Antibiotic Trends Amid Multidrug-Resistant Gram-Negative Infections in Intensive Care Units

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KEYWORDS

• Antibiotic resistance • Multidrug-resistant • Gram-negative bacteria • ICU

KEY POINTS

- Multidrug-resistant (MDR) gram-negative bacteria are emerging as the most common nosocomial infections acquired in ICUs worldwide.
- There are multiple strategies with strong supporting evidence that can be used to combat the emergence of MDR gram-negative bacteria.
- Initially inappropriate antibiotic treatments are the leading cause of the emergence of bacterial resistance as the organisms mutate rapidly to protect themselves.
- *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are the leading pathogens worldwide demonstrating virulence against antibiotics.
- Novel treatments and strategies have been proved effective against the emergence of MDR gram-negative pathogens.

ICU admission is significant risk factor for nosocomial bacterial infections.[1,2] Isolates from ICUs internationally most commonly find MDR gram-negative bacteria.[1–8] Multiple studies indicate the leading factor perpetuating antimicrobial resistance is antibiotic misuse.[9–16] The purpose of this article is to discuss the significant impact MDR gram-negative infections are having on ICUs , the threat on health and mortality, and effective and new approaches aimed to combat MDR gram-negative infections in the critically ill population.

BACKGROUND AND PROBLEM

Mechanisms of Antibiotic Resistance

Bacteria become resistant to antibiotics via gene mutations. Gene mutations of the bacteria can occur in 2 ways, intrinsically or from acquired mutations. Intrinsic

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mutations occur as a defense mechanism to protect against an antibiotic. Acquired resistant gene mutations occur by the transfer of a gene to neighboring bacteria during plasmid exchange.[1,17]

Bacteria demonstrate antibiotic resistance in 4 ways. Bacteria can express enzymes that inactivate or destroy an antibiotic. For instance, bacteria resistant to penicillin produce lactamase. Lactamase breaks down the structure of penicillin, thereby inhibiting its ability to kill or stagnate a microorganism. Despite pharmaceutical companies developing antibiotics able to combat this resistance with β-lactamase inhibitors (β-lactam antimicrobials), the prevalence of extended-spectrum β-lactamase (ESBL) emerged more in the United States than in the rest of the world. Germs expressing ESBL became resistant to most β-lactams, penicillins, third-generation and fourth-generation cephalosporins, and aztreonam. Unfortunately, as the name suggests, ESBL-producing bacteria continue to mutate and some strains have developed coresistance to trimethoprim-sulfamethoxazole, fluoroquinolones, and aminoglycosides.[1]

A second resistance mechanism affects intracellular accumulation of the medications by modifying the target molecule's drug transporters in the microorganism's membrane.[17] The third mechanism involves mutations at the drug's binding site. This limits the ability of the antibiotic to bind tightly to the organism.[1] The last mechanism by which bacteria demonstrate resistance to antibiotics is down-regulating the outer membrane's porin channels and preventing the antibiotic from entering the microorganism's cell.[1]

Biofilm formation and colonization

Many bacteria are capable of protecting themselves by creating a protective coating around the cell known as a biofilm. This coating protects them from the activity of the antibiotic and facilitates resistance.[5,17–20] The biofilm creates protected colonies of the bacteria that are resistant to host defenses and treatments. *A baumannii* is one of the MDR germs that is capable of creating a biofilm.[18–20] These organisms can seed different areas of the body, such as the lung, and cause infections later when a host's immunity is weakened again.[17]

Epidemiology and Emergence of Gram-Negative Bacterial Resistance in ICUs

The Study for Monitoring Antimicrobial Resistance Trends (SMART) reports a global increase and spread of antimicrobial resistance in bacteria causing hospital-associated and community-associated infections.[2] Specifically in ICUs, isolates of gram-negative bacteria have demonstrated MDR trends worldwide increasingly for more than 10 years.[3,5,8,9,13,21] Patients admitted to ICUs for noninfectious causes are at high risk for MDR nosocomial infections due to contamination of equipment, mechanical ventilation, invasive lines/catheters, contamination of surfaces, and contamination of ICU staff.[4–6] Although an MDR gram-negative infection has not been found a single predictor of mortality, the presence of this infection compounded by ICU admission greater than 48 hours, the presence of invasive lines, and other comorbidities greatly increases the overall ICU mortality rate in comparison with non-MDR gram-negative infection diagnoses.[6]

Sepsis related to intraabdominal or pulmonary sources is a diagnosis associated with the highest ICU mortality rates secondary to MDR gram-negative organisms.[2] Patients who have undergone severe burns of the head and neck region are identified at high risk for MDR gram-negative infections as well.[22] In addition to the already troubling and lethal risks for death, those patients colonized with MDR gram-negative bacteria (eg, nursing home residents, individuals with chronic renal disease,