Novel Antibiotic Combinations against Infections with Almost Completely Resistant *Pseudomonas aeruginosa* and Acinetobacter Species

James J. Rahal
Infectious Disease Section and Lang Research Center, New York Hospital Queens, and Department of Medicine, Weill College of Medicine, Cornell University, New York, New York

For infections with antibiotic-susceptible strains of *Pseudomonas aeruginosa*, most studies have suggested that combination therapy, usually with a β-lactam antibiotic plus an aminoglycoside, is preferable for patients with bacteremia and neutropenia. Against infections with *Pseudomonas aeruginosa* or *Acinetobacter baumannii* isolates that are resistant to all antibiotics except the polymyxins, several novel antibiotic combinations demonstrate increased activity in vitro compared with that of any single agent. Whether these combinations yield outcomes that are improved over those seen with a polymyxin or other agent alone remains to be determined. However, against infections with species resistant to all antibiotics, including polymyxins, novel combinations are the only remaining therapeutic option.

Antibiotic combinations have long been used to provide antibacterial activity against multiple potential pathogens for initial empirical treatment of critically ill patients. Here, I review the rationale and clinical experience supporting the use of antibiotic combinations against a single invasive pathogen, either *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. The clinical use of such therapy for gram-negative infections in general can be divided into 2 categories. In the first category, such therapy is used to improve clinical outcomes of infections with strains that are susceptible to one or more individual antibiotics. The primary rationale for combining 2 agents is to enhance the activity of either by achievement of a synergistic effect. This effect, synergy, is defined as significantly greater activity provided by 2 agents combined than that provided by the sum of each agent alone. A secondary rationale is to allow lower doses of either antibiotic to reduce toxicity. Third, use of 2 antibiotics might prevent the emergence of resistance to either. The second category of antibiotic combination use has evolved during the past 10–15 years, during which certain clinical species have become resistant to all available antibacterial agents or to all except a single agent. In this circumstance, the achievement of synergy is no longer a required result of combination therapy, because any clinical activity of an antibiotic combination is preferable to the inactivity of each drug alone. Thus, an acceptable effect may result from additive or subadditive activity of the combination. An acceptable result may also derive from enhancement of a single active agent by an otherwise inactive agent. In this case, prevention of resistance to the active agent may be possible.

**COMBINATION ANTIBIOTIC THERAPY AGAINST SUSCEPTIBLE PATHOGENS**

Prior reviews have synthesized studies of antibiotic combination therapy for gram-negative infection conducted from the 1970s to the 1990s. The consensus is that combination therapy is probably more effective than monotherapy only for infections with *P. aeruginosa* and primarily among patients with bacteremia and neutropenia [1–4]. The potential increased value of combination therapy over monotherapy for nosocomial gram-negative pneumonia has been controversial for many years. A recent consensus opinion from the Amer-
ic Thoracic Society and the Infectious Diseases Society of America suggests that monotherapy with newer agents (quinolones, late-generation cephalosporins, β-lactam–β-lactamase inhibitor combinations, or carbapenems) is preferred for patients with no risk of infection with drug-resistant organisms and without severe infection [5]. The apparent advantage of combination therapy noted in reviews of early studies [1–4] may not relate to current therapeutic options with quinolones, late-generation β-lactam agents, and β-lactamase inhibitors. Early studies were conducted primarily with ticarcillin or piperacillin, with or without an aminoglycoside. Thus, monotherapy with any of these agents, particularly for pulmonary infection, would not now be considered equivalent to monotherapy with modern agents. The most recent meta-analysis of randomized controlled trials compared β-lactam monotherapy with therapy with a β-lactam plus an aminoglycoside, against a variety of mixed infections [6]. Eight trials were analyzed, 6 of which used late-generation agents as monotherapy. The results showed no difference between monotherapy and combination therapy in mortality or emergence of resistant pathogens. In contrast, analysis of a historical cohort of 115 episodes of P. aeruginosa infection compared monotherapy and combination therapy, each categorized as adequate or inadequate on the basis of susceptibility results [7]. The results were further categorized as empirical initial therapy or definitive therapy, given when susceptibility was known. Monotherapy regimens included piperacillin or piperacillin-tazobactam, ceftazidime, imipenem, cefepime, or ciprofloxacin. Aminoglycosides were not used as monotherapy. Combination therapy consisted of one of these agents plus an aminoglycoside. The risk of death at 30 days was significantly greater for patients receiving adequate empirical monotherapy than for those receiving adequate empirical combination therapy. However, adequate definitive combination therapy did not improve survival over that seen with adequate definitive monotherapy. These results support the concept that combination therapy is superior to monotherapy as the initial empirical approach to Pseudomonas bacteremia. However, completion of therapy with a single effective agent after susceptibility data are known appears to be equivalent to continued combination therapy.

In summary, demonstration of in vitro synergy by combining 2 antibiotics and early clinical data using less potent antibiotics support an extrapolated conclusion that combination therapy is probably preferable for treatment of serious infection with antibiotic-susceptible gram-negative pathogens, particularly as empirical therapy for bacteremia due to P. aeruginosa. Such combination therapy has usually included a β-lactam drug plus an aminoglycoside or quinolone. This tentative conclusion is based on in vitro and clinical studies in which each antibiotic used in combination is active against the infecting pathogen. As noted previously, the evolution of resistance to all, or almost all, antibiotics among P. aeruginosa and A. baumannii isolates has made necessary the use of antibiotic combinations consisting of one or more agents to which the organism may be resistant. Selection of such drugs and their potential for providing increased activity in combination depends on an understanding of mechanisms of action and of resistance.

**COMBINATION ANTIBIOTIC THERAPY AGAINST HIGHLY RESISTANT PATHOGENS**

In 1983, Zuravleff et al. [8] demonstrated that clinical isolates of P. aeruginosa that were resistant to ticarcillin and tobramycin, alone and in combination, were killed by the addition of rifampin. Thus, despite the organism’s resistance to each of the 3 drugs alone, killing was achieved by the triple combination and by the double combination of ticarcillin plus rifampin. These results were validated in a neutropenic mouse model of P. aeruginosa infection. Triple therapy with ticarcillin, tobramycin, and rifampin yielded significantly lower mortality than did ticarcillin plus tobramycin [9]. The same group of investigators subsequently compared a triple therapy regimen including an antipseudomonal β-lactam, an aminoglycoside, and rifampin with double therapy (without rifampin) among 121 patients with bacteremia due to P. aeruginosa. No significant difference in mortality occurred in the 2 groups. However, bacteriologic cure occurred significantly more frequently in the group treated with triple therapy. Also, breakthrough or relapsing bacteremia occurred in 2% of patients treated with triple therapy and 14% of those treated with double therapy [10]. These novel results were followed by other attempts to exploit the anti-gram-negative activity of rifampin in enhancing the effect of other agents against multidrug-resistant pathogens. The following combinations have been shown to provide enhanced activity, compared with that of any single agent, against A. baumannii: polymyxin B or colistin plus rifampin, imipenem, or azithromycin; rifampin plus azithromycin; sulfactam plus rifampin, azithromycin, or a quinolone; and the triple combination of polymyxin B, imipenem, and rifampin [11–18]. Against multidrug-resistant P. aeruginosa, increased activity in vitro has been achieved by combinations of polymyxin B plus rifampin; ceftazidime or cefepime plus a quinolone; cefazidime plus colistin; clarithromycin plus tobramycin; and azithromycin plus tobramycin, doxycycline, trimethoprim, or rifampin [19–23]. The mechanisms of positive interaction between these agents are not known, with few exceptions. The combined action of polymyxins and imipenem appears to exist primarily against bacterial strains in which a permeability barrier, created by the loss of an effective outer membrane porin channel, is responsible for relatively low-level imipenem resistance. That polymyxin increases bacterial membrane permeability appears to explain its enhancement of imipenem’s activity [16]. The effect of sulfactam alone or in combination with other agents appears
to be due to its attachment to penicillin-binding proteins, specifically in *A. baumannii* [24]. The enhancing action of rifampin and macrolides against multidrug-resistant gram-negative pathogens remains relatively unknown.

Despite the above-noted studies demonstrating enhanced activity of novel antibiotic combinations against multidrug-resistant *A. baumannii* and *P. aeruginosa*, reports of clinical trials of such combinations are extremely rare. In a nosocomial outbreak of pulmonary infection with multidrug-resistant *P. aeruginosa*, cefepime and amikacin were found to be the “least inactive” antibiotics and to be highly synergistic by checkerboard and killing curve methods. All patients were treated with this combination, and 44 of 64 recovered [25]. In another cohort study, 25 critically ill patients with respiratory tract infections due to multidrug-resistant *A. baumannii* or *P. aeruginosa* were treated with intravenous and/or aerosolized polymyxin B in combination with ≥1 of the following agents: imipenem or meropenem (65%), amikacin (28%), tobramycin (10%), cefepime (10%), ampicillin-sulbactam (10%), a quinolone (7%), or aztreonam (3%). Twelve of the 25 infecting isolates were resistant to all available antibiotics except polymyxin B. It is noteworthy that rifampin was not included in the therapeutic regimens [26]. Nevertheless, 79% of treated patients survived to the end of therapy, and 41% of 22 patients achieved microbiological clearance. These results compare favorably with those of multiple studies in which polymyxin B or colistin alone was used for the same type of infection [27–33]. Other single-drug regimens against which the use of novel combinations must be compared include ampicillin-sulbactam or imipenem alone [34–39]. These drugs, however, are used only against isolates to which susceptibility has been retained. Thus, comparative studies are needed to determine whether novel combinations improve the results of therapy with polymyxins, ampicillin-sulbactam, or imipenem alone against infecting strains that may be susceptible to these agents. Strains that are resistant to all antibiotics including polymyxins are rare, although their incidence is increasing [23]. Antibiotic combinations that yield some degree of susceptibility in vitro are the only recourse in such situations. Experimental polypeptides may ultimately provide a new approach to this problem [40–42]. Tigecycline, recently approved for clinical use, is active in vitro against many multidrug-resistant isolates of *A. baumannii* [43]. Its clinical effect, alone or in combination with other agents, remains to be determined.

In summary, few treatment options remain for serious infections caused by multidrug-resistant *A. baumannii* and *P. aeruginosa*. Carbapenems and amikacin remain active against some isolates of both species. Sulbactam, available as ampicillin-sulbactam, may also be active against *A. baumannii*. The polymyxins remain the most consistently effective agents in vitro against both *A. baumannii* and *P. aeruginosa*. However, more than an occasional isolate is resistant to all of the above agents. In this situation, novel antibiotic combinations with in vitro activity, as described above, become the only treatment option (table 1). Infections with isolates that are susceptible to only one or a few agents may be treated with a single drug, but the

### Table 1. Enhanced activity of antibiotic combinations against multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: in vitro and clinical evidence.

<table>
<thead>
<tr>
<th>Pathogen (type of evidence), antibiotic combination</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em> (in vitro)</td>
<td></td>
</tr>
<tr>
<td>Ticarcillin, tobramycin, rifampin</td>
<td>[8]</td>
</tr>
<tr>
<td>Cephalosporins, quinolones</td>
<td>[21]</td>
</tr>
<tr>
<td>Ceftazidime, colistin</td>
<td>[22]</td>
</tr>
<tr>
<td>Macrolides, tobramycin, trimethoprim, rifampin</td>
<td>[20]</td>
</tr>
<tr>
<td>Polymyxin B, rifampin</td>
<td>[19]</td>
</tr>
<tr>
<td><em>A. baumannii</em> (in vitro)</td>
<td></td>
</tr>
<tr>
<td>Polymyxin B, imipenem, rifampin</td>
<td>[16]</td>
</tr>
<tr>
<td>Polymyxin B, cecropin</td>
<td>[41, 42]</td>
</tr>
<tr>
<td>Polymyxin B, rifampin, ampicillin-sulbactam</td>
<td>[12]</td>
</tr>
<tr>
<td>Polymyxin B, rifampin, imipenem</td>
<td>[16]</td>
</tr>
<tr>
<td>Colistin, rifampin</td>
<td>[13, 15]</td>
</tr>
<tr>
<td><em>A. baumannii</em> and <em>P. aeruginosa</em> (clinical)</td>
<td></td>
</tr>
<tr>
<td>Cefepime, amikacin</td>
<td>[25]</td>
</tr>
<tr>
<td>Polymyxin B plus 1 or more of the following: a carbapenem, aminoglycoside, quinolone, or β-lactam</td>
<td>[26]</td>
</tr>
</tbody>
</table>
risk of progressive resistance must be considered. Controlled therapeutic trials will be necessary to determine whether novel antibiotic combinations provide greater efficacy and less progressive resistance in this setting.

Acknowledgments

Financial support. This work was supported by the BMA Medical Foundation, the Beatrice Snyder Foundation, and Agnes Varis. Potential conflicts of interest. J.J.R. has received recent research and educational funding from Merck and Co., Roche Pharmaceuticals, and Ortho-McNeil Pharmaceuticals Inc. and is a consultant and speaker for Wyeth, Merck, and Hemispherx Biopharma Inc.

References