Beware of broad-spectrum generalizations: ceftazidime-avibactam compared to meropenem for the treatment of gram-negative pneumonia

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Comment on: Torres A, Zhong N, Pachl J, *et al.* Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 2018;18:285-95.

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Nosocomial pneumonia remains a serious challenge to modern healthcare and accounts for a substantial proportion of healthcare associated infections. Frequently, nosocomial pneumonia, and in particular ventilator-associated pneumonia, is caused by multi-drug resistant (MDR) Gram-negative organisms, leaving clinicians few effective therapeutic options. A recent study published by Torres and colleagues in *The Lancet Infectious Diseases* (1), suggests that ceftazidime-avibactam (CA) may be a valuable option for treatment of nosocomial pneumonia. The addition of avibactam extends ceftazidime's spectrum of activity to include carbapenem-resistant Enterobacteriaceae (CRE) due to Ambler class A carbapenemases, while it does not augment the efficacy of ceftazidime against *Pseudomonas aeruginosa*, nor does it target metallo-β-lactamases. Based on this study, demonstrating non-inferiority, CA gained approval for hospital-acquired and ventilator-associated pneumonia (HAP, VAP). This combination of a third-generation, antipseudomonal cephalosporin with a novel β-lactamase-inhibitor was initially approved by the Food and Drug Administration (FDA) in 2015 for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). REPROVE represents an important contribution to the field by expanding the clinical indications for CA, and was conducted to attain an FDA approval for pneumonia. However, from a clinical application standpoint, many questions remain on how we will best be able to translate these trial findings into the clinical setting.

REPROVE was a prospective, randomized controlled phase 3 non-inferiority trial, conducted in 23 countries thus representing a wide geographic range of antibiotic resistance. Adult patients aged 18 to 90 were eligible if they were hospitalized, had nosocomial pneumonia with a respiratory specimen for Gram stain and culture 48 h before randomization. The exclusion criteria were quite numerous and are important to consider. These included infectious aspects (lung abscess, pleural empyema, concurrent infection) but also notably lung and heart transplant patients and immunocompromised patients due to HIV, recent chemotherapy, neutropenia, or immunosuppressant therapies. The exclusions were unfortunate because these populations represent the highest at risk individuals for MDR-GNR infections in general and CRE infections in particular (2). Notably, the study also excluded patients with a creatinine clearance (CrCl) less than 16 mL/min and those receiving hemodialysis (HD) or other renal support, which are also populations of key interest since CA resistance has been documented to occur in patients receiving renal replacement (3,4). Additionally, patients previously treated with CA were excluded, but there was no such exclusion for MERO. Patients received an anti-

MRSA agent empirically (linezolid or vancomycin), which is noteworthy because CA lacks Gram-positive coverage. Additionally, open label aminoglycosides were permitted while awaiting culture results for 24 to 72 hours unless there was a contraindication or if risk of multi-drug resistance was deemed low. More than 50% of included patients did receive an aminoglycoside for less than 72 hours and ~20% for more than 72 hours.

The average CrCl of study participants was over 100 mL/min on average with approximately 80% with a CrCl >50 mL/min. Antibiotics were given for a total of 7 to 14 days. Patients with a CrCl of 50 mL/min or greater received standard CA dosing of 2.5 grams (2 gm of ceftazidime and 500 mg of avibactam) every 8 hours by intravenous (IV) infusion over 2 hours. Both ceftazidime and avibactam are renally eliminated and dosage adjustments were made at a CrCl of ≤50 mL/min to CA to 1.25 gm q8h, ≤30 mL/min to 0.94 gm q12h, ≤15 mL/min to 0.94 gm q24h, and ≤5 mL/min to 0.94 gm q48h. The CA dosing in the REPROVE study changed during the study period after a protocol amendment in patients with renal impairment. The newer dosing is the same as labeled dosing for cUTI and cIAI.

The primary endpoint in this study was clinical cure at the test-of-cure visit with additional secondary endpoints including all-cause 28-day mortality. Ultimately, 405 patients received CA and 403 received MERO. CA was found to be non-inferior to MERO. In the intent-to-treat group, 69% of patients in the CA group were clinically cured at the test-of-cure visit compared with 73% in the MERO group. Similarly, 77% in the CA group and 78% in the MERO group achieved clinical cure in the clinically evaluable population. All-cause mortality rates were 8% and 7% in the CA and MERO groups respectively. There were no differences between the two groups in the sub-group populations including high APACHE score, late VAP, with concurrent bacteremia, and moderate to severe renal impairment.

The clear strengths of this study include randomization, stratification by infection type (ventilator or non-ventilator-associated), placebo-control, double-dummy design with a large patient population spanning four continents. However, considering that the added benefit of avibactam comes from targeting Ambler class A carbapenemases, it would have been ideal to gain information on how CA compares to MERO plus polymyxin in patients with pneumonia caused by CRE. Understandably, it is challenging to recruit a sufficient number of CRE infected patients because of the relatively low frequency of these pathogens. Also, the FDA might be reluctant to recommend polymyxin as a comparator as it is commonly used as a last resort choice due to safety reasons (5).

Additional limitations need to be considered. The unbound plasma concentrations of ceftazidime above MIC correlate best with its antibacterial activity. A pharmacokinetic/pharmacodynamic (PK/PD) modeling study determined that CA 2.5 gm infused over 2 hours every 8 hours was optimal for lung penetration (6). Therefore, CA was optimally dosed in REPROVE. However, the same was not true for MERO, which was given over 30 minutes thus giving CA an unfair advantage. In a population pharmacokinetics study using Monte Carlo simulations comparing MERO 1 and 4 hours infusions in critically ill patients, the probability of target attainment of 80% time above MIC for free drug increased from 84% to 94% for an MIC of 1 and 74% to 88% for an MIC of 2. Predictably, MERO 2 gm over 4 hours performed best at the highest MICs (7). In terms of pharmacokinetics, the penetration of CA in the lung is approximately 25–35% of concentration in the plasma. This is lower compared to other Gram-negative agents such as piperacillin (40–50%), MERO (50%, but varies widely), and 53% for vaborbactam in terms of penetration into the epithelial lining fluid (ELF) (8). For this reason, it would be useful to see efficacy data for CA in patients with more severe pneumonia, are critically ill with a higher metabolic state and augmented renal clearance, or with elevated MICs to determine if lung penetration is sufficient in such cases.

The REPROVE study also raises some safety concerns. In the CA group there were higher rates of serious adverse events (19% *vs.* 13%) such as diarrhea and liver abnormalities, which lead to study drug discontinuation as well as more adverse events leading to study drug discontinuation compared to MERO (4% *vs.* 2.7%). Further studies are needed to address these observations.

What do we know to date about the efficacy of CA to treat pneumonia due to CRE infections in clinical practice? Thus far, only a limited number of reports have emerged (4,9,10). In a 2017 paper from University of Pittsburg looking at blood stream infections from carbapenem-resistant *Klebsiella pneumoniae*, CA was compared to alternative therapies (9). Of the 109 patients, 13 received CA and 30 received a carbapenem plus colistin. Overall, patients receiving CA did relatively well, achieving a higher rate of clinical success compared to the alternative regimens (P=0.02), but there were only three patients in the CA group with pneumonia. In a 2018 paper from the same group, 77 patients with CRE infections were analyzed to better

understand risk factors associated with treatment failure and the development of resistance to CA (4). Nearly half of the treated patients in this study had pneumonia (43%), and 26% had bacteremia. The most common pathogen was carbapenem-resistant *K. pneumoniae*, which constituted 78% of the isolates. CA was used as monotherapy in 69% and in combination in 31% the patients and dosed as 2.5 grams intravenously (IV) every 8 hours for a median duration of 14 days. The median age of patients was 62, and about a quarter of patients (26%) were transplant recipients. The 30-day survival rate was 81% with clinical success achieved in 55% of patients. Success rates were highest for patients with urinary tract infections (88%) and primary bacteremia (75%), but lower for pneumonia (36%). By multivariate analysis, pneumonia (OR =3.10, 95% CI: 1.03–9.34; P=0.045) and receipt of renal replacement therapy (OR =4.78, 95% CI: 1.03–22.2; P=0.046) were independent predictors of clinical failure. Furthermore, pneumonia was the only predictor of microbiological failure (OR =2.71, 95% CI: 1.53–14.57; P=0.007). Fifty-eight percent and 35% of the *K. pneumoniae* isolates carried bla_{KPC-2} and bla_{KPC-3} respectively. CA resistance developed in 10% of patients, entirely in KPC-3 harboring isolates. Because CA use will largely be used in infections from CRE as opposed to MERO-susceptible isolates, this paper provides important and relevant data when considering its use in a real life manner. Lastly, *de novo* resistance (11) and evolution of resistance during CA treatment (including for pneumonia) have also been reported from other centers (3,12). This raises the possibility of a relatively low barrier to resistance for CA and has important implications for antibiotic stewardship programs. Given the potential benefit of the CA combination to treat CRE infections (10), prudence should be exercised to limit widespread use of CA for culture negative infections or when more narrow spectrum antibiotics are effective.

What explains the discordant findings from REPROVE (showing non-inferiority of CA compared to MERO for nosocomial pneumonia) compared to the 2018 Pittsburg group study (showing pneumonia to be an independent risk factor for clinical failure when using CA)? Two possible explanations come to mind. First, patients in the real world setting who receive CA are generally more medically complicated with comorbidities including immunosuppressed state and renal failure. Many of these patients were excluded from the REPROVE study. In the Pittsburg study however, 26% of patients were transplant recipients, more than half (57%) were in the ICU at disease onset. And of the 8 who developed resistance, 5 (63%) were receiving renal replacement therapy. The other explanation has to do with the pathogen. While the REPROVE study examined CA against mostly Enterobacteriaceae, they were largely meropenem-susceptible while the Pittsburg group included meropenem-resistant isolates. It is not reasonable to suggest that pharmaceutical companies study their drugs in all patient populations and for reasons stated above and it may not have been feasible to study CA against MERO plus polymyxin for CRE pneumonias. However, combining *in vitro* data demonstrating excellent activity of CA against CRE with clinical data showing activity in pneumonia does not seem to be sufficient to confidently use it in the real-world setting. Further studies need to clarify if pathogen-specific factors predispose to the rapid development of CA resistance in select clonal backgrounds, or if dosing adjustments or a combination with other antimicrobials may lead to better outcomes in patients with pneumonia.

In summary, REPROVE demonstrated that CA is a potentially valuable alternative in the treatment of nosocomial pneumonia, including VAP. Exclusion of high-risk populations such as transplant recipients and those with severe impairment of renal function or on HD, lack of a direct comparisons to CRE infections as well as some concerns regarding CA's safety profile still raise concerns about the clinical utility of CA in the treatment of CRE infections. These limitations require urgent future investigations, in particular in light of recent reports of higher treatment failures in patients with renal failure and renal replacement therapy, before CA can be considered part of first line for the treatment of pneumonia.

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Footnote

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