Introduction

Optimizing the use of carbapenems in the face of increasing Gram-negative resistance

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Among the worrisome complications in the treatment of serious bacterial infections is antibiotic resistance, both pre-existing and emerging during therapy. The consequences of this phenomenon have repeatedly been analyzed, with the conclusion that infections with resistant pathogens generally result in increased patient morbidity and mortality, and an increase in the societal financial burden. Much of this resistance, particularly among Gram-negative organisms, is directed against often used classes of antibiotics, such as the third-generation cephalosporins, fluoroquinolones, and broad-spectrum penicillins. Thus, there has been increasing use of carbapenems for empiric and definitive therapy in institutions in which resistance among Gram-negative organisms is frequently observed. The articles included in this supplement review optimization of therapy, focusing on the following issues: appropriate first-line therapy, de-escalation, antibiotic-related adverse events, and pharmacokinetic-pharmacodynamic principles of antibiotic infusion.

Thomas G Slama (Clinical Professor of Medicine at Indiana University School of Medicine) reviews the clinical and economic significance of antibiotic resistance [1]. The Antimicrobial Availability Task Force, created by the Infectious Diseases Society of America, identified six pathogenic microorganisms, including three key Gram-negative pathogens, as being significant concerns. Dr Slama reviews the role of these Gram-negative organisms in infections and the impact that they have. *Acinetobacter* has now reared its head in North America after being widely recognized as an important problem in European and Asian intensive care units. It is now considered to be a battlefield organism. He also briefly reviews the prevalence, costs, and mortality associated with infections caused by extended β-lactamase producing bacteria, emphasizing that delays in appropriate therapy result in increased mortality.

Dr Slama also discusses the real costs of antibiotic resistance. In addition to patient care costs, there are costs associated with surveillance, testing, and isolation procedures. His commentary on new drug development is worth a read.

Robert C Owens Jr (Co-Director of the Antimicrobial Stewardship Program at Maine Medical Center in Portland, Maine) focuses on the adverse events associated with antimicrobial agents [2]. Antimicrobial agents lead all drug classes in terms of associated adverse events. The adverse events that are characteristic of a particular class of antimicrobials, such as β-lactams, remain manageable. However, the drug classes that contain unique, unpredictable harms, such as the fluoroquinolones, must be viewed with caution and subject to scrutiny. Importantly, although not typically considered an adverse event, the emergence of resistance plays an integral role in the process of deciding on the initial therapeutic regimen. Emergence of resistance becomes an even greater concern because carbapenems (members of the β-lactam class with activity against a broad spectrum of resistant pathogens) are increasingly being utilized in first-line therapy protocols for the treatment of serious bacterial infections.

James J Rahal (Professor of Medicine at Weill Medical College of Cornell University and New York Hospital in New York) reviews the importance of appropriate initial antibiotic therapy and de-escalation [3]. Drawing on his lengthy and broad experience in dealing with resistant Gram-negative bacteria, he emphasizes the role of carbapenems in institutions that are plagued by extended-spectrum β-lactamase producers, but he also points out the downside to carbapenem use based on his first-hand published experience. He also emphasizes careful de-escalation to a narrow spectrum of antibiotic therapy after identification of the infecting organism, and appropriate short-course therapy to limit the emergence of resistance to carbapenems.

David P Nicolau (Director of the Center for Anti-Infective Research and Development at the Hartford Hospital, Hartford, Connecticut) discusses the pharmacokinetic-

pharmacodynamic principles required to optimize antibiotic administration and so improve clinical outcomes [4]. The goals of antibiotic use are to achieve and maintain therapeutic drug levels that eradicate the pathogen, while simultaneously preventing the emergence of resistance. He suggests how both goals can be attained by targeting the pathogen-specific minimum inhibitory concentration and altering infusion strategies. Continuous infusion strategies, as opposed to the commonly employed intermittent (1 hour) infusion, have been reported in a few small studies to yield enhanced clinical response rates. He points out that it is not necessary to exceed the minimum inhibitory concentration for the entire duration of the dosing regimen. An alternative strategy uses the same dose at the same frequency of administration but extends the period of infusion. The extended infusion protocol appears to have almost identical efficacy with a low dose as with a higher dose infused over a shorter period of time, while also reducing cost, toxicity, and the possibility of emergence of resistance.

These reviews should serve as starting points for optimal use of carbapenems to prolong their useful life, given the demonstrated need for carbapenems resulting from the emergence of more resistant Gram-negative organisms. However, it should be noted that no long-term data on some of the strategies suggested in these reviews exist. The proof that prolonging infusion times will minimize the development of resistance is still lacking, and whether outcomes will be better must still be demonstrated in large-scale studies. Thus, careful data collection and reporting are needed if we are to obtain a better appreciation of the utility of such strategies.

Competing interests

The author declares that they have no competing interests.

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