International Journal of Antimicrobial Agents 54 (2019) 527–529

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Carbapenem-resistant Enterobacteriaceae in hematological patients: Outcome of patients with Carbapenem-resistant Enterobacteriaceae infection and risk factors for progression to infection after rectal colonization

Sir,

Carbapenem-resistant Enterobacteriaceae (CRE) are resistant to any carbapenem antimicrobial and any antimicrobial that produces carbapenemase [1]. Infections with CRE are associated with considerable mortality, particularly in hematological patients, who frequently experience neutropenia and immunosuppression. We conducted a retrospective study at our institute from January 2012 to December 2017 with the aim to assess risk factors for CRE infection and seek appropriate therapy to reduce CRE-related mortality.

Isolate identification and antimicrobial susceptibility tests were conducted using the Vitek 2 automated system (bioMérieux). CRE rectal colonization was defined as the isolation of CRE from a rectal swab in patients with no clinical signs of infection. CRE infection was defined as detection of CRE in a clinical specimen from a patient with signs and symptoms of invasive infection. Bacteremia, pneumonia, urinary tract infection and other site infections were defined according to the Centers for Disease Control and Prevention (CDC) criteria [2]. Acute leukemia (AL) in complete remission (CR), lymphoma in CR or partial remission, refractory anemia of myelodysplastic syndrome (MDS) and severe aplastic anemia (SAA) untreated were defined as standard risk; and AL in induction failure or relapse, lymphoma in stable disease or progression, and MDS/SAA transfusion dependence with no response to treatment were classified as high risk [3,4]. Early appropriate therapy was considered when at least one in vitro-sensitive agent was administered within 48 h of onset of CRE infection. Monotherapy was defined as a single active drug in the regimen and combined therapy described when two or more active drugs were initiated against CRE. Duration of follow-up for CRE infections was 30 days after onset of infection, and the primary endpoint was CRE-related death. Patients who were rectal carriers of CRE were followed until they developed CRE infection.

There were 50 patients with CRE infection between 2012 and 2017 and the number of cases increased each year (supplementary Fig. 1). Main patient characteristics are summarized in Table 1. The most common CRE infection was bacteremia (31/50), followed by pneumonia (10/50), perianal infection (6/50), pharyngeal infection (1/50), gum infection (1/50) and urinary tract infection (1/50). A total of 28 infections were caused by *Escherichia coli*, 18 by *Klebsiella pneumoniae*, and 2 each by *Enterobacter cloacae* and *Enterobacter aerogenes*. The incidences of isolates susceptible to antibiotics were as follows: 82% to tigecycline, 80% to amikacin, 22% to gentamicin, 14% to ciprofloxacin, 8% to moxifloxacin, and 4% each to piperacillin-tazobactam and cefepime. A total of 28 patients received monotherapy; the other 22 patients received combination therapy. Tigecycline plus aminoglycoside with/without a carbapenem was the most common combination therapy (supplementary Table 1).

Patient 30-day overall survival is depicted in supplementary Fig. 2. A total of 17 (34%) patients died of CRE infection (bacteremia or pneumonia) within 30 days. Univariate analysis showed that patients with high-risk hematological diseases, prolonged neutropenia (≥14 days) and monotherapy had increased mortality rates. In multivariate analysis, prolonged neutropenia (odds ratio [OR], 6.48; $P = 0.042$) was the independent risk factor for mortality, whereas active combined therapy (OR, 0.15; $P = 0.014$) was associated with improved survival (supplementary Table 2).

Carbapenem was combined with at least one active drug in 22 patients. In contrast to other studies [5,6], patients whose regimens included a carbapenem had a similar mortality rate to those whose regimens did not include a carbapenem (31.8% vs. 35.7%, $P = 0.773$). The discrepancy was mainly because of a high level of carbapenem resistance in our study (62% had meropenem MICs ≥16 μg/mL) whereas the reported improved outcomes were generally detected with meropenem MICs ≤8 μg/mL and carbapenems were administered with high doses and prolonged infusions.

A total of 7625 patients with 21 699 rectal swabs were screened during the study, and 55 patients were identified for CRE colonization (supplementary Table 3). The most common isolates were *E. coli* (n = 28), followed by *K. pneumoniae* (n = 18), then *E. cloacae* (n = 6) and *E. aerogenes* and *Proteus mirabilis* (n = 1 for each). One further case was multimicrobial, colonized with *E. coli* and *K. pneumoniae*. Overall, 14 (25.5%) patients developed CRE infection after rectal colonization, including 11 bacteremia and 3 pneumonias. In univariate analysis, high-risk diseases and mucositis were variables associated with subsequent CRE infection (supplementary Table 3). Male patients also had a trend towards higher risk for CRE infection ($P = 0.065$). Multivariate analysis revealed that mucositis (OR, 5.20; 95% confidence interval [CI], 1.09 to 24.79; $P = 0.038$) and male sex (OR, 6.58; 95% CI, 1.06 to 41.67; $P = 0.043$) were independent risk factors for CRE infection after rectal colonization.

In conclusion, our study confirmed the severity of CRE infection in hematological patients. Active combined therapy was the independent factor in improved survival rates. Patients who were CRE rectal carriers, particularly males and those complicated with mucositis, were at high risk of progressing to CRE infection. Therefore, these patients should be under active surveillance and tested for CRE infection upon the onset of febrile neutropenia.

https://doi.org/10.1016/j.ijantimicag.2019.06.023

Table 1
Characteristics of 50 CRE infection patients.

	N	%
Patients	50	
Male sex	37	74
Age (years), median (IQR)	35 (20-51)	
Charlson comorbidity score		
2	40	80
3-4	10	20
Underlying hematological disease		
Acute leukemia	32	64
Myelodysplastic syndrome	8	16
Severe aplastic anemia	8	16
Non-Hodgkin lymphoma	2	4
HSCT recipients	12	24
MDRO carriage/infection in the previous 3 months previous	29	58
Antibiotics used in the previous 3 months		
Cephalosporins	41	82
Carbapenems	39	78
Fluoroquinolones	12	24
Penicillins	9	18
Aminoglycosides	6	12
Glycopeptides	17	34
Infection site		
Bacteremia	31	62
Pneumonia	10	20
Perianal infection	6	12
Other infection sites	3	6
Mucositis	16	32
Invasive devices (CVC or PICC)	43	86
CRE isolates		
Escherichia coli	28	56
Klebsiella pneumoniae	18	36
Enterobacter cloacae	2	4
Enterobacter aerogenes	2	4
Neutropenia at the onset of CRE infection	40	80
Prolonged neutropenia (≥14 days)	33	66
Meropenem MICs (mg/L)		
≥16	31	62
≤8	19	38

CRE, carbapenem-resistant Enterobacteriaceae; IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; MDRO, multidrug-resistant organism; CVC, central venous catheter; PICC, peripherally inserted central catheters; MIC, minimum inhibitory concentration

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.06.023.

Declarations

Funding: This work was supported by the National Megaproject on Key Infectious Diseases (grant number 2017ZX10202102); the CAMS Initiative for Innovative Medicine (grant number 2016-I2M-1-017) and the Natural Science Foundation of Tianjin, China (grant number 18JCZDJC34400).

Competing interests: No conflicts of interest.

Ethical approval: Not required.

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Received 19 October 2018
Accepted 27 June 2019