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

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) recognize that antimicrobial resistance is a pressing global health concern, (2) appreciate the epidemiology, risk factors for, and the treatment of infections caused by resistant gram-negative bacilli, and (3) recognize that a holistic approach is required to combat the global spread of antimicrobial resistance.

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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]

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