Impact of Antibiotic Resistance in Gram-Negative Bacilli on Empirical and Definitive Antibiotic Therapy

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Serious infections with gram-negative pathogens continue to be associated with considerable mortality. Increasing antibiotic resistance in organisms such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae is contributing to difficulties with choosing antibiotics to prescribe for these infections. Optimization of therapy against these organisms starts with the initial empirical antibiotic choice. Surveillance data and hospital or unit antibiograms may inform this decision, although individualization of the initial regimen on the basis of prior antibiotic use and prior isolation of resistant pathogens may be more important. Combinations of antibiotics are often required empirically, and “combination antibiograms” may need to be developed for this purpose. Preliminary data suggest that extending the time over which a dose of antipseudomonal β-lactam antibiotics is infused may improve clinical outcomes; however, this idea remains to be confirmed in randomized trials. The role of direct susceptibility testing in aiding more-rapid initiation of appropriate antibiotic therapy is also being studied. When identification and susceptibility testing is complete, the antibiotic regimen for infections due to gram-negative pathogens can be “fine tuned.” On some occasions, this fine tuning necessitates the introduction of “salvage” antibiotics, such as colistin or tigecycline; on others, it necessitates de-escalation and early termination of therapy. The lack of new antibiotic options against gram-negative pathogens underscores the need for optimization of current therapies and prevention of the spread of these organisms.

Available evidence shows that the proportion of gram-negative bacilli resistant to commonly used antibiotics is increasing [1–5]. Prominent examples include fluoroquinolone resistance in Escherichia coli, cephalosporin resistance in a variety of the Enterobacteriaceae, carbapenem resistance in Acinetobacter baumannii and Pseudomonas aeruginosa, and now even resistance to antibiotics used as “salvage” therapy, such as tigecycline and the polymyxins [6]. The mechanisms of this resistance are often complex but include production of multiple β-lactamase types, outer-membrane impermeability, up-regulated efflux pumps, and target-site mutation [3, 5].

While the rate of antibiotic resistance is worsening, the antibiotic armamentarium available for use against gram-negative bacilli is barely increasing [7]. The purpose of the present article is to discuss optimization of antibiotic choice for serious infections with gram-negative bacilli. Points of discussion include (1) methods for determining initial empirical antibiotic choice for infections suspected to be caused by gram-negative bacilli; (2) optimizing choice for therapy when the organism is known but susceptibility test results are not yet available; and (3) “fine tuning” therapy when identification is completed and susceptibility test results have been obtained.

METHODS FOR DETERMINING INITIAL EMPIRICAL ANTIBIOTIC CHOICE FOR INFECTIONS SUSPECTED TO BE CAUSED BY GRAM-NEGATIVE BACILLI

On a daily basis, clinicians are forced to choose an antibiotic for a patient with symptoms and signs of a
serious infection before identification of the bacteria and before susceptibility test results are available. Such treatment can be described as initial empirical therapy.

When choosing to use initial empirical therapy, clinicians should be aware that some patients with symptoms and signs of a serious infection do not, in fact, have an infection at all. Examples include patients with pulmonary edema or hemorrhage with radiologic appearances similar to those of ventilator-associated pneumonia (VAP) [8], as well as patients with cerebral hemorrhage, advanced cirrhosis, severe burns, malignancy, or autoimmune conditions with fever or hypotension (symptoms that normally would be expected in a severe infection). In these situations, antibiotic therapy creates an increased risk of disturbance of endogenous flora, potentially leading to Clostridium difficile infection or colonization with antibiotic-resistant bacteria [9, 10].

Habitual use of the same antibiotic regimen for all patients with suspected significant bacterial infection may lead to increased resistance [11] and/or increased rates of inadequate coverage. As described by Kollef [12], in this situation, inadequate initial empirical therapy is associated with increases in adverse patient outcomes.

Three methods can be used to increase the probability that initial empirical antibiotic choice will be adequate: (1) individualizing therapy on the basis of a formal review of previously isolated organisms and prior antibiotic use, (2) using unit-based antibiograms, and (3) using data from surveillance studies.

Use of data from surveillance studies. Masterton [13] outlined the various types of national and international antibiotic resistance surveillance programs in place and their role in informing antibiotic policy. At the individual patient level, these surveillance programs assist clinicians in ensuring that their antibiotic prescribing choices have a substantial probability of effectiveness. For example, antibiotic resistance surveillance programs indicate that, in most parts of the world, E. coli has a substantial likelihood of being resistant to ampicillin or amoxicillin [13]. Therefore, amoxicillin would be a poor empirical choice for treatment of an infection in which E. coli is a probable cause, such as urinary tract infection. National and international trends in antibiotic resistance, derived from sequential examination of surveillance data, can also alert clinicians to a need to reexamine their empirical antibiotic choices. For example, the emergence of substantial degrees of fluoroquinolone resistance in P. aeruginosa described in national surveillance studies [2] necessitates cautious use of fluoroquinolones as the sole therapy for infections such as VAP.

Individualizing initial empirical therapy. Every patient differs according to factors such as underlying comorbidities, severity of illness, type of infection, prior antibiotic use, allergies, and colonization with antibiotic-resistant organisms. Thus, it is reasonable to consider that these variables necessitate an individualization of initial empirical antibiotic therapy for every seriously ill patient. Infection type is a major determinant of the initial empirical regimen. Regimens aimed against gram-negative pathogens can be divided into those that require antipseudomonal therapy and those that do not. Infections in which P. aeruginosa is a pathogen that needs to be covered in initial empirical therapy include VAP, fever in neutropenic patients, and most cases of undifferentiated infection in critically ill patients. In contrast, skin and soft-tissue infections (including foot infection in diabetic patients), community-acquired pneumonia, community-onset intra-abdominal infections, and community-acquired bacterial meningitis do not typically require empirical antipseudomonal coverage [14–17]. There is also a need to consider whether therapy active against methicillin-resistant Staphylococcus aureus is necessary; the present article, however, pertains strictly to considerations regarding therapy against gram-negative bacilli.

β-Lactam, aminoglycoside, and fluoroquinolone antibiotics form the core antipseudomonal drugs. Aminoglycosides are rarely used as monotherapy, except in the treatment of urinary tract infection [18]. Studies performed >10 years ago showed that fluoroquinolones were as effective as β-lactam therapy for some infections with gram-negative bacilli, such as VAP [19]. However, most surveillance studies have shown that the resistance of gram-negative bacilli (especially P. aeruginosa) to fluoroquinolones has been increasing during the past decade [2]. Similarly, the resistance of P. aeruginosa and many Enterobacteriaceae to aztreonam is substantial [3]. Thus, β-lactam antibiotics have remained the most widely used antibiotics for initial empirical therapy, especially when P. aeruginosa may be present. Reasonable evidence suggests that 2 factors—recent receipt of antibiotics and colonizing flora—have a substantial effect on the adequacy of initial empirical therapy.

Bhat et al. [20] recently showed how such knowledge could be used to improve the adequacy of initial empirical therapy; after reviewing 158 episodes of serious infection with P. aeruginosa occurring in 140 intensive care unit (ICU) patients, they found that initial empirical antibiotic therapy was microbiologically adequate in only 67% of these episodes [20]. The rate of adequacy of initial empirical antibiotic choice could have been improved to 82% by universally recommending an antipseudomonal carbapenem (imipenem or meropenem) as the first-line choice. Routinely adding amikacin to the carbapenem would have improved the adequacy of the initial empirical antibiotic choice to 95%.

However, mathematical modeling suggests that homogeneity of antibiotic regimens is inferior to heterogeneity of antibiotic regimens. Thus, algorithms were developed in which piperacillin/tazobactam or cefepime could also be used as initial empirical antibiotic choices. (It is noteworthy that the addition of tazobactam to piperacillin does not add to piperacillin’s anti-
pseudomonal spectrum; however, it does add to its activity against class A β-lactamase–producing organisms [3].) Thirty-seven percent of patients who used piperacillin/tazobactam in the month before the current infection were now infected with a piperacillin/tazobactam-resistant strain, and 64% of patients who had isolation of piperacillin/tazobactam-resistant gram-negative bacilli in the month before the current infection were now infected with piperacillin/tazobactam-resistant P. aeruginosa. Therefore, piperacillin/tazobactam was considered to be appropriate initial empirical therapy only if, during the past month, the patient neither had received the antibiotic nor had isolation of a piperacillin/tazobactam-resistant organism. (The use of a 1-month cutoff for prior antibiotic use or prior isolation of resistant organisms was purely arbitrary; it is not known whether the use of other time periods would change the utility of this algorithm.) Comparable findings and recommendations were made with respect to cefepime. By use of this algorithm, antibiotic heterogeneity was maintained, because substantial proportions of patients used piperacillin/tazobactam, cefepime, or an antipseudomonal carbapenem as initial empirical therapy.

Use of unit-based antibiograms and combination antibiograms. Unit-based antibiograms are cumulative antibiotic susceptibility reports for patients in a particular ward of the hospital (for example, a specific ICU) in a specified time period. They are potentially more useful than international, national, or hospital-specific antibiograms for a prescriber making decisions about antibiotic therapy in a specific ICU. Unit-based antibiograms have been shown to have substantially different antibiotic susceptibility results, compared with those of hospital-wide antibiograms [21].

Traditional antibiograms provide data on the susceptibility of organisms to a range of antibiotics, but they do not answer the question of what antibiotic combinations may be optimal against any given organism. Combination antibiotic therapy is necessary as initial empirical antibiotic therapy for infections in which P. aeruginosa is prominent, such as VAP [22]. It is important to point out that combination therapy for P. aeruginosa infection does not prevent the emergence of resistance [23]. Its purpose is to maximize the possibility that the infecting organism will be “covered,” because, in most ICUs, <90% of P. aeruginosa strains are susceptible to any particular antipseudomonal β-lactam. A traditional antibiogram does not give data regarding what aminoglycoside or fluoroquinolone should be used in combination with a core antipseudomonal β-lactam (e.g., an antipseudomonal penicillin, cephalosporin, or carbapenem) to ensure that initial empirical coverage is optimized. Mizuta et al. [24] discussed the role of the “combination antibiogram” to address this question. A combination antibiogram provides information on the percentage of isolates susceptible to a particular antibiotic if the isolate is resistant to a core antipseudomonal antibiotic. For example, Bhat et al. [20] showed that, of the P. aeruginosa isolates resistant to cefepime in their institution, 19.5% were resistant to amikacin, 100% to aztreonam, 82.9% to ciprofloxacin, 43.9% to gentamicin, 87.8% to levofloxacin, and 39.0% to tobramycin. Therefore, combinations of cefepime plus amikacin would be much more likely to improve the adequacy of initial empirical antibiotic therapy than would a combination of cefepime plus a fluoroquinolone.

Unit-based, combination antibiograms can be constructed to complement individualized antibiotic choices. The following strategies should be used to optimize empirical antibiotic administration for seriously ill patients:

- Use unit antibiograms to determine potentially useful antibiotics, especially those active against P. aeruginosa (e.g., cefepime, ceftazidime, piperacillin/tazobactam, imipenem, doripenem, and meropenem, all of which have been found to be active in vitro against >80% of P. aeruginosa isolates from an ICU in the past 12 months).
- Determine antibiotics used by the patient in the past month and avoid these antibiotics as empirical therapy for the current infection (e.g., if piperacillin/tazobactam was used 2 weeks ago, avoid it for treating the current infection).
- Scrutinize past microbiological records to determine whether organisms have been isolated that are resistant to potentially useful antibiotics; avoid antibiotics that have not demonstrated in vitro activity against gram-negative bacilli isolated from the patient in the past month (e.g., if Enterobacter cloacae resistant to ceftazidime was isolated 2 weeks ago, avoid ceftazidime for the current infection).
- Use a local combination antibiotic to determine an optimal secondary antibiotic for the current infection. A combination antibiogram shows that, for example, if P. aeruginosa from the ICU is cefepime resistant, there is a 90% chance that it is susceptible to tobramycin but only a 30% chance that it is susceptible to ciprofloxacin; if P. aeruginosa from the ICU is resistant to an antipseudomonal carbapenem, then there is an 80% chance that it is susceptible to tobramycin but only a 40% chance that it is susceptible to ciprofloxacin, which leaves tobramycin as a sensible antibiotic choice for empirical combination therapy with cefepime or an antipseudomonal carbapenem.
- Optimize the dosing of the preferred antibiotic regimen on the basis of pharmacodynamic principles (e.g., if the preferred antibiotic regimen is tobramycin plus cefepime, the aminoglycoside should be dosed aiming for a high peak: MIC ratio and the β-lactam dosed as an extended infusion).

THE IMPORTANCE OF DOSE, FREQUENCY, AND DURATION IN OPTIMIZING THE REGIMEN

Once the decision regarding the choice of antibiotic regimen has been made, it is necessary to ensure that the dose, frequency...
of administration, and duration over which the antibiotic is infused are optimized. The product information of each antibiotic mentioned thus far gives some guidance for appropriate dosage regimens; however, some exceptions exist. For example, guidance regarding dosage regimens for patients receiving continuous renal replacement therapy typically is absent from approved product information. Furthermore, a few lines of evidence suggest that some adjustment of dosage regimens may optimize pharmacodynamic parameters and could potentially result in superior clinical outcomes [25]. At present, most of these data do not come from randomized controlled trials.

Lodise et al. [25] examined the impact of a novel dosing regimen of piperacillin/tazobactam on outcome. They compared the clinical outcomes of patients who received the antibiotic in doses of 3.375 g infused over 30 min every 4–6 h (conventional dosing) with those who received the antibiotic in doses of 3.375 g infused over 4 h every 8 h (extended-infusion dosing). Among patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of ≥17 who were infected with *P. aeruginosa*, 14-day mortality was significantly lower among those treated with the extended-infusion strategy than those given conventional dosing (12.2% vs. 31.6%; *P* = .04). These data come from a cohort study rather than a randomized controlled trial, but they do provide preliminary evidence to suggest that the dosing of piperacillin/tazobactam should be altered for seriously ill patients with suspected *P. aeruginosa* infection.

The product information for cefepime, approved by the US Food and Drug Administration, suggests a range of possible doses, from 0.5 g every 12 h to 2 g every 8 h, for patients with normal renal function. Dosing at the lower end of this range may be appropriate for urinary tract infection but is most likely inappropriate for patients with serious infections with organisms that may have cefepime MICs in the higher portion of the susceptible range. Specifically, *P. aeruginosa* and extended-spectrum β-lactamase–producing Enterobacteriaceae may have cefepime MICs of 8 μg/mL and yet may be reported by laboratories using Clinical and Laboratory Standards Institute breakpoints as cefepime susceptible. A recent analysis of 204 patients with bloodstream infection with gram-negative bacteria primarily treated with cefepime showed that patients infected with an organism with a cefepime MIC of 8 μg/mL had a 28-day mortality rate of 56.3%, compared with 24.1% for those with a cefepime MIC <8 μg/mL [26]. Pharmacodynamic assessments using Monte Carlo simulation suggest that dosing regimens of 1–2 g administered over 30 min every 12 h have a low probability of “target attainment” when the cefepime MIC is 8 μg/mL [26]. Again, these data do not come from a randomized trial but suggest that cefepime should be administered empirically at a dose of 2 g every 8 h or as an extended infusion, to adequately treat infection with *P. aeruginosa* and extended-spectrum β-lactamase–producing Enterobacteriaceae, which may have cefepime MICs as high as 8 μg/mL.

The antipseudomonal carbapenems (imipenem, meropenem, and doripenem) share with antipseudomonal penicillins the pharmacodynamic characteristic that best predicts antimicrobial activity—that is, the percentage of time during the dosing interval during which the serum concentration exceeds the MIC. As Nicolau and colleagues [27, 28] point out, Monte Carlo simulation predicts that extending the infusion duration of meropenem from 30 min to 3 h increases the probability of bactericidal target attainment. In a nonrandomized assessment, Lorente et al. [29] assessed outcomes of patients with VAP who were given meropenem by continuous infusion (1 g over 360 min every 6 h) or by 30-min infusions (1 g over 30 min every 6 h). The group receiving meropenem by continuous infusion had a clinical cure rate superior to that of the group receiving the 30-min infusions (cure rate, 90.5% vs. 59.6%; *P* <.001). Extended infusions of meropenem or imipenem are not approved by any regulatory agency. An extended-infusion dosing regimen for doripenem is currently under review by the US Food and Drug Administration.

**OPTIMIZING CHOICE FOR THERAPY WHEN THE ORGANISM IS KNOWN BUT SUSCEPTIBILITY DATA ARE NOT YET AVAILABLE**

When blood samples are collected for culture, they are placed in specialized equipment, which regularly assesses for changes in the bottle that are consistent with bacterial growth. If growth occurs (typically 8–24 h after the blood sample is collected for culture), microbiology technicians perform a Gram stain on the broth within the bottle and indicate the Gram stain appearance to the clinician. The broth is then plated onto solid media, incubated, and examined for growth after another 12–16 h. At this point, the microbiologist is usually able to differentiate *Pseudomonas*-like organisms from coliforms. Simple biochemical tests may be able to provide species identification (e.g., *E. coli*) at this point. However, most laboratories use semiautomated identification and susceptibility testing methodologies, which take another 8–16 h to provide results. Thereafter, final identification and susceptibility test results are typically available.

Close liaison with clinical microbiologists may allow clinical use of preliminary identification data. Antipseudomonal therapy must be ensured if *P. aeruginosa* is provisionally identified. An important role of the microbiology laboratory is to alert prescribers to the possibility of the presence of an organism not routinely covered by standard antipseudomonal therapy. For example, the provisional identification of *Stenotrophomonas maltophilia* should allow coverage of this organism with trimethoprim/sulfamethoxazole if a clinically significant infection is apparent. Earlier appropriate antibiotic therapy may be ini-
tiated for infection with multidrug-resistant epidemic organisms, such as carbapenem-resistant *A. baumannii* or KPC- or extended-spectrum β-lactamase–producing *K. pneumoniae*, if the characteristic phenotype of these organisms is observed on incubation of specimens on solid media [3]. Despite these not being final identifications or susceptibilities, a 24-h “head start” on the initiation of therapy with antibiotics not typically used as empirical therapy, such as colistin or trimethoprim/sulfamethoxazole, may provide some clinical benefit.

Direct susceptibility tests, although clearly not standardized, may also provide a similar benefit. Bouza et al. [30] performed a prospective trial in which patients with VAP were randomized into 2 groups: one group had conventional respiratory specimen culture results reported using standard procedures, whereas the intervention group had a rapid antibiotic susceptibility result obtained by the immediate placement of E-test strips (AB Biodisk) on respiratory tract samples. Patients in the group with rapid reporting of susceptibility testing had fewer days of fever, decreased antibiotic consumption, decreased rates of *C. difficile* infection, and fewer days of receiving mechanical ventilation. Rapid PCR-based identification methods for gram-negative bacilli are on the horizon [31], although the diversity and complexity of mechanisms of resistance are likely to make rapid determination of antibiotic resistance much more difficult.

**FINE TUNING THERAPY WHEN IDENTIFICATION AND SUSCEPTIBILITY DATA ARE COMPLETE**

When identification and susceptibility testing results are available to the clinician, antibiotic regimens can be fine tuned. Recommendations for antibiotic therapy for infections with a range of gram-negative organisms are listed in table 1. Even with the best efforts at optimizing initial empirical regimens, surprises sometimes occur, necessitating intensification of antibiotic therapy. The need for intensification of antibiotic therapy may imply a necessity for the use of salvage options, such as polymyxins or tigecycline. The polymyxins were developed in the 1950s, when knowledge of pharmacodynamics was undeveloped [32]. As a result, few assessments have been made of optimal dosing strategies for polymyxin B or colistin. Much-needed work is now proceeding in this area. Tigecycline has activity against some β-lactamase–producing organisms that are resistant to all β-lactam therapies [33]. This antibiotic has unusual pharmacokinetic properties, resulting in low blood concentrations but somewhat higher tissue levels. The utility of the drug must be considered suspect in therapy for bloodstream infections with organisms that have relatively high tigecycline MICs [34]. Evolution of resistance during therapy has been observed, raising further concerns about the drug [35]. The utility of tigecycline in therapy for serious infections, such as VAP, is not yet known.

In some circumstances, empirical antibiotic regimens may be broader than is required on the basis of antibiotic susceptibility testing. In this circumstance, de-escalation is required. Penicillins are appropriate antibiotics for de-escalation (e.g., from piperacillin/tazobactam to piperacillin for *P. aeruginosa* infections and from antipseudomonal β-lactams to ampicillin for some infections with *Enterobacteriaceae*). It is debatable whether it is appropriate to de-escalate to cephalosporins or fluoroquinolones, because these antibiotics are prone to cause considerable “collateral damage” [36]—that is, promoting resistance not only to that antibiotic but to other classes of antibiotics as well. An important consideration in de-escalation is assessment of the need to discontinue antibiotic therapy. Increasingly, clinical data suggest that many infections with gram-negative bacilli require a shorter duration of therapy than has historically been thought necessary [37].

In summary, clinicians should apply logic in their selection and use of antibiotics in treating severely ill patients, rather than using a “tradition-based” method of selecting treatment. Tradition is hard to break, but it results in patients receiving inappropriate antibiotics and contributes to the development of resistance in bacteria through increased selection pressure. Information is available with which to make a more logical choice of antibiotic, and closer liaison with a microbiologist

<table>
<thead>
<tr>
<th>Organism</th>
<th>Recommended therapy</th>
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<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Antipseudomonal β-lactam</td>
</tr>
<tr>
<td>ESBL-producing <em>Enterobacteriaceae</em></td>
<td>Carbapenem</td>
</tr>
<tr>
<td>Cefazidime resistant <em>Enterobacter cloacae</em></td>
<td>Fluoroquinolone, carbapenem, or cefepime</td>
</tr>
<tr>
<td>Carbapenem resistant <em>Acinetobacter baumannii</em></td>
<td>Colistin/polymyxin B, tigecycline, or ampicillin/sulbactam, depending on susceptibility and location of infection</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>Trimethoprim/sulfamethoxazole plus ticarcillin/clavulanate</td>
</tr>
</tbody>
</table>

**NOTE.** ESBL, extended-spectrum β-lactamase.
will greatly facilitate the decision-making process. Clinicians must be prepared to alter the dose and or infusion rates for certain patients, relying on evidence from small clinical trials to support such actions until they are confirmed in larger clinical trials.

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