6. Carbapenem-Resistant *Enterobacteriaceae*

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Introduction

Background

Carbapenem-resistant *Enterobacteriaceae* (CRE) encompass a family of gram-negative bacteria that cause infections with high mortality rates and few therapeutic options due to their ability to confer resistance to many different antibiotics.[1] Different mechanisms cause the carbapenem resistance, with carbapenemase-producing CRE (CP-CRE) considered primarily responsible for the increase in the spread of CRE.[2] CP-CRE produce enzymes that break down many antibiotics: penicillins, cephalosporins, monobactams, and carbapenems. This trait is most commonly seen in *Enterobacteriaceae*, which include clinically important bacterial species such as *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae*.[3]

Because of the public health risk CRE poses, predominantly attributed to the rapidly spreading CP-CRE, healthcare facilities must implement stringent infection control practices to reduce CRE-associated transmission and to ensure that healthcare settings remain safe for patients. Many toolkits and guidance documents exist to assist healthcare workers and infection control specialists to design and implement their CRE prevention policies. This systematic literature review assesses the implementation and effectiveness of contact precautions to prevent CRE in healthcare settings. The review's key findings are located in the box on the next page.

Importance of Harm Area

CRE is commonly associated with clusters and outbreaks in healthcare settings and is responsible for increasing morbidity, mortality, and healthcare costs worldwide.[3] In the United States, 42 States over the past decade have had at least one type of CRE infection diagnosed in their medical facilities. About 4 percent of hospitals and 18 percent of long-term acute care hospitals (LTACHs) had a patient with a CRE infection in 2012.[4] A study of blood and cerebrospinal fluid isolated from invasive *Klebsiella pneumoniae* infections in Europe showed an increase in carbapenem resistance from 4.6 percent in 2010 to 8.3 percent in 2013.[5]

Carbapenem resistance can be transferred between patients and between different species of bacteria via plasmids, allowing the rapid spread of the resistance gene within healthcare and community settings.[6] Although CRE are largely associated with nosocomial transmission, species within the *Enterobacteriaceae* family (such as *E. coli*) have been associated with community-acquired infections and outbreaks in the past.[2] Therefore, as CRE becomes more prevalent, both nosocomial and community transmission should be considered when developing prevention efforts.

Mortality among patients with CRE infections can be as high as 40 to 50 percent due to both the severity of the infections and the lack of effective antibiotics with which to treat them.[2] Because of their increasing global incidence and associated morbidity and mortality, the World Health Organization recently identified CRE as critical pathogens requiring focused prevention research.[7]

Prolonged inpatient stays increase the risk of exposure to and colonization by CRE.[8] Additionally, patients in long-term care facilities or those who received medical care in CRE-endemic regions are at increased risk for colonization.[2] Other risk factors include intensive care unit (ICU) stay, poor functional status, underlying medical conditions, and receipt of antibiotics.[9]

Key Findings:

- Contact precautions have been shown to reduce transmission of CRE as part of infection control bundles in a variety of healthcare settings, including long-term care facilities and acute care facilities.
- Active surveillance is recommended in outbreak scenarios, in highly endemic regions, and in healthcare facilities or units with ongoing transmission.
- Further research is needed to develop accurate risk assessment tools for determining risk of CRE colonization at hospital admission in order to inform preemptive contact precaution policies.
- Comprehensive policies are needed to ensure appropriate use of contact precautions, regular compliance monitoring, and ongoing staff education.
- Additional research is needed to determine whether there is an appropriate time to discontinue contact precautions based on duration of CRE carriage.

Methods for Selecting Patient Safety Practices (PSPs)

CRE are predominantly transmitted through person-to-person contact in healthcare settings (the other route being contact with environmental fomites). Transmission-based precautions are the most important means of eliminating nosocomial transmission. Organism-independent PSPs (such as general hand hygiene and environmental cleaning practices) are covered in greater detail in Chapter 5 of this report, “General MultiDrug-Resistant Organisms.” This chapter specifically focuses on transmission-based precautions for CRE prevention.

References for Introduction

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6.1 PSP: Contact Precautions To Prevent CRE Infections

Contact precautions are one of three types of transmission-based precautions to control the spread of infectious diseases, the other two being airborne and droplet precautions. Contact precautions are currently recommended to prevent nosocomial transmission of CRE for patients with known or suspected infections or at an increased risk of infection with CRE.[1,2] Maintaining appropriate contact precautions can be challenging for patients undergoing procedures or those who are critically ill and require intensive patient care. Contaminated stool and bodily fluids can transmit CRE, making environmental contamination a concern for patients who are incontinent, who have draining wounds or secretions, or who require high levels of care.[1] Patient transport within and between healthcare facilities also complicates strict adherence to contact precautions. However, when successfully implemented, contact precautions have been shown to reduce transmission of CRE in healthcare facilities.

6.1.1 Practice Description

Contact precautions include appropriate patient placement (e.g., single-patient spaces), use of personal protective equipment, a reduction in the movement and transportation of the patient, the use of disposable or dedicated patient-care equipment, and the frequent and thorough cleaning of patient spaces (especially high-touch surfaces and equipment in close proximity to the patient).[3] Variations on implementation of contact precautions differ by setting, risk of transmission, and the type of care being provided.

Some level of patient isolation should also be a part of contact precautions when feasible. This may include:

- Isolating carriers or individuals infected with CRE in single rooms with attached bathrooms.
- Isolating carriers into rooms shared only by other patients colonized or infected with the same pathogen.
- Cohorting staff (to reduce staff-to-patient transmission), defined as using a dedicated team of healthcare staff to care for patients infected with a particular multi-drug resistant organism (MDRO).
- Prioritizing patients at higher risk of transmission for single rooms, and rooming the remaining carriers or infected individuals together.

Of these options, single patient rooms are always preferred whenever possible. The placement of appropriate signs outside patient rooms is essential to alert staff and visitors to the isolation status of the patient(s) whose room(s) they are entering.

In addition to the contact precaution practices described above—particularly during invasive procedures—contact precautions may include full-head protection and/or face masks. Molter and colleagues advised, when feasible, individual supplies and equipment dedicated to a colonized patient should be used.). However, more studies are needed to determine which variations or additions to contact precautions improve control of CRE transmission.

6.1.2 Methods

To answer the question, “What are effective contact precautions for CRE in healthcare settings?” we searched three databases (CINAHL®, MEDLINE®, and Cochrane) for “Carbapenem-resistant

Enterobacteriaceae" as a keyword term, as well as "cross-infection," "contact precautions," "dedicated staff," "prevention and control," "patient isolation," and similar synonyms. English-language articles published from January 2009 through December 2018 were included. The initial search yielded 69 results. After 13 duplicates were removed, the remaining 56 articles were reviewed and 52 full-text articles were retrieved. Of those, 21 were selected for inclusion in this review. Articles that were excluded had insufficient detail, were of limited rigor, or were not available in English.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

6.1.3 Review of Evidence

Of the 21 articles we reviewed, 3 were systematic reviews and 18 were studies. One of the systematic reviews had a general focus on CRE in healthcare settings, whereas the other two focused specifically on hospitals and outbreaks in acute care hospitals. Of the 18 studies, 11 took place in international settings and only 1 took place in the United States. These studies included:

- 10 pre-post intervention studies.
- 3 outbreak investigations.
- 2 cross-sectional surveys.
- 1 model-based study.
- 1 prospective observational study.
- 1 ambidirectional cohort study.

All but one study included contact precautions as part of an intervention with multiple PSPs. Studies also included active surveillance (n=7), staff/patient/equipment cohorting (n=7), patient isolation (n=6), staff education (n=5),hand hygiene (n=4), monitoring and feedback (n=4), and other topics (n=6). Other topics included: environmental cleaning, chlorhexidine bathing, personal protective equipment use, staff attitudes toward contact precautions, an interdisciplinary outbreak intervention team, and antimicrobial stewardship.

6.1.3.1 Initiating Contact Precautions

Contact precautions are often initiated following a positive screening test. Active screening using perirectal swabs or swabs of other body sites may be used to screen patients for CRE colonization for the purpose of initiating contact precautions. The European Centers for Disease Control and Prevention (ECDC) recommends active screening on admission to specific wards or units (e.g., oncology units), during outbreak scenarios, and upon admission to a hospital.[4]

Active surveillance (upon admission) may not be appropriate in all settings. In units that regularly perform contact precautions, such as ICUs, active screening may be unnecessary. For some organisms, such as extended-spectrum beta-lactamase (ESBL)-producing bacteria, active surveillance has not been found to reduce transmission.[5] Active surveillance also may not be appropriate in settings where the prevalence is low. A study in a large tertiary care hospital in South Korea found that transmission of CRE was reduced without implementing active screening, which they deemed inefficient given the hospital's location in a low-prevalence setting.[6] That hospital's multi-faceted intervention included antibiotic stewardship measures, contact isolation, and enhanced monitoring of hand hygiene practices. Passive surveillance may be sufficient to reduce transmission in low-endemicity settings—initiating contact precautions only if a CRE infection is identified during the course of clinical care, as opposed to screening upon admission.

Pre-emptive isolation relies on identifying CRE carrier risk factors at admission to the facility, which requires information about potential risks. The Centers for Disease Control and Prevention (CDC, 2015) recommends isolating patients who transfer from high-risk settings (e.g., hospitals in endemic areas or facilities with known outbreaks).[1] Djibré et al. (2017) used risk factors to predict carrier status and to reduce unnecessary additional contact precautions in an ICU setting. Their prediction model had a low positive predictive value of 18 percent but a relatively high negative predictive value of 93 percent for predicting carriage of any MDRO, which allowed them to reduce unnecessary contact precautions. The risk factors in their model included: exposure to antibiotics within the preceding 3 months (odds ratio [OR]: 1.64, 95% confidence interval (CI), 0.68 to 3.94, p=0.27), chronic dialysis (OR: 2.16, 95% CI, 0.53 to 8.69, p=0.28), and recent (within the past year) prior hospital stay for more than 5 days (OR: 2.38, 95% CI, 1.04 to 5.46, p=0.04).[7]

A meta-analysis performed by van Loon et al. (2017) pooled ORs from 43 studies to assess risk factors for acquiring a CRE. This meta-analysis found that the greatest pooled ORs were for carbapenem exposure (OR = 4.71, 95% CI, 3.54 to 6.26) and cephalosporin use (OR = 4.49, 95% CI, 2.42 to 8.33).[8]

Further research is needed to design a decision tree or risk score that can be used as a simple and accurate screening tool in a variety of settings. A study performed at the Johns Hopkins Hospital found that despite their assessed risk factors at admission (history of vancomycin-resistant *Enterococcus,* methicillin-resistant *Staphylococcus aureus*, and/or multi-drug-resistant gram-negative organisms), 57 percent of CRE-colonized patients and 50 percent of patients colonized with CP-CRE were not isolated with contact precautions (Goodman et al., 2018).[9] The Johns Hopkins study demonstrates that even with a review of a patient's history at the time of hospital admission, many CRE carriers are missed, and are placed on contact precautions only after a positive clinical culture is isolated. This type of study is valuable for determining the positive predictive value of existing methods for preemptively assessing risk, and similar research is needed to assess the risk prediction models suggested in other studies and guidance documents.

6.1.3.2 Contact Precautions Examples and Summary

The literature we reviewed included many examples of successful contact precautions that reduced CRE transmission in various settings, as shown in Table 1. All these interventions combined contact precautions with other interventions, including screening, patient and staff cohorting or isolation, staff education, pre-emptive contact isolation using risk factor analysis, environmental cleaning, compliance monitoring, and/or hand hygiene. Studies reporting on bundled interventions are limited in their ability to attribute successful reductions in transmission to any one intervention. This weakens the evidence in support of contact precautions significantly and should be taken into consideration when reading this review. Additionally, most of these studies were pre-post interventions and took place during nosocomial outbreaks of CRE.

Table 1: Summary of Studies on Contact Precautions

Study	Intervention(s)	Results
Arena et al., 2018[10]	• Presumptive and standard contact precautions and cohorting • Admission/weekly screening	At admission, 11.6% of patients were colonized, and 9.9% of those negative at admission subsequently became colonized. The intervention was associated with a decline in the incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) colonization in the Severe Brain Injury ward (from 17.7 to 7.2 acquisitions/100 at-risk patient-weeks, p<0.05), but not in other wards. The change was not statistically significant.
Ben-David et al., 2014[12]	• Contact isolation • Active surveillance • Periodic on-site assessments of infection control policies and resources	In long-term acute care hospital (LTACHs), prevalence among those not known to be carriers decreased from 12.1% to 7.9% (p=.008[1]). Overall carrier prevalence decreased from 16.8% to 12.5% (p=0.013[1]). Appropriate use of gloves was independently associated with lower incidence of new CRE carriers.
Ben-David et al., 2019[13]	• Population-tailored contact precautions • Staff education • Active surveillance • Real-time notification of healthcare facilities when cases were detected upon transfer or admission screening, by establishing a repository of all CRE carriers and events of acquisition	Incidence per 10,000 patient-days declined to approximately 50% of baseline (p<0.001), from 2.5 to 1.2 for post-acute care hospitals, from 2 to 0.8 for skilled nursing facilities (SNFs and from 0.5 to 0.3 for nursing homes (NHs. The number of SNFs and NHs experiencing ≥ 5 CRE acquisitions annually decreased from 35 to 11. The incidence of CRE acquisition declined between 2009 and 2015 in all facility types, as expressed by an incidence rate ratio (IRR) of <1/year (PACHs: 0.90, 95% confidence interval (CI), 0.88 to 0.92, p< 0.001; SNFs: 0.87, 95% CI, 0.85 to 0.90, p<0.001; NHs: 0.93, 95% CI, 0.91 to 0.95, p<0.001).
Borer et al., 2011[15]	• Pre-emptive and standard contact precautions • Patient cohorting • 1:4 nursing ratio • Improved signage • Dedicated staff and equipment • Visitor education	CRE incidence declined from 5.26 to 0.18 per 10,000 patient-days (p<0.001[2]) with carbapenem-resistant *Klebsiella pneumonia* in a tertiary care teaching hospital.
DalBen et al., 2016[20]	• Contact precautions • Hand hygiene • Compliance monitoring of hand hygiene and contact precautions (audit and feedback)	CRE R_0 decreased from 11 to 0.42 (range, 0-2.1[2]); and median prevalence of patients colonized with CRE decreased from 33% to 21%.[2] The authors used a mathematical model to provide a real-time decision report to an ongoing before-after trial in an ICU.
Djibré et al., 2017[7]	• Reductions in preemptive advanced contact precautions based on risk factors	The rate of acquired multi-drug resistant organisms (MDRO) (positive screening or clinical specimen) was similar during both periods (respectively, 10%, n=15 and 11.8%, n=15; p=0.66[2]).
Jalalzaï et al., 2018[5]	• Universal contact precautions • Active surveillance cultures (ASCs)	Intensive care unit (ICU)-acquired extended-spectrum beta-lactamase (ESBL)-positive clinical *Enterobacteriaceae* infections occurred in 1.1% of patients admitted during the ASC period and 1.5% of patients admitted during the no-ASC period (p=0.64). An admission during the no-ASC period had no impact on the risk of ESBL infections (odds ratio, 1.16, 95% CI, 0.38 to 3.50, p=0.79), in-ICU death (hazard ratio, 1.22, 95% CI, 0.93 to 1.59, p=0.15), and extended length of stay (standardized hazard ratio[3] of discharge for admission during the no-ASC period, 0.89, 95% CI, 0.79 to 1.01, p=0.08).
Kim et al., 2014[6]	• Contact precautions • Hand hygiene • Monitoring and feedback	In a South Korean teaching hospital, CRE incidence increased from 1.61 in 2008 to 5.49 in 2009, and 9.81 per 100,000 patient days in early 2010. After intervention, CRE incidence declined to baseline levels in 2011 and the decrease was sustained (p<0.001).

Study	Intervention(s)	Results
Molter et al., 2016[17]	• "Extended" contact precautions (hand hygiene, gowns, gloves, face masks, head protection, cohorted staff and patients, individual supplies/equipment, separate communal facilities for carriers) • Weekly staff education • Interdisciplinary outbreak intervention team	After the implementation of the intervention during an outbreak in a tertiary care hospital, there was no contamination of environmental surfaces or equipment and no new cases after 4 days.
Robustillo-Rodela et al., 2017[11]	• Contact precautions • Staff education • Environmental cleaning • Chlorhexidine bathing	During an ICU outbreak, the cumulative incidence of OXA-48-like carbapenemase producing *Enterobacteriaceae* decreased 77% (p<0.05), from 3.48% to 0.79%. Incidence of multidrug-resistant *Acinetobacter baumannii* did not change following the intervention.
Rossi Gonçalves et al., 2016[16]	• Contact precautions • Bedside alcohol gel • Active screening	A CRE outbreak in a university hospital in Brazil was not contained. Poor compliance with infection control measures such as contact precautions and hand hygiene led to the dissemination of colistin-resistant KPC-producing *Klebsiella pneumoniae*.
Schwaber et al., 2011[14]	• Contact isolation • Evaluation and feedback • Patient/staff/equipment cohorting	Pre-intervention, the monthly incidence of nosocomial CRE was 55.5 cases per 100,000 patient-days. During intervention, increase in incidence stopped and eventually reduced to 11.7 cases per 100,000 patient-days (p=0.001). There was a direct correlation between compliance with guidelines and success in containment of transmission (effect estimate -0.06, 95% CI, -0.11 to -0.1, p=0.02) (as shown in Table 1 in article).
Sypsa et al., 2012[18]	• Contact precautions • Hand hygiene • Active surveillance • Isolation/cohorting	Mathematical modeling of the interventions suggested that, assuming 60-80% hand hygiene compliance, this multifaceted intervention would result in a 60-90% reduction in number of colonized patients.
Toth et al., 2017[19]	• Enhanced contact isolation • Active surveillance	The model's intervention effect on transmission reduction ranged from 79% to 93%.
Viale et al., 2015[28]	• Contact precautions • Cohorting carriers • Staff education • Antimicrobial stewardship • Active surveillance	In an Italian teaching hospital, CRE colonization incidence reduced significantly over 30 months, with risk reductions of 0.96 (95% CI, 0.92 to 0.99, p<0.0001) and 0.96 (95% CI, 0.95 to 0.97, p<0.0001), respectively.

Four of these studies reported on the effects of preemptive contact precautions, active screening, cohorting, and advanced contact precautions in ICU settings. One study found no statistically significant change in transmission after implementing active surveillance in an ICU. This ward already used universal contact precautions due to the sensitive population.[5] Two other studies found that implementing preemptive contact precautions had no effect on CRE transmission, including one study in an ICU[7] and one hospital-wide study that included a severe brain-injury unit.[10] The latter study also included active screening and patient cohorting as part of the multi-faceted intervention, which was not found to have a statistically significant effect either facility-wide and within individual units. Thus, this review found little evidence to support preemptive contact precautions, advanced contact precautions, and active screening in ICU settings. However, one study in an ICU found a reduction in cumulative incidence of CRE as a result of a multi-faceted intervention that included staff education, environmental cleaning, and chlorhexidine bathing in addition to contact precautions.[11] Further research is needed to strengthen the evidence in support of these other practices to reduce CRE transmission in ICU settings.

Seven facility-wide studies reported on variations in CRE infection control practices in settings ranging from long-term care (e.g., LTACHs, skilled nursing facilities [SNFs], and nursing homes [NHs]) to tertiary care hospitals. Three of these studies reported on the successful multi-faceted intervention in Israeli healthcare settings. These national interventions included active surveillance, on-site policy and implementation assessments, and contact isolation. With this large-scale and heavily resourced intervention, Israel successfully reduced CRE transmission in LTACHs, post-acute care hospitals, SNFs, and NHs.[12-14]

Two teaching hospitals also successfully reduced CRE transmission with their multi-faceted interventions: one included preemptive contact precautions, cohorting (staff, equipment, and patients), improving signage, and visitor education,[15] and one included standard contact precautions and hand hygiene monitoring.[6] Because of the multifaceted nature of these interventions—which also included antibiotic stewardship, new emergency flagging systems, and environmental cleaning policies—it is difficult to associate success with any one factor. Another study (of implementing active screening and contact precautions during a CRE outbreak) found that poor implementation of contact precautions impeded the intervention and resulted in a continuation of the outbreak.[16] This is a cautionary tale of the importance of monitoring ongoing infection control practices as well as CRE-positive cultures. Lastly, one outbreak study implemented extended contact precautions and used an interdisciplinary outbreak intervention team to successfully stem a CRE outbreak.[17]

In addition to studies, this review included three mathematical models.[18-20] One model of a hyperendemic surgical unit found that a multi-faceted approach was necessary to reduce colonization prevalence.[18] This model found that hand hygiene alone was insufficient, and had to be paired with contact precautions and patient isolation/cohorting to successfully reduce prevalence. Active surveillance and enhanced contact isolation were found to be successful in one model of LTACHs, Acute Care Hospitals (ACHs), and NHs in Utah.[19] This model lends support to these practices in facilities in regions with ongoing outbreaks. Lastly, one mathematical model was used to provide real-time decision support and to predict observed outcomes during a successful before-after study in an ICU.[20]

6.1.3.3 Discontinuation of Contact Precautions

There is currently no global consensus on whether it is appropriate, or when it is appropriate, to discontinue contact precautions. A study of 15 hospitals in Canada found that 6.7 percent discontinued contact precautions after one negative specimen, 26.7 percent discontinued after three negative specimens separated by 1 week, and 53.3 percent continued until the patient was discharged.[21] Even within this review, several different strategies on discontinuation of contact precautions were mentioned. In post-acute care hospitals in Israel, discontinuation of contact precautions is recommended only in sub-acute medical wards when 3 months have passed since the last positive culture. For all other wards in post-acute care hospitals, discontinuation is not recommended.[13] Current Israeli national guidelines state that contact precautions should not be discontinued less than 1 month after a positive culture, and state that 3 months since the last culture is recommended for community, general hospital, and long-term care facility (LTCF) settings.[22] In a pre-post intervention study in a South Korean tertiary care hospital, contact isolation was discontinued after three consequent negative cultures were taken at least 3 days apart.[6] In a literature review by French et al. (2017), one study kept patients on contact precautions for the duration of their hospitalization.[23]

The CDC (2015) recommends that contact precautions be continued indefinitely.[1] However, Banach et al. (2018) recommend discontinuation on a case-by-case basis if: (1) at least 6 months have elapsed since a positive culture, and (2) at least two consecutive negative cultures were collected at least 1 week apart.[24] This guidance does not recommend discontinuation for organisms found to be susceptible to two or fewer antibiotics, when a symptomatic patient is infected with a known or suspected CRE, or when a patient is treated with a broad-spectrum antibiotic (which could select for CRE).

Zimmerman et al., (2013) produced an ambidirectional cohort study in an Israeli teaching hospital on the length of CRE carriage to help inform discontinuation of contact precautions. They found that the mean time to CRE negativity was 387 days (95% CI, 312 to 463). They also found that repeat hospitalization was positively associated with increased carriage time ($p=0.001$).[25] More studies like this are needed to assess risk factors for increased carriage in a variety of settings and populations. By creating more specific models on the length of CRE carriage for different patients, we can make safer and more responsible recommendations on the discontinuation of contact precautions, which are burdensome to patients, staff, and the healthcare system.

6.1.4 Implementation

Fostering a workplace environment that encourages consistent use of contact precautions requires multi-institutional stakeholder involvement. Local health departments and large health systems may mandate contact precautions for patients with CRE infections. On a facility level, administrators and infection control specialists should encourage appropriate contact precautions by implementing monitoring and compliance audits as well as education of staff, patients, and visitors. This section focuses on the evidence identifying key supporting factors and systemic challenges to consistent use of contact precautions.

6.1.4.1 Staff Compliance With Contact Precautions

Cross-sectional surveys have been used to better understand how workplace environments can improve staff compliance with contact precautions and thus reduce transmission of CRE. A study of 420 healthcare workers in an acute care hospital and post-acute care hospital in Israel found that CRE acquisition was negatively correlated with workplace factors such as lack of staff engagement in infection control efforts ($r = -0.25$; $p < 0.05$) and the impression that the work environment is overwhelming, stressful, and chaotic ($r = 0.22$; $p = 0.06$).[26] Efforts should be made to engage staff in infection prevention and to ensure that understaffing and disorganization are not hindering these efforts.

Training, monitoring, compliance auditing, and feedback systems are also effective for improving compliance and appropriate use of contact precautions. An impressive example is the work that has been done on a national level by Israel's Ministry of Health task force.[14] To control CRE transmission among 27 acute care hospitals, the task force visited hospitals to evaluate infection control policies and intervened when compliance and implementation were poor. This led to reduced nosocomial CRE transmission from a monthly incidence of 55.5 cases per 100,000 patient-days to 11.7 cases per 100,000 patient-days ($p<0.001$). Other Israeli research involved a prospective cohort interventional study that scored 16 infection control features, with feedback reported to 13 post-acute care hospitals. Overall carrier prevalence in the 13 facilities declined from 16.8 to 12.5 percent ($p=0.013$).[12] This study also found that appropriate use of gloves was independently associated with lower CRE carrier incidence (New carrier prevalence is defined as the prevalence of carriers detected during screening who were not previously known to be carriers. Thus, the denominator of this measure excludes known carriers.). As another example, one quasi-experimental study by DalBen et al. (2016) found that weekly audit and feedback improved compliance with hand hygiene and contact precautions from 66 percent to 84 percent over a 24-week intervention period, and reduced weekly median R_0 from 11 during the baseline period to 0.42 during the intervention period.[20]

6.1.4.2 Facilitators

6.1.4.2.1 Policy

Infection control policies vary at a national, regional, or facility level and can influence use of contact precautions to prevent CRE. For example, in a 13-facility intervention in Israel, a task force monitored infection control policies and resources during periodic site visits, and developed national guidelines for CRE prevention. By the end of this national intervention, CRE carrier prevalence in post-acute care hospitals had decreased from 16.8 percent to 12.5 percent (p=0.013).[12] Schwaber et al. (2011) also found that because of this intervention in Israel, the incidence of nosocomial transmission decreased among 27 acute-care hospitals (p<0.001).[14] Additionally, a study of 15 hospitals in Canada found that only one-third of the facilities had written infection control policies for CRE.[21] However, this study was conducted in 2012, only shortly after Canada had released guidance for CRE. It is possible that additional hospitals have developed policies since then.

The CDC recommends that healthcare facilities implement policies for important CRE prevention practices such as hand hygiene and antibiotic stewardship, and that policies be enforced through continuous monitoring, auditing, and feedback.[1] Additionally, the CDC recommends that facilities "strictly enforce CDC guidance for CRE detection, prevention, tracking, and reporting."[27] Guidance documents are available on the CDC website.

6.1.4.2.2 Education

The presence of a policy alone may not be enough to facilitate consistent control methods for CRE. Education must accompany any new policy to ensure effective implementation. Awareness about infection control policies is crucial to consistently and successfully implementing these procedures. Staff education has been part of several intervention bundles that have been successful in reducing CRE transmission.[11,13,17,28] Additionally, the CDC recommends that all staff working with patients with CRE should be educated on practicing appropriate contact precautions.[1]

6.1.4.3 Other Challenges

Adherence to contact precautions alone may not be enough to reduce transmission of CRE. An ICU in Brazil had to halt new admissions when contact precautions failed to stem an outbreak (compliance was not reported).[16] Delay of implementation can reduce the efficacy of contact precautions and may be to blame in some of the outbreaks. In a model for CRE transmission in LTACHs, delaying interventions until the 20th CRE case reduced transmission to 60 to 79 percent, below the reduction rate for immediate intervention of 79 to 93 percent.[19]

6.1.4.4 Resources To Assist With Implementation

There are many toolkits to aid facilities in implementing institution-specific infection control programs specifically targeting transmission of CRE or other important multi-drug resistant organisms.

- The CDC healthcare facility guidance lists recommendations for specific types of healthcare facilities, excluding certain long-term care facilities such as nursing homes and assisted living facilities.[1]

- A systematic review performed by the European Centre for Disease Prevention and Control also lists recommendations based on findings from several studies, including contact precautions (n=6), dedicated/cohorted staff (n=6), isolating patients (n=4), and educating staff (n=3), all of which are effective methods for reducing CRE transmission.[4]
- Additional guidance documents and reviews available for CRE prevention are by Banach et al. (2018), Carmeli et al. (2010), Magiorakos et al. (2017), Friedman et al. (2017), and Parker et al. (2014).[2,24,29-31]

6.1.5 Gaps and Future Directions

Future research is needed to improve the sensitivity of risk factor analysis at patient intake in order to determine whether pre-emptive contact precautions should be implemented. A number of risk factors are being used to determine the risk of carriage, such as international travel to areas with increased transmission and prevalence of MDROs in healthcare settings, history of dialysis or chemotherapy, or history of CRE carriage.[29] However, quantitative analysis of the predictive value of these risk factors is needed to focus resources and avoid inconveniencing patients who ultimately test negative upon screening.

Currently there is no consensus on an appropriate timeline for discontinuation of contact precautions, although a handful of studies address average length of CRE carriage, and one guidance document was found containing discontinuation recommendations.[24] Only one study in this review investigated the average length of carriage of CRE to inform discontinuation policies. Zimmerman et al. (2013) obtained follow-up cultures from 97 patients who had a positive culture during a hospitalization at an Israeli teaching hospital. Using Kaplan-Meier survivor analysis, the authors found a mean time to culture negativity of 387 days (95% CI: 312–463 days; range: 26–1,025 days) and a median time of 295 days (95% CI: 192–398 days). Seventy-eight percent of the patients had positive cultures at 3 months, 65 percent had positive cultures at 6 months, and 39 percent had positive cultures at 1 year. Repeat hospitalization was an independent risk factor for CRE carriage ($p<0.001$), reemphasizing that healthcare exposure is a crucial factor in CRE transmission.[25] This study and future studies may help predict the length of carriage for patients with varying risk factors and contribute to more-evidence-based recommendations on an appropriate timeline for discontinuation of contact precautions.

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Conclusion

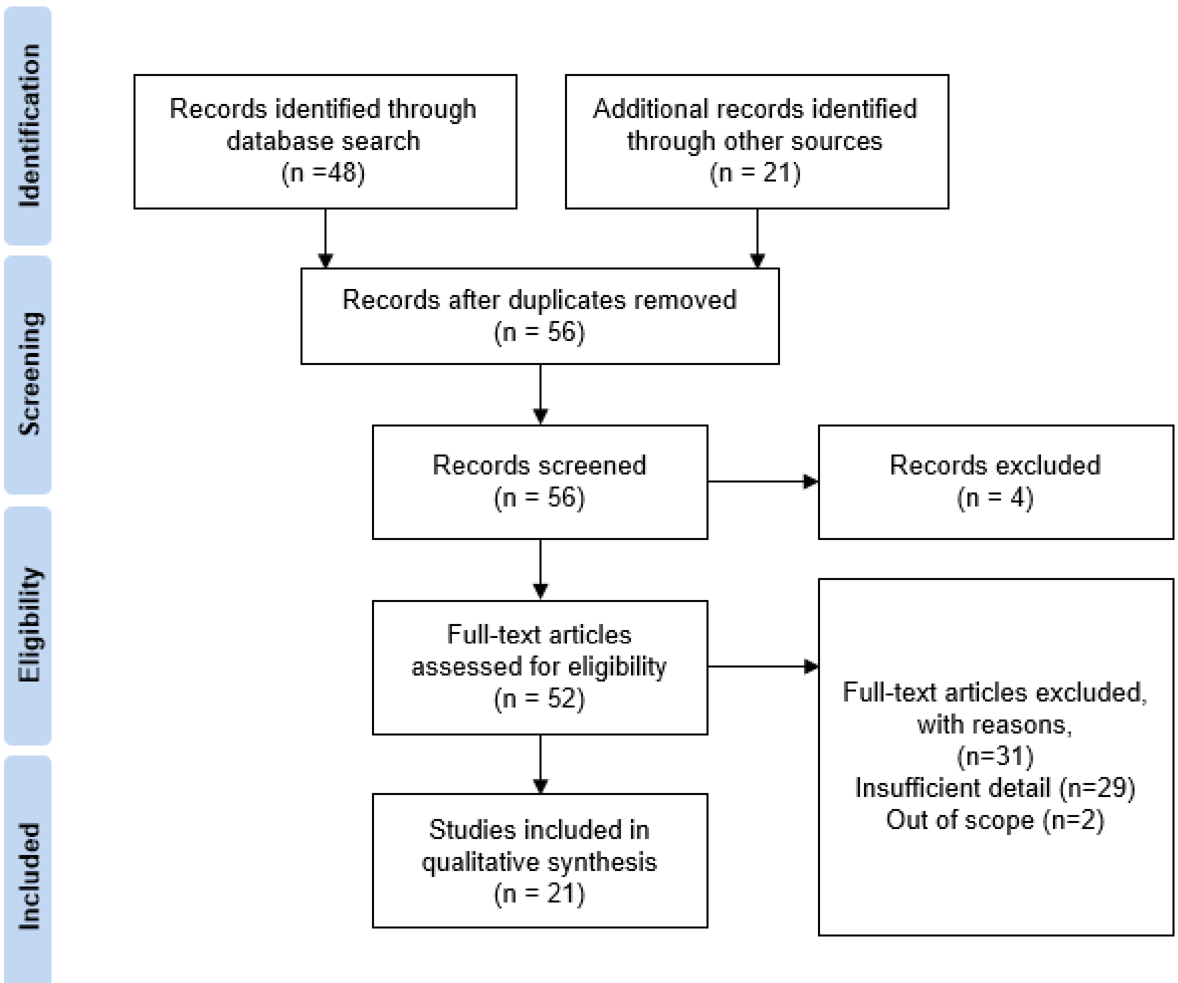
Based on the evidence found in this review, contact precautions are strongly recommended for patients infected with or colonized by CRE. There is little evidence to support universal active surveillance for CRE. However, active surveillance is recommended in outbreak scenarios, in highly endemic regions, and in healthcare facilities or units with ongoing transmission. In units already using universal contact precautions, the evidence suggests that active surveillance does not have a significant impact on reducing transmission. There was little evidence in this study to support preemptive contact precautions for high-risk patients. However, it is recommended that CDC guidelines be followed for this practice.

In all settings, ongoing monitoring, staff feedback, and education on the implementation of contact precaution and infection control policies are highly recommended. Although no study singles out the association of these practices with a successful intervention, they are often part of successful multi-faceted interventions.

There is no strong support for discontinuation of contact precautions when an individual has been placed on contact precautions due to a positive CRE culture. Such patients should remain on contact precautions at each healthcare facility they are admitted to until they are discharged into the community.

Appendix A. Carbapenem-Resistant *Enterobacteriaceae*: PRISMA Diagram

Figure A.1: Carbapenem-Resistant *Enterobacteriaceae* Transmission-Based Precautions—Study Selection for Review



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Appendix B. Carbapenem-Resistant *Enterobacteriaceae*: Evidence Tables

Table B.1: Carbapenem-Resistant *Enterobacteriaceae*, Transmission-Based Precautions—Systematic Reviews

Note: Full references are available in the Section 6.1 reference list.

Author, Year	Description of Patient Safety Practice	Setting(s) Population(s)	Summary of SR Findings	Implementation Themes/Findings	Notes
French et al., 2017[23]	Multicomponent infection control measures, including: patient screening, personal protective equipment (PPE), hand hygiene, staff education or monitoring, environmental cleaning/ decontamination, patient and/or staff cohorting, and patient isolation	Carbapenemase-producing *Enterobacteriaceae* (CPE) outbreaks in acute care settings	Ninety-eight reports on CPE outbreaks were included, with 53 reports from Europe. The number of cases (CRE infection or colonization) involved in outbreaks varied widely, from 2 to 803. Although the risk of bias for selected reports was high, the literature suggests that CPE outbreaks can be controlled using multi-component interventions. Outbreak scenarios that were unsuccessful in controlling transmission may be underrepresented in literature.	Compliance may impact effectiveness, although it is often unmonitored or unreported in literature. The findings indicate that CRE outbreaks can be controlled using combinations of existing measures. However, the quality of the evidence base is weak, and further high-quality research is needed, particularly on the effectiveness of individual infection control measures.	Organism: CPE
Tomczyk et al., 2018[32]	Multimodal strategies comprising three or more components, including contact precautions (CP), active surveillance, patient isolation, audit, feedback, and monitoring	Healthcare facilities	Ninety percent of studies had implemented CP; 80% had monitoring, audit, and feedback of preventive measures; 70% had patient isolation or cohorting. Of the nine studies that reported implementing CP, eight reported patient isolation or cohorting, and eight found that monitoring and audits were associated with a significant reduction in slope and/or level. Study quality was low.	Multimodal infection prevention and control (IPC) strategies (>=3 components implemented in an integrated way) were found to be highly effective for CRE prevention and control. Active surveillance was found to be effective for identifying CRE carriers or infections, but varied in terms of policies from institution to institution, depending on definitions of high-risk populations. Because most studies reviewed were of multimodal IPC strategies, it was difficult to determine the effectiveness of individual interventions.	Organisms: CRE, Carbapenem-resistant *Acinetobacter baumannii* and Carbapenem-resistant *Pseudonomonas aeruginosa*

Author, Year	Description of Patient Safety Practice	Setting(s) Population(s)	Summary of SR Findings	Implementation Themes/Findings	Notes
Van Loon et al., 2017[8]	Use of physical barriers (PPE), patient cohorting, and other contact precautions	Hospitalized patients	Author searched for articles published up to 2017. One hundred sixty-two studies were included in the systematic review, of which 69 studies regarding risk factors for CRE acquisition were included in the random-effects meta-analysis studies. The meta-analyses regarding risk factors for CRE acquisition showed that the use of medical devices generated the highest pooled estimate (odds ratio [OR]=5.09; 95% confidence interval [CI], 3.38 to 7.67), followed by carbapenem use (OR=4.71; 95% CI, 3.54 to 6.26). Based on data from 95 studies, use of a physical barrier and/or CP were found to be most successful intervention (n=71), followed by patient cohorting (n=68).	To control hospital outbreaks, bundled interventions are needed, including the use of barrier/ contact precautions for patients colonized or infected with CRE, In addition, it is necessary to optimize the therapeutic approach, which is an important message to infectious disease specialists, who need to be actively involved in a timely manner in the treatment of patients with known CRE infections or suspected CRE carriage.	Organism: CRE

Table B.2: Carbapenem-Resistant *Enterobacteriaceae*, Transmission-Based Precautions—Single Studies

Note: Full references are available in the Section 6.1 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Arena et al., 2018[10]	Screening at admission, active surveillance and preemptive contact isolation, including contact precautions, single-bed rooms, and rehabilitation treatments inside the room	Pre-post intervention, 1,084 long-term acute care facility (LTACF) patients; included a 25-bed severe brain injury ward with patients who have extended lengths of stay; mean=97+/-72 days	LTACF with 100 beds (Italy)	The intervention was associated with a decline in the incidence of CRE colonization in the severe brain injury (SBI) ward (from 17.7 to 7.2 acquisitions/100 at-risk patient-weeks), but not in other wards. The decline was not statistically significant.	Not provided	The majority of CRE carriers were in the SBI (20/25). SBI admission screening positive results/in-hospital transmission/cross-transmission were all higher there than in other wards. The SBI ward experienced a decreasing trend in in-hospital colonization throughout the program (not significant), whereas the trend in other wards remained stable. Limitations: 1-year length, limited pre-intervention data, and no analysis of genetic variation in strains.	Moderate	Organism: *Klebsiella pneumoniae* carbapenemase-producing K. *pneumoniae* (KPC-KP)

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Ben-David et al., 2014[12]	Active surveillance and contact isolation for carriers, cross-sectional surveys to determine carrier prevalence, and periodic on-site assessments of facility infection control policies	Pre-post intervention study, hospitalized patients	Thirteen long-term acute care hospitals (LTACHs) in Israel (median, 209 beds; range, 104–320 beds)	Prevalence of carriage among those not known to be carriers decreased from 12.1% to 7.9% (p=0.008). Overall carrier prevalence decreased from 16.8% to 12.5% (p=0.013). The appropriate use of gloves was independently associated with lower new carrier prevalence.	Not provided	A multifaceted intervention was initiated between 2008 and 2011 as part of a national program involving all Israeli healthcare facilities. The intervention has included: Periodic on-site assessments of infection control policies and resources, using a score comprising 16 elements Assessment of risk factors for CRE colonization Development of national guidelines for CRE control in long-term acute care hospitals involving active surveillance and contact isolation of carriers Three cross-sectional surveys of rectal carriage of CRE that were conducted in representative wards.	Moderate	Organism: CRE

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Ben-David et al., 2019[13]	Implementation of a national real-time notification system for transfers and admission screenings, population-tailored contact precautions (CP), supervised inter-facility information exchange, and directed intervention at the institutional level during local outbreaks	Pre-post intervention study; 25,000 beds in over 300 institutions	Israeli Long-term care facility, including 15 LTACHs, 15 skilled nursing facilities (SNFs), and 300 nursing homes	The intervention included implementation of population-tailored CP and early detection of carriers. During the study period, incidence declined in all facility types, to approximately 50% of the baseline ($p<.001$). The number of SNFs and nursing homes experiencing ≥5 CRE acquisitions annually decreased from 35 to 11 during this period. The point prevalence of newly detected CRE carriage in long-term acute care hospitals decreased from 12.3% in in 2008 to 0.8% in 2015 ($p<0.001$).	Not provided	A key element was real-time notification of healthcare facilities upon detection of such cases (transfers/admission screenings), enabling timely contact tracing and local preventive measures. Uptake and implementation may have varied across institutions. There was implementation of population-tailored CP and early detection of carriers, a real-time repository of all CRE carriers and events of acquisition, supervised information exchange between healthcare facilities, and directed intervention at the institutional level during local outbreak.	High	This is a national-level real-time notification system and multi-facility intervention.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Borer et al., 2011[15]	Multicomponent intervention that included preemptive contact precautions for high-risk patients, improved signage for patients on contact precautions, dedicated staff and equipment (e.g., x-ray machines and monitors, visitor restriction and CP education, and assigned patient transport)	Pre-post intervention stud;, 8,376 patients	1,000-bed tertiary-care university teaching hospital, Israel	The CR-KP infection density was reduced from 5.26 to 0.18 per 10,000 patient-days (p<0.001), and no nosocomial infections were diagnosed.	Not provided	Researchers implemented "enforcement of CP compliance." Upon admission for high-risk patients: strict, preemptive CP; signage; 1:4 ratio of trained nurses to patients. In cohort ward: signage; strict isolation; dedicated nursing staff and equipment, including an x-ray machine and monitors. Visitors required patient permission and were educated about hand hygiene, use of gowns, gloves, etc. There was also assigned transport of patients.	Moderate to low	Organism: *Klebsiella pneumoniae* carbapenemase-producing K. *pneumoniae* (KPC-KP)

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
DalBen et al., 2016[20]	Compliance monitoring and feedback for hand hygiene and contact precautions	Pre-post intervention with a 44-week baseline period and 24-week intervention period; 14 bed intensive care unit (ICU) (all patients admitted); mathematical model of intervention	ICU of a tertiary care teaching hospital; 14 beds; Brazil	During the baseline period, the calculated R_0 was 11; the median prevalence of patients colonized by CRE in the unit was 33%, and three times it exceeded 50%. In the intervention period, the median prevalence of colonized CRE patients went to 21%, with a median weekly R_0 of 0.42 (range, 0 to 2.1).	Not provided	Compliance was monitored using an audit and feedback routine with weekly meetings. During the baseline period, the ICU had to be closed three times as a measure to stop the spread of CRE. The prevalence of CRE-colonized patients on these occasions exceeded 50%. Each time the unit was reopened, prevalence rates soared rapidly. The goals for compliance with hand hygiene and CP were reached on the third week of the intervention period and were kept above target levels in all but weeks 6 and 8. Rates of compliance with CP went from 66% in the baseline period to a median of 84% in the intervention period.	Moderate	Organism: mainly KP, but study includes all CREs. Contact rates were assumed to be the same for every patient, which is generally not true and could bias the model.

Djibré et al., 2017[7]	Multicomponent intervention that included active surveillance and preemptive contact precautions for high-risk patients, improved CP signage, patient/visitor CP education, and use of personal protective equipment (PPE) (gowns and gloves)	Pre-post intervention study; Phase 1: n=413, Phase 2: n=368; medical and surgical ICU patients	20-bed medical and surgical ICU of a French university-affiliated hospital	The rate of acquired multidrug-resistant organisms (MDRO) (positive screening or clinical specimen) was similar during both periods (respectively, 10%, n=15 and 11.8%, n=15; p=0.66). The risk estimate of MDRO carriage using selected risk factors was feasible, and a zero-risk estimate had a very good negative predictive value, allowing a 19% reduction rate of the use of additional CP.	Not provided	Phase 1: admit screenings with preemptive additional CP; Phase 2: admit screenings with additional CP for patients with one or more risk factors. There was also weekly screening. Risk factors: exposure to antibiotics within the preceding 3 months, hospitalization within the preceding year, admission to another hospital department with a hospital stay of more than 5 days, immunosuppression, chronic dialysis, transfer from rehab, Long-term care unit, or nursing home, and travel abroad within 1 year. Standard precautions included hand hygiene, protective gowns and gloves in case of risk of contact with blood or bodily fluids, and gloves in case of lesions of the healthcare worker's hands. Additional CP included wearing gowns during contact with patient and bodily fluids, wearing gloves as part of standard precautions, door signs at the room entrance stating, "isolation screening" or "isolation confirmed," and oral education of the patients and relatives. Authors did not measure hand hygiene and CP compliance. Acquisition rates were estimated in 50% of population due to relatively short median length of stay	High	

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
						and lack of follow-up or discharge sample.		
Fedorowsky et al., 2015[26]	N/A	Cross-sectional study; self-administered questionnaires; 420 healthcare workers, including: registered/ academic nurses, practical nurses/ auxiliary staff, physicians, and paramedical staff	One acute care hospital and 1 LTACH in Israel (same HMO)	Staff engagement was negatively correlated with CRE acquisitions (r^2=0.25; p<0 .05), overwhelmed/ stress-chaos was positively correlated with CRE acquisitions (r^2=0.22; p<0.06), and hospital leadership showed no significant correlation with CRE acquisition (r^2=0.09; p>.05).	Not provided	When staff engagement was high, the probability of staff reporting compliance with patient isolation was 2x as high as the probability of their reporting noncompliance (p<0.01). High overwhelmed/stress-chaos scores also increased the probability of staff reporting not knowing what precautions to take before caring for a CRE carrier or the environment (p<0.05).	Moderate	Focuses on how work environment can affect CP compliance. Employees with <12 months on the job and students were excluded.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Jalalzaï et al., 2018[5]	Active surveillance in settings with universal contact precautions	Retrospective, uncontrolled pre-post intervention study; n=1,069; all patients admitted for 3 or more days during two consecutive 1-year periods with and without active surveillance cultures (ASC)	ICU of 1,100 bed French hospital	An ICU-acquired extended-spectrum beta lactamase *Enterobacteriaceae* (ESBL-E) infection occurred in 1.1% and 1.5% of patients admitted during the ASC and the no-ASC periods (p=0.64). An admission during the no-ASC period exerted no impact on the hazards of ESBL-E infections (adjusted OR 1.16, 95% CI, 0.38 to 3.50, p=0.79), in-ICU death (SHR 1.22, 95% CI, 0.93 to 1.59, p=0.15), and extended LOS (SHR for discharge 0.89, 95% CI, 0.79 to 1.01, p=0.08).	Not provided	Because universal CP are already in place in ICU settings, the study found active surveillance screening to be unnecessary and to have no effect on incidence of ICU-acquired infections. This study defined CP as single-use gloves and gowns in case of close contact with patients and potential exposure to body fluids during nursing, physiotherapy and other care not requiring full-barrier precautions.	Moderate to low	Organism: extended-spectrum beta-lactamase producing *Enterobacteriaceae*

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Kim et al., 2014[6]	Discontinuation of CP after three consecutive negative cultures taken 3 days apart, passive surveillance using only clinical samples, and strict CP with single-use gowns and gloves	Pre-post intervention study; n=5,790 isolates	Nine hundred-bed tertiary care university teaching hospital in South Korea	CRE incidence rates rose from 1.61 in 2008 to 5.49 in 2009; they rose further to 9.81 per 100,000 patient days in early 2010. After adoption of strict infection control measures, CRE frequency fell back in 2011 and remained at baseline afterward. Resistance rates began to decline, reaching baseline in 2011 ($p<0.001$), and remained at this level afterward.	Not provided	CP kept until three consecutive negative clinical cultures of the same specimen taken at least 3 days apart. Reduced incidence was accomplished without active surveillance. CP were implemented only with positive clinical samples (likely due to lower rates of CRE compared with in the United States). Hospital used strict individual CP with single-use gowns and gloves.	Moderate to low	Organisms: beta lactamase-producing CREs *(E. coli and K. pneumoniae)*

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Lowe et al., 2012[21]	Facility policies on CP discontinuation, risk factor-based screening, and patient isolation	Cross-sectional survey; 15 facilities (6 academic and 9 community hospitals)	Toronto, Canada	There was wide variation in the use of infection control practices for ESBL-E and CRE, respectively, including admission screening (53% and 53%), CP (53% and 100%), and isolation (60% and 100%). Of hospitals performing admission screening, 75% used risk factor-based screening for ESBL-E and CRE.	Not provided	One hundred percent of respondents' facilities use CP on all patients, 6.7% discontinue after one negative specimen, 26.7% discontinue after three negative specimens separated by 1 week, 53.3% continue until discharge, 13.3% have unknown practices, and 33.3% have written infection control policies. The study was conducted only shortly after Canadian guidance for CRE had been released, and hospitals may have been in the process of developing or modifying their practices with respect to CRE. Because of the low prevalence of CRE in Toronto, there is limited experience managing CRE infected/colonized patients from an infection control perspective.	High	Organism: CRE

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Molter et al., 2016[17]	Multicomponent intervention that included weekly staff education, an interdisciplinary outbreak response team, PPE use including facemasks and head protection, dedicated equipment, and patient cohorting with dedicated staff and equipment	Outbreak study, n=10	Tertiary care hospital with 18 bed medical intensive care unit and 18 bed surgical intensive care unit, Germany	There was no contamination of environmental surfaces or equipment, and no new cases, after 4 days of intervention.	Suspected breaches in infection control such as incomplete environmental cleaning and poor hand hygiene may have led to prolonged dissemination of carbapenem-resistant *Acinetobacter baumannii*.	Researchers implemented weekly educational sessions for all personnel. Crucial to the successful outbreak containment was the rapid establishment of an interdisciplinary outbreak intervention team, which instituted infection control measures, including closing the ICU for new admissions, and extended CP including hand hygiene, gowns, gloves, face masks, head protection, cohorted staff and patients and contact patients, individual supplies/ equipment, and separate communal facilities.	Moderate to high	Organism: Carbapenem-resistant *Acinetobacter baumannii*
Robustillo-Rodela et al., 2017[11]	Multicomponent intervention that included staff education, patient and staff cohorting, and in-depth environmental cleaning of the ICU	Outbreak study; ICU	Acute care hospital in Bolivia	Cumulative incidence of OXA-48 (a type of carbapenemase) decreased 77% ($p<0.05$), whereas multidrug-resistant *Acinetobacter baumannii* did not change.	Not provided	The ICU already had strict CP before the outbreak, including gowns and gloves for any contact with patient. During outbreak, CP training was given to staff, among other interventions.	Moderate to high	Organisms: OXA-48 *Enterobacteriaceae,* multidrug-resistant *Acinetobacter baumannii*

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Rossi Gonçalves et al., 2016[16]	Multicomponent intervention that included hand hygiene promotion and education, environmental cleaning monitoring, dedicated equipment, and active surveillance.	Outbreak study; n=111	University hospital in Brazil	Infection control measures were strengthened at the time of the first outbreak to include hand hygiene promotion and supervised cleaning of bed spaces and rooms. Sharing of patient equipment was limited as much as possible, and a program of structural repairs on the AICU was implemented.	Outbreak was not contained, and the ward was eventually closed to new admission.	CP were implemented during outbreak in addition to bedside alcohol gel and active screening. Poor CP/infection control compliance is implicated, but monitoring was not done. There was anecdotal observation of inappropriate use of gloves.	Moderate to high	Organism: KP-KPC
Schwaber et al., 2011[14]	National policy development that implemented intervention monitoring using active surveillance and daily feedback, patient isolation and cohorting, and dedicated staff and equipment	Pre-post intervention study; 1,275 cases; 27 acute care hospitals (ACHs) with 13,040 beds	Israeli ACHs	Pre-intervention, the monthly incidence of nosocomial CRE was 55.5 cases per 100,000 patient-days. During intervention the increase in incidence stopped, and eventually it reduced to 11.7 cases per 100,000 patient-days (p=0.001). There was a direct correlation between compliance with guidelines and success in containment of transmission (p=0.02).	Not provided	The Israeli Ministry of Health task force paid site visits at acute-care hospitals, evaluated infection control policies and laboratory methods, supervised adherence to the guidelines via daily census reports on carriers and their conditions of isolation, provided daily feedback on performance to hospital directors, and intervened additionally when necessary. There was also placement of patients in self-contained nursing units—either single rooms or cohorts—containing all materiel needed for their care and staffed by dedicated nurses on all shifts.	Moderate to low	Organism: CRE Author is consultant of MSD, Johnson & Johnson, and Intercell.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Sypsa et al., 2012[18]	Mathematical model that measured the effects of improved hand hygiene compliance, active surveillance, and patient isolation and cohorting	Prospective observational study and mathematical model of intervention; n=850 surgical unit patients	30-bed Greek tertiary care hospital	Simulation results: Hand hygiene alone did not decrease colonization prevalence in model. With 60-80% hand hygiene compliance there would be a 60-90% reduction in number of colonized admissions.	Not provided	The Ross-Macdonald model for vector-borne diseases was applied to obtain estimates for the basic reproduction number R_0 and assess the impact of infection control measures on CP-KP (Carbapenemase-producing *Klebsiella pneumoniae*) containment in endemic and hyperendemic settings.	Moderate to high	Organism: CP-KP
Toth et al., 2017[19]	Mathematical model that measured the effects of enhanced contact isolation and improved outbreak response time	Model-based intervention study	One LTACH, 6 nursing homes, 3 ACHs; Utah-based data	Model showed reductions in CRE transmissions by 79-93%.	Delaying intervention until the 20th case reduced transmissions by only 60-79%.	Model was for LTACH-focused intervention in a previously CRE-free region. The enhanced isolation model accounted for patients contributing 75% less to transmission rate compared with 50% for standard isolation.	High	Organism: CRE COI: Author received personal fees from Promise Hospital of Salt Lake.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Viale et al., 2015[28]	Multicomponent intervention that included active surveillance for high-risk units or roommates of CRE-positive patients, patient isolation/ cohorting with strict CP, and staff education on CP and hand hygiene	Pre-post intervention study; n=1,571 CRE-positive cultures	1,420-bed teaching hospital in Italy	Following the intervention, the incidence rate of CRE bloodstream infections (risk reduction 0.96, 95% CI, 0.92 to 0.99, p=0.03) and CRE colonization (risk reduction 0.96, 95% CI, 0.95 to 0.97, p<0.0001) significantly decreased over a period of 30 months.	Not provided	The intervention consisted of the following: (a) rectal swab cultures were performed in all patients admitted to high-risk units (ICUs, transplantation, and hematology) to screen for CRE carriage, or for any roommates of CRE-positive patients in other units; (b) cohorting of carriers, managed with strict CP; (c) intensification of education, cleaning, and handwashing programs; and (d) promotion of an antibiotic stewardship program (carbapenem-sparing regimen). Researchers stated that targeted screening of populations and units expected to be at high risk for serious CRE infection makes definitive calculation of CRE carrier incidence rates impossible, and that these rates are potentially underestimated.	Moderate	Organism: CRE

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias	Comments
Zimmerman et al., 2013[25]	N/A	Ambidirectional cohort study; 137 patients; adult hospitalized patients with at least one CRE-positive culture	700-bed teaching hospital in Israel	N/A	Not provided	Mean time to CRE negativity was 387 days (95% confidence interval: 312 to 463). Seventy-eight percent of patients (64/82) had a positive culture at 3 months, 65% (38/58) at 6 months, and 39% (12/30) at 1 year. Duration of carriage was affected by repeated hospitalization (p=0.001) and clinical, as opposed to surveillance, culture (p=0.002).	Moderate to low	Relevant to discontinuation of CP

Appendix C. Carbapenem-Resistant *Enterobacteriaceae* Search Terms

Methods	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review	CRE: Transmission-based Precautions: Contact Precautions, Patient Isolation, Dedicated Staff	((MH “Patient Isolation”) OR (AB “Contact Precautions” OR “Contact Precaution” OR “Patient Isolation” OR “Transmission-Based Precaution*” OR “Transmission Based Precaution*” OR “Dedicated Staff”)) AND ((MH “Carbapenem-Resistant Enterobacteriaceae”) OR (AB “Carbapenem-Resistant Enterobacteriaceae”)))	(((MH “Patient Isolation”) OR (AB “Contact Precautions” OR “Contact Precaution” OR “Patient Isolation” OR “Transmission-Based Precaution*” OR “Transmission Based Precaution*” OR “Dedicated Staff”)) AND ((MH “Carbapenem-Resistant Enterobacteriaceae”) OR (AB “Carbapenem-Resistant Enterobacteriaceae”)))

• Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			

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