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# Clinical profile and outcome of patients with pancreatic necrosis infected with carbapenem resistant infections (PanCRI): A prospective observational study

*Keywords:*
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Tigecycline

*Dear Editor,*

We read with interest the article by Lin C et al. that has shown high sensitivity and negative predictive value of metagenomic next-generation sequencing in the diagnosis of infections among patients with pancreatic necrosis. The authors stressed upon the importance of having confirmed microbiological diagnosis and possible harms associated with empiric antibiotics. This is especially important in countries with a high burden of carbapenem resistant infections as carbapenems are usually considered as antibiotics of choice owing to their good pancreatic concentrations.

We conducted a single-center prospective observational study from June 5, 2022 to December 31, 2022 among patients diagnosed with carbapenem resistant organisms (CRO)-infected necrotizing pancreatitis (approval number AIG/EIC-BH&R 29/06.2022–05). Consecutive patients diagnosed with CRO pancreatic infections were recruited from wards and intensive care units after taking written informed consent. Data including baseline characteristics at the time of diagnosing CRO infection, interventions performed, organisms isolated, antibiotics received, and superadded infections were noted. The primary objective was to study the treatment outcomes of CRO-infected pancreatic necrosis on day 28 and determine the clinical failure predictors. CRO infection was defined in a patient with pancreatic necrosis not improving on empiric antibiotics who had a pancreatic tissue sample or a drain growing a micro-organism that was found to be resistant to carbapenem on susceptibility testing. Patients with CRO infection were followed to the hospital until day 28 or discharge/death (whichever was earlier) from the recruitment day. The outcome was a clinical success if the patient improved clinically and was either discharged or showed stabilization/improvement in Serial Organ Failure Assessment score (SOFA) by day 28 from the time of recruitment. Conversely, the outcome was a clinical failure if the patient had expired or had deterioration in SOFA score by more than two from the time of recruitment.

During the study period, we recruited 48 patients with pancreatitis infected with CRO (Table 1 and Table 2). Of 48 patients with CRO-infected pancreatitis, ten patients succumbed to illness (20.8%). Clinical success was observed in 32 (66.6%) patients on Day 28 after diagnosis of CRO infection, whereas 16 patients had a clinical failure (33%). In univariate analysis, high SOFA score, APACHE II score, total leucocyte count (TLC), alanine transaminase (ALT), elevated blood urea, the requirement of oxygen, the requirement of vasopressors, and low albumin at the time of diagnosis of CRO infection were associated with higher clinical failure rates (Table 1). There was a trend toward increased adverse outcomes in patients who developed *Candida auris* infection.

Delayed drainage and debridement approach for treating infected necrotizing pancreatitis is favored as the collections take approximately 3–4 weeks to form walled-off necrosis and liquefy. In between, patients receive empiric antibiotics and other supportive care, with which a proportion of patients are rescued from intervention [1,2]. Traditionally, carbapenem antibiotics are preferred over other antibiotics due to their better penetration into the pancreatic tissue [3]. However, the increased prevalence of carbapenem-resistant infections poses a significant challenge to this approach [4]. Unlike severe acute pancreatitis, where culture isolation from the extra pancreatic site is more common, most patients with pancreatic necrosis are diagnosed with CRO infection only after drainage [5]. More importantly, 56% of patients were on ineffective empiric antibiotics against the eventually isolated bacteria. In this context, where empiric therapy is ineffective in many cases and the role of early microbiological diagnosis using invasive techniques or metagenomic next generation sequencing needs to be discussed. In previous studies, the role of fine needle aspiration (FNAC) cultures for diagnosing infected pancreatic necrosis was discredited due to no difference in diagnostic accuracy compared to clinical features and imaging [6]. However, clinical features and imaging cannot differentiate carbapenem-resistant infections from carbapenem-sensitive infections. Therefore, in areas with a high prevalence of carbapenem-resistant infections, the

*Abbreviations:* ALT, Alanine transaminase; BL-BLI, Beta Lactam-Beta Lactamase Inhibitor; CRO, Carbapenem Resistant Organisms; CT, Computed Tomography; DEN, Direct Endoscopic Necrosectomy; EUS, Endoscopic ultrasound; FNAC, Fine Needle Aspiration Cytology; NDM, New Delhi Metallo-beta-lactamase; SOFA, Serial Organ Failure Assessment; TLC, Total leucocyte counts.

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**Table 1**
Comparison of clinical characteristics and outcomes of patients with CRE-infected pancreatic necrosis.

| Parameters | | Clinical success (n = 32) | Clinical failure (n = 16) | p-value |
|---|---|---|---|---|
| Age | | 39.4 ± 10.8 | 43.2 ± 14.8 | 0.075 |
| Male gender | | 31 (96.8%) | 13 (81.2%) | 0.065 |
| Diabetes mellitus | | 11 (34.3%) | 3 (18.8%) | 0.262 |
| Hypertension | | 8 (25%) | 5 (31.2%) | 0.646 |
| SOFA score | | 1 [1,2] | 6 (2–9) | .000 |
| APACHE II SCORE | | 6 (4–10) | 12 (9–16) | .001 |
| Fever | | 17 (53.1%) | 10 (62.5%) | 0.537 |
| Oxygen requirement | | 8 (25%) | 12 (75%) | 0.01 |
| Vasopressor requirement | | 1 (3.1%) | 8 (50%) | <0.001 |
| Parenteral requirement | | 2 (6.3%%) | 3 (18.8%) | 0.181 |
| *Klebsiella pneumoniae* | | 26 (81.3%) | 12 (75%) | 0.358 |
| *Candida auris* | | 3 (9.4%) | 5 (31.3%) | 0.055 |
| Time from admission to *Candida* isolation | | 29.3 ± 13 | 35.4 ± 2.7 | 0.017 |
| *Enterococci* | | 6 (18.8%) | 5 (31.3%) | 0.331 |
| Time to *Enterococci* isolation | | 34.8 ± 15.1 | 32 ± 8.8 | 0.205 |
| Polymicrobial infection | | 4 (12.5%) | 1 (6.3%) | 0.504 |
| Resistance | Colistin | 4/32 | 2/16 | 0.359 |
| | Minocycline | 22/31 | 11/16 | 0.765 |
| | Tigecycline | 7/32 | 3/14 | 0.124 |
| | Fosfomycin | 6/7 | 6/9 | 0.038 |
| | Amikacin | 18/32 | 11/16 | 0.404 |
| | Ceftazidime | 29/31 | 16/16 | 0.449 |
| Before culture | Carbapenem | 19 (59.37%) | 13 (81.25%) | 0.13 |
| | BL-BLI | 21 (65.6%) | 9 (56.2%) | 0.527 |
| | Aminoglycoside | 5 (15.6%) | 1 (6.2%) | 0.355 |
| | Tigecycline | 9 (28.1%) | 9 (56.2%) | 0.058 |
| | Minocycline | 1 (3.1%) | 0 | 0.475 |
| | Polymyxins | 5 (15.6%) | 5 (31.2%) | 0.209 |
| After culture | Ceftazidime-avibactam ± Aztreonam | 11 (34.4%) | 7 (43.7%) | 0.527 |
| | Polymyxins | 8 (25%) | 8 (50%) | 0.083 |
| | Minocycline | 3 (9.4%) | 1 (6.25%) | 0.712 |
| | Tigecycline | 21 (65.6%) | 8 (50%) | 0.297 |
| | Fosfomycin | 2 (6.25%) | 2 (12.5%) | 0.46 |
| | Amikacin | 10 (31.25%) | 2 (12.5%) | 0.157 |
| Procalcitonin (Median) | | 0.77 (0.32–1.96) | 0.83 (0.6–7.9) | 0.458 |
| Open necrosectomy | | 9 (28.12%) | 6 (37.5%) | 0.509 |
| PCD | | 24 (75%) | 15 (93.7%) | 0.117 |
| EUS drainage | | 10 (31.25%) | 4 (25%) | 0.653 |
| DEN | | 6 (18.8%) | 2 (12.5%) | 0.584 |
| Time from admission to culture positive | | 10 (6.5–19) | 10 (5–26) | .869 |
| TLC (cells/mm3) | | 13,300 (10,050–15800) | 20,700 (10,300–38100) | .012 |
| Albumin level (grams/dl) | | 2.6 (2.2–3) | 2.3 (2.1–2.7) | .010 |
| Blood Urea (mg/dl) | | 21 (18–25.5) | 56 (34–63) | <0.001 |
| Creatinine (mg/dl) | | 0.7 (0.68–0.74) | 0.7 (0.67–0.86) | .662 |
| Total Bilirubin (mg/dl) | | 0.9 (0.6–1.15) | 1.2 (0.8–2.2) | .057 |
| AST | | 25 (17–51) | 38 (29–90) | .067 |
| ALT | | 15 (11–33.5) | 30 (21–69) | .015 |
| Duration of antibiotics | | 14 (8.5–21) | 12 (7–23) | .574 |

SOFA- Serial organ failure assessment; APACHE II- Acute Physiology and Chronic health evaluation II; PCD- Percutaneous drainage; EUS-Endoscopic ultrasound; DEN-Direct endoscopic necrosectomy; TLC-Total leucocyte count; AST- Aspartate transaminase; ALT-Alanine transaminase.

role of FNAC cultures needs to be reinvestigated. The role of metagenomic next generation sequencing for suspected infected pancreatic necrosis should be further studied not only to identify the causative microorganism but also to understand the genomic resistance to improve the patient outcomes.

## Author contributions

Praveen T, Shravani E and Siva K contributed to study conception. Anand G, Hardik R and Haripriya C contributed to design of study. Shravani E and Chandu D carried out the study. Chandu D, Nitin G and Aniruddha P analyzed and interpreted the data. Sadhana V, Naveen P and Santhosh S drafted the article. All authors reviewed and approved the final version of manuscript.

**Table 2**
Outcomes of Ceftazidime-avibactam and Aztreonam in managing CR *Klebsiella pneumoniae* isolates.

| Sn | Age/ sex | Duration of ceftazidime-avibactam + aztreonam | Antibiotics received before Ceftazidime avibactam + aztreonam | Carba R test | Phenotypic double disc test for synergy | Outcomes |
|---|---|---|---|---|---|---|
| 01 | 25/M | 17 days | Meropenem, Cefoperazone -Sulbactam, Polymyxin B | Not done | Not done | Survived |
| 02 | 18/M | 6 days | Tigecycline, Imipenem - Cilastatin | NDM & OXA-48 | Not done | Survived |
| 03 | 45/M | 16 days | Tigecycline, Imipenem - Cilastatin | NDM & OXA-48 | Not done | Survived |
| 04 | 23/M | 28 days | Tigecycline, Imipenem - Cilastatin | Not done | Synergy positive | Survived |
| 05 | 24/M | 10 days | Cefoperazone - sulbactam, Imipenem - Cilastatin | NDM | Not done | Survived |
| 06 | 36/M | 14 days | Colistin, Minocycline | NDM | Not done | Survived |
| 07 | 56/F | 17 days | Meropenem, Cefoperazone - sulbactam | NDM &OXA-48 | Not done | Survived |
| 08 | 55/M | 08 days | Meropenem, Tigecycline | NDM &OXA-48 | Not done | Expired |
| 09 | 34/M | 10 days | Meropenem, Amikacin | Not done | Synergy positive | Survived |
| 10 | 53/M | 02 days | Meropenem, Cefoperazone -sulbactam, Tigecycline, Polymyxin - B | Not done | Not done | Mortality |
| 11 | 40/M | 08 days | Meropenem, Tigecycline, Colistin | NDM &OXA-48 | Not done | Survival |
| 12 | 49/M | 22 days | Meropenem, Cefoperazone + -sulbactam, Tigecycline, Polymyxin - B | Not done | Not done | Mortality |
| 13 | 35/M | 22 days | Tigecycline, Meropenem | Not done | Synergy positive | Survived |
| 14 | 45/M | 28 days | Polymyxin B, Tigecycline, Meropenem | Not done | Synergy positive | Survived |
| 15 | 44/M | 06 days | Cefoperazone -Sulbactam, Piperacillin -Tazobactam | Not done | Synergy positive | Survived |
| 16 | 36/M | 25 days | Meropenem | Not done | Synergy positive | Survived |
| 17 | 55/M | 05 days | Imipenem + Cilastatin, Tigecycline. | Not done | Synergy positive | Survived |
| 18 | 31/M | 12 days (Ceftazidime + Avibactam) alone | Cefoperazone + sulbactam, Imipenem + Cilastatin | OXA-48 | Not done | Survived |

NDM - New Delhi metallo-beta-lactamase.

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## Declaration of competing interest

The authors have no conflicts of interest to disclose.

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