Multi-resistant Gram-Negative (MRGN) Infections: An Emerging Problem in Hospitals and Health Care Facilities Worldwide

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Multiresistant Gram-negative (MRGN) infections are an increasing worldwide concern, contributing to significant nosocomial morbidity and mortality (up to 50%). These infections are produced mainly by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., all of them very familiar in our field.

Over the last several years, a growing number of *Enterobacteriaceae* resistant to all of our antibiotics—including carbapenems—have emerged. Historically, carbapenems have been our last line of defense in treating *Enterobacteriaceae*; therefore, the development of resistance to these last-line agents has been a significant concern in healthcare. To protect patients and prevent transmission, healthcare professionals need to take specific steps.

The overuse of antimicrobial agents has led to the development of different resistance mechanisms that can be shared easily with other Gram-negative species. In the area of globalization, bacteria can spread rapidly, passing quickly through geographic barriers. Therefore, we need aggressive infection control measures and prevention efforts when resistant-epidemic clones are detected. Clinicians should be aware of this rising problem and practice/maintain a rational use of current drugs.

The terms “multidrug-resistant” (MDR), “extensively drug-resistant” (XDR), and “pan-drug resistant” (PDR) gram-negative bacilli infections are used with different meanings. People frequently confuse these terms and use them inappropriately. The correct terminology is as follows:

- **Multidrug-resistant (MDR):** defined as a pathogen that is resistant to at least 3 antimicrobial classes of agents to which it could have been susceptible.
- **Extensively drug-resistant (XDR):** resistant to 1 or 2 antimicrobial options.
- **Pan-drug resistant (PDR):** term implies resistance to all commercially available antimicrobial agents.

Currently, the most important resistance mechanism is beta-lactamase production. Extended-spectrum β-lactamases (ESBLs) are most often found in *E. coli* and *K. pneumoniae*; however, other Gram-negative bacilli, including *Enterobacter* spp., *Proteus mirabilis*, *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*, and to lesser extent *P. aeruginosa*, have also been found to produce these enzymes. Some of these bacilli can also...
produce other β-lactamases, including chromosomal or plasmid mediated AmpC-type enzymes, metallo-
lactamase or other carbapenemases, so they can also be resistant to the β-lactams, β-lactamase inhibitors
combinations, antipseudomonal cephalosporins, and carbapenems.

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We have very limited options of treatment (Table 1). These include Carbapenems, Aztreonam, beta-
lactamics, Polymyxins, Tigecycline, and Fosfomycin. All of these drugs may be used alone or in combination.
In the pipeline there are few options in early phase: ACHN-490 neoglycoside, CXA 101, Ceftazidime/NXL104,
Ceftalorine. In addition, we can use other routes of antimicrobial therapy as inhaled therapy for respiratory
infections. Nebulized therapy with colistin or aztreonam lysine is an attractive option in these cases. A high
concentration of antibiotic can be achieved in the infection’s location without systemic side effects. Finally,
despite the lack of scientific evidence, combined IV and nebulized therapy is currently a very good option for
MRGN respiratory infections.

In summary, the limited therapeutic armamentarium has been the reason for the development of novel
approaches such as old antibiotics, new routes, doses and combination therapies. A tailored therapeutic
approach is recommended in these cases. Since new antibiotics continue to be required, we must avoid
returning to the pre-antibiotic era. Bacteria are evolving faster than companies can bring new antibiotics to
market. Bacteria are tricky; by changing quickly in response to antibiotics, they can grow resistant, creating
even more harmful and life-threatening infections.

Please, when you treat the next nosocomial infection, keep in mind that bacteria are cleverer than us. It is an
unequal battle for several reasons. First, bacteria grow faster than human beings, preventing new antibacterial
drugs from becoming available in time. Second, bacteria quickly develop resistance mechanisms shared with
other Gram-negative species. Finally, they spread easily in this globalized world without effective drugs to
combat them.
Meanwhile, strict application of infection control measures is the cornerstone of nosocomial infection prevention. Antibiotic stewardship, exemplified by appropriate duration of therapy and de-escalation policies, is paramount and must not be overlooked.

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