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Antimicrobial Resistance in Hospital-Acquired Gram-Negative Bacterial Infections

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Aerobic gram-negative bacilli, including the family of Enterobacteriaceae and non-lactose fermenting bacteria such as *Pseudomonas* and *Acinetobacter* species, are major causes of hospital-acquired infections. The rate of antibiotic resistance among these pathogens has accelerated dramatically in recent years and has reached pandemic scale. It is no longer uncommon to encounter gram-negative infections that are untreatable using conventional antibiotics in hospitalized patients. In this review, we provide a summary of the major classes of gram-negative bacilli and their key mechanisms of antimicrobial resistance, discuss approaches to the treatment of these difficult infections, and outline methods to slow the further spread of resistance mechanisms. CHEST 2015; 147(5):1413-1421

ABBREVIATIONS: CRE = carbapenem-resistant Enterobacteriaceae; ESBL = extended-spectrum β-lactamase; FDA = US Food and Drug Administration; KPC = *Klebsiella pneumonia* carbapenemase

Mutations that confer antibiotic resistance to bacteria are evolutionarily ancient and widespread in nature, having arisen in response to selection pressures that predate human activity.[1,2] These resistance mechanisms have found a permissive niche in the modern hospital environment, where a high density of susceptible patients, intense selection pressure for antibiotic resistance, and manifold opportunities for transmission intersect. Antimicrobial resistance rates are highest in ICUs because of antibiotic overuse, imperfect isolation practices, and prolonged stays of patients who are highly susceptible to nosocomial infections because of comorbidities and the use of indwelling devices, such as endotracheal and nasogastric tubes, urinary catheters, and central venous catheters.[3] The clonal spread of resistant organisms among geographically distant regions has added further momentum to the explosive rise in antibiotic resistance in recent years.[4,5] This global spread of antimicrobial resistance is fueled by poor hygiene and common use of over-the-counter antibiotics in developing countries, veterinary practices that overuse antibiotics, and the frequency of international travel.[6,7]

As a group, aerobic gram-negative bacilli are the most common causes of nosocomial infections and the most common causes of infection in the ICU,[3] including most cases of hospital-acquired pneumonia and urinary tract infections and 25% to 30% of

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bloodstream and surgical site infections.[8-10] A subset of gram-negative bacilli, the Enterobacteriaceae are part of the normal commensal flora of the human gut and, in the context of acute illness, asymptomatically colonize the upper aerodigestive tract and skin in most hospitalized patients and nearly all critically ill individuals. Once established as colonizers, these organisms cause hospital-acquired infections from microaspiration or their introduction into sterile sites; in addition, the colonizing bacteria are progressively displaced by antibiotic-resistant strains in the ICU setting.[11] Gram-negative bacilli possess multiple modes of antibiotic resistance and are highly efficient in horizontally transferring them between species. The dramatic increase in antibiotic resistance among gram-negative bacteria in recent decades was identified by the Centers for Disease Control and Prevention as among the most important threats to human health worldwide (Table 1).[12]

The Pathogens

The most common causes of nosocomial gram-negative infections are members of the family Enterobacteriaceae, which can grow in the presence of bile salts and use lactose as an energy source on MacConkey's agar. In contrast, gram-negative bacilli that cannot use lactose (the so-called "non-lactose fermenters") include, most prominently, *Pseudomonas* and *Acinetobacter* species, as well as less common organisms *Stenotrophomonas, Burkholderia*, and *Achromobacter* species. Because *Pseudomonas* infections were the subject of reviews in this journal,[13,14] we will discuss the other pathogens in this section.

Enterobacteriaceae are part of the resident microbiota of the mammalian intestinal tract and include multiple genera (eg, *Enterobacter*, *Citrobacter*, *Escherichia coli*, *Klebsiella*, *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia*). As part of the normal response to systemic illness, they colonize the upper aerodigestive tract and can then be transmitted via hand carriage and fomites. Aspiration of colonizing pharyngeal Enterobacteriaceae result in nosocomial and, less commonly, community-acquired pneumonia, and the introduction of skin organisms into sterile sites can cause infections of the urinary tract, surgical sites, and venous catheters.[15-18] According to the National Healthcare Safety Network, from 2009 to 2010, *E coli* (accounting for 12% of hospital-acquired infections), *Klebsiella pneumonia* and *Klebsiella oxytoca* (8%), *Pseudomonas aeruginosa* (8%), and *Enterobacter* species (5%) were, in descending order, the most common causes of gram-negative nosocomial infections in the United States.[9] The global pandemic of antimicrobial resistance among Enterobacteriaceae in the past 2 decades has been, in large part, caused by the emergence and dissemination of extended-spectrum β-lactamases (ESBLs) and carbapenemases in these organisms,[19] as discussed later in this review.

TABLE 1] Estimated Incidence and Mortality of Selected Antibiotic-Resistant Gram-Negative Pathogens in the United States

Organism	Annual No. of Cases	Annual Deaths
Carbapenem-resistant Enterobacteriaceae	9,300	610
Extended-spectrum β-lactamase producing Enterobacteriaceae	26,000	1,700
Multidrug resistant *Acinetobacter* species	7,300	500
Multidrug resistant *Pseudomonas aeruginosa*	6,700	440

Adapted from the Centers for Disease Control and Prevention.[12]

Acinetobacter species are encapsulated, nonmotile, aerobic coccobacilli that are nonfermenters of lactose. The majority of infections are caused by the *Acinetobacter calcoaceticus-baumannii* complex, which includes the *Acinetobacter baumannii*, *Acinetobacter calcoaceticus, Acinetobacter nosocomialis*, and *Acinetobacter pittii* genotypes.[20] *Acinetobacter* species are important causes of nosocomial infections and also cause community-acquired pneumonia and soft tissue infections in warm and humid climates. The National Nosocomial Infection Surveillance System implicated *Acinetobacter* species in 7% of nosocomial pneumonias and 2% each of nosocomial blood stream, surgical site, and urinary tract infections in ICUs in the United States in 2003.[21] Importantly, *Acinetobacter* was the only gram-negative bacillus that increased significantly in incidence as a cause of ventilator-associated pneumonia compared with 1986. In the SENTRY study from January 2009 to December 2011, *Acinetobacter* species were implicated in 7% of ICU infections in the United States and Europe.[22] Infections with *Acinetobacter* are an independent risk factor for death and carry a crude mortality rate of 30% to 75%, which is partly attributable to comorbidities of the hosts and incorrect choices of antimicrobial therapy.[20,23-25] Regarding the latter factor, a study of *A baumannii* isolates from 803 US health-care facilities noted that 60% were resistant to three classes of antibiotics and 34% to four classes.[26]

Apart from *Acinetobacter* and *Pseudomonas* species, several less common non-lactose-fermenting gram-negative pathogens can cause significant nosocomial infections in the ICU environment. *Stenotrophomonas maltophilia (*previously classified in the *Pseudomonas* and subsequently the *Xanthomonas* genus) is an important cause of nosocomial pneumonia and bacteremia, particularly in immunocompromised hosts.[27] The mortality rate of *Stenotrophomonas* infections is close to 40%, with 100% mortality reported in nosocomial pneumonia in immunocompromised hosts.[28,29] The *Burkholderia cepacia* complex, best recognized as causing respiratory infection in patients with cystic fibrosis, consists of 17 closely related species.[30] These organisms can cause nosocomial outbreaks of pneumonia and bacteremia in critically ill patients without cystic fibrosis,[31] and are sometimes associated with contaminated medications and toiletries.[32,33] *Achromobacter xyloxidans (*previously classified as *Alcaligenes* species) is ubiquitous in water environments but is an uncommon nosocomial pathogen, causing pneumonia, bacteremia, and catheter-associated infections that disproportionately afflict immunocompromised patients with underlying malignancy.[34,35] It, like *Burkholderia*, has been isolated from aqueous solutions used in health-care facilities, including IV and dialysis solutions, and it can colonize medical equipment.[36]

Resistance Mechanisms

Disruption of β-lactam rings of antibiotics by enzymatic hydrolysis is the most common resistance mechanism among gram-negative bacilli. More than 900 individual bacterial β-lactamase enzymes have been described. β-lactamases are categorized into classes A to D based on molecular structure, and functionally into groups 1 to 3 based on the antibiotic they degrade (Table 2).[37] In the latter system, group 1 β-lactamases are encoded in the chromosomes of many gram-negative bacilli; they are more active against cephalosporins and aztreonam than penicillins but are only active against carbapenems at high concentrations. Group 2 enzymes, the serine β-lactamases, are the largest and most structurally diverse group of β-lactamases, many of which are encoded by plasmids and are, therefore, readily transmissible between species. Group 2 enzymes include several penicillinases inhibited by β-lactamase inhibitors, such as sulbactam, clavulanic acid, or tazobactam; the ESBLs (discussed subsequently); enzymes that hydrolyze extended-spectrum cephalosporins; and most recently, the serine carbapenemases. Group 3 enzymes, the metallo-β-lactamases, are distinguished from other β-lactamases by their requirement for zinc at their enzymatic binding site. These enzymes are potent hydrolyzers of carbapenems and are not inhibited by β-lactamase inhibitors. Group 3 enzymes were first described as chromosomal genes in nonfermenting bacteria but, in recent years, have become encoded by transposons and plasmids, thus greatly increasing their interspecies transmissibility and prevalence.

Extended-Spectrum β-Lactamases

The ESBLs arose in Europe from single amino-acid substitutions in TEM and SHV group 2 β-lactamases in the 1980s, temporally corresponding to the introduction of third-generation cephalosporins. ESBLs became prevalent in the 1990s and are now ubiquitous worldwide, with > 300 individual enzymes described.[19] The most common ESBLs belong to the TEM, SHV, and, beginning in the 2000s, the CTX-M family. The CTX-M ESBLs appear to have been acquired from a nonpathogenic Enterobacteriaceae.[38] All ESBLs are plasmid encoded and are most commonly expressed by Enterobacteriaceae. ESBLs hydrolyze penicillins, aztreonam, and most cephalosporins but are inactive against the cephamycins (such as cefotetan and cefoxitin) and carbapenems.

TABLE 2] Classification of β-Lactamases

Functional Group	Category Name	Molecular Class	Target	Examples
1	…	C	Cephalosporins	*Escherichia coli* AmpC
2	Serine β-lactamases	A	Penicillins, cephalosporins, aztreonam	TEM-1, TEM-2, SHV-1; includes most ESBLs and some carbapenemases such as KPC
		D	Extended spectrum cephalosporins, some carbapenems	OXA family; includes several carbapenemases
3	Metallo-β-lactamases	B	Carbapenems	IMP family, VIM family, NDM-1

ESBL = extended-spectrum β-lactamase; KPC = *Klebsiella pneumoniae* carbapenemase.

Although widespread worldwide, the prevalence of ESBLs varies greatly by geographic region: In epidemiologic surveys, the prevalence of ESBL-expressing *Klebsiella* and *E coli* species have been highest in Latin American countries and lowest in the United States and Canada,[39,40] although the prevalence in the United States and Canada has increased approximately 10-fold per decade.[41,42] In addition, the TEM and SHV ESBLs are being replaced by the CTX-M strains in most countries. Human gut carriage is thought to represent the largest reservoir of ESBLs, but other documented sources include rivers, wild and domesticated animals, and retail foods.[17] In addition to endemic prevalence, clonal outbreaks of ESBLs have been documented both within and between hospitals, clinics, and long-term care facilities in a geographic location.[15,43]

Infection and colonization by ESBL-carrying pathogens occur most commonly in hospital and ICU settings and are associated with length of stay, prior β-lactam or fluoroquinolone use, comorbidity and severity of illness, and presence of indwelling devices (eg, central venous catheters, endotracheal tubes, urinary catheters, and gastrostomy tubes).[44,45] Once exclusively a cause of hospital-acquired infections, ESBL organisms increasingly cause community-acquired infections in patients with recent health-care contact.[46,47]

Carbapenemases

The first carbapenemase-producing Enterobacteriaceae was described in a Japanese patient in 1991, and carbapenem-resistant Enterobacteriaceae (CRE) have since become widespread globally. Carbapenemase enzymes belong to either group 2 serine β-lactamases (in molecular classes A or D), or to group 3 metallo-β-lactamases in molecular class B. The importance of the CRE resistance mechanism is that it eliminates a class of antibiotics that was previously highly active against gram-negative organisms (eg, those producing ESBLs), thus severely limiting the antibiotic armamentarium to older antibiotics with considerable toxicity and newer drugs with limited effectiveness, as discussed later in this review. Furthermore, CRE often possess additional resistance mechanisms that confer resistance to most antibiotics,[48] and bloodstream infections caused by CRE are associated with high mortality rates, significantly higher than those associated with carbapenem-susceptible Enterobacteriaceae.[49]

The most common carbapenemase in the United States is a *Klebsiella pneumonia* carbapenemase (KPC), a class A serine β-lactamase that was first isolated from a *K pneumoniae* isolate in North Carolina in 1996[50] and has since become widespread: As of February 2014, KPC had been reported in every state in the United States except Idaho, Maine, and Alaska.[51] The KPC gene is plasmid borne and has thus been reported from multiple Enterobacteriaceae species and *Pseudomonas*. The KPC resistance mechanism is strongly associated with hospital outbreaks, with 45 such outbreaks reported in peer-reviewed literature at the time of writing. The prevalence of KPC is increasing in the United States, with 4% of Enterobacteriaceae and 10% of *Klebsiella* species reported as containing KPC in 2011.[48]

Another important carbapenemase enzyme, NDM-1, is a metallo-β-lactamase that was first isolated in 2008 in a *K pneumoniae* isolate from a Swedish patient after a hospital stay in India[52] but has been retrospectively detected in samples from the Indian subcontinent dating back to 2006.[53] NDM-1 was reported in several European and African countries and the United States in 2010, and it is now distributed globally.[19] The prevalence of NDM-1 in the United States is low but increasing, with 27 cases reported from 2009 to 2013 and a further 69 cases reported in 2013.[54] NDM-1 has the potential for rapid dissemination among bacterial species by plasmid-mediated horizontal transfer; consistent with this, the most common bacteria that carried NDM-1 in 2012 were *Klebsiella* species (40% of isolates) and *E coli* (30%), followed by *Acinetobacter* species (10% of isolates).[55] There is a clinically significant association between incidence of NDM-1 and recent hospitalization in India or Pakistan.[56]

A third, emerging group of CRE enzymes are the OXA family carbapenemases, classified as class D serine β-lactamases.[19,24] Most of these enzymes are plasmid borne and transferred horizontally among Enterobacteriaceae and *A baumannii* complex. This resistance mechanism has been reported most commonly in Middle Eastern and Mediterranean countries and is, as yet, uncommon in North America.

Other Resistance Mechanisms

As noted previously, hydrolysis of β-lactam rings is the most common mode of antibiotic resistance among gram-negative bacilli. Other mechanisms of resistance among gram-negative bacteria include enzymatic inactivation of other antibiotics, alteration of the bacterial target of the antibiotic, reduction in the permeability of bacterial cells to the antibiotic, and efflux pumps that actively remove the antibiotic from the bacterial cytoplasm.[19] Like β-lactamases, the genes

responsible for these mechanisms may be intrinsic and may be encoded by the bacterial chromosomes or by mobile genetic elements such as transposons and plasmids, allowing their interspecies transfer. Finally, genes encoding multiple resistance mechanisms to different classes of antibiotics are often transferred on the same mobile genetic element, resulting in wholesale acquisition of resistance to multiple antibiotic classes that greatly limits treatment options; for example, a recent report documented plasmid-mediated acquisition of an ESBL and two other β-lactamases together with inhibition of porin-mediated antibiotic permeability by an *E coli* during treatment.[57]

Treatment

Colonization by resistant gram-negative bacteria is more common than infection and does not benefit from antimicrobial therapy. Using clinical criteria to distinguish infection from colonization is, therefore, important. Removal, drainage, or debridement of the infection source, when feasible, is a critical part of therapy.

Extended-Spectrum β-Lactamase-Producing Organisms

Carbapenems are the drugs of choice for the treatment of infections caused by ESBL-carrying pathogens. In observational studies, the treatment with imipenem-cilastatin or meropenem of patients with bacteremia caused by ESBL-producing *Klebsiella* has been associated with reduced mortality, as compared with other choices.[58,59] There are fewer data available regarding doripenem and ertapenem, but their effectiveness against ESBL-producing organisms is thought to be comparable to the older carbapenems.[60,61]

ESBL-carrying organisms demonstrate in vitro susceptibility to cephamycin antibiotics, which include cefotetan, cefmetazole, and cefoxitin, but clinical data on the use of these antibiotics during ESBL infections are very limited, and their use is discouraged.[62] Similarly, cefepime and piperacillin-tazobactam can have in vitro activity against some ESBL-carrying organisms, but treatment failures are common, and resistance has been reported to emerge during therapy; as a result, these antibiotics are considered inferior to carbapenems for ESBL-producing pathogens.[63]

Few data are available on the effectiveness of other antibiotic classes, or antibiotic combinations, against ESBL-producing organisms. Fluoroquinolone resistance is very common in ESBL-producing pathogens, and ciprofloxacin is inferior to carbapenems even for the treatment of fluoroquinolone-sensitive ESBL isolates.[58] Aminoglycoside resistance among ESBL pathogens is also increasing[64] and, with the possible exception of urinary tract infections, this class should not be used as monotherapy; combination therapy that includes an aminoglycoside in the treatment of infections caused by ESBL-producing pathogens has not been studied specifically to date. Tigecycline, the first of a class of tetracycline-analog glycylcycline antibiotics, was active in vitro against nearly all ESBL-producing Enterobacteriaceae isolated in a surveillance trial between 2005 and 2011 in the United States[65]; however, tigecycline has poor penetration into the urinary system (a common site of gram-negative infections), and there are limited clinical data on its use against ESBL-producing organisms. Most importantly, meta-analyses of noninferiority trials have demonstrated increased mortality and treatment failure rates associated with the use of tigecycline as compared with other antibiotics.[66] The increased risk was greatest in patients treated with tigecycline for ventilator-associated pneumonia, a use for which the US Food and Drug Administration (FDA) has not approved the drug, but the risk was also noted when tigecycline was used for FDA-approved indications. As such, the FDA black box warning recommends against the use of tigecycline for infections caused by organisms (such as those producing ESBLs), for which an alternative antibiotic agent is available.

Carbapenemase-Producing Organisms

The choice of antibiotics for the treatment of carbapenemase-producing pathogens is very limited. Carbapenemase-producing Enterobacteriaceae are universally resistant to cephalosporins and penicillins, and as noted previously, this resistance mechanism is often cotransmitted with genes that mediate resistance against multiple other antibiotic classes. As such, no antibiotic regimen is universally effective against CRE pathogens, and the choice of antibiotics should be based on the specific susceptibility pattern of a given organism. Combination therapy, using two or three classes of antibiotics to which the organism is sensitive, is strongly recommended based on data from observational studies showing the emergence of resistance and poorer outcomes with monotherapy.[67]

Polymyxin antibiotics, including polymyxin-B and colistin, target the negatively charged bacterial cell membranes by virtue of their cationic charge and then disrupt the membrane with their detergent properties. Systemic administration of colistin, the most commonly

used polymyxin, is complicated by dose-dependent and reversible nephrotoxicity in > 10% of patients.[68] The other major complication of colistin, neurotoxicity, is uncommon (occurring in about 3% of patients) and is manifested as paraesthesia, ataxia, seizures, and, rarely, neuromuscular blockade and consequent respiratory failure.[68] Contemporary studies have shown that, overall, these toxicities have been manageable. The optimal dosing regimen for colistin has not been established, but individualized regimens based on body weight, creatinine clearance, or form of renal replacement therapy, and the minimal inhibitory concentration of the pathogen, have been proposed.[69] Colistin should be used only in combination with other antibiotics because resistance can develop during treatment.

CRE pathogens are often sensitive to tigecycline, with the caveats noted previously: Specifically, tigecycline should not be used as monotherapy or in treatment of urinary infections. CRE pathogens usually have in vitro sensitivity to fosfomycin, a bacterial cell wall-active antibiotic that is unrelated to β-lactams. Fosfomycin, available only as an oral drug in the United States, is an appropriate choice for urinary tract infections with sensitive pathogens in patients who are not systemically ill; the data on its use in pneumonia and blood-stream infections are limited.[70] In addition, the optimal dose and duration of treatment of multidrug-resistant pathogens have not been established.

Antibiotic-Resistant Acinetobacter, Pseudomonas, *and Other Non-Lactose Fermenters*

The treatment of drug-resistant non-lactose fermenters is among the most challenging problems in contemporary medicine, because these organisms often do not respond to most cephalosporins, penicillins, or fluoroquinolones. Among these pathogens, *S maltophilia* is unusual in that it is typically sensitive to trimethoprim; the treatment of choice for infections with this pathogen is, therefore, IV trimethoprim-sulfamethoxazole.[27] For other non-lactose fermenters, provided the organism is sensitive, β-lactams are an appropriate first choice. Among carbapenems, imipenem-cilastatin or meropenem are active against many *Pseudomonas* and *Acinetobacter* species, whereas ertapenem has poor activity against non-lactose fermenters and should not be used against these pathogens. For organisms that retain sensitivity to β-lactams, the role of combination antibiotic therapy, typically with a β-lactam and aminoglycoside, remains undefined: Clinical studies have not shown any benefit from combination therapy over monotherapy if the organism is sensitive to the selected antibiotic.[71,72]

Combination therapy is appropriate for the treatment of infections caused by carbapenem-resistant *Pseudomonas* and *Acinetobacter* species. Polymyxins are effective against most of these organisms in vitro and constitute a mainstay of therapy. The addition of aerosolized to IV colistin has been reported as beneficial in pneumonia caused by such highly resistant isolates in some studies, but not others.[73,74] Tigecycline is active against most *Acinetobacter,* but not *Pseudomonas,* species. For *Acinetobacter* species, the sulbactam component of ampicillin-sulbactam can be an effective therapy.[75] Other choices, including aminoglycosides (most often amikacin), aztreonam, fosfomycin, and rifamycins, may be considered, based on sensitivity testing.

Prevention

It is an inescapable fact of evolutionary biology that the use of any antimicrobial will result in a selection pressure that, in time, will result in the development of resistance to that drug. The rapidity of the emergence of resistance is related to the intensity of the selection pressure caused by ubiquitous antibiotic use in the ICU environment, and the short generation time of bacteria. Viewed from this perspective, the rise in antibiotic resistance can be mitigated but not prevented. Fundamentally, there are four ways to slow the increase in antibiotic resistance:

1. Reduce the pool of patients susceptible to nosocomial infections. This can be achieved by implementing ICU practices that minimize the use of indwelling vascular lines, GI tubes, and urinary catheters and enforcing strict sterile technique during procedures.[76] In addition, measures that reduce the risk of microaspiration reduce the rate of hospital- and ventilator-associated pneumonia. These include minimizing the implementation of mechanical ventilation and sedation and maintaining patients in the semirecumbent position.[77] Newer methodologies aimed at attenuating colonization, such as oropharyngeal and GI decontamination, are attractive in principle but await validation.[78,79]
2. Reduce the selection pressures that favor the development of antibiotic resistance among bacteria. This involves reducing the duration of exposure of bacteria to antibiotics and reducing the number of antibiotics to which they are exposed. This requires the implementation of antibiotic stewardship programs to prohibit inappropriately broad or prolonged antibiotic

administration and the establishment of institution-wide policies for antibiotic selection in specific infections, to minimize antibiotic use to a limited and nonduplicative formulary.[80]

3. Prevent transmission in the hospital environment. This requires good general hygiene practices such as hand washing and decontaminating equipment between patients, systematic monitoring for antibiotic resistant bacteria as part of hospital epidemiology to identify colonized patients, and strict enforcement of isolation procedures as part of infection control.
4. Develop novel antimicrobials. This is an indispensable component of combating antibiotic resistant infection, but the rate of development of new antimicrobials has lagged far behind the rate of bacterial acquisition of resistance. Policies that prioritize antibiotic research at universities and provide financial incentives for research and development to the pharmaceutical industry have the potential to stimulate the development of new antibiotic classes.

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