EDITORIAL

# Therapeutic Options for the Treatment of Carbapenem-resistant Enterobacteriaceae Infections: Hope in the Times of Hype and Despair

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"May your choices reflect your hopes, not your fears"—Nelson Mandela

## Background

Antimicrobial resistance is the most imminent threat to public health, and in the absence of an effective antimicrobial stewardship program, it threatens our healthcare delivery system to an unprecedented level of disruption.[1,2]

Acquisition of hospital-acquired infections is affected by a multitude of factors like underlying comorbidities, immune status, therapeutic interventions, prior antimicrobial exposure, and hospital infection control practices.[3,4] Among all the multidrug-resistant organisms, carbapenem-resistant Enterobacteriaceae (CRE) are of the highest concern due to their rising incidence and associated mortality.[5]

## Current Evidence

Barring a few consensus statements, there is a serious paucity of high-level evidence on managing CRE infections and an urgent need to find effective drugs in the post-carbapenem era.[6] Most CRE organisms have multiple resistance mechanisms (Ambler class A, B, and D), and a rapid screening for genetic mechanisms is possible with either conventional multiplex PCR or Xpert Carba-R assay.[7,8] Coproduction of NDM-1 with OXA-48 has been increasingly encountered in our intensive care units (ICUs) along with frequent possession of 16S rRNA methylase gene in NDM-producing Enterobacteriaceae.[9–11] In light of this, it becomes imperative for the clinician to use combination therapies in seriously ill patients with CRE infections as an initial inappropriate antibiotic regime has been associated with increased mortality or prolonged ICU stay.[12] Polymyxins (B and E) have exhibited their superiority for the treatment of CRE infections and remain the cornerstone molecule for both empiric monotherapy and combination regimes.[13,14] A preference for combination therapy in patients with high mortality risk score [INCREMENT-CPE score (ICS)] or worsening SOFA scores (>2) would be the right strategy in NDM-prevalent Indian setting.[15,16] Also, tigecycline and fosfomycin have shown considerable potential to counter CRE menace when used in combination regimes based on site of infection, PK/PD characteristics, and molecular resistance phenotypes.

Novel anti-infectives like CZA (ceftazidime + avibactam) or MER-VAB (meropenem + vaborbactam) do not provide cover against NDM which seriously limits their utility in Indian setting.[17-19] Although CZA salvage therapy for severe KPC (*Klebsiella pneumoniae* carbapenemase) infections including bacteremia has been well established, its utility would be of limited import for our CRE infections.[20]

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## The Study in the Current Issue

In this issue of the journal, a retrospective observational study taken up between February 2019 and January 2020 at two tertiary care centers has evaluated "Clinical outcomes of patients on CZA and combination therapy in CRE infections" with focus on underlying resistance mechanism and clinical cure rates[21]. The authors have explored the feasibility of CZA as monotherapy or in combination with AZT (aztreonam) and other agents based on the predominant phenotype of the CRE isolates. They have also documented a "Zone of Hope" by stacking CZA and AZT discs and/or MIC strips in close approximation to witness synergy and clearing zones of more than 18 mm. Out of a total 121 CRE isolates examined by Xpert Carba-R for rapid detection of gene sequences, only 57 patients were included for treatment comparison. Majority of the tested isolates were *Klebsiella pneumoniae* (83%) while remaining strains were *Escherichia coli* (17%) with OXA-48 (33%) and NDM (28%) being the dominant mechanisms of resistance. Nearly half of all the *Klebsiella* isolates were NDM + OXA-48 coproducers. There was a high degree of acute illness in the studied populations with majority of patients admitted in ICU (72%). Majority of them were afflicted with intra-abdominal (31.5%) and nosocomial pneumonia (26.3%) as the leading source of infection. CZA was used for OXA-48 producers either alone (23%) or in combination (77%) with other agents like polymyxin, tigecycline, or fosfomycin. For all NDM or NDM + OXA-48 coproducers, CZA + AZT was used in 30% of patients as synergistic combination while another agent like polymyxin

or fosfomycin was added to the remaining 70% of subjects. An overall clinical cure rate without relapse or death (within 30 days) was reported in 78% of patients with a crude mortality of around 21% in the studied population.

A similar retrospective study published recently from our country studied the impact of CZA in clinical outcomes of CRE infections in a total of 103 patients with a matching clinical cure rate of 73% with all-cause mortality of 27%. They reported an impressive 79% sensitivity to CZA on E-tests (Epsilometer test), demonstrating its feasibility as a viable therapeutic option though no association was identified between E-test sensitivity and overall mortality (20). The study in consideration has tried to offer real-world data and highlights the burden of serious infection especially *Klebsiella* species (NDM + OXA-48 coproducers) as the "Thanos" of CRE era. In conjunction with other established antimicrobial agents, CZA + AZT can rise to the occasion as a possible therapeutic option in an algorithmic-MIC-based approach against the rising menace of CRE. To name a few shortcomings, there appears an overgeneralization of outcome, lack of homogeneity, survivorship bias (the treatment arm comprised less than half of CRE isolates studied), and a quick estimate of the potential "Zone of Hope."

## Author's View

There is no hiding from the growing burden of CRE in Indian tertiary healthcare setting, the need for identification of resistance mechanisms, and the growing utility of combination therapies (cornerstone antibiotic with companion/adjuvant drugs) in treating this subset of critical patients. Further research with high-quality prospective/retrospective studies, case series, and meta-analyses to address this menace is a pressing priority.

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