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Commentary

# Carbapenems as First-Line Therapy for Hospital-Acquired Pneumonia

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## DESCRIPTION

Carbapenems are frequently recommended to pneumonia patients in the hospital. Approximately 75% of carbapenem-treated patients are treated empirically, most typically for respiratory infections. Despite the apparent mortality advantage, the 2016 HAP/VAP Guidelines did not preferentially advocate empiric carbapenem therapy.

A systematic process and meta-analysis to evaluate the comparison of carbapenem with non-carbapenem antibiotics for patients with Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia (HAP/VAP). This evaluation incorporates new evolutions and expands on the guidelines. The study's findings have consequences for diagnostic and antimicrobial stewardship, Carbapenem are routinely prescribed to hospitalised pneumonia patients. Approximately 75% of carbapenem-treated patients are treated empirically, with the majority of them being treated for respiratory infections.

The majority of included studies were to increases the risk of resistance while providing little benefit. The current study contains a number of sub analyses that give essential context for the observed drop in death rates. Specifically, the mortality benefit of carbapenem seemed stronger in studies that were conducted before 2000, involved >66% of patients with VAP, and enrolled patients with low and intermediate Acute Physiology and long term Physiological Evaluation II scores.

The following effects of each analysis were considered: It is tempting to speculate that carbapenem efficiency has declined due to increased resistance among HAP/VAP bacteria. However, because these are mostly registration trials, known carbapenem resistance is ruled out. The possibility is that overall critical care has improved and that salvage medicines for treatment failures are now available, cancelling out the mortality cost of failed therapy. As the authors point out, this finding is difficult to interpret. Although there was a mortality benefit when VAP was more prevalent, clinical cure did not differ in this stratum. Patients with VAP are more Immunocompromised than those with HAP, Especially if the HAP is not severe enough to necessitate ventilation. Effective antibiotics are perhaps more important than HAP. This data could point to a "Goldilocks" window of sickness intensity above which the likelihood of mortality plays an outsized impact. In contrast, antibiotic pharmacokinetic exposures in critically sick patients are diverse, which can result in poorer outcomes. Meropenem pulmonary pharmacokinetic exposures, for example, can range from 3.7%to 178% that of plasma, hence determining if a certain patient's pharmacokinetics is acceptable is impossible without monitoring it.

The crucial question is which demographic would benefit from the carbapenem-associated mortality benefit that would support empiric use. Those afflicted with *Pseudomonas aeruginosa* are a tempting answer. However, meta-regression failed to show a link between *P aeruginosa* prevalence and the risk of death. In other words, the fluctuation in *P aeruginosa* prevalence was not associated with an increased risk of death. Importantly, the prevalence of carbapenem resistance in *P aeruginosa* has grown from around 12% (median, 10% [ward] and 13.2% [ICU]) 10% to nearly 20% in more recent investigations. As a result, given current resistance rates, it is unclear if the mortality advantage reported predominantly in older study still applies. HAP/VAP caused by extended-spectrum beta-lactamase-producing Enterbacterales is another population that may benefit from carbapenems.

Meropenem outperformed piperacillin/tazobactam in terms of mortality in the MERINO study. A post-hoc analysis, however, discovered that the mortality benefit was reduced when the piperacillin minimum inhibitory concentration was 16 m/L. Because genotypic resistance does not necessarily correspond with phenotypic, carbapenems should continue to be the first-line treatment for HAP/VAP caused by extended-spectrum beta-lactamase Enterbacterales.

If alternative agents were universally inferior, carbapenems would be favored. The authors did a subgroup analysis and discovered that, with the exception of cephalosporins, the mortality benefit of carbapenem treatment was lost. Notably, ceftazidime was utilized in five of the eight studies included in this analysis (with or without an aminoglycoside). ASPECT-NP observed that ceftolozane-tazobactam was not inferior to meropenem, implying that not all cephalosporins are equal. Similarly, a prior meta-analysis found no differences in death or clinical failure between

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carbapenems and alternative beta-lactam monotherapy. As a result, considerations such as local susceptibility and patient-specific data should affect the decision between carbapenems and other beta-lactams. These subanalyses suggest avenues for future research but also underscore the need for aggressive pursuit of microbiologic etiology in patients with HAP/VAP.

Notably, the 2016 Guidelines recommended against invasive microbiologic sampling (eg, BAL, nonbronchoscopic BAL). Yet, invasive sampling is essential if reductions in empiric carbapenem use are to be achieved. Rapid diagnostic technologies, such as multiplex polymerase chain-reaction amplification, can identify pathogens and resistance mechanisms thatnecessitate carbapenem use, specifically ctx-M. BAL with quantitative cell counts and cultures discriminates between colonization and infection with much greater accuracy than tracheal aspirate although antibiotic stewardship can also reduce some unnecessary carbapenem use (absent a clear microbiologic diagnosis), empiricism will continue to drive carbapenem consumption.

Overall, the findings of this outstanding analysis strongly support the need for more exploration, aggressive pursuit of microbiologic aetiology, fast de-escalation, and sensible prescribing to avoid resistance while maximizing carbapenem therapeutic advantages.