Resistant Gram-Negative Infections

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KEYWORDS

• Enterobacteriaceae • *Pseudomonas aeruginosa* • *Acinetobacter* species
• Gram-negative bacilli • Septic shock • Antibiotic resistance

KEY POINTS

- Worldwide increased incidence of multidrug-resistant gram-negative bacilli (GNB) has been associated with worse outcomes.
- Strategies including combination therapy and extended antimicrobial infusion are increasingly being used in attempts to treat these infections.
- Source control remains an important part of managing septic shock as clinicians are faced with increasing incidence of multidrug-resistant GNB, a paucity of new agents, and ineffectiveness of older agents.

BACKGROUND

The global crisis in antimicrobial resistance continues to escalate. Infections caused by multidrug-resistant (MDR) gram-negative bacilli (GNB) are particularly challenging, with little immediate help forthcoming in the antimicrobial pipeline.[1–3] The crisis of MDR infections is especially vexing in the intensive care unit (ICU), where the highest rates of MDR GNB are found.[4] In the ICU, early effective antimicrobial therapy improves survival of patients with septic shock and other life-threatening infections, but selective pressures from intense antimicrobial exposure contribute to the emergence of MDR bacteria, including extensively drug-resistant (XDR) and even pan–drug-resistant (PDR) organisms.[5] MDR pathogens colonizing patients in ICUs can "leak" into the long-term patient population and even into the community setting, when former ICU patients cycle through the acute and chronic health care system.

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This article reviews the major classes of resistant and MDR GNB and their current prevalence in ICUs worldwide. The authors discuss the older and new drugs of potential use in treating these infections, and current strategies to maximize their effectiveness, including rational combination therapy and dosing schemes optimizing the pharmacodynamics of these agents. Treatment options are presented for specific classes of resistant GNB encountered in the ICU, including extended β-lactamase (ESBL)-producing, AmpC-producing, and carbapenem-resistant Enterobacteriaceae (CRE), MDR and carbapenem-resistant *Acinetobacter baumannii* (ACCB), and MDR *Pseudomonas aeruginosa* (PA).

EPIDEMIOLOGY

Antimicrobial resistance is a major public health catastrophe. Following the introduction of each new antimicrobial, reports of resistance rapidly appear. In the late 1970s, reports described mechanisms of resistance of GNB to aminoglycoside and the newly introduced cefamandole.[6] More recently, the lag from introduction of new agents to reports of resistance has markedly decreased, with resistance often identified even before release of the drug. A wide variety of resistance mechanisms are described in GNB. Some mechanisms, such as ESBL production, are found in many species. Others are highly specific, such as overexpression of the MexAB-OprM efflux pump in PA.[7] GNB resistance mechanisms are reviewed elsewhere.[8,9] Important classes of resistance are summarized in **Table 1**.

The trend toward increased resistance among GNB is reported in numerous local, regional and international studies. Recent data from a few of these studies are shown in **Table 2**. In the United States, 10-year surveillance from the Tracking Resistance in the United States Today (TRUST) study describes the steady increase in resistant and MDR GNB isolated in 26 institutions.[10] For example, imipenem-resistant PA increased from 5% in 2003 to 15% in 2009. The prevalence of ESBL-producing *Escherichia coli* increased from 20.8% to 65 % over 7 years among intra-abdominal infection isolates in China.[11] This trend toward increased resistance has been especially significant in ICUs in both tertiary care centers and community hospitals worldwide.[12,13] ACCB are particularly problematic, with resistance rates of up to 60% to 70% in international studies.[11,14] Studies also demonstrate that colonization with MDR GNB is a risk for subsequent infections and bacteremia with same organism.[15] The US Centers for Disease Control and Prevention (CDC) is currently performing population-based surveillance of infection caused by CRE and MDR ACCB through the Multi-Site Resistant Gram-Negative Bacilli Surveillance Initiative (MuGSI), with data expected in 2013.[16] The goals of this project are to determine the extent of CRE and MDR ACCB infections in the United States, identify those most at risk for infection, and measure trends of disease over time.

DEFINITIONS AND DIAGNOSIS OF INFECTIONS CAUSED BY RESISTANT AND MDR GNB

Until recently there was little consensus on the definitions of MDR, XDR, and PDR.[17–22] To remedy the issue, an expert panel sponsored by CDC and the European Center for Disease Prevention and Control (ECDC) met in 2008 to establish interim standard definitions for MDR, XDR, and PDR for epidemiologically significant microorganisms, as well as to begin to establish consistency in categorization of “susceptible” and “nonsusceptible” for different organisms and antimicrobial classes.[23] These definitions were developed specifically for public health and epidemiology purposes and not for clinical management. An organism was designated as nonsusceptible to an antibiotic when it tested intermediate or resistant when using clinical breakpoints as interpretive criteria.