Gram-Negative Bacterial Resistance: Evolving Patterns and Treatment Paradigms

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Successful treatment of patients with nosocomial pneumonia depends primarily on providing adequate initial antibiotic treatment in a timely manner, because an inappropriate course is closely associated with increased mortality. Gram-negative bacteria are commonly responsible for nosocomial pneumonia, and the increasing prevalence of drug resistance among these bacteria complicates decision making with regard to treatment with antibiotics. Infections due to *Pseudomonas aeruginosa* are particularly problematic because of their intrinsic resistance to multiple classes of antibiotics and their ability to acquire adaptive resistance during a therapeutic course. Numerous strategies, including the use of combination therapy followed by de-escalation of antibiotics, have shown promise in the treatment of these serious infections. However, future success in treating nosocomial infections depends on the appropriate and responsible use of antibiotics in the intensive care unit, to ensure that the antibiotics available today maintain their effectiveness in the future.

Despite the availability of modern medical devices and potent antibiotics, nosocomial pneumonia remains the second leading cause of hospital-acquired infection and the leading cause of mortality due to nosocomial infections. Mechanical ventilation remains the greatest risk factor for the development of nosocomial pneumonia, with studies showing an associated incidence rate of up to 3%/day of intubation [1]. In addition to increasing the risk of death among severely ill patients, nosocomial pneumonia significantly extends the length of stay in the intensive care unit (ICU), resulting in a heavy economic burden on hospitals. Each case of ventilator-associated pneumonia (VAP) in the ICU has been estimated to cost an additional $12,000–$40,000 [2, 3]. Many of these cases can be prevented with proper hospital procedures, and education programs directed to health-care personnel in the ICU have been effective in reducing the incidence of and mortality and costs associated with VAP [4].

One of the difficulties of treating patients with nosocomial pneumonia is the high incidence of antibiotic-resistant bacteria in the ICU. Gram-negative bacilli account for most common causative pathogens of nosocomial pneumonia, and resistance to various classes of antimicrobials has gradually increased during the past decade [5, 6]. Resistance to third-generation cephalosporins by *Klebsiella pneumoniae* and *Enterobacter* species approaches 9% and 36%, respectively. The resistance of *Pseudomonas aeruginosa* to the quinolones and imipenem is ∼20%–25%. In examining the susceptibility of gram-negative bacilli in ICUs in the United States, Neuhauser et al. [7] found that, between 1994 and 2000, nearly all antimicrobials tested showed a decrease in susceptibility of ≤6%. The one exception was a 10% decrease in susceptibility for ciprofloxacin. Further analysis illustrated a strong correlation between the use of fluoroquinolone and resistance to ciprofloxacin, providing evidence that judicious use of antibiotics will be necessary to reverse the current trends in bacterial resistance. Local susceptibility data should be evaluated when deciding on an appropriate treatment, particularly for patients who are at risk of acquiring antibiotic-resistant bacterial infections.

Numerous studies have attempted to delineate risk factors associated with an antibiotic-resistant infection [8]. Previous antibiotic use is commonly associated with these infections, including those caused by both gram-positive and -negative pathogens. Other risk factors include mechanical ventilation for at least 7 days, prior use of a broad-spectrum antibiotic, prolonged length of hospital stay, or residence in a long-term care facility. It is imperative...
that physicians recognize these risk factors, to implement an optimal antibiotic regimen that will provide adequate coverage for individual patients.

Successful treatment depends critically on administration of appropriate and adequate therapy at the first sign of infection. Clinical studies consistently show that mortality rates are significantly higher for patients who receive inappropriate therapy (i.e., therapy that is not effective against the causative pathogen) [9–12]. Patients with VAP who receive inadequate antimicrobial therapy can have mortality rates that are nearly double those of patients who receive adequate therapy. Delaying antimicrobial treatment until culture results are available will also contribute to higher mortality rates [11, 13]. Furthermore, adjusting the choice of antimicrobials after the pathogen has been identified does not necessarily improve clinical outcomes. The greatest likelihood of successful outcomes occurs when initial empirical therapy provides appropriate coverage. With the high prevalence of antibiotic-resistant pathogens, providing appropriate coverage becomes a daunting task for today’s physicians in the ICU. However, various strategies have been used to maximize the probability of providing adequate coverage for patients with VAP.

Initial combination therapy that provides broad coverage may improve the chance of providing effective empirical coverage. In a pivotal study by Ibrahim et al. [14], all patients initially suspected of having VAP were treated, within 12 h of clinical suspicion of infection, with a combination of imipenem, ciprofloxacin, and vancomycin, to provide broad coverage of gram-positive and -negative pathogens. Importantly, after the pathogen was identified, de-escalation of antibiotic doses was performed to minimize drug overuse. As a result, for 98% of patients with VAP, treatment with 1 or 2 antibiotics was ended within 48 h of initial treatment. Compared with patients who were treated before implementation of these guidelines, patients treated with the combination were more likely to receive adequate therapy (94.2% vs. 48.0%; \( P < .001 \)), had a shorter average duration of antimicrobial treatment (8.6 days vs. 14.8 days; \( P < .001 \)), and were less likely to develop a second episode of VAP (7.7% vs. 24.0%; \( P = .030 \)). Mortality was slightly higher in association with the use of combination therapy but was not statistically significant.

De-escalation of antibiotic doses can allow the proper balance between providing initial adequate treatment and reducing the risk of the emergence of antimicrobial-resistant bacteria. The administration of unnecessary antibiotics will only contribute to the problem of resistance in the ICU. Narrowing the antimicrobial coverage can be accomplished after the pathogen has been identified and its susceptibility profile has been determined. In addition, the duration of therapy should be limited to the shortest effective course, because several studies have shown that this strategy can successfully treat specific infections without adversely affecting patients’ outcomes [14–17]. Other strategies also show promise for successfully treating nosocomial pneumonia and/or reducing the development of resistance, including the use of computerized “automatic antibiotic consultant” programs [18], involvement of infectious disease specialists in diagnosis and treatment selection [19], and antibiotic cycling and restricted use programs [20]. Regardless of the intervention program in question, each hospital must carefully evaluate whether a strategy will be clinically successful and cost effective for the treatment of patients with nosocomial pneumonia.

In this supplement to Clinical Infectious Diseases, several articles address the options for treatment of antibiotic-resistant respiratory infections, particularly nosocomial pneumonia caused by P. aeruginosa. These infections are particularly worrisome because of the high associated treatment failure and mortality rates observed among severely ill patients. This pathogen possesses high intrinsic resistance to various antimicrobials, in part because of its semipermeable outer membrane and its several efflux systems that efficiently reduce the intracellular concentration of antimicrobial agents. In addition, to acquire high levels of resistance to a particular agent, P. aeruginosa frequently mutates during a course of therapy. Because of this phenomenon, current effective treatment options are limited, and initial empirical treatment is commonly inadequate for successful eradication of this pathogen. However, clinical results can improve when clinicians recognize which patients are at risk for P. aeruginosa infection and then follow through with an effective treatment regimen in a timely manner.

Surveillance studies can provide useful information to physicians attempting to determine an appropriate antimicrobial for an identified pathogen. Numerous studies now exist that track P. aeruginosa resistance trends. In an article by Karlowsky et al. [21], data are presented from the Tracking Resistance in the United States Today surveillance study, which collected 2394 P. aeruginosa isolates throughout the United States during 2001–2003. Among the agents tested, piperacillin-tazobactam, cefepime, and ceftazidime were the most active against P. aeruginosa, although susceptibility to any agent tested was still <90%. The susceptibility of P. aeruginosa to ciprofloxacin or levofloxacin was found to be similar (≈67%). Approximately 9% of the isolates were multidrug resistant (i.e., resistant to ≥3 classes of antibiotics), and the prevalence of multidrug-resistant isolates increased from 7.2% in 2001 to 9.9% in 2003. Given the susceptibility data, combination therapy with an antipseudomonal β-lactam plus gentamicin or a fluoroquinolone will provide better coverage than monotherapy.

In a review article, Burgess [22] provides an overview of the pharmacokinetic (PK) and pharmacodynamic (PD) evidence used to determine optimal antibiotic dosing strategies for treating P. aeruginosa infections. As the field of pharmacodynamics has expanded in recent
years, information gathered from in vitro and animal models has altered dosing regimens to achieve maximal killing of bacteria and to reduce the risk of the emergence of antimicrobial-resistant bacteria. Concentration-independent agents, such as the β-lactams, are effective when the drug concentration remains greater than the MIC for most of the dosing interval. Concentration-dependent agents, such as aminoglycosides and fluoroquinolones, can effectively eradicate an infection when the maximum serum concentration:MIC or area under the serum concentration–time curve:MIC ratios meet target values. A compilation of the currently available PK/PD studies of *P. aeruginosa* clearly show that further studies are needed, particularly with regard to newer agents. The PK/PD targets required for successful eradication of *P. aeruginosa* would also be difficult for some agents to meet on a consistent basis. For this reason, combination therapy may improve treatment outcomes, particularly in association with agents that exhibit synergy against *P. aeruginosa*.

Lister and Wolters [23] use an in vitro PD model to test the killing of *P. aeruginosa* clinical isolates with levofloxacin and imipenem, either alone or in combination. The β-lactam/fluoroquinolone combination was specifically chosen, because each agent is susceptible to separate efflux mechanisms in *P. aeruginosa*. In theory, efflux mutants that efficiently reduce the activity of one agent will still be susceptible to the second agent. Monotherapy with either agent consistently showed initial killing, followed by regrowth and the emergence of a resistant subpopulation after 24 h of exposure to drugs. This result was expected, because previous studies showed rapid emergence of antimicrobial resistance with the strains used. However, the use of combination therapy eradicated all 3 clinical isolates and failed to produce any resistant subpopulation. Careful drug selection for combination therapy can improve clinical outcomes when treating *P. aeruginosa* infections, and the use of the levofloxacin-imipenem combination for this purpose should be investigated in a clinical setting.

The fluoroquinolones have become a popular choice for the treatment of nosocomial pneumonia. However, clinical data supporting the use of fluoroquinolones for the treatment of nosocomial pneumonia are limited, particularly in studies designed to show superiority over another class of antimicrobials. Shorr et al. [24] provide a meta-analysis of all prospective, randomized, controlled studies of nosocomial pneumonia using quinolones in a treatment arm. Only 5 studies (4 studies using ciprofloxacin and 1 study using levofloxacin) met all inclusion criteria. Analysis showed that there was no statistical difference in clinical results or mortality when the fluoroquinolone treatments were compared by use of comparators, although the quinolones did show a slight survival advantage. Only 3 studies reported the emergence of antimicrobial resistance, and the small number of *P. aeruginosa* isolates limited the ability to determine differences among the treatment options. The quinolones appear to be an acceptable choice for the treatment of nosocomial pneumonia, and they offer a number of advantages over other agents, including once-daily dosing, convenient iv-to-oral dose switching, and a favorable tolerability profile.

The last article in this supplement is a retrospective analysis of several clinical trials involving levofloxacin for the treatment of pneumonia (community acquired or nosocomial) attributed to *P. aeruginosa* or *Stenotrophomonas maltophilia* [25]. Overall, clinical success with levofloxacin reached 76.5%, although most patients with nosocomial pneumonia received adjunctive therapy with an antipseudomonal β-lactam. Resistance of and superinfection by *P. aeruginosa* remained low in these patients. These results support the notion that consideration should be given to the inclusion of levofloxacin as part of a combination regimen for the treatment of these infections, particularly when given in a 750-mg dose. At this higher dose, the concentration of drug at the site of infection approximately doubles, compared with the 500-mg dose, and it increases the probability of meeting the PK/PD targets necessary for successful clinical outcomes. In addition, the article addresses the concept that pseudomonal respiratory infections are not necessarily limited to nosocomial pneumonia. One study determined that 7% of cases of community-acquired pneumonia among hospitalized patients were attributed to *P. aeruginosa* [26]. However, that report may have included cases of health care–associated pneumonia, which can have an etiology similar to that of nosocomial infections [27, 28]. This can have significant consequences when deciding on an appropriate empirical therapy for cases of community-acquired pneumonia, particularly for patients with risk factors for *P. aeruginosa* infection (such as pulmonary comorbidity and previous hospital admission).

In the absence of breakthrough antimicrobials with high potency against *P. aeruginosa*, physicians must use the available agents responsibly and effectively to extend their usefulness for years to come. Numerous strategies exist for optimizing treatment decisions for patients with nosocomial pneumonia, and hospital personnel must develop strategies that work best for their particular setting to reduce the risk of developing resistance while providing appropriate initial therapy.

References


