2-hour Symposium

Bloodstream infections in the era of MDR and XDR Gram-negative bacteria

Initial and definitive therapy - do we have sufficient evidence for guidance?

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According to the current definitions, multidrug- resistant (MDR) bacteria are those that have acquired resistance to at least three antimicrobial classes while extensive-drug resistant (XDR) those that have acquired resistance to all but one or two classes. Gram-negative bacteria that produce extended-spectrum β-lactamases and/or carbapenemases fulfill these criteria.

The clinical evidence to guide treatment decisions for infections caused by MDR or XDR bacteria is surprisingly scarce and mostly relies on observational studies from prospective or retrospective cohorts and case series. On the other hand, several authors have shown that early appropriate antimicrobial therapy is the only modifiable risk factor that drives mortality in these patients.

A type one carbapenem remains the agent of choice for the initial treatment of bacteremia in patients with risk factors for ESBL-producing Gram-negative bacteria. Once the susceptibility results are available, the patient's condition is stable and adequate source control has been achieved, de-escalation to a carbapenem-sparing regimen may be considered. β Lactam/β-lactamase inhibitor combinations (piperacillin-tazobactam or amoxicillin-clavulanate) have been effective in this setting for bacteria that are susceptible *in vitro*. Quinolones or aminoglycosides would be reasonable choices for urinary tract infections, if the MICs are low.

In a setting where the prevalence of carbapenem resistant Gram-negative bacteria is high, the empiric therapy should include combination of two agents with a high probability of activity against the infecting organism (i.e. a carbapenem plus colistin or an aminoglycoside), depending on the site of infection and the local epidemiology.

For directed therapy, combination schemes appear to hold the most promise, particularly for severe infections in critically ill patients. Carbapenems may be preferred in these combinations provided that the MIC is ≤ 8mg/L and a high-dose/prolonged infusion regimen is administered to attain acceptable drug exposure. For cases where no β-lactam agent can be used, combination of two agents with *in vitro* activity against the infecting organism is recommended (i.e. colistin or aminoglycoside + tigecycline, colistin or aminoglycoside + fosfomycin). Recently, our understanding of the appropriate dosing regimen for colistin was expanded by PK studies that showed the importance of a loading dose and an extended dosing interval of 12 hours in order to optimize exposure to this agent.

For carbapenem-resistant *Acinetobacter* or *Pseudomonas aeruginosa* the need for combination regimens has not been established.

There is an urgent need for new drugs and for better clinical studies investigating the efficacy and safety of old active drugs and combinations.