ICU MANAGEMENT & PRACTICE

ICU Volume 5 - Issue 3 - Autumn 2005 - Cover Story:Outreach

Antibiotics in the ICU: Current Use and Future Strategies

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Professor Niederman discusses the reasons for increased antibiotic resistance, how to address these failings and innovative strategies for the future.

Nosocomial infection remains a major cause of morbidity and mortality in ICU patients throughout the world. Currently, the management of serious nosocomial infections is complicated by the high frequency of antibiotic resistance among the etiologic pathogens commonly present in critical care units. A number of factors, many under the control of physicians, contribute to this rising rate of antibiotic resistance (Niederman 2003):

• Using the wrong drug in the wrong patient;

• Overuse: antibiotics are not always needed;

• Failure to use the correct dose and optimize pharmacokinetics;

• Use of agents with broader spectrum than needed;

• Use of therapy for longer than needed.

There are three possible strategies to avoid excessive antibiotic usage: limiting use through better diagnosis, restricted access through antibiotic control programs, and “de-escalation”, an approach of limited use after initial aggressive empiric therapy. This can be facilitated by the results of bacterial cultures and the patient’s clinical response to initial therapy. De-escalation may be the most promising, assuring adequate therapy of infection while avoiding excessive use of antimicrobials (Hoffken and Niederman 2002; Ibrahim et al. 2001; Micek et al. 2004: Rello et al. in press).

Improving diagnostic methodology is a logical approach to avoid the overuse of antibiotics. For many infections (especially ventilator-associated pneumonia), antibiotics are used in patients who may not have infection, but perhaps fever and leukocytosis. Antibiotics could be used more rationally if they were limited to patients who definitely had infection, and improved diagnostic methodology might promote this goal. Unfortunately, in clinical practice, this approach can lead to some patients receiving therapy only when infection is far advanced and it is possibly too late to improve outcome. This controversy is most evident in the management of ventilator -associated pneumonia, where proponents of using a bacteriologic diagnosis have advocated the withholding of antibiotics unless lower respiratory tract samples confirm, or at least suggest, a high concentration of bacteria in lower respiratory secretions. Although such an approach can improve the specificity of diagnosis and use of antibiotics, it may do so at the expense of sensitivity and lead to certain patients being treated late in the course of illness (Luna et al. 2003; Niederman et al. 2005).

Control of resistance through restricted access to specific antibiotics has been attempted for years and this approach has been successful for altering and manipulating problem pathogens, but has not generally been successful at eliminating the problem of antibiotic resistance. One dramatic example of this experience occurred in a hospital in New York City in the mid- 1990’s, which experienced an epidemic of ceftazidime-

resistant Klebsiella infections. The response to this epidemic was a restriction of the use of cephalosporins, which led to an 80% reduction in cephalosporin use and a 44% reduction in resistant Klebsiella organisms. Unfortunately, because antibiotic use could not be stopped completely, the reduction in cephalosporin use was accompanied by a 140% increase in the use of carbapenems, which resulted in a 68% increase in carbapenem-resistant Pseudomonas infection (Rahal et al. 1998). The editorial which accompanied the report of this epidemic described this phenomenon as “squeezing the balloon”; restricted access to antibiotics successfully manipulated the problem pathogens, without eliminating antimicrobial resistance.

De-escalation, which implies aggressive empiric therapy, using multiple antibiotics followed by narrowing, focusing, and shortening duration of therapy, as culture and clinical data become available, seems a more logical approach. De-escalation has been employed in patients with ventilator-associated pneumonia and has effectively led to good outcomes (Hoffken and Niederman 2002; Ibrahim et al. 2001; Micek et al. 2004: Rello et al. In press). In studies of this approach, the use of an algorithm for initial empiric therapy has resulted in a high frequency of initially appropriate therapy, which in turn has permitted a protocol-driven reduction in duration of therapy, with less total antibiotic usage, while still preserving good clinical outcomes. There are many opportunities to further enhance our use of de-escalation in patients with ventilator-associated pneumonia (Niederman 2004). These include stopping antibiotic administration in patients with negative cultures and an improving clinical course, since these patients may not even have infection. It may also be possible to shorten the durations of therapy, and also avoid the prolonged use of combination therapy in patients who are infected with highly resistant pathogens such as Pseudomonas aeruginosa. Future studies are needed to explore the limits of de-escalation therapy and its potential.

One way to further control antibiotic resistance is to optimize our treatment of infection, and often this requires the use of “adequate” therapy. Adequate therapy, as defined in the 2005 ATS/IDSA Nosocomial Pneumonia Guidelines, implies not only using an antibiotic that matches the sensitivities of the etiologic organism, but also using that antibiotic in the correct dose and having it penetrate to the site of infection (Niederman et al. 2005). Use of incorrect dosing has been a major problem in the treatment of seriously ill patients and current guidelines for nosocomial pneumonia have emphasized the need to maximize dosing to rapidly kill bacteria and minimize the selection of antibiotic resistance.

In the future, new approaches will be needed to combat antimicrobial resistance. These will focus on both the responsible usage of antibiotics and the development of new antimicrobial agents. While our current antibiotics are being challenged, responsible usage programs that emphasize the avoidance of therapy when not needed and the use of a tailored spectrum of therapy appropriate for the identified pathogens, is an achievable objective. More challenging is the development of new antimicrobial antibiotics.

Over the past decade we have seen a dramatic rise in antimicrobial resistance, accompanied by a decline in research and development into new antimicrobial agents. From 1983 to 2002, there has been a 50% decline in the United States’ Food and Drug Administrations approval of new antimicrobial agents, and the majority of new molecular entities being developed by the pharmaceutical industry are focused on chronic diseases and not acute infections (Spellberg et al. 2004). Even in the area of infectious diseases, many new agents are being developed for HIV infection and not for bacterial diseases. Of the new products that have appeared in the last several years, there is very little innovation and generally products have been minor modifications of existing agents.

One challenge for the future will be to develop new drugs with new mechanisms of action (Cassell and Mekalanos 2001). For example, many bacteria, both gram-positive and gram-negative, develop antimicrobial resistance through efflux mechanisms, which act to remove antibiotics from the interior of the microbe. Development of a strategy to combat bacterial efflux mechanisms could potentially restore the efficacy of our existing agents. Other approaches could include the development of “xenobiotics”, which are non-natural compounds never seen by bacteria that could potentially thwart antimicrobial resistance mechanisms; these could be achieved by synthetic chemistry advances. At the same time, bacterial genomics can help us to find new targets in the bacteria for the development of new types of therapy. Genomics would allow us to avoid adverse events by identifying agents that have bacterial targets that are different from human genes. In addition, functional genomics could define targets that are essential for bacterial growth, by identifying which genes are over-expressed during an episode of infection. In addition, genomics can help us identify bacterial virulence factors which are expressed during infection and these virulence factors themselves can be targeted with a variety of agents, including immunotherapy. Microchip gene arrays can help identify which bacterial genes are expressed during infection, and these too can be targeted by new agents.

A number of novel antibacterial substances could also be developed, which differ from our current antibiotics (Bryskier 1999). For example, peptides with antimicrobial activity currently exist, but are not used in humans. Protegrins are an example of an animal host defense system of peptide antimicrobials, which have the potential to serve as novel antibacterial agents for humans. Unfortunately, a recent clinical trial with iseganan, a peptide antimicrobial, was unsuccessful in preventing ventilator-associated pneumonia. Another approach would be the development of probiotics, which can be defined as microorganisms that can be put into patients because of their beneficial effects to humans. For example, bacteria that produce lactic acid could be applied to mucosal surfaces, where they could compete for nutrients and adhesion space with pathogenic bacteria. These organisms could also be immunomodulating, producing exo-products, which are inherently antibacterial.

Ultimately the challenge for the future will be a careful blending of preserving our current antimicrobial agents through a responsible usage program, and the development of new knowledge to better target bacteria and develop new antimicrobial agents. Unfortunately, the motivation for industry to do this may be limited by economics, at a time when these new agents are most needed for the well-being of our patients.

Published on : Thu, 20 Oct 2011