Treatment of Hospital or Ventilator-Associated Pneumonia Due to Carbapenem-Resistant Enterobacteriaceae: Leveraging Molecular Resistance Testing and Combination Therapy to Improve Outcomes

TO THE EDITOR—The recently published updated Infectious Diseases Society of America guideline on the management of adults with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) recommend that patients with HAP/VAP due to “carbapenem-resistant pathogens” susceptible only to polymyxins should receive, in addition to colistin by inhalation, systemic monotherapy with either polymyxin B or colistin [1]. This recommendation ignores the molecular heterogeneity of resistance mechanisms in these organisms and conflicts with accumulating data supporting the use of combination therapy for bacteremic infections due to some carbapenem-resistant Enterobacteriaceae (CRE), particularly those due to Klebsiella pneumoniae [2–4].

These retrospective studies provide evidence that, despite the presence of phenotypic carbapenem resistance, the addition of a carbapenem to a polymyxin to which the organism is susceptible is associated with improved outcomes in the treatment of infection due to carbapenemase-positive organisms. This has best been demonstrated with bacteremic infections due to carbapenemase-producing K. pneumoniae (KPC) that, have relatively low minimum inhibitory concentrations (MICs) (ie, \( \leq 8 \mu g/mL \)) [5,6]. Although the relevant studies deal with bacteremic infections, there is no reason to presume that the same principles do not apply to the treatment of HAP/VAP.

The predictability of response is, however, complicated by the fact that CRE often express more than one mechanism of resistance. For example, KPC-producing K. pneumoniae may possess altered porin expression and function, the presence of which is an independent risk factor for poor outcomes in KPC-infected patients treated with colistin and doripenem in combination [6]. Furthermore, the specific
type of carbapenemase also affects the response to therapy with at least one new antimicrobial, ceftazidime-avibactam. As a consequence, molecular analysis of pathogens may assist clinicians in their choice of optimal antimicrobial therapy for serious CRE-related infections, such as HAP/VAP [4].

Microbiology laboratories now have the option to use commercially available Food and Drug Administration–approved real-time polymerase chain reaction assays targeting the 5 most common carbapenemase genes KPC, New Delhi metallo-

B-lactamase-1 (NDM-1), imipenemase (IMP), Verona imipenemase (VIM), and OXA-48. In addition, timely carbapenem MIC testing by E-test can be performed, offering precise carbapenem MIC values. Identification of metallo-β-lactamases alerts the infectious disease clinician against the use of ceftazidime-avibactam, which is inactive against metallo-β-lactamases such as NDM-1, VIM and IMP. A further potentially confounding factor is the detection of CRE isolates in the United States with ceftazidime-avibactam MIC values ≥8 µg/mL, associated with the presence of the KPC gene blaKPC-2 [7]. Therefore, determining the MIC for ceftazidime-avibactam is critical to guiding antibiotic therapy. The availability of this information in the first 24 hours after the isolation of a CRE facilitates an educated treatment decision by the infectious disease clinician. The predicted impact of molecular resistance testing on patient outcomes, however, remains to be demonstrated in clinical trials.

In addition to potentially improved outcomes associated with carbapenem-containing combination therapy, such an approach may be important in determining the emergence of resistance to polymyxins, the propensity for which is enhanced in the face of monotherapy [8]. Polymyxin monotherapy also raises concern about the accelerated spread of plasmid-mediated polymyxin resistance especially because mcr-1 has been detected in organisms carrying carbapenemases, including New Delhi metallo-

β-lactamase [9]. These observations indicate that strong consideration should be given to the optimization of laboratory evaluation and the use of combination antibiotic therapy in patients with HAP/VAP due to CRE.

Note

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References


