

CARBAPENEM INTERMEDIATE or RESISTANT - ACINETOBACTER SPECIES, KLEBSIELLA SPECIES & *E. COLI* (CRAB, CRE- Klebsiella Species or *E. coli*)

✓ DISEASE AND EPIDEMIOLOGY

Clinical Description:

CRAB, which stands for carbapenem-resistant Acinetobacter, and carbapenem-resistant Enterobacteriaceae (CRE), which includes *Klebsiella pneumoniae* and *E. coli*, is a family of germs that are difficult to treat because they have high levels of resistance to antibiotics. CRAB and CRE are an important emerging threat to public health. CRAB causes a variety of diseases, ranging from pneumonia to serious blood or wound infections, and the symptoms vary depending on the disease. CRAB may also “colonize” or live in a patient without causing infection or symptoms, especially in tracheostomy sites or open wounds. CRE can cause a variety of skin and soft tissue infections, as well as cause invasive disease including bacteremia, endocarditis, toxic shock syndrome, etc.

Causative Agent:

CRAB and CRE are bacteria that have acquired resistance (complete or intermediate resistance) to the carbapenem antibiotics known as meropenem, ertapenem, doripenem, and imipenem.

Differential Diagnosis:

None applicable as diagnosis is made based on laboratory findings.

Laboratory identification:

CRAB and CRE may be diagnosed serologically or by culture. Lab definitions are based on current Clinical and Laboratory Standards Institute (CLSI) interpretative criteria. See below.

Agent	Previous Breakpoints (M100-S19) MIC (µg/mL)			Current Breakpoints (M100-S22) MIC (µg/mL)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Doripenem	-	-	-	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty Second Informational Supplement (January 2012). CLSI document M100-S22. Wayne, Pennsylvania, 2012.

Treatment:

CRE and CRAB have been susceptible to very specific antibiotics. There is concern, however, about the possibility that an extremely resistant bacteria could emerge from a case of CRE or CRAB.

The decision to decolonize carriers of CRE or CRAB should be made by the primary care physician in conjunction with hospital infection control and public health.

Case fatality:

If the organism is susceptible to licensed antibiotics, the case fatality rate should approximate that of a non-carbapenem resistant organism. If the organism is resistant to licensed antibiotics, then the case fatality rate could rise due to lack of treatment options.

Reservoir:

Enterobacteriaceae can be found in the intestines of healthy individuals. Acinetobacter can be found in the soil.

Transmission:

To get a CRE or CRAB infection, a person must be exposed to CRE or CRAB bacteria. CRE or CRAB bacteria are usually spread person-to-person through contact with infected or colonized people, particularly through contact with wounds or stool. CRE or CRAB cause infections when they enter the body, often through introduction of contaminated medical devices like ventilators, intravenous catheters, urinary catheters, or wounds caused by injury or surgery.

Susceptibility:

CRAB infections typically occur in intensive care units and healthcare settings housing very ill patients. CRAB infections rarely occur outside of healthcare settings.

CRE primarily affects patients in acute and long-term healthcare settings who are being treated for another condition. CRE are more likely to affect those patients who have compromised immune systems or have invasive devices like tubes going into their bodies. Use of certain types of antibiotics might also make it more likely for patients to get CRE.

Incubation period:

Not applicable, but colonization is an important factor in disease transmission.

Period of communicability:

A person with CRE or CRAB is infectious until the person has completed appropriate antibiotic therapy.

Epidemiology:

CRE, which includes *Klebsiella pneumoniae* and *E. coli* have emerged as one of the most common gram-negative bacteria encountered by physicians worldwide. At present,

carbapenem-resistant *Klebsiella pneumoniae* is the CRE species most commonly encountered in the United States. CRE are more likely to affect those patients who have compromised immune systems or have invasive devices like tubes going into their bodies. Use of certain types of antibiotics might also make it more likely for patients to get CRE.

These organisms have increased in prevalence in US hospitals over the last three decades, have important implications for patient safety, have extremely limited options for treatment, and are associated with increased lengths of stay, medical costs, and mortality. They are resistant to almost all drugs, difficult to treat, and are associated with high death rates (up to 40% in some studies).

CRAB is another pathogenic gram negative bacteria that was the cause of an outbreak in Utah in 2009. It has the same public health implications as CRE, but is more common in Utah.

✓ PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:

- **IMMEDIATELY NOTIFY UDOH AND HEALTHCARE INFECTION CONTROL. CRAB and CRE are infection control emergencies.**
- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation form.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify clusters or outbreaks of this disease.
- Identify sources of exposure and stop further transmission.

Prevention:

The likelihood of acquiring this disease is minimized by judicious use of antibiotics when treating individuals with severe infections, along with appropriate hand washing and other infection control measures.

Chemoprophylaxis:

The decision to decolonize healthcare workers should be made by occupational health services, the infection control team, the healthcare worker, public health, and the worker's personal physician.

The decision to decolonize non-healthcare worker contacts should be made by the contact, their primary care physician, and public health authorities.

Vaccine:

None.

Isolation and quarantine requirements:

Isolation: Cases will be strictly isolated. See case investigation process.

Hospital: Hospitals will institute strict infection control policies. See case investigation process.

Quarantine: Quarantine measures on colonized individuals are possible. See case investigation process.

CASE INVESTIGATION

Reporting:

Report any illness to public health authorities that meets the following criteria:

- Report any human patient that has had isolation of Acinetobacter species:
 - From any specimen source, AND
 - For which the MIC of imipenem or meropenem was ≥ 8 $\mu\text{g/mL}$ OR
 - That was identified as possessing a carbapenemase gene or phenotypically producing carbapenemase.
- Report any human patient that has had isolation of Klebsiella species or Escherichia coli:
 - From any specimen source, AND
 - For which the MIC of imipenem, doripenem, or meropenem was ≥ 2 $\mu\text{g/mL}$ (see table below) OR
 - For which the MIC to Imipenem, or Meropenem was ≥ 8 $\mu\text{g/mL}$; Ertapenem was ≥ 4 $\mu\text{g/mL}$, or if using current CRE Breakpoints, MIC to Imipenem, Meropenem, or Doripenem was ≥ 1 $\mu\text{g/mL}$; Ertapenem was ≥ 0.5 $\mu\text{g/mL}$ (see table below) OR
 - That was identified as possessing a carbapenemase gene or phenotypically producing carbapenemase.
- All Utah patients, regardless of whether they have an infection or are colonized and without symptoms, are reportable. Patients are reportable regardless of hospitalization status.
- All susceptibility results for the isolate (including those for non-penem antibiotics, as well as all antibiotics to which the isolate is susceptible) shall be reported, including those results that may have been suppressed to the clinician.
- If Minimum Inhibitory Concentrations (MIC's) were obtained, then the report should list the MIC value as well as the interpretation of that result (susceptible, intermediate, resistant).
- All cases of this condition should be reported within 3 days of identification.
- Reporting should be on-going and routine.

All isolates of CRAB with a MIC intermediate or resistance ≥ 8 to meropenem or imipenem, and a CRE including carbapenem intermediate or resistant *Klebsiella species* or *E. coli* with an MIC for the following antibiotic from any sites are reportable:

Agent	CRE Previous Breakpoints (M100-S19) MIC ($\mu\text{g/mL}$)			CRE Current Breakpoints (M100-S22) MIC ($\mu\text{g/mL}$)			CRAB
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Intermediate or Resistant
Doripenem	-	-	-	≤ 1	2	≥ 4	-
Ertapenem	≤ 2	4	≥ 8	≤ 0.5	1	≥ 2	-
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4	≥ 8
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4	≥ 8

Case definition:

CRAB/CRE - *Klebsiella species* or *E. coli* (Utah, proposed 2012):

Laboratory Criteria

Confirmed:

- Isolation of Acinetobacter species and:
 - MIC to Imipenem or Meropenem of $\geq 8 \mu\text{g/mL}$, or
 - Positive Modified Hodge test, or
 - PCR positive for carbapenemase gene
- Isolation of Klebsiella species or Escherichia coli and:
 - MIC to Imipenem, or Meropenem of $\geq 8 \mu\text{g/mL}$, Ertapenem of $\geq 4 \mu\text{g/mL}$, or if using current CRE Breakpoints, MIC to Imipenem, Meropenem, or Doripenem of $\geq 1 \mu\text{g/mL}$, Ertapenem of $\geq 0.5 \mu\text{g/mL}$ or
 - Positive Modified Hodge test, or
 - PCR positive for carbapenemase gene

Case Classification

A confirmed case is one that meets the laboratory criteria above.

Case Investigation Process:

- Upon receipt of a positive laboratory result, the LHD/UDOH should immediately notify UDOH/LHD and the Infection Preventionist at the local hospital.
- All further steps of the case investigation will be carried out with representatives from the UDOH, LHD, and healthcare facility.

- UDOH will develop a written plan to determine infection control actions that will be taken with all individuals who are identified as carriers. This plan will include treatment protocols, follow-up cultures (how and when obtained), when carriers will be considered free of colonization, and quarantine protocols for carriers. This plan should be written and agreed upon prior to any culture work-ups of contacts.
- Healthcare facility will identify all contacts and categorize their contact as extensive, moderate, or minimal, according to their level of interaction with the colonized or infected patient.
 - Examples of extensive interaction would involve:
 - Patients who shared a room with the case patient.
 - Healthcare providers and staff who:
 - Clean/bathe/rotate/ambulate the patient
 - Change dressings
 - Make more than three visits per day to the patient
 - Handle secretions and body fluids (including respiratory secretions)
 - Care for wound dressings or perform debridement
 - Conduct physical exams on the patient
 - Have documented prolonged patient contact, including physical therapy, rehabilitation personnel, dialysis, and respiratory technicians
 - Family members who:
 - Provide primary care
 - Have close contact with patient (e.g., sleep in the same bed, or same room)
 - Examples of moderate interaction include:
 - Healthcare providers and staff who:
 - Deliver medications
 - Cross-cover patient only
 - See the patient on daily rounds without conducting extensive exams
 - Perform surgical or invasive procedures where sterile barriers or aseptic techniques are used
 - Monitor patient-care equipment without handling secretions
 - Have limited interactions (e.g. radiology technicians)
 - Examples of minimal interaction include:
 - Healthcare providers and staff who:
 - Work on the same floor without formal cross-coverage of patient
 - Perform predominately administrative duties
 - Consult without extensive exam
 - Visit during teaching rounds only
 - Provide dietary or maintenance services that do not interact directly with the patient.
- Healthcare facility will collect surveillance cultures as deemed necessary.
 - Patient:
 - Culture nares, wounds, drains, and other clinically relevant sites.
 - Healthcare providers and staff with extensive interaction:
 - Culture nares and all skin lesions/wounds.

- If no one in this group is identified as colonized with CRAB or CRE (*Klebsiella species* or *E. coli*), surveillance cultures for individuals with moderate or minimal interaction are not necessary.
- If CRAB or CRE (*Klebsiella species* or *E. coli*) colonization of contacts is identified, OR until the case is no longer colonized or infected:
 - Culture the nares of contacts with extensive interaction weekly to assess the efficacy of infection control precautions.
 - Place a log book at the entrance of the patient's room to identify and track patient contacts.

Outbreaks:

An outbreak will be defined as:

- A substantial increase of CRAB or CRE (*Klebsiella species* or *E. coli*) in a facility in Utah.
- Defining “a substantial increase” will depend on the reporting facility's history with CRAB or CRE. For example:
 - A single case of CRAB or CRE (*Klebsiella species* or *E. coli*) in a facility in Utah without prior cases would be considered an outbreak as long as the case did not have a history of transfer from a facility with known cases.
 - For facilities that regularly identify CRAB or CRE in their facility, double the expected amount of CRAB or CRE cases in a month may be considered an outbreak.

Identification of case contacts:

See above.

Case contact management:

See above.

REFERENCES

1. Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing *Enterobacteriaceae* in Acute Care Facilities. MMWR March 20, 2009 / 58(10);256-260.
2. CDC, Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in healthcare settings, 2006. Atlanta, GA: US Department of Health and Human Services, CDC, Healthcare Infection Control Practices Advisory Committee; 2007. Available at <http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroguideline2006.pdf>.
3. Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE). 2012 CRE Toolkit. Atlanta, GA: National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion. Available at: <http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf>