Infection and Drug Resistance

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ORIGINAL RESEARCH

Impact of individualized active surveillance of carbapenem-resistant enterobacteriaceae on the infection rate in intensive care units: a 3-year retrospective study in a teaching hospital of People's Republic of China

This article was published in the following Dove Press journal:
Infection and Drug Resistance

Shu Li[1]
Fu-Zheng Guo[2]
Xiu-Juan Zhao[1]
Qi Wang[3]
Hui Wang[3]
You-Zhong An[1]
Feng-Xue Zhu[1,2]

[1]Department of Critical Care Medicine, Peking University People's Hospital, Beijing, People's Republic of China; [2]Trauma Centre, Peking University People's Hospital, Beijing, People's Republic of China; [3]Department of Clinical Laboratory, Peking University People's Hospital, Beijing, People's Republic of China

Purpose: Active surveillance of carbapenem-resistant Enterobacteriaceae (CRE) may contribute to the decline of the infection rate. Individualized active surveillance of CRE could cost less than screening all patients. However, the impact of individualized active surveillance on the CRE infection rate in intensive care units (ICUs) has not been well described.

Patients and methods: We retrospectively studied the clinical data of all patients admitted in the ICUs of a tertiary-care hospital in China from 2015 to 2017 during two periods, before and after the implementation of individualized active surveillance. During period 1 (January 2015–April 2016), no screening protocol was used. During period 2 (May 2016–December 2017), we implemented active CRE screening for selected patients according to their clinical characteristics. The trend of CRE rate infection was analyzed by a joinpoint regression model, and multivariate analysis was performed to analyze the association of active surveillance, Acute Physiology and Chronic Health Evaluation (APACHE) II score, prior antimicrobial use, length of mechanical ventilation (MV) before infection, and other risk factors with CRE infection rate.

Results: A total of 5,372 patients were included. After assessing the patients' clinical characteristics, 72.3% (3,882/5,372) were considered to be at high risk of CRE infection. During period 1, the infection percent of CRE increased by 13.04% every month (95% CI: 5.2–21.5). During period 2, the infection rate decreased (monthly percent change, −3.57%; 95% CI −6.9 to −0.1, $P<0.05$). Multivariate analysis showed that individualized active surveillance (odds ratio, 0.146; 95% CI, 0.061–0.347; $P<0.001$) was associated with a reduction of the CRE infection rate, whereas APACHE II score, prior antimicrobial use, and length of MV before infection were independent risk factors.

Conclusion: Individualized active surveillance may be associated with a reduction of the overall CRE infection rate in ICUs.

Keywords: CRE, screening, risk factors, incidence, carbapenems, critical care

Correspondence: Feng-Xue Zhu
Department of Critical Care Medicine, Trauma Centre, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044 100044, People's Republic of China
Tel +86 139 1100 5275
Fax +86 10 8832 4488
Email zhu_fengxue@163.com

Introduction

Enterobacteriaceae are the most common human pathogens causing health care-associated infections. The carbapenems are the mainstay of therapy for treating serious and life-threatening infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamase.[1] In 2001, carbapenem-resistant Enterobacteriaceae (CRE)

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http://doi.org/10.2147/IDR.S201644

was first identified. Since then, CRE has disseminated widely. The overall annual CRE incidence is 2.93 per 100,000 individuals in the US.[2] The national bacteria resistance surveillance report of 2015 (People'sRepublic of China) demonstrates that *Escherichia coli* and *Klebsiella pneumoniae* are the two most frequently detected Gram-negative bacteria, and their carbapenem resistance rates are 1.9% and 7.6%, respectively. However, in some major cities, the resistance rate is up to 20%, which is significantly higher than that in 2014.[3]

Resistant strains emerge and rapidly spread via two main pathways: 1) patient-to-patient transmission (ie, from another patient, through the health care staff, through the proximal environment, or through shared equipment); and 2) emergence of resistance.[4] Human transmission is the most important cause of the CRE epidemic and outbreaks in health care facilities.[5] Very few antibiotics are effective against CRE infection. Therefore, among strategies to control CRE infection, prevention is of utmost importance. Active surveillance involves CRE screening of patients who might not be epidemiologically linked to known CRE patients but who meet certain pre-specified criteria. This form of CRE screening is considered a supplemental measure in the Facility Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE) November 2015 Update[6] and by many other national and international bodies.[7,8] Facilities that employ this approach often target patients admitted to high-risk units. Patients in intensive care units (ICUs) are a high-risk population for CRE infection because critical patients have more high-risk factors, such as severe underlying conditions, invasive treatment, long hospital stays, and exposure to high doses of carbapenems.[9]

However, high costs make it difficult to implement active surveillance.[10] In particular, the economic burden of active surveillance outweighs its benefits in low medical resource areas with a relatively low infection rate.[11] In People's Republic of China, most ICUs admit mixed patient populations from different sources with varying diagnoses, disease severities, and hospital stays.[12,13] Therefore, active CRE surveillance based on patient source or hospital department may include a significant number of patients at low risk for CRE infection, resulting in unnecessary costs.

Studies have demonstrated that patients at high risk for CRE infection share similar clinical features, including exposure to antimicrobials,[14] high co-morbidity indexes, deteriorated functional status and/or cognition at baseline, recent LTCF stay, and recent invasive procedures or permanent implantation of foreign devices.[15,16] Moreover, ICU patients at high risk for CRE infection have a significantly higher infection rate than do non-high-risk patients.[17] Therefore, we speculate that active surveillance based on patient risk level, rather than hospital department, may be a more targeted approach and effective in reducing the CRE infection rate.

The infection management and control department of Peking University People's Hospital has been conducting on-going surveillance of multi-drug resistant bacterial infections over the years and has implemented a series of measures to manage and control infections in ICUs. Since the second half of 2016, active surveillance has been added in our clustered infection control measures to combat the rising CRE infection rate. Given the high costs of surveillance, we have developed surveillance criteria based on our previous study and other literature and implemented active surveillance only in patients at high risk for CRE infection. In this study, we retrospectively analyzed CRE surveillance data from the ICU of our hospital between 2015 and 2017, reported the 3-year infection rate and trend in the ICU, and evaluated the association of active surveillance of CRE for high-risk patients with the CRE infection incidence in the ICU.

Patients and methods

Setting

The study was conducted in two ICUs of Peking University People's Hospital, a tertiary teaching hospital in Beijing, People's Republic of China. The ICUs have an average of 1,800 admissions per year. Patients are transferred from all the other wards in the hospital and other health care institutions. Most patients are cared for in two-bed rooms or in single-bed rooms. In this study, CRE was defined as either meropenem- or imipenem-resistant according to the minimum inhibitory concentrationsbreakpoints defined by the Clinical and Laboratory Standards Institute.[18]

Study design and population

We performed a retrospective cohort study of all patients admitted to the ICUs from January 2015 to December 2017. Patients diagnosed with CRE infection before admission were not included in the data analysis. Since the second half of 2016, active surveillance for high-risk patients has been implemented. The 3-year CRE infection rate and trend over time in the ICUs were analyzed. We also assessed the

impact of active surveillance for high-risk patients on the incidence of CRE infection and identified risk factors associated with CRE infection.

High-risk patients were defined as patients with any of the following characteristics: age >65 years old; transferred from other health institutions; hospital stay >7 days; carbapenems, third- or fourth-generation cephalosporin or fluoroquinolone treatment for >3 days during 2 weeks before admission to the ICU; haematological malignancies; and immunosuppressive agent treatment for >1 week during 1 month before admission to the ICU.

Patients with a positive blood culture or any other sterile source culture were directly defined as infected. Positive cultures from respiratory, urine, and surgical wounds were defined as infections according to the Centers for Disease Control and Preventionand National Healthcare Safety Network criteria.[19]

Active surveillance and data collection

Active surveillance for high-risk patients was conducted beginning in the second half of 2016 as follows: high-risk patients were screened for CRE rectal colonization at the time of admission, on day 3 and day 7, and every other week. The results were reported to the nosocomial infection control department in the hospital and ICU doctors through an early warning information system.

A CRE infection control intervention was conducted at the time of CRE infection diagnosis or when the screening result was positive throughout the study period. The control intervention consisted of a number of measures, including cohorting of carriers, managed with strict contact precautions; intensification of education, cleaning and hand-washing programmes; and promotion of an antibiotic stewardship programme of carbapenem-sparing regimens.

Patients' clinical characteristics were extracted from medical records. Variables analyzed as risk factors included sex, age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and treatments and procedures performed prior to the infection (such as steroid administration, dialysis, surgery, and exposure to antibiotics). The length of mechanical ventilation (MV) and previous ICU hospitalization before infection acquisition were also considered.

Culture and laboratory methods

The active surveillance involved performing a rectal culture using a dry rayon swab. Alternatively, instead of a rectal culture, a culture could be obtained from the perirectal area (if visible stool was present) or from a fecal incontinence bag. All swabs were transported to the central laboratory in liquid Stuart medium (Copan, Italia) within 2 hrs.

China Blue Agar Medium (XFL Medical Sales Co., Ltd, Beijing, People'sRepublic of China) was used for the isolation of Enterobacteriaceae from rectal culture samples. Identification and antimicrobial susceptibility testing were performed in the clinical microbiology laboratory using a Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France). Carbapenem (meropenem and/or imipenem) resistance was confirmed by the E-test method according to the manufacturer's instructions (AB Biodisk, Solna, Sweden). CRE isolates were tested for carbapenemase genes (bla_{KPC}, bla_{NDM} and bla_{IMP}) using PCR.[20,21] Multilocus sequence typing (MLST) was performed according to the protocol described on the *K. pneumoniae* MLST website (www.pasteur.fr/mlst). Internal fragments of seven housekeeping genes for *K. pneumoniae* (*gapA, infB, mdh, pgi, phoE, rpoB*, and *tonB*) were amplified, sequenced, and analyzed. Alleles and sequence types (STs) were determined according to the MLST database (www.pasteur.fr/mlst/Kpneumoniae.html).

Statistical analyses

SAS statistical software (SAS Institute Inc., Cary, NC, USA), version 9.1, was used for the statistical analyses. Measurement data are expressed as means±standard deviations or medians (25th–75th percentile). Enumeration data are expressed as absolute frequencies and percentages. Student's *t* test was used for normally distributed measurement data, and the rank sum test was used for non-normally distributed measurement data. The χ^2 test was used for comparisons of rates. The institutional monthly incidence of CRE infection was analyzed by the Joinpoint Regression Program 4.5.0.1 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Logistic regression models were used to analyze risk factors for CRE infection. All of the tests were conducted at a level of significance of α=0.05.

Results

Patient inclusion and baseline characteristics

A total of 5,416 patients were admitted to the ICU of our hospital between January 2015 and December 2017. Of these, 2 patients were excluded from this study because they had been diagnosed with CRE infection before ICU

admission, and 42 patients were excluded due to incomplete data. Finally, a total of 5,372 patients were included in this study. Active surveillance for high-risk patients was conducted beginning in the second half of 2016. Patients admitted per month, high-risk patients per month, and demographic and clinical characteristics were similar before and after the active surveillance was conducted (Table 1).

Incidence of CRE infection

Seventy-eight patients were diagnosed with CRE infections during the study period, and the overall CRE infection rate was 1.45% (78/5372). During the pre-intervention period, the monthly percent change (MPC) of CRE infection rate was 13.04% (Figure 1A. 95% CI: 5.2–21.5, $P<0.05$). In April 2016, 162 patients admitted in the ICU. Of these, 7 patients were diagnosed with CRE infection. The infection rate peaked at 4.32% (7/162). Then, the active surveillance programme for high-risk patients was initiated. During the following intervention period, a total of 2,162 high-risk patients were admitted to the ICU. The majority of these patients (1,916/2,063; 92.9%) qualified for CRE active screening. The incidence of CRE colonization significantly decreased, with an MPC of −3.02% (Figure 1B. 95% CI: −4.7 to −1.3, $P<0.05$). Meanwhile, the incidence of CRE infection significantly decreased, with an MPC incidence of −3.57% (Figure 1A. 95% CI: −6.9 to −0.1, $P<0.05$).

The most common types of infection were respiratory tract infections (n=42; 53.8%), followed by bloodstream infections (n=25; 32.1%), urinary tract infections (n=5; 6.4%), intra-abdominal infections (n=4; 5.1%), and wound and soft tissue infections (n=2; 2.6%).

Clinical characteristics of high-risk patients and non-high-risk patients

The 5,372 patients were divided into two groups according to whether they had high-risk factors for CRE infection. There were 3,882 (72.3%) high-risk patients and 1,490 (27.7%) non-high-risk patients. The clinical features and prognosis were analyzed. Age, APACHE II score, ICU stay, and 28-day mortality were significantly lower or shorter in the non-high-risk group than in the high-risk group. Moreover, the CRE infection rate of non-high-risk patients was significantly lower than that of high-risk patients (0.3% and 1.9%, respectively; $P<0.001$) (Table 2).

Microbiological data

During the study period, a total of 267 non-duplicate CRE-positive cultures were detected in the respiratory tract (n=128, 47.9%), bloodstream (n=94, 35.2%), and urine (n=22, 8.2%) and from drainage catheters or surgical specimens (n=14, 5.2%), invasive sampling of the gastrointestinal tract (bile cultures, or ascites fluid; n=2, 0.7%) and skin or wound culture (n=7, 2.6%).

Table 1 Patient demographic and clinical characteristics before and after the active surveillance period (n=5372)

Variable	Pre-intervention period (N=2637)	Intervention period (N=2735)	*P*-value
Admissions per month, mean±SD	146.5±18.6	151.9±18.4	0.974
High-risk patients per month, mean±SD	113.4±16.7	102.3±12.4	0.416
Age, y, mean±SD	62.5±17.5	63.5±17.3	0.077
Male sex, n (%)	1,485 (56.3)	1,469 (53.7)	0.058
Transfer from the ER or other health institutions, n (%)	719 (27.3)	765 (28)	0.583
Diabetes mellitus, n (%)	218 (8.3)	253 (9.3)	0.210
APACHE II score at admission, median (IQR)	16 (12, 20)	16 (14, 19)	0.082
Transplant receipt, n (%)	9 (0.3)	7 (0.3)	0.623
Dialysis, n (%)	36 (1.4)	29 (1.1)	0.320
Prior surgery, n (%)	1,925 (72.0)	1,931 (70.6)	0.052
Prior antimicrobial use, n (%)	497 (18.5)	529 (18.9)	0.652
Prior corticosteroid use, n (%)	117 (4.4)	103 (3.8)	0.216
Length of MV before infection, hours, median (IQR)	7 (2, 24)	6 (2, 26)	0.071
LOS-ICU before infection, d, median (IQR)	1 (1, 6)	1 (1, 5)	0.105
LOS-ICU, d, median (IQR)	1 (1, 6)	1 (1, 6)	0.650
In-ICU mortality, n (%)	232 (8.8)	247 (9.0)	0.774

Abbreviations: ER, emergency room; APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation; LOS-ICU, length of stay-intensive care unit; IQR, interquartile range.

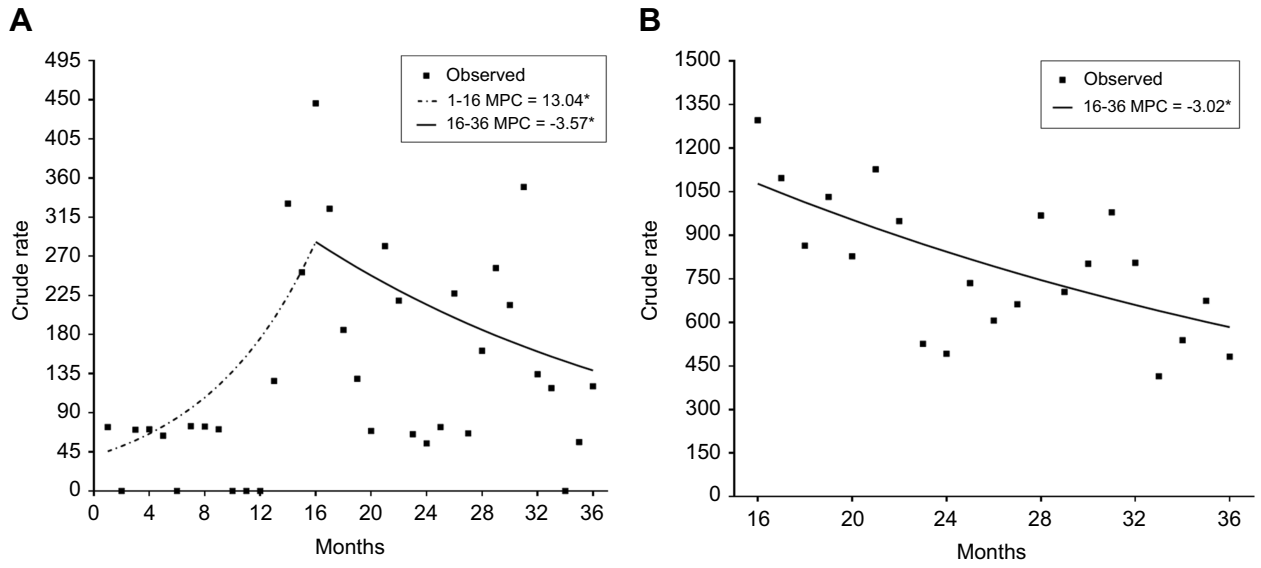

Figure 1 The trend of the CRE infection incidence (**A**) and colonization incidence (**B**). A significant decrease in the monthly incidence of CRE infection and colonization found by joinpoint regression after initiating active surveillance for high-risk patients. *Indicates that the MPC was significantly different from zero at the alpha =0.05 level.
Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; MPC, monthly percent change.

Table 2 Patient demographic and clinical characteristics according to risk classification (n=5372)

Variable	CRE high-risk patients (N=3882)	CRE non-high-risk patients (N=1490)	*P*-value
Age, y, mean±SD	67.7±16.8	50.8±12.1	<0.001
Male sex, n (%)	2190 (56.4)	764 (51.3)	0.001
APACHE II score at admission, median (IQR)	16 (14, 20)	15 (12, 18)	<0.001
Length of ICU stay, days, median (IQR)	2 (1, 8)	1 (1, 2)	<0.001
28-day mortality, n (%)	415 (10.7)	72 (4.8)	<0.001
CRE infection, n (%)	73 (1.9)	5 (0.3)	<0.001

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CRE, carbapenem-resistant Enterobacteriaceae; IQR, interquartile range; ICU, intensive care unit.

K. pneumoniae was the most frequently isolated CRE (n=246, 92.1%). Other CRE isolates included *Enterobacter cloacae* (n=7, 2.6%), *Escherichia coli* (n=4, 1.5%), *Enterobacter aerogenes* (n=4, 1.5%), *Serratia marcescens* (n=4, 1.5%), and *Citrobacter freundii* (n=2, 0.7%).

Carbapenemase production and ST types

Seventy-eight non-duplicated CRE strains were tested for their ability to produce carbapenemase and for the presence of carbapenemase genes. Fifty-five of the 78 CRE (70.5%) were found to produce a carbapenemase gene. The KPC-2-type carbapenemase gene (bla_{KPC-2}) was the most dominant type (83.6%, 46/55), followed by NDM-1 (10.9%, 6/55) and NDM-5 (5.5%, 3/55). Among the 78 CRE strains, 54 strains were *K. pneumoniae*. ST11 was the major type (98.1%, 53/54); 1 strain was ST1876. In addition, one carbapenem-resistant *E. coli* strain was ST167, and one carbapenem-resistant *E. cloacae* strain was ST121.

Risk factors for CRE infection

Univariable analysis demonstrated that the risk factors associated with CRE infection included APACHE II score, active surveillance, prior surgery, prior antimicrobial use, prior corticosteroid use, length of ICU stay before infection, and length of MV before infection. By multivariable analysis, the APACHE II score, prior antimicrobial use, and length of MV before infection were independent risk factors associated with CRE infection. Active surveillance was a protective factor for CRE infection (OR, 0.146; 95% CI, 0.061–0.347; *P*<0.001) (Table 3).

Discussion

In this study, we reported the CRE infection rates and trends in an ICU of a tertiary hospital in a major city in People'sRepublic of China and analyzed the association of active surveillance of CRE for only high-risk patients with

Table 3 Summary of risk factors associated with CRE infection

Risk factor	CRE patients (N=78)	Non-CRE patients (N=5294)	Univariable analysis OR (95% CI)	*P*-value	Multivariable analysis OR (95% CI)	*P*-value
Age, y, mean ±SD	61.6±19.1	62.9±17.4	1.026 (0.752, 1.042)	0.621		
Male sex, n (%)	43 (55.1)	2,911 (55.0)	1.408 (0.858, 2.312)	0.174		
Transfer from ER or other health institutions, n (%)	21 (26.9)	1,463 (27.6)	0.965 (0.583, 1.597)	0.889		
APACHE II score at admission, median (IQR)	23 (16, 28)	16 (13, 19)	1.119 (1.090, 1.150)	<0.001	1.080 (1.043, 1.117)	<0.001
Active surveillance, n (%)	7 (9.0)	1,909 (36.1)	0.175 (0.080, 0.381)	<0.001	0.146 (0.061, 0.347)	<0.001
Prior surgery, n (%)	59 (75.6)	3,797 (71.7)	1.224 (0.728, 2.060)	0.455		
Prior antimicrobial use, n (%)	37 (47.7)	989 (18.3)	3.928 (2.505, 6.159)	<0.001	3.030 (1.742, 5.263)	<0.001
Prior corticosteroid use, n (%)	8 (10.3)	212 (4.0)	2.740 (1.302, 5.767)	0.006	1.762 (0.755, 4.112)	0.190
Dialysis, n (%)	2 (2.6)	63 (1.2)	2.185 (0.525, 9.093)	0.271		
Length of ICU stay before infection, days, median (IQR)	8 (2, 14)	1 (1, 5)	1.021 (1.009, 1.034)	0.001	1.016 (0.992, 1.041)	0.191
Length of MV before infection, hours, median (IQR)	84 (2, 268)	6 (2, 24)	1.002 (1.002, 1.003)	<0.001	1.001 (1.000, 1.002)	0.001

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation; ICU, intensive care unit; CRE, carbapenem-resistant Enterobacteriaceae; IQR, interquartile range.

the CRE infection rate of all patients. The results show that the CRE infection rate was 1.45% during the 3-year study period. The monthly infection rate was 0–4.32%. According to the 2015 report of the China Antimicrobial Resistance Surveillance System, the detection rate is 6.8% for imipenem-resistant *K. pneumoniae* and 1.4% for imipenem-resistant *E. coli*. The resistance rate of *Enterobacter* spp. is highest in tertiary hospitals in major cities such as Beijing, and the ICU has the highest CRE infection rate among hospital departments. Therefore, the results of this study may partly reflect the condition of a hospital department with the highest CRE infection rate in People's Republic of China. Few studies have reported the incidence of CRE infection in People's Republic of China. It was reported that among 326 ICU patients, CRE infections developed in 26 patients (8%) within 30 days in an ICU in the US.[22] In another study carried out in Israel, 5.5% of the ICU patients developed CRE infection.[23] The incidence of CRE infection was relatively low in the ICU of our hospital. However, an epidemiology survey with a large sample size is needed.

Passive surveillance data demonstrated that the CRE infection rate in our hospital has risen significantly since 2016, especially in the ICU. Therefore, active surveillance of CRE was added to the existing infection control measures. Considering the economic burden, we implemented active surveillance for high-risk patients only. In this study, we analyzed patients admitted to the ICU of our hospital during the 3-year period and found that 27.7% were non-high-risk patients for CRE infection. Significant differences were observed with respect to CRE infection rate, disease severity, hospital stay, MV time, and mortality between high-risk patients and non-high-risk patients. Based on these results, we speculated that active surveillance for high-risk patients may be more targeted, as it excludes patients at low risk for infection, thereby reducing unnecessary waste of health care resources. However, studies on cost-effectiveness are needed in the future.

We analyzed the CRE infection rate trend and found that the CRE infection rate decreased since the second half of 2016 (MPC, −3.57%), when active surveillance for high-risk patients was performed. Then, the multivariate analysis of multiple risk factors revealed that active surveillance remained a protective factor for reducing the CRE infection rate after controlling for several confounding factors. This indicates that active surveillance for high-risk patients may help to reduce the overall CRE infection rate. With any screening program, decisions regarding which patients to screen should be based on local epidemiological data. In Israel, the national guidelines in 2008 required all facilities to implement a CRE screening policy.[7] Screening is recommended for all new admissions who are transferred directly from an acute-care hospital or patients admitted from home with extensive health care

exposure. In the US, facilities that employ this approach often target patients admitted to high-risk units (eg, ICU) or those admitted from long-term acute care hospitals.[2] However, most ICUs and hospitals in People's Republic of China admit mixed patient populations from different sources with varying diagnoses, and the epidemiological data of most hospitals are not clear. Our study may help to identify which populations are candidates for screening.

In this study, 78 patients were diagnosed with CRE infections, primarily respiratory and bloodstream infections. A total of 267 CRE-positive cultures were detected from these patients, and the most common strain was *K. pneumoniae*, which was consistent with the findings from other large tertiary hospitals in People's Republic of China.[24] MLST assay revealed that in this study, most carbapenem-resistant *K. pneumoniae* strains were ST11. Among all 78 non-duplicate CRE strains, 55 produced carbapenemase, primarily KPC-2. Since 2001, several studies have reported CRE mediated by carbapenemases in People's Republic of China, especially KPC-2.[25,26] Our study has demonstrated the same results with respect to carbapenemase distribution.

In this study, multivariate analysis revealed that additional independent risk factors for CRE infection included APACHE II score, prior antimicrobial use, and length of ventilation before infection, which was consistent with the findings of other studies on risk factors for CRE infection in different medical facilities, different hospital departments (ICU and non-ICU), and different patient populations.[27,28] These data suggest that active surveillance for high-risk patients should not be limited to the ICU. The same or similar screening criteria for high-risk factors may be applicable to different departments of large general hospitals and even different hospitals in different regions. Nevertheless, further research is needed to investigate how to scientifically select risk factors or establish screening criteria or systems for high-risk patients.

Although this study demonstrates the impact of active surveillance for high-risk patients in the ICU, it has some limitations. First, as in any observational study, our results may be confounded by unmeasured patient or programme characteristics. Second, this is a single-center retrospective observational study, and the sample size was small. More large sample size studies are needed to investigate the epidemiology of CRE infection. These are metrics that we plan to evaluate in the future.

Conclusion

CRE active surveillance is associated with reduction of the overall CRE infection rate in ICUs when it is targeted toward high-risk patients. Because CRE status is unclear at the time of admission, strategies such as active surveillance could be effective at preventing the rising CRE trends.

Ethics approval and informed consent

This study was approved by the Institution of Human Subjects Committee at Peking University People's Hospital. The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study. Because all patient data were analyzed in anonymity, no additional informed consent was required.

Acknowledgments

This work was supported by the Capital's Funds for Health Improvement and Research (2018-2-4082). We thank Huixin Liu and Qingqi Zeng for providing support in the statistical analysis.

Author contributions

All authors contributed to data analysis, drafted and revised the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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