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Original Article

Carbapenemase Production is Not Associated with Increased Mortality in Carbapenem-Nonsusceptible Enterobacteriaceae (CNSE) Bacteremia Patients: A Retrospective Study

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SUMMARY

Objectives: The aims of this study were to identify whether underlying carbapenem-nonsusceptible Enterobacteriaceae (CNSE) resistance mechanism was associated with clinical outcomes, and to evaluate risk factors for 7-day and 28-day mortality in patients with CNSE bacteremia
Material and methods: A retrospective cohort study was conducted at a 2108-bed tertiary medical center. All medical charts of adult patients with carbapenem-resistant Enterobacteriaceae bacteremia from January 2013 to December 2018 were reviewed and included. The PCR techniques was used to screen the bacterial isolates collected for the presence of carbapenemase genes.
Results: Of 99 patients with CNSE bacteremia, 13 (13.1%) were infected with carbapenemase-producing CNSE (CP-CNSE), and 86 (86.9%) with non-CP-CNSE. Risk factors for seven-day mortality in CNSE bacteremia included failure to prescribe at least one active antibiotic within three days of culture availability, respiratory failure after onset of bloodstream infection (BSI), steroid use ≤ 3 days prior to onset of BSI, septic shock at time of BSI, and underlying hematologic malignancies. Risk factors for twenty-eight mortality included failure to prescribe at least one active antibiotic within three days of culture availability, respiratory failure post BSI, septic shock at time of BSI, and use of mechanical ventilation at the time of BSI. Carbapenemase production and patient age did not affect 7-day or 28-day mortality.
Conclusions: The results of this study indicate that prescribing at least one active antibiotic post culture availability reduces mortality in those with CNSE bacteremia. Carbapenemase production is not a risk factor for mortality in those with CNSE bacteremia.

1. Introduction

Enterobacteriaceae are common pathogens in both hospital and community settings. When these pathogens gain the ability to resist powerful and versatile antibiotics such as carbapenems they can wreak devastating consequences.[1] Infections caused by carbapenem-nonsusceptible Enterobacteriaceae (CNSE) with production of various carbapenemases have been reported to be associated with high (≥ 30%) case-fatality rates even with the currently available antibiotic armaments.[2–4] CNSE blood-stream infection is a public health concern not only because it is associated with high mortality rates, but also with a rapidly increasing global spread, and a propensity for multidrug resistance.[5] Mechanisms of carbapenem resistance included carbapenemase production, a combination of AmpC hyper-production and/or extended spectrum beta-lactamase (ESBL) production, and porin mutation.[6] The primary aim of this study is to determine and compare the mortality rates associated with carbapenemase producing CNSE (CP-CNSE) and non-carbapenemase-producing CNSE (non-CP-CNSE). Furthermore, we hope to elucidate the patient risk factors that may contribute to CNSE mortality and bacteremia.

2. Methods

2.1. Bacterial isolates

From January 2013 to December 2018, blood isolates of *Enterobacteriaceae* were collected at MacKay Memorial Hospital, a tertiary medical center in Taiwan. Collected isolates were identified using Vitek 2 system (bioMe'rieux Vitak System Inc., Hazelwood, MO, USA). For patients with more than one positive blood culture, only the first isolate was included. Antibiotics susceptibility testing were interpreted according to the Clinical Laboratory Standards Institute (CLSI) guidelines.[7] Carbapenem-nonsusceptibility was defined as ertapenem MIC ≥ 1. Isolates were kept frozen at -70 °C in trypticase soy broth (BC, Sparks, MD, USA) containing 20% glycerol (v/v) until further testing.

2.2. Gene detection

The isolates were placed in sterile water and boiled for the duration of 10 minutes. The supernatant was collected to serve as

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DNA sources for the PCR. The reaction mix employed in this study consisted of 1X S-T Gold buffer, 1.5 mM or $MgCl_2$, 0.3 mM of dNTPs, 20 pmol of primers, and 0.4 units of Super-Therm polymerase. The PCR techniques was used to screen the bacterial isolates collected for the presence of carbapenemase genes and β-lactamase genes. Gene products were subsequently presented on agarose gel, followed by ABI prism 3730 XL DNA analyzer (Applied Biosystems, Foster City, CA, USA) sequence analysis of the amplicons.

2.3. Study population and data collection

The medical charts of all patients with CNSE bloodstream infection were reviewed retrospectively. Bloodstream infection of CNSE was defined as the isolation of CNSE from one or more blood cultures with clinical features of infection. Patients with age < 20 were excluded from this study. Patient demographic data including age and sex, comorbidities, and past medical histories were collected. Furthermore, any use of broad-spectrum antibiotics within 30 days prior to the time of bacteremia was collected.

An active and adequate empirical therapy was defined as the administration of at least one antimicrobial agents to which pathogen was sensitive to *in-vitro* within 48 hours of bacteremia; moreover, administration must be of appropriate route and dosage for end organ function, prior to the availability of culture results. Effective culture-directed antibiotic was defined as the administration of at least one antimicrobial agent within 72 hours of culture result availability, to which the bacteria is sensitive to *in-vitro*. The primary outcomes of interest were 7-day and 28-day patient mortality rates. This retrospective study was approved by the MacKay Memorial Institutional Review Broad (protocol numbers 20MMHIS394e).

2.4. Statistical analysis

Categorical variables were presented as numbers and percentages (or positive rates). Continuous variables were presented as the mean ± standard deviation (SD) or the median with inter-quartile range (IQR). Categorical variables were analyzed using the chi-square test, Pearson $\chi 2$ test or Fisher's exact test as appropriate. Binary logistic regression was used to identify independent risk factors for the 7-day and 28-day mortality. Odds ratios (OR) and 95% confidence intervals (CI) were analyzed separately for each of the risk factor variables by the univariate analysis. Subsequently, all significant variables with p value ≤ 0.05 in the univariate analysis were carried into the multivariate analysis of the binary logistic regression (method: forward conditional). All reported p values were based on two-tailed tests and were considered statistically significant if they were < 0.05. Data were analyzed using IBM SPSS release 21.0 (IBM, Armonk, New York).

3. Results

From January 2013 to December 2018, a total of 113 Enterobacteriaceae isolates were collected. Among the collected isolates, 74 were determined to be *Klebsiella pneumonia*, 23 *E. coli*, 16 *Enterobacter cloaecae*, 1 *Proteus mirabilis*, and 1 *Serratia marcensens*. Four isolates were excluded from the study due to collection from samples other than blood. A total of 111 blood isolates collected from 99 patients were eventually included in the current study. The mean age of study population was 70.15 years old, with standard deviation of 12.46. The median length of stay was 32 days, with interquartile range of 47. Fifty-seven (57/99 or, 57.6%) of the patients included were male and forty-two patients (42/99 or, 42.4%) were female. Thirty-three (33/99 or, 33.3%) patients were younger than 65 years old and sixty-six (66/99 or, 66.7%) patients were over 65 years of age.

Among the study group, 22 patients (22/99 or, 22.2%) had history of steroid use prior to the onset of bacteremia. Furthermore, 52 (52/99 or, 52.5%) patients had an indwelling catheter prior to the onset of bacteremia, and 18 (18/99 or 18.2%) patients had a history of recent surgical interventions or interventions with an invasive procedure prior to the onset of bacteremia. Moreover, among the study population 27 (27/99 or, 27.3%) patients had respiratory failure requiring mechanical ventilation prior to the onset of bacteremia. In terms of patient co-morbidities, 37 patients (37/99 or, 37.4%) had solid tumors; 43 patients (43/99 or, 43.4%) had diabetes; 20 patients (20/99 or, 20.2%) had chronic kidney disease requiring regular renal replacement therapy. Baseline characteristics of the study population are shown in Supplementary Table 1.

Sixteen (16/111, or 14.4%) isolates were CP-CNSE and ninety-five (95/111, or 85.5%) isolates were non-CP-CNSE. The susceptibility profiles of the carbapenem-nonsusceptible *Enterobacterales* included in this study is as shown in Table 1. Among the CP-CNSE isolates, 12 (12/16, or 75%) were identified as *Klebsiella pneumoniae*, 3 *E. coli* (3/16, or 18.8%), and 1 *Enterobacter cloacae* (1/16, or 6.25%). The types of carbapenemase identified in this study included one OXA48, one VIM, two NDM, five IMP, and seven KPC isolates. Among the non-CP-CNSE isolates 60 (60/95, or 75.4%) were identified as *Klebsiella pneumonia*, 19 *E. coli* (19/95, or 20%), and 14 *Enterobacter cloacae* (14/95, or 14.7%). The mechanisms of resistance among the non-CP-CNSE isolates were identified to be conferred mostly by production of one or more than one other β-lactamases, including CTX-M group 1 (11/95, or 11.6%), CTM-X group 9 (41/95, or 43.2%), SHV (60/95, or 63.2%), TEM (31/95, or 32.6%), DHA (52/95, or 54.7%), and CMY (16/95, or16.8%). No carbapenemase or β-lactamases genes were detected among the *Proteus mirabilis*, and *Serratia marcensens* isolates. The identifications of β-Lactamase genes are provided in Supplementary Table 2.

Thirty-eight (38/99 or, 38.4%) patients died within 28 days, while nineteen (19/99 or, 19.2%) patients died within the first 7 days. Among the thirteen CP-CNSE bacteremia patients, five patients died within 28 days, while three patients died within the first 7 days. After adjusting for possible confounders, the odds of mortality within 28-days between CP-CNSE and non-CP-CNSE study groups was 1.004 (CI = 0.303–3.329, p = 0.995), while the odds of mortality within 7-days was 1.312 (CI = 0.324–5.322, p = 0.703). Multivariate analysis showed that respiratory failure at the onset of bacteremia (odds ratio = 5.327, CI = 2.084–13.616, $p \leq 0.001$) was an independent risk factor for 28-day mortality, and prescription of ≥ 1 active culture directed antibiotic within 3 days after culture availability (odds ratio = 0.296, CI = 0.105–0.832, p = 0.021) was an independent protective

Table 1
Susceptibility profiles of the carbapenem-nonsusceptible *Enterobacterales*.

	CP-CNSE				Non-CP-CNSE			
	Total	S	R	R(%)	Total	S	R	R(%)
Ertapenem	13	0	13	100%	86	0	86	100%
Imipenem	12	0	12	100%	85	21	64	21.71%
Meropenem	0	0	0	--	31	29	2	6.45%

Resistance rate includes resistant and intermediate isolates, based on CLSI criteria.
CP-CNSE, carbapenemase-producing carbapenem nonsusceptible Enterobacteriaceae isolates containing carbapenemase producing genes: bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{OXA-48} and bla_{NDM}; Non-CP-CNSE: non-carbapenemase-producing carbapenem nonsusceptible Enterobacteriaceae isolates not containing carbapenemase producing genes: bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{OXA-48} and bla_{NDM}.

factor for 28-day mortality (Table 2). For 7-day mortality, multivariate analysis showed respiratory failure at the onset of bacteremia (odds ratio = 3.991, CI = 1.217–13.094, p = 0.022), and steroid use within 3 days prior to onset of bacteremia (odds ratio = 4.723, CI = 1.206–18.501, p = 0.026) as independent risk factors. Prescription of ≥ 1 active antibiotic within 3 days after culture availability (odds ratio = 0.131, CI = 0.035–0.481, p = 0.002) was an independent protective factor for 7-day mortality (Table 3).

4. Discussion

The use of carbapenems against multidrug-resistant pathogen infections has been severely compromised due to the increasing prevalence of carbapenem-resistant gram-negative bacteria.[8] Previous studies have documented an increase in mortality associated with serious infections caused by CNSE relative to CSE infections among adults in the hospital settings.[9] Furthermore, Tamma et al.[10] observed that CP-CNSE confers a four-times-higher 14-day mortality risk than non-CP CNSE infections. Villegas et al.[11] in comparing the clinical outcomes of patients with carbapenemase producing (CP) bacteremia and non-carbapenemase producing (non-CP) bacteremia in a multicenter observational study noted that patients with CP-CNSE bacteremia had 4 times the odds of death within 28 days compared with non-CP bacteremia. However, contrary evidences showing no apparent association between CP-CNSE and mortality have also been reported. Kassem et al.[12] found that non-CP-CNSE colonized patients had a higher in-hospital mortality rate. Moreover, Seo et al.[13] in a retrospective cohort study showed a lack of significant difference in 14-day mortality between CP-CNSE and non-CP-CNSE bacteremia patients. Similarly, our results show CP-CNSE bacteremia does not result in significant increases in 7-day and 28-day mortality rates.

Felipe et al.[14] in a retrospective study involving patients with VAP caused by CNSE showed age to be an independent mortality risk factor. De Maio Carilho et al. also showed in a prospective study that age was an independent risk factor for CNSE infection-related death.[15] However, age as a mortality risk factor in association with CP-CNSE and non-CP-CNSE bacteremia has yet to be investigated. Segagni et al.[16] in a case-control study observed that exposure to a healthcare facility in a high CNSE prevalence region was an independent risk factor for CP-CNSE acquisition. As age is associated with increased severe underlying conditions and healthcare facility exposure, patient age was hypothesized to be a potential independent mortality risk factor for CP-CNSE patients. Interestingly, in the present study, patient age was not found to be significantly associated with mortality risks for CP-CNSE bacteremia patients. Instead, multi-

Table 2
Twenty-Eight-Day Mortality for Patients with CNSE bacteremia.

Covariate	Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Prescribed at least 1 active antibiotics ≤ 3 days of culture result	0.253 (0.097–0.659)	**0.005**	0.296 (0.105–0.832)	0.021
Respiratory failure after onset of BSI	6.261 (2.529–15.499)	**< 0.001**	5.327 (2.084–13.616)	< 0.001
Septic shock at time of BSI	4.127 (1.739–9.794)	**0.001**	-	-
Mechanical ventilation at the time of BSI	4.129 (1.626–10.483)	**0.003**	-	-
CP-CNSE bacteremia	1.004 (0.303–3.329)	0.995	-	-
Age ≥ 65	0.776 (0.330–1.820)	0.559	-	-
Hematologic malignancies	7.059 (0.758–65.733)	0.086	-	-
Solid tumors	0.964 (0.417–2.228)	0.931	-	-
Diabetes mellitus	1.090 (0.482–2.465)	0.837	-	-
End-stage renal disease	1.821 (0.677–4.904)	0.235	-	-
Liver cirrhosis	0.640 (0.118–3.480)	0.605	-	-
Acute kidney injury ≤ 3 days of BSI	2.524 (0.977–6.523)	0.056	-	-
Gave ≥ 1 active empiric antibiotic treatment after culture collection	2.133 (0.893–5.096)	0.088	-	-
Steroid use ≤ 3 days prior to onset of BSI	2.400 (0.913–6.311)	0.076	-	-

BSI, bloodstream infection; CP-CNSE, carbapenemase-producing carbapenem nonsusceptible Enterobacteriaceae isolates containing carbapenemase producing genes: bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{OXA-48} and bla_{NDM}.
Method: Simple and Multiple Logistic regression (method: forward conditional).

Table 3
Seven-Day Mortality for Patients with CNSE bacteremia.

Covariate	Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Prescribed ≥ 1 active antibiotics ≤ 3 days of culture result	0.162 (0.055–0.476)	**0.001**	0.131 (0.035–0.481)	0.002
Respiratory failure after onset of BSI	5.712 (1.931–16.900)	**0.002**	3.991 (1.217–13.094)	0.022
Steroid use ≤ 3 days prior to onset of BSI	3.325 (1.130–9.778)	**0.029**	4.723 (1.206–18.501)	0.026
Septic shock at time of BSI	2.931 (1.011–8.495)	**0.048**	-	-
Hematologic malignancies	7.312 (1.129–47.365)	**0.037**	-	-
CP-CNSE bacteremia	1.312 (0.324–5.322)	0.703	-	-
Age ≥ 65	1.508 (0.492–4.620)	0.472	-	-
Mechanical ventilation at the time of BSI	2.335 (0.820–6.647)	0.112	-	-
Solid tumors	0.972 (0.345–2.740)	0.958	-	-
Diabetes mellitus	2.710 (0.963–7.628)	0.059	-	-
End-stage renal disease	2.176 (0.706–6.710)	0.176	-	-
Liver cirrhosis	0.725 (0.082–6.428)	0.773	-	-
Acute kidney injury ≤ 3 days of BSI	2.991 (0.877–10.200)	0.080	-	-
Gave ≥ 1 active empiric antibiotic treatment after culture collection	1.739 (0.619–4.884)	0.294	-	-

BSI, bloodstream infection; CP-CNSE, carbapenemase-producing carbapenem nonsusceptible Enterobacteriaceae isolates containing carbapenemase producing genes: bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{OXA-48} and bla_{NDM}.
Method: Simple and Multiple Logistic regression (method: forward conditional).

variate analysis in the current study showed an increase in seven-day mortality in CNSE patients with steroid use within 3 days of bacteremia onset, and respiratory failure post bacteremia onset. A decrease in seven-day mortality rate in CNSE patients prescribed with culture-directed active antibiotic within 3 days of culture result was also noted. A reason for increased mortality in association with prior steroid use may be because glucocorticosteroid treatment increases the risk of both CP-CNSE colonization and non-CP-CNSE colonization as shown by Kassem et al.[12] Glucocorticosteroids are immunosuppressive agents that may lead to downregulation of the immune system, which might be followed by a higher incidence of infectious complications in patients receiving glucocorticosteroids[17] and subsequently associated with an increase in CNSE mortality rates. Respiratory failure post bacteremia developed in 35.4% of the patients and was found to be an independent mortality risk factor in CNSE patients. As demonstrated by Zilberberg et al. in a multicenter observational cohort, the presence of CNSE increases the risk of receiving inappropriate empiric therapy substantially,[18] which in turn may be associated with an increase in the rate of respiratory failure followed by a rise in hospital mortality. The rationale could be that an abnormally low level of oxygen in blood (hypoxemia) may fail to meet the metabolic demands of vital organs, which would eventually lead to poor prognosis.[19] These collective findings suggest that the differences in mortality rates may be due to treatment-related factors rather than patient-related factors.

Early interventions against CNSE bacteremia are often emphasized,[20] but the optimal timing of initiation of therapy remains obscure. One study noted that therapy with at least one active antibiotic at the correct doses improves the 30-day mortality rate if it is administered within 5 days or less.[21] Similarly, Wang et al.[22] found that prescription of at least one active drug at conventional doses within 5 days or less after the onset of bacteremia resulted in survival benefits. Kohler et al.[20] in a meta-analysis noted that the rate of survival from CNSE infection increases with therapy using ≥ 1 active antimicrobial agent within 48 hours at the correct doses. In our current study we found that survival benefits may be derived from using ≥ 1 active antibiotic at the correct doses within 72 hours of culture availability. Interestingly, no additional survival benefit was observed from a similar empiric antibiotic regimen administered at the time of blood culture collection. These collective results, suggest that administration of ≥ 1 active antimicrobial agent within 72 hours after culture availability, in conjunction with timely antimicrobial sensitivity testing, may improve clinical outcomes.

There are several limitations associated with this study. First, this study included patients from a single tertiary medical center in Taiwan. Although the distribution of carbapenemase-gene may be similar to other Taiwanese medical centers, it may differ from those in other regions of the world, thus compromising generalizability. Second, the low prevalence of CP-CNSE in our study population undermines the power of the results, possibly preventing significant differences from being detected. Thirdly, although the inclusion of all variables identified as being associated with poor outcomes for patients with CNSE bacteremia was attempted, the possibility of residual confounding factors unaccounted for, which could influence the treatment outcomes between CP-CNSE and non-CP-CNSE cases, cannot be excluded. Lastly, the limited sample size of current study precluded analysis of certain subgroups, such as differences in various antibiotic dosing, and differences in certain carbapenemase-specific genes.

In summary, we confirm that the presence of carbapenem resistance itself rather than carbapenemase production is associated with an increase in mortality associated with CNSE bacteremia. Furthermore, our findings support that treatment-related as opposed to organism- or patient-related risk factors are associated with CNSE patient outcomes. These cumulative findings highlight the urgent need for expanding currently available therapeutic options, refining established infection managements, and further identifying risk factors for poor prognosis in patients with CNSE infections.

Disclosure

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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This retrospective study was approved by the MacKay Memorial Institutional Review Board. Judgement protocol number was designated 20MMHIS394e.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=22.

References

1. Satlin MJ, Chen L, Patel G, et al. Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE) in the CRE epicenter of the United States. *Antimicrob Agents Chemother.* 2017;61(4):e02349–16.
2. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. *Clin Infect Dis.* 2012;55(7):943–950.
3. Jean SS, Lee NY, Tang HJ, et al. Carbapenem-resistant Enterobacteriaceae infections: Taiwan aspects. *Front Microbiol.* 2018;9:2888.
4. Jean SS, Lee WS, Lam C, et al. Carbapenemase-producing Gram-negative bacteria: current epidemics, antimicrobial susceptibility and treatment options. *Future Microbiol.* 2015;10(3):407–425.
5. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2013.* Atlanta, USA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2013.
6. Pasteran F, Mendez T, Guerriero L, et al. Sensitive screening tests for suspected class A carbapenemase production in species of Enterobacteriaceae. *J Clin Microbiol.* 2009;47(6):1631–1639.
7. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement*. CLSI document M100-S24. Pennsylvania, USA: Clinical and Laboratory Standards Institute; 2014.
8. Akova M, Daikos GL, Carmeli Y, et al. Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria. *Clin Microbiol Infect.* 2012;18(5):439–448.
9. Martin A, Fahrbach K, Zhao Q, et al. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to Enterobacteriaceae: Results of a systematic literature review and meta-analysis. *Open Forum Infect Dis.* 2018;5(7):ofy150.
10. Tamma PD, Huang Y, Opene BN, et al. Determining the optimal carbapenem MIC that distinguishes carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae. *Antimicrob Agents Chemother.* 2016;60(10):6425–6429.
11. Villegas MV, Pallares CJ, Zurita J, et al. Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing Enterobacteriaceae in seven Latin American countries. *PLoS One.* 2016; 11(4):e0154092.
12. Kassem A, Raed A, Michael T, et al. Risk factors and outcomes of patients colonized with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae. *Infect Control Hosp Epidemiol.* 2020;41(10):1154–1161.

13. Seo H, Lee SC, Chung H, et al. Clinical and microbiological analysis of risk factors for mortality in patients with carbapenem-resistant Enterobacteriaceae bacteremia. *Int J Antimicrob Agents.* 2020;56(4):106126.
14. Tuon FF, Graf ME, Merlini A, et al. Risk factors for mortality in patients with ventilator-associated pneumonia caused by carbapenem-resistant Enterobacteriaceae. *Braz J Infect Dis.* 2017;21(1):1–6.
15. de Maio Carrilho CM, de Oliveira LM, Gaudereto J, et al. A prospective study of treatment of carbapenem-resistant Enterobacteriaceae infections and risk factors associated with outcome. *BMC Infect Dis.* 2016; 16(1):629.
16. Segagni Lusignani L, Presterl E, Zatorska B, et al. Infection control and risk factors for acquisition of carbapenemase-producing Enterobacteriaceae. A 5 year (2011-2016) case-control study. *Antimicrob Resist Infect Control.* 2020;9(1):18.
17. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis.* 1989;11(6):954–963.
18. Zilberberg MD, Nathanson BH, Sulham K, et al. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infect Dis.* 2017;17(1):279.
19. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care.* 2008, 12(6):R156.
20. Kohler PP, Volling C, Green K, et al. Carbapenem resistance, initial antibiotic therapy, and mortality in Klebsiella pneumoniae bacteremia: A systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2017;38(11):1319–1328.
21. Gutierrez-Gutierrez B, Salamanca E, de Cueto M, 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(7):726–734.
22. Wang X, Wang Q, Cao B, et al. Retrospective observational study from a Chinese network of the impact of combination therapy versus monotherapy on mortality from carbapenem-resistant Enterobacteriaceae bacteremia. *Antimicrob Agents Chemother.* 2018;63(1):e01511-18.