Serious Infections in the Intensive Care Unit: *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

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Infectious disease physicians have long recognized *Pseudomonas aeruginosa* as a pathogen with notable virulence characteristics and the ability to exhibit antibiotic resistance. *Acinetobacter* species, although less common overall, have been associated with numerous outbreaks of infection, particularly in intensive care units (ICUs). Unfortunately, many of us have now been confronted with *P. aeruginosa* and *Acinetobacter* isolates resistant to all β-lactam and quinolone antibiotics.

In May 2004, a symposium was held at the University of Pittsburgh Medical Center to gather together leading researchers in the field of antibiotic resistance. A number of topics were covered: the epidemiological profile of antibiotic resistance in gram-negative bacilli; mechanisms of antibiotic resistance; strategies for prevention, including both infection control and modifications in antibiotic use; and use of “old” and new drugs for the management of infections with gram-negative bacilli resistant to all other alternatives.

Analysis of the epidemiological profile of antibiotic-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species shows an increased risk of infection in patients in ICUs [1]. It is particularly noteworthy that clonal dissemination of multidrug-resistant *P. aeruginosa* and *Acinetobacter* species occurs commonly. There is, therefore, a need for clinical microbiology laboratories to provide molecular epidemiological support to infection control personnel. Investigation of environmental sources of infection and the introduction of contact isolation precautions may be necessary in the control of these infections. Additionally, the use of specific antibiotic classes may be linked to infection with multidrug-resistant *P. aeruginosa* and *Acinetobacter* species. There is, thus, a potential role for antibiotic management in the reduction of incidence of these infections.

In this supplement issue of *Clinical Infectious Diseases*, Bonomo and Szabo [2] review the mechanisms of multidrug resistance in *P. aeruginosa* and *Acinetobacter* species. Both organisms produce chromosomally encoded β-lactamas and also have the ability to acquire genes that encode other β-lactamas. The specter of acquisition of genes encoding metalloenzymes is a particularly important one, because these encode resistance to all β-lactam antibiotics except aztreonam. Hyperproduction of chromosomally encoded β-lactamas can lead to aztreonam resistance and, thereby, to resistance to all β-lactam antibiotics. Target site mutations in quinolone resistance-determining regions, acquisition of genetic elements encoding aminoglycoside resistance, and the presence of outer membrane protein deficiencies and overexpressed efflux pumps can result in *P. aeruginosa* or *Acinetobacter* species becoming truly “panresistant.”

There is also the threat of transferable genetic elements that encode proteins that block the active site of quinolones. These *qnr* genes appear to be spreading worldwide, although neither has yet been found in either *P. aeruginosa* or *Acinetobacter*. Finally, resistance to colistin and polymyxin B is now very real, eliminating all options from the antibiotic formula.

What of control of selection or the spread of multidrug-resistant *P. aeruginosa* and *Acinetobacter* species? In this supplement issue, leaders in the field describe their views on various control measures for multidrug-resistant gram-negative bacilli in the ICU. Harris et al. [3] define some important terms in the understanding of colonization with resistant gram-negative organisms. They discuss current evidence for and against introduction of contact isolation precautions against multidrug-resistant gram-negative bacilli. Bonten [4] reviews the potential use of selective digestive tract decontamination in the prevention of pneumonia with multidrug-resistant gram-negative bacilli. The risk of the selective digestive tract decontamination regimens currently used is that they may select for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in ICUs in which these organisms are endemic. Thus, although positive results have been reported in some ICUs in the Netherlands, selective digestive tract decontamination may not be a panacea in many ICUs around the world.
world. Donskey [5] reviews the potential for antibiotics to alter gastrointestinal tract flora and, therefore, to promote colonization with multidrug-resistant organisms or *Clostridium difficile*. He provides convincing evidence that antibiotics with antianaerobic activity should be avoided if antianaerobic coverage is not required.

The role of antibiotic cycling in prevention of selection of multidrug-resistant organisms is frequently discussed at medical meetings. In this supplement, Kollef [6] provides a comprehensive review of the data pertaining to antibiotic cycling. It seems that initial enthusiasm for antibiotic cycling or rotation in ICUs is being replaced by the reality that antibiotic cycling is not a practical option in the “real world.” Insistence on the use of the scheduled antibiotic may be at odds with providing appropriate and adequate empirical antibiotic therapy. Chastre et al. [7] review 2 important practical elements for care of the patient in the ICU. First, reducing the duration of therapy is a practical way of limiting the volume of antibiotics used. Second, the use of quantitative cultures in differentiating true infection from colonization has been proven to be useful in a randomized trial comparing an “invasive approach” to the diagnosis of ventilator-associated pneumonia with the standard “end of the bed” approach. Mortality was lower in patients managed using quantitative cultures, presumably because empirical antibiotic treatment could be discontinued and antibiotic resistance reduced. Although I personally favor the use of quantitative cultures in the management of suspected ventilator-associated pneumonia, there may be other approaches to managing this common scenario, as advocated by Fujitani and Yu [8].

Despite our best efforts at controlling multidrug-resistant *P. aeruginosa* and *Acinetobacter* species, many physicians are faced with difficult treatment decisions. The use of colistin or polymyxin B is difficult because dosage regimens have not been optimized for many subpopulations of critically ill patients. Linden and Paterson [9] review published clinical experience with intravenous colistin therapy. Rahal [10] reviews the potential for combination therapy, including combinations involving the polymyxins, in the treatment of infections with multidrug-resistant *P. aeruginosa* or *Acinetobacter* species. Unfortunately, clinical data on the use of many such combinations are lacking; indeed, we cannot agree on the use of combination therapy for susceptible strains of *P. aeruginosa*. Controlled trials are needed to optimize the use of polymyxins or combination therapies for these increasingly common pathogens.

Most of you are aware of the “Bad Bugs, No Drugs” campaign by the Infectious Diseases Society of America. Rice [11] reviews the challenges facing the development of new drugs active against multidrug-resistant *P. aeruginosa* or *Acinetobacter* species. It is unlikely that any new classes of antibiotics will be available for clinical use against these pathogens in the next 5 years. This underscores the importance of improving our control measures and optimizing our use of currently available agents against these pathogens.

I trust that you will find this material interesting and relevant to clinical practice. Continuing medical education (CME) credits are available for readers of this supplement. CME credit is provided by the University of Pittsburgh Center for Continuing Education in the Health Sciences.

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