Antibiotic Dosing in Multiple Organ Dysfunction Syndrome

Marta Ulldemolins, Jason A. Roberts, Jeffrey Lipman and Jordi Rello

_Chest_ 2011;139;1210-1220
DOI 10.1378/chest.10-2371

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
http://chestjournal.chestpubs.org/content/139/5/1210.full.html

_Chest_ is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2011 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.

(http://chestjournal.chestpubs.org/site/misc/reprints.xhtml)
ISSN: 0012-3692
Despite decades of clinical experience with antibiotic use, treatment of severe infections remains a challenge for clinicians. Over the past years, two important phenomena have made even more essential the need to improve the use of presently available antibiotics and to extend the effective life of a drug: (1) the escalation in the incidence of bacteria resistant to the available antibiotics; and (2) the dearth of antimicrobial drugs with new mechanisms of action in development. One mechanism to improve optimization of antibiotic use may be improvement of antibiotic dosing because a causal relationship is thought to exist among inappropriate dosing, clinical outcome, and the development of bacterial resistance. From a clinical perspective, optimization of antibiotic use is particularly important for critically ill patients in whom early and appropriate antibiotic prescription has been shown to reduce mortality. The physiologic and pharmacokinetic derangements in antibiotics have been reviewed previously for patients with sepsis; however, there is an absence of guidance on rational approaches to antibiotic dosing in patients with multiple organ dysfunction syndrome (MODS) who have higher levels of sickness severity and whereby effective antibiotic therapy may be even more important to clinical outcome. The purpose of this article is to review, using examples from the literature, the key concepts likely to affect antibiotic pharmacokinetics and pharmacodynamics and to provide dose recommendations for the treatment of critically ill patients with MODS.

**Search Strategy and Selection Criteria**

Data were identified by a systematic search in PubMed (1966-October 2010) for original articles that evaluated the variations in antibiotic pharmacokinetics and pharmacodynamics (PK/PD) in MODS. Key words used were “sepsis” or “systemic inflammation response syndrome” or “septic...
shock” or “multiple organ failure” and “antibacterial agents” or “antibiotics” and “pharmacokinetics” or “pharmacodynamics” and “critically ill patient” or “intensive care unit” or “critical care.” A total of 167 articles were returned, of which only 48 were deemed relevant for critically ill patients with MODS or some level of organ dysfunction. Numerous articles also were identified through searches of the extensive files of the authors.

Overview of Antibiotic Physicochemistry, Pharmacokinetics, and Pharmacodynamics

The term “antibiotic” includes a variety of chemical compounds that exhibit great differences among them in terms of mechanism of action and physicochemical, pharmacokinetic, and pharmacodynamic characteristics. The uniqueness of each class makes independent study essential to provide accurate characterization of antibiotic behavior.

Physicochemistry

A simple, but useful chemical classification for antibiotics is by their affinity for water. Hydrophilic drugs predominantly distribute into intravascular and interstitial water but are unable to passively cross the lipid cellular membrane and, therefore, do not penetrate intracellularly in meaningful concentrations. Hence, their volume of distribution (Vd) is equiva-

Pharmacokinetics

Pharmacokinetics is the study of the interrelationship between drug dose and variations in concentrations in plasma and tissue over time. The most relevant pharmacokinetic parameters include the following:

- peak concentration achieved after a single dose (Cmax)
- Vd: the apparent volume of fluid that contains the total drug dose administered at the same concentration as in plasma
- clearance (CL): quantification of the irreversible loss of drug from the body by metabolism and excretion
- elimination half-life: time required for the plasma concentration to fall by one-half
- protein binding: proportion of drug binding to plasma proteins
- AUC0-24: total area under the concentration curve over 0 to 24 h

Pharmacodynamics and PK/PD

Pharmacodynamics is the study of the relationship between drug concentrations and effect. The PK/PD approach seeks to establish a relationship between dosage and pharmacological effect. Figure 1 represents the relationship among pharmacokinetics, pharmacodynamics, and PK/PD. Antibiotics can be categorized in three different classes depending on the PK/PD indices associated with their optimal killing activity.

Time-Dependent Antibiotics: Optimal activity is achieved when unbound plasma concentrations are maintained above the minimum inhibitory concentration (MIC) of the bacteria (fT > MIC) for a defined fraction of the dosing interval.

Concentration-Dependent Antibiotics: Optimal activity correlates with Cmax, quantified by its ratio with the MIC of the bacteria (Cmax/MIC).
Concentration-Dependent Antibiotics With Time Dependence: A defined ratio between the unbound AUC\(_{0-24}\) and the MIC of the bacteria (fAUC\(_{0-24}/\)MIC) correlates with optimal activity.

**Pathophysiology of MODS and Effect on Drug Vd and CL**

Sepsis-related MODS has been defined as the worsening of organ function due to a severe infection such that homeostasis cannot be maintained without intervention, usually involving two or more organ systems. Endotoxins have a cascade effect on the production of endogenous molecules that act on the vascular endothelium, leading to vasodilatation and transcapillary leakage of fluid and proteins into the extracellular space. Moreover, sepsis is known to produce myocardial dysfunction. These hemodynamic alterations lead to sepsis-induced tissue hypoperfusion, which can affect pharmacokinetics. Because antibiotics are a group of drugs with “silent” pharmacodynamics (ie, the pharmacologic effect is not perceivable immediately after administration), it is almost impossible to assess whether therapeutic concentrations are being achieved during the early phase of therapy. Therefore, consideration of the scenarios likely to alter antibiotic pharmacokinetics and necessitate dosage adjustment are necessary to enable individualization of antibiotic therapy.

**Tissue Hypoperfusion**

In the first stage of septic shock (warm shock), arteries dilate, decreasing peripheral arterial resistance and causing a reflex increase in cardiac output. Later, typical features of septic shock may appear, including a decrease in cardiac output and BP. This sepsis-mediated altered blood flow may have important effects on drug delivery to tissues.

During the warm shock phase, hypoperfusion of vital organs (eg, brain or lung) occurs, whereas peripheral tissues and nonvital organs still receive high blood flow as a consequence of peripheral vasodilation and increased cardiac work. Vital organs hypoperfusion can lead to suboptimal delivery of antibiotic and subtherapeutic levels at the target site during the initial stages of the infection in vital organ infections (eg, respiratory tract infections). However, a challenge for interpretation is the absence of pharmacokinetic data specifically targeting the effects of warm shock on drug distribution, and more research is required in this area.

Peripheral tissue hypoperfusion can occur during the second phase of septic shock as a result of the body’s attempt to increase perfusion of the vital organs. Because peripheral tissues frequently are the source of infection, hypoperfusion can lead to a failure to attain therapeutic concentrations at the site of infection. A similar scenario may be observed in patients with fluid shifts, capillary leak, and edema. In this case, despite increased movement of plasma and solutes (eg, hydrophilic antibiotics) to the extravascular compartment, drug concentrations at the target site could decrease because of a dilution effect. Alternative approaches to drug administration, such as continuous or extended infusion, have been shown to reach more consistent antibiotic concentrations in tissue for time-dependent antibiotics in these scenarios and should be considered when treating infections by poorly susceptible bacteria. Monte Carlo simulations can be used to this end to compare...
the relative PK/PD target attainments for different dosing approaches for antibiotics, particularly for time-dependent antibiotics. These analyses have shown consistently that extended infusions (>3 h) or continuous infusions of time-dependent antibiotics achieve PK/PD targets more successfully than intermittent infusions (≤30 min).24-26 Monte Carlo simulations also can be used to show the effect of renal dysfunction on the achievement of PK/PD targets. Figure 2 has been adapted from Roberts et al.22 and describes how administering the same dose of meropenem in different levels of renal dysfunction will provide different levels of achievement of PK/PD targets. Use of extended or continuous infusions in this context could serve to further increase the achievement of PK/PD targets.

Renal Dysfunction

Several factors can precipitate acute kidney injury (AKI) in critically ill patients.27 Early identification of AKI and accurate assessment of renal function are essential for daily dose adjustment of hydrophilic antibiotics. The estimations of creatinine clearance (CrCL) as a surrogate for glomerular filtration rate (GFR) using formulas such as Cockroft-Gault and modified diet in renal disease (MDRD) must be interpreted carefully in critically ill patients because despite having well-documented clinical value in specific patient populations (eg, patients with chronic kidney disease), they are yet to be validated in critically ill patients. Because plasma creatinine concentrations can vary for many reasons other than renal function in these patients (eg, decreases due to immobility-related cachexia) and are rarely at steady state, these formulas may lead to inaccurate estimations of GFR and lead to inappropriate dose adjustments.28,29 Where possible, it is preferable to use either 8-, 12-, or 24-h urinary CrCL to estimate GFR in critically ill patients.30-32

When using urinary CrCL, dose recommendations in the product information for estimated GFR by MDRD or Cockcroft-Gault also apply. The main issue here is not the change in drug CL relative to GFR that is problematic; rather, it is how GFR is calculated. If GFR is not accurately estimated, then any dose adjustment is likely to be suboptimal.

Hepatic Dysfunction

The most common causes of liver failure in critically ill patients are infection-related cholestasis and hepatocellular injury, which occur in response to bacterial toxins and to the toxins themselves.33 In the first case, bacterial toxins and released cytokines can affect the uptake and excretion of bile by hepatocytes, leading to jaundice. In the second case, endotoxins and bacteria are phagocytized by Kupffer cells that release several hepatotoxic molecules, leading to cellular damage.33 Hepatic dysfunction also may result from organ hypoperfusion, hemolysis, or concomitant administration of hepatotoxic drugs (eg, rifampicin).33,34 Assessment of the degree of hepatic dysfunction in acute liver failure is mainly clinical and may include signs and symptoms such as elevations in liver enzymes, bilirubin, or ammonia and decreases in the concentration of liver-produced proteins (eg, albumin, α₁-acid glycoprotein, coagulation factors). Hepatic dysfunction may impair metabolism and, therefore, lead to accumulation of hepatically cleared antibiotics.35,36 A decrease in the hepatic production of albumin and α₁-acid glycoprotein also can alter pharmacokinetics of highly protein-bound antibiotics.

Albumin is the most frequent drug carrier in the bloodstream. The drug-protein interaction is rapid and dynamic, and an equilibrium depends on the concentration of both drug and protein.39 In the presence of hypoalbuminemia, a larger number of unbound drug molecules are able to distribute from the bloodstream into tissues to a larger extent than when there is normal protein binding; pharmacokinetically, this is translated into a larger Vd.39

Furthermore, clinical management of severe hepatic failure may include renal replacement therapy (RRT) and the use of adsorbent columns for removing excess ammonia and other waste products in the blood.40 The additive effect of these interventions and endogenous renal function on the excretion of renally cleared antibiotics has to be considered when dosing with hydrophilic antibiotics.

Figure 2. The effect of varying levels of renal dysfunction on the achievement of pharmacokinetics/pharmacodynamics targets for the same dose of meropenem. This example describes the probability of target attainment (fT>MIC) for meropenem administered by intermittent bolus (infused over 5 min), in a man aged 50 years and weighing 70 kg with Cr of 50, 100, 200, and 300 mmol/L. Cr = plasma creatinine concentration; fT>MIC = time over the minimum inhibitory concentration; MIC = minimum inhibitory concentration. Adapted with permission of Oxford University Press from Roberts et al.22

www.chestpubs.org
Optimizing Initial Dosing of Antibiotics in MODS

Pharmacokinetic alterations mediated by MODS should be considered during antibiotic prescription in critically ill patients. During the initial phase of sepsis, increased Vd and CL are common, and dosing must be adjusted, which has been confirmed by two recent studies. The first study, by Roberts et al, was a β-lactam therapeutic drug monitoring (TDM) evaluation in critically ill patients, including patients with MODS, that found that ~70% of patients did not achieve appropriate antibiotic concentrations, with requirement of 50.4% and 23.7% dose increases and decreases, respectively, on the initial phase of therapy. The second was a multicenter study by Taccone et al that showed that conventional initial dosing for many β-lactams frequently used in critically ill patients was insufficient for achieving PK/PD targets on the first day of therapy. In this study, only 28% of the patients on ceftazidime, 16% on cefepime, and 44% on piperacillin/tazobactam achieved the PK/PD targets on the first day of therapy. The authors found that 40% of patients receiving piperacillin/tazobactam had plasma concentrations of less than four times MIC within 90 min after administration.

The results of both studies are likely to be due to an increased Vd for these patients. It is important to note that in the study by Taccone et al, 27% of the patients had AKI, and despite having been prescribed with standard non-AKI initial doses, most of them had suboptimal concentrations after the first dose. In contrast, in the study by Roberts et al, 19% of patients had AKI (with or without dialysis requirements), and on days 2 through 5, 72% of these patients required a dose decrease. The data from both studies suggest that initial antibiotic dosing needs to account for the increased Vd that occurs in critically ill patients with MODS; therefore, higher-than-standard doses should be considered in the initial phase of therapy. This concept will be referred throughout this review as “front-loaded” dosing and especially applies to hydrophilic drugs whose Vd dramatically increases in this scenario.

This concept was demonstrated by Marik, who showed a twofold increase in the Vd of amikacin in critically ill patients with gram-negative infections. This pharmacokinetic alteration will significantly affect the achievement of therapeutic peak concentrations (Cmax/MIC ≥ 10). Recent research also supports administration of front-loaded doses for aminoglycosides (eg, 25 mg/kg for amikacin) on the first day of therapy for severe sepsis and septic shock.

For lipophilic drugs, front-loaded doses based on total body weight should be considered for patients with a higher proportion of adipose tissue to achieve therapeutic concentrations. This is the same principle by which loading doses of drugs such as amiodarone and phenytoin are required. Further, evidence supports that even the Vd of hydrophilic antibiotics is increased in obese patients due to the increased interstitial fluid, connective tissue, and muscle mass also present in obesity. Therefore, obesity must be a factor to consider for initial dosing. In this context, use of an equation that assists calculation of lean body weight should be used.

Table 1 provides broad recommendations for optimizing initial dosing in patients with increased Vd. Table 2 provides guidance for specific drugs in these scenarios.

Optimizing Maintenance Dosing of Antibiotics in MODS

Maintenance dosing must be guided by drug CL. Depending on the organ systems impaired by MODS, the effect on antibiotic CL can vary widely. The most relevant organ systems that may affect pharmacokinetics (mainly renal and hepatic systems) will be considered individually.

Table 1 provides general principles for maintenance dosing in renal failure, hepatic failure, and RRT. Table 2 provides guidance for specific drugs in these scenarios. Figure 3 summarizes the scenarios likely to alter pharmacokinetics in MODS.

Renal Dysfunction

Hydrophilic antibiotics are mostly renally cleared by glomerular filtration and tubular secretion. Decreased CL of these drugs is well described in renal dysfunction, and as such, dose reductions or extended dosing intervals are required to prevent drug accumulation and toxicity. Dose adjustments to prevent toxicity are especially relevant for antibiotics with a narrow therapeutic window, such as glycopeptides and aminoglycosides, that can produce nephrotoxicity, and, hence, its accumulation may lead to a vicious circle of injury in the damaged kidney that may lead to greater antibiotic accumulation.

When dose reducing, it is essential to consider antibiotic pharmacodynamics to ensure that targets are still attained where possible. For instance, a more appropriate dose reduction of time-dependent antibiotics would be to reduce the dose rather than the frequency of administration as a strategy to preserve the fT>MIC (eg, recommended dosing of meropenem for an estimated GFR <15 mL/min would be a front-loaded dose of 1,000 mg to provide therapeutic concentrations followed by a maintenance dose of 500 mg every 12 h to enable continued optimization of fT>MIC without toxicity). For concentration-dependent drugs,
Table 1—Broad Guidelines for Loading and Maintenance Dosing of Antibiotics in Critically Ill Patients With MODS

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Solubility</th>
<th>Main Organ Systems Responsible for Clearance</th>
<th>PD Parameter Associated With Maximal Activity</th>
<th>LD in Patients With Increased Vd</th>
<th>MD in Acute Kidney Injury</th>
<th>MD in Hepatic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>$fT &gt; MIC$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Dose decreases preferred to increased time between intervals</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>Cmax/MIC</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Increased time intervals preferred to dose decreases, titrate dosing according to TDM results</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>AUC$_{0-24}$/MIC</td>
<td>Administer high LD on day 1, as Vd will be significantly increased</td>
<td>Titrate dosing according to TDM results</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Lipophilic</td>
<td>Renal and hepatic (ciprofloxacin, moxifloxacin, levofloxacin)</td>
<td>AUC$_{0-24}$/MIC and Cmax/MIC</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction and principal organ system responsible for clearance</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lipophilic</td>
<td>Renal and hepatic (ciprofloxacin, moxifloxacin, levofloxacin)</td>
<td>AUC$_{0-24}$/MIC and $fT &gt; MIC$</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>$fT &gt; MIC$ and AUC$_{0-24}$/MIC</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>Cmax/MIC</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Decrease dosing if severe hepatic failure</td>
</tr>
<tr>
<td>Cyclic lipopeptides</td>
<td>Amphiphilic</td>
<td>Renal</td>
<td>Cmax/MIC</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Increase dosing interval</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Glycyacyclines</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>AUC$_{0-24}$/MIC</td>
<td>Administer LD per product information</td>
<td>Normal dosing</td>
<td>Decrease dosing</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>AUC$_{0-24}$/MIC and $fT &gt; MIC$</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
</tbody>
</table>

AUC$_{0-24}$/MIC = area under the concentration curve over 0 to 24 h-to-minimum inhibitory concentration ratio; Cmax/MIC = peak concentration-to-minimum inhibitory concentration ratio; $fT > MIC$ = time over the minimum inhibitory concentration; LD = front-loaded dose; MD = maintenance dose; MIC = minimum inhibitory concentration; MODS = multiple organ dysfunction syndrome; PD = pharmacodynamic; TDM = therapeutic drug monitoring; Vd = volume of distribution.
<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Antibiotic Name</th>
<th>Recommended LD for Patients With 7 Vd (Day 1)</th>
<th>Recommended MD for Patients With Hepatic Failure a</th>
<th>Recommended MD for Patients With Acute Kidney Injury a</th>
<th>Recommended MD for Patients With RRT b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Lactams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Meropenem</td>
<td>1-2 g q8h</td>
<td>1 g q8h</td>
<td>500 mg q12h</td>
<td>500 mg q8h</td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
<td>500 mg q12h</td>
<td>500 mg q8-12h</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Piperacillin/tazobactam</td>
<td>4.5 g q4-6h</td>
<td>4.5 g q6h</td>
<td>4.5 g q8h or 2.25 g q6h</td>
<td>4.5 g q8h</td>
</tr>
<tr>
<td></td>
<td>Ticaricillin/clavulanate</td>
<td>3.1 g q4-6h</td>
<td>3.1 g q6h</td>
<td>2 g q4-6h</td>
<td>2 g q4-6h</td>
</tr>
<tr>
<td></td>
<td>Isoxazolyl penicillins (cloxacillin, flucloxacillin, dicloxacillin)</td>
<td>2 g q4h</td>
<td>2 g q4h</td>
<td>2 g q6h-1 g q4h</td>
<td>2 g q6h-1 g q4h</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Ceftriaxone</td>
<td>1-2 g q12h</td>
<td>1 g q12h</td>
<td>500 mg q12h</td>
<td>500 mg q8h</td>
</tr>
<tr>
<td></td>
<td>Cefazidime</td>
<td>2 g q8h</td>
<td>1 g q8h</td>
<td>1-2 g q8h</td>
<td>1 g q8h</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>1-2 g q8-12h</td>
<td>1-2 g q8-12h</td>
<td>500 mg q12h</td>
<td>500 mg q8-12h</td>
</tr>
<tr>
<td>Monobactams</td>
<td>Aztreonam</td>
<td>1-2 g q8h</td>
<td>1 g q8h</td>
<td>1-2 g q8h</td>
<td>1-2 g q8h</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Amikacin</td>
<td>25 mg/kg q24h to achieve a Cmax/MIC = 10</td>
<td>15 mg/kg q24h to achieve a Cmax/MIC = 10</td>
<td>Monitor Cmin after 24 h, aiming for levels &lt; 5 mg/L</td>
<td>Monitor Cmin after 24 h, aiming for levels &lt; 5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Gentamycin, tobramycin</td>
<td>7 mg/kg as a LD on day 1 to achieve a Cmax/MIC = 10</td>
<td>5 mg/kg q24h to achieve a Cmax/MIC = 10</td>
<td>Monitor Cmin after 24 h, aiming for levels &lt; 5 mg/L</td>
<td>Monitor Cmin after 24 h, aiming for levels &lt; 5 mg/L</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>20-30 mg/kg LD c</td>
<td>15-20 mg/kg q12h</td>
<td>Use TDM (Cmin) on day 3, aiming for range 15-20 mg/L (20-25 mg/L if CI). Dosing should be titrated to this range</td>
<td>Use TDM (Cmin) on day 3, aiming for range 15-20 mg/L (20-25 mg/L if CI). Dosing should be titrated to this range</td>
</tr>
<tr>
<td></td>
<td>Teicoplanin</td>
<td>12 mg/kg q12h for three doses</td>
<td>3-6 mg/kg q12h, titrate dosing on day 4 guided by TDM, aiming for Cmin &gt; 10 mg/L</td>
<td>Prescribe 3 mg/kg q12h from the fourth dose and titrate dosing on day 4 guided by TDM, aiming for Cmin &gt; 10 mg/L</td>
<td>Prescribe 3 mg/kg q12h from the fourth dose and titrate dosing on day 4 guided by TDM, aiming for Cmin &gt; 10 mg/L</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin</td>
<td>400 mg q8h</td>
<td>400 mg q12-24h</td>
<td>400 mg q12-24h</td>
<td>400 mg q12-24h</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin</td>
<td>500-750 mg q24h</td>
<td>500-750 mg q24h</td>
<td>250 mg q24-48h</td>
<td>500 mg q48 or 250 mg q24h</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg q24h</td>
<td>400 mg q24h</td>
<td>400 mg q24h</td>
<td>400 mg q24h</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lincomycin</td>
<td>600 mg q6-8h as an LD on day 1</td>
<td>600 mg q12-24h</td>
<td>600 mg q12-24h</td>
<td>600 mg q12-24h</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>600 mg q6-8h as an LD on day 1</td>
<td>600 mg q12-24h</td>
<td>600 mg q12-24h</td>
<td>600 mg q12-24h</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Clarithromycin</td>
<td>500 mg q12h</td>
<td>500 mg q12h</td>
<td>In severe renal failure, 250 mg q12h</td>
<td>500 mg q12h</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>500 mg q24h</td>
<td>500 mg q24h</td>
<td>500 mg q24h</td>
<td>500 mg q24h</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Antibiotic Name</th>
<th>Recommended LD for Patients With Acute Kidney Injury</th>
<th>Recommended LD for Patients With Hepatic Failure</th>
<th>Recommended LD for Patients With RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>500 mg q8h</td>
<td>500 mg q12-24h in severe hepatic failure</td>
<td>600 mg q12h</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>6-8 mg/kg q24h</td>
<td>6 mg/kg q24h</td>
<td>6 mg/kg q48h</td>
</tr>
<tr>
<td></td>
<td>Glycylcyclines</td>
<td>Tigecycline dose 1 12 h after LD, administer 25 mg q12h</td>
<td>12 h after LD, administer 50-100 mg q12h</td>
<td>12 h after LD, administer 50-100 mg q12h</td>
</tr>
<tr>
<td></td>
<td>Oxazolidinones</td>
<td>Linezolid 600 mg q8-12h</td>
<td>600 mg q12h</td>
<td>600 mg q12h</td>
</tr>
</tbody>
</table>
|                  |                 | Data are modified from the product information of each individual drug. Note that the product information for many of the hydrophilic antibiotics included in the table is not available. The recommendations should be used as guidelines and adjusted based on individual patient needs. To provide optimal attaining of therapeutic concentration, Cmin should be monitored. RRT = renal replacement therapy. See Table 1 legend for expansion of other abbreviations.

Antibiotics like aminoglycosides, it is suggested to prolong the interval between doses rather than to decrease the dose so that the peak concentration required for optimal bacterial killing is still achieved. However, despite these theoretical recommendations, uncertainty is always present when prescribing antibiotics in patients with MODS because organ function is very likely to fluctuate from day to day during therapy. It follows that TDM is a very useful tool to titrate antibiotic dosing in MODS. TDM is widely used with aminoglycosides and glycopeptides to ensure appropriate exposure and minimize the incidence of toxicity. However, the potential and usefulness of TDM as a strategy for optimizing antibiotic doses of β-lactams (the most frequently prescribed class of antibiotics) has not yet been confirmed. Recent research has assessed its usefulness with a broad group of critically ill patients. Roberts et al showed that in the maintenance phase of therapy, many patients with renal dysfunction required a dose decrease due to high concentrations (about 10 times MIC), despite empirical dose adjustment for renal dysfunction. However, other patients with renal failure or on RRT exhibit suboptimal concentrations with this adjusted dosing, which evidences that concentrations do not depend exclusively on renal function but on various other factors.

### Renal Replacement Therapy

As renal function deteriorates, waste products will accumulate, and commencement of RRT should be considered. The main determinants of CL during RRT are the modality and settings prescribed. Hemodialysis, hemofiltration, hemodiafiltration, and peritoneal dialysis all have different mechanisms of removing metabolic waste and have a different effect on the extent to which each drug is cleared. Other factors that determine the extraction ratio are drug molecular weight (drugs with a molecular weight greater than the pores of the filter membrane are not able to be removed), protein binding (only unbound molecules can be removed), drug affinity for filter adsorption, whether replacement fluid is added prefilter or postfilter, and the ultrafiltration rate. The implications of RRT on drug dosing have been reviewed recently, and a further discussion is beyond the scope of this article. However, Table 1 provides some recommendations for dosing in RRT.

### Hepatic Dysfunction

Liver impairment may have a significant impact on the CL of both lipophilic and hydrophilic drugs. Lipophilic drugs may undergo metabolism in the liver to increase the hydrophilicity of the compound. The CL of hepatically eliminated drugs depends on...
Figure 3. Clinical scenarios likely to alter antibiotic PK in MODS. MODS = multiple organ dysfunction syndrome; PK = pharmacokinetics.

The hepatic blood flow and intrinsic clearance (i.e., degree of enzymatic activity) are distinct. Therefore, two kinds of scenarios can be distinguished. CL of highly extracted drugs is mainly correlated with hepatic blood flow (e.g., lidocaine), whereas in less-extracted drugs, CL is determined by intrinsic CL and degree of protein binding (e.g., nitroimidazoles, fluoroquinolones). Hepatic failure may imply modification of both factors, leading to decreased drug elimination, accumulation, and potential toxicity. For example, in liver failure, metronidazole oxidation by microsomes may be decreased because of reduced enzyme expression and enzymatic activity, leading to potential toxicities, including seizures and peripheral neuropathy. Other drugs may be cleared by biliary excretion, which may be substantially decreased in hepatic impairment (e.g., tigecycline). A study comparing patients with different degrees of hepatic failure found that tigecycline CL was reduced by 55%, and elimination half-life was prolonged by 43% in patients with severe hepatic impairment. In this context, a dose reduction is suggested to avoid toxicity.

Additionally, the decreased synthesis of albumin and α1-acid glycoprotein in liver dysfunction, together with the transcapillary distribution of these proteins due to capillary leakage, may alter the pharmacokinetics of highly protein-bound antibiotics. Hypoalbuminemia has been shown to cause significant increases in the Vd and CL of drugs such as ceftriaxone (85%-95% protein bound), ertapenem (85%-95%), fluclaxacinil (95%), and teicoplanin (90%-95%). Therefore, front-loaded doses should be considered when prescribing these drugs in critically ill patients with MODS and hypoalbuminemia. Initial dosing recommendations for highly bound hydrophilic antibiotics (Table 2) account for this scenario. Maintenance dosing should be guided by the level of organ function and in the context of the main elimination pathways for the drug and, where possible, guided by TDM. Decreased plasma concentrations of α1-acid glycoprotein increase substantially erythromycin Vd (73%-81% protein bound), whereas CL decreases by 60% in the presence of metabolic impairment. Other antibiotics that bind substantially to this protein include trimethoprim and the lincosamides.

As a final consideration for organ dysfunction, it is noteworthy that critically ill patients can present with underlying comorbidities, such as chronic renal or hepatic dysfunction, unrelated to sepsis. In this case, the previously mentioned dosing principles for initial and maintenance dosing also should apply. Dose adjustments should always be made according to the degree of organ function and the estimated level of drug Vd and CL present in the patient, regardless of preexisting dysfunction. Preexisting dysfunction should only be considered as a guide to the likely level of organ function in the maintenance phase of therapy.

Conclusions

Appropriate antibiotic dosing in MODS is complex and depends on several drug- and patient-related factors. Consideration of antibiotic physicochemical and pharmacodynamic characteristics and disease-related alterations in pharmacokinetics is essential for designing dosing regimens that avoid suboptimal dosing. There are two important phases in antibiotic therapy in MODS. During the first day of therapy, front-loaded dosing is required and must be guided by the

1218

© 2011 American College of Chest Physicians
predicted Vd, which is likely to be increased in critically ill patients despite impaired organ function. From day 2 onward, maintenance dosing can be adjusted in line with the CL associated with the organ dysfunction. The requirements for dose adjustment for antibiotics should be considered individually depending on the organ system that is failing and the drug CL pathway. Because of the great variability of organ function during a septic insult, TDM should be regarded as a useful tool to individualize dosing and ensure appropriate exposure to the antibiotic. Further research on dose adjustment in MODS is required for improving patient quality of care and outcomes in this population.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Roberts serves as a consultant for AstraZeneca and Janssen-Cilag. Dr Lipman serves as a consultant for AstraZeneca and Wyeth and has received grant support from AstraZeneca. Drs Ulldemolins and Rello have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES

Antibiotic Dosing in Multiple Organ Dysfunction Syndrome
Marta Ulldemolins, Jason A. Roberts, Jeffrey Lipman and Jordi Rello
Chest 2011;139; 1210-1220
DOI 10.1378/chest.10-2371

This information is current as of May 4, 2011

Updated Information & Services
Updated Information and services can be found at:
http://chestjournal.chestpubs.org/content/139/5/1210.full.html

References
This article cites 57 articles, 15 of which can be accessed free at:
http://chestjournal.chestpubs.org/content/139/5/1210.full.html#ref-list-1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.chestpubs.org/site/misc/reprints.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.chestpubs.org/site/misc/reprints.xhtml

Citation Alerts
Receive free e-mail alerts when new articles cite this article. To sign up, select the "Services" link to the right of the online article.

Images in PowerPoint format
Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online figure for directions.