REVIEW ARTICLE

CURRENT CONCEPTS

Hospital-Acquired Infections Due to Gram-Negative Bacteria

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Hospital-acquired infections are a major challenge to patient safety. It is estimated that in 2002, a total of 1.7 million hospital-acquired infections occurred (4.5 per 100 admissions),[1] and almost 99,000 deaths resulted from or were associated with a hospital-acquired infection,[1] making hospital-acquired infections the sixth leading cause of death in the United States[2]; similar data have been reported from Europe.[3] The estimated costs to the U.S. health care budget are $5 billion to $10 billion annually.[4] Approximately one third or more of hospital-acquired infections are preventable.[5]

Infections caused by gram-negative bacteria have features that are of particular concern. These organisms are highly efficient at up-regulating or acquiring genes that code for mechanisms of antibiotic drug resistance, especially in the presence of antibiotic selection pressure. Furthermore, they have available to them a plethora of resistance mechanisms, often using multiple mechanisms against the same antibiotic or using a single mechanism to affect multiple antibiotics (Fig. 1). Compounding the problem of antimicrobial-drug resistance is the immediate threat of a reduction in the discovery and development of new antibiotics.[6] Several factors have contributed to this decline, including the increasing challenges of screening for new compounds, the high capital costs and long time required for drug development, the growing complexity of designing and performing definitive clinical trials, and the concern about reduced drug longevity due to the emergence of resistance. As a consequence, a perfect storm has been created with regard to these infections: increasing drug resistance in the absence of new drug development.

TYPES OF INFECTIONS

Hospital-acquired infections are most commonly associated with invasive medical devices or surgical procedures. Lower respiratory tract and bloodstream infections are the most lethal; however, urinary tract infections are the most common.

Recent data from the U.S. National Healthcare Safety Network indicate that gram-negative bacteria are responsible for more than 30% of hospital-acquired infections, and these bacteria predominate in cases of ventilator-associated pneumonia (47%) and urinary tract infections (45%).[7] In intensive care units (ICUs) in the United States, gram-negative bacteria account for about 70% of these types of infections, and similar data are reported from other parts of the world.[8] A range of gram-negative organisms are responsible for hospital-acquired infections, the Enterobacteriaceae family being the most commonly identified group overall (see the table in the Supplementary Appendix, available with the full text of this article at NEJM.org). Unfortunately, multidrug-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase (ESBL)–producing or carba-

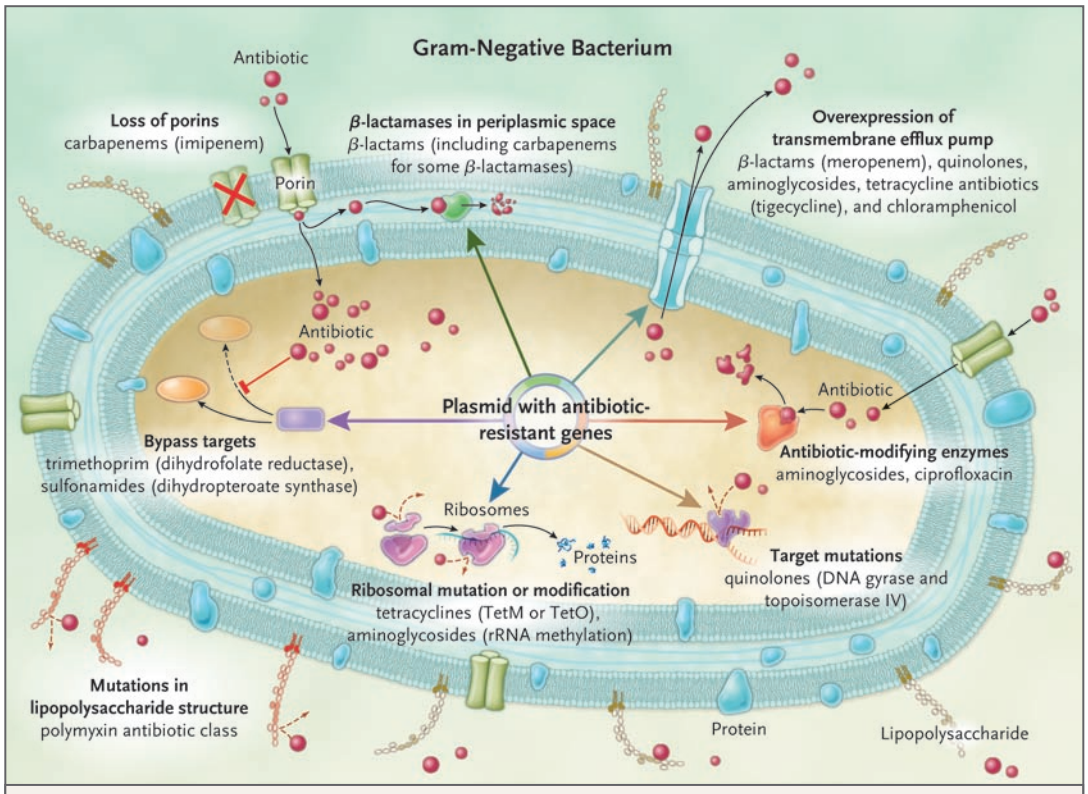

Figure 1. Mechanisms of Resistance in Gram-Negative Bacteria, and the Antibiotics Affected.

Seven mechanisms of resistance are shown in the gram-negative bacterium, with some being mediated by a mobile plasmid. These mechanisms include the loss of porins, which reduces the movement of drug through the cell membrane; the presence of β-lactamases in the periplasmic space, which degrades the β-lactam; increased expression of the transmembrane efflux pump, which expels the drug from the bacterium before it can have an effect; the presence of antibiotic-modifying enzymes, which make the antibiotic incapable of interacting with its target; target site mutations, which prevent the antibiotic from binding to its site of action; ribosomal mutations or modifications, which prevent the antibiotic from binding and inhibiting protein synthesis; metabolic bypass mechanisms, which use an alternative resistant enzyme to bypass the inhibitory effect of the antibiotic; and a mutation in the lipopolysaccharide, which renders the polymyxin class of antibiotics unable to bind this target. Red spheres indicate antibiotics.

penemase-producing Enterobacteriaceae, are increasingly being reported worldwide.

PNEUMONIA

Hospital-acquired pneumonia is the most common life-threatening hospital-acquired infection, and the majority of cases are associated with mechanical ventilation. Ventilator-associated pneumonia occurs in approximately 10 to 20% of patients who are on ventilators for longer than 48 hours and is associated with significant increases in length of hospital stay, mortality, and costs.[9] Gram-negative organisms predominate in hospital-acquired pneumonia, particularly *P. aeruginosa*, *A. baumannii*, and the Enterobacteriaceae.[8] Between 1986 and 2003, acinetobacter species were the only gram-negative organisms that increased significantly as a cause of pneumonia in ICUs in the United States.[8] Unfortunately, the resistance of these organisms to antibiotics, particularly to carbapenems, has posed important therapeutic challenges. In a recent survey, 26.4% of 679 *P. aeruginosa* isolates and 36.8% of 427 *A. baumannii* isolates that caused ventilator-associated pneumonia were resistant to carbapenems (imipenem or meropenem).[7] Similar data have been reported from other parts of the world, with countries such as Greece reporting rates of carbapenem resistance of up to 85% among ICU isolates.[10] Of greatest concern are reports of infections caused by organisms that are resistant to all currently available antibiotics, including the polymyxins.[11,12]

A more recent clinical entity that physicians need to be aware of is health care–associated

Table 1. Risk Factors for Health Care–Associated Infections and Infection with Drug-Resistant Bacteria.*

Risk factors for health care–associated infections
Hospitalization for ≥2 days in preceding 90 days
Residence in a nursing home or long-term care facility
Home infusion therapy, including antimicrobial agents
Long-term dialysis within 30 days
Home wound care
Family member with multidrug-resistant pathogen
Risk factors for infection with drug-resistant bacteria
Antimicrobial therapy in preceding 90 days
Current hospitalization for ≥5 days
High frequency of antibiotic resistance in the community or in the specific hospital unit
Immunosuppression

* Risk factors are from the Infectious Diseases Society of America and the American Thoracic Society guidelines.[15]

pneumonia — that is, cases of pneumonia acquired in the community by patients who have had direct or indirect contact with a health care or long-term care facility and are subsequently hospitalized. Such patients are more likely to have a coexisting illness and to receive inactive empirical antibiotic therapy and are at greater risk for death than patients who have true community-acquired pneumonia.[13,14] As a consequence, antibiotics with a broader spectrum of coverage — particularly those with activity against *P. aeruginosa*, other multidrug-resistant gram-negative bacilli, and drug-resistant *Staphylococcus aureus*[14] — should be considered for patients who have defined risk factors and who present to the emergency room with pneumonia (Table 1).[15,16] In order to minimize the overuse of broad-spectrum antibiotics, further research is required to determine the true predictive value of each of these risk factors for resistant bacteria.[17] Recent hospitalization or antibiotic exposure and residence in a long-term care facility should be considered the most important risk factors.

Apart from being associated with increased morbidity and mortality, suspected hospital-acquired pneumonia in the ICU can lead to the inappropriate use of antibiotic drugs, contributing to bacterial drug resistance and increases in toxic effects and health care costs. To optimize the appropriateness of antibiotic use, physicians must be aware of the management paradigms for hospital-acquired pneumonia (Table 2). The diagnosis of ventilator-associated pneumonia remains challenging, with no easily obtained reference standard. Apart from clinical criteria, microbiologic assessment is important to help guide therapy. For patients in whom ventilator-associated pneumonia is suspected, a sample from the lower respiratory tract should be obtained by means of endotracheal aspiration, bronchoalveolar lavage, or a protected specimen brush (depending on the resources available)[18,19] for microscopy and culture before antibiotics are administered. Although each sampling method has its limitations, the most important point is to obtain the sample in a timely manner. The alternative techniques appear to be associated with similar outcomes, on the basis of recent systematic reviews.[20,21] When the patient is severely ill, the administration of empirical antibiotic therapy should not be delayed on account of the diagnostic procedure.[15]

To assist the treating physician in determining whether a cultured organism signifies colonization or infection, it has been recommended that quantitative cultures be obtained, either by measuring the colony-forming units (CFU) per milliliter or by grading the bacterial growth as light, moderate, or heavy (semiquantified approach). In bronchoalveolar-lavage fluid, a cutoff value of less than 10^4 CFU per milliliter is more likely to indicate colonization; however, this information needs to be interpreted on the basis of the patient's clinical state. Quantitative culture results are subject to possible sampling variability, and there is no evidence that quantitative cultures, as compared with qualitative cultures, are associated with reductions in mortality, the length of the ICU stay, the duration of mechanical ventilation, or the need to adjust antibiotic therapy.[20] Nevertheless, quantitative cultures are more helpful in differentiating between colonization and true infection and thus are less likely to lead to unnecessary antibiotic therapy. To further improve such differentiation in patients with ventilator-associated pneumonia, promising biomarkers are being studied in combination with clinical and microbiologic factors. These biomarkers include procalcitonin, C-reactive protein, and soluble triggering receptor expressed on myeloid cells (sTREM-1).[22,23]

Once a diagnosis of pneumonia has been made, empirical antibiotic therapy needs to be tailored to

the institution's microbial ecology and the length of time the patient was in the hospital before pneumonia developed. With a hospital stay of 5 days or longer, as compared with a shorter stay, the patient is at greater risk for infection with more resistant pathogens, and empirical treatment with broad-spectrum antimicrobial agents should be prescribed (see discussion of treatment below). Growing evidence suggests that early, appropriate antibiotic therapy improves outcomes,[24,25] and such therapy should therefore be a goal; however, this strategy needs to be coupled with an early reassessment of both diagnosis and therapy, usually within 48 to 72 hours. In the majority of cases, the antibiotic coverage can then be reduced to a more targeted regimen based on the results of respiratory cultures or even discontinued, if an alternative diagnosis is identified.[26] When respiratory cultures are not available, therapy needs to be tailored to the most likely causative organisms for the given institution, with close monitoring for clinical failure, recently defined as lack of improvement in the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen and persistence of fever after 3 days of treatment.[27]

When definitive antibiotic therapy is warranted, a relatively short course (8 days) should be prescribed for patients with uncomplicated ventilator-associated pneumonia who receive appropriate antibiotic therapy initially.[28] For patients infected with nonfermenting gram-negative organisms such as *P. aeruginosa*, however, the rate of relapse is higher with short-course therapy, and thus the longer course of therapy (15 days) should be prescribed. Finally, the importance of preventive measures for ventilator-associated pneumonia deserves specific mention, particularly a bundled approach (Table 3).[5] Institutions that adhere to such measures report a significant reduction in the rates of ventilator-associated pneumonia.[9]

Table 2. Diagnostic Criteria and Management Guidelines for Ventilator-Associated Pneumonia.*

Diagnostic criteria
Presence of a new or progressive infiltrate on chest radiography and two of the following three clinical features:
Temperature >38°C (100.4°F)
Leukocytosis or leukopenia
Purulent respiratory secretions
Positive respiratory culture
For quantitative cultures, a bacterial density of at least
10^6 CFU/ml for an endotracheal aspirate
10^4 CFU/ml for a bronchoalveolar-lavage specimen
10^3 CFU/ml for a protected-specimen brush
For semiquantitative cultures, at least moderate growth of bacteria
Key management steps
Make the appropriate diagnosis
Use local antimicrobial-susceptibility data and the length of the hospital stay before pneumonia developed to determine the most effective empirical antibiotic coverage
Reassess the patient and recheck culture results at 48 to 72 hours, with the goal of tailoring antibiotic therapy to the susceptibilities of the cultured bacteria
Initiate a short course of therapy (8 days) for most organisms with the exception of nonfermenting gram-negative organisms (e.g., *Pseudomonas aeruginosa*), for which a course of 15 days is recommended
Implement a bundled prevention program for ventilator-associated pneumonia

* CFU denotes colony-forming units.

BLOODSTREAM INFECTION

Infection of the bloodstream remains a life-threatening occurrence and is most commonly associated with the presence of a central vascular catheter but may also be associated with a gram-negative infection in other areas of the body, such as the lung, genitourinary tract, or abdomen. Approximately 30% of hospital-acquired bloodstream infections in ICUs in the United States are due to gram-negative organisms,[8] although this proportion is lower when hospital-wide data are examined.[7]

Given an adequate portal of entry, almost any gram-negative organism can cause bloodstream infection; however, the most common organisms include klebsiella species, *Escherichia coli*, enterobacter species, and *P. aeruginosa*. As described above for organisms that cause hospital-acquired pneumonia, resistance is an emerging problem, particularly resistance against extended-spectrum cephalosporins and carbapenems. For example, of bloodstream isolates of *Klebsiella pneumoniae* from hospitals throughout the United States, 27.1% (from 483 isolates tested) were resistant to third-generation cephalosporins and 10.8% (from 452 isolates tested) were resistant to carbapenems.[7] Higher rates of resistance are reported from parts of Europe.[10]

The most recent challenge has been the spread

Table 3. Evidence-Based Guidelines for the Prevention of Hospital-Acquired Infections.*

Ventilator-Associated Pneumonia	Central Venous Catheter–Associated Bloodstream Infection	Catheter-Associated Urinary Tract Infection
Follow effective hand-hygiene procedures	Before insertion, educate health care personnel involved with central venous catheterization about prevention of infection	Implement written catheter-care protocols, including guidelines on catheter insertion
Educate health care personnel who care for patients on ventilators about the local epidemiology of VAP, risk factors, and outcomes	Use a catheter-insertion checklist to ensure adherence to infection-prevention practices	Insert urinary catheter only when necessary and leave in only as long as indicated
Implement policies and practices for disinfection, sterilization, and maintenance of respiratory equipment according to evidence-based standards[29]	Follow hand-hygiene procedures before catheter insertion or manipulation	Consider other methods for management, including condom catheters or in-and-out catheterization, as appropriate
Provide regular antiseptic oral care according to product guidelines	Avoid use of the femoral vein in adults	Maintain a sterile, continuously closed drainage system
Ensure that patient is in a semirecumbent position, unless contraindicated	Use an all-inclusive catheter kit and maximal sterile-barrier precautions during catheter insertion	Do not disconnect the catheter and drainage tube unless the catheter must be irrigated
Use noninvasive ventilation in appropriately selected patients with respiratory failure†	Use a chlorhexidine-based antiseptic for skin preparation in patients >2 mo of age	Maintain unobstructed urine flow
Conduct active surveillance for VAP and institute preventive measures	After insertion, disinfect catheter hubs, needleless connectors, and injection ports before accessing the catheter; remove nonessential catheters	Empty the collecting bag regularly, using a separate collecting container for each patient, and take care not to let the drainage spigot touch the collecting container
In hospitals with suboptimal infection control using basic practices, use an endotracheal tube with in-line and subglottic suctioning for all eligible patients	For nontunneled catheters in adults, change transparent dressings and perform site care with a chlorhexidine antiseptic every 5 to 7 days (every 2 days for gauze dressings), or more frequently if dressing is soiled, loose, or damp‡	Cleaning the meatal area with antiseptic solutions is unnecessary; routine hygiene is appropriate
	Replace administration sets not used for blood products or lipids at intervals not longer than 96 hr	Do not routinely use silver-coated or other antibacterial catheters
	Use antimicrobial ointments for hemodialysis-catheter insertion sites	Do not screen for asymptomatic bacteriuria in catheterized patients
	Perform surveillance for bloodstream infection	Avoid catheter irrigation if possible
	In hospitals with suboptimal infection control using basic practices, bathe ICU patients >2 mo of age with a chlorhexidine preparation daily, use antiseptic-impregnated or antimicrobial-impregnated catheters for adult patients, use chlorhexidine-containing sponge dressings in patients >2 mo of age, and use antimicrobial locks for central venous catheters	Do not use systemic antibacterial agents routinely as prophylaxis

* These guidelines have been adapted from recent guidelines published by professional societies and organizations committed to improving patient safety and quality of care.[5] We report only those strategies with grade I quality of evidence (i.e., from one or more properly randomized, controlled trials) or grade II quality of evidence (i.e., from one or more well-designed, nonrandomized clinical trials). ICU denotes intensive care unit, and VAP ventilator-associated pneumonia.

† This strategy is considered grade I in the American Thoracic Society guidelines[15] but grade III in the guidelines published more recently by the collaborative group of societies and organizations.[5]

‡ Central venous or arterial catheters should not be routinely replaced.

of carbapenemase-producing Enterobacteriaceae.[30] The β-lactamase responsible for this phenotype, also known as *K. pneumoniae* carbapenemase, or KPC, confers reduced susceptibility to all cephalosporins (including cefepime), monobactams (aztreonam), and the carbapenems.[30] Carbapenemase-producing Enterobacteriaceae have now been identified in hospitals in at least 20 states in the United States, as well as in other parts of the world, including South America, Israel, China, and, less commonly, Europe.[30] The genetic relatedness of the strains responsible for outbreaks within and between countries highlights the importance of strict infection control to prevent ongoing dissemination.[31] These β-lactamases are encoded on mobile genetic elements, mostly plasmids and transposons, which probably explains their spread among gram-negative genera. Furthermore, they often coexist with other resistance genes, including the most widespread of the ESBLs (the $bla_{\text{CTX-M-15}}$ gene), aminoglycoside-resistance determinants, and plasmid-mediated quinolone-resistance genes (*qnrA* and *qnrB*),[30] thus leaving the physician with few therapeutic options. As has been described for the nonfermenting gram-negative organisms, *K. pneumoniae* strains that are resistant to all currently available antibiotics, including the polymyxins, have been reported.[10]

As with hospital-acquired pneumonia, delays in the administration of appropriate antibiotic therapy are associated with excess mortality among patients with hospital-acquired bloodstream infection,[32] although the data reflect predominantly gram-positive infections. Data on the clinical effect of initial therapy for gram-negative bloodstream infection are more heterogeneous. Empirical antibiotic coverage for gram-negative bacteria should be considered for patients who are immunosuppressed, those in the ICU, those with a femoral catheter, those with gram-negative bacterial infection at another anatomical site (particularly the lung, genitourinary tract, or abdomen), and those with other risk factors for resistant organisms (Table 1). Moreover, patients who present at the hospital with suspected bloodstream infection who have health care–associated risk factors should be treated initially with broad-spectrum empirical antibiotics, pending the results of blood cultures.[33] Detailed guidelines for the management of central vascular catheter–related bloodstream infections have recently been published.[34]

Prevention of bloodstream infections associated with central catheters is of paramount importance. Adherence to evidence-based interventions has proved highly successful (Table 3),[35] and hospitals worldwide should be adopting such cost-effective, preventive measures. Evidence is also emerging in support of other interventions, such as the use of catheters impregnated with an antiseptic, an antibiotic, or both[36] or the use of chlorhexidine-impregnated dressings[37]; however, when the described interventions for best practice are adhered to, the cost-effectiveness of these interventions is less clear.

URINARY TRACT INFECTION

Gram-negative organisms predominate in hospital-acquired urinary tract infections, almost all of which are associated with urethral catheterization. After the second day of catheterization, it is estimated that the risk of bacteriuria increases by 5 to 10% per day. The majority of cases of bacteriuria are asymptomatic, and the most effective management is removal of the catheter rather than antibiotic treatment. In rare cases, local and systemic complications ensue, and antibiotic treatment should be initiated for asymptomatic bacteriuria in patients who are about to undergo urologic surgery or implantation of a prosthesis.[38] Such therapy should also be considered in immunocompromised patients. Bloodstream infection appears to be a well-defined but rare complication of catheter-associated urinary tract infection.[39]

Recent U.S. data indicate that *E. coli* is the most common etiologic gram-negative organism, followed in descending order of frequency by *P. aeruginosa*, klebsiella species, enterobacter species, and *A. baumannii*.[7] Uropathogenic *E. coli* strains infect the urinary tract through a range of mechanisms, including specialized adhesins, fimbriae, biofilm, and aversion of host responses.[40] The emergence of resistance to quinolones and extended-spectrum cephalosporins remains a considerable challenge, since these agents are often used as first-line therapy. Traditionally, the SHV-type and TEM-type ESBLs have predominated among hospital-acquired organisms, and this is still the case in the United States. The epidemiology of ESBLs is changing, however, and CTX-M–type ESBLs are becoming more common worldwide. In particular, CTX-M-15 is the most widespread, and this β-lactamase has frequently been associated with a uropathogenic *E. coli* clone

Table 4. Recommended Empirical Therapy to Cover Gram-Negative Organisms That Cause Hospital-Acquired Infections.*

Hospital-Acquired Infection	Recommended Therapy and Dosage
Hospital-acquired pneumonia (includes VAP and HCAP)	
Length of hospital stay <5 days before pneumonia developed†	One of the following regimens: ceftriaxone, 1 g given intravenously every 24 hr; ampicillin–sulbactam, 3 g given intravenously every 6 hr; levofloxacin, 750 mg given orally or intravenously every 24 hr; moxifloxacin, 400 mg given orally or intravenously every 24 hr; or ertapenem, 1 g given intravenously every 24 hr
Length of hospital stay ≥5 days before pneumonia developed or diagnosis of HCAP	One of the following antipseudomonal β-lactam regimens: cefepime, 2 g given intravenously every 12 hr; ceftazidime, 2 g given intravenously every 8 hr; piperacillin–tazobactam, 4.5 g given intravenously every 6–8 hr; ticarcillin–clavulanate, 3.1 g given intravenously every 6 hr; meropenem, 1–2 g given intravenously every 8 hr; imipenem, 500 mg given intravenously every 6 hr; doripenem, 500 mg given intravenously every 8 hr or as a 1-hr or 4-hr infusion; or aztreonam, 1 g given intravenously every 8 hr‡ Plus one of the following regimens: ciprofloxacin, 400 mg given intravenously every 8–12 hr; levofloxacin, 750 mg given intravenously every 24 hr; gentamicin or tobramycin, 5–7 mg/kg of body weight given intravenously every 24 hr; or amikacin, 15–20 mg/kg given intravenously every 24 hr
Bloodstream infections (including health care–associated infections)	Same as for hospital-acquired pneumonia
Catheter-associated urinary tract infection	One of the following regimens: cefepime, 1 g given intravenously every 12 hr; ceftazidime, 1 g given intravenously every 8 hr; piperacillin–tazobactam, 3.75 g given intravenously every 8 hr; meropenem, 500 mg given intravenously every 8 hr; imipenem, 500 mg given intravenously every 8 hr; aztreonam, 500 mg given intravenously every 8 hr‡; ciprofloxacin, 400 mg given orally or intravenously every 12 hr; or gentamicin, 5 to 7 mg/kg given intravenously every 24 hr

* Therapy for staphylococcus or legionella species, which may also require initial empirical coverage, is not described in this article. These recommendations are based on the treatment of adults with normal renal function.[15] HCAP denotes health care–associated pneumonia, and VAP ventilator-associated pneumonia.
† These recommendations apply when there are no risk factors for a multidrug-resistant pathogen.
‡ Aztreonam is an alternative for patients who are allergic to β-lactams except when allergy is to ceftazidime, in which case a cross-reaction with aztreonam can occur.

known as sequence type 131.[41] Unfortunately, the plasmids carrying these ESBL genes often carry resistance determinants targeting fluoroquinolones as well. To reduce the morbidity associated with hospital-acquired urinary tract infections and prevent the dissemination of drug-resistant gram-negative organisms, adherence to evidence-based prevention guidelines is strongly recommended (Table 3). Until further data are available, we do not recommend the use of antibiotic-impregnated or silver-coated urinary catheters.

TREATMENT OPTIONS

The importance of knowing local antimicrobial susceptibility to direct empirical antibiotic therapy cannot be overemphasized. Recommendations regarding empirical therapy for the hospital-acquired infections discussed here and definitive therapy for infections caused by drug-resistant gram-negative organisms are presented in Tables 4 and 5, respectively.

The polymyxins (colistin and polymyxin B) are an older antibiotic class that has seen a resurgence of use in recent years and deserves mention. Discovered in the late 1940s, polymyxins have specificity for lipopolysaccharides on the outer cell membrane of gram-negative bacteria. Organisms inherently resistant to polymyxins include serratia, proteus, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and flavobacterium. Their use was initially hampered by nephrotoxicity and then rapidly declined with the advent of newer antibiotics. However, this class of antibiotic has been reinstated as a key therapeutic option for carbapenem-resistant organisms, particularly *P. aeruginosa*, *A. baumannii*, and carbapenemase-producing Enterobacteriaceae (Table 4). It is still a challenge to determine the appropriate dosage, since the polymyxins were never subjected to the rigorous drug-development process we now expect for new antimicrobial agents.[42] Despite in vitro data suggesting that colistin's antimicrobial activity is de-

Table 5. Recommended Definitive Therapy for Serious Infections, Including VAP and Bloodstream Infections, Caused by Drug-Resistant Gram-Negative Bacteria.*

Drug-Resistant Pathogen	Recommended Therapy
Extended-spectrum β-lactamase–producing Enterobacteriaceae	Meropenem, 1–2 g given intravenously every 8 hr; or imipenem, 500 mg given intravenously every 6 hr; doripenem, 500 mg given intravenously every 8 hr or as a 1-hr or 4-hr infusion
Carbapenemase-producing Enterobacteriaceae	Colistin, 2.5–5.0 mg of colistin base/kg of body weight/day given in 2 to 4 divided doses† (equivalent to 6.67–13.3 mg of colistimethate sodium/kg /day); or tigecycline, 100 mg given intravenously as a loading dose, then 50 mg given intravenously every 12 hr
Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*	For *P. aeruginosa*: Colistin as for carbapenemase-producing Enterobacteriaceae For *A. baumannii*: Colistin as for carbapenemase-producing Enterobacteriaceae; or ampicillin–sulbactam, up to 6 g of sulbactam given intravenously per day; or tigecycline, 100-mg intravenous loading dose, then 50 mg given intravenously every 12 hr‡ Possible alternatives: Extended infusion of meropenem, 1–2 g given as an intravenous infusion over a 3-hr period every 8 hr; of doripenem, 500 mg–1 g given as an intravenous infusion over a 4-hr period every 8 hr; or of imipenem, 1 g given as an intravenous infusion over a 3-hr period every 8 hr; combination therapy with a nontraditional antibiotic, including rifampin, minocycline or doxycycline, or azithromycin§ For pneumonia: Nebulized colistimethate sodium, 1 million to 3 million IU/day in divided doses (diluted in sterile normal saline), administered with a conventional nebulizer; or nebulized aminoglycosides

* The bacteria listed here are often resistant to fluoroquinolones and aminoglycosides; however, these agents can be used if the bacteria are susceptible to them.
† This regimen is based on the current parenteral formulation in the United States (Coly-Mycin M Parenteral [Parkdale Pharmaceuticals]).
‡ This regimen would not be recommended for bloodstream infection, owing to low serum drug levels.
§ Use of these antibiotics is based on in vitro data and animal models and on clinical case reports and studies of small series of patients.

pendent on the peak blood concentration and that its effectiveness could be enhanced by once-daily administration, selection for colistin-resistant mutants, regrowth, and increased toxicity in an animal model have been reported with this dosing frequency.[43,44] Therefore, two to four divided doses per day are currently recommended.

Recently licensed agents with activity against gram-negative bacteria include tigecycline, which is a parenteral glycylcycline antibiotic, and doripenem, which is a parenteral carbapenem that appears to have activity similar to that of meropenem. Tigecycline, a minocycline derivative with a broader spectrum of activity, is approved for the treatment of complicated skin, soft-tissue, and intraabdominal infections. In vitro activity of tigecycline against a range of troublesome gram-negative organisms, including ESBL-producing and carbapenemase-producing Enterobacteriaceae, acinetobacter species, and *Stenotrophomonas maltophilia*, has been reported (*P. aeruginosa* and proteus species are intrinsically resistant to the drug). Clinical experience with treating these multidrug-resistant bacteria remains limited, however. The urine concentrations of tigecycline are low, so it is not suitable for the treatment of urinary tract infections. Furthermore, it was shown to be inferior to imipenem–cilastatin for the treatment of ventilator-associated pneumonia in a randomized, double-blind trial.[45] Given its rapid movement from the bloodstream into tissues after administration, peak tigecycline serum levels are low (0.63 μg per milliliter) with standard dosing (a 100-mg loading dose followed by 50 mg every 12 hours). Thus, its use for bloodstream infection due to organisms with a minimum inhibitory concentration of 1 μg per milliliter or more also remains limited and requires caution.[46]

There is still much debate about the role of combination therapy versus monotherapy for gram-negative infections. The results of earlier studies and meta-analyses are difficult to interpret, but more recent evidence is starting to clarify this issue. For empirical treatment, combination therapy improves the likelihood that a drug with in vitro activity against the suspected organism is being administered (often defined as appropriate therapy).[47] This effect is more pronounced in institutions with a greater prevalence of multidrug-resistant organisms. The antibiotics selected for the combination, however, need to be tailored to local susceptibility data, because the benefits can be lost in the presence of high cross-resistance, such as to fluoroquinolones and third-generation cephalosporins. When the antibiotic susceptibili-

ties of the infecting organism are known, monotherapy and combination therapy have similar outcomes, including rates of emergence of resistance and recurrence of infection.[48] Exceptions include monotherapy with aminoglycosides for *P. aeruginosa*, which is inferior to any other monotherapy regimen, and possibly monotherapy for patients who have cystic fibrosis. Therefore, we recommend institution-tailored combination therapy for the empirical treatment of serious hospital-acquired gram-negative infections, followed by de-escalation to monotherapy once susceptibilities have been determined. Although clinicians have historically preferred dual therapy for serious pseudomonal infections, the data support single-agent therapy as long as an active β-lactam can be chosen.

Other strategies currently used to treat multidrug-resistant gram-negative infections include prolonged infusion (3 to 4 hours) or continuous infusion of β-lactams and aerosolized antibiotics for the treatment of ventilator-associated pneumonia. These strategies are particularly useful for infections caused by multidrug-resistant organisms (Table 5). For example, according to pharmacokinetic and pharmacodynamic data in hospitalized patients, prolonging the infusion of β-lactams such as cefepime, piperacillin–tazobactam, and the carbapenems significantly improves bactericidal target attainment (i.e., time above the minimum inhibitory concentration for at least 50% for cefepime and piperacillin–tazobactam and 40% for the carbapenems), especially for organisms with an elevated minimum inhibitory concentration (8 to 16 μg per milliliter).[49] Furthermore, the emergence of resistance has been prevented in in vitro models.[50] Clinical data for extended-infusion β-lactams remain sparse, with some retrospective studies showing improved outcomes, but results of prospective trials are less consistent. Nebulized antibiotics such as tobramycin, amikacin, and colistimethate sodium attempt to minimize systemic toxicity and improve drug delivery at the site of infection. For severe or refractory cases of pneumonia or those caused by highly drug-resistant organisms, nebulized antibiotics given as an adjunct to systemic antibiotics should be thought of as a therapeutic option (Table 5). Respiratory toxicity such as bronchospasm has been reported and may be diminished or prevented by the administration of bronchodilators before dosing. Moreover, a recent Food and Drug Administration alert informed physicians about the importance of using aerosolized colistimethate sodium soon after preparation to prevent lung toxicity from the active colistin form. Prospective studies should be focused on determining the clinical benefits and safety of nebulized antibiotics and extended-infusion β-lactams, especially for infections caused by nonfermenting gram-negative bacteria.

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