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Carbapenemase-producing *Enterobacteriaceae* infections in General Surgery patients: Our experience☆

Infecciones por Enterobacterias productoras de carbapenemasas en pacientes de Cirugía General: análisis de nuestra experiencia

During the last decade, infections caused by carbapenemase-producing *Enterobacteriaceae* (CPE) have been dramatically increased worldwide. Numerous publications have focused on the epidemiology and risk factors for CPE-related infections,[1–3] although studies about surgical patients are scarce. Recognizing patterns in patients admitted to a General Surgery Department (GSD), could be essential to ensure a more rational antibiotic use in this specific setting. We performed a retrospective review including nosocomial CPE infections inpatients admitted to the GSD from January 2013 to December 2016. We analyzed patients with at least one (new) positive culture 48 h after admission for a CPE at any location and associated clinical signs or symptoms of infection. The probable infectious source was defined according to microbiological results and the analysis of clinical findings by two physicians in accordance with Centers for Disease Control definitions.[4] Patient's samples were collected and incubated based on standard recommendations.[5] We investigated the clinical and microbiological characteristics, treatment, complications, antimicrobial susceptibility and risk factors for mortality.

We included 40 patients with a CPE clinical infection: 50% were male, with a mean age of 69.4 ± 13.4 years. Charlson's comorbidity index median value was 3 (range 1–5). The rate of CPE infections in the GSD increased annually from 1.2% in 2013, to 4.7% in 2016.

Carbapenemase-producing *Klebsiella pneumoniae* strains were the most commonly identified (92.5%), all with the OXA-48-like carbapenemase. Prior to the CPE infection, other non-resistant microorganisms isolated were Gram-negative bacteria (52.5%), Gram-positive bacteria (65%), and fungi (40%). Intra-abdominal site was the most frequent source of infection (55%), followed by surgical wound (22.5%). CPE were susceptible to amikacin (100%), tigecycline (97%), and colistin (76%), and showed increased MICs but acceptable susceptibility to meropenem (64.3%) and imipenem (52.5%). CPE isolates showed low susceptibility rates to ertapenem (8.8%) and ciprofloxacin (5.3%).

Median hospital stay was 41.5 days (range 26.2–74.5). A surgical procedure had been performed in 35 patients in the previous 30 days, including emergency surgery in 15 cases. A major complication occurred in 23 patients, with a mortality rate of 17.1% in patients who underwent a surgery. A postoperative intra-abdominal infection (IAI) was present in 19 cases. The reoperation rate was 32.5%, without differences regarding mortality compared to non-reoperation. All patients received antibiotic therapy, of which 28 patients received carbapenem therapy. Table 1 shows the analysis of factors associated with mortality. Six patients received an appropriate empirical antibiotic regime, according to the *in vitro* activity. Appropriate definitive antimicrobial treatment was administered to 32 patients. The mortality rate at 30 days was 15%. Factors associated with mortality were: blood transfusions ($p = 0.021$), and lower rate of major complications (Clavien-Dindo ≥ III) ($p = 0.031$). A combined definitive two-drug targeted scheme was protector for mortality ($p = 0.048$).

This study summarizes the outcomes of patients with CPE infections in a GSD. The specific characteristics of this population were age >65 years, previous comorbidities (solid tumor, diabetes, and renal insufficiency), some risk factors for multidrug-resistant infections (including prior hospitalization and antibiotic therapy), all previously described.[1,2,6] In our series, antibiotic therapy had been previously prescribed in all patients (carbapenem therapy in 70%), with high rates of previous hospitalizations, surgery and endoscopic procedures. These findings agree with those of a recently published study of patients admitted in a surgical ICU from a tertiary-care Spanish hospital.[6] In addition, other investigations detailed that factors related with the acquisition of a CPE infection in solid organ recipients are poor functional status and frequent antimicrobial therapy, which more frequently occurs in the early post-transplant period.[7]

Intra-abdominal location was the most common source of CPE infection in our patients (the majority of patients had undergone an abdominal surgery). A two-drug scheme was a protective factor for mortality, and this combination is recommended by current guidelines on the treatment of IAI.[8,9] Despite this, several studies have not identified these differences in all patients and propose appropriate monotherapy for patients with low-mortality risk scores.[10]

Although this study only represents a review of an experience in a GSD of a single-institution with a limited number of patients, it shows a current vision of an increasing problem in a less analyzed population. As physicians prescribing antimicrobials, we may need to pay attention to patients with a specific clinical profile, using a targeted treatment for each patient. Future studies on CPE-related intra-abdominal infections could determine more definite features and outcomes in specific settings with surgical patients.

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Table 1
Analysis of factors associated with mortality in patients with infection caused by carbapenemase-producing *Enterobacteriaceae* (CPE).

Characteristic	Total, *n* = 40	Survivors, *n* = 34 (85%)	Non-survivors, *n* = 6 (15%)	*p* value	OR (95% CI)
Patient-related					
Male	20 (50)	17 (50)	3 (50)	0.93	0.89 (0.16–5.04)
Age (years), mean ± SD	69.4 ± 13.4	68.9 ± 13.8	71.7 ± 12.3	0.65	NA
Cardiovascular disease	8 (20)	5 (14.7)	3 (50)	0.08	5.80 (0.90–37.28)
COPD	4 (10)	4 (11.8)	0 (0)	0.94	NA
Solid tumor	17 (42.5)	12 (35.3)	5 (83.3)	0.07	9.17 (0.96–87.78)
Immunodeficiency	7 (17.5)	4 (11.8)	3 (50)	0.05	7.5 (1.11–50.66)
Diabetes	10 (25)	10 (29.4)	0 (0)	0.31	NA
Chronic renal failure/dialysis	10 (25)	9 (26.5)	1 (16.7)	0.89	0.56 (0.06–5.42)
Charlson comorbidity index, median (IQR)	3 (1–5)	3 (1–5)	6.5 (3–9)	0.12	NA
Pre-infection intervention					
Hospitalization[a]	26 (65)	21 (61.8)	5 (83.3)	0.40	3.09 (0.32–29.53)
Surgery[b]	35 (85)	28 (82.4)	6 (100)	0.56	NA
Antibiotic therapy[b]	40 (100)	34 (100)	6 (100)	0.95	NA
Prior carbapenem therapy[b]	28 (70)	23 (67.6)	5 (83.3)	0.65	2.39 (0.25–23.01)
Dialysis[c]	3 (7.5)	2 (5.9)	1 (16.7)	0.39	3.2 (0.24–42.18)
ICU[d]	13 (32.5)	10 (29.4)	3 (50)	0.37	2.4 (0.41–13.98)
Endoscopy[c]	15 (37.5)	12 (35.3)	3 (50)	0.65	1.83 (0.32–10.53)
Central venous catheter[c]	24 (60)	19 (55.9)	5 (83.3)	0.37	3.95 (0.42–37.49)
Parenteral nutrition[c]	23 (57.5)	18 (52.9)	5 (83.3)	0.22	4.44 (0.47–42.17)
Blood transfusion	21 (52.5)	15 (44.1)	6 (100)	0.021	NA
ASA score III or IV	26 (76.5)	20 (71.4)	6 (100)	0.30	NA
Reoperation[c]	13 (32.5)	11 (32.4)	2 (33.3)	0.91	1.04 (0.17–6.60)
Infection-related					
Intra-abdominal source	22 (55)	17 (50)	5 (83.3)	0.19	5.00 (0.53–47.43)
Surgical wound	9 (22.5)	9 (26.5)	0 (0)	0.82	NA
Catheter-related	1 (2.5)	1 (2.9)	0 (0)	0.90	NA
Urinary	6 (15)	5 (14.7)	1 (16.7)	0.84	0.93 (0.09–9.51)
Pneumonia	2 (5)	2 (5.9)	0 (0)	0.91	NA
Septic shock	13 (32.5)	9 (26.5)	4 (66.7)	0.07	5.56 (0.86–35.71)
Treatment-related					
Adequate empirical antimicrobial treatment	6 (15)	6 (17.6)	0 (0)	0.87	NA
Adequate post-antibiogram treatment	32 (80)	28 (82.3)	4 (66.7)	0.73	0.92 (0.08–10.15)
Post-antibiogram combination therapy	30 (75)	26 (76.5)	4 (66.7)	0.45	0.40 (0.03–4.83)
Two-drug combination	28 (70)	27 (79.4)	1 (16.7)	0.048	0.09 (0.01–0.96)

Data are expressed as *n* (%), unless otherwise stated.
[a] During the 12 months preceding infection onset.
[b] During the 30 days preceding infection onset.
[c] During the current hospitalization.
[d] ICU (intensive care unit) admission includes only stay >48 h.
ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NA: non-applicable; OR: odds ratio; SD: standard deviation.

Conflicts of interest

The authors report none conflict of interest to declare for the present study.

Bibliografía

1. Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH. Global dissemination of Carbapenemase-producing *Klebsiella pneumoniae*: epidemiology, genetic context, treatment options, and detection methods. Front Microbiol. 2016;7:895.
2. Mariappan S, Sekar U, Kamalanathan A. Carbapenemase-producing Enterobacteriaceae: risk factors for infection and impact of resistance on outcomes. Int J Appl Basic Med Res. 2017;7:32–9.
3. Dimopoulos G, Akova M. An overview on severe infections in Europe. Intensive Care Med. 2017;43:686–9.
4. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128–40.
5. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. Version 1.0, December 2013. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_v1.0_20131211.pdf [accessed July 2014].
6. Maseda E, Salgado P, Anillo V, Ruiz-Carrascoso G, Gómez-Gil R, Martín-Funke C, et al. Risk factors for colonization by carbapenemase-producing Enterobacteria at admission to a Surgical ICU: a retrospective study. Enferm Infecc Microbiol Clin. 2017;35:333–7.
7. Pouch SM, Satlin MJ. Carbapenem-resistant *Enterobacteriaceae* in special populations: Solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. Virulence. 2017;8:391–402.
8. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt). 2017;18:1–76.
9. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
10. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis. 2017;17:726–34.

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