Epidemiology and Management of Emerging Drug-Resistant Gram-Negative Bacteria

Extended-Spectrum β-Lactamases and Beyond

Daniel P. Boyle, MD*, Teresa R. Zembower, MD

KEYWORDS

- Antibiotic resistance • Extended-spectrum β-lactamases
- Carbapenem-resistant enterobacteriaceae • New Delhi metallo–β-lactamase
- Carbapenem-resistant *Acinetobacter baumannii* • Multidrug-resistant *Pseudomonas aeruginosa*

KEY POINTS

- Antibiotic resistance is increasing at an alarming rate primarily due to antibiotic overuse.
- The most common classes of resistance encountered in gram-negative bacteria include extended-spectrum β-lactamase (ESBL)–containing organisms, carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and multidrug-resistant (MDR) *Pseudomonas.*
- Urinary tract infections (UTIs) are the most commonly encountered infections with these MDR bacteria, and infections with these organisms result in increased morbidity and mortality.
- The antimicrobials used to treat these infections are termed, *drugs of last resort*, and often carry a high risk of adverse drug events.
- Antimicrobial stewardship and infection prevention programs are the most proved modalities used to stop the development and spread of antimicrobial resistance.

INTRODUCTION

In the past couple of decades, worldwide prevalence of antimicrobial resistance has increased at a startling rate. Many factors play a role in increasing drug resistance; however, the main driver remains antibiotic overuse. In addition, person-to-person spread of resistant bacteria and the passage of resistance genes between bacteria also play a large role. With the increase in global travel and trade, resistance mechanisms are easily transmitted worldwide.[1] Each year in the United States, it is estimated that more than 2 million individuals suffer an infection from a resistant bacteria and more than 23,000 deaths are attributed to these organisms.[2] Because of these alarming numbers, President Obama issued an Executive Order in 2014 outlining a national plan to detect, prevent, and control the spread and

Division of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue, Suite 900, Chicago, IL 60611, USA
* Corresponding author. Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue, Suite 900, Chicago, IL 60611.
E-mail address: daniel.boyle@northwestern.edu

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Abbreviations	
CAUTIs	Catheter associated urinary tract infections
CLABSIs	Central line associated bloodstream infections
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended spectrum β-lactamase
HAIs	Healthcare associated infection
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	Multidrug-resistant
NDM-1	New Delhi metallo-β-lactamase
SSIs	Surgical site infections
UTI	Urinary tract infection
VAPs	Ventilator associated pneumonias

emergence of antimicrobial resistance. This plan emphasizes implementation of strong antimicrobial stewardship programs aimed at preventing antibiotic misuse and infection prevention programs aimed at decreasing person-to-person transmission of these resistant bacteria.[2]

When resistant bacteria are encountered in the clinical setting, decisions regarding management are difficult. The first decision to be made is whether the isolated bacteria represents a true infection versus colonization. In those who are colonized (have no signs or symptoms consistent with infection), treatment is not warranted, because treatment increases the risk for an adverse drug event and drives further resistance. When treatment is warranted, antibiotic options are often limited and many of the choices carry a significant risk of side effects (ie, polymyxins and renal failure).

This review discusses emerging gram-negative resistance patterns. For each resistance pattern, the mechanisms of resistance, risk factors, type of infections, treatment, and outcomes are highlighted. Common side effects associated with the antimicrobial therapies and the tools the medical community is using to combat the continued spread of resistant bacteria also are discussed.

EXTENDED-SPECTRUM β-LACTAMASE–CONTAINING BACTERIA

Definition and Types

ESBLs are plasmid-mediated enzymes that mediate resistance to extended-spectrum (third-generation) cephalosporins (eg, ceftazidime, cefotaxime, and ceftriaxone) and monobactams (eg, aztreonam) but do not affect cephamycins (eg, cefoxitin and cefotetan) or carbapenems (eg, meropenem or imipenem).[3] These enzymes disrupt the β-lactam antibiotics through hydrolysis, resulting in an opening of the β-lactam ring, rendering these antibiotics inactive. In addition to β-lactam resistance, many organisms carrying these enzymes also have resistance to other classes of antibiotics, including fluoroquinolones, aminoglycosides, and sulfonamides through different mechanisms of resistance, further complicating therapeutic choices.[4] The first clinical case involving an ESBL-producing organism was reported in 1983 in Germany and occurred in a *Klebsiella* species found to have resistance to a newer class of antibiotics, oxyimino-cephalosporins, which had been specifically designed to combat β-lactam–producing organisms.[5] In 1988, the first cases of infections due to ESBL-producing organisms in the United States were discovered.[6] Today, ESBL-producing organisms are a problematic cause of infections worldwide.[3]

ESBLs are most commonly encountered in organisms belonging to the Enterobacteriaceae family, and *Klebsiella pneumoniae* and *Escherichia coli* are the most common species found to produce ESBLs.[4] The first ESBL enzyme was termed, *SHV-2*, and over time, researchers have identified numerous genetic mutations leading to multiple classes of ESBLs, the most common belonging to the SHV, TEM, CTX-M, and OXA classes of β-lactamases.[7]

Although these mutations are predominantly seen in bacteria recovered from patients in the health care setting, a growing body of literature supports the existence of these resistant bacteria in the community, especially in patients with UTIs. Numerous environmental reservoirs for these bacteria have been detected, including poultry and other meats,[8,9] drinking and river water,[10,11] and companion animals.[12]

Epidemiology and Risk Factors

Estimates of the prevalence of ESBL-producing organisms are difficult to perform because of the labor required to identify these organisms