THE ROLE OF PHARMACODYNAMICS IN EFFECTIVE TREATMENT OF COMMUNITY-ACQUIRED PATHOGENS

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ABSTRACT

Pharmacodynamics is commanding a greater role in the study of antibiotic efficacy and determination of dosing regimens. The simple measurement of serum, tissue, and body fluid antibiotic concentration do not provide sufficient information concerning the rate of pathogen killing at the site of any postantibiotic effects that may be occurring. This article discusses the pharmacokinetic and pharmacodynamic parameters that are now being used to determine antibiotic dosing regimens and will be used to set new breakpoints of susceptibility. Understanding the relationship between the 24-hour area under the serum concentration vs time curve, the minimum inhibitory concentration, and the peak serum level can have profound effects on the appropriate antibiotic choice for a given infection and the dosing regimen. This article will provide an overview of the key pharmacodynamics studies in animals and humans with a focus on pathogens associated with community-acquired infections.

MEASURING ANTIBIOTIC ACTIVITY

The primary measure of antibiotic activity or potency has been the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC). The MIC is the test upon which all susceptibility and breakpoint measurements are made. MIC and MBC are useful indicators of antibiotic potency, but they reveal nothing about the time course of antimicrobial activity. For example, the MBC cannot indicate the rate of killing or whether this rate is enhanced by increasing concentration. Furthermore, the MIC does not indicate whether there are persistent effects that can last after antibiotic exposure. These persistent effects may delay the time required by the organism to recover from exposure to the drug. And, in fact, the rate of killing and persistent effects are really the best parameters to define the optimal time course of antimicrobial activity.

Historically, an antibiotic dosing regimen has been determined by pharmacokinetic (PK) parameters. However, pharmacodynamics (PD) play an equal, if not more important, role because the drug concentrations in the tissues and body fluids as well as at the site of infection are considered. Tissue and body fluid concentrations determine the pharmacological and toxicological effects, while drug concentration at the site of infection determines the antimicrobial effect. In this age of increasing antibiotic resistance, pharmacodynamics becomes even more important because these parameters may be used to counteract and/or prevent resistance.

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The rate of killing is determined by either the length of time necessary to kill (i.e., time-dependent killing) or the effect of increasing concentrations (i.e., concentration-dependent killing). Persistent effects can include a postantibiotic effect, a postantibiotic sub-MIC effect (PASME), or a postantibiotic leukocyte enhancement effect (PALE), in which the bacteria in the postantibiotic phase are more susceptible to intracellular killing or to phagocytosis by leukocytes.2-4 Using these parameters, antibiotics can be divided into 3 categories. Table 1 summarizes the characteristics of each group and provides examples of each type.1 A more detailed discussion follows below.

**TYPE I: CONCENTRATION-DEPENDENT KILLING AND PROLONGED PERSISTENT EFFECTS**

For Type I antibiotics, higher concentrations result in faster and more extensive bacterial killing with prolonged persistent effects. Antibiotics in this group include aminoglycosides, quinolones, and, among the newer antibiotics under investigation, daptomycin and the ketolides. The dosing regimen goal for this type of drug would be to maximize concentration because the higher the concentration, the more extensive and the faster is the degree of killing. Therefore, as expected, the area under the serum-concentration-versus-time curve (AUC), or the peak serum level in relationship to the MIC, would be the important determinant of efficacy.5,6 Figure 1 shows the results from a murine thigh infected with *Streptococcus pneumoniae* and treatment with levofloxacin. By using multiple dosing regimens, this animal model can determine which of the different parameters (e.g., 24-hour AUC to MIC ratio [AUC/MIC], peak serum level to MIC ratio [peak/MIC], and time above MIC) are important for in vivo efficacy. Figure 1 shows the results from a Type I drug in which the AUC/MIC and peak/MIC clearly are the strongest determinants of efficacy.7

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Drugs</th>
<th>Dosing Goal</th>
<th>Parameter Correlating with Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I: Concentration-dependent killing and prolonged persistent effects</td>
<td>Aminoglycosides, quinolones</td>
<td>Maximize concentrations</td>
<td>Peak level/MIC and AUC/MIC</td>
</tr>
<tr>
<td>Type II: Time-dependent killing and minimal to moderate persistent effects</td>
<td>Penicillins, cephalosporins, carbapenems, clindamycin, macrolides</td>
<td>Optimize duration of exposure</td>
<td>Time above MIC</td>
</tr>
<tr>
<td>Type III: Time-dependent killing and prolonged persistent effects</td>
<td>Vancomycin, azithromycin, tetracyclines</td>
<td>Optimize daily amount of drug</td>
<td>AUC/MIC</td>
</tr>
</tbody>
</table>

**Table 1. Patterns and Parameters of Antimicrobial Activity**


Figure 1. Correlation of PK/PD Parameters with Efficacy of Levofloxacin against *S* pneumoniae in Thighs of Neutropenic Mice

The dotted line represents the number of organisms at the start of therapy. Points above the dotted line represent growth; points below represent killing. The AUC/MIC and peak/MIC are clearly correlated with antimicrobial effect, whereas the time above MIC shows essentially a scattergram. Therefore, levofloxacin shows concentration-dependent killing.
**Type II: Time-dependent Killing with Minimal to Moderate Persistent Effects**

Type II antimicrobials demonstrate the complete opposite type of killing compared with Type I. These drugs use time-dependent killing, which indicates that higher concentrations will not kill the organism faster. The only way to achieve greater killing is to maintain adequate drug levels at the site of infection for a longer period of time. These organisms also recover very quickly from exposure to the drug, so the drugs have minimal to moderate persistent effect.5,6

β-Lactam antibiotics (ie, penicillin, cephalosporin, mono-bactam, carbapenems) all have this Type II pattern of activity, as well as clindamycin, macrolides, and, among the newer agents, linezolid. The dosing regimen goal is to optimize duration of exposure because the time above MIC is the parameter that most correlates with efficacy, as demonstrated in Figure 2. Of note, a relatively static effect is achieved when the time above MIC is reached during only 30% to 40% of the dosing intervals. However, maximum killing is seen when the time above MIC is 70% of dosing intervals.5,6

**Type III: Time-dependent Killing with Prolonged Persistent Effects**

Type III drugs offer time-dependent killing but have prolonged persistent effects which keeps the duration of exposure from being an important determinant of activity; thus the AUC is the parameter that correlates with efficacy. Type III antibiotics include glycopeptides (eg, vancomycin), tetracyclines, and azithromycin. Newer drugs such as the dalfopristin-quinupristin combination are Type III drugs.

Tetracycline can be dosed q 2 d in a mouse to achieve the same effect as q 6 h. So, how did we decide to dose q 6 h in humans? PK/PD studies can help to better define appropriate dosing regimens.

**PK/PD Parameters**

A variety of studies have suggested that the magnitude of the parameter required for efficacy is the same in animal species and humans. For example, the time above MIC required for a β-lactam to demonstrate activity in a mouse appears to be the same time above MIC required to demonstrate efficacy in humans.5,8,9 This relationship holds true for antibiotics (and not other types of drugs) because the receptor is the same for humans and animals; the receptor is the bacteria. With antihypertensive agents, eg, the receptor in the animal could be entirely different from the receptor in humans. So, an increasing number of antimicrobial agents have been studied in both humans and animals, and the parameters in animals are predictive of the parameters in humans.

The other observation is that the magnitude of the parameter required for efficacy does not vary with the dosing regimen. So, if a Type II drug is given q 6 h or q 12 h, the same percentage of the dosing interval is required for efficacy. If optimal killing occurs with time above MIC at 70%, as is seen with lefotaxime for treating S pneumoniae, and if it is dosed q 8 h, the time above MIC needs to be 4.2 hours. If cefotaxime is dosed q 12 h, the time above MIC needs to be 8.4 hours.
The magnitude of the parameter does not vary with similar drugs in the same class. For example, one carbapenem will have the same magnitude required for efficacy as another carbapenem, providing that protein binding is accounted for. Clearly, the free, unbound drug concentration is most important in determining activity so highly protein-bound drugs require a higher magnitude than a nonprotein-bound drug. If that is corrected for in the dosing, and the free drug concentrations are used, then the magnitude is the same.

Interestingly, studies comparing a variety of acute infections (eg, the pneumonia model, peritonitis models, bacteremia models, and skin and soft tissue models) show that these types of infections have roughly the same magnitude of the parameter required for efficacy.5,6 On the other hand, the required parameter magnitudes for each antibiotic vary by different organisms. For example, staphylococci succumb with less time above MIC with penicillin and cephalosporins than pneumococci or gram-negative bacilli, and this can be explained by the postantibiotic effect. β-Lactams demonstrate a prolonged postantibiotic effect with staphylococci and streptococci in the test tube, but this has not been shown with streptococci in any in vivo animal model. Another example is with fluoroquinolones, because pneumococci, in the presence of neutrophils, succumb to killing with a 3- to 4-fold smaller AUC in relationship to the MICs than is required by gram-negative bacilli.5,6

One of the prominent concerns in recent times is the extent to which increasing resistance will affect the magnitude of the parameter required for effective killing. As will be discussed later, for many of the organisms that have been studied, the magnitude of the parameter does not vary much with resistant strains, especially with penicillin-resistant pneumococci. Figure 3 shows the relationship between the time above MIC and the MIC for numerous strains of pneumococci, some of which are penicillin resistant.5,10 Clearly, the time above MIC required for a static effect is the same regardless of strain or susceptibility to penicillin (ie, regardless of MIC). However, drug concentrations will need to increase with higher MICs in order to stay above the MIC for the same period of time, but the percentage of the time required to be above the MIC is not affected by the presence of altered penicillin-binding protein.

**Table 2. Magnitude of Time Above MIC Determining Efficacy of β-Lactams Against Common Pathogens**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Time Above MIC (% of Dosing Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>40%-50% for streptococci and gram-negative bacteria (60%-70% for maximum kill)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>25%-30% for staphylococci (50% for maximum kill)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>25%-30% (40%-50% for maximum kill)</td>
</tr>
</tbody>
</table>

Numerous strains of S pneumoniae with MICs ranging from 0.016 to 4 for amoxicillin and 16 for cefpodoxime were analyzed. No change in time above MIC was required over a 24-hour period, regardless of MIC. However, doses will have to increase to meet the time above MIC requirement.
One of the major benefits of using animal studies to predict the required magnitude of the efficacy parameter is in situations where collecting sufficient clinical data is difficult (ie, with any new emerging resistance). Clinical data collection for an antibiotic takes years and emergence of resistance can occur within just a few years of introduction of a new antibiotic. Using pharmacodynamics, clinicians can begin to predict the most effective dosage regimens and, as the clinical data become available, those regimens can be fine-tuned.

Mechanisms of Resistance

There are a variety of mechanisms for resistance, including drug inactivation (most notably β-lactams, aminoglycoside-modifying enzymes), target modification (eg, altered penicillin-binding proteins, DNA gyrase mutations), and decreased permeability/increased drug efflux (eg, altered outer membrane porins, altered specific drug pumps). It is difficult to compensate for drug inactivation using pharmacodynamics because the MICs are so much higher. On the other hand, target modification results in a more modest or gradual change in the MIC that can often be overcome with higher doses. However, second-step mutations (ie, additional mutations in the same or other genes that are targets of antibiotics) may cause even higher MICs that would be difficult to overcome with higher drug concentrations. Decreased permeability or increased efflux also result in a more moderate form of resistance that may be overcome by giving higher doses.

Resistance genes can be disseminated by plasmids, transposons, transformation, and clonal spread. Many investigators are now studying the role of pharmacodynamics in clonal spread—more specifically, which pharmacodynamic parameters are required to eliminate pneumococcus from the nasopharynx and thereby reduce the chances of its spread.

Time Above MIC and Dosing Regimens

Table 2 summarizes the magnitudes of time above MIC required with different drugs for common pathogens. Of note, carbapenems require a shorter time above MIC to improve efficacy than penicillins and cephalosporins because carbapenems exhibit postantibiotic effects with pneumococci, gram-negative organisms, and staphylococci while penicillins and cephalosporins show postantibiotic effects only with staphylococci. However, the major reason is considered to be that the rate of killing by carbapenems is significantly faster than by penicillins and cephalosporins. So both the postantibiotic effects and the rate of killing probably contribute to these differences.

The National Committee on Clinical Laboratory Standards (NCCLS) has begun using pharmacodynamics to establish and/or reevaluate breakpoints but, so far, the only organism that significantly has been studied and affected by this information over the last few years is S pneumoniae. Many of the older breakpoints for staphylococci and gram-negative organisms are probably no longer accurate. Table 3 shows the time above MIC for β-lactams with Staphylococcus aureus. Cefazolin, as an example, has an MIC₉₀ of 1 µg/mL, and provides serum levels above that value for 8 hours. Cefazolin is currently dosed q 8 h, which should be effective because the magnitude of the time above MIC required for killing is 50% (Table 2). On the other hand, cefotaxime is now dosed 1g q 12 h in some situations. The MIC₉₀ is 4 µg/mL and

<table>
<thead>
<tr>
<th>Drug (Dose)</th>
<th>Half-life (hr)</th>
<th>MIC₉₀ (µg/mL)</th>
<th>T&gt;MIC (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafcillin (2 g)</td>
<td>0.5</td>
<td>0.25</td>
<td>3.0</td>
</tr>
<tr>
<td>Oxacillin (2 g)</td>
<td>0.4</td>
<td>0.2</td>
<td>2.45</td>
</tr>
<tr>
<td>Cefazolin (1 g)</td>
<td>1.5</td>
<td>1</td>
<td>7.8</td>
</tr>
<tr>
<td>Cefotaxime (1 g)</td>
<td>1.0</td>
<td>4</td>
<td>4.2</td>
</tr>
<tr>
<td>Ceftriaxone (1 g)</td>
<td>7.0</td>
<td>4</td>
<td>8.0</td>
</tr>
<tr>
<td>Ceftazidime (1 g)</td>
<td>2.0</td>
<td>16</td>
<td>3.8</td>
</tr>
<tr>
<td>Cefepime (1 g)</td>
<td>1.5</td>
<td>16</td>
<td>3.2</td>
</tr>
<tr>
<td>Imipenem (0.5 g)</td>
<td>1.0</td>
<td>0.03</td>
<td>10</td>
</tr>
</tbody>
</table>

the time above the MIC is 4 hours. So, dosing the drug q 12 h means that the time above MIC is now around 30%, which can be effective but, for staphylococci, 50% is maximal. Dosing q 12 h is borderline and if the MIC increases to 8, the dose is essentially ineffective but the NCCLS still considers S. aureus susceptible at that concentration. Similarly, ceftriaxone has an MIC of 4 µg/mL with S. aureus, but there are some organisms with an MIC of 8 µg/mL, which essentially removes 1 half-life. So there are clear examples in which the current breakpoint would not provide what we would now consider pharmacodynamically adequate drug concentrations. On the other hand, imipenem is dosed q 6 h with 500 mg. For S. aureus, the time above MIC is 10 hours, so imipenem could easily be dosed q 12 h while maintaining efficacy.1

Escherichia coli tends to produce much longer times above MIC because the organisms have lower MIC values. Cefazolin, eg, has an MIC of 16, which is susceptible right at the breakpoint by NCCLS standards. However, dosing q 8 h means that the time above MIC is less than 2 hours, which is less than 25% (ie, much less than the time required for effective killing) and far below that required for a gram-negative bacteria (Table 2). Yet, dosing of cefazolin q 8 h is still recommended for any susceptible organism.1

Table 4 shows the PK/PD parameters required for treating community-acquired pathogens. Of note, the AUC/MIC for azithromycin is 25 to 35. In other words, the magnitude for efficacy is 1 x MIC for each 24 hours, which gives an AUC/MIC of 24. For aminoglycosides, the magnitude is 100 or an average of 4 x MIC. To prevent selection of resistant mutants, it is best to have peak levels at least 8 times the MIC.

PD in Humans

Studies with multiple β-lactams in otitis media have demonstrated a strong association between bacteriological eradication and time above MIC. High rates of bacterial eradication of S. pneumoniae and Haemophilus influenzae are seen when serum levels exceed the MIC for at least 40% to 50% of the dosing interval.1 This correlates very well with the animal studies. Ambrose et al recently showed similar data in humans for fluoroquinolones. A total of 58 patients were enrolled in a comparative trial of levofloxacin and gatifloxacin. The

Table 4. Magnitude of PK/PD Parameters Determining Efficacy Against Community-acquired Pathogens for Different Antimicrobials

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK/PD Parameter</th>
<th>Magnitude for Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides, clindamycin</td>
<td>T &gt; MIC</td>
<td>40%-50% of dosing interval</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>24-hr AUC/MIC</td>
<td>25-35 (average 1 X MIC)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>24-hr AUC/MIC</td>
<td>100 (average 4 X MIC)</td>
</tr>
<tr>
<td></td>
<td>Peak/MIC</td>
<td>8-10</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>24-hr AUC/MIC</td>
<td>100-125 for gram-negative bacteria and staphylococci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-35 for pneumococci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-10 for gram-negative bacteria + staphylococci</td>
</tr>
</tbody>
</table>

Figure 4. Pharmacodynamics of Fluoroquinolones against S. pneumoniae in Community-acquired Respiratory Tract Infections

AUC was calculated in relation to the MIC. As shown in Figure 4, 100% eradication was achieved with 24-hour AUC/MIC (ie, free drug) of 41 or higher. Below 41, treatment failures occurred in 25% to 35% of cases. The actual breakpoint was at an AUC/MIC of 33.7, but these data clearly support the predictive value of PK/PD studies of antibiotics in animal models.13

Of recent interest are the activities of different fluoroquinolones in humans against S pneumoniae, S aureus, and gram-negative bacilli. Table 5 shows the extent to which fluoroquinolones are meeting the goals associated with optimal dosing for this pathogen. There is currently no established breakpoint by the NCCLS for pneumococci with ciprofloxacin. The MIC50 is about 1 µg/mL but the 24-hour AUC/MIC is only 20. As discussed previously, the target 24-hour AUC/MIC for fluoroquinolones is 25 to 35 so 20 is suboptimal. With staphylococci, the AUC/MIC is 40 but the optimal 24-hr AUC/MIC is 100 to 125. For both of these organisms, the newer fluoroquinolones give more adequate values. With gram-negative organisms, all the agents provide an adequate 24-hr AUC/MIC (100 to 125) if we use the MIC50. However, for organisms with MICs at the susceptibility breakpoint, the 24-hr AUC/MIC is only 12 to 20. These organisms would still be classified as susceptible in the microbiology laboratory, but the 24-hr AUC/MIC values are clearly suboptimal.

For anthrax, the MIC with ciprofloxacin is 0.03 mg/mL. Compared with the MIC of 1 mg/mL for pneumococci, the MIC is at least 16-fold less for anthrax, which yields a 24-hr AUC/MIC in the hundreds. Therefore, ciprofloxacin is predicted to be effective in treating anthrax. Many of the other newer fluoroquinolones, which tend to have higher AUCs and lower MICs for some of the gram-positive organisms, might have even higher values for anthrax. In any case, the MIC is required to perform these types of calculations.

**PK/PD versus Emergence of Resistance**

Thomas et al studied the effect of pharmacodynamics in preventing the selection of Type 1 β-lactamase-producing strains with β-lactam monotherapy (ie, penicillin or cephalosporins). The 24-hr AUC/MICs were extraordinarily high, which would correlate with levels that exceeded the MIC for 100% of the dosing interval. Still resistance developed in 50% to 75% of the cases. Carbapenems, however, are not susceptible to this type of β-lactamase, so combination therapy is recommended when using penicillins and/or cephalosporins for treatment of these kinds of organisms.13

They also studied ciprofloxacin monotherapy and, as expected, a value of greater than 100 (24-hr AUC/MIC) resulted in the emergence of resistance in 100% of the cases. Resistance was still not completely eliminated at higher values. Nevertheless, 24-hr AUC/MIC values greater than 100 reduced the emergence of resistance to 25% for Pseudomonas aeruginosa and 7% for other gram-negative bacteria.13

**Conclusion**

Pharmacokinetic and pharmacodynamic parameters can be used to develop more effective dosing regimens to improve efficacy of antimicrobial agents, reduce the emergence of resistance, develop new drugs and new formulations, consider during guideline formation and development, and establish susceptibility breakpoints. The NCCLS has used these data primarily with pneumococci, but there is ample opportunity and need to apply this information to other organisms.

### Table 5. 24-hour AUC/MIC for Fluoroquinolones at the MIC Susceptibility Breakpoint/MIC50

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pneumococci</th>
<th>Staphylococci</th>
<th>Gram-negative organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>— / 20</td>
<td>20 / 40</td>
<td>20 / 333</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>18 / 36</td>
<td>18 / 72</td>
<td>18 / 300</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>24 / 96</td>
<td>12 / 200</td>
<td>12 / 200</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>28 / 112</td>
<td>14 / 112</td>
<td>14 / 225</td>
</tr>
</tbody>
</table>

REFERENCES

Case Study

A 57-year-old man with multiple health problems including type 2 diabetes, obesity, peripheral vascular disease, and venous insufficiency.

HISTORY
AB is a 57-year-old man who is a farmer with multiple health problems including type 2 diabetes, obesity, peripheral vascular disease, and venous insufficiency. He has chronic edema and recurrent ulcers on his lower legs, which have been treated at times with oral antibiotics. For the past week, he has had an open ulceration in the pretibial area of his right lower leg. About 3 days ago, he developed pain and erythema around the ulcer. He self-medicated with oral dicloxacillin, but the swelling, pain, and erythema progressed. He also developed a fever and night sweats and was admitted to the hospital.

PHYSICAL EXAMINATION
His temperature was 38.8°C, with a pulse of 108, respirations 24 beats per minute, and BP 150/85 mm Hg. His lungs were clear. The heart showed tachycardia and a grade 2/6 systolic ejection murmur along the LSB. Abdomen was obese but nontender. The right lower leg was swollen with erythema from the ankle to the knee. A pretibial ulcer with purulent drainage was present but could not be probed to bone. The patient had decreased sensation in his feet.

LABORATORY RESULTS
Laboratory evaluation showed a normal hemoglobin and hematocrit, a WBC of 15,600 with 89% PMNs. Creatinine was 1.5 mg/L. LFTs were normal. C-reactive protein was elevated at 16 (normal 0-2). An X-ray of the leg did not show any air or underlying osteomyelitis. A Gram stain of the exudate showed >25 PMNs, many gram-positive cocci in pairs and clumps, and many gram-negative rods.

INTERVENTION
He is started on ceftriaxone 1 g IV q 24 h after consideration of cefotaxime 1 g q 12 h, ciprofloxacin 400 mg IV q 12 h, ampicillin/sulbactam 1.5 g IV q 6 h, and imipenem 500 mg IV q 6 h or ertapenem 1 g IV q 24 h. Although his fever decreases, he continues to have night sweats and erythema of the leg. His WBC remains elevated. The laboratory has identified the pathogens as Staphylococcus aureus susceptible to nafcillin but resistant to penicillin and Enterobacter cloacae susceptible to ceftriaxone and many other antibiotics.

DISCUSSION
Ceftriaxone was clearly not an appropriate choice for initial therapy because, if the infection was due to staphylococcus, the MIC would be 4 to 8. MICs for S aureus are relatively high for ceftriaxone, and organisms with high MICs are usually poorly treated because the time above MIC is too short. Ceftriaxone is also not a good choice for Enterobacter because of the significant emergence of resistance with derepressed mutants producing excessive amounts of β-lactamase. Cefotaxime q 12 h would also not be appropriate because the half-life is 1 hour and the time above the MIC is 4.2 hours with an MIC₉₀ of 4. Ciprofloxacin 400 mg IV q 12 h would be of concern due to the selection of resistant organisms. The MIC for S aureus with ciprofloxacin is high enough to possibly select out resistant variants. Ampicillin sulbactam might be an appropriate choice provided that there is sufficient evidence of an anaerobic infection.

Once the pathogen was identified, the most appropriate antibiotic would be imipenem or ertapenem. Monotherapy with other β-lactams may increase the chance of selecting out a resistant organism. Ciprofloxacin could be used but only in combination with another antibiotic for the S aureus. Enterobacter is not covered by ampicillin/sulbactam.