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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]