Carbapenem’s Role in Empiric and Directed Therapy for Bacterial Infections in Cardiothoracic Transplantation: Are All Carbapenems Created Equal?

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The spectrum of potential pathogens in the cardiothoracic transplant recipient (CT TX) is vast and has varied over time with the evolution of novel immunosuppressant regimens, and with the exposure to both prophylaxis regimens employed to avert infections and increasingly resistant nosocomial and community acquired bacteria. Successful clinical management of a bacterial infection in the CT TX includes appropriate empiric therapy at the time of presentation of an infectious disease followed by directed therapy for the identified pathogen(s). The carbapenems play a major role in empiric or pathogen directed therapy in these patients due to their broad spectrum of activity to pathogens resistant to other classes of antibiotics and also atypical pathogens that can infect this cohort of patients, like Listeria and Nocardia spp. Carbapenems are a class of broad-spectrum β-lactam antibiotics consisting of Invanz® (ertapenem), Primaxin® (imipenem/cilastatin), Merrem® (meropenem), and Doribax® (doripenem).1-4 This article aims to highlight the key differences that may influence therapeutic decisions by comparing and contrasting these carbapenems in terms of spectrum of activity, evolving resistance mechanisms, metabolism, pharmacokinetics/dynamics properties, differing tissue penetration capabilities and adverse effects of the individual drugs.

The carbapenems bind to penicillin-binding proteins (PBP), preventing bacterial cell wall synthesis. These agents are similar structurally and share similar spectrums of activity for the most part with some clinically important exceptions that will be discussed.1-4 Resistance to carbepenems can occur via several mechanisms. Pathogens may develop a reduced affinity of the target PBPs or an increased expression of efflux pump components. Gram negative bacteria may adapt a decreased permeability of the outer membrane due to diminished production of porins causing reduced bacterial uptake or may produce antibiotic-destroying enzymes like carbapenemases, metallo-ß-lactamases and others.5-9

Gram Positive Organisms:1-4,10-17 All carbapenems have activity against Staphylococcus aureus (methicillin susceptible), penicillin sensitive Streptococcus pneumoniae, other aerobic and anaerobic Streptococcal spp, and Bacteroides fragilis. Enterococcus faecium and methicillin fesistant Staphilococcus aureus are resistant to the carbapenems due to poor binding affinity for the necessary penicillin binding proteins.13 Imipenem/cilastatin is considered the most active of the group against gram positive organisms and is the only agent that should be used to simultaneously to treat Enterococcus faecalis (ampicillin susceptible) and other non-faecium species in a polymicrobial infection.12 Listeria1-4 and nocardia spp1-4,15-18 have demonstrated in vitro sensitivity and clinical successes are reported but no large clinical trials have been achieved nor likely will be due to infrequency of these diseases.17
Norcardia: All carbapenems have good to excellent activity against all strains of Nocardia, except Nocardia brasiliensis where 20-30% of isolates tested were sensitive to imipenem, and N. otitiscaviarum where 0% of isolates were sensitive. Treatment recommendations for Nocardia asteroides, N. farcinica, N. nova, and N. transvalensis include ®imipenem/cilastatin (which has the most evidence for treatment of nocardiosis), or meropenem in addition to 1 or 2 other classes of potentially active drugs empirically until the sensitivities of the specific Nocardia ssp pathogen are available. Meropenem may be the preferred carbapenem over imipenem with a much lower seizure threshold in this disease that may be associated with central nervous system (CNS) involvement. Doripenem, with little CNS penetration with an intact blood brain barrier (BBB) and no data demonstrating CNS penetration with an infamed BBB, should be avoided in any infectious process involving the CNS. A CT TX presenting later than 30 days after transplantation with a pneumonia should consider Nocardia in the differential of possible pathogens and CNS penetration of the empiric therapeutic regimen is warranted till the definitive diagnosis is known.

Gram Negative Organisms: The carbapenem class of drugs until recently has maintained broad gram negative antimicrobial activity due to their stability against most β-lactamases produced by gram negative bacteria, including extended spectrum beta lactamases (ESBL) and Amp-C β-lactamases. Carbapenem resistance has been increasingly detected due to the production of carbapenem hydrolyzing enzymes in the Enterobacteriaceae spp (carbapenem resistant Enterobacteriacea or CRE) and other Gram-negative organisms. In the United States, according to the National Healthcare Safety Network (NHSN) 2006-2007 survey, E. coli with CRE were 4% and Klebsiella spp with CRE were 10.8% of isolates associated with certain device related infections. Different regions of the world vary greatly in the percentage of carbapenem resistant isolates that are in the endemic flora.

Excellent activity persists for the Enterobacteriaceae without CRE, E. coli (including those producing extended spectrum β-lactamases (ESBL)), Klebsiella spp (including ESBL), Haemophilus influenzae (β-lactamases- and non-β-lactamases-producing), Neisseria meningitidis, Morganella spp, Enterobacter spp, Citrobacter spp, Salmonella spp, Shigella spp, Proteus mirabilis, and with the exception of ertapenem, Pseudomonas aeruginosa and Acinetobacter spp. Compared to the other carbapenems, meropenem and doripenem have similar susceptibility patterns and slightly lower MICs against many of the gram negative bacteria in published series.

Gram Negative Pseudomonas: Imipenem/cilastatin, meropenem and doripenem are the anti-pseudomonal carbapenems. Ertapenem does not have anti-pseudomonal activity. Carbapenem resistance among Pseudomonas aeruginosa isolates is variable within this class of drugs. Pseudomonas can become resistant to imipenem/cilastatin with the loss of the OprD porin, while meropenem and doripenem require both the upregulation of the MexA-MexB-OprM multidrug efflux pump combined with the loss of OprD. Imipenem is not affected by upregulation of MexA-MexB-OprM, as it is not subject to efflux. While uncommon, these varied mechanisms of resistance to carbapenems allow for certain pseudomonal isolates to have different MICs to imipenem/cilastatin vs. meropenem/doripenem. The clinical pearl is that if pseudomonas is the suspected pathogen prior to the MICs becoming available, meropenem or doripenem would be the most likely carbapenem to be active against the pathogen of concern. If CNS involvement is suspected in the disease, doripenem should be avoided as previously discussed.
Metabolism: Imipenem differs from the other carbapenems in that it is extensively metabolized by renal dehydropeptidase-1, and as such, is formulated with cilastatin, which inhibits this enzyme. All carbapenems are renally excreted (70-80%) and all require renal dose adjustments, with ertapenem having the highest protein binding and longest half-life allowing for once daily dosing.\textsuperscript{1-4}

Pharmacokinetics/dynamics properties: The efficacy of the carbapenems, like other $\beta$-lactams, is associated with the time above the MIC, where a percentage of the dosing interval during which the concentration is greater than the MIC (T>MIC) of approximately 20% is considered bacteriostatic and 40% is considered bactericidal. Imipenem, meropenem, and doripenem, the anti-psuedomonal carbapenems, easily achieve this 40% T>MIC target against a Pseudomonas isolate with an MIC of 1 mcg/ml using standard dosing. However, against a pseudomonal isolate with an MIC at the respective breakpoints (4mcg/ml for imipenem and meropenem, 2mcg/ml doripenem) the probability of achieving the T>MIC target of 40% is dependent on the infusion time using standard doses/frequencies. The ability to achieve these targets decreases as an organism’s MIC increases and as the infusion time decreases. This is evidence that the choice of a carbapenem with a more favorable MIC (vs. one where the MIC is at the break-point of susceptibility) and administration over an extended infusion time may be beneficial.\textsuperscript{19-21}

Tissue Penetration: Carbapenems are thought to penetrate a variety of fluids/tissues. Only meropenem is approved for meningitis treatment. Imipenem’s safety for CNS infections has not been established and incidence of seizures is a concern. Imipenem is recommended for treatment of serious infections caused by susceptible strains of microorganisms. All carbapenems have approved indications for polymicrobial intra-abdominal infections and complicated urinary tract infections.

The carbapenems are useful for their broad spectrum coverage as empiric therapy and are powerful therapeutic agents as directed therapy for atypical pathogens or resistant nosocomial or community acquired susceptible pathogens. It is imperative that we safeguard the efficacy of this class of antibiotics by preventing the spread of the newly resistant strains of pathogens with effective infection control measures globally.

Disclosure Statement:
The authors have no conflicts of interest to disclose.

References