15-ID-05

Committee: Infectious Disease

Title: Standardized definition for Carbapenem-resistant Enterobacteriaceae (CRE) and recommendation for sub-classification and stratified reporting

I. Statement of the Problem

Carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE) are an emerging public health problem in the United States. Interventions to control the spread of CP-CRE require:
1) Comparable measures of CRE and CP-CRE both within and across public health jurisdictions to facilitate reporting of CRE and CP-CRE data to professional audiences, policy makers, and the public
(2) Actionable epidemiology for healthcare facilities about CRE and CP-CRE detection and response

II. Background and Justification

Background

CP-CRE are an emerging and epidemiologically important threat. Since first detection of CP-CRE in the United States in 1996 (1), CP-CRE have spread rapidly, with cases reported in 48 of 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. CP-CRE contain mobile resistance elements that facilitate transmission of resistance to other Enterobacteriaceae (4). Early detection and aggressive implementation of infection prevention and control strategies are necessary to prevent further spread of CP-CRE. These strategies require an understanding of the prevalence or incidence of CP-CRE. The development and use of a standardized definition is central to this process.

The detection of and definitions for CRE are complicated. Unlike other antibiotic-resistant organisms like methicillin-resistant *Staphylococcus aureus*, which represent a single species and a single resistance mechanism, Enterobacteriaceae are a family of more than 70 organisms and carbapenem resistance can be due to a variety of mechanisms (5). CRE are Enterobacteriaceae that are nonsusceptible (i.e., intermediate or resistant) to at least one carbapenem. Carbapenemase production, most commonly *Klebsiella pneumoniae* carbapenemase (KPC), has been primarily responsible for the emergence of CRE in the United States over the last decade (5). For this reason, CP-CRE have become an important target for prevention. However, there is wide variability in the capacity of clinical and public health laboratories to test for carbapenemase production as the mechanism for carbapenem resistance. CRE definitions that include all isolates testing as nonsusceptible to at least one carbapenem are sensitive but might lack specificity for the most common CP-CRE currently found in the United States (KPC). Due to this limitation, certain phenotypic definitions have been developed to identify likely CP-producing CRE to define priorities for aggressive prevention interventions. Regardless of the definition, any organism nonsusceptible to a carbapenem may be considered a multidrug-resistant organism and warrant the use of transmission-based precautions for patients admitted to a healthcare facility (e.g., Contact Precautions).

A CDC–CSTE working group was created to develop a definition for CRE that allows for the following objectives to be met:

(1) Comparable measures of CRE both within and across public health jurisdictions to facilitate reporting of CRE data to professional audiences, policy makers, and the public
(2) Actionable epidemiology for healthcare facilities about CRE detection and response

In 2014, CDC conducted an evaluation of the 2012 CRE definition (used by the Emerging Infections Program (5) and in the 2012 CDC CRE toolkit (6)) using 312 *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. isolates nonsusceptible to at least one carbapenem (7). Results from these analyses demonstrated that the 2012 CDC definition misclassified 13% of carbapenem nonsusceptible *Klebsiella* spp. and 21% of KPC-producing *Klebsiella* spp. as non-CP. A CRE definition (the 2015 definition proposed here) that included isolates resistant to any carbapenem (including ertapenem) rarely missed CP strains, but captured a higher proportion of non-CP strains (55%). Adding the modified Hodge test (MHT) to this definition decreased the non-CP-CRE captured from 55% to 12%.

In addition to the CDC findings, other challenges exist with the 2012 definition for hospitals, laboratories, and public health authorities:

- It is complicated, has proven difficult to implement by hospitals for reporting and response purposes, and has led to confusion about what interventions should be used for carbapenem-nonsusceptible strains not meeting the CRE definition (i.e., if they do not meet the CDC CRE definition, it is mistakenly thought that no infection prevention action is needed).
- In the past, ertapenem has been the only carbapenem tested on some susceptibility panels.

Based on these challenges and the findings from the CDC evaluation, reasons for case definition changes include the need to:

- Remove the cephalosporin requirement (i.e., resistance to all third-generation cephalosporins tested). This requirement did not appear to add specificity for CP-CRE to the definitions for the CDC isolates.
- Add ertapenem to the definition. This requirement appeared to have improved sensitivity for CP-CRE, especially among *Klebsiella* spp. for the CDC isolates.
- Change the susceptibility requirement from nonsusceptible (i.e., intermediate or resistant) to resistant for carbapenems. This requirement appears to have improved specificity and did not substantially affect sensitivity for identifying CP-CRE for the CDC isolates.

The 2012 definition for CRE was: *E. coli, Klebsiella* spp., *and Enterobacter* spp. nonsusceptible to imipenem, meropenem, or doripenem and resistant to all third-generation cephalosporins tested (e.g., ceftriaxone, cefotaxime, and ceftazidime). Note: ertapenem was excluded. (5, 6)

The proposed 2015 definition for CRE is: *E. coli, Klebsiella* spp., *and Enterobacter* spp. resistant to imipenem, meropenem, doripenem, or ertapenem or production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP)

The change in definition is expected to have the following benefits:

- The proposed definition is simpler than the 2012 definition and is expected to be more easily implemented across a wide range of laboratories.
- The proposed definition corresponds better to the stratified prevention recommendations described in Section VII.
- The proposed definition encourages use of mechanism testing as these tests become more widely available.

III. Statement of the desired action(s) to be taken

☒1. Utilize standard sources (e.g. reporting*) for case ascertainment for CRE. Surveillance for CRE should use the following recommended sources of data to the extent of coverage presented in Table III.

Table III. Recommended sources of data and extent of coverage for ascertainment of cases of CRE

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	X	X
Laboratory reporting	X	X
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers)	X	X
Death certificates	X	X
Hospital discharge or outpatient records	X	X
Extracts from electronic medical records	X	X
Telephone survey		
School-based survey		
Other _____		

2015 Template

☒2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for CRE but do not add CRE to the *Nationally Notifiable Condition List*. If requested by CDC, jurisdictions (e.g. States and Territories) conducting surveillance according to these methods may submit case information to CDC.

3. Jurisdictions should stratify reports of cases of CRE using the methods outlined in Section VII.

4. CSTE requests that CDC adopt this revised, standardized reporting definition of CRE, including the revised laboratory criteria.

5. CSTE recommends that health departments and public health laboratories should work with clinical laboratories to collaborate around the identification and timely reporting of CRE to infection control and public health authorities to ensure timely communication. Interfacility communication should be strongly encouraged (also see CSTE position statement 13-ID-09: Communication of possible healthcare-associated infections across healthcare settings (8)).

CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined above.

Terminology:
* Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local or state public health.
**Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Condition List TO CDC.

IV. Goals of Surveillance

To provide information on the temporal, geographic, and demographic occurrence of CRE and CP-CRE to facilitate its prevention and control.

V. Methods for Surveillance: Surveillance for CRE should use the recommended sources of data and the extent of coverage listed in Table III.

The primary source of data will be the microbiology laboratory and the laboratory should report CRE to public health authorities. Healthcare facilities and clinicians who become aware of patients with CRE should report these to public health authorities. Other data sources (e.g., death certificates or hospital discharge data) may be used as supplementary case finding methods; their yield is unknown)

VI. Criteria for case identification

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

Report to public health authorities any of the following laboratory results:

Enterobacter spp, *E.coli* or *Klebsiella* spp:

> Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem)
> OR
> Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP)

Report to public health authorities a person whose healthcare record contains a diagnosis of CRE, CP-CRE, KPC, NDM, OXA-48, IMP or VIM or a person whose death certificate lists CRE, CP-CRE, KPC, NDM, OXA-48, IMP or VIM as a cause of death or significant condition contributing to death.

B. Table of criteria to determine whether a case should be reported to public health authorities

Criterion	**CRE**	**CRE**	**CP-CRE**	**CP-CRE**
Clinical Evidence				
Health record diagnosis of CRE	S			
Health record diagnosis of CP-CRE			S	
Health record diagnosis of KPC			S	
Health record diagnosis of NDM			S	
Health record diagnosis of OXA-48			S	
Health record diagnosis of IMP			S	
Health record diagnosis of VIM			S	
Death certificate lists as cause of death or significant condition contributing to death: CRE	S			
Death certificate lists as cause of death or significant condition contributing to death: CP-CRE			S	
Death certificate lists as cause of death or significant condition contributing to death: KPC			S	
Death certificate lists as cause of death or significant condition contributing to death: NDM			S	

Death certificate lists as cause of death or significant condition contributing to death: OXA-48			S	
Death certificate lists as cause of death or significant condition contributing to death: VIM			S	
Death certificate lists as cause of death or significant condition contributing to death: IMP			S	
Laboratory Evidence				
Klebsiella spp.*;* *Escherichia coli;* *Enterobacter* spp*.*		N		N
Resistant to imipenem, meropenem or doripenem (MIC** ≥4 mcg/ml)		O		
Resistant to ertapenem (MIC ≥ 2 mcg/ml)		O		
PCR for KPC positive				O
PCR for NDM positive				O
PCR for OXA-48 positive				O
PCR for IMP positive				O
PCR for VIM positive				O
Modified Hodge test (MHT) positive				O
Carba NP positive				O
Metallo-β-lactamase testing (e.g., E-test) positive				O

Notes:
S = This criterion alone is Sufficient to report a case.
N = All "N" criteria in the same column are Necessary to report a case.
O = At least one of these "O" (Optional) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to report a case.
* A requisition or order for any of the "S" laboratory tests is sufficient to meet the reporting criteria.
**MIC: Minimum inhibitory concentration

C. Disease-specific data elements
None

VII. Case Definition for Case Classification

To meet objective 1 (i.e., comparability within and across public health jurisdictions) CRE reporting by public health authorities should be:

1) Restricted at the present time (March 2015) to *Klebsiella* spp., *E. coli*, and *Enterobacter* spp. and stratified by these three genera.
2) 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 screening cultures (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.

3) Stratified by whether additional information is available on the mechanism of carbapenem resistance (e.g., likely carbapenemase producer (i.e., likely CP-CRE); likely non-carbapenemase producer (i.e., likely non-CP-CRE) and unknown carbapenemase production status (i.e., not tested or data not available or insufficient data available). This may be helpful, because the definition of CRE still may lack specificity for CP-CRE, which has infection control implications. In light of this, some health departments that have access to additional CRE mechanism testing might choose to stratify the definition further into three groups: likely carbapenemase producer (i.e., likely CP-CRE); likely non-carbapenemase producer (i.e., likely non-CP-CRE),

For objective 2 (actionable epidemiology for healthcare facilities about CP-CRE detection and response), health departments should consider including other species of Enterobacteriaceae beyond just *Klebsiella* spp., *E. coli*, and *Enterobacter* spp. See Appendix B for additional guidance about other Enterobacteriaceae species. In general, any patient colonized or infected with an organism that is nonsusceptible to a carbapenem warrants the use of Standard Precautions, Contact Precautions and other transmission-based precautions as indicated by the patient's status in acute care settings, to decrease the risk for transmission of these organisms. However, for isolates known or suspected to be carbapenemase producers (i.e., likely CP-CRE or unknown CP-CRE) consideration should be given to implementation of more aggressive interventions including screening cultures of known contacts, cohorting of patients and staff, interfacility communication (i.e., communicating patient's CRE status to receiving facility upon patient transfer or when results become available and report CRE to previous care setting following recent transfer).

As of March 2015, no single test is adequate to exclude each of the 5 most common carbapenemases in all species of Enterobacteriaceae. Tests for carbapenemases should be able to identify the most common U.S. carbapenemases which currently are KPC and New Delhi metallo-β-lactamase (NDM). Testing for other carbapenemases should be considered based on local epidemiology and patient exposures (e.g., healthcare exposure outside the United States) and for isolates that are highly carbapenem-resistant but negative for NDM and KPC. Additional carbapenemases include the Verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP), and oxacillinase-48-like carbapenemase (OXA-48). Testing for carbapenemases that laboratories might perform include metallo-β-lactamase screening tests (e.g., MBL E-test), PCR, Carba NP, or MHT). Due to intrinsic production of AmpC beta-lactamase, non-CP *Enterobacter* spp. may produce a false positive modified Hodge test. Therefore, caution is advised when interpreting modified Hodge test results for these organisms. Other phenotypic tests for carbapenemase production should be used, if available.

A. Narrative: Description of criteria to determine how a case should be classified.

Confirmed: meets below laboratory criteria.
Probable: not applicable
Suspect: not applicable

CSTE recommends that CRE cases be further stratified into likely CP-CRE, likely non-CP-CRE and unknown mechanism of carbapenem resistance. These sub-classifications have infection control implications listed below. Please also see Appendix A for additional notes on laboratory interpretation

Clinical Criteria
None

Laboratory Criteria

E. coli, *Klebsiella* spp., or *Enterobacter* spp. that is:

Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem)
OR
Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, modified Hodge test (MHT), Carba NP, or metallo-β-lactamase testing (e.g., MBL E-test or other screening method))

Sub-classifications of CRE

1. Likely CP-CRE
   - Positive for production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, modified Hodge test (MHT), Carba NP, or metallo-β-lactamase testing (e.g., MBL E-test or other screening method))
2. Likely non-CP-CRE (if OXA-48 has not been identified in jurisdiction or is very rare)
   - Negative molecular assay for KPC and NDM if performed (and negative for other recognized tests or no other recognized test performed)
   - Negative MHT (and negative for other recognized tests or no other recognized test performed)
   - Negative MHT and negative MBL E-test (and negative for other recognized tests or no other recognized test performed)
   - Negative Carba NP (and negative for other recognized tests or no other recognized test performed)
   - Negative Carba NP and negative PCR for OXA-48 (and negative for other recognized tests or no other recognized test performed)
   - Negative MBL E-test and negative PCR for KPC (and negative for other recognized tests or no other recognized test performed)
   - Negative MBL E-test, negative PCR for KPC, and negative PCR for OXA-48 (and negative for other recognized tests or no other recognized test performed)
3. Likely non-CP-CRE (if OXA-48 identified in jurisdiction or surrounding geographic area or history of overseas travel)
   - Negative PCR for KPC, NDM, and OXA-48 if performed (and negative for other recognized tests or no other recognized test performed)
   - Negative MHT (and negative for other recognized tests or no other recognized test performed)
   - Negative Carba NP and negative PCR for OXA-48 (and negative for other recognized tests or no other recognized test performed)
   - Negative MBL E-test and negative PCR for KPC (and negative for other recognized tests or no other recognized test performed)
   - Negative MHT and negative MBL E-test (and negative for other recognized tests or no other recognized test performed)
4. Unknown mechanism of carbapenem resistance
   - No recognized test performed
   - Negative PCR for KPC and no other tests performed*
   - Negative PCR for NDM and no other tests performed*
   - Negative PCR for OXA-48 and no other tests performed*
   - Negative PCR for VIM and no other tests performed*
   - Negative PCR for IMP and no other tests performed*
   - Negative MBL E-test and no other tests performed*
   - No positive result by a recognized test*

*Testing for additional carbapenemase (e.g., IMP, VIM, OXA-48) should be considered if local epidemiology suggests that these enzymes are circulating in the area, or patient has

exposures that suggest additional carbapenemases might be present (e.g., hospitalization outside the United States, exposure to patient with another carbapenemase, high MICs to carbapenems but negative for KPC and NDM.) Please refer to Appendix B for additional notes on laboratory testing

Infection Control Implications

1. Likely CP-CRE: Standard Precautions + Contact Precautions (+ additional transmission-based precautions per patient status (e.g. Droplet) in addition to more aggressive interventions (e.g. screening, cohorting of staff/patients). Interfacility communication
2. Likely non-CP-CRE: Standard Precautions + Contact Precautions (+ additional transmission-based precautions per patient status (e.g. Droplet). Interfacility communication
3. Unknown CP production status: Standard Precautions + Contact Precautions (+ additional transmission-based precautions per patient status (e.g. Droplet) + strongly consider more aggressive interventions (e.g. screening, cohorting of staff/patients); based on the clinical circumstance, patient history of travel, and local CRE epidemiology. Interfacility communication

Epidemiologic Criteria

- For subclassification: Likely non-CP-CRE (if OXA-48 has not been identified in jurisdiction or is very rare)
    - OXA-48 not identified in jurisdiction or is very rare
    - No history of overseas travel in patient
- For subclassification: Likely non-CP-CRE (if OXA-48 in jurisdiction or surrounding geographic area or history of overseas travel)
    - OXA-48 identified in jurisdiction or surrounding geographic area
      OR
    - History of overseas travel in patient

Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance

- Classify cases by clinical isolate vs. screening isolate (i.e., rectal, peri-rectal, or stool cultures)
- For clinical isolates, a new event should be counted after a 30 day interval since previous clinical isolate
- For colonization (screening culture), count patient only once regardless of the interval between testing (assumes patient is always colonized)
- If clinical isolate and colonization isolates are recovered from the same patient within same 30 day period, count once as clinical isolate, do not count future colonization
- Different organism/species are counted as separate events from other species (30 day time interval does not apply)

B. Classification Table

Criterion	Confirmed
Laboratory Evidence	
Klebsiella spp.*; Escherichia coli; Enterobacter* spp*.*	N
Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem)	O
Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain	O

reaction, modified Hodge test (MHT), Carba NP, or metallo-β-lactamase testing (e.g., MBL E-test or other screening method))	

Sub-classification Table

	CRE			
Criterion	**Unknown mechanism of carbapenem resistance**	**Likely CP-CRE**	**Likely Non-CP-CRE If OXA-48 has not been identified in jurisdiction or very rare**	**Likely Non-CP-CRE If OXA-48 in jurisdiction or surrounding geographic area or history of overseas travel**
Laboratory evidence				
Klebsiella spp.*; Escherichia coli; Enterobacter* spp.	N	N	N	N
No other tests* performed	S			
PCR for KPC positive	A	S	A	A
PCR for both KPC and NDM negative if performed	A		S	
PCR for KPC, NDM and OXA48 negative if performed	A		S	S
PCR for KPC negative and no other tests performed*	S			
PCR for NDM	A	S	A	A

positive				
PCR for NDM negative and no other tests performed*	S			
PCR for OXA48 positive	A	S	A	A
PCR for OXA48 negative and no other tests performed*	S			
PCR for VIM positive	A	S	A	A
PCR for VIM negative and no other tests performed*	S			
PCR for IMP positive	A	S	A	A
PCR for IMP negative and no other tests performed*	S			
MHT positive	A	S	A	A
MHT negative and no other tests performed*	A		S	S
Carba NP positive	A	S	A	A
Carba NP negative	A		S	
Carba NP negative and PCR for OXA 48 negative	A	A	S	S
MBL Etest positive	A	S	A	A
MBL Etest negative	A		S	

and PCR for KPC negative				
MBL Etest negative and PCR for KPC negative and PCR for OXA48 negative	A		S	S
MBL Etest negative and no other tests performed*	S			
MHT negative and MBL Etest negative	A		S	S
Epidemiological Evidence				
OXA-48 not identified in jurisdiction or is very rare			N	A
OXA-48 identified in jurisdiction or surrounding geographic area			A	O
History of overseas travel in patient			A	O
Criteria to distinguish a new case:				
Not counted as a new case if occurred within 30 days of initial case of same genera and species and	N	N	N	N

clinical isolate				
If have positive clinical culture, do not count subsequent or concurrent screening cultures/tests if same genera and species regardless of time interval	N	N	N	N
For screening cultures, count isolate only once	N	N	N	`N

*Other tests performed include: PCR for KPC, NDM, OXA-48, VIM, IMP or modified Hodge test (MHT), Carba NP or metallo-ß-lactamase. Please see appendix A for additional information on test performance characteristics of MHT and CarbaNP.

Notes:
S = This criterion alone is Sufficient to classify a case.
N = All "N" criteria in the same column are Necessary to classify a case. A number following an "N" indicates that this criterion is only required for a specific disease/condition subtype (see below).
A = This criterion must be absent (i.e., NOT present) for the case to meet the classification criteria.
O = At least one of these "O" (Optional) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case. (These optional criteria are alternatives, which means that a single column will have either no O criteria or multiple O criteria; no column should have only one O.) A number following an "O" indicates that this criterion is only required for a specific disease/condition subtype.

VIII. Period of Surveillance

Surveillance is expected to be ongoing, as this is an emerging pathogen.

IX. Data sharing/release and print criteria
At present, there are no expectations for sharing of case data with CDC

X. References

1. Yigit H, et al. Novel Carbapenem-Hydrolyzing Beta-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*. Antimicrob Agent Chemother 2001; 45:1151-1161
2. CDC. Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae in the United States. Available at http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html . Last viewed 5 March 2015
3. Patel G, et al. Outcomes of Carbapenem-Resistant *Klebsiella pneumoniae* Infection and the Impact of Antimicrobial and Adjunctive Therapies. Infect Control Hosp Epidemiol 2008; 29:1099-1106
4. Gupta N, et al. Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis 2011; 53:60-67
5. CDC. Vital Signs: Carbapenem-Resistant *Enterobacteriaceae*. MMWR Morb Moral Wkly Rep. 2013;62:165-170
6. Centers for Disease Control and Prevention (CDC): Guidance for control of Carbapenem Resistant Enterobacteriaceae (CRE): 2012 CRE toolkit available at: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html
7. Chea N, Bulens SN, Kongphet-Tran T et al An evaluation of phenotypic definitions for the identification of carbapenemase-producing carbapenem-resistant Enterobacteriaeceae, United States. Emerging Infectious Diseases (in press)
8. CSTE position statement 13-ID-09: Communication of possible healthcare-associated infections across healthcare settings

XI. Coordination

Agencies for Response

(1) Centers for Disease Control and Prevention
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Appendix A: Laboratory guidance and notes

1. Changes have been made to the Clinical and Laboratory Standards Institute (CLSI) MIC breakpoints for both carbapenems and cephalosporins in the past decade. It is important to note that clinical laboratory adoption of the most current breakpoints for these antibiotic classes may vary, both in laboratory philosophy and software or panel updates for automated systems. Therefore, susceptibility results received should be interpreted accordingly. Quantitative (numeric values) as well as qualitative (interpretation) results should be reported.

Clinical and Laboratory Standards Institute. 2014. Performance standards for antimicrobial susceptibility testing: 24th informational supplement CLSI document M100-S24. Clinical and Laboratory Standards Institute, Wayne, PA.

2. Due to intrinsic production of AmpC beta-lactamase, non-CP *Enterobacter* spp. or *Citrobacter* spp. may produce a false positive Modified Hodge Test. False positive results may also be observed with organisms carrying extended-spectrum beta-lactamases of the CTX-M type. Therefore, caution is advised when interpreting results for these organisms. Other phenotypic tests for carbapenemase production should be used, if available.

Carvalhaes CG, Picao RC, Nicoletti AG, Xavier DE, Gales AC. Cloverleaf test (modified Hodge test) for detecting carbapenemase production in *Klebsiella pneumoniae*: be aware of false positive results. *J Antimicrob Chemother*. 2010; 65(2):249–51.

Hung KH, Yan JJ, Lu JJ, Chen HM, Wu JJ. Characterization of the modified Hodge test-positive isolates of Enterobacteriaceae in Taiwan. *J Microbiol Immunol Infect.* 2013; 46(1):35-40.

Girlich D, Poirel L, Nordmann P. Value of the modified Hodge test for detection of emerging carbapenemases in Enterobacteriaceae. *J Clin Microbiol*. 2012; 50(2):477–9.

3. Metallo-beta-lactamase carbapenemases require the presence of metal ions such as zinc to hydrolyze carbapenems. Lack of appropriate zinc ion supplementation in Mueller Hinton Agar media used in the Modified Hodge Test may lead to false negative results for NDM and other metallo-beta-lactamase

enzymes. In addition, it has been observed that Modified Hodge Test results for NDM carbapenemases may vary depending on the carbapenem used for the test (i.e., ertapenem, meropenem, imipenem).

Girlich D, Poirel L, Nordmann P. Value of the modified Hodge test for detection of emerging carbapenemases in Enterobacteriaceae. *J Clin Microbiol*. 2012; 50(2):477–9.

4. Due to the inherently weak carbapenem hydrolysis activity of OXA-48 and OXA-48-like enzymes, delayed, weak, indeterminate, or negative reactions may be observed with the Carba NP test. Therefore, a Carba NP indeterminate or negative result should not be considered sufficient to rule out the presence of OXA-48 or OXA-48-like enzymes, particularly in patients with a history of previous medical care in endemic regions.

Österblad M, Hakanen AJ, and Jalava J. Evaluation of the Carba NP Test for Carbapenemase Detection. *Antimicrob Agents Chemother.* 2014; 58(12):7553.

5. Example language used in guidance to laboratories reporting CRE to Public Health

Escherichia coli, from clinical specimen and resistant to at least one carbapenem OR production of carbapenemase (e.g., *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

Enterobacter species, from clinical specimen and resistant to at least one carbapenem OR production of carbapenemase (e.g., *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

Klebsiella species, from clinical specimen and resistant to at least one carbapenem OR production of carbapenemase (e.g., *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

6. Example language used in guidance to laboratories reporting CRE to Public Health if jurisdiction is participating in MuGSI surveillance as part of the Emerging Infections Program

Escherichia coli, from clinical specimen and nonsusceptible (i.e., intermediate- or resistant) to at least one carbapenem OR production of carbapenemase (i.e. *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

Enterobacter species, from clinical specimen and nonsusceptible (i.e., intermediate- or resistant) to at least one carbapenem OR production of carbapenemase (i.e. *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], the imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

Klebsiella species, from clinical specimen and nonsusceptible (i.e., intermediate- or resistant) to at least one carbapenem OR production of carbapenemase (i.e. *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], the imipenemase [IMP] metallo-β-lactamase, OXA-48 carbapenemase) demonstrated by recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP). Include all

susceptibility results (quantitative, and qualitative interpretation, breakpoints used), plus all results regarding carbapenemase production (positive or negative)

Appendix B: Expanded definition of CRE

For jurisdictions that would like to capture other CRE (beyond *E. coli*, *Klebsiella* spp., *Enterobacter* spp.)

Other Enterobacteriaceae *(*apart from *E.coli, Enterobacter* spp., *Klebsiella* spp.):

Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem*, and doripenem or ≥ 2 mcg/ml for ertapenem)

OR

Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP)

* Note: do not use imipenem for *Proteus* spp., *Providencia* spp. and *Morganella* spp.

Table VIb

Criterion	***Proteus* spp., *Providencia* spp., and *Morganella* spp.**	**Other CRE**	**Likely CP-CRE**
Laboratory Evidence			
Proteus spp., *Providencia* spp., and *Morganella* spp.	N	A	O
Other Enterobacteriaceae *(*non *Klebsiella* spp.*, E coli, Enterobacter* spp.*)*	A	N	O
Resistant to imipenem, meropenem, or doripenem (MIC ≥4 mcg/ml)		S	

Resistant to meropenem or doripenem (excluding imipenem) (MIC ≥4 mcg/ml)	S		
Resistant to ertapenem (MIC ≥ 2 mcg/ml)	S	S	
PCR for KPC positive			S
PCR for NDM positive			S
PCR for OXA-48 positive			S
PCR for IMP positive			S
PCR for VIM positive			S
MHT positive			S
Carba NP positive			S
MBL testing (e.g., E-test) positive			S

Laboratory criteria:

Any Enterobacteriaceae (not just *E. coli*, *Klebsiella* spp., *Enterobacter* spp.) that is:

Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem)

OR

Production of a carbapenemase e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP)

- For *Proteus* spp., *Providencia* spp., and *Morganella* spp. which can be intrinsically nonsusceptible to imipenem, results for carbapenems other than imipenem should be used to determine if an isolate meets the CP-CRE definition
- At this time (March, 2015) acceptable tests for carbapenemases includes: polymerase chain reaction, modified Hodge test (MHT), Carba NP, or metallo-β-lactamase testing (e.g., MBL E-test or other screening method)

Table VIIb. . Criteria for Sub-Classifying a case of CRE Enterobacteriaceae *(*non *Klebsiella* spp.*, E coli, Enterobacter* spp.*)*

	CRE			
Criterion	**Unknown mechanism of carbapenem resistance**	**Likely CP-CRE**	**Likely Non-CP-CRE If OXA-48 has not been identified in jurisdiction or very rare**	**Likely Non-CP-CRE If OXA-48 in jurisdiction or surrounding geographic area or history of overseas travel**
Laboratory evidence				
Other Enterobacteriaceae *(*non *Klebsiella* spp.*, E coli, Enterobacter* spp.*)*	N	N	N	N
No other tests* performed	S			
PCR for KPC positive	A	S	A	A
PCR for both KPC and NDM negative if performed	A		S	
PCR for KPC, NDM and OXA48	A		S	S

negative if performed				
PCR for KPC negative and no other tests performed*	S			
PCR for NDM positive	A	S	A	A
PCR for NDM negative and no other tests performed*	S			
PCR for OXA48 positive	A	S	A	A
PCR for OXA48 negative and no other tests performed*	S			
PCR for VIM positive	A	S	A	A
PCR for VIM negative and no other tests performed*	S			
PCR for IMP positive	A	S	A	A
PCR for IMP negative and no other tests performed*	S			
MHT positive	A	S	A	A
MHT negative and no other tests performed*	A		S	S
Carba NP positive	A	S	A	A

Carba NP negative	A		S	
Carba NP negative and PCR for OXA 48 negative	A	A	S	S
MBL Etest positive	A	S	A	A
MBL Etest negative and PCR for KPC negative	A		S	
MBL Etest negative and PCR for KPC negative and PCR for OXA48 negative	A		S	S
MBL Etest negative and no other tests performed*	S			
MHT negative and MBL Etest negative	A		S	S
Epidemiological Evidence				
OXA-48 not identified in jurisdiction or is very rare			N	A
OXA-48 identified in jurisdiction or surrounding geographic area			A	O
History of overseas travel in patient			A	O
Criteria to distinguish a new case:				

Not counted as a new case if occurred within 30 days of initial case of same genera and species and clinical isolate	N	N	N	N
If have positive clinical culture, do not count subsequent or concurrent screening cultures/tests if same genera and species regardless of time interval	N	N	N	N
For screening cultures, count isolate only once	N	N	N	`N

*Other tests performed include: PCR for KPC, NDM, OXA-48, VIM, IMP or modified Hodge test (MHT), Carba NP or metallo-ß-lactamase. Please see appendix A for additional information on test performance characteristics of MHT and CarbaNP.

Notes:
S = This criterion alone is Sufficient to classify a case.

N = All "N" criteria in the same column are Necessary to classify a case. A number following an "N" indicates that this criterion is only required for a specific disease/condition subtype (see below).
A = This criterion must be absent (i.e., NOT present) for the case to meet the classification criteria.
O = At least one of these "O" (Optional) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case. (These optional criteria are alternatives, which means that a single column will have either no O criteria or multiple O criteria; no column should have only one O.)

Case investigation
Details captured will depend on available resources and local epidemiology. If in low incidence area for CP-CRE, or low incidence area for a particular mechanism (e.g., OXA-48), then consider collecting the

following information. Note: 12 month time-frame is more sensitive; 6 month exposure time-frame is more specific.

Exposures in last 12 months:

- Overseas travel , if yes - country(ies), dates of travel, and any healthcare exposures
- Complex medical devices (e.g., duodenoscopes) if yes - facility name, date(s) and type(s) of procedures performed (e.g., ERCP), type(s) of invasive devices(s) used
- Hemodialysis
- Long term care facility stay, if yes – facility name, date(s) of stay
- Long term acute care hospital (LTACH) stay, if yes – facility name and date(s) of stay
- Acute care hospital stay, if yes – facility name and date(s)

Other details of interest:

- Was there evidence of infection, was CRE isolate identified as part of a screening protocol, active surveillance testing, or contact investigation?
- Previous CRE isolated?

If in low incidence area, consider adding:

- Exposure to healthcare in areas in US with high rates of CRE or CP-CRE during the past year
- Other healthcare exposures in past year, including admissions, surgeries, dialysis
- Medical devices (catheters, foley, trach, etc) in place within 2 calendar days prior to culture?
- Antibiotic exposures last 30 days

Examples of case investigation forms from several jurisdictions (low incidence areas) can be found here:

- http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/ReportingCommunicableDisease/ReportingForms/Documents/cre_form.pdf
- http://www.doh.wa.gov/Portals/1/Documents/5100/420-098-ReportForm-CRE-Supplemental.pdf