Carbapenem-resistant Enterobacterales (CRE) is an urgent public health threat of significant global concern that accounted for more than 1100 deaths per the 2019 CDC report for antibiotic resistance.1 CRE is associated with higher mortality rate, with an approximately 2-fold increase in mortality compared with infections with carbapenem-susceptible Enterobacterales.2 Carbapenemases produced by CRE have been classified into three different groups according to Ambler classification: class A [e.g. Klebsiella pneumoniae carbapenemase (KPC)], class B or MBL (e.g. VIM) and class D [e.g. oxacillinase (OXA-48)].2,3 Local data that describe the molecular epidemiology of CRE in Saudi Arabia found that OXA-48 accounted for 71.2% (n = 292) of 410 carbapenemase-producing CRE isolates, followed by NDM (n = 85; 20.7%) and NDM + OXA-48 (n = 33; 8%).4 Alqahtani et al. The new □-lactam/□-lactamase inhibitors have gained significant interest for their favourable outcomes in terms of clinical efficacy and safety profile.5 Ceftazidime/avibactam is a combination of a third-generation cephalosporin, ceftazidime, and the novel, non-□-lactam □-lactamase inhibitor avibactam, which possesses the ability to treat carbapenemase-producing CRE (CP-CRE).5 Ceftazidime/avibactam was approved by the FDA in 2015 for complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs) and, in 2018, for the treatment of hospital-acquired pneumonia (HAP) and ventilator- associated pneumonia (VAP).6 Few observational studies have evaluated the clinical outcomes for treatment of CP-CRE harbouring OXA-48 with ceftazidime/avibactam.7,8 Findings of these studies showed lower 30 day mortality with ceftazidime/avibactam ranging between 8.3% and 22%.7,8 Notably, the small sample size of both studies would affect its generalizability and increase the value in other studies with larger sample sizes. Considering the high prevalence of Gram-negative resistant pathogens, particularly CP-CRE, at our institution,9 the aim of this study was to evaluate the clinical efficacy of ceftazidime/avibactam for treatment of CP-CRE harbouring OXA-48 and/or NDM. Methods Study design and setting This was a retrospective, observational, single-centre study conducted at King Abdulaziz Medical City (KAMC) from January 2018 to November 2020. KAMC is a Joint Commission International (JCI)-accredited 1500-bed tertiary care academic medical centre in Riyadh, Saudi Arabia. Study population The inclusion criteria of patients were if they were adults (age ≥18 years) and had received ceftazidime/avibactam alone or in combination for ≥72 h as treatment of a confirmed infection secondary to CP-CRE with a detected gene encoding for carbapenemase production. At least one isolate was collected and isolated from each case for microbiological analysis. All patients were stratified into two groups: those who had received ceftazidime/avibactam alone (monotherapy group) and those who had combination therapy added to ceftazidime/avibactam for treatment of CP-CRE as per definition (combination therapy group). Patients with polymicrobial infections and those who did not receive aztreonam in combination with ceftazidime/avibactam for CP-CRE encoded with NDM were excluded. The study was approved by the

institutional review board at King Abdullah International Medical Research Center (KAIMRC). Clinical data were collected from electronic medical records and de-identified for further review. Relevant information, including demographic data, baseline comorbidities, Charlson comorbidity index, infection and treatment-related variables, was recorded. Microbiological tests Microbiological tests for bacterial identification and susceptibility testing were performed in the laboratory department in accordance with CLSI protocols. Susceptibility tests were conducted by an automated susceptibility testing system via the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France). Per local microbiology lab protocol, isolates were subjected for further work-up when susceptibility tests showed resistance to ertapenem, meropenem or imipenem/cilastatin, defined as when MICs are at the resistance cut-off of the susceptibility breakpoints determined by CLSI protocol (≥1 mg/L for meropenem and imipenem/cilastatin and 2 ≥0.5 mg/L for ertapenem). Such isolates would undergo PCR-based testing to identify the presence of any gene coding for carbapenemase production and thus classified as CP-CRE. Ceftazidime/avibactam MICs were determined by Etest (bioMérieux). Broth microdilution was used to determine colistin MICs. The results were interpreted in accordance with the CLSI clinical breakpoints (≤2 mg/L interpreted as susceptible or intermediately susceptible, after recent updates of CLSI in 2020). Carbapenemase gene content was detected using the GeneXpert Carba-R PCR assays (Cepheid, Sunnyvale, CA, USA) targeting blaKPC, blaOXA-48-like, blaVIM, blaNDM and blaIMP. Antimicrobial therapy Ceftazidime/avibactam is a restricted medication at KAMC for critical care, haematology/oncology and infectious disease (ID), and it can be dispensed for 72 h without an ID approval. Therapy with ceftazidime/avibactam was usually started by the primary treating physician, which was often followed by an ID consultation. Dosage set was 2.5 g every 8 h to be infused over 2 h. Other antibiotics that were frequently used as a combination therapy for CP-CRE were colistin, amikacin, gentamicin, tigecycline and aztreonam. Definitions The infection source was determined based on the CDC/National Healthcare Safety Network criteria. Treatment regimens were classified as monotherapy (treatment with ceftazidime/avibactam alone) or combination therapy, defined as the addition of other IV antimicrobials with in vitro activity against the clinical isolate or the addition of aztreonam to ceftazidime/avibactam for isolates with NDM genes detected. Concomitant treatment with metronidazole (when required for anaerobic coverage) was not considered as combination therapy. Acute kidney injury (AKI) was defined as an increase in serum creatinine by 0.3 mg/dL over 48 h or a reduction in urine output to 0.5 mL/kg/h over 6 h. Outcomes Primary outcomes were determined to be clinical cure at completion of therapy and 30 day mortality rate. For the secondary outcomes, 60 day mortality and relapse rate within 30 days of completion of ceftazidime/ avibactam therapy for primary infection were determined. Safety outcomes include development of adverse drug reactions related to ceftazidime/avibactam. Clinical cure was defined as clinical improvement with no signs or symptoms of systemic infection (absence of fever, leucocytosis and elevated inflammatory markers) at the completion of therapy. Relapse was defined as reinfection with the same organism within 30 days after completion of ceftazidime/avibactam therapy. s A total of 233 confirmed infections with CRE were identified between January 2018 and November 2020. Twenty-two patients were excluded for not fully meeting the inclusion criteria. A total of 211 patients received ceftazidime/avibactam for CP-CRE infection during the study period (Figure 1). For those who

received ceftazidime/avibactam as monotherapy (n = 119), the average age was 66 years and the majority of these were male (55.6%). Combination therapy was prescribed for 92 patients (61% male) with an average age of 56 years. HTN and DM followed by heart disease were the most frequently seen comorbidities in monotherapy and combination therapy groups [(70% versus 48%; P = 0.015); (69% versus 49%; P = 0.031); (54% versus 48%; P = 0.259)], respectively. There were 61 (51.3%) patients with a Charlson index score of 5 or higher in the monotherapy group and 36 (39%) in the combination group (P = 0.08). Infection biochemical markers, including leucocytosis, elevated procalcitonin, high erythrocyte sedimentation rate and C-reactive protein, were elevated in both groups with no statistically significant differences (Table 1). Compared with the monotherapy group, more patients in the combination group were in ICUs when cultures were collected (61% versus 43%; P = 0.025). The number of patients receiving invasive MV and vasopressors was significantly higher in the combination group compared with the monotherapy group (55% versus 39%; P = 0.021 and 46% versus 32.8%; P = 0.051, respectively). The most frequently isolated pathogens from 211 patients were K. pneumoniae (189/211; 90%), Escherichia coli (9/211, 4.3%) and Enterobacter spp. (9/211; 4.3%). The majority of collected specimens were from the respiratory tract (sputum, tracheal aspirate, bronchoalveolar lavage) (31.3%), followed by urine (27.5%) and blood (25.6%). More than 80% of isolates (171/211; 81%) carried OXA-48 genes, followed by NDM ± OXA-48 (40/211; 19%). Ceftazidime/avibactam susceptibility was done for 76 isolates (44 and 32 in the monotherapy group and combination groups, respectively); these were all susceptible and carried the OXA-48 gene. Pneumonia (HAP and VAP) was the most frequently encountered ID (31.3%) followed by UTIs (26.5%) and bacteraemia (25.6%) (Figure 2). The appropriateness of ceftazidime/avibactam dosing was observed in 77.7% of the total cohort; however, 6% received higher doses since they were determined to have resolved AKI secondary to sepsis, and 17% received lower doses than recommended. The median time between identifying CP-CRE and ceftazidime/avibactam initiation was 24 h in both groups. The mean duration of ceftazidime/avibactam therapy was prolonged in combination therapy (17 versus 14 days; P = 0.08). Combination therapy was prescribed for 92 patients, 45% of whom received aztreonam; 27%, colistin; 20%, gentamicin; and the remaining received tigecycline (17.4%) and amikacin (11%) (Table 2).