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The Cost-Effectiveness of an Environmental Intervention on Carbapenem-Resistant *Klebsiella pneumonia* Healthcare-Associated Infection Control

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Research Article

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ABSTRACT

Aim: Conducted environmental intervention on Carbapenem-Resistant *Klebsiella Pneumoniae* (CRKP) to evaluate the effect and cost.

Background: Environmental disinfection is important prevention and control measures for Carbapenem-Resistant *Enterobacteriaceae* (CRE).

Methods: During pre-intervention phase, monitored disinfection effect of environment around patients randomly through microbiological tests quarterly and feedback to supervise environment disinfection. During intervention phase, targeted microbiological monitoring disinfection effect of environment around CRKP patients, used multiple monitoring methods including fluorescent labelling, Adenosine Triphosphate (ATP) to strengthen monitoring. Compared CRKP Healthcare-Associated Infections (HAI) rates and surroundings monitoring qualification rates, calculated the increased cost and effect.

Results: 44 CRKP positive patients were included from January 2018 to June 2019. CRKP HAI rate decreased from 6.49/1000 admissions in pre-intervention phase to 3.08/1000 in intervention phase, microbiological monitoring qualification rate increased from 79.09% to 90.50%. Total environmental intervention cost was CNY6211.00. CRKP HAI and death cases decreased 3.33, 2.50 respectively. Increased CNY1865.17 environmental intervention cost could prevent one CRKP HAI case, increased CNY2484.40 cost could reduce one CRKP death case.

Conclusion: CRE infection is persistent threat. Environmental intervention could be cost-effectively measure.

Keywords: Cost-effectiveness; Environmental intervention; Carbapenem-resistant *Klebsiella pneumonia*; Healthcare-associated infection; Admissions

INTRODUCTION

The prevention and control of CRE infections is growing concern due to high fatality and serious adverse effects [1,2].

The surrounding environment of CRE patients is infection cross-spread medium, which can cause outbreak if mishandled [3-5]. Facility guidance for control of CRE [6] and guidelines for the prevention and control of CRE, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities [7] emphasized the essential of environmental disinfection.

However, environmental disinfection consumes manpower, material and financial resource. The cost and effect of environmental disinfection have not been elucidated. Our study was to analyze cost and effect of environmental disinfection on prevention and control of CRE HAI. We conducted an environmental intervention study on the most common CRE bacterial strain CRKP, to find out whether targeted increase of environmental disinfection monitoring could effectively control spread of CRKP, evaluated its cost and effect.

MATERIALS AND METHODS

Research design

Conducted environmental intervention study in ICU, with 30 sickbeds, 15 sickbeds were for surgery patients, the other 15 sickbeds for respiratory medicine patients. CRKP patients and their surrounding environment were research objects. During pre-intervention phase (from January 2018 to December 2018), took routine environmental management measures, monitored disinfection effect of environment around patients randomly through microbiological tests every quarter and feedback to supervise environment disinfection. During intervention phase (from January 2019 to June 2019), on the basis of quarterly environmental microbiological tests, targeted microbiological monitoring disinfection effect of environment around CRKP patients, meanwhile used multiple monitoring methods including fluorescent labelling and ATP to strengthen monitoring. Compared CRKP, HAI rates and surrounding environment monitoring qualification rates, calculated increased cost and effect. Calculated expected infection cases and death cases if environmental intervention not taken, compared with actual cases, employed expected decreased cases as effect, calculated increased cost of environmental intervention, evaluated cost-effectiveness of environmental intervention on CRKP HAI prevention and control.

Research proposal

Pre-intervention phase: Performed routine environmental management, including

- Single-room isolation or with other CRKP patient when CRKP positive.
- Infection prevention and control management professionals instructed clinical staff to disinfect patients surrounding environment when identified CRKP-positive case.
- Monitoring disinfection effect of environment through microbiological tests every quarter, randomly chosen patients surrounding environments and feedback to supervise environment disinfection.

Intervention phase: On the basis of quarterly environmental microbiological tests and supervision, adopt intensive environmental management for CRKP-positive patients, including:

- Targeted microbiological monitoring disinfection effect of environment around CRKP patients, meanwhile used multiple monitoring methods including fluorescent labelling and ATP detection to strengthen monitoring. Upon detection of CRKP-positive case, conducted microbiological monitoring of environment

around CRKP patients during his stay, conducted another microbiological monitoring of environment after the patient discharged and terminal disinfection had been completed. Additionally, performed fluorescence labelling and ATP analysis after the CRKP-positive case was detected during his stay to strengthen monitoring, urging to increase disinfection frequency. Separately collected samples for each monitoring method. The environmental disinfection procedures were strengthened if sampling outcome ineligible.

- Performed terminal disinfection after patients discharge, transfer, or death. Another patient could be admitted in case no CRKP was detected in environment and all environment monitoring was eligible.

Data collection

Protein-Protein Interaction (PPI) network analysis is essential in identifying molecular players that mediate important cellular processes in the progression of hypertrophic cardiomyopathy. We constructed a high-connectivity PPI network using data obtained from querying public databases for independent effector genes. Cytoscape plugins were utilized for network visualization, analysis and publication.

Cell culture

Clinical materials: A clinician collected and submitted a specimen of each suspected infection site for analysis, using drug sensitivity tests and resistance labelling, followed by their registration in the Laboratory Information System (LIS). Hospital infection management professionals received clinical data of CRKP-positive patients through HAI monitoring system, which was connected to LIS. Sent messages to urge clinical to undertake contact isolation measures, including single-room isolation, environmental disinfection, hand hygiene and proper personal protection procedures. Based on the standard Centres for Disease Control and Prevention (CDC). National Healthcare Safety Network (NHSN) surveillance definitions for specific types of infections, 2015 update, hospital infection management professionals analysed the clinical symptoms and signs, infection-related examinations, imaging results, reports and antibacterial drug use of each CRKP-positive patient, determined patient's infection status and whether was a HAI.

Forty-four CRKP-positive patients from January 2018 to June 2019, clinical characteristics are listed in Table 1.

Table 1. Clinical characteristics of CRKP-positive patients.

Items	Category	No	Proportion %
Gender	Male	30	68.18
	Female	14	31.82
Age	>65	27	61.36
	≤ 1	17	38.64
ICU type	Respiratory	19	43.18
	Surgical	16	36.36
	Emergency	9	20.45
Specimen type	Sputum	30	68.18
	Rectal swab	9	20.45
	Drainage fluid	3	6.82
	Blood	2	4.55
Outcome	Death	23	52.27
	Better	20	45.45
	Unchanged	1	2.27
Total		44	100

Environmental monitoring

Environmental monitoring site: The surrounding environment of CRKP-positive patients, hands of clinical staff, reusable medical equipment were sampling points. Surrounding environment included sickbed bars, bedside tables, treatment tables, ventilator panels, monitor panels, infusion pump/micro pump panels and nursing tables. Reusable medical equipment consisted of non-critical and semi-critical equipment. Non-critical equipment included medical devices such as stethoscopes and blood pressure cuff that would had contact with intact skin but not with mucous membranes. Semi-critical equipment involved medical devices, such as ventilator air inlets/outlets, simple breathing apparatuses, humidifying tanks and other medical devices that would had contact with intact mucosa without contacting sterile human body tissues, organs, the bloodstream and damaged skin and mucosa.

Surroundings sampling

Hospital infection management: Professionals took a sample, sent specimens for analysis following the national industry standards of hygienic standard for disinfection in hospitals: GB15982-2012 and regulation of disinfection technique in healthcare settings: WS/T 367-2012.

Surface and reusable medical equipment sampling: Surface and reusable medical equipment sampling was performed after disinfected. Placed a 5 cm × 5 cm sterilized specification plate on the surface of tested object and used a cotton swab soaked in 0.03 mol/L sterile Normal Saline (NS) sampling solution to smear the sample plate horizontally and vertically five times each. Rotated the cotton swab accordingly during sampling and continuously sampled four specification plate areas. If the collected surface was ≤ 100 cm^2, all the surfaces were included in the sample. If the area was more than 100 cm^2, only 100 cm^2 was used as a sampling area following the aforementioned methodology. Removed the hand contact part of the cotton swab and placed the rest in a test tube containing 10 mL of sterile eluent.

Hand surface: Used a cotton swab soaked in 0.03 mol/L of sterile Normal Saline (NS) sampling solution. Moved the swab back and forth on the finger surfaces of both hands from the finger root to the tip twice each (approximately 30 cm^2 for each hand) and refer to the specific methods above.

Detection methods: Professional microbiology laboratory technicians conducted the strain culture and isolation according to national clinical examination operating procedures. 0.5 mL of the solution was taken and inoculated by being poured into petri dishes with melted nutrient agar medium cooled to 40°C-45°C, followed by incubation in an incubator at 36°C for 48 h. Then, the number of colonies was counted and detection of the target microorganism was performed. The results were reported to hospital infection management professionals and feedback to clinic staff to supervised re-disinfection.

Calculations:

$$\text{Total colonies number of surface } (\text{CFU/cm}^2) = \frac{\text{colonies per plate } \times \text{ dilution ratio } (20)}{\text{sampling area } (100 \text{ cm}^2)}$$

$$\text{Total colonies number of hand } (\text{CFU/cm}^2) = \frac{\text{colonies per plate } \times \text{ dilution ratio } (20)}{\text{sampling area } (60 \text{ cm}^2)}$$

$$\text{Total colonies number of equipment } (\text{CFU}) = \text{colonies per plate } \times \text{ dilution ratio } (20)$$

Classification of results obtained:

- If total colonies number of surface was ≤ 5 CFU/cm^2 and no pathogenic bacteria were detected, it was eligible, otherwise, it was ineligible.
- If total colonies number on the hand was ≤ 10 CFU/cm^2 and no pathogenic bacteria were detected, it was eligible; otherwise, it was ineligible.
- If number of bacteria colonies detected in one device of semi-critical equipment was ≤ 20 CFU, number of bacteria colonies detected in one device of non-critical equipment was ≤ 200 CFU and none of them were pathogenic, it was eligible, otherwise it was ineligible.

ATP analysis: When a CRKP-positive case was established, conducted ATP assessment during the patient's stay. Ten samples were randomly collected from each CRKP patient during the intervention period. A cotton swab was wetted with sterile water in a bioluminescence test tube and then sampling (for sampling methods, see the surroundings sampling methods described above) the swab was placed into the bioluminescence test tube. The top of the tube was quickly broken and squeezed to ensure the lysate and luciferase have quickly squeezed in. Then, the completely closed-up test tube was transferred into the handheld detector, where a 15 sec examination was performed and the Relative Light Unit (RLU) value of the monitored surface was obtained. The results were classified into the following categories according to the ATP product description: RLU ≤ 100 was considered to be eligible and RLU>100 was considered ineligible.

Fluorescent labelling: When a CRKP-positive sample was detected during patients stay, conducted fluorescent labelling. Ten samples were collected from each patient during intervention period. Fluorescent marking of CRKP-positive patient's bed units was performed before disinfection. The marking sites included the head, the end and gear of bed, bedside table and oxygen equipment belt. Used UV lamp to check the clear or not after disinfection. No fluorescence residue meant removal, whereas the presence of residue indicated unsuccessful removal. Calculated the fluorescent label removal rate by formula number of fluorescent label removals/number of spots × 100%.

Data analysis

Cost-effectiveness: Summarized cost of intensive environmental monitoring during intervention period, including materials of additional sampling, ATP detection and fluorescent labelling, all material costs were calculated as incremental costs. The expected reduction in number of CRKP HAI cases was considered as effectiveness, based on CRKP HAI rate in pre-intervention phase, calculated the expected infection and death cases of intervention period, compared with actual cases, using decreased CRKP HAI and death cases as effectiveness. Calculated cost-effectiveness ratio and assessed the incremental costs of reducing one CRKP HAI case and one CRKP death.

Statistical methods: Summarized cost of intensive environmental monitoring during intervention period, including materials of additional sampling, ATP detection and fluorescent labelling, all material costs were calculated as incremental costs. The expected reduction in number of CRKP HAI cases was considered as effectiveness, based on CRKP HAI rate in pre-intervention phase, calculated the expected infection and death cases of intervention period, compared with actual cases, using decreased CRKP HAI and death cases as effectiveness. Calculated cost-effectiveness ratio and assessed the incremental costs of reducing one CRKP HAI case and one CRKP death.

RESULTS

CRKP isolation and infection type

44 CRKP-positive were established from January 2018 to June 2019. Incidence of CRKP was 15.6/1000 admissions (44/2823) and 34.09% (15/44) were HAI, community source accounted for 65.91% (29/44). The composition of CRKP HAI in intervention phase (23.08%) was lower than that in pre-intervention phase (38.71%).

The composition of 44 CRKP-positive specimens was as follows: Respiratory specimens 68.18%, including 45.45% sputum and 22.73% bronchoscope secretions rectal swab specimens 20.45%, drainage fluid and blood samples accounted for 6.82% and 4.55%, respectively. Tables 2 and 3 specify the details.

Table 2. Isolation and composition of CRKP.

Infection type	Pre-intervention period		Intervention period		Total	
	No	Proportion %	No	Proportion %	No	Proportion %
Health care-associated	12	38.71	3	23.08	15	34.09
Community source	19	61.29	10	76.92	29	65.91
Total	31	100	13	100	44	100

Table 3. Composition of the CRKP-positive specimens and their infection types.

Specimen type	HAI	Community source	Total	Specimen composition %
Sputum	8	12	20	45.45
Bronchoscope secretions	4	6	10	22.73
Rectal swab	0	9	9	20.45
Drainage fluid	2	1	3	6.82
Blood	1	1	2	4.55
Total	15	29	44	100

Intensive environmental monitoring and cost

330 samples were collected in pre-intervention phase, 261 were eligible and qualification rate was 79.09% (261/330). During intervention phase, 242 samples were collected (120 routine quarterly samples and 122 samples

for determination of the additional investment in intensive environmental management). 219 were eligible, with a qualification rate of 90.50% (219/242). ATP detection and fluorescence labelling were conducted in 90 samples, respectively eligible samples were 51 and 74 correspondingly, with qualification rates of 56.67% and 82.22%, respectively, Table 4 shows the details.

Table 4. Environmental monitoring of different methods at different phases.

Test items	Samples no	Qualified no	Qualified rate (%)	χ^2	P
Surroundings sampling at pre-intervention phase	330	261	79.09	13.455	0
Surroundings sampling at intervention phase	242	219	90.5		
ATP detection at intervention phase	90	51	56.67	-	-
Fluorescence labelling at intervention phase	90	74	82.22	-	-

During intensive environmental management phase, the incremental cost was CNY 6211.00, including costs of 122 additional investment in intensive environmental samplings and 28 positive strains were identified (122 sampling reagents, 122 inoculating plates, 28 strain identification), 90 ATP detections cost 90 sampling rods and 90 fluorescent labelling cost 5 sets of fluorescent labels the details are presented in Table 5.

Table 5. Intensive environmental monitoring cost in the intervention period.

Test items	Samples no	Price per unit (¥)	Total (¥)
Sampling reagent	122	5.50	671.00
Inoculating plates	122	5.00	610.00
Strain identification	28	60.00	1680.00
ATP detection	90	35.00	3150.00
Fluorescence labelling	5	20.00	100.00
Total			6211.00

Cost-effectiveness of intensive environmental management

CRKP HAI rate was 6.49/1000 admissions (12/1848) in pre-intervention phase and mortality rate of CRKP HAI was 83.33% (10/12), whereas CRKP HAI and mortality rates in intervention phase were 3.08/1000 admissions (3/975) and 0.00% (0/3) the details are listed in Table 6.

Table 6. CRKP HAI and death rates in the different study phases.

Phases	Admission	CRKP HAI no	Mortality no	HAI rate	Mortality rate
Pre-intervention	1848	12	10	6.49/1000	83.33%
Intervention	975	3	0	3.08/1000	0.00%

Based on CRKP HAI rate (6.49/1000 admissions) and mortality rate (83.33%) in pre-intervention phase, the expected CRKP HAI cases in intervention phase was 6.33 (975 × 6.49/1000) if no intervention taken, whereas actual number

was 3. The expected CRKP HAI death cases was 2.50 (3.00 × 83.33%), whereas exact death cases was 0, which indicated that intensive environmental management reduced 3.33 CRKP HAI cases and 2.50 death cases. According to estimation based on cost-effect ratio, prevent 1 CRKP HAI case required CNY1865.17 (CNY6211.00/3.33) incremental environmental monitoring costs, reduce 1 CRKP HAI death cost CNY 2484.40 (CNY6211.00/2.50 cases) see Table 7 for details.

Table 7. Cost-effect values associated with the reduction of CRKP HAI and death during the intervention phase.

Items	Expected rate	Admission	Expected no	Actual no	Reduced no	Unit cost CNY
CRKP HAI	6.49/1000	975	6.33	3.00	3.33	1,865.17
CRKP HAI death	83.33%	3.00	2.50	0.00	2.50	2,484.40

DISCUSSION

A persistent threat: Carbapenem-resistant *Enterobacteriaceae*

The dissemination of CRE is a global public health threat. CRE infection rate has been increasing all over the world. According to CDC's estimation, more than 9000 infections in United States are caused by CRKP or *Escherichia coli* and approximately 600 deaths annually. However, options for treatment of CRE infections remain limited [8]. ICU patients are especially exposed to this risk, with CRE prevalence in ICUs of Europe, Asia and United States of 2%-7% [9]. Earlier evidence revealed that patients in long-term care facilities had a high CRE acquisition and prolonged CRE carriage duration after colonization [10]. Additionally, CRE infection rates in ICUs of hospitals in United States were 1.5%-8.7%, whereas those in non-ICUs ranged from 0.9%-4.9% [11]. CRE infections are associated with poor outcomes and high mortality, with few treatment options. Another study [12] showed that CRE caused severe illness, especially critical for infections caused by *Klebsiella pneumoniae*, with fatality rate reaching 18.9%-48.0%.

A study in a tertiary care center in Bahrain on epidemiology of CRE infections found that *Klebsiella pneumoniae* was the most common CRE organism, accounting for 87.0%, which presents considerable challenge to clinical treatment and HAI prevention and control. Moreover, rapid increase in CRE incidence was observed, which reached a peak in 2015 with 4.54/1000 admissions and HAI was present in 87% of CRE cases, indicating that community sources accounted for 13% [13]. In our investigation, CRKP incidence was 15.6/1000 admissions, which was much higher than established in aforementioned research conducted in Bahrain (4.54/1000). Notably, 65.91% were community source and 34.09% HAI. The proportion of HAI was lower than those in above studies (13%).

The aforementioned literature evidence and data of our study suggest that CRKP HAI prevention and control causes tremendous pressure in ICUs. Therefore, early identification and isolation of patients need to be promoted, especially during epidemics or periods of high incidence. Previous studies [14] have shown that early identification of CRE and active screening can effectively prevent and control occurrence of HAI.

Nevertheless, the best site for active screening has not yet been established. Several studies have recommended active screening of rectal or anal swabs. In our research, 20.45% of 44 CRKP-positive specimens were rectal swab. However, the proportion of the positive rectal swab specimens would have been higher if active screening had been performed in all admissions during the study period. A previous study [15] showed that digestive system is commonly colonized by *Klebsiella pneumoniae*, *Escherichia coli* and other *Enterobacteriaceae* bacteria. Unreasonable use of antibacterial agents would increase pathogen resistance, leading to a rise in the quantities of drug-resistant strains

in digestive system. Thus, active screening of rectal swab would be a valuable tool for improving positive rate of screening and early isolation of CRE patients.

Intensive environmental management can effectively control CRKP HAI

CRE infection spreads mainly through contact. Strict infection prevention and control measures are of utmost importance, especially environment disinfection. Environment surroundings are an essential transmission pathway for CRE. Therefore, continuous efforts are necessary to strengthen the application of environment disinfection [16]. Studies revealed that CRE can survive in medical environment, on hand skin of medical personnel, surfaces of ambient objects and medical devices and cause infection outbreaks [17,18]. Israeli epidemiologists examined the environment contamination CRE carriers surroundings and found that sheet surfaces, personal bedside tables and infusion pumps were contaminated. The environmental contamination decreased with the increase in distance from the patient location [19]. Therefore, environment disinfection are critically important. Our study also confirmed the significant effect of environmental management on infection spread. On the basis as other interventions keep unchanged, intensive environmental management decreased CRKP HAI incidence and effectively increased the sampling qualification rate. The CRKP HAI rate dropped from 6.49/1000 admissions in pre-intervention phase to 3.08/1000 admissions in intervention phase. Composition of CRKP HAI in intervention phase (23.08%) was lower than that in pre-intervention phase (38.71%). The sampling qualification rate increased from 79.09% in pre-intervention phase to 90.50% in intervention phase. A related study established that the standardized intervention measures of environmental disinfection in ICU significantly reduced CRE HAI [20].

Intensive environmental management: A worthwhile investment?

Environmental intervention is one of the key measures to prevent and control CRKP HAI. Extensive research has been carried out to evaluate the effectiveness of environmental intervention. In this respect, Squire et al. conducted a study on the cost-effectiveness of multifaceted built environment interventions for reducing the transmission of pathogenic bacteria in healthcare facilities and found that improving the built environment through cost-effective resource allocation effectively controlled the infection and reduced the transmission of bacterial pathogens [21]. The aforementioned research of Squire's team on environmental control interventions within hospitals to reduce CRE infection, showed that the application of hospital environment intervention improved the control of CRE infections. The average direct cost of a CRE infection was $1535, whereas the benefits of CRE infection reduction, including its direct economic benefits, were 52% ($460.5 K), 58% ($203 K) and 50% ($37 K) in large hospitals, community hospitals and small acute care hospitals, respectively, indicated environmental intervention is a low-cost and high-efficiency investment [22,23].

CONCLUSION

In our study, we summarized the incremental cost of intensive environmental monitoring during intervention period, considered the expected reduction in the number of CRKP HAI and their death cases as the effectiveness. Prevention and control one CRKP HAI case, incremental cost was CNY 1865.17. Reducing one CRKP HAI death, incremental cost was CNY 2484.40. A case-control study conducted by U.S researchers showed that one case of a single CRE infection would cause average economic loss of $22,484-$66,031 for the hospital, $10,440-$31,621 for the patient and

$37,778-$83,512 for the society, hence, prevent and control one case CRE infection could bring immense benefits, add a small amount cost of environment disinfecting can bring huge benefits.

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PATIENT CONSENT FOR PUBLICATION

Human participants was not involved in this study,

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval and consent was not needed, this was approved by the Ethical Review Committee of Peking University People's Hospital.

COMPETING INTERESTS

The authors have declared that no competing interest exists.

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REFERENCES

1. Abboud CS, et al. Carbapenem-resistant *Enterobacteriaceae* on a cardiac surgery intensive care unit: Successful measures for infection control. J Hosp Infect. 2016;94:60-64.
2. Landry J, et al. The emerging threat from carbapenem-resistant *Enterobacteriaceae*. Nurs Womens Health. 2013;17:519-524.
3. Garcia-Arenzana N, et al. Carbapenem-resistant *Enterobacteriaceae* outbreak in a medical ward in spain: Epidemiology, control strategy and importance of environmental disinfection. Microb Drug Resist. 2020;26:54-59.
4. Mularoni A, et al. Epidemiology and successful containment of a carbapenem-resistant *Enterobacteriaceae* outbreak in a southern Italian transplant institute. Transpl Infect Dis. 2019;21:e13119.
5. Lee JY, et al. Outbreak of imipenemase-1-producing carbapenem-resistant *Klebsiella pneumoniae* in an intensive care unit. Korean J Crit Care Med. 2017;32:29-38.
6. CDC. Facility guidance for control of Carbapenem-resistant *Enterobacteriaceae* (CRE). 2015.
7. World Health Organization. Guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities. Geneva. 2017.

8. Morrill HJ, et al. Treatment options for carbapenem-resistant *Enterobacteriaceae* infections. Open Forum Infect Dis. 2015;2:ofv050.
9. Ruppe E, et al. Mechanisms of antimicrobial resistance in gram-negative bacilli. Ann Intensive Care. 2015;5:61.
10. Chen HY, et al. Carbapenem-resistant *Enterobacterale*s in long-term care facilities: A global and narrative review. Front Cell Infect Microbiol. 2021;11:601968.
11. Martirosov DM, et al. Emerging trends in epidemiology and management of infections caused by carbapenem-resistant *Enterobacteriaceae*. Diagn Microbiol Infect Dis. 2016;85:266-275.
12. Akova M, et al. Interventional strategies and current clinical experience with carbapenemase-producing gram-negative bacteria. Clin Microbiol Infect. 2012;18:439-448.
13. Saeed NK, et al. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in a tertiary care center in the kingdom of Bahrain. J Lab Physicians. 2019;11:111-117.
14. Viale P, et al. Impact of a hospital-wide multifaceted programme for reducing carbapenem-resistant *Enterobacteriaceae* infections in a large teaching hospital in northern Italy. Clin Microbiol Infect. 2015;21:242-247.
15. Potter RF, et al. The rapid spread of carbapenem-resistant *Enterobacteriaceae*. Drug Resist Updat. 2016;29:30-46.
16. Blanco N, et al. Transmission pathways of multidrug-resistant organisms in the hospital setting: A scoping review. Infect Control Hosp Epidemiol. 2019;40:447-456.
17. Chen M, et al. Environmental distribution characteristics of carbapenem-resistant *Klebsiella pneumoniae*. Chin J Infect Control. 2017;16:956-959.
18. O'Horo JC, et al. Carbapenem-resistant *Enterobacteriaceae* and endoscopy: An evolving threat. Am J Infect Control. 2016;44:1032-1036.
19. Lerner A, et al. Environmental contamination by carbapenem-resistant *Enterobacteriaceae*. J Clin Microbiol. 2013;51:177-181.
20. Gupta R, et al. Getting to zero: Reduction in the incidence of multidrug-resistant organism infections using an integrated infection control protocol in an intensive care unit. Am J Infect Control. 2016;44:1695-1697.
21. Squire MM, et al. Cost-effectiveness of multifaceted built environment interventions for reducing transmission of pathogenic bacteria in healthcare facilities. HERD. 2019;12:147-161.
22. Squire MM, et al. Optimal design of paired built environment interventions for control of MDROs in acute care and community hospitals. HERD. 2021;14:109-129.
23. Bartsch SM, et al. Potential economic burden of Carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States. Clin Microbiol Infect. 2017;23:48-49.