

## Optimizing Antimicrobial Therapy and Emerging Pathogens

*Based on a presentation by David P. Nicolau, PharmD*

### **Presentation Summary**

Based on the current understanding of antimicrobial pharmacodynamics, several strategies can be used to optimize antimicrobial efficacy. However, the method used depends on the class of antimicrobial chosen. For agents (eg,  $\beta$ -lactams, clindamycin, vancomycin, macrolides) for which the rate and extent of killing stay essentially constant when concentrations are approximately four times the minimum inhibitory concentration (MIC) of the organism, the goal is to maximize the time the drug concentration remains above the MIC (Time>MIC) during the dosing interval. Therefore, whereas simply increasing the dosage or dosing frequency relative to the conventional regimen will increase the Time>MIC, this method is inefficient from a drug utilization perspective because it will result in an increase in drug cost, a decrease in patient compliance, or both. As a result of these shortcomings, the maximization of Time>MIC is best achieved by selecting agents that optimize their pharmacodynamic profile through improvements in microbiological activity and/or pharmacokinetics.

However, when considering the optimal agent based on the anticipated pharmacokinetic profile, attention must be given not only to the peripheral profile (eg, plasma or serum concentration) but also to the concentration at the site of infection. Consideration of this issue is paramount, because optimal bactericidal activity can only exist if sufficient drug concentrations are in the vicinity of the infecting organism. Therefore, high antimicrobial concentrations at this site maximize the rate and extent of bactericidal activity, which should not only optimize clinical outcomes but also reduce the potential for the development of resistance.

This presentation addresses another aspect relative to the effort to optimize antibiotic therapy, that is, the emergence of atypical pathogens as more common causes of infection and coinfection than previously thought. Although data on the incidence of atypical pathogens are difficult to obtain, recent studies have demonstrated that several of these organisms may play a more prominent role in lower respiratory infections, particularly community-acquired pneumonia.

**T**he basis of infectious diseases is the interaction between the host, the drug, and the bug (Figure). Although ongoing efforts are being directed at optimizing the host response to infection with various immunomodulating agents and cytokine therapies, this approach is not currently available for wide-scale clinical application, according to David P. Nicolau, PharmD, coordinator for Research, Departments of Medicine, Division of Infectious Diseases and Pharmacy, Hartford Hospital, Hartford, Connecticut. Similarly, whereas a variety of investigational techniques are being studied to modify the pathogen (for example, using the macrolide antibiotics to either down-regulate virulence factors and/or biofilm production in pseudomonas species), the broad clinical application of this technique is yet to be used.<sup>1,2</sup>

Therefore, although future clinical emphasis will probably be directed at modulating both the host and infecting pathogen, the optimization of a given antibiotic's pharmacodynamic profile against the selected pathogen offers a contemporary approach to enhance the potential for a good clinical outcome, Dr. Nicolau said.

#### Pharmacodynamic Issues

"It is important to integrate pharmacodynamic parameters into the anti-

microbial decision-making process," Dr. Nicolau observed, noting that "the basis of antimicrobial pharmacodynamics is the correlation between drug concentration and bacterial killing."

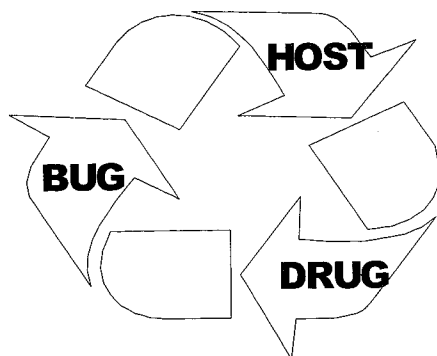
At one time, it was thought that a drug with a long half-life, low protein binding, and a low minimum inhibitory concentration (MIC) was the ideal agent, but these parameters in and of themselves do not provide information about the influence of the drug concentration on the rate or extent of bactericidal activity or the antimicrobial effects that can persist after drug exposure, such as the "postantibiotic effect" (PAE).

"Although the exact mechanism of the PAE is not known, and there is very little if any data on the ultimate contribution of the PAE for microbial eradication in humans, this concept deserves consideration in the design of the optimal antimicrobial regimen," Dr. Nicolau said.

"We now know that the effect of increasing drug concentrations on bactericidal activity and the presence or absence of a PAE gives a much better description of the time course of antimicrobial activity than what is provided solely by the MIC," Dr. Nicolau said.<sup>3</sup> "Furthermore," he continued, "it is necessary for the drug to be delivered to the site of infection for an appropriate duration and at a critical concentration, in addition to having an affinity for the bacterial binding site."<sup>4</sup>

One difficulty with antimicrobial pharmacodynamics is the inability to easily determine the drug concentration at the infection site. Instead, it is assumed that measurable drug concentrations in blood, serum/plasma, or urine are proportional to the drug concentration at the active site of the bacteria. The pharmacokinetic parameters of the area under the drug concentration-time curve (AUC), maximum observed drug concentration (peak), and drug half-life are often linked with the MIC of the pathogen to produce pharmacodynamic parameters such as the AUC/MIC ratio, the peak/MIC ratio, and the time that

**Figure.** Optimization of Clinical Outcome



the concentration remains above the MIC (time>MIC), Dr. Nicolau explained.

"These pharmacodynamic parameters are different for various antimicrobials, making it inappropriate to choose an antibiotic because of microbiologic activity alone. Instead, an agent must be selected according to its complete pharmacodynamic profile," Dr. Nicolau said.<sup>5</sup>

For example, when using concentration-dependent agents such as the fluoroquinolones, bactericidal effects can be maximized by pushing the peak/MIC ratio high enough. However, with other drugs, the influence of the peak concentration on the overall bactericidal activity is less important, and the time of exposure should be optimized so that with macrolides and cephalosporins, the focus is on maximizing the time above the MIC.

#### Maximizing the Time Above the MIC

With agents such as the macrolides,  $\beta$ -lactams, vancomycin, and clindamycin, it is not enough to simply increase peak drug concentration; instead, strategies must be designed to increase the time above the MIC or to increase the amount of time the pathogen is exposed to adequate bactericidal concentrations.<sup>3</sup>

"There is some debate as to what is the optimal time above the MIC, because of variations in the estimation of the pharmacokinetic profile, the inability to determine precise MIC values, and the immunocompetence of the host," Dr. Nicolau said. "However, for most drug-pathogen combinations in the non-neutropenic host, such as is the case in the majority of respiratory tract infections, the minimally effective time above the MIC that should result in acceptable levels of clinical cure should approximate 50% of the dosing interval."<sup>6</sup>

How can clinicians increase the time above the MIC for these agents? An obvious solution is to administer higher doses or more frequent doses. "These

solutions tend to compromise patient compliance, increase cost, and may cause problems with patients' abilities to tolerate the higher doses," Dr. Nicolau said. Increasing the dose also does not produce a proportional increase in time above the MIC. "By doubling the dose," he explained, "you only achieve the duration of one additional half-life above the MIC. Therefore, time above the MIC is proportionally increased with a higher dose."

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Continuous infusion is appropriate in hospitalized patients, and it may be an option for some outpatients. Studies have shown that continuous infusion maintains the drug concentration above the MIC continuously, unlike intermittent dosing regimens that allow concentrations to drop below the MIC for various periods of time. Continuous infusion also requires much less drug than intermittent dosing.<sup>7-9</sup>

Another way to maximize the time above the MIC is to choose agents with longer half-lives. However, Dr. Nicolau cautioned that clinicians must also realize that when the drug stays around for a long period of time there is the potential for resistance to develop. Resistance may be one problem with this approach, because the longer half-life agent may not only provide an increased time above the MIC but may also provide an extended duration of sub-MIC concentrations that may select for resistant microorganisms.

### Drug Activity

"Considering all the pharmacodynamic variables, perhaps the best way to choose an antibiotic agent is to choose only ones with both an excellent pharmacokinetic profile and a high level of microbiological activity," Dr. Nicolau continued.

With this approach there is a tendency to optimize both sides of the pharmacodynamic equation. For example, in one study, healthy patients were given multiple doses of cefuroxime, azithromycin, and clarithromycin in standard dosing regimens. Blood was then drawn and inoculated with penicillin-susceptible pneumococcus and tested for serum bactericidal activity. Cefuroxime and azithromycin appeared to provide bactericidal activity throughout 50% of the dosing interval, which is considered minimally effective. However, clarithromycin, because of its pharmacokinetic profile, provided bactericidal activity over the entire 12-hour dosing interval.<sup>10</sup>

"We also know that the drug distribution of the macrolides is very, very different from other antibiotics such as the cephalosporins in the respiratory tract," Dr. Nicolau added, explaining that recent studies involving the intrapulmonary disposition of the newer macrolides provide important information concerning the achievable concentrations in both the epithelial lining fluid (which is relevant for pathogens residing in extracellular or interstitial space) and in the alveolar macrophages (which is relevant for intracellular pathogens). Such information can assist in distinguishing the optimal pharmacokinetic profile at the site of infection. Whereas conventional pharmacodynamic analyses have typically incorporated plasma or serum concentration data, information on the site-specific concentration of these new agents provides new insight into the relationship within the drug-bug-host triad.<sup>11,12</sup>

"We want to achieve high drug concentrations in the vicinity of infection during the dosing interval, and the opti-

mal mode of administration may depend on whether the drug is concentration-dependent or independent," Dr. Nicolau explained, adding that "we like to think that high concentrations of drug enhance bacterial eradication, thereby decreasing the development of resistance. This is an emerging area in pharmacodynamics; if the drug completely eradicates the pathogen, then obviously the pathogen cannot become resistant."

### Atypical Pathogens

A significant problem in optimizing antibiotic therapy has been the recent increase in infections, particularly those of the upper respiratory tract, as a result of atypical pathogens or coinfection with atypical pathogens. "These pathogens cannot be cultured by routine methods, they cannot be seen on a gram stain, and they are often going unnoticed," Dr. Nicolau said.

However, several recent studies have demonstrated that these pathogens are cause for concern. Estimates of pneumonia caused by unidentifiable pathogens range from 35% to 60%, and atypical pathogens are now thought to account for 17% to 40% of these cases, depending on the geographic region and whether it is an inpatient or outpatient population that is being surveyed. The numbers can also vary greatly, depending on the method of diagnosis.

There are relatively new data on the incidence of atypical pathogens in both the inpatient and outpatient population with community-acquired pneumonia. One study of 149 ambulatory adult pneumonia patients who underwent a battery of serologic testing showed that mycoplasma was identified in 23% of cases and chlamydia in about 11%. The incidence of coinfection with both mycoplasma and chlamydia occurred in 3.4%. As a result, the authors conclude that atypicals account for nearly 50% of the identifiable etiology in their outpatients with community-acquired pneumonia.<sup>13</sup>

Another study of 346 hospitalized adults with community-acquired pneu-

monia who underwent a very rigorous serologic and microbiological evaluation found an identifiable pathogen in 81% (279/346) of the reported cases. Pneumococcus was present in 43%, mycoplasma in 29%, chlamydia in 18%, and legionella in 16%. "Another important point was that coinfection, which often occurs with a typical (eg, pneumococcus) and an atypical pathogen, reached a level of nearly 40%," Dr. Nicolau noted.<sup>14</sup>

Another issue that recently emerged from various data involving the etiology of community-acquired pneumonia is that contrary to popular belief the atypical pathogens can be quite prevalent in the elderly hospitalized population. In fact, one report showed that chlamydia was second only to pneumococcus in pneumonia patients older than age 55 years,<sup>14</sup> whereas another report revealed the potential importance of mycoplasma in this subset of hospitalized patients.<sup>15</sup>

### Conclusion

"We know these atypical pathogens are out there and that they may be more common than we have thought," Dr. Nicolau said, adding that "we also are beginning to understand that these pathogens may play an important role in the evolution of the infectious process, either by acting as a coinfection or as a sequential pathogen that may make the host more susceptible to the typical etiologies of the disease. Therefore, when choosing an antibiotic we need to consider adequate coverage for not only typical bacterial but also for the atypicals as well, because many of the patients with community-acquired pneumonia may have their treatment course complicated by the presence of multiple comorbidities.

"Most of our therapy is empiric and based on data from our own institutions or geographic regions, so our therapy decisions can be largely intuitive," Dr. Nicolau said, "but the key point is not to delay therapy using an agent that is appropriate for the possible pathogens involved. If adequate treatment is de-

layed, there is an increased potential for morbidity and mortality, as well as higher healthcare costs.

"Remember that patients who are considered treatment failures tend to go back to square one with regard to antibiotic therapy, thereby resulting in a prolonged treatment course and added costs," Dr. Nicolau concluded.

### ... DISCUSSION ...

*After his presentation, Dr. Nicolau responded to colleagues' questions.*

**Question:** *Does the use of serologic investigation in large studies make you uneasy about the incidence statistics that result?*

**Dr. Nicolau:** Certainly. Serology is not perfect, and even the use of cultures to determine pathogens is not. What you grow doesn't necessarily mean that it is what is causing the infection, but I think such studies give us more insight into the real incidence of various pathogens.

**Question:** *Regarding the incidence of legionella, is it reasonable to extrapolate data from studies done in one geographic region to populations in other regions? In the West, for example, a finding of legionella is extremely rare.*

**Dr. Nicolau:** I agree. Again, these statistics are used simply to point out the need to consider atypical pathogens.

**Question:** *Nationwide, what is the number one pathogen responsible for community-acquired pneumonia?*

**Dr. Nicolau:** Pneumococcus is still the most commonly isolated pathogen in the respiratory tract, and there is good data to suggest that people colonized with it are subsequently more prone to infection with the same pathogen. And,

to correlate, pneumococcus is the major cause of death from pneumonia. However, one of the reasons there is good data to show this is that pneumococcus has been relatively easy to culture. One does not have to rely on the specificity and sensitivity of various serologic tests to identify pneumococcus. For the other pathogens, I think eventually we will have to move toward an increased use of polymerase chain reaction to determine which pathogens are present and which are causing coinfection more often.

**Question:** *How important are multi-drug-resistant organisms, such as streptococcus pneumonia, and how are they going to affect common therapies?*

**Dr. Nicolau:** Changes in microbiology have definitely had an impact on the way we treat patients, and they are also certainly having an effect on the way in which we optimize antibiotic therapy. Eventually, there are some antibiotics we are not going to be able to use.

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