Emerging Issues in Gram-Negative Bacterial Resistance: An Update for the Practicing Clinician

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Abstract

The rapid and global spread of antimicrobial-resistant organisms in recent years has been unprecedented. Although resistant gram-positive infections have been concerning to clinicians, the increasing incidence of antibiotic-resistant gram-negative infections has become the most pressing issue in bacterial resistance. Indiscriminate antimicrobial use in humans and animals coupled with increased global connectivity facilitated the transmission of gram-negative infections harboring extended-spectrum β-lactamases in the 1990s. Carbapenemase-producing Enterobacteriaceae, such as those containing *Klebsiella pneumoniae* carbapenemases and New Delhi metallo-β-lactamases, have been the latest scourge since the late 1990s to 2000s. Besides β-lactam resistance, these gram-negative infections are often resistant to multiple drug classes, including fluoroquinolones, which are commonly used to treat community-onset infections. In certain geographic locales, these pathogens, which have been typically associated with health care—associated infections, are disseminating into the community, posing a significant dilemma for clinicians treating community-onset infections. In this Concise Review, we summarize emerging trends in antimicrobial resistance. We also review the current knowledge on the detection, treatment, and prevention of infection with these organisms, with a focus on the carbapenemase-producing gram-negative bacilli. Finally, we discuss emerging therapies and areas that need further research and effort to stem the spread of antimicrobial resistance.

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Although antimicrobial resistance is complex and longstanding, what has recently and appropriately garnered attention is that the evolution of resistant microbes has outpaced the development of antibiotics. From the emergence of penicillin and methicillin resistance in *Staphylococcus aureus* to vancomycin-resistant enterococci, we are now faced with the specter of resistant superbug gram-negative infections, some of which have become virtually untreatable.

Although resistant gram-positive infections have been of most concern, the spread of resistant gram-negative infections is currently the most pressing emerging issue in bacterial resistance. In this Concise Review, we present current knowledge with respect to the detection, treatment, and prevention of infection with these organisms, with a focus on the carbapenemase-producing gram-negative bacilli (CPGNB). We also discuss emerging therapies and areas that need further efforts and research to stem the spread of antimicrobial resistance.
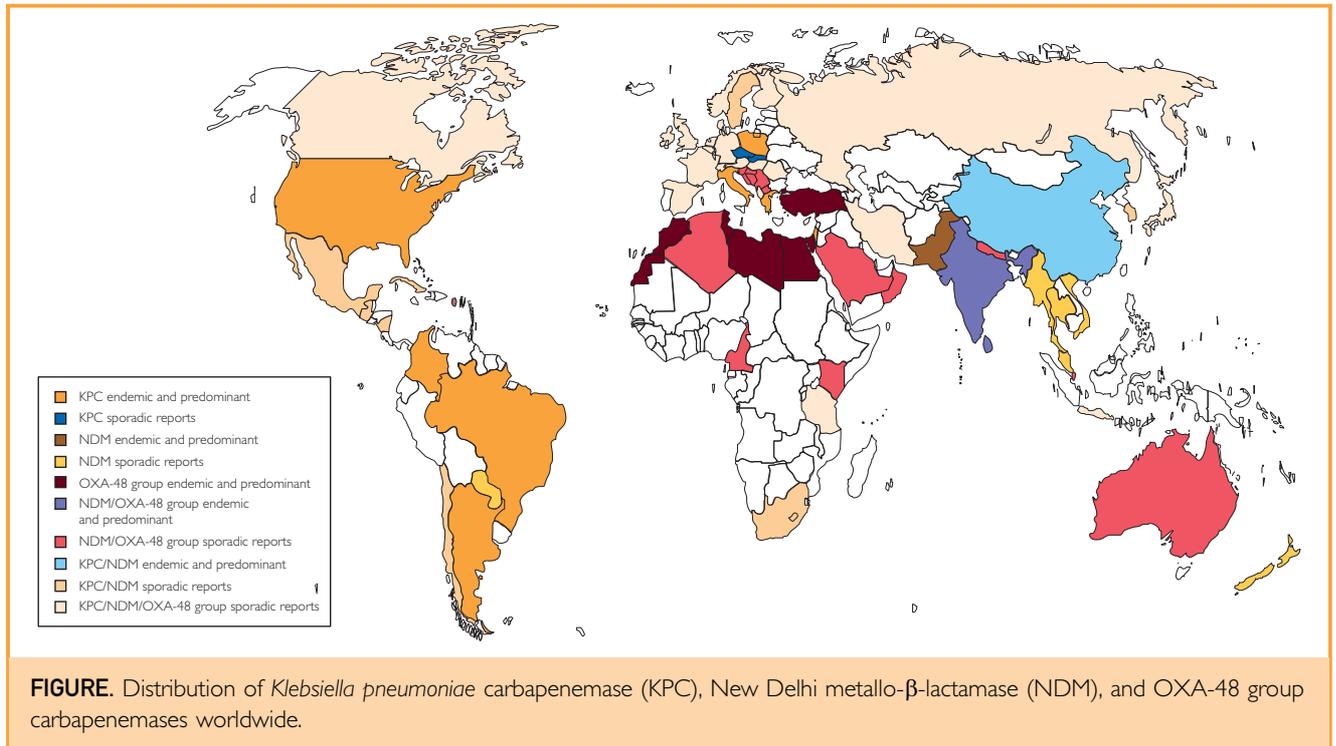
WHY SHOULD WE BE CONCERNED?

Antimicrobial resistance should concern clinicians for several important reasons. First, treatment options are limited and sometimes nonexistent. Among the Enterobacteriaceae (eg, *Escherichia coli, Klebsiella,* and *Enterobacter*), the extended-spectrum β-lactamases (ESBLs) mediate resistance to the first- through fourth-generation cephalosporins. The more recently developed carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPCs) and New Delhi metallo-β-lactamases (NDMs), also hydrolyze carbapenems, the preferred agents of the β-lactam class when treating serious ESBL gram-negative infections. Both ESBL and CPGNB often exhibit multiclass resistance. Non-Enterobacteriaceae gram-negative bacilli (GNB), such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are significant nosocomial pathogens found in the environment and on medical equipment that frequently possess multiple-resistance mechanisms beyond β-lactamases. These pathogens are especially problematic in intensive care units, where multi- or even pan-drug resistance is commonly encountered.

Second, resistance has spread widely on several fronts. On a biologic level, genes that encode resistance are often carried on plasmids, which are shared easily among the GNB, in particular the Enterobacteriaceae. This exchange of resistance genes can occur within a host[1] and in the environment.[2] Gram-negative organisms, such as *E coli* and *K pneumoniae,* are important causes of community-onset and health care—associated infections, respectively, and these 2 species have been most frequently associated with ESBL and carbapenemase carriage. Geographically, resistant gram-negative infections have caused outbreaks on a locoregional level[3,4] and also worldwide[5,6] (Figure), the latter facilitated by increased international travel and medical tourism. Currently, KPC is endemic in parts of the United States, certain Latin American countries (Colombia and Brazil), and the Mediterranean (Italy, Greece, and Israel), and NDM is endemic in the Indian subcontinent, Balkan States, North Africa, and the Arabian Peninsula, with sporadic outbreaks occurring in the United States.[6] In the Indian subcontinent, NDM has disseminated into the community and has been found in drinking water sources.[2] Household spread of KPC has also been reported.[7]

Third, dissemination and acquisition may be silent and pose significant challenges for infection control. Because the Enterobacteriaceae form part of the normal gut microbiota, individuals can be colonized asymptomatically and unknowingly serve as a reservoir for spread to others; a subset eventually develops infections due to these bacteria.[3]

Fourth, infections are associated with increased mortality and economic costs. A recent meta-analysis found that mortality was twice as high in patients with carbapenem-resistant Enterobacteriaceae bacteremia compared with those with bacteremia due to carbapenem-susceptible Enterobacteriaceae; mortality attributable to carbapenem-resistant Enterobacteriaceae infection was up to 44%.[8] A lack of initial, active antibiotic therapy is an independent predictor of mortality in infections caused by KPC-producing *K pneumoniae*.[9] Overall, antimicrobial resistance is estimated to cost $55 billion in the United States yearly.[10] The ESBL *E coli* and *Klebsiella* species infection was found in a matched-cohort study to have an additional attributable cost of $16,450 per patient and a mean additional 9.7 days of hospitalization.[11] Similar findings have been described for KPC infections.[12]

FIGURE. Distribution of *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and OXA-48 group carbapenemases worldwide.

WHAT ARE THE MECHANISMS OF β-LACTAM RESISTANCE IN GNB?

The mechanisms of resistance in GNB seem daunting, partly because of the alphabet soup and the somewhat arbitrary nature of β-lactamase nomenclature. A basic understanding, however, is necessary to appreciate the epidemiology, treatment options, and infection control implications. Several important definitions are reviewed in Table 1. The Ambler classification system classifies β-lactamases into 4 groups (class A, B, C, and D) on the basis of their amino acid sequences and their active site (Table 2).

Class A enzymes include the ESBLs and KPC enzymes. These enzymes are most commonly found in Enterobacteriaceae and are usually plasmid-borne. The ESBLs hydrolyze penicillins, first- through fourth-generation cephalosporins, and aztreonam but may be inhibited by β-lactam/β-lactamase inhibitor (BLBLI) combinations, such as amoxicillin-clavulanate and piperacillin-tazobactam. Cephamycins such as cefoxitin also retain susceptibility despite these enzymes. However, in serious ESBL infections (eg, bacteremia or high-inoculum infections), BLBLIs may not be reliable, making the existing combination products unsuitable; therefore, carbapenems are the β-lactams of choice. In addition to possessing the hydrolytic activity of ESBLs, KPCs also hydrolyze carbapenems. Few choices are left for treatment because other resistant determinants (eg, to fluoroquinolones and aminoglycosides) are almost invariably cocarried on plasmids. Among the aminoglycosides, however, gentamicin seems to retain the most activity against the KPC producers.[5]

Class B enzymes are metallo-β-lactamases and examples include NDM, imipenem (IMP), and Verona integron-encoded metallo-β-lactamase (VIM). Metallo-β-lactamases hydrolyze penicillins, first- through fourth-generation cephalosporins, BLBLIs, and the carbapenems. Of interest, the monobactam aztreonam retains activity. However, because most isolates coproduce ESBLs, aztreonam is usually rendered ineffective.

The class C enzymes are the cephalosporinases or AmpC enzymes. These enzymes are chromosomally encoded and inherent in species such as the MY SPACE organisms (*M*organella, *Y*ersinia, *S*erratia, *P*seudomonas/*P*roteus/*P*rovidencia, *A*eromonas/*A*cinetobacter, *C*itrobacter, and *E*nterobacter species). In some of these (eg, *Enterobacter, Serratia*, and *Citrobacter*), AmpC can become induced during treatment with cephalosporins. Organisms initially testing

TABLE 1. Definitions of Common Terms Used to Describe Resistant Gram-Negative Bacilli

β-lactam antibiotics:	These antibiotics comprise the penicillins, cephalosporins, and carbapenems, which share the common basic chemical structure of a 4-member β-lactam ring.
β-lactamases:	These enzymes hydrolyze the β-lactam ring and inactivate the β-lactam class of antibiotics.
Ambler classification:	This is a classification system for β-lactamases on the basis of their amino acid sequences and their active site residue.
Extended-spectrum β-lactamases (ESBLs):	These are broad-spectrum, Ambler class A β-lactamases, which hydrolyze the penicillins, and first- to fourth-generation cephalosporins, which are cefoxitin susceptible and are inhibited by the β-lactamase inhibitors (eg, clavulanate).
Cephalosporinases:	ESBLs are technically cephalosporinases, but the term *cephalosporinase* is generally reserved to describe Ambler class C AmpC β-lactamases, which are cefoxitin resistant, hydrolyze the penicillins and first to third-generation cephalosporins, and are not inhibited by the β-lactamase inhibitors, such as clavulanate.
Carbapenemases:	These are broad-spectrum β-lactamases (usually Ambler class A, B, or D), which have the ability to hydrolyze carbapenems, in addition to the penicillins and also the first- to fourth-generation cephalosporins, although activity may vary depending on the exact type of carbapenemase.
Carbapenem-resistant gram-negative bacilli (CRGNB) and carbapenem-resistant Enterobacteriaceae vs carbapenemase-producing gram-negative bacilli (CPGNB) and carbapenemase-producing Enterobacteriaceae:	CPGNB are most often CRGNB (susceptibility testing may yield rare isolates and may have low carbapenem minimum inhibitory concentrations); however, not all CRGNB are carbapenemase producers. Carbapenem resistance may be mediated by ESBL or AmpC production, for example, associated with porin loss (see text for details). The Enterobacteriaceae are a large family of gram-negative bacilli, which ferment glucose. Nonfermenting gram-negative bacilli (non-Enterobacteriaceae) include *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

susceptible to cephalosporins (eg, ceftriaxone) may develop resistance during treatment with this class. This is an important point for clinicians to note and especially a problem with *Enterobacter* species; one study with 213 isolates found that 38% possessed inducible AmpC.[13] AmpCs are sometimes plasmid encoded and also inducible but sporadically found in other Enterobacteriaceae; one study in 70 sites and 25 US states found an incidence of plasmid-borne AmpC to be 4% in *E coli* and 8.5% in *K pneumonia*.[14] AmpCs hydrolyze the penicillins, first- to third-generation cephalosporins, BLBLIs, and aztreonam. Cefepime, a fourth-generation cephalosporin, is poorly hydrolyzed by AmpCs, so many isolates test susceptible, and cefepime may be effective as treatment. In high-inoculum or serious infections, however, carbapenems are generally considered to be more reliable.[15]

Class D enzymes are oxacillinases or OXA enzymes, so named because of their high hydrolytic activity against oxacillin. They are, however, a very diverse group, with some members being narrow-spectrum β-lactamases and others including carbapenemase activity. Unlike class A enzymes, they are not inhibited by the β-lactamase inhibitors. More recently, the OXA-48 group has emerged to become a predominant carbapenemase in some Mediterranean countries with sporadic cases reported in the United States.[6] This group is plasmid borne, has disseminated among Enterobacteriaceae (predominantly *K pneumoniae*, unlike the other OXA types),

TABLE 2. Characteristics of Important β-Lactamases and Potential Treatment Options[a]

Enzyme	ESBL	AmpC	KPC	NDM	OXA-48 group
Activity	ESBL	Cephalosporinases	Carbapenemases		
Ambler class	A	C	A	B	D
Active site residue	Serine	Serine	Serine	Zinc	Serine
Resistance gene location	Plasmid	Chromosomal (inherent in some genera, such as *Enterobacter, Serratia, Citrobacter*), occasionally plasmid	Plasmid	Plasmid	Plasmid
β-lactams inactivated[b]	First-generation to fourth-generation cephalosporins, aztreonam, older BLBLIs	First-generation to third-generation cephalosporins, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, aztreonam, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, carbapenems; however, may have variable or diminished hydrolysis of third-generation or fourth-generation cephalosporins
Examples of current treatment options[c]	Carbapenems Possibly BLBLIs, such as piperacillin-tazobactam, in carefully select patients (low inoculum, nonsevere infections, such as cystitis)	Cefepime (in select patients, such as those needing only a short course of therapy, low-inoculum, nonsevere infections) Carbapenems	More data needed Polymyxins, tigecycline, and aminoglycosides Combination treatment, consider including a carbapenem Cystitis: fosfomycin (oral) nitrofurantoin	More data needed Polymyxins, tigecycline, and aminoglycosides Aztreonam[d] Combination treatment, consider including a carbapenem Cystitis: fosfomycin (oral), nitrofurantoin	More data needed Polymyxins, tigecycline, and aminoglycosides Consider using a β-lactam in combination with the above, choice dependent susceptibility testing; third-generation cephalosporin (eg, ceftazidime) may retain activity and may be preferable to carbapenems

[a]BLBLI = β-lactam/β-lactamase inhibitor; ESBL = extended-spectrum β-lactamases; KPC = *Klebsiella pneumoniae* carbapenemase; NDM = New Delhi metallo-β-lactamase.
[b]Older BLBLIs are amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanate. Novel BLBLIs, such as ceftazidime-avibactam and aztreonam-avibactam, have activity against ESBLs, AmpCs, and KPCs. Aztreonam-avibactam has activity against NDMs.
[c]Not all options have been listed. Treatment needs to be individualized, considering susceptibility results, pharmacokinetic and pharmacodynamic factors, infection site, and patient factors (allergies or intolerances). Note that the polymyxins are limited by nephrotoxicity and neurotoxicity and have no activity against *Proteus, Providencia*, and *Serratia*. Tigecycline has no activity against *Pseudomonas, Proteus*, and *Providencia*, is a bacteriostatic agent, and achieves poor serum and urine levels; thus, it should not be used as monotherapy in bloodstream infections or in urinary tract infections.
[d]Aztreonam is intrinsically active against the metallo-β-lactamases but often inactivated by the organism's concomitantly produced ESBLs. The aztreonam-avibactam combination, however, is expected to be active.

and has been implicated in multiple nosocomial outbreaks.[6]

Of note, carbapenem resistance does not always necessarily stem from carbapenemase production. Isolates that are ESBL or AmpC producers when coupled with a porin loss may be resistant to carbapenems. Porins are protein channels that allow entry of solutes into the bacterial cell, including antibiotics. Resistance to carbapenems may also result from efflux pumps, which extrude antibiotics from the bacterial cell.

WHY ARE ESBL AND CPGNB OFTEN RESISTANT TO OTHER (NON−β-LACTAM) DRUG CLASSES?

Plasmids encoding β-lactamases often carry other antibiotic-resistance genes, for example, enzymes that modify antibiotic targets (eg, ribosomal RNA methylation conferring high-level aminoglycoside resistance), or antibiotics themselves (eg, acetyltransferases modifying quinolones and aminoglycosides). Plasmids can also encode various efflux pumps that extrude

TABLE 3. Typical Antibiograms of ESBL, AmpC, and CPGNB Isolates[a]

Antibiotic	ESBL producer	AmpC producer	CPGNB		
			KPC	NDM	OXA-48 group
Ampicillin	R	R	R	R	R
Ampicillin-sulbactam	R	R	R	R	R
Amoxicillin-clavulanate	**V**[b]	R	R[b]	R	R
Piperacillin-tazobactam	**V**[b]	R	R[b]	R	R
Cefoxitin	**S**	**R**	V/R	R	V/R
Cefazolin	R	R	R	R	R
Ceftriaxone or ceftazidime	**R**	**R**	**R**	**R**	**V**[c]
Cefepime	**R**	**S**	**R**	**R**	**V**[c]
Aztreonam	R	R	R	**V/R**[d]	V
Ertapenem	**S**[e]	**S**[e]	**R**	**R**	**R**[c]
Meropenem or imipenem	**S**[e]	**S**[e]	**R**	**R**	**R**[c]
Ciprofloxacin or levofloxacin	V/R	V/R	V/R	V/R	V/R
Amikacin	V	V	V	V	V
Gentamicin	V	V	**V/S**	V	V
Tobramycin	V	V	V/R	V/R	V
Trimethoprim-sulfamethoxazole	V/R	V/R	V/R	V/R	V/R
Tigecycline	V/S	V/S	V/S	V	V/S
Colistin or polymyxin B	V/S	V/S	V/S	V/S	V/S
Ceftazidime-avibactam[f]	S	S	S	**R**	V/S
Aztreonam-avibactam[f]	S	S	S	**S**	V/S

[a]CPGNB = carbapenemase-producing gram-negative bacilli; ESBL = extended-spectrum β-lactamases; KPC = *Klebsiella pneumoniae* carbapenemase; NDM = New Delhi metallo-β-lactamase; R = resistant; S = susceptible; V = variable; V/S = variable, often susceptible; V/R = variable, often resistant. Bolded fields indicate a typical susceptibility pattern that may be helpful in deducing the underlying resistance mechanism. In general, the antibiogram profile does not reliably distinguish the various CPGNB, and further confirmatory testing (eg, phenotypic or molecular [polymerase chain reaction]) is needed.

[b]Class A enzymes, which include ESBLs and KPC, can test susceptible to β-lactam/β-lactamase inhibitor combinations.

[c]OXA-48 group CPGNB are difficult to detect because they may retain susceptibility to third- and fourth-generation cephalosporins and may have only slightly elevated minimum inhibitory concentrations (low level resistance) to the carbapenems.

[d]Metallo-β-lactamases (class B), such as NDM, are intrinsically susceptible to aztreonam (a monobactam) but often test resistant because of coproduction of ESBLs in the same isolate.

[e]ESBLs and AmpC producers can test resistant to the carbapenems if associated with a porin loss or an efflux pump.

[f]Ceftazidime-avibactam and aztreonam-avibactam are novel β-lactam/β-lactamase inhibitor combinations that are not approved by the Food and Drug Administration yet.

not only β-lactams but also quinolones, amino-glycosides, and tetracyclines.[16]

WHO IS AT RISK FOR ACQUIRING RESISTANT GNB?

Risk factors for acquiring ESBL and CPGNB include prior and recent antibiotic use, residence in long-term acute care facilities, admission to an intensive care unit, presence of indwelling medical devices or wounds, poor functional status, increased age, solid organ or stem cell transplant, and receipt of health care in or travel to endemic areas.[17] In addition, resistance to a particular antibiotic may not necessarily be associated with exposure to antibiotics from the same class but may follow exposure to other classes. For example, one study on *Acinetobacter baumannii* bacteremia found that fluoroquinolone exposure was associated strongly with

carbapenem-resistant isolates; this association could be due to activation of intrinsic mechanisms of resistance (eg, efflux pumps).[18]

HOW ARE INFECTIONS WITH RESISTANT GNB DIAGNOSED?

Diagnosis of infection is via culture of clinical specimens with bacterial identification and susceptibility testing. Most isolates have a susceptibility pattern with a typical ESBL or CPGNB phenotype (Table 3).[19] Confirmatory testing for ESBL or carbapenemase production can be performed for infection control purposes but is not currently routinely recommended by the Clinical Laboratory Standards Institute. The CPGNB isolates may sometimes test susceptible (using clinical breakpoints) to one or more of the extended-spectrum cephalosporins (ceftriaxone, cefotaxime, and/or cefepime) and

only have modest increases in carbapenem minimum inhibitory concentrations; this is especially a problem with the OXA-48–producing isolates. Confirmation of ESBL or carbapenemase production typically comprises a phenotypic test (eg, a double disk diffusion test for ESBLs and the modified Hodge test, Carba NP test, or other inhibitor-based tests for carbapenemases) or a molecular test, which typically is a polymerase chain reaction assay for a specific resistance gene encoding the β-lactamase (eg, KPC and NDM).[17,20] Identification of colonized patients is important as part of infection control because asymptomatic carriage is a reservoir for further propagation. Patients at risk may include those who have had direct contact with another actively infected or colonized patient, patients transferred from other facilities (especially long-term care facilities), or those who have been hospitalized overseas within the past 6 months. Such screening can be performed via culture or molecular methods (eg, polymerase chain reaction of rectal surveillance swabs or stool).

WHAT IS THE OPTIMAL TREATMENT OF INFECTIONS WITH RESISTANT GNB?

Definitive therapy should always be guided by susceptibility testing. Expert consultation with an infectious disease specialist is recommended. Carbapenems are the treatment of choice for invasive or high-inoculum infections caused by ESBL and AmpC producers. For CPGNB, treatment options are even more limited. Often the polymyxin (colistin or polymyxin B), tigecycline, and sometimes select aminoglycosides are the only active agents (Table 2 and Table 3). The polymyxins are limited by nephrotoxicity and neurotoxicity and have no activity against *Proteus, Providencia, Morganella*, and *Serratia*. We have only started to understand how to optimize the pharmacodynamic and pharmacokinetic properties of these agents. Tigecycline has no activity against *Pseudomonas, Proteus, Providencia*, and *Morganella*. In addition, it is a bacteriostatic agent, achieves poor serum and urine levels, and thus should not be used as monotherapy in bloodstream or urinary tract infections. Other legacy antimicrobials, such as oral fosfomycin and nitrofurantoin, can be used if found to be active, but their use is generally limited to lower urinary tract infections. Trimethoprim-sulfamethoxazole

or the quinolones may also be used if these test susceptible, but this is uncommon. For the acutely ill or septic patient, empiric therapy with agents active against ESBL and CPGNB may have to be considered if the patient possesses appropriate risk factors; clinicians should also take into account the local epidemiology of ESBL and CPGNB in their area of practice. A local hospital antibiogram can be very helpful in this respect. State or public health departments may also publish such data and be a useful resource.

Data from prospective, randomized trials are lacking for combination therapy for CPGNB; however, in vitro studies and accumulated retrospective experience suggest that, at least for KPC infections, combination therapy, including a carbapenem (eg, polymyxin-carbapenem or aminoglycoside-carbapenem), may have a mortality benefit.[21] Extended infusions with carbapenems may be considered to increase the probability of achieving optimal bactericidal killing, although more data from randomized trials are needed.[22] Clinical data are scant for treatment of OXA-48 and NDM infections; a recent retrospective, observational study suggested that for bacteremia from OXA-48 producers, combination therapy that included colistin produced a mortality benefit.[23] Clearly, new and effective agents are needed for CPGNB infections, and recent stimuli for development, such as the Generating Antibiotics Incentives Now Act, are much welcomed initiatives. Avibactam is a novel β-lactamase inhibitor furthest along in development and expected to be introduced into clinical use soon. It has good activity against KPCs when combined with ceftazidime, and although it does not intrinsically inhibit metallo-β-lactamases, it has potent activity against metallo-β-lactamases, such as NDM, when combined with aztreonam.[24,25]

HOW ARE RESISTANT GRAM-NEGATIVE INFECTIONS PREVENTED?

A proactive approach to combating antimicrobial resistance should take place on the prescriber and local level and on the regional or national and international level.

Prescriber and Local Level

Health Care Worker Education. In a study by Giblin et al,[26] clinicians were more likely to believe that antimicrobial resistance was a

problem nationally than at their own practice or institution. It is difficult to engage physicians and other health care workers when they do not believe a problem exists. Hard data should be presented and made readily accessible (eg, via Web portals), such as a local antibiogram (ideally stratified for both inpatient and outpatients) and local hand hygiene or isolation precautions adherence rates. A local antibiogram is essential to facilitate rational empiric antibiotic prescribing. Education of health care professionals is important and should begin during initial training and be featured regularly as part of ongoing education programs. Special efforts should be targeted toward the greatest barriers identified in one's local context. In the study by Giblin et al, for example, the chief barriers were identified as (1) resisting the urge to treat colonization rather than true infection, (2) discontinuing use of antimicrobials when infection is cured or unlikely, and (3) practicing antimicrobial control.

Infection Control and Antimicrobial Stewardship. Such efforts should be spearheaded by multidisciplinary teams (involving physicians, pharmacists, microbiologists, and nurses). Antimicrobial stewardship should extend beyond inpatients to the outpatient setting (including emergency departments), where most patients are seen.

Active Surveillance and Interrupting the Chain of Transmission. Active surveillance of at-risk patients should be part of routine infection control activities—a bundled approach, including early detection, isolation and cohorting, and skin decontamination in select patient groups (eg, daily chlorhexidine bathing) can help interrupt the chain of transmission.[27] Novel approaches may help in decreasing environmental contamination (eg, adenosine triphosphate bioluminescence or UV monitoring for effectiveness of environmental cleaning,[28,29] hydrogen peroxide vapor decontamination,[30] and use of copper-coated surfaces[31]); however, more studies will be needed to validate and standardize such approaches, keeping in mind that each method has inherent limitations. Laboratories, depending on local hospital epidemiology, should determine the optimal method for CPGNB screening and be aware

that no one method is perfect (molecular methods only detect resistance targets identified in the assay, whereas phenotypic methods may be less sensitive overall and are generally more labor intensive).

Regional or National and International Level Information Sharing. Given the potential for rapid regional dissemination of resistant GNB with increased interfacility transfers for medical care, novel methods to accurately identify patients who are at risk of or who are known CPGNB carriers during transfer of care will help ensure that appropriate infection control measures will be continued. Regional antimicrobial surveillance networks, such as the Healthcare-Associated Infections-Community Interface, European Antimicrobial Resistance Surveillance Network, and Asian Network for Surveillance of Resistant Pathogens, play an important role in providing necessary data for policy making and resource allocation.

Decrease in Nonhuman Use of Antimicrobials. Currently, only the European Union has banned (since 2006) the use of antibiotics for nontherapeutic uses in farm animals. It has been estimated that 80% of antimicrobial use in the United States is for nontherapeutic uses in livestock. Further inroads globally should be made into regulating such use because this has been linked to antimicrobial-resistant human infections.[32]

CONCLUSIONS

Antimicrobial resistance, in particular resistant GNB, is a formidable threat to human health. Although the climate for the development of novel, active agents against CPGNB has improved somewhat in recent years, and indeed several new agents are in the pipeline, these agents will most certainly not be a panacea. A holistic approach must be embraced, including continued health care professional education, attention to infection control, adoption of new technologies and algorithms in screening, diagnosing and interrupting the chain of infection, antimicrobial stewardship in both humans and animals, and greater regional and international collaboration.

Abbreviations and Acronyms: **BLBLI** = β-lactam/β-lactamase inhibitor; **CPGNB** = carbapenemase-producing gram-negative bacilli; **ESBL** = extended spectrum β-lactamase; **GNB** = gram-negative bacilli; **KPC** = *Klebsiella pneumoniae* carbapenemase; **NDM** = New Delhi metallo-β-lactamases

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