients with febrile neutropenia (22). Clinical cures in the subset of patients with documented infections (odds ratio [OR], 1.56; 95% CI, 1.05 to 2.31) and mortality (OR, 0.85; 95% CI, 0.54 to 1.35) were no different between the two groups; however, nephrotoxicity (OR, 0.30; 95% CI, 0.16 to 0.59) was notably decreased in patients receiving combination therapy incorporating fluoroquinolones.

According to the available evidence, *in vitro* synergy does not necessarily translate into a clinical benefit. *In vitro* synergy studies are conducted in well-controlled environments where precise concentrations of multiple antibiotics are tested against known inocula of microorganisms, which can be very different from the unpredictable drug concentrations and microorganism burdens of actual patients. Additionally, *in vitro* studies cannot take into account the added contribution of the host immune system.

**Synergy testing in the microbiology laboratory.** The use of combination antibiotic susceptibility testing to guide clinical decisions is generally limited to multidrug-resistant organisms in the cystic fibrosis population. Previous studies suggest that this method of testing yields reproducible results (1, 213–215). However, clinical studies have not consistently correlated *in vitro* synergy results with improved clinical outcomes, and thus such testing is performed on a very limited basis (3, 230). Often, by the time synergy testing on an isolate is complete, the resistance profile for the organism infecting a patient has already changed. Additionally, synergy testing is generally performed on planktonically growing bacteria (i.e., free-floating bacteria) as opposed to bacteria in biofilms. Bacteria growing in biofilms are generally significantly more resistant, and biofilms often coat the airways of patients with cystic fibrosis (2, 61, 176, 229) Lastly, synergy testing is performed on the sickest patients with highly resistant organisms who have a very poor prognosis, and synergistic combinations may provide minimal improvements in clinical outcomes.

## Prevention of Resistance

The available evidence shows that the proportion of Gram-negative organisms resistant to commonly used antibiotics is increasing (97, 184, 192, 202). Resistance is even observed with antibiotics considered "salvage" therapy, such as tigecycline and colistin (193). Unfortunately, as antimicrobial resistance is worsening, the antimicrobial armamentarium against Gram-negative bacilli remains relatively constant (236). Carmeli et al. published one of the first studies to address outcomes associated with antimicrobial resistance in Gram-negative pathogens (40). The emergence of resistance was associated with a 3-fold-greater risk of death ($P = 0.02$) and a 1.7-fold-longer duration of hospital stay ($P < 0.001$). The estimated mean adjusted increase in duration of hospitalization was 5.7 days. Lautenbach et al. found higher in-hospital mortality among patients infected or colonized with aztreonam-resistant or fluoroquinolone-resistant *P. aeruginosa* strains than among patients with more susceptible *P. aeruginosa* strains (87, 88, 149).

One possible rationale for the use of combination antimicrobial therapy is to prevent or delay the emergence of resistance during treatment (178). However, convincing clinical data supporting this theory are lacking (39, 218, 220).

***In vitro* evidence for prevention of resistance.** A notable example of successful use of combination antimicrobial therapy for prevention of resistance is the treatment of infections due to *Mycobacterium tuberculosis*. Combination therapy for *M. tuberculosis* infections significantly decreased the rate of development of resistance to rifampin (43). However, with the relatively slower growth of *M. tuberculosis* and slower emergence of resistance mutations, combination therapy may not yield comparable results for infections with Gram-negative bacteria. An *in vitro* study of the combination of azlocillin and tobramycin was undertaken to assess the development of resistance in eight *P. aeruginosa* isolates recovered from patients with cystic fibrosis after 12 to 16 treatments. Upon exposure to azlocillin and tobramycin combinations using the checkerboard method, the MICs of neither azlocillin nor tobramycin changed significantly; however, there was some evidence of an increase in MICs when the individual antibiotics were used alone (250). Similarly, in two small *in vitro* studies of five strains and three strains of *P. aeruginosa*, respectively, the combination of levofloxacin and imipenem appeared to delay the emergence of resistance (155, 156).

**Clinical data supporting combination therapy for prevention of resistance.** In general, most clinical studies comparing combination therapy and monotherapy focus primarily on clinical effectiveness and toxicities and are generally not designed to study the

emergence of antimicrobial resistance as a primary outcome. Most clinical studies have had inadequate samples sizes to make conclusions regarding emergence of resistance when comparing combination therapy to monotherapy.

Gribble et al. compared piperacillin as a single agent with carboxypenicillin-aminoglycoside combinations in a prospective, randomized trial of 50 adults with serious bacterial infections (101). The difference in the clinical response rates between the two regimens was not significant; however, the emergence of resistant organisms during therapy was more frequent among patients receiving piperacillin alone (42%) than among patients receiving combination therapy (17%) ($P < 0.05$). The authors concluded that the use of piperacillin as a single agent in the treatment of serious bacterial infections should not be advocated.

The incidence of emergence of resistance was also evaluated by retrospective review of 173 studies encompassing over 14,000 patients (78). Bacterial resistance occurred among 5.6% of infections and appeared to be significantly more frequent with penicillin and aminoglycoside monotherapy. Lower rates were associated with broader antimicrobial combinations such as carbapenems and combination therapy. Of importance, aminoglycoside therapy used alone can be an independent risk factor for resistance, and it is unknown if these results would have been replicated if monotherapy was limited to agents other than aminoglycosides (152, 167).

In a retrospective study of 1,403 episodes of lower respiratory tract infection, Kosmodis and Koratzanis reported that a lower rate of emergence of resistance was noted among patients with nosocomial pneumonia and among patients in the ICU receiving antibiotic combinations (including β-lactams and aminoglycosides) than among those receiving monotherapy (139). Monotherapy frequently consisted of aminoglycoside therapy used alone.

In a Cochrane meta-analysis from 2005 comparing monotherapy versus combination therapy for patients with cystic fibrosis exacerbations, the authors determined that there was insufficient evidence to conclusively determine the effects of the different treatment approaches on the emergence of resistance to *P. aeruginosa* (67). In summary, the theoretical advantage of minimizing emergence of resistant mutants has not been confirmed conclusively in clinical studies.

**Clinical data not supporting combination therapy for prevention of resistance.** Although initial clinical studies evaluating the addition of an aminoglycoside to a β-lactam antibiotic suggested that the combination delays the development of antimicrobial resistance, monotherapy often consisted of aminoglycoside therapy alone in early studies (112). Aminoglycoside monotherapy can be effective for urinary tract infections, as aminoglycosides can achieve high concentrations in the kidneys (152). However, for infections of other body sites, patients treated with an aminoglycoside as the single effective drug have worse clinical outcomes than patients treated with a single β-lactam drug (247). One review of a large number of clinical trials found that resistance during therapy for infections with Gram-negative bacteria ranged from a low of 4.7% for imipenem to a high of more than 13% for aminoglycosides (167). The emergence of resistance was associated with therapeutic failure in approximately half of cases; however, in patients treated with aminoglycosides, development of resistance resulted in treatment failure in 85% of the cases. After these initial studies, combination therapy became the norm and monotherapy with aminoglycosides fell out of favor. With the advent of broad-spectrum β-lactam antibiotics, however, the postulated beneficial effect of combination therapy needs to be reassessed.

A prospective cohort study of 271 adults examined the emergence of resistance to ceftazidime, imipenem, ciprofloxacin, and piperacillin during therapy with the respective agents (39). Resistance emerged for all agents and was not delayed or prevented with the addition of aminoglycoside therapy. Several comparative studies of combination therapy and monotherapy addressing the outcome of resistance have not shown an added benefit of aminoglycosides in preventing or delaying the emergence of resistance (6, 48, 51, 151).

A meta-analysis of 8 randomized, controlled trials comparing β-lactam monotherapy with β-lactam and aminoglycoside combination therapy was conducted, with the primary outcome of emergence of resistance and a secondary outcome of the development of a superinfection (23). Antimicrobial-resistant organisms were defined as bacterial isolates that became resistant to the administered drug during therapy with a change from "susceptible" to "intermediate" or "resistant" or from "intermediate" to "resistant." The summary OR for the emergence of resistance suggested that combination therapy and monotherapy were equivalent in the development of subsequent resistant organisms (OR, 0.90; 95% CI, 0.56 to 1.47). The authors of the meta-analysis defined a superinfection as the isolation of a pathogen responsible for a subsequent infection and of a species different from the initially isolated pathogen. Pathogens categorized as superinfecting pathogens were often significantly more resistant than the pathogen initially isolated. Results from the meta-analysis showed that β-lactam monotherapy was associated with fewer superinfections than combination therapy (OR, 0.62; 95% CI, 0.42 to 0.93). In one of the included studies, there were significantly more superinfections with methicillin-resistant *S. aureus* in the combination arm than in the monotherapy arm, and the authors attributed this to multiply resistant staphylococci that could be induced by gentamicin, possibly by plasmid transfer, as others have previously described (41, 55, 81, 179). An additional meta-analysis demonstrated a trend toward fewer bacterial superinfections with monotherapy than with combination therapy (relative risk [RR], 0.76; 95% CI, 0.59 to 1.06) (194).

## ADVERSE EVENTS ASSOCIATED WITH COMBINATION THERAPY

### Nephrotoxicity

Aminoglycosides accumulate in the kidney, with approximately 85% of the drug found in the renal cortex (222). They bind to glycoproteins on the brush borders of renal tubular cells, which is necessary for internalization of the drug (181). When there is significant accumulation of the drug in the cytosol, aminoglycosides activate apoptosis, causing cell death (226). These findings have also been demonstrated clinically. In a randomized, prospective study of 876 febrile, neutropenic episodes, comparing ceftazidime with piperacillin and gentamicin, the incidence of renal toxicity was significantly higher in the combination therapy group ($P < 0.001$); five patients required hemodialysis, and one patient died with renal insufficiency (58). Similarly, in a randomized, prospective trial of 280 patients with severe sepsis comparing imipenem with imipenem and netilmicin, nephrotoxicity attributed to anti-

biotics was observed in none of the patients receiving monotherapy compared with six of the patients receiving combination therapy ($P = 0.03$) (51). Additionally, in a prospective study of 109 patients, following trauma, creatinine rose from normal concentrations to greater than 1.5 mg/dl in 2.6% of monotherapy patients compared to 7.1% of combination therapy patients ($P < 0.02$). One patient in the combination group required dialysis (55). A retrospective study of 225 children receiving antibiotic therapy for *P. aeruginosa* bacteremia found that 9 of 66 (13%) children receiving monotherapy and 49 of 159 (31%) children receiving combination therapy developed acute renal injury while receiving antibiotic therapy ($P < 0.01$) (240).

Several meta-analyses of RCTs have shown that renal toxicity is more common in patients who receive aminoglycoside therapy than in those patients who do not (194, 196, 198, 199). In fact, these meta-analyses have shown that monotherapy was protective against nephrotoxicity, ranging from 17% to 70%. Of concern is that patients with Gram-negative sepsis are often exposed to several nephrotoxins, including intravenous contrast agents, additional antibiotics associated with acute renal injury, and diuretics. They also are often volume depleted and have metabolic acidosis. The addition of an aminoglycoside to these other agents in critically ill patients could result in synergistically worse nephrotoxicity.

Even low-dose gentamicin has been associated with nephrotoxicity. A secondary analysis evaluating safety data from a randomized, controlled trial of 236 patients with *S. aureus* bacteremia found that even 4 days of low-dose gentamicin (one milligram per kilogram per dose every 8 h) significantly increased the risk of nephrotoxicity (53).

### Ototoxicity

An additional concern with aminoglycoside use is the potential for ototoxicity. Aminoglycosides penetrate into the vestibular and cochlear tissue, damaging the sensory air cells in the cochlea and labyrinth (32, 63). The relationship between aminoglycoside pharmacokinetic parameters and auditory toxicity is unclear. An animal study demonstrated that aminoglycoside ototoxicity is related to the concentration of the drug in the inner ear over time and is not proportional to the absolute concentration at a single point in time (19). Existing data suggest that prolonged therapy for 10 or more days, preexisting renal impairment, and prior treatment with aminoglycosides are risk factors for ototoxicity (174).

### *Clostridium difficile* Infection

Another known adverse consequence of antibiotic use is *C. difficile* infection. Any antibiotic, including β-lactams and aminoglycosides, has the potential to result in overgrowth of *C. difficile* and infection. Comparative studies of combination therapy and monotherapy have not specifically evaluated *C. difficile* infection as an outcome to draw conclusions regarding the increased risk, if one exists, with the addition of an aminoglycoside. Ample evidence exists, however, that fluoroquinolones are an independent risk factor for *C. difficile* infection (201, 221).

### Additional Disadvantages to Prescribing Combination Therapy

There are additional risks associated with combination therapy, including the risk of fungal overgrowth and the need for frequent catheter access, placing the patient at risk for subsequent infections (212). Patients at risk for infections with Gram-negative bacteria are likely to be receiving multiple medications with complex treatment schedules, potentially leading to drug interactions and further toxicities. Drug acquisition, preparation, and administration costs are also increased. A substantial advantage can be gained with a simple antibiotic regimen with one agent, provided the agent is effective (including appropriate dosage, interval, and route of administration) and well tolerated.

## CLINICAL STUDIES EVALUATING THE EFFECTIVENESS OF COMBINATION THERAPY

Few studies comparing monotherapy with combination therapy are well designed to conclusively determine the regimen that optimizes clinical outcomes. Comparisons are complicated by the various study designs. The quality of data collection may be limited in retrospective studies. Additionally, evaluating treatment effects from observational data can be problematic. Prognostic factors may influence treatment decisions, producing a type of bias referred to as confounding by indication (122). It is possible that patients appearing to be severely ill are more likely to be prescribed combination therapy. Certainly, a patient appearing relatively well would be expected to have a better prognosis than an ill patient, and the former may be more likely to receive monotherapy while the latter receives combination therapy.

Prospective, randomized studies addressing the question are often not blinded, are designed primarily to show noninferiority and so have small sample sizes, and do not assess data using intention-to-treat analyses. Frequently, severely ill patients are excluded, the adequacy of empiric therapy is not evaluated, a large portion of patients have no pathogen identified. when pathogens are identified different bacteria with various virulences are often grouped together, and β-lactams with differing spectra of activity are administered in the two treatment arms. The body site of infection within and between studies may vary; e.g., a urinary tract infection is compared to an intra-abdominal abscess. Subjective endpoints are often used; sometimes clinical failure is defined as the need to prescribe an additional antibiotic, which is concerning as the threshold for initiating broader-spectrum coverage varies among physicians. These inherent weaknesses can be a deterrent to comparisons of existing studies.

### *Pseudomonas aeruginosa* Infections

The importance of optimizing therapy for *Pseudomonas* sp. infections is highlighted by their prominent place among all pathogens in case-fatality rates (44, 245, 248). The prognosis of infections with *P. aeruginosa* remains poor, with a crude mortality rate of as high as 50% (21, 246, 249). The ability of this organism to simultaneously express multiple mechanisms of resistance adds to the challenge of effectively treating it (104, 157). Several studies evaluating morbidity and mortality with dual and single antipseudomonal agents for the treatment of *P. aeruginosa* infections have been conducted, as outlined below (7, 15, 44, 70, 112, 152, 180, 211, 224, 227, 228, 246).

**Studies supporting combination therapy for *Pseudomonas aeruginosa* infections.** Bodey et al. conducted a retrospective observational study examining 410 episodes of *P. aeruginosa* bacteremia in patients with malignancies over a 10-year period. Patients who received an antipseudomonal β-lactam antibiotic and aminoglycoside had a significantly higher cure rate (defined as eradication of all signs and symptoms of pseudomonal infections)

than patients who received only an aminoglycoside (72% versus 29%; $P < 0.001$) (25). However, patients who received an antipseudomonal penicillin plus aminoglycoside did not have a higher cure rate than patients who received only an antipseudomonal penicillin (72% versus 71%).

The effectiveness of monotherapy versus combination therapy on mortality in patients with *P. aeruginosa* bacteremia was evaluated in a prospective, multicenter study of 200 patients (112). Mortalities were 27% and 47% in the combination therapy and monotherapy groups, respectively ($P < 0.02$). Among a subgroup of patients who were severely ill (defined as having a need for mechanical ventilation, presence of hypotension, or presence of coma), survival was 53% with combination therapy versus 8% with monotherapy ($P < 0.02$). *In vitro* synergy testing was performed, but the presence of synergy did not correlate with clinical outcome ($P = 0.10$). The validity of results may be compromised by the fact that the vast majority (84%) of monotherapy patients received inadequate monotherapy with an aminoglycoside. Therapeutic drug concentrations of aminoglycosides were not reported and it is unclear whether appropriate serum concentrations of aminoglycoside were attained. As previously discussed, patients with Gram-negative bacteremia treated only with an aminoglycoside have been shown to be at a disadvantage in a number of studies (25, 26, 69, 114, 128, 138, 152).

**Studies not supporting combination therapy for *Pseudomonas aeruginosa* infections.** In a prospective, observational study, a subgroup analysis of 172 patients with *P. aeruginosa* bacteremia had no survival advantage when prescribed combination therapy (OR, 0.7; 95% CI, 0.3 to 1.8) (152). Similarly, in a prospective study of 189 consecutive episodes of *P. aeruginosa* bacteremia, the investigators found that survival was no greater in patients who received two or more antibiotics with *in vitro* activity against *P. aeruginosa* (therapies not specified) than in patients who received a single agent with *in vitro* activity (246). A prospective, randomized clinical trial comparing ceftazidime monotherapy with ceftriaxone and tobramycin for serious infections with Gram-negative bacteria, including *Pseudomonas* spp., showed similar mortality between the groups (211). The authors' definition of combination therapy was essentially aminoglycoside monotherapy for *Pseudomonas* spp. (i.e., the second agent was largely not effective against *Pseudomonas* spp.) and may have biased the results toward the null. A retrospective cohort study of 123 episodes of *P. aeruginosa* bacteremia similarly showed that mortality was no different between the monotherapy (an appropriate antipseudomonal cephalosporin, carbapenem, or fluoroquinolone) and combination therapy (the agent in the monotherapy arm in combination with an aminoglycoside) groups (228).

Several meta-analyses have investigated the impact of combination therapy on the outcome of Gram-negative bloodstream infections, with subgroup analysis frequently performed on *Pseudomonas* spp. (Table 1). The results of the various meta-analyses are limited by the quality of the included studies. Nonetheless, the majority of meta-analyses did not find a clinical advantage to combination therapy for pseudomonal infections (131, 194, 196, 198, 199). One meta-analysis, however, concluded that combination therapy should be used when bloodstream infections with *P. aeruginosa* are suspected (212). Importantly, a large number of patients included in this meta-analysis received monotherapy with an aminoglycoside.

Although the need for definitive combination therapy is questionable, delays in initiating appropriate antimicrobial therapy for pseudomonal infections (which often consists of combination therapy) have been associated with higher mortality (27, 117, 123, 124, 157, 165, 166). A proposed strategy for clinicians is to initiate empirical therapy with two antipseudomonal agents in critically ill patients with risk factors for pseudomonal infections. It is prudent to avoid readministering recently prescribed antibiotics when initiating empirical therapy, since the development and persistence of resistance have been shown with virtually all antipseudomonal agents (65, 206). In cases of proven *P. aeruginosa* bacteremia, however, combination therapy could be narrowed to monotherapy on the basis of the specific susceptibility results for the isolate.

### Neutropenia

Some believe that patients with significant neutropenia benefit from the enhanced bactericidal activity offered by β-lactam and aminoglycoside combination therapy (9, 127, 129). Clinical benefits of synergistic combinations were evident in early studies involving neutropenic patients (57). More recent studies, however, have shown no striking differences between monotherapy and multidrug combinations for the treatment of fever in neutropenic patients (198). With the availability of new antibiotics with increasingly broad spectra of activity, empiric treatment of bacterial infection in patients with febrile neutropenia with a single antibiotic, rather than a standard combination of drugs, may be a reasonable option.

Comparing outcomes of infections with Gram-negative bacteria in neutropenic and nonneutropenic patients can be inherently problematic. Neutropenic patients generally have associated comorbid illnesses that may independently result in a poorer prognosis. Additionally, the prognosis for neutropenic patients may be more dependent on the return of the neutrophil count than on the antibacterial agents administered, and the definition of neutropenia varies significantly between studies.

**Studies supporting the use of combination therapy for neutropenic patients with infections with Gram-negative bacteria.** The European Organization for Research and Treatment of Cancer performed a prospective, randomized trial of ceftazidime plus definitive therapy with amikacin for 9 days compared with ceftazidime plus empirical therapy with amikacin for 3 days for in 129 neutropenic patients with Gram-negative bacteremia (69). In the subgroup with an absolute neutrophil count (ANC) of $<100$ cells/mm$^3$, 50% of patients receiving definitive combination therapy had clinical cure, compared with 6% who received combination therapy only empirically ($P = 0.03$). The investigators defined treatment failure as persistence of fever for greater than 3 days. Because defervescence could be dependent on a number of factors, including catheter removal, abscess drainage, underlying malignancy, adverse drug events, or return of neutrophil count, this may not be an accurate surrogate marker for treatment failure.

**Studies not supporting the use of combination therapy for neutropenic patients with infections with Gram-negative bacteria.** A multicenter, randomized, controlled trial was undertaken to compare piperacillin and tobramycin with ceftazidime for the treatment of 876 episodes of fever and neutropenia (58). As a single agent, ceftazidime was as effective as the combination of piperacillin and tobramycin with respect to mortality (6% versus 8%). Eradication of the infecting organisms was achieved in 79% of bacteremic episodes treated with ceftazidime, compared with

TABLE 1 Summary of meta-analyses comparing monotherapy with combination therapy for the definitive treatment of presumed or proven infections with Gram-negative bacteria

| Reference | Trials included | Clinical outcome(s) | Clinical outcome summary statistics | | | | | Conclusion(s) |
|---|---|---|---|---|---|---|---|---|
| | | | Overall | *Pseudomonas* infections | Neutropenia | Resistance and superinfections | Acute renal injury | |
| 80 | 29 RCTs; 4,795 febrile and neutropenic episodes | Clinical failure[a] | OR, 0.87; 95% CI, 0.75-1.01 | Not evaluated | OR, 0.91; 95% CI, 0.77-1.09 (<500 cells/μl) | Not evaluated | Not evaluated | Monotherapy as effective as combination therapy |
| 198 | 68 RCTs; 7,524 febrile and neutropenic episodes | Mortality, treatment failure[b] | RR, 0.87; 95% CI, 0.75-1.02 (mortality); RR, 1.11; 95% CI, 1.02-1.21 (treatment failure) | RR, 0.87; 95% CI, 0.34-2.24 (mortality); RR, 1.41; 95% CI, 0.90-2.22 (treatment failure) | RR, 0.68; 95% CI, 0.37-1.24 (mortality); RR, 1.48; 95% CI, 1.12-1.96 (<100 cells/μl) (treatment failure) | RR, 1.00; 95% CI, 0.86-1.18 (bacterial superinfections)[c] RR, 0.70; 95% CI, 0.49-1.00 (fungal infections) | RR, 0.45; 95% CI, 0.35-0.57 | Monotherapy as effective as combination therapy; increased nephrotoxicity with combination therapy |
| 199 | 47 RCTs; 8,803 febrile and neutropenic episodes | Mortality, treatment failure[d] | RR, 0.85; 95% CI, 0.72-1.02 (mortality); RR, 0.92; 95% CI, 0.85-0.99 (treatment failure) | RR, 0.78; 95% CI, 0.24-2.56 (mortality); RR, 1.46; 95% CI, 0.23-9.41 (treatment failure) | RR, 0.66; 95% CI, 0.35-1.26 (mortality); RR, 1.49; 95% CI, 1.13-1.97 (<100 cells/μl) (treatment failure) | RR, 0.97; 95% CI, 0.82-1.14 (bacterial superinfections) RR, 0.75; 95% CI, 0.51-1.10 (fungal infections) | RR, 0.49; 95% CI, 0.36-0.65 | Monotherapy as effective as combination therapy; increased nephrotoxicity with combination therapy |
| 194 | 64 RCTs; 7,586 patients | Mortality, clinical failure[e] | RR, 0.90; 95% CI, 0.77-1.06 (mortality); RR, 0.87; 95% CI, 0.78-0.97 (clinical failure) | RR, 1.50; 95% CI, 0.07-32.84 (mortality); RR, 1.01; 95% CI, 0.68-1.49 (clinical failure) | Not evaluated | RR, 0.79; 95% CI, 0.59-1.06 (bacterial superinfections); RR, 0.78; 95% CI, 0.38-1.58 (fungal infections) | RR, 0.36; 95% CI, 0.28-0.47 | Monotherapy as effective as combination therapy; increased nephrotoxicity with combination therapy |
| 212 | 17 studies (15 retrospective or prospective cohort, 2 RCTs); 3,077 patients | Mortality | OR, 0.96; 95% CI, 0.70-1.32 | OR, 0.50; 95% CI, 0.30-0.79 | Not evaluated | Not evaluated | Not evaluated | Monotherapy as effective as combination therapy; combination therapy beneficial for *Pseudomonas* bacteremia[f] |
| 23 | 8 RCTs; 1,394 patients | Mortality, treatment failure[g] | OR, 0.70; 95% CI, 0.40-1.25 (mortality); OR, 0.62; 95% CI, 0.38-1.01 (treatment failure) | Not evaluated | Not evaluated | OR, 0.90; 95% CI, 0.56-1.47 (resistance)[h] OR, 0.62; 95% CI, 0.42-0.93 (superinfections)[i] | Not evaluated | Monotherapy as effective as combination therapy; fewer superinfections with monotherapy |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 67 | 27 RCTs; 356 cystic fibrosis patients | Clinical improvement,[j] bacteriologic improvement[k] | No difference in clinical or bacteriologic improvement (no overall summary statistic) | OR, 5.63; 95% CI, 2.12-14.94 (eradication of *Pseudomonas* infections) | Not evaluated | OR, 0.44; 95% CI, 0.17-1.14 (resistant strains at 2-8 wk) | OR, 1.54; 95% CI, 0.15-15.56 | Monotherapy as effective as combination therapy; no conclusive results |
| 196 | 64 RCTs and quasi-RCTs; 7,586 patients | Mortality, clinical failure[l] | RR, 1.01; 95% CI, 0.75-1.35 (mortality); RR, 1.11; 95% CI, 0.95-1.29 (clinical failure) | Not detailed but "no significant disparities" (mortality); RR, 1.02; 95% CI, 0.68-1.51 (clinical failure) | Not evaluated | RR, 0.76; 95% CI, 0.57-1.01 (bacterial superinfections)[m] 0.79; 95% CI, 0.42-1.48 (fungal infections); RR, 0.88; 95% CI, 0.54-1.45 (bacterial resistance) | RR, 0.30; 95% CI, 0.23-0.39 | Monotherapy as effective as combination therapy; increased nephrotoxicity with combination therapy |
| 142 | 50 studies (37 retrospective or prospective cohort, 13 RCTs); 8,504 pts | Mortality/clinical response (aggregate outcome) | OR, 0.86; 95% CI, 0.71-1.03OR, 0.49; 95% CI, 0.35-0.70 (severely ill) | Not evaluated | Not evaluated | Not evaluated | Not evaluated | Combination therapy improves survival in patients with septic shock |
| 161 | 52 RCTs; >6,643 episodes | Mortality, clinical failure[n] | RR, 0.96; 95% CI, 0.78-1.18 (mortality); RR, 0.88; 95% CI, 0.74-1.05 (clinical failure) | RR, 3.18; 95% CI, 0.49-20.65 (mortality); RR, 1.55; 95% CI, 1.24-1.93 (clinical failure) | RR, 0.84; 95% CI, 0.61-1.14 (mortality); 1.16; 95% CI, 1.07-1.26 (clinical failure) (neutropenia not defined) | RR, 1.15; 95% CI, 0.89-1.50 (bacterial superinfections); RR, 0.67; 95% CI, 0.41-1.10 (fungal infections) | RR, 0.77; 95% CI, 0.67-0.87 (adverse effects) | Monotherapy as effective as combination therapy; increased adverse effects with combination therapy; further studies needed for *Pseudomonas* infections |

[a] Defined as modification of the initially allocated regimen or death during treatment.
[b] A composite endpoint of one or more of the following: death; persistence, recurrence, or worsening of clinical signs or symptoms of presenting infection; any modification of the assigned empirical antibiotic treatment.
[c] Defined as new, persistent, or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen (different susceptibility) or the development of a new site of infection.
[d] Defined as death, persistence, recurrence, or worsening of presenting infection, any modification of presenting infection, and any modifications to the assigned antibiotic treatment.
[e] Defined as death, nonresolving primary infection, any modification to allocated antibiotics, or any therapeutic invasive intervention not defined by protocol.
[f] Eighty-four percent of patients in monotherapy arm received aminoglycosides; meta-analysis was reconducted excluding aminoglycoside monotherapy patients, with an OR of 1.31 and a 95% CI of 0.62 to 2.79 (194a).
[g] Defined as no response to treatment, no clinical improvement, clinical deterioration, or death from infection.
[h] Defined as reisolation of an organism with changes in susceptibility to a more resistant phenotype (i.e., from initially susceptible to intermediate or resistant or from initially intermediate to resistant).
[i] Defined as isolation of a pathogen thought to be responsible for an infection that was of a different species from the initially isolated pathogen.
[j] Defined as improvement in spirometric lung function (e.g., forced expiratory volume in 1 s and forced vital capacity), reported at 10 to 14 days.
[k] Defined as improvement in quantitative bacteriology of sputum.
[l] Defined as death and/or one or more serious morbid events (persistence, recurrence, or worsening of clinical signs or symptoms of presenting infection, any modification of the assigned empirical antibiotic treatment, or any therapeutic invasive intervention required [not defined in the protocol]).
[m] Recurrent infections defined as new, persistent, or worsening symptoms and/or signs of infection associated with isolation of a new pathogen (different pathogen or same pathogen with different susceptibilities) or the development of a new site of infection.
[n] The definitions of failure in each study (time frame, clinical findings defining failure, and attribution of deaths) were accepted.

68% of the episodes treated with combination therapy (OR, 1.76; 95% CI, 0.92 to 3.38). Nephrotoxicity was more evident in the combination therapy group, and clinically apparent ototoxicity was limited to the group receiving combination therapy, with five patients reporting hearing loss, tinnitus, or both. This study suggests that an antipseudomonal β-lactam alone may be a reasonable option for therapy for fever and neutropenia.

A meta-analysis of 21 RCTs compared imipenem-cilastatin with a β-lactam–aminoglycoside combination for the treatment of febrile and neutropenic patients (59). The β-lactam prescribed in the control arms of 18 of these studies had antipseudomonal activity. Imipenem-cilastatin demonstrated a beneficial treatment effect over that achieved by aminoglycoside-containing regimens, yielding an OR of 0.77 (95% CI, 0.61 to 0.98). Similarly, a meta-analysis of 8 RCTs reported that ceftazidime monotherapy was equal in efficacy to combination regimens for the treatment of febrile neutropenic patients when mortality was assessed; because of the inability to extract data on patients with absolute neutrophil counts (ANCs) of $<100/mm^3$, no conclusions could be made about this subgroup (219).

In a more recent meta-analysis, published in 2002, of 29 RCTs from 4,795 febrile and neutropenic episodes, including 1029 bacteremic patients, monotherapy with an antipseudomonal agent was shown to be as effective as aminoglycoside-containing combinations for the treatment of febrile neutropenia (OR of 0.88 and 95% CI of 0.78 to 0.99 for overall clinical failure; OR of 0.70 and 95% CI of 0.54 to 0.92 for clinical failure in bacteremic patients) (80). Monotherapy was considered preferable to combination therapy, as it resulted in fewer treatment failures, defined as in-hospital mortality or the need to modify the initial empirical regimen. This held true for ANCs of below 1,000 cells/μl and 500 cells/μl; however, the authors were unable to perform a subgroup analysis of patients with an ANC of <100 cells/μl. These results indicate that antipseudomonal β-lactams can be at least as effective for the treatment of febrile neutropenia as a combination containing an aminoglycoside.

The evidence supporting the use of fluoroquinolone-based monotherapy for the management of febrile neutropenia is, however, more limited. Several studies assessing the efficacy of fluoroquinolone monotherapy compared with combination therapy showed no difference in treatment effect between fluoroquinolone monotherapy and combination therapy (93, 111, 121, 159). However, these results did not have adequate power to reliably demonstrating efficacy. Fluoroquinolone monotherapy should be used with caution in potentially bacteremic patients because it has been shown to be an independent risk factor for subsequent emergence of resistance (190).

Guidelines issued by the Infectious Diseases Society of America (IDSA) for the treatment of febrile, neutropenic patients do not recommend combination therapy as first-line therapy (79). Monotherapy with an antipseudomonal β-lactam agent, such as cefepime, a carbapenem, or piperacillin-tazobactam, is recommended. The addition of a second agent should be reserved for patients with complications, including hypotension or pneumonia, or where there is suspicion of antimicrobial resistance. In summary, when weighing all existing evidence comparing various antimicrobial management strategies for febrile neutropenic patients, monotherapy with an antipseudomonal agent appears to be preferable to the use of combination treatment. The choice of the antipseudomonal agent should be based on careful review of institution-specific antibiograms.

### Hospital-Acquired Pneumonia

Several epidemiologic studies have suggested that the empiric administration of inadequate antibiotic treatment for hospital-acquired pneumonia (HAP) is an important determinant of hospital mortality (42, 244). This appears to be especially concerning with organisms associated with high resistance rates, including *Pseudomonas* spp., *Serratia* spp., *Enterobacter* spp., and *Acinetobacter* spp. (78). HAP has been associated with relatively high rates of antimicrobial resistance, especially in patients in ICUs or those requiring mechanical ventilation (78).

In a multicenter, retrospective study conducted in five ICUs analyzing 183 cases of *P. aeruginosa* VAP, rates of appropriate empiric therapy (at least one effective antibiotic based on *in vitro* antibiotic susceptibilities) were higher in patients who were prescribed combination therapy than in those prescribed monotherapy (91% versus 57%, respectively; $P < 0.0001$) (86).

The 2005 Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines for the treatment of HAP recommend empirical combination therapy for patients at risk for multidrug-resistant pathogens (8). Risk factors for multidrug-resistant pathogens causing HAP include antimicrobial therapy in the preceding 90 days, current hospitalization of >5 days, a high frequency of antimicrobial resistance in the specific hospital unit, immunosuppression, and hospitalization for ≥2 days in the preceding 90 days (8). The guidelines suggest that therapy can be narrowed to a single agent if lower respiratory tract cultures do not demonstrate resistant pathogens. It has been shown that this approach of deescalation contributes to the preservation of antimicrobial susceptibilities (8, 110).

Although national guidelines are useful, the importance of local epidemiology to guide empiric treatment choices cannot be overemphasized. Both Ibrahim et al. and Soo Hoo et al. conducted before-and-after studies demonstrating that treatment guidelines incorporating local epidemiology can greatly improve clinical outcomes of HAP (118, 235). Beardsley and colleagues developed institution-specific guidelines for the treatment of HAP after retrospectively evaluating the pathogens associated with HAP in 111 patients (18). They found monotherapy to be appropriate for pneumonia developing within 10 days of hospitalization, while a β-lactam antibiotic in combination with an aminoglycoside was appropriate for late-onset HAP, and they concluded that local antimicrobial susceptibility data should guide institution-specific recommendations for the treatment of HAP.

In a randomized trial conducted at 22 centers involving 111 patients evaluating empiric therapy for HAP, Sieger et al. compared meropenem monotherapy with ceftazidime-tobramycin combination therapy (227). The investigators assessed clinical and microbiologic responses at the end of treatment. They found satisfactory clinical responses in 89% and 72% of the patients in the meropenem and ceftazidime-tobramycin arms, respectively ($P = 0.04$). Similarly, corresponding microbiologic response rates were 89% and 67% ($P = 0.006$). In a randomized, open-label study comparing meropenem to ceftazidime and amikacin in 140 patients with VAP, a satisfactory clinical response was observed in 83% of patients receiving meropenem and 66% of patients receiving ceftazidime-amikacin ($P = 0.04$) (7). A randomized prospective trial of 280 patients with HAP comparing imipenem mono-

therapy with imipenem and netilmicin combination therapy found similar clinical response rates in the two groups ($P = 0.19$) (51). Importantly, the addition of netilmicin significantly increased nephrotoxicity, and it did not prevent the emergence of *P. aeruginosa* resistant to imipenem.

The broader spectrum of activity of carbapenems may have contributed to the improved response in these studies and suggests that the use of an appropriately broad β-lactam agent may invalidate the need for the addition of an aminoglycoside. Additionally, the lack of Gram-positive coverage with the combination of ceftazidime and an aminoglycoside compared to carbapenems may have also influenced results. The relatively poor penetration of aminoglycosides into bronchial secretions should also be considered when weighing the risks and benefits of additional aminoglycoside therapy (13).

A meta-analysis of RCTs evaluating monotherapy compared with combination therapy for the empiric treatment of VAP was conducted in 2008 (4). The authors identified 41 trials randomizing 7,015 patients. Although the methodological quality of the eligible studies was low, including lack of double-blind design and allocation concealment in most studies, they found that rates of mortality and treatment failure for monotherapy and combination therapy were similar (RR of 0.94 and 95% CI of 0.76 to 1.16 for monotherapy and RR of 0.88 and 95% CI of 0.72 to 1.07 for combination therapy).

In summary, although there may be an added benefit of empiric combination therapy for patients at risk for HAP caused by MDRGNs, this does not seem to apply for all patients. This is especially the case for patients without risk factors for MDRGNs or patients receiving sufficiently broad β-lactam coverage. A recent multicenter, observational study found that compliance with the ATS and IDSA recommendations for empiric therapy for HAP was associated with increased mortality, suggesting that the guidelines may need to be revised after future RCTs evaluating this question are conducted (125). In the meantime, if combination therapy is initiated empirically, deescalation once antimicrobial susceptibilities are known is warranted, as continued combination therapy has not been found to be effective.

### Intra-Abdominal Infections

The majority of intra-abdominal infections (IAIs) are polymicrobial, with enteric Gram-negative pathogens contributing heavily; in health care-associated IAIs, highly resistant Gram-negative pathogens may predominate. In 2002, the Study for Monitoring Antimicrobial Resistance Trends (SMART) was initiated to monitor annual trends in antimicrobial susceptibility of Gram-negative enteric organisms associated with community- and hospital-associated IAIs (107). A total of 3,160 clinical isolates of *Escherichia coli* from IAIs during 2008 and 2009 from 13 European countries were evaluated, and 11% were found to produce extended-spectrum β-lactamases (ESBLs) (107). The SMART report for 2008 U.S. *E. coli* strains from IAIs indicated that about 4.7% of strains produced ESBLs (113). Emphasizing the importance of geographic trends, the rate of ESBL-producing *E. coli* strains from the Asia-Pacific region was 36.8% using SMART data from this region (47).

For intra-abdominal infections (IAIs), surgical management can be critical, as ongoing infection may result from persistence of the source of the infection. Once adequate source control is obtained, appropriate antimicrobial therapy improves outcomes (71, 172, 175, 251). Mortality secondary to intra-abdominal sepsis has been approximated at 25 to 35% but can exceed 70% (16, 17, 75, 83).

The majority of RCTs comparing monotherapy versus combination therapy for the treatment of IAIs, define "combination therapy" differently from other studies included in this review. In the IAI literature, "combination therapy" consists of agents with significantly different spectra of activity, for example, ticarcillin-clavulanate versus clindamycin and gentamicin or imipenem versus clindamycin, metronidazole, and tobramycin, etc.(12, 49, 76, 115, 164, 188, 204, 223, 231, 232, 234, 251). To our knowledge, there is only one RCT comparing the clinical efficacy of a β-lactam to that of a β-lactam plus an aminoglycoside for IAIs. Piperacillin-tazobactam monotherapy was compared with piperacillin-tazobactam combined with amikacin for the treatment of severe peritonitis in 227 eligible patients, and in an adjusted model, mortality rates were similar for the different treatment regimens (64).

Evidence-based guidelines for the management for IAIs were compiled by the Surgical Infection Society and IDSA in 2010 (233). Although based on very limited clinical data, the guidelines state the following: "The routine use of an aminoglycoside or another second agent effective against Gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy" (233).

### Severely Ill Patients

Although it is relatively undisputed that empiric combination therapy can play an important role in severe sepsis, a number of studies have also suggested that there is a benefit of definitive combination therapy for the severely ill (48, 112, 138). In a prospective multicenter study comparing the efficacy of monotherapy versus combination therapy on mortality in 200 patients with *P. aeruginosa* bacteremia, in a subgroup of patients who were severely ill (as defined by the need for mechanical ventilation, presence of hypotension, or presence of coma), survival was 53% with combination therapy versus 8% with monotherapy ($P < 0.02$) (112). The vast majority of patients receiving monotherapy received only an aminoglycoside, and 7% of patients did not receive appropriate antipseudomonal therapy.

Similarly, a prospective, multicenter observational study of 230 patients with *Klebsiella* bacteremia demonstrated no difference in mortality between patients who received combination therapy (82%) and those who received monotherapy (80%) (138). However, for a subgroup of patients who experienced hypotension within 3 days of the positive blood culture, 76% (22/29) who received combination therapy survived, compared to 50% (13/26) who received monotherapy ($P < 0.05$). The median duration of antibiotic therapy is unclear, and it is possible that for a large portion of, patients combination therapy was prescribed solely on an empiric basis.

In a prospective, multicenter observational study of 129 patients with *Enterobacter* bacteremia, overall survival was not different between patients who received combination therapy (84%) and those who received monotherapy (83%) (48). However, in a subgroup of severely ill patients, as defined by vital sign abnormalities, decreased mental status, mechanical ventilation, or cardiac arrest, those who received combination therapy had improved survival (73%) compared to those who received monotherapy (50%), but statistical significance was not achieved ($P = 0.17$).

These studies were conducted in the late 1980s and early 1990s, and results may change with newer, more potent agents.

Paul et al. performed a meta-analysis of 64 randomized trials comprising 7,568 patients, comparing β-lactam and aminoglycoside combination therapy with β-lactam monotherapy for severe infections in hospitalized patients with sepsis, and observed no difference in mortality between the treatment groups (RR, 0.90; 95% CI, 0.77 to 1.06) (196). This meta-analysis did not require a stringent criterion for "sepsis," making it possible that the advantage of combination therapy in critically ill patients may be diluted by the inclusion of less severely ill patients.

Kumar and colleagues performed a meta-analysis assessing whether the benefit of combination therapy is restricted to patients presenting with septic shock (142). The definition of "septic shock" was left to the discretion of the authors of the individual studies. Increased efficacy of combination therapy was observed in the subgroup with septic shock (OR, 0.49; 95% CI, 0.35 to 0.70; $P < 0.0001$). Interpretations of the findings were limited by the inclusion of observational studies. Aminoglycosides were prescribed for various amounts of time in the included studies, sometimes for short durations that mimic combination "empiric" therapy. Although the authors attempted to extract studies of aminoglycoside monotherapy or studies lacking microbiological susceptibility data, this was not always successful. One-third of the studies included in the septic shock subgroup analysis were performed before 1992, and the β-lactams prescribed frequently did not have antipseudomonal activity. Further, well-designed studies need to be conducted to ascertain whether combination therapy is beneficial for the most critically ill patients.

### Meta-Analyses

As there have been a number of studies conducted to assess the appropriateness of combination therapy for infections caused by Gram-negative organisms, several meta-analyses have been compiled to summarize these data (Table 1) (23, 67, 68, 80, 161, 194, 196–199, 212). In general, meta-analyses of observational studies have shown a benefit of combination therapy, while those including RCTs have not demonstrated such a benefit (161). The available clinical evidence does not support the routine use of combination antimicrobial therapy for the treatment of infections with Gram-negative bacteria. As trials are lacking for the subgroup of patients with septic shock, further analysis needs to be conducted to determine if this subpopulation may benefit from the addition of an aminoglycoside.

## OTHER ANTIBIOTIC COMBINATIONS FOR INFECTIONS WITH MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

The emergence of carbapenem-hydrolyzing β-lactamases has threatened the clinical utility of carbapenems and exemplifies the challenge of emerging antimicrobial resistance in Gram-negative organisms. Resistance to antibiotics other than β-lactams is equally concerning for these organisms. Resistance to quinolones in carbapenemase producers approaches 98%, and resistance to aminoglycosides is approximately 50% (31). Remaining agents with activity against carbapenemase producers include polymyxins (colistin and polymyxin B), tigecycline, and fosfomycin; however, resistance to these agents has been described as well (72). Table 2 summarizes some comparative clinical studies evaluating monotherapy and combination therapy for infections with highly resistant Gram-negative bacteria (52, 73, 74, 103, 150, 154, 243). These regimens are generally considered "salvage therapy" for MDRGN infections. As the data are still very limited and generally confined to observational studies, selection of therapy in these situations should be determined on a case-by-case basis and in consultation with an infectious diseases specialist. Although data are still emerging, some experts advocate consideration of combination therapy when prescribing polymyxins, tigecycline, or fosfomycin (although not currently available in the United States in intravenous formulations) because of concerns regarding the development of resistance when used alone (92).

## CONCLUSION

Although there are theoretical reasons why combination antimicrobial therapy may, in certain patients and situations, be superior to monotherapy for the treatment of infections with Gram-negative bacteria, the clinical data supporting these theories are neither overwhelming nor definitive. On the contrary, meta-analyses that have been conducted exclusively evaluating RCTs demonstrate no difference in clinical outcomes between the two treatment strategies for definitive management of infections with Gram-negative bacteria, but there are well-documented increased toxicities with combination therapy. This suggests that patients with infections with Gram-negative bacteria are served best by receiving definitive treatment with a single appropriate antibiotic.

In contrast, due to the greater mortality associated with delays in appropriate and effective antimicrobial treatment, initiating broad-spectrum empiric antimicrobial treatment (which often means combination therapy) at the first suspicion of infection in critically ill patients is prudent. For patients at risk of MDRGN infections, including patients with compromised immune systems, those with previous ICU admissions, or recent recipients of broad-spectrum antibiotics, empiric antimicrobial treatment should include coverage of pathogens that may be resistant to previously administered antibiotics, and empiric combination therapy may be appropriate. However, in attempts to avoid further emergence of resistance and adverse side effects such as *C. difficile* infection, nephrotoxicity, and ototoxicity, the antimicrobial regimen should be promptly narrowed or discontinued based on the patient's clinical course and culture and susceptibility profile results.

Given the lack of evidence supporting the routine use of combination antimicrobial therapy for definitive treatment of infections with Gram-negative bacteria, clinicians need to be judicious in antibiotic use. A large proportion of the rise in MDRGNs can be attributed to selective pressure from excessive antimicrobial use (36, 208). There are few, if any, new agents in the drug development "pipeline" to rescue us from this dilemma in the near future (160). Many large pharmaceutical companies have terminated their antibacterial research programs as they focus on more lucrative therapeutic areas. At the same time, MDRGNs have emerged and spread rapidly, highlighting the need to optimize the use of the remaining antimicrobial agents. Rather than simply adding a second agent, optimization of antimicrobial therapy includes selection of appropriate antibiotic agent(s), dose, frequency, route, and duration. It also may include prolonged antibiotic infusion strategies to exploit the time above the MIC mechanism of β-lactams when combating organisms with elevated MICs (239, 242).

## SUMMARY

The findings from this review as well as from several meta-analyses do not support the use of combination antimicrobial therapy for

**TABLE 2** Comparative clinical studies assessing the benefit of monotherapy compared with combination antibiotic therapy for infections with multidrug-resistant Gram-negative bacteria

| Reference | Design (*n*) | Infection | Drug combination | Outcome(s) (monotherapy vs combination therapy) | Conclusion(s) |
|---|---|---|---|---|---|
| 52 | Prospective, randomized (53) | *Pseudomonas aeruginosa* cystic fibrosis exacerbations | Colisin (2 million IU q8h) vs colistin plus aztreonam, piperacillin, ceftazidime, imipenem, or ciprofloxacin | 100% vs 100% (clinical response at day 12); significant decrease in creatinine clearance in combination therapy group (nephrotoxicity) | No difference in response rates; nephrotoxicity increased with combination therapy |
| 55a | Prospective, observational (162) | Metallo-β-lactamase-producing *Klebsiella pneumoniae* bacteremia | Single active agent vs carbapenem plus either colistin or aminoglycoside | 27% vs 8.3% (mortality) | Patients treated with a carbapenem plus either colistin or an aminoglycoside tended to have higher survival that those treated with a single active drug |
| 74 | Retrospective (71) | MDRGN infections (multiple sites) | Colistin vs colistin plus meropenem | 85.7% vs 68.4% (clinical response); 0% vs 37% (mortality); 0% vs 7% (nephrotoxicity) | No difference in response and nephrotoxicity rates; survival significantly higher in patients treated with colistin monotherapy |
| 73 | Retrospective (258) | MDRGN infections (multiple sites) | Colistin vs colistin plus meropenem, ampicillin-sulbactam, or piperacillin-tazobactam | 90% (colistin) vs 83% (colisin plus meropenem) vs 55% (colistin plus piperacillin-tazobactam or ampicillin-sulbactam) (clinical response) | Favorable outcomes of MDRGN infections can be observed with colistin monotherapy or colistin in combination with meropenem |
| 103 | Retrospective (33) | Carbapenem-resistant *Acinetobacter baumannii* | Tigecycline vs tigecycline plus aminoglycoside | 100% (tigecycline) vs 32% (tigecycline plus aminoglycoside) (clinical failure) | Improved outcomes when tigecycline was used in combination with an aminoglycoside |
| 150 | Prospective, observational (16) | Carbapenem-resistant *K. pneumoniae* bacteremia | Polymyxin B vs polymyxin B plus tigecycline | 25% vs 0% (increase in polymyxin B MIC) | Treatment with combination of polymyxin B and tigecycline may prevent emergence of resistance to these agents |
| 154 | Prospective, observational (23) | MDR *P. aeruginosa* (multiple sites) | Colistin (1-5 mg/kg/day) vs colistin plus amikacin or antipseudomonal β-lactam | 60% vs 62% (clinical response) | No difference in response rates |
| 243 | Retrospective (8) | MDR *P. aeruginosa* diabetic foot infections | Colistin (1 million IU q12h) vs colistin plus rifampin or imipenem | 75% vs 50% (response rates); 25% vs 0% (nephrotoxicity) | No difference in response and nephrotoxicity rates |

definitive treatment of infections with Gram-negative bacteria. It should be noted that combination therapy may have some value in a specific subset of patients with severe sepsis, and well-controlled randomized studies are necessary to answer this question. Many of the early studies that supported the concept of combination therapy used aminoglycoside monotherapy as the comparator group, a clinical strategy that has been subsequently shown to be inferior. With the advent of broad-spectrum antipseudomonal β-lactam agents, studies have not shown an advantage to adding a second agent.

There are three potential advantages to combination antimicrobial therapy for infections with Gram-negative bacteria that are generally cited: (i) an increased likelihood that the infective pathogen will be susceptible to at least one of the components of an empiric combination regimen, (ii) the synergistic effect afforded by the use of two agents, and (iii) protection against emergence of resistance with combination therapy. With regard to the first point, the use of empiric combination therapy for critically ill patients is certainly appropriate to broaden the spectrum of activity and to increase the likelihood that the regimen contains a single agent that is active against the pathogen, but there is insufficient evidence showing a benefit of a second agent for continued therapy once pathogens and antimicrobial susceptibilities are known. Although synergy may have a role when treating a highly resistant organism with MICs in the intermediate to resistant range, assuming that the pathogen is susceptible to one antibiotic, there does not appear to be a "synergistic" benefit that translates to an incremental clinical benefit with the addition of a second agent. Finally, clinical studies of infections with Gram-negative bacteria have shown no difference in the emergence of resistance during antimicrobial therapy with combination therapy versus monotherapy. Ensuring that the dose, frequency of administration, and duration over which an antibiotic is infused are optimized is likely more important in the prevention of resistance than the addition of a second agent. As the flow of new antibacterial drugs into the market has slowed coupled with the increasing prevalence of MDRGN infections, saving the second agent for when actually necessary is vital in the war against antimicrobial resistance.

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