Is double coverage of gram-negative organisms necessary?

SARAH J. JOHNSON, ERIKA J. ERNST, AND KEVIN G. MOORES

Infections caused by gram-negative bacilli typically occur in the lungs, in the urinary tract, at surgical sites, and in the bloodstream and are a significant cause of morbidity and mortality.1,2 The gram-negative bacilli most commonly responsible for infection in humans are *Enterobacter* species, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter* species, and *Serratia marcescens.*1 Depending on the site of infection and a patient’s comorbid conditions, mortality related to infections caused by gram-negative bacilli ranges from 20% to 60%. Inappropriate initial antimicrobial therapy and a delay in drug administration are associated with poorer patient outcomes.3,4

When a patient is suspected of having a gram-negative infection, initial antimicrobial coverage is often directed at *P. aeruginosa*, because this pathogen has been associated with higher mortality rates compared with other gram-negative organisms.6,8 Initial antimicrobial regimens often include two agents that are active against *P. aeruginosa*. The rationale for prescribing two antimicrobial agents originates from a 1989 study that found significantly lower mortality rates among patients who received combination therapy versus monotherapy (27% versus 47%, *p* < 0.02); however, most of the patients receiving monotherapy were treated with an aminoglycoside.9 This study was published when aminoglycosides and β-lactam antibiotics were...
the primary agents available to treat infections caused by *P. aeruginosa*. The results of the study are not pertinent to current practice for several reasons: (1) aminoglycosides are now dosed based on their pharmacokinetic and pharmacodynamic parameters, (2) fluoroquinolones have largely replaced aminoglycosides as the agents used in combination with β-lactam antibiotics, and (3) susceptibilities of the targeted microorganisms have changed over the years. Regardless of these factors, clinicians often prescribe two antibiotics for coverage of infections caused by *P. aeruginosa*.10,11 The usual regimens consist of a β-lactam antibiotic (i.e., antipseudomonal penicillin, third- or fourth-generation antipseudomonal cephalosporin, carbapenem, or aztreonam), plus an aminoglycoside or a fluoroquinolone. All of these agents have activity against *P. aeruginosa*; however, resistance mechanisms have been identified for these antipseudomonal antibiotics, and resistance to all of these agents is increasing.6

The use of combination therapy to treat gram-negative infections remains controversial. Results from studies that compared the efficacy of combination therapy with that of monotherapy against gram-negative bacilli conflict.9,18 Strong evidence to support the use of two antimicrobials to treat gram-negative organisms is lacking. Unnecessary antimicrobial use may lead to antimicrobial resistance, increased adverse effects, and increased costs. No guidelines exist regarding double coverage of extended-spectrum β-lactamase-producing gram-negative organisms, and 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 treatment.17 Similarly, the IDSA–American Thoracic Society guidelines for the treatment of hospital-acquired pneumonia recommend empirical combination therapy for late-onset pneumonia only or in patients at risk for multidrug-resistant pathogens.18 This article examines the appropriateness of combination therapy for gram-negative infections.

**Empirical antimicrobial therapy against gram-negative pathogens**

Risk factors for infections with gram-negative organisms include increased length of stay in the hospital, admission to the intensive care or burn unit, comorbid conditions (e.g., diabetes, human immunodeficiency virus infection, hematologic malignancy, liver failure), use of an i.v. or urinary catheter, mechanical ventilation, and hemodialysis.19 When initiating empirical antimicrobial therapy in patients at risk for infection with gram-negative bacilli, including *P. aeruginosa*, the antimicrobial regimen should include an antipseudomonal agent with a broad spectrum of coverage. Selection of the specific empirical antimicrobial regimen should be based on hospital-specific susceptibility data (e.g., antibiogram) for the organisms most likely to be causing the infection and on the hospital formulary. Once susceptibility data are available for a particular organism, therapy should be targeted and narrowed to cover the isolated pathogen. If *P. aeruginosa* is not isolated, discontinuation of the antipseudomonal antibiotic should be considered.

The initial use of double coverage for gram-negative infections is often justified by one of three reasons: (1) the potential for synergistic activity between two classes of antimicrobial agents (the potential for improved outcomes), (2) the broad empirical coverage provided by two antimicrobial agents with differing spectra of activity and resistance patterns (an effort to ensure the organism is adequately covered), or (3) the prevention of resistance development during antimicrobial therapy. Disadvantages of using combination therapy are increased drug toxicity, increased costs, and increased risk of superinfection with more-resistant bacteria or fungi or *Clostridium difficile*.20

**Use of two antimicrobials for synergy.** Synergy between two antimicrobial agents is defined as greater than a 2-log increase in bactericidal activity in vitro compared with the bactericidal activity of each agent alone.21 Before fluoroquinolones became available, empirical therapy for a suspected gram-negative infection usually consisted of a β-lactam agent plus an aminoglycoside. The rationale for this combination was based on data suggesting that aminoglycoside monotherapy is associated with worse outcomes; however, there is also the potential for synergistic effects between these two classes of antibiotics. The β-lactam opens the cell wall and facilitates the entry of the aminoglycoside to reach the ribosomal RNA of the bacteria. In vitro data have suggested that synergistic activity exists between β-lactams and aminoglycosides; but these susceptibility-testing methods have been questioned.7 Although the clinical rationale of synergy makes sense, as does avoiding aminoglycoside monotherapy, the routine use of aminoglycosides has fallen out of favor due to its associated toxicities (e.g., nephrotoxicity, ototoxicity) and more-complicated dosing and additional monitoring requirements (e.g., serum aminoglycoside levels, serum creatinine levels) compared with fluoroquinolones. However, fluoroquinolones are associated with adverse effects, and limited data suggest that synergistic activity ex-
ists between the fluoroquinolones and other antimicrobials. The only data available are in vitro data of a possible synergistic effect between antipseudomonal cephalosporins (cefepime and ceftazadime) and quinolones (ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin); synergy was only noted for *P. aeruginosa* that was resistant to one of the two agents.22

Based on the available data, a combination regimen consisting of a β-lactam antibiotic plus an aminoglycoside will provide the most synergistic effect. For serious gram-negative infections, the peak aminoglycoside serum concentration should be 8–12 times the minimum inhibitory concentration (MIC) of the pathogen to achieve the best bactericidal activity. Attaining such MICs has been associated with less emergence of bacteria with subsequent higher MICs and faster onset to recovery from infection.23,24 Larger aminoglycoside doses may also facilitate higher drug concentrations in the lungs. Patients receiving higher doses should also be monitored for nephrotoxicity and signs and symptoms of hearing loss or vestibular toxicity. In addition, serum aminoglycoside levels should be monitored routinely. It is important to note that there is no clear evidence that a β-lactam antibiotic in combination with an aminoglycoside is superior to β-lactam monotherapy for hospitalized patients with serious infections.16,20 A meta-analysis of studies showed similar or better outcomes with β-lactam monotherapy in immunocompetent patients treated for sepsis compared with β-lactam and aminoglycoside combination therapy.16 Combination therapy provided no advantage over monotherapy in patients with gram-negative infections, including bacteremias caused by *P. aeruginosa*. In addition, there was no difference in the development of antimicrobial resistance between β-lactam monotherapy and combination therapy. Nephrotoxicity was more common in patients receiving an aminoglycoside. Another meta-analysis of combination therapy for gram-negative bacteremia found no mortality benefit with combination therapy.20 The authors did report mortality benefits in a subgroup of patients with *P. aeruginosa* bacteremia treated with combination therapy; however, this conclusion was based on only five studies, the largest of which compared combination therapy with monotherapy with an aminoglycoside.9 Of note, this study was published in 1989, before the adoption of current aminoglycoside dosing recommendations. The authors concluded that their findings did not support the routine use of combination antimicrobial therapy for gram-negative bacteremia.20

A recent retrospective study conducted at a large academic medical center explored the influence of combination β-lactam aminoglycoside therapy to β-lactam therapy alone.25 While there was no survival benefit overall with combination therapy, a subgroup analysis indicated a strong survival benefit with combination therapy in patients with shock or neutropenia. This study is also noteworthy in that, while drug dosages were not specified, local guidelines during the study period recommended the use of extended-interval dosing of aminoglycosides.

The efficacy of other combination therapies, such as fluoroquinolones plus β-lactam antibiotics, has also been studied retrospectively. A meta-analysis was conducted to compare the efficacy and toxicity of ciprofloxacin plus a β-lactam with those of an aminoglycoside plus a β-lactam for treatment of inpatients with febrile neutropenia.26 A total of eight randomized controlled trials were included in the meta-analysis. Comparable clinical outcomes were reported for both treatment groups. The authors concluded that the combination of ciprofloxacin with a β-lactam antibiotic should be considered in patients who have not received fluoroquinolone prophylaxis for febrile neutropenia. A recent retrospective, single-center study compared β-lactam monotherapy with a β-lactam in combination with a fluoroquinolone for bacteremia caused by gram-negative bacilli.27 In critically ill patients, no significant difference was observed in 28-day mortality rates between the two treatment groups. However, in less-severely ill patients, combination therapy was associated with a significantly lower 28-day mortality rate (*p* = 0.044). It is important to note that an overwhelming number of less-severely ill patients treated with a fluoroquinolone had bacteremia from a urinary source (*p* < 0.01). Data from outpatient settings suggest that fluoroquinolones are superior to β-lactams for the treatment of urinary tract infections24; this may help explain why the combination was beneficial in less-severely ill patients but not in critically ill patients.

Use of two antimicrobials for expanded spectrum of activity. Resistance of gram-negative bacilli to antimicrobials continues to increase.6 According to data from the National Nosocomial Infections Surveillance (NNIS) System report in 2003, resistance rates for *P. aeruginosa* isolates from the intensive care unit were 22.3% for imipenem, 30% for cephalosporins, and 33% for quinolones.6 *P. aeruginosa* is particularly problematic because the organism acquires resistance via several different mechanisms, including target-site mutations in topoisomerases II and IV, derepression of AmpC β-lactamases, upregulation of efflux pumps, and membrane impermeability through porin changes.29 NNIS data from 2004 indicate that resistance rates to third-generation cephalosporins among critically ill patients in the United States are 20.6% for *K. pneumoniae*, 31.1% for *Enterobacter* species, and 5.8% for *E. coli*.30
Given the increased resistance patterns observed in gram-negative bacilli, two antimicrobial agents may be prescribed empirically to increase the spectrum of activity. Suitable antimicrobial combinations should be selected based on individual hospital susceptibility data. It is common for a β-lactam antibiotic such as piperacillin–tazobactam to be prescribed in combination with a fluoroquinolone for a suspected gram-negative infection. For example, if an institution had a reported cumulative annual _P. aeruginosa_ resistance rate of 5% for piperacillin–tazobactam but a reported cumulative annual resistance rate of 25% for the fluoroquinolones, the rationale for adding the fluoroquinolone is to provide coverage for the 5% of organisms that would not be susceptible to piperacillin–tazobactam. Based on this example, the fluoroquinolone could be beneficial if the organism is resistant to piperacillin–tazobactam and susceptible to the fluoroquinolone. However, based on current data, there is a significant likelihood that the organism would also be resistant to the fluoroquinolone. Data from our institution indicate that the addition of a fluoroquinolone to an antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, or meropenem) does not broaden the spectrum of activity against _P. aeruginosa_. Only 1–2% of isolates resistant to an antipseudomonal β-lactam were susceptible to ciprofloxacin. It is interesting to note that 4–7% of the β-lactam-resistant _P. aeruginosa_ isolates were susceptible to tobramycin.31 We intend to use this information, as part of our antimicrobial stewardship program, to discourage the use of combination antimicrobial therapy with little perceived benefit. Beardsley and colleagues32 used similar findings to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia, where they suggested monotherapy for pneumonia developing within 10 days and a β-lactam antibiotic in combination with an aminoglycoside for late-onset hospital-acquired pneumonia.

The use of combination regimens with the same mechanism of action, such as two β-lactam antibiotics, may also be considered. The theoretical rationale for the use of two β-lactams is that they would each have affinity for different penicillin-binding proteins. No clinical data support the use of two β-lactams targeting _P. aeruginosa_, such as an antipseudomonal penicillin or third-generation cephalosporin plus aztreonam. Studies investigating the combination of two β-lactams in neutropenic children are two small and do not contain adequate comparison groups to draw conclusions.33,34 Older literature in this area typically includes combinations that are not used today (e.g., cefotaxime plus aztreonam compared with cefotaxime plus an aminoglycoside for the treatment of nosocomial pneumonia).35 Since cefotaxime does not adequately treat _P. aeruginosa_, the aminoglycoside treatment was essentially monotherapy.35 On the other hand, there may potentially be antagonistic effects of combination β-lactam antibiotics, as one agent may inactivate the other by inducing β-lactamases.36,37 Most importantly, if two agents will be prescribed as empirical therapy, the spectrum of activity should be increased by the addition of the second agent.

Regardless of what is chosen as empirical therapy, once culture and susceptibility results are known, the therapy should be directed at the pathogen; thus, one of the two agents should be discontinued. If possible, the antimicrobial spectrum should also be narrowed in an effort to avoid the development of resistant organisms (e.g., carbapenem-resistant _P. aeruginosa_, _K. pneumoniae_, or _Acinetobacter_ species).38,39 The decision to continue or discontinue a specific antimicrobial agent depends on a number of factors, including the need for oral therapy, cost of the agents, and other hospital-specific protocols.

**Prevention of antimicrobial resistance.** Another reason for using combination regimens is for prevention of antimicrobial resistance during treatment. Studies have shown that there is no difference in the emergence of resistance during antimicrobial therapy with combination therapy versus monotherapy.40,41,42 In one study, monotherapy was associated with less risk of bacterial superinfection and bacterial colonization.41 One small animal study did find that antimicrobial resistance was less common with combination therapy versus monotherapy.42

**Adverse consequences related to combination antimicrobial use.** The use of combination antimicrobial therapy can lead to increased toxicity, cost, and the possibility of superinfection. Nephrotoxicity, ototoxicity, and vestibular toxicity have deterred the widespread use of aminoglycosides. However, aminoglycoside-containing regimens have the most support in the medical literature. Although it is tempting to prescribe several antimicrobials in an attempt to provide the best coverage against suspected microorganisms, it is important to remember that the overuse of antimicrobial agents contributes to antimicrobial resistance as well as serious superinfections such as candidemia or infections caused by _C. difficile_. The frequency of _C. difficile_ infections has increased significantly over the past 15 years, and more virulent strains of the toxin produced by _C. difficile_ have been identified.43,44 _C. difficile_ infection can lead to severe consequences, including pseudomembranous colitis, colectomy, and death. The infection recurs in approximately 25% of patients and in many cases is refractory to treatment.45 The increase in rates of _C. difficile_ infections has been linked to other drug therapies such as acid-suppressing agents; however,
C. difficile infections are strongly associated with the use of antibiotics. Of the antibiotics used for the treatment of gram-negative infections, fluoroquinolones and the third-generation cephalosporins are the most commonly associated with C. difficile infections. Similarly, the rate of fungal infections has increased in recent years, and mortality attributed to these infections is significant.

Conclusion
The available clinical evidence does not support the routine use of combination antimicrobial therapy for treatment of gram-negative infections. Patients with shock or neutropenia may benefit from combination therapy that includes an aminoglycoside.

References
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