



Disease Investigation Guideline: Carbapenem-resistant Enterobacteriaceae (CRE)

Contents

Case Definition	3
Clinical Criteria	3
Laboratory Criteria	3
Case Classification	4
Laboratory Analysis	6
Isolate Submission to KHEL	6
Figure 2: Isolate Submission and Testing Criteria	7
Submission and Reporting Instructions:	7
Epidemiology	8
Standard Case Investigation and Control Methods	9
Case Investigation	10
Contact Investigation	10
Control Measures	11
Containment Strategy	11
Detection	11
Infection Control	11
Contact Screening	11
Figure 3: Approach to Screening Healthcare Contacts	12
Resources and References	13
Patient Resources	13
Healthcare Provider and Facility Resources	13
State Health Department Resources	13
References	13



Healthcare-Associated Infections & Antimicrobial Resistance Program



Revision History

Date of Revision	Changes made	Revision by
02/21/2019	Formatted for publishing.	M. Ella Vajnar
6/01/2018	Submission requirement, added Containment Strategy, and various formatting changes	Justin Blanding
2/12/2018	Updated case definition, formatting, and investigation guidance	Justin Blanding
9/15/2017	Created CRE Disease Investigation Guideline	Justin Blanding

Case Definition

Clinical Criteria

Carbapenem-resistant Enterobacteriaceae (CRE) cases shall be reported and classified based on whether cultures obtained were clinical (i.e. collected for the purpose of diagnosis or treating disease in the course of normal care) versus for screening/surveillance (i.e. collected for the detection of colonization and not for the purpose of diagnosing or treating disease). Because it can be difficult to differentiate screening cultures from clinical cultures based on microbiology records, screening tests should generally be limited to rectal, peri-rectal or stool cultures. Cultures from such sites can be assumed to be for screening unless specifically noted otherwise.

Laboratory Criteria

Laboratory evidence of carbapenemase production in an isolate by a phenotypic method or positive for a known carbapenemase resistance mechanism by specific testing methods, such as:

Phenotypic methods for carbapenemase production:

- CarbaNP positive
- Metallo- β -lactamase testing (e.g., E-test) positive
- Modified Carbapenem Inactivation Method (mCIM) positive or indeterminate
- Carbapenem Inactivation Method (CIM) positive
- Modified Hodge Test (MHT) positive
- Positive for phenotypic carbapenemase production (e.g., mCIM, CIM, CarbaNP) but negative by polymerase chain reaction (PCR) (e.g., Xpert Carba-R) for all known resistance mechanisms (e.g., *Klebsiella pneumoniae* Carbapenemase [KPC], New Delhi metallo- β -lactamase [NDM], oxacillinase-48 [OXA-48], Verona integron-encoded metallo- β -lactamase [VIM], imipenemase [IMP])

Molecular methods for resistance mechanism:

- PCR positive (for KPC, NDM, OXA-48, IMP, or VIM)
- Xpert Carba-R positive (for KPC, NDM, OXA-48, VIM, IMP)
- PCR or Xpert Carba-R positive for novel carbapenemase

Case Definition

Confirmed CP-CRE Cases (CDC 2018)

Carbapenemase producing CRE (CP-CRE) is defined as *Escherichia coli*, *Klebsiella* spp., or *Enterobacter* spp. where the isolate is:

- Positive for known carbapenemase resistance mechanism (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized tested (e.g., PCR, Xpert Cara-R)
- **--OR--**
- Positive on a phenotypic test for carbapenemase production (e.g., metallo- β -lactamase test, modified Hodge test, Carba NP, Carbapenem Inactivation Method [CIM] or modified CIM).

Note: KDHE will classify CP-CRE as any bacteria that is positive by a phenotypic method or positive for known carbapenemase resistance mechanism. National reporting to CDC will only occur for cases that meet CDC's CP-CRE definition.

Probable CP-CRE Cases (KDHE Use Only)

Any carbapenem-resistant bacteria that is tested positive by a phenotypic test and/or a molecular test for carbapenemase production that has been more than 30 days but no more than 12 months since prior positive CP-CRE. Must be same organism, species, and carbapenemase. Used for data management purposes.

Suspect CP-CRE Cases (KDHE Use Only)

Any carbapenem-resistant bacteria that is not available for testing at KHEL for carbapenemase production. Used for data management purposes.

Not a Case (KDHE Use Only)

Any carbapenem-resistant bacteria tested negative on a phenotypic test (e.g. mCIM) performed at KHEL or through CDC's Antimicrobial Resistance Laboratory Network (ARLN).

Criteria to Distinguish a New CP-CRE Case from an Existing CP-CRE Case

- Different organisms/species/carbapenemases are counted as separate events from other organisms/species/carbapenemases and each such event will separate CMR events
- There is at least a 12-month interval from previous CMR event for clinical cases
- Person with a clinical case should NOT be counted as a screening/surveillance case thereafter (e.g., patient with known infection who later has colonization of GI tract is not counted as more than one case)
- Person with a screening case that develops infection (e.g., patient with positive peri-rectal screening swab who later develops blood stream infection)



Case Classification Comments

1. Cases involving isolates that are phenotypically positive for carbapenemase production (e.g., mCIM), but negative for KPC, NDM, OXA-48, VIM, and IMP should be counted as confirmed CP-CRE. Isolates should be submitted to the regional laboratories of the ARLN for further characterization (potential novel carbapenemase).
2. A positive Modified Hodge Test (MHT) can be used to confirm CP-CRE for *Klebsiella* spp. and *E. coli* but not *Enterobacter* spp. An isolate that tests positive on MHT but negative PCR for KPC, NDM, OXA-48, VIM and IMP should have additional characterization performed with another phenotypic test for carbapenemase such as mCIM. CLSI updated guidelines for carbapenemase testing recommend mCIM as the preferred method and removed the recommendation for MHT.
3. If isolate is indeterminate on mCIM and negative by PCR for KPC, NDM, OXA-48, VIM and IMP, isolate should be tested using CarbaNP (at state public health laboratory or regional ARLN lab).
4. CP-CRE should be stratified by the 3 subtypes (genera): *Klebsiella* spp., *Enterobacter* spp. and *E. coli*. Each subtype/ genus should be stratified by whether the cultures were clinical (i.e., collected for the purpose of diagnosing or treating disease in the course of normal care) versus for screening/surveillance (i.e., collected for the detection of colonization and not for the purpose of diagnosing or treating disease). Because it can be difficult to differentiate screening cultures from clinical cultures based on microbiology records, screening tests should generally be limited to rectal, peri-rectal or stool cultures. Cultures from such sites can be assumed to be for screening unless specifically noted otherwise. Laboratory may also note screening culture for other sites (e.g., wounds, tracheostomy or central line sites). Laboratories do not need to change their practice; public health wants to identify all CP-CRE whether they come from screening or clinical cultures.
5. For bacteria that have intrinsic imipenem nonsusceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), resistance to a carbapenem other than imipenem is required.

Laboratory Analysis

The Kansas Health and Environmental Laboratories (KHEL) performs carbapenemase testing on carbapenem-resistant bacteria. Isolates submitted for carbapenemase testing is used for epidemiological and infection control purposes only. KHEL performs the below testing on any isolate that meets testing criteria (Figure 2). No change in the interpretation of carbapenem susceptibility test results is necessary for mCIM positive specimens (CLSI, M100-S28).

Description of Carbapenemase Testing for Enterobacteriaceae and Pseudomonas aeruginosa (CRE, CRPA):

All carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) isolates will be characterized using the following testing workflow:

1. Species identification by mass spectrometry (MALDI-ToF)
2. Phenotypic detection of carbapenemase enzymes by mCIM (modified Carbapenem Inactivation Method)
3. mCIM positive isolates will be tested for the five most common carbapenemase (KPC, NDM, IMP, VIM, OXA-48; Xpert Carba-R)
4. mCIM positive, PCR negative isolates are submitted to the Minnesota Department of Health – Public Health Laboratory for further characterization (with some exceptions)

Description of Carbapenemase Testing for Acinetobacter baumannii:

All carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates received at KHEL will be forwarded to the Minnesota Department of Health – Public Health Laboratory for carbapenemase testing. CRAB isolates will be characterized using the following testing workflow:

- Species identification by mass spectrometry (MALDI-TOF)
- Carbapenemase PCR for five most common carbapenemases (KPC, NDM, IMP, VIM, OXA-48; Cepheid CarbaR)
- OXA Variant PCR testing for OXA-23, OXA-24, OXA-58 (real-time multiplex PCR)

Isolate Submission to KHEL

Kansas Administrative Regulation (K.A.R. 28-1-18) requires laboratories to submit isolates of any bacteria that is resistant to any carbapenem antimicrobial (i.e., doripenem, ertapenem, imipenem, meropenem) to KHEL. Resistance breakpoints are defined from the current Clinical and Laboratory Standards Institute M100 document (Figure 2).

Additionally, for bacteria that have intrinsic imipenem nonsusceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), should also be resistant to either doripenem, ertapenem, or meropenem. Resistance breakpoints for *Pseudomonas aeruginosa* and *Acinetobacter* spp. exclude resistance to ertapenem, but resistant to doripenem, imipenem, or meropenem (≥ 8 $\mu\text{g/mL}$).



See section below for instructions on submission and reporting requirements.

Figure 2: Isolate Submission and Testing Criteria

Enterobacteriaceae family (CRE) ¹	<i>Acinetobacter</i> spp. (CRAB)	Non-mucoid <i>Pseudomonas aeruginosa</i> (CRPA) ²
Resistant to any carbapenem: Ertapenem ≥2 µg/mL or ≤18 mm Doripenem ≥4 µg/mL or ≤19 mm Imipenem ≥4 µg/mL or ≤19 mm Meropenem ≥4 µg/mL or ≤19 mm	Resistant to any carbapenem: Ertapenem N/A (excluded) Doripenem ≥8 µg/mL or ≤14 mm Imipenem ≥8 µg/mL or ≤18 mm Meropenem ≥8 µg/mL or ≤14 mm	Resistant to any carbapenem: Ertapenem N/A (excluded) Doripenem ≥8 µg/mL or ≤15 mm Imipenem ≥8 µg/mL or ≤15 mm Meropenem ≥8 µg/mL or ≤15 mm
OR		
Any CRE, CRAB, or CRPA positive for carbapenemase by CIM, mCIM, CarbaNP, or PCR		
Values shown are MIC breakpoints and zone sizes for disk diffusion from the current CLSI M100 document, 28th edition. Any specimen that meets any one (1) of the above criteria must be submitted to KHEL for carbapenemase testing with below exceptions. 1. <i>Morganella morganii</i> , <i>Proteus</i> spp., and <i>Providencia</i> spp. only non-susceptible to imipenem are not to be submitted. These must test resistant to doripenem, ertapenem, or meropenem. 2. Exclude CRPA sputum isolates from cystic fibrosis patients. Non- <i>aeruginosa Pseudomonas</i> are not required to be submitted. 3. Any CRE, CRAB, or CRPA that is only intermediate to carbapenems do not qualify for testing/submission to KHEL. Description of carbapenemase testing: species ID by mass spectrometry (MALDI-ToF), phenotypic detection by mCIM, and genotypic detection by PCR for mCIM positives		

Submission and Reporting Instructions:

Facilities should follow the below submission and reporting instructions for any bacteria that is resistant to carbapenems or documented production of carbapenemase as outlined by the Carbapenem-Resistant Organism Submission Guidelines (Rev. 08/2018)(Figure 2) document available online at www.kdheks.gov/epi/disease_reporting.html.

1. Reporting to KDHE Bureau of Epidemiology and Public Health Informatics:
 - a. Laboratorians must submit culture results and non-suppressed susceptibility report with numerical values along with isolate submission (unless this information is submitted by Electronic Laboratory Reporting [ELR]). Isolates submitted without susceptibility report may be rejected.
 - b. Infection Preventionists/Mandatory Reporters should submit the Multi-Drug Resistant Organism (MDRO) Reporting Form and laboratory results for any carbapenem-resistant bacteria eligible for carbapenemase testing. The MDRO form is available at www.kdheks.gov/epi/disease_reporting.html
2. Submitting isolates to KHEL:
 - a. Specimens needs to be isolated (raw material not accepted)
 - b. Submitted on typical slant media (blood, chocolate, TSA, etc.)
 - c. Shipped in Category B shipper at room temperature with Universal Submission Form
 - d. For additional information, call **KHEL Customer Service 785-296-1620**

Epidemiology

Carbapenem-resistant Enterobacteriaceae (CRE), Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and Carbapenem-resistant *Acinetobacter baumannii* (CRAB) are a family of bacteria that are difficult to treat because they have high levels of resistance to antibiotics. Common Enterobacteriaceae include *Klebsiella* species and *Escherichia coli* (*E. coli*). These bacteria are found in normal human intestines (gut). Sometimes these bacteria can spread outside the gut and cause serious infections, such as urinary tract infections, bloodstream infections, wound infections, and pneumonia. Enterobacteriaceae can cause infections in people in both healthcare and community settings.

Unlike other multi-drug resistant organisms (MDRO) like MRSA for which a single mechanism leads to methicillin resistance, CRE can become nonsusceptible to carbapenems due to many mechanisms. Before the recent emergence of carbapenamases like KPC (*Klebsiella pneumoniae* carbapenemase), most CRE in the United States likely were resistant to carbapenems through a combination of mechanisms (e.g., a beta-lactamase combined with a porin mutation that limited the ability of carbapenems to get into the bacteria). In 2001, a *K. pneumoniae* isolate that possessed a novel carbapenemase called KPC was recognized in the United States. The genes that code for KPC are on a highly mobile genetic element that can be transmitted from one bacterium to another thereby spreading resistance. KPC-producing bacteria have spread widely across the United States. In addition to KPC, a number of other carbapenemases exist that can lead to carbapenem resistance; examples of these include New Delhi Metallo-beta-lactamase (NDM), Verona Integron-Encoded Metallo-beta-lactamase (VIM), and Imipenemase Metallo-beta-lactamase (IMP). These metallo-beta-lactamases are more common outside the United States but have been identified rarely in this country, most commonly in patients with exposure to healthcare in endemic countries. Of note, some Enterobacteriaceae are intrinsically nonsusceptible to the carbapenem imipenem, such as *Morganella morganii*, *Proteus* species, and *Providencia* species.

Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CP-CRE) are an emerging and epidemiologically important threat. Since the first detection of CP-CRE in the United States (1), CP-CRE have spread rapidly, with cases reported in all 50 states (2). Infections with CP-CRE are difficult to treat and associated with high mortality rates (3). Carbapenem antibiotics are often used as the last line of treatment for infections caused by highly resistant bacteria, including those in the Enterobacteriaceae family. Increased antimicrobial resistance limits treatment options (4). CP-CRE contain mobile resistance elements that facilitate transmission of resistance to other Gram-negative bacilli (5). Early detection and aggressive implementation of infection prevention and control strategies are necessary to prevent further spread of CP-CRE, especially novel CP-CRE. These strategies require an understanding of the prevalence or incidence of CP-CRE.

Notification to Public Health Authorities

Confirmed cases of Carbapenem-resistant bacteria (infection or colonization) shall be reported within 24 hours, except if the reporting period ends on a weekend or state-approved holiday, the report shall be made by 5:00 p.m. on the next business day after the 24-hour period:

1. Healthcare providers and hospitals: report to the local public health jurisdiction or KDHE-BEHI (see below)
2. Local public health jurisdiction: report to KDHE-BEPHI (see below)
3. Laboratories: report to KDHE-BEPHI

Kansas Department of Health and Environment (KDHE)
Bureau of Epidemiology and Public Health Informatics (BEPHI)
Phone: 877-427-7317
Fax: 877-427-7318

Further responsibilities of state and local health departments to the CDC:

As a nationally notifiable condition, CRE cases require a ROUTINELY NOTIFIABLE report to the Centers for Disease Control and Prevention (CDC).

1. ROUTINE reporting requires KDHE-BEPHI to file an electronic report for cases within the next reporting cycle.
 - a. KDHE-BEPHI will file electronic reports weekly with CDC.
2. The local public health jurisdiction will:
 - a. Ensure that all reports of carbapenem-resistant bacteria are forwarded to KDHE-BEPHI on the same day received (or next business day if afterhours).
3. KDHE-BEPHI will:
 - a. Ensure that all information is entered in the Kansas EpiTrax system as soon as possible, ensuring that the electronic form is completed within 7 days of receiving a notification of a report.

Standard Case Investigation and Control Methods

Case Investigation

Healthcare exposures are the main risk factor for CRE infection; therefore, the Healthcare-Associated Infections and Antimicrobial Resistance (HAI/AR) Program at KDHE will conduct CRE disease investigations in Kansas. Despite investigations being performed by HAI/AR at KDHE, local health departments can view any CRE cases that reside in their jurisdiction in EpiTrax. Please report any suspect CRE cases to KDHE, so that an investigation can be initiated. If you have any questions or need to report suspect CRE, contact the HAI/AR Program's Antimicrobial Resistance Epidemiologist at the Epidemiology Hotline (877-427-7317). The case investigation will generally consist of the information and actions below.

- 1) If the index case is currently in an inpatient healthcare setting (e.g., nursing home, hospital) ensure that they have been placed on appropriate isolation (i.e. Contact + Standard) in accordance with CDC's "Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007)." Additionally, ensure that the patient's medical record is "flagged" so isolation precautions can be applied in future inpatient healthcare visits.¹
- 2) Coordinate with diagnostic laboratory for submission of CRE organism to KHEL for carbapenemase testing.
- 3) Contact medical provider to request copy of medical records.
- 4) Contact the patient to access for risk factors of acquisition of multi-drug resistance organisms.²
- 5) Performing contact investigation (see section below).

¹ Doctor office visits or other outpatient settings have less of a risk of transmission of CP-CRE to others and standard precautions (e.g. hand hygiene) should be observed. In cases where the organism is negative for carbapenemase, there is no definitive guidance on the discontinuation of Contact Precautions in inpatient healthcare settings. General recommendations are to use the same isolation practices as ESBL-producing organisms for non-carbapenemase producing CRE.

² CRE patients will generally only be interviewed in cases of confirmed carbapenemase production and for a carbapenemase enzyme not readily detected in Kansas (e.g., NDM, OXA-48).

Contact Investigation

Contact investigation will consist of screening and identifying high-risk contacts for MDRO acquisition. Screening will be based on CDC's "Interim Guidance for a Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs)." Response will be based on the tier type of organism/mechanism. The primary goals of prompt response and containment include:

- 1)** Identifying if transmission/dissemination is occurring, **2)** Identifying affected patients, **3)** Ensuring appropriate control measures are promptly initiated/implemented to contain potential spread, and **4)** Characterizing the organism or mechanism in order to guide further response actions, patient management, and future responses.

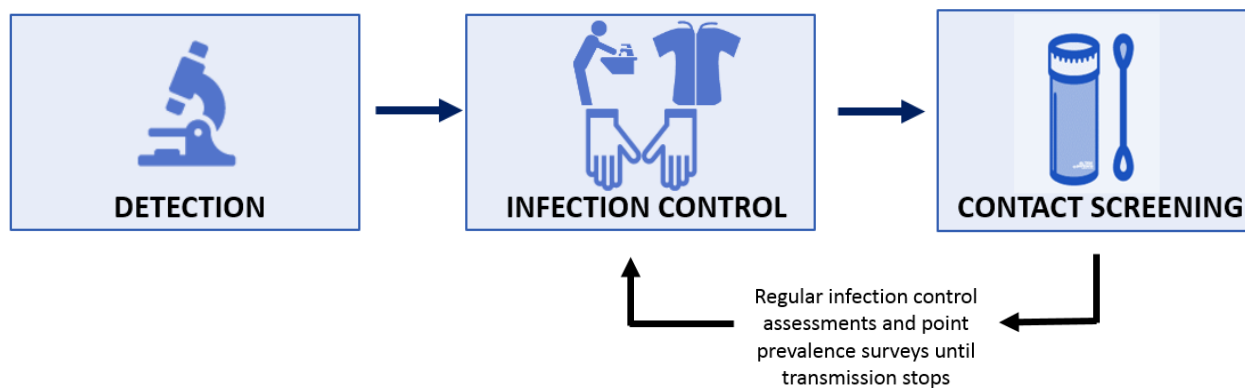


Control Measures

For each person hospitalized with a carbapenem-resistant organism, contact precautions shall be followed during infection or colonization (refer to Requirements for Isolate and Quarantine of Specific Infectious or Contagious Disease document for additional information).

Containment Strategy

KDHE implements CDC's Containment Strategy to control the spread of carbapenemase. The Containment Strategy is a systematic and aggressive approach led by public health and designed to slow the spread of antimicrobial resistance. It has three central elements: detection, infection control, and contact screening.



Detection

Detection focuses on identifying emerging resistance and launching a public health investigation in response to a single case. This is differentiated from past approaches, in which the threshold was two or more clinical cases with suspicion for transmission.

Infection Control

The infection control element includes on-site assessments at facilities where the patient has been admitted in the prior 30 days. All facility types are targeted, with a special emphasis on facilities that care for high acuity patients with longer lengths of stay, which have previously been shown to be amplifiers of transmission.

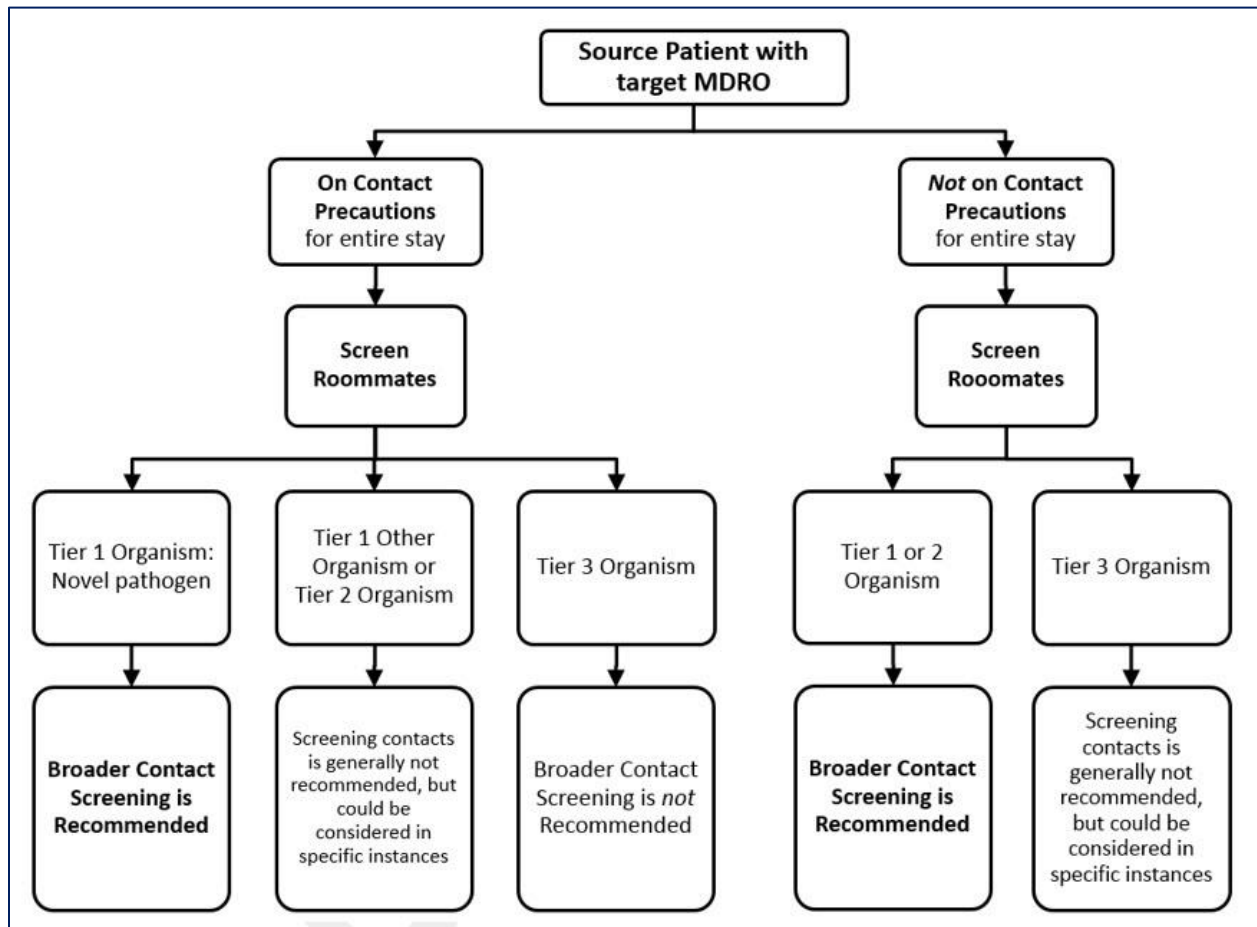
Contact Screening

Contact screening aims to detect asymptomatic colonization, to stop the silent spread of AR. Healthcare contacts of index patients, such as roommates or other patients on a unit or wing, are screened to identify transmission.

When transmission is identified, regular infection control assessments and point prevalence surveys are conducted until transmission stops.



Figure 3: Approach to Screening Healthcare Contacts



Note:

If Contact Precautions are ordered but are not being adhered to regularly, consider the patient as not on Contact Precautions.

If more than one new patient identified with the same mechanism, more widespread screening should be conducted.

Resources and References

Patient Resources

CDC CRE Overview: <https://www.cdc.gov/hai/organisms/cre/cre-patients.html>

CDC Patient FAQ: <https://www.cdc.gov/hai/organisms/cre/cre-patientfaq.html>

Healthcare Provider and Facility Resources

Reporting Form and Submission Guidelines: http://www.kdheks.gov/epi/disease_reporting.html

KDHE HAI/AR Program Website and Contact Information: <http://www.kdheks.gov/epi/hai.htm>

State Health Department Resources

CDC MDRO Outbreak Response: <https://www.cdc.gov/hai/organisms/cre/cre-statehealth.html>

CDC Guidance for Targeted MDROs: <https://www.cdc.gov/hai/outbreaks/docs/Health-Response-Contain-MDRO.pdf>

References

1. Yigit H., et al. Novel Carbapenem-Hydrolyzing Beta-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*. *Antimicrobial Agents and Chemotherapy*, 2001. 45 (4):1151-1161. DOI: 10.1128/AAC.45.4.1151-1161.2001
2. CDC. Healthcare-associated Infections: Tracking CRE. Available at <http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>.
3. Patel G., et al. Outcomes of Carbapenem-Resistant *Klebsiella pneumoniae* Infection and the Impact of Antimicrobial and Adjunctive Therapies. *Infection Control and Hospital Epidemiology*, 2008. 29(12): 1099 -1106. DOI: 10.1086/592412
4. Papp-Wallace, K.M., et al. Carbapenems: Past, Present, and Future. *Antimicrobial Agents and Chemotherapy*, 2011. 55(11): 4943-4960. DOI: 10.1128/AAC.00296-11
5. Gupta N., et al. Carbapenem-Resistant *Enterobacteriaceae*: Epidemiology and Prevention. *Clinical Infectious Diseases*, 2011. 53(1): 60-67. DOI: 10.1093/cid/cir202