How Soon Is Now? The Urgent Need for Randomized, Controlled Trials Evaluating Treatment of Multidrug-Resistant Bacterial Infection

David L. Paterson and Benjamin A. Rogers
University of Queensland Centre for Clinical Research, Royal Brisbane and Women’s Hospital Campus, Brisbane, Australia

(See the article by Kofteridis et al, on pages 1238–1244.)

Antibiotic resistance among gram-negative bacilli shows no signs of abatement. Resistance of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and the Enterobacteriaceae to multiple antibiotic classes is a growing clinical problem worldwide [1]. Two trends are particularly noteworthy. First, there has been increased recognition of successful antibiotic-resistant clones appearing in multiple geographic regions. Multilocus sequence typing analyses of contemporary collections of multidrug-resistant strains have shown that carbapenem-resistant *A. baumannii* ST92 [2], *K. pneumoniae* carbapenemase–producing *K. pneumoniae* ST258 [3], and extended-spectrum β-lactamase–producing *Escherichia coli* ST131 [4] are global problems. Second, new mechanisms of multidrug resistance are becoming evident. These include aminoglycoside 16S ribosomal RNA methylation [5] and production of the New Delhi metallo-β-lactamase [6].

From a clinical viewpoint, the end result of these and other mechanisms of antibiotic resistance is loss of susceptibility to all penicillins (including combinations with β-lactamase inhibitors), cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones. There are desperately few treatment options available for strains with this resistance profile. Possibilities for “salvage therapy” include polymyxins (eg, colistin) [7], tigecycline [1], and fosfomycin [8]. As is illustrated in the article by Kofteridis et al [9] in this issue of *Clinical Infectious Diseases*, much attention has been paid to the potential use of novel salvage regimens, including combinations of different antibiotics or use of multiple modes of antibiotic administration.

Kofteridis et al [9] evaluated the combination of aerosolized plus intravenous colistin in contrast with monotherapy with intravenous colistin. They concluded that this combination of administration routes did not provide additional therapeutic benefit in patients with ventilator-associated pneumonia (VAP) due primarily to *A. baumannii*. Before this therapeutic strategy is “written off” as ineffective, it is useful to look more deeply into the design and results of this study. Using a matched case-control study design, Kofteridis and colleagues demonstrated that 54% of patients in the dual–administration route arm had clinical cure, compared with 32.5% in the intravenous only arm (*P* = .05). There were also trends toward superiority in the end points “clinical success” (74% vs 60%; *P* = .10) and mortality in the intensive care unit (24% vs 42%; *P* = .066). In a multivariable model, trends toward superior clinical cure with the dual route of administration persisted (odds ratio, 2.375; 95% confidence interval, 0.901–6.258; *P* = .08) [9].

There are a number of potential reasons why these results should not lead to the combination of aerosolized plus intravenous colistin being discarded as a potential treatment option. First, the study methods give no indication of sample size deliberations; it may well be that the study was underpowered to truly show a significant difference between the 2 treatment options. Second, the diagnosis of VAP is always fraught with difficulties, even when quantitative cultures are used. Given that patients with airway colonization may have been labeled as having VAP, we have a real chance of bias toward the null hypothesis, because the outcomes for patients with airway colonization should not be affected by therapy, thereby necessitating an even greater sample size to show a real difference. Third, the dosages of colistin were not based on modern pharmacokinetic analyses, and it is possible that dosing regimens were not optimal.
In addition, few details are provided about the mode of aerosolization of colistin. The science of aerosolization of drugs has advanced rapidly in the past decade [10]. A different approach to drug delivery is necessitated in the intubated versus the awake patient because of characteristics including the patient’s supine position, artificial airway, and the use of humidified air [10]. With use of a traditional jet nebulizer, it is estimated that only 6%–10% of the nominal dose would be inhaled by the patient [11]. Newer technologies, such as the vibrating-mesh nebulizer, significantly improve delivery and have yielded promising results in the nebulized delivery of other antimicrobials, such as amikacin, in this setting [12].

Although the combination of aerosolized plus intravenous colistin is potentially promising for the treatment of VAP due to multidrug-resistant gram-negative bacteria, combinations of different antibiotics also need to be considered. James Rahal and Carl Urban from New York City have pioneered the study of combination therapy and have shown synergistic effects of the combination of carbapenems, rifampin, and a polymyxin against carbapenem-resistant Gram-negative organisms [13, 14]. A number of other combinations have been assessed by a variety of groups [14]. A number of other combinations have been assessed by a variety of groups [14].

It is important to temper the potential advantages of combination therapy with experience from management of serious, antibiotic-susceptible P. aeruginosa infection. The parallels are significant. In vitro, synergy has been widely shown between certain combinations of antibiotics (eg, antipseudomonal β-lactam antibiotics plus aminoglycosides) [16]. Some observational studies have shown substantial benefits of combination therapy, including significant reductions in mortality when combination therapy is used [17]. Yet, there is a paucity of randomized, controlled trials showing superiority of combination therapy versus monotherapy. Indeed, meta-analyses of randomized, controlled trials have shown no benefit of combination therapy over monotherapy for P. aeruginosa or other common serious infections with gram-negative bacteria [18, 19].

We desperately need randomized, controlled trials in the field of treatment of infections with multidrug-resistant gram-negative bacilli. We acknowledge that the severity of illness and the clinical complexities of patients usually affected by multidrug-resistant gram-negative bacilli greatly hamper conduct of such studies. Furthermore, substantial resources are needed to conduct randomized, controlled trials: the pharmaceutical industry will not fund such studies until new antibiotics are developed that have significant activity against multidrug-resistant organisms. Even then, industry is likely to take the easy way out and conduct studies of conditions such as urinary tract infection or complicated intraabdominal infections. Therapy for multidrug-resistant organisms will continue to be regarded as an off-label use, with clinicians persisting to use therapy without data from randomized, controlled trials. It is hoped that the US Food and Drug Administration would demand studies of patients at high risk of developing infection due to multidrug-resistant organisms. Whether this imposition of additional hurdles on the path to drug approval would discourage development of new drugs active against these organisms is highly contentious.

It may be several years before the pharmaceutical industry has sufficient new compounds to be studied. In the meantime, is there a way we can rigorously study existing options? The National Institutes of Health is to be congratulated for their program to fund “Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance.” A randomized, controlled trial comparing the combination of colistin and imipenem versus colistin monotherapy for multidrug-resistant A. baumannii infection has recently been funded by this program (K. Kaye, personal communication). On the basis of the work of Kofteridis et al [9], it would seem that an randomized, controlled trial comparing the combination of aerosolized plus intravenous colistin versus monotherapy with intravenous co-

Table 1. Potential Randomized, Controlled Trials in the Arena of Treatment of Infection with Gram-Negative Bacilli That Could Be Evaluated for Fast-Tracked Funding

| Beta-lactam antibiotics plus aminoglycosides versus beta-lactam antibiotics alone for serious P. aeruginosa infection |
| Pharmacodynamically optimized versus standard therapy for serious infections due to gram-negative bacilli |
| Combinations including colistin versus colistin alone for bacterial infections resistant to all other options |
| Inhaled plus intravenously administered antibiotics versus intravenous administration alone for ventilator-associated pneumonia |
| Short-course versus long-course therapy for bloodstream infection due to gram-negative bacilli |

Table 2. Predicted Issues in Gram-Negative Bacteria Resistance in the Next Decade

| Widespread occurrence of carbapenem resistance in hospitalized patients necessitating “routine” use of polymyxins or tigecycline |
| Resistance to polymyxins and tigecycline commonplace in some hospitals |
| Loss of improvement in intensive care unit survival rates due to impact of resistance in gram-negative bacilli |
| Calls for universal screening for multidrug-resistant gram-negative bacilli at hospital admission |
| Increased acquisition of carbapenem-resistant organisms outside of hospitals |
| Increased hospitalizations for community-onset urinary tract infections due to pathogens resistant to all orally administered antibiotics |
Colistin may also be a reasonable proposition (Table 1). Studies evaluating combinations with rifampin may also be worthy of further consideration.

The sad news is that multidrug-resistant *A. baumannii* and *P. aeruginosa* have been noted for more than a decade [20]. On the basis of the global epidemiology of infection, we need to be planning randomized, controlled trials for treatment of a variety of infections with a high probability of being widespread in the next decade (Table 2). How soon should we act? Now!

**Acknowledgments**

**Potential conflicts of interest.** D.L.P. has participated in advisory boards sponsored by Cubist, Merck, AstraZenica, Novartis, Johnson & Johnson, Pfizer, and LEO Pharmaceuticals. B.R.: no conflicts.

**References**