Global Action in Healthcare Network Antimicrobial Resistance Module (GAIHN-AR) Interim Laboratory Guidance for Clinical Culture of Carbapenem-resistant Enterobacterales

This guidance is intended for global healthcare settings participating in GAIHN-AR.

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Centers for Disease Control and Prevention
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Glossary

Alert: GAIHN-AR testing results that require immediate notification of infection prevention personnel. Specific alert criteria are defined within the document in the "Communications of Alerts and Actions" section.

Antimicrobial-resistant organisms: Some bacteria and fungi are naturally (intrinsically) resistant to certain antimicrobials. For the purposes of this document, this term refers to bacteria that are resistant to one or more classes of antimicrobials to which they are usually susceptible.

Broad phenotypic carbapenemase production testing: Laboratory testing that detects carbapenemase activity. Examples of phenotypic carbapenemase testing methods include modified carbapenem inactivation method (mCIM), Blue Carba, and Carba NP. These methods cannot identify specific carbapenemase genes/enzymes but may be useful, particularly in areas of low carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE) prevalence, to reduce the number of carbapenem-resistant Enterobacterales (CRE) isolates requiring carbapenemase gene or enzyme identification testing and inform infection prevention and control (IPC) actions.

Carbapenem-resistant organisms (CROs): Gram-negative bacteria, such as Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, that test resistant to at least one carbapenem against which they are not intrinsically resistant.

Carbapenemases: Types of beta (β)-lactamase enzymes that can hydrolyze penicillins, and cephalosporins, and carbapenem antibiotics. Bacteria that produce carbapenemases can cause difficult-to-treat infections. Carbapenemase genes, which encode these enzymes, are often carried on mobile genetic elements, such as plasmids, and have the potential for rapid spread in healthcare settings.

Carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE): Enterobacterales that test resistant to at least one carbapenem agent and produce or carry genes that encode for at least one carbapenemase. CP-CRE are associated with high levels of antimicrobial resistance and difficult-to-treat infections. For more information about CP-CRE, visit https://www.cdc.gov/hai/organisms/cre/technical-info.html.

Carbapenemase-producing organisms (CPOs): Organisms that produce or carry a gene that encodes a carbapenemase.

Clinical culture: Clinical cultures collected as part of routine patient care (e.g., blood culture, urine culture, etc.). For public health purposes, identification of antimicrobial-resistant organisms such as CP-CRE allows for the implementation of appropriate IPC actions and for the detection of carbapenemases for which containment strategies should apply. In some cases, the patient may be asymptomatically colonized with an antimicrobial-resistant organism (e.g., finding CP-CRE in urine culture obtained from an asymptomatic patient); however, infection control actions such as initiating Contact Precautions or containment (if appropriate) should still be pursued due to the risk of transmission to other patients.

Colonization screening: The use of laboratory testing to determine if a patient is asymptomatically colonized (i.e., a carrier) with antimicrobial-resistant organisms such as CP-CRE to enact appropriate IPC actions during their care to limit transmission to others.

Confirmed novel or non-targeted carbapenemase: A carbapenemase that has never been detected or is not one of the targeted cabapenemases (*Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), Verona Integron-encoded metallo-β-lactamase (VIM), Imipenemase metallo-β-lactamase (IMP), and oxacillinase (OXA)-48-like) and is unusual for the healthcare facility. Identification of a novel carbapenemase requires the use of whole genome sequencing (WGS), and non-targeted carbapenemases may be confirmed by PCR or WGS. The epidemiological understanding of novel carbapenemases and some non-targeted carbapenemases is unclear (e.g., populations at risk, modes of transmission, etc.) and will require Tier 1 containment response.

Containment response: Activities described in the GAIHN-AR Interim Guidance for Containment Activities that are implemented in response to detecting a single antimicrobial-resistant threat. While containment can be used for various antimicrobial-resistant organisms, GAIHN-AR currently focuses on implementing a containment response for CP-CRE containing a novel carbapenemase or a rare targeted or non-targeted carbapenenemase.

Healthcare facility (HCF): In this document, refers to the hospital setting.

Molecular/enzymatic carbapenemase identification: Laboratory testing methods such as polymerase chain reaction (PCR) or immunochromatography that aim to identify five specific targeted carbapenemase genes/enzymes: KPC, NDM, VIM, IMP, and OXA-48-like.

Non-targeted carbapenemase: A carbapenemase other than KPC, NDM, IMP, VIM and OXA-48-like. Non-targeted carbapenemase genes may be detected by supplemental PCR, if available, or may require WGS.

Pan-resistant organism: In this guidance, a pan-resistant organism is resistant to all relevant antimicrobials tested at the clinical laboratory that serves the healthcare facility. Relevant antimicrobials for CP-CRE are those that have activity against Enterobacterales and are available for treatment in the healthcare facility. Confirmation of pan-resistance and additional characterization by a reference laboratory is recommended for all potentially pan-resistant organisms.

Priority organisms: Priority CRE organisms for GAIHN-AR include ***Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella* (formerly *Enterobacter*) *aerogenes,*** and ***Enterobacter* spp**. (If species cannot be obtained in some of the isolates, use the genus). HCFs may target additional CROs as desired, according to local epidemiology and resources available.

Suspected novel or non-targeted carbapenemase: Isolates that test positive for carbapenemase production using a phenotypic test method (e.g., mCIM) but test negative for ALL targeted carbapenemase genes (including at least KPC, NDM, VIM, IMP, and OXA-48-like) may harbor a novel or non-targeted carbapenemase gene. Novel carbapenemase genes are only detectable through WGS.

Targeted carbapenemases: In this document, the carbapenemases of interest for GAIHN-AR include KPC, NDM, VIM, IMP, and OXA-48-like for which ample epidemiological information is currently known. Targeted carbapenemases may also include others that are of local and/or national importance.

Acronyms

Acronym	Definition
AST	Antimicrobial Susceptibility Testing
CDC	U.S. Centers for Disease Control and Prevention
CLSI	Clinical and Laboratories Standards Institute
CP-CRE	Carbapenemase-Producing Carbapenem-Resistant Enterobacterales
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	U.S. Food and Drug Administration
GAIHN-AR	Global Action in Healthcare Network - Antimicrobial Resistance Module
HCF	Healthcare Facility
ICT	Immunochromatography Test
IFU	Instructions for Use
IMP	Imipenemase metallo-β-lactamase
IPC	Infection Prevention and Control
KPC	*Klebsiella pneumoniae* carbapenemase
NDM	New Delhi metallo-β-lactamase
OXA	Oxacillinase
PCR	Polymerase Chain Reaction
POC	Point-of-contact
RT-PCR	Real-time Polymerase Chain Reaction
TAT	Turnaround time
VIM	Verona Integron-encoded metallo-β-lactamase
WGS	Whole Genome Sequencing

Introduction

As members of CDC's Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR), participating laboratories from the local to the global level collaborate to detect and characterize antimicrobial-resistant threats. Once detected, these antimicrobial-resistant threats are rapidly communicated from clinical and reference network laboratories to the affected healthcare facility (HCF) and infection prevention and control (IPC) partners. This facilitates appropriate responses such as the initiation of additional IPC actions ranging from use of Contact Precautions to triggering a containment response.

Note: Additional information regarding containment activities following the identification of certain targeted CP-CRE can be found in "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Laboratories participating in GAIHN-AR rapidly identify and characterize carbapenem-resistant Enterobacterales (CRE) isolates to detect targeted carbapenemase-producing (or carbapenemase gene-positive) CRE (CP-CRE). Carbapenemases are enzymes that can break down (hydrolyze) a variety of antimicrobials, including carbapenems. Carbapenemase genes, which encode these enzymes, are often carried on mobile genetic elements (such as plasmids) and can rapidly spread resistance between bacteria through horizontal gene transfer; resistant bacteria can spread between patients and HCFs. Since their discovery in the 1990s, mobile carbapenemases have spread worldwide with sporadic to endemic prevalence depending on the region[1].

The clinical and reference laboratories in GAIHN-AR provide HCFs with access to advanced testing for antimicrobial-resistant organisms, when indicated, and will initiate a coordinated approach to provide additional testing and characterization capacity when needed.

Using shared decision making and available epidemiological information, local laboratories share agreed upon isolates and associated isolate-level deidentified data with other network laboratories to enhance their understanding of, response to, and preparation for new and known antimicrobial-resistant threats.
This document outlines expectations for GAIHN-AR laboratories' testing of clinical culture isolates including: priorities and strategies for testing, overall structure of the referral laboratory network, recommended laboratory testing methods, workflow considerations, communication of results, isolate storage, and data management, analysis, and retention.

General Considerations

When using this document, GAIHN-AR laboratories should consider:

- This document recommends options for laboratory testing methods. Methods used by laboratories are not limited to these options; however, alternative testing methods should identify and characterize CP-CRE with similar turnaround times (TATs) and accuracy to those recommended here.
- Each Network laboratory should designate a laboratory point-of-contact (POC) to lead laboratory coordination with other laboratories in their GAIHN-AR network as well as national and local IPC teams. This POC should have expertise in antimicrobial resistance detection and clinical diagnostics. Up-to-date POC contact information must be shared with relevant GAIHN-AR partners.

Note: Use of trade names and commercial sources in this document is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

Priority Organisms and Targeted Carbapenemases

Priority organisms for GAIHN-AR include carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE), specifically ***Escherichia coli, Klebsiella pneumoniae*[1,2]*, Klebsiella oxytoca*[1]*, Klebsiella* (formerly *Enterobacter*) *aerogenes, and Enterobacter* spp**. (If species cannot be identified in some of the isolates, categorize by genus.) Carbapenemases targeted for GAIHN-AR detection are KPC, NDM, VIM, IMP, OXA-48-like. However, GAIHN-AR also aims to detect additional non-targeted carbapenemases, with particular focus on suspected and confirmed novel[3] carbapenemases. If a country's priorities include antimicrobial-resistant organisms or carbapenemases in addition to those targeted by GAIHN-AR, these priorities may be included in their country-specific GAIHN-AR protocols.

GAIHN-AR laboratories will detect prioritized antimicrobial-resistant threats from two sources: clinical culture and colonization screening. This guidance focuses on detection of CP-CRE from clinical cultures collected from inpatients and outpatients[4] during their routine course of care. For colonization screening guidance, please refer to the "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Laboratory Guidance for Colonization Screening for Carbapenem-resistant Organisms."

For diagnostic clinical culture, only priority organisms identified as potential pathogens by bacteriology staff performing routine culture workup should be included for GAIHN-AR. These should receive core testing. A subset may require supplemental testing as indicated in the following sections.

Technical Notes:

- Laboratories should target Enterobacterales that test **resistant** to at least one carbapenem using Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) carbapenem breakpoints.
- Initial CP-CRE detection: If the same CP-CRE is first detected from multiple sources in a patient on the same day, perform core testing on the most invasive isolate source.
- Subsequent CP-CRE detection: Once a CP-CRE clinical isolate has been identified in a patient, subsequent CRE isolates of the same species from clinical cultures during that patient's same admission do *not* require phenotypic or genotypic carbapenemase testing unless changes in resistance pattern indicate full GAIHN-AR testing. However, if resistance patterns change in subsequent isolates, then phenotypic or genotypic carbapenemase testing is recommended. If the same CP-CRE from a subsequent culture acquires an additional carbapenemase gene or develops pan-resistance to the routine clinical AST panel, then the HCF IPC team should be notified (via a new Alert) to determine the appropriate response. Supplemental laboratory testing may be warranted depending on the situation.
- GAIHN-AR testing recommendations should not detract from any additional testing performed as part of a facility's routine practice.

[1] Clinical laboratories unable to speciate *Klebsiella* should perform core testing and inform IPC on all *Klebsiella* genus isolates.
[2] For MALDI users, identification to the level of Klebsiella pneumoniae complex is sufficient.
[3] Isolates that test positive for carbapenemase production using a phenotypic test method (e.g., mCIM) but test negative for ALL targeted carbapenemases may harbor a novel or non-targeted carbapenemase gene.
[4] Scope of lab testing may be tailored to IPC goals and resource availability for CP-CRE testing beyond the TPUs at sites.

Network Laboratory Referral Structure

GAIHN-AR relies on a network of laboratories, including clinical laboratories at participating hospitals and supporting reference laboratories at the subnational, country, regional, and global levels to detect and characterize CP-CRE. To achieve rapid detection and characterization for immediate IPC action, GAIHN-AR laboratories should coordinate a system of testing and referral based on available capacities at each laboratory in their referral network. At minimum, core testing should be completed for all GAIHN-AR priority CRE organisms recovered from a clinical culture. If carbapenemase production is detected, CP-CRE should undergo additional testing to determine the type(s) of carbapenemase present. Select CP-CRE may require additional testing, particularly if a novel or non-targeted carbapenemase is suspected (see section C below, "Additional characterization for select CP-CRE"). All testing workflows should be conducted to optimize TAT of laboratory results to improve patient care and allow for rapid IPC response.

A. Core Testing for All Priority CRE

All GAIHN-AR priority organisms recovered from clinical cultures should undergo core testing at the clinical laboratory supporting the HCF. Core GAIHN-AR testing includes:

- Organism identification, including speciation as available
- Antimicrobial susceptibility testing (AST), (see **Table 2**)
- Broad phenotypic testing for detection of carbapenemase production (e.g., mCIM, CarbaNP) performed concurrently with AST or within 24 hours of CRE detection.

Carbapenemase inhibitor-based phenotypic methods, including those that differentiate between serine carbapenemases and metallo-β-lactamases, such as boronic acid and Ethylenediaminetetraacetic acid (EDTA)-based tests, may be included in the laboratory workflow, but should not be substituted for a broad phenotypic method and should not be used in place of gene or enzyme identification.

B. Core Testing for All Priority CP-CRE

All GAIHN-AR priority CP-CRE organisms recovered from clinical cultures should be tested for all targeted carbapenemases, including at least KPC, NDM, VIM, IMP, and OXA-48-like. (Additional carbapenemases may be included per local or country priorities and capacities.) Core CP-CRE testing includes:

- Molecular test (RT-PCR preferred) to identify targeted carbapenemase genes
  OR
- Immunochromatography test (ICT) to identify targeted carbapenemase enzymes (e.g. Carba-5)

On-site core CP-CRE testing by the clinical laboratory is preferred. Laboratories that cannot complete core testing for CP-CRE on-site may refer isolates to a GAIHN-AR reference laboratory; however, rapid TAT is crucial to enable a robust IPC response. Ideally, processes and procedures should be in place to ensure shipment to the reference lab can take place within 24 hours, and that the reference laboratory can return results to the submitting lab within 3 working days of isolate receipt.

C. Additional Characterization for Select CP-CRE

CP-CRE isolates suspected of pan-resistance[5] or suspected to have novel or non-targeted carbapenemase genes may need to undergo additional characterization, including:

- AST for antimicrobials not routinely tested at the submitting clinical laboratory (see **Appendix A**)
- PCR for additional known but non-targeted carbapenemases, if available
- Whole genome sequencing (WGS) to detect and identify novel carbapenemases

[5] Refer to Glossary for definition of pan-resistant organism.

If additional characterization is performed at a reference laboratory, reference laboratories should at least confirm the submitting laboratory's organism identification prior to testing. Further confirmation of the submitter's other testing results may be warranted based on the testing requested and is at the discretion of the reference laboratory. Ideally, confirmatory testing is performed using alternative methods to the submitting laboratories whenever possible. For example, if the submitting laboratory used an automated testing instrument to conduct AST, the reference laboratory should confirm with a reference AST method, such as broth microdilution.

As the GAIHN-AR global reference laboratory, CDC may request submission of some isolates to CDC for additional characterization, including isolates confirmed to be harboring a novel or unusual resistance mechanism. With permission of the country, a subset of these isolates may be deposited to the CDC & FDA Antimicrobial Resistance Isolate Bank (https://www.cdc.gov/drugresistance/resistance-bank/index.html).

Communication of Alerts and Actions

GAIHN-AR testing results that should trigger immediate review by infection prevention personnel are known as **alerts**. For isolates meeting alert criteria (see **Table 1**), laboratories should immediately notify healthcare facility IPC teams, thereby facilitating immediate IPC action, such as implementation of Contact Precautions and possible initiation of containment activities. For isolates meeting alert criteria, a tiered system (Tier 1, Tier 2, and Non-Tier 1 or 2) was developed to help facilities prioritize which alerts to consider responding to with containment. This tiered system is described in detail in the document, "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Hospitals and reference laboratories may use or adapt their own established data systems to communicate alerts within their hospital and to the national level (if indicated) according to their local protocols. Hospitals or countries that do not have an integrated laboratory and IPC data or communication system in place should work internally and with their implementing partner as needed to create a system for communication of alerts. Ideally, local data systems would automatically notify IPC when CP-CRE meeting alert criteria are entered in a reporting database.

Table 1. Clinical Culture Testing Alert Criteria and Actions

The footnotes immediately follow the table.

Alert Criteria	Inclusion Criteria	Organisms[1]	Actions
Carbapenemase production detected	Isolate tests positive for carbapenemase production by phenotypic method	At minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, or *Enterobacter* spp.	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification As soon as possible: ■ Perform gene or enzyme testing if available ■ If gene or enzyme testing unavailable, send isolate to country-level reference laboratory
Targeted[2] carbapenemase gene or enzyme detected (at least: IMP, KPC, NDM, VIM, or OXA-48-like)[3] (Tier 2)	Isolate tests positive for a targeted carbapenemase gene or enzyme using PCR or ICT tests	At minimum: *E. coli, Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella aerogenes, Enterobacter* spp.	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification If organism contains a targeted carbapenemase that is Tier 2 by the healthcare facility: ■ Contact colonization screening is recommended and should initiated if capacity is available[4]
Suspected novel or non-targeted carbapenemase (suspect Tier 1)	Positive broad phenotypic carbapenemase production test (e.g., mCIM) but negative for ALL targeted[2] carbapenemase genes or enzymes tested	At minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Enterobacter* spp.[5]	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification ■ Send isolate to country-level reference laboratory or other Network level laboratory for applicable confirmatory or supplemental testing and, if warranted, WGS If laboratory and IPC teams determine that there is high concern this isolate represents a Tier 1 carbapenemase prior to WGS results: ■ Contact colonization screening is recommended and should be initiated if capacity is available[4]
Confirmed novel or non-targeted carbapenemase (Tier 1)	Novel or non-targeted carbapenemase confirmed by supplemental PCR or WGS	At minimum: *E. coli, Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella aerogenes, Enterobacter* spp.	Within 24 hours: ■ Notify IPC and all appropriate hospital administration and public health authorities ■ Record date and time of IPC notification ■ Notify CDC. Share isolate(s) and WGS data, as allowed by local regulations. If organism contains a carbapenemase gene that is defined as Tier 1: ■ Contact colonization screening is recommended and will likely be initiated if capacity is available[4]

[1] GAIHN-AR's activities are currently focused on carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE), but a facility may choose to expand alerts to include other carbapenemase-producing organisms. Additionally, depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are non-carbapenemase-producing.

Footnotes Continued

[2] Targeted genes/enzymes MUST include KPC, NDM, VIM, IMP, and OXA-48-like. May also include other carbapenemases of local and/or national importance.

[3] Facilities may make epidemiology-based decisions to exclude alerts for certain GAIHN-AR targeted carbapenemases detected depending on the prevalence of those carbapenemases present.

[4] For laboratory guidance regarding colonization screening, refer to, "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Laboratory Guidance for Colonization Screening for Carbapenem-resistant Organisms." For more guidance on the response tiers to alerts, refer to, "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

[5] Please exclude *Enterobacter* spp. isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and is associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile is indicative of a possible presence of IMI or NMC carbapenemases.

Laboratory Testing Methods

This guidance recommends options for laboratory testing methods. Methods used by GAIHN-AR laboratories are not limited to these options; however, alternative testing methods should yield comparable results, TAT, and accuracy to those recommended here. All methods selected should be properly verified/validated[6] for use in each laboratory. The verification/validation process provides objective evidence that the method will meet the laboratory's acceptance criteria and intended use. Laboratories are responsible for understanding limitations associated with selected test methods and should always refer to current manufacturer instructions for use (IFU) for the most up-to-date information.

A. Organism Identification

Genus and species should be determined using one of the methods listed below:

- MALDI-TOF mass spectrometry
- Automated testing instruments (e.g., VITEK 2, MicroScan, Phoenix, MIDI, etc.)
- Biochemical tests (e.g., API strips, tube methods, spot reagents)

B. Antimicrobial Susceptibility Testing (AST)

Organisms should be tested for antimicrobial susceptibility using one of the following methods:

- Disk diffusion
- Automated testing instruments (e.g. VITEK 2, MicroScan, and Phoenix)
- Gradient diffusion (e.g., Etest, MIC Test Strip [MTS])
- Broth microdilution (e.g., Sensititre)

All network laboratories are encouraged to incorporate the antimicrobials listed in **Table 2** into their routine AST panels for GAIHN-AR priority organisms.

Table 2. Recommended Core Antimicrobials for Susceptibility Testing

The table's footnotes immediately follow the table.

Drug class	Antimicrobials
Carbapenems	ertapenem **AND** at least 1 additional carbapenem
Cephalosporins[1]	cefepime, ceftazidime, and cefotaxime or ceftriaxone[2]
Monobactams	aztreonam

[1] Testing may aid in identifying less common carbapenemases (SME, IMI, NMC) or other mechanisms conferring carbapenem resistance (hyper production of AmpC in certain species).

[2] Or other third-generation cephalosporin.

[6] Validations and verifications are processes used to confirm the validity and accuracy of laboratory tests and techniques. To support validations and verifications, the following templates are available on the GAIHN-AR External SharePoint Drive: Cepheid Gene Xpert verification, mCIM validation, NG-Test Carba 5 verification, RT-PCR validation. Additionally, well characterized isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank that correspond to the templates are available to GAIHN-AR partners.

Laboratories should target Enterobacterales that test **resistant** to at least one carbapenem using CLSI or EUCAST carbapenem breakpoints.

In addition to performing confirmatory AST, **reference laboratories** are encouraged to offer additional AST for public health, epidemiological, and clinical purposes and to report the results to CDC. Additional AST results can be used to investigate CP-CRE phenotypes to inform GAIHN-AR priorities for containment and supplemental genotypic characterization (including WGS), investigate suspected pan-resistance, and monitor emerging resistance to newer antimicrobial agents available in the country for treatment of patients infected with CP-CRE. Recommendations for additional AST can be found in **Appendix A**.

Please note: The antimicrobials listed in **Appendix A** are included for public health and epidemiological purposes only. They are not intended to replace the list of antimicrobials used or tested by laboratories to prepare clinical reports or to contribute to therapeutic decision making, but rather to facilitate the detection, notification, and monitoring of targeted antimicrobial-resistant threats for GAIHN-AR.

C. Broad Phenotypic Carbapenemase Production Testing

These tests can be used to determine if carbapenemase production is present, but they cannot identify the specific enzyme(s) or gene(s) responsible. Carbapenemase inhibitor-based phenotypic methods, including those that differentiate between serine carbapenemases and metallo-β-lactamases, such as boronic acid and EDTA-based tests, may be included in the laboratory workflow but should not be substituted for a recommended method and should not be used in place of gene or enzyme identification.

Recommended test methods are listed in **Table 3** (below).

Table 3. Performance Characteristics of Broad Phenotypic Carbapenemase Production Test Methods[1]

The footnotes immediately follow the table.

Recommended

Test Name	Organisms	Turnaround Time	Performance [5,6]	Limitations [5,6]
Modified Carbapenem Inactivation Method (mCIM)	Enterobacterales *Pseudomonas*	18-24 hours	Sensitivity: 97–98% Specificity: 95–99%	False-positives may occur with Amp-C positive *E. cloacae* complex[2]. Procedure for Enterobacterales and *P. aeruginosa* differs slightly.

Recommended Alternatives

Test Name	Organisms	Turnaround Time	Performance [5,6]	Limitations [5,6]
CarbaNP (including commercially available, e.g. Rosco, Rapidec)	Enterobacterales *Pseudomonas*	30 minutes to 2 hours	Sensitivity: 84–98% Specificity: 98–100%	False-negatives reported with mucoid strains (for example, some *Klebsiella* or *Pseudomonas* strains) or weak carbapenemases (ex. SME, GES, OXA-48-like). Poor diagnostic sensitivity (38%–86%) for detection of carbapenemase production from OXA-48-like.

Continued

Test Name	Organisms	Turnaround Time	Performance [5,6]	Limitations [5,6]
Blue Carba Test (BCT), including commercially available BCT tests	Enterobacterales *Pseudomonas* *Acinetobacter*	<2 hours	Sensitivity: 97% Specificity: 96%	Poor diagnostic sensitivity (40%–80%) for detection of OXA-48-like carbapenemase production.

Not Recommended

Test Name	Organisms	Turnaround Time	Performance [5,6]	Limitations [5,6]
Modified Hodge Test (MHT)	Enterobacterales	18-24 hours	Sensitivity: 95% Specificity: 91%	**Not recommended for use by CLSI or EUCAST** due to poor specificity when used on *Enterobacter* spp., difficult interpretation, and suboptimal sensitivity in some cases[3]. False-positives may occur with ESBL or Amp-C positive isolates. False-negatives with metallo-β-lactamases (MBLs) (**sensitivity is 11% for MBLs**).

[1] Table is not comprehensive of all available broad phenotypic carbapenemase detection tests. Laboratories are not limited to these options; however, alternative methods should yield comparable sensitivity, specificity, and TAT to those recommended here. Any test system selected for use should be thoroughly validated prior to implementation to understand limitations associated with gene variants, particularly those known to be circulating in your local region.

[2] Please exclude *Enterobacter* spp. isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and is associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile is indicative of a possible presence of IMI or NMC carbapenemases.

[3] Testing may aid in identifying less common carbapenemases (SME, IMI, NMC) or other mechanisms conferring carbapenem resistance (hyper production of AmpC in certain species).

D. Carbapenemase Identification Methods

All CP-CRE isolates must be tested for all targeted carbapenemases, which should include at least KPC, NDM, VIM, IMP, and OXA-48-like. Additional carbapenemases may be included for routine or reference testing per local or country priorities. Recommended carbapenemase identification test methods are listed in **Table 4**.

All test methods selected should be properly verified/validated[7] for use in each laboratory. For carbapenemase identification methods, this includes verification that regionally circulating variants are detectable using the method of choice. Deviation from the manufacturer's IFU would require validation, a more comprehensive process than verification.

[7] Validations and verifications are processes used to confirm the validity and accuracy of laboratory tests and techniques. To support validations and verifications, the following templates are available on the GAIHN-AR External SharePoint Drive: Cepheid Gene Xpert verification, mCIM validation, NG-Test Carba 5 verification, RT-PCR validation. Additionally, well characterized isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank that correspond to the templates are available to GAIHN-AR partners.

Table 4. Recommended Carbapenemase Gene and Enzyme Identification Methods[1]

The footnotes immediately follow the table.

Manufacturer	Instrument	Test Name	Method	Test Type	Specimen Type	Carbapenemase Genes or Enzymes Detected[2]
In-house or lab-developed		PCR	PCR	Molecular	Isolate	bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, $bla_{OXA\text{-}48\text{-}like}$
Streck	ABI 7500 Fast ABI 7500 Fast Dx ABI QuantStudio 7 Bio-Rad CFX96 Touch™ QIAGEN Rotor-Gene® Q	ARM-D Kit, β-lactamase (CE-IVD)	PCR	Molecular	Isolate	bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, $bla_{OXA\text{-}48\text{-}like}$
Cepheid	GeneXpert®	Xpert Carba-R	PCR	Molecular	Isolate or rectal swab	bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, $bla_{OXA\text{-}48\text{-}like}$
Coris Bioconcept	*N/A*	RESIST series and various K-Sets	ICT	Enzymatic	Isolate	KPC, NDM, VIM, IMP, OXA-48-like
Hardy Diagnostics	*N/A*	NG-Test Carba 5	ICT	Enzymatic	Isolate	KPC, NDM, VIM, IMP, OXA-48-like

[1] This table is not comprehensive of all available carbapenemase gene or enzyme detection tests. Laboratories are not limited to these options; however, alternative methods should yield comparable sensitivity, specificity, and TAT to those recommended here. Any test system selected for use should be thoroughly validated prior to implementation to understand limitations associated with gene variants, particularly those known to be circulating in your local region.

2 Refer to manufacturer IFU and published literature for information regarding the specific variants detectable by a particular test method. *In silico* predictions should not serve as a basis for use and would require additional validation per applicable regulations. Laboratories must be aware of specific limitations when selecting a test system.

Workflow Considerations and Suggestions

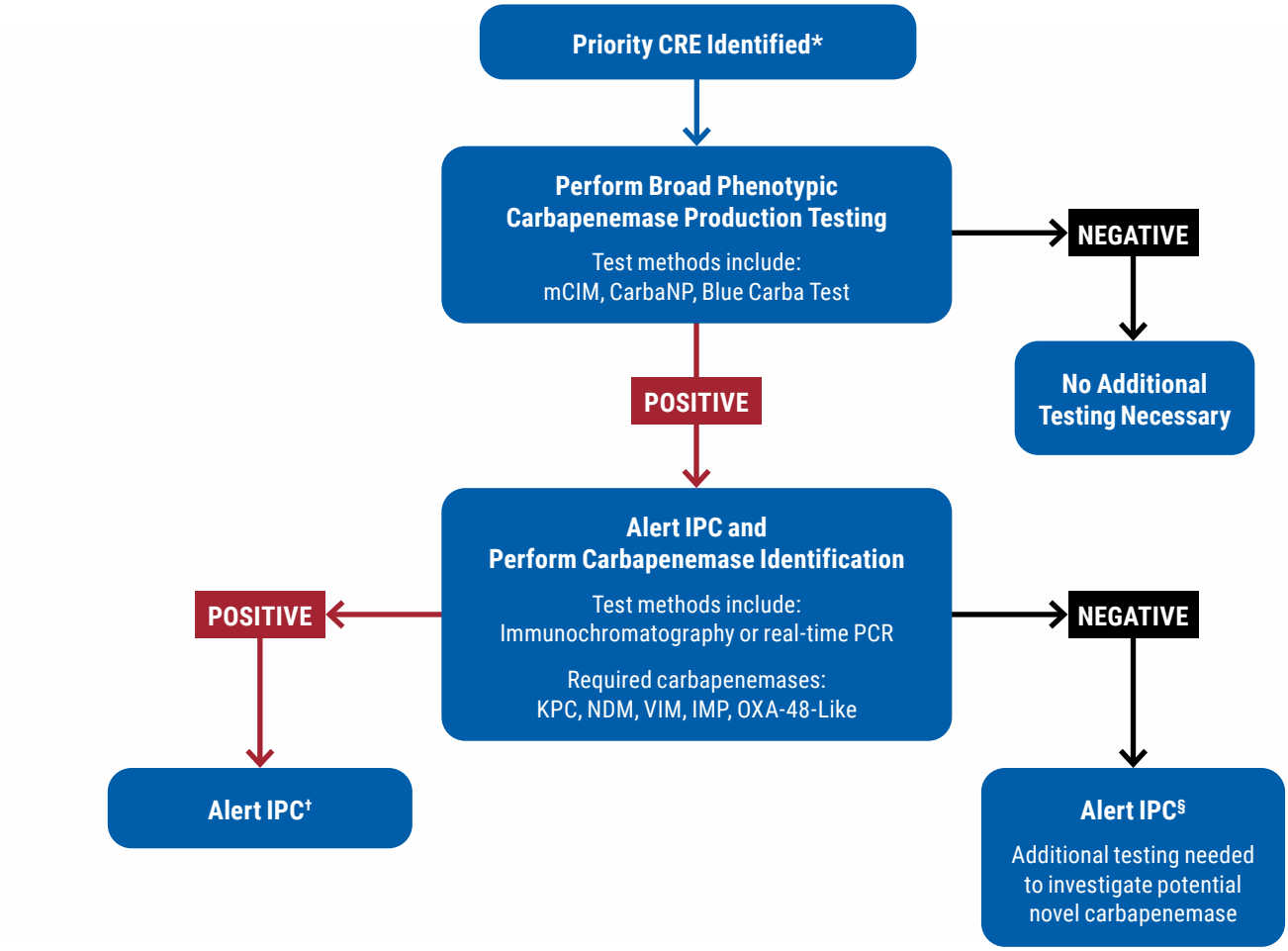
The specific test methods selected for use in a laboratory, as well as the workflows used for testing isolates, will depend on multiple factors. Factors may include:

- Anticipated test volume
- Test cost
- TAT
- Staffing availability and expertise
- CP-CRE prevalence
- Carbapenemase gene distribution
- Equipment and supply availability
- Maintenance/support availability

Workflow suggestions are provided below for testing of culture isolates from clinical samples with targeted CRE identified. In areas where the prevalence of CP-CRE is low, the workflow in **Figure 1** (below) may be favorable to save costs on carbapenemase detection and identification. In areas where the prevalence of CP-CRE is high, the workflow in **Figure 2** may be favorable to achieve rapid TAT. CDC can also provide customized recommendations for test and workflow selection.

Figure 1. Suggested Workflow for CP-CRE Identification in Areas of **Low** Prevalence

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix B on page 21.



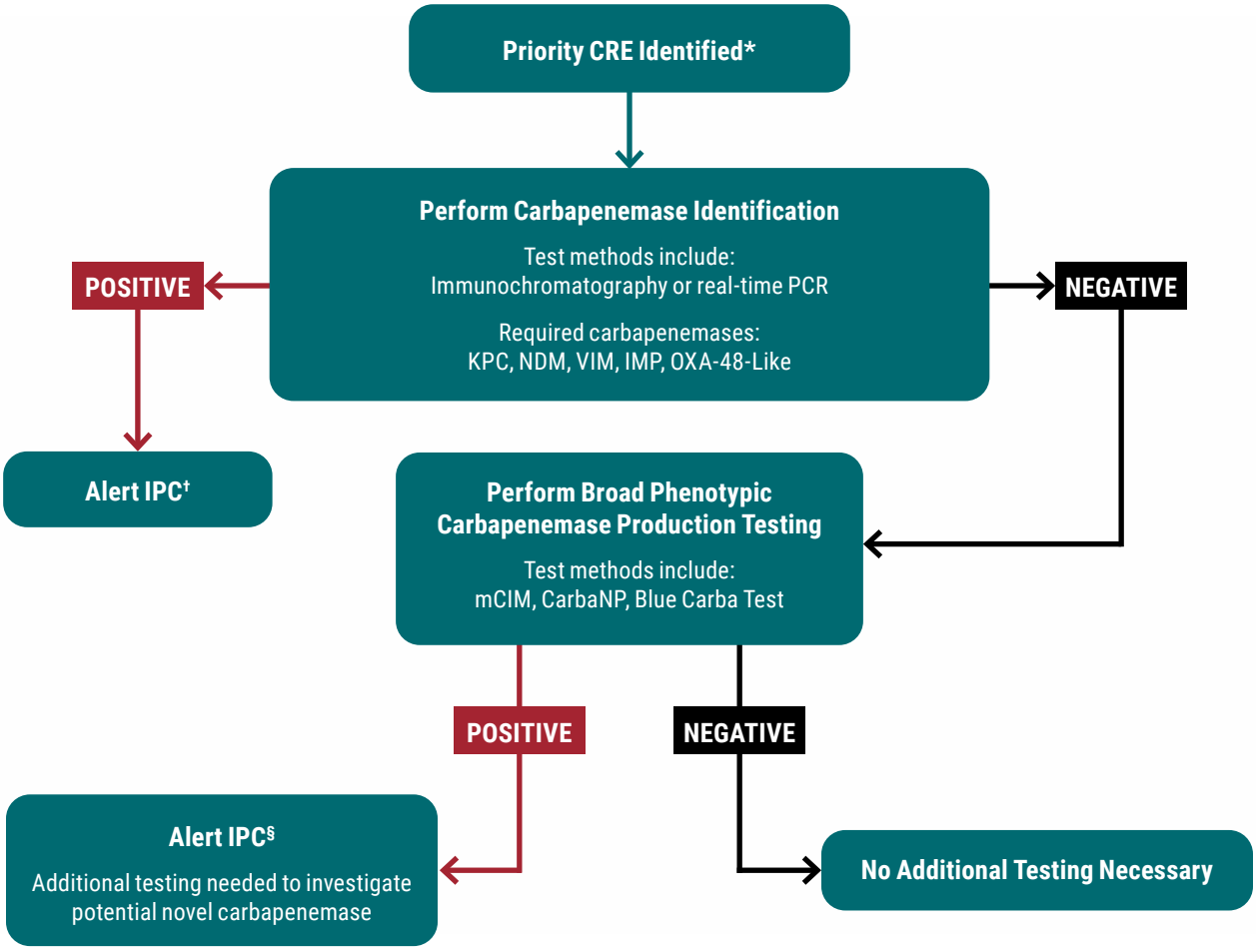
* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are non–carbapenemase-producing.

† Carbapenemases triggering alerts may vary depending on epidemiology within facility.

§ When alerting IPC about *Enterobacter* spp. that is carbapenemase production positive but negative for carbapenemase genes or enzymes, exclude isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile for *Enterobacter* is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile is indicative of a possible IMI or NMC carbapenemase.

Figure 2. Suggested Workflow for CP-CRE Identification in Areas of **High** Prevalence

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix B on page 21.



* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are non-carbapenemase-producing.

† Carbapenemases triggering alerts may vary depending on epidemiology within facility.

§ When alerting IPC about *Enterobacter* spp. that is carbapenemase production positive but negative for carbapenemase genes or enzymes, exclude isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile for *Enterobacter* is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile is indicative of a possible IMI or NMC carbapenemase.

Recording Laboratory Results

Laboratories should record testing results for all priority CRE isolates tested for GAIHN-AR, including both CP-CRE and non-CP-CRE. Ideally, laboratories will incorporate all core and supplemental GAIHN-AR test results into their existing electronic laboratory information system (LIS) used for diagnostic clinical culture or referral isolate workup. Doing so will minimize duplicate data entry, enable real-time data use, and facilitate future data extraction, analysis, and reporting. If adapting the LIS to accommodate GAIHN-AR test methods is not possible, an alternative electronic system that creates an isolate-level line list including all core and supplemental test results is strongly recommended. If additional antimicrobials are tested, laboratories should also include these results when communicating testing results to the submitter and to CDC.

Reporting Laboratory Data

As a global network that aims to be on the forefront of detecting emerging AR in healthcare, sharing and analysis of isolate/specimen-level data, WGS data, and isolates is essential.

CDC requests that sites share:

- Isolates and WGS data from Tier 1 responses. Select isolates from Tier 2 responses may also be requested. We recommend sharing WGS data via an accessible repository (e.g., the GAIHN-AR BioProject: ID 962934 - BioProject - NCBI (nih.gov), a component of the CDC International HAI/AR Seq NCBI Umbrella Project).
- De-identified isolate-level data for all GAIHN-AR CRE priority organisms tested, at least every six months, including results generated by:
  - ☐ Organism identification
  - ☐ AST
  - ☐ Phenotypic carbapenemase production testing
  - ☐ Carbapenemase identification
  - ☐ WGS, if performed

CDC recognizes that some sites may have barriers to sharing isolates and certain isolate level data. CDC will work with partners and countries to establish any necessary data use agreements and to adapt processes as is feasible to help them meet these requirements.

GAIHN-AR sites will also be required to report GAIHN-AR indicators to implementing partners and CDC every 6 months. Some of the indicator data requested relies on summarized laboratory testing results. Indicator data will be used to:

- Monitor progress and impact of GAIHN-AR activities over time
- Support quality improvement efforts for laboratory, IPC, and communication
- Identify and advocate for Network resources
- Provide feedback and recommendation reports to each site

More information about requirements and use for data and isolates shared to CDC can be found in the document, "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Core Principles."

Data and Isolate Retention

Laboratories should maintain a database of test results. Testing results should be retained for a minimum of 2 years or according to local or national requirements, whichever is longer.

All CP-CRE isolates should be retained by either the clinical or reference laboratory at -70°C for a minimum of 2 years. If -70°C storage capacity is limited, prioritize retention as follows:

1. Isolates with a confirmed novel or non-targeted carbapenemase
2. CP-CRE that are not susceptible to the newest[8] antimicrobials for treating infections caused by CP-CRE
3. Pan-resistant CP-CRE
4. Isolates with >1 targeted carbapenemase
5. Other carbapenemase-producing/-positive isolates. Additional retention criteria based on specific genes and/or organism-gene combinations will depend on local and national epidemiology. Contact CDC for assistance determining retention priorities if needed.

[8] Will vary by country based on availability; examples include but are not limited to: ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, aztreonam-avibactam, cefiderocol, etc.

If sending an isolate to their reference laboratory, clinical laboratories should store CP-CRE isolates at -20°C or -70°C at least until the reference lab has: completed testing, resolved any discrepancies, and confirmed isolates will be retained for a minimum of 2 years.

Laboratories performing WGS should back-up WGS data locally and deposit WGS data meeting the required quality standards in a recommended accessible repository (e.g., the GAIHN-AR BioProject: ID 962934 - BioProject - NCBI (nih.gov), a component of the CDC International HAI/AR Seq NCBI Umbrella Project), with minimum levels of metadata to protect patient privacy.

Laboratory Quality Considerations

- **Quality Control:** Quality control for organism identification, AST, phenotypic carbapenemase production testing, and molecular or enzymatic carbapenemase identification, and WGS should be performed according to manufacturer recommendations or in compliance with national regulatory standards. Generated WGS data should meet quality standards per CDC guidance for HAI/AR isolates.
- **Assay verification or validation:** Upon request, CDC can assist laboratories with implementation of select testing methods by providing isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank, verification and validation templates, and expertise in methods and results interpretation.
- **Proficiency Testing (PT):** All Network laboratories should participate in routine bacteriology PT for organism identification, AST, phenotypic carbapenemase production testing, and molecular or enzymatic carbapenemase identification, as applicable to their specific test menu. Laboratories should work with their implementing partner and other in-country or Network laboratories as needed to create a PT plan.
- **External Quality Assessment (EQA):** GAIHN-AR will support EQA for Cepheid GeneXpert CARBA-R for Network reference laboratories.

References

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2. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 33rd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2023.
3. CLSI. *CLSI Subcommittee on Antimicrobial Susceptibility Testing CLSI AST News Update*. Vol 2, Issue 1. Clinical and Laboratory Standards Institute; Jun 2017.
4. EUCAST. *EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance*. Version 2.0. European Committee on Antimicrobial Susceptibility testing. Jul 2017.
5. Pasteran F, Veliz O, Ceriana P,et al. ReLAVRA Network Group. *Evaluation of the Blue-Carba test for rapid detection of carbapenemases in gram-negative bacilli*. J Clin Microbiol. 2015 Jun;53(6):1996-8. doi: 10.1128/JCM.03026-14. PMID: 25809971
6. Tamma PD, Simner PJ. *Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates*. J Clin Microbiol. 2018 Oct 25;56(11):e01140-18. doi: 10.1128/JCM.01140-18. PMID: 30158194

Appendix A: Recommended Supplemental AST at Reference Laboratories

Reference laboratories are encouraged to offer supplemental AST for antimicrobials that go beyond confirmatory testing of drugs tested by the submitting clinical laboratory and to report these testing results to GAIHN-AR. AST results can be used to investigate CP-CRE phenotypes to inform both local and global activities and priorities, set priorities for containment and supplemental genotypic characterization (including WGS), investigate suspected pan-resistance, and monitor emerging resistance to the newer antimicrobial agents for treating CP-CRE that are available for patient treatment in the country. **Countries with existing protocols for providing supplemental AST of CP-CRE need not change their existing protocols** to accommodate GAIHN-AR recommendations but are asked to report all AST results to GAIHN-AR. Countries without existing CP-CRE AST protocols may find the recommendations in **Table 4** helpful for developing protocols relevant to their priorities but should modify as needed.

Please note: The antimicrobials recommended for GAIHN-AR testing in Appendix A are intended for public health and epidemiological purposes only. They are not intended to replace the list of antimicrobials used or tested by laboratories to prepare clinical reports or to contribute to therapeutic decision making, but rather to facilitate the detection, notification, and monitoring of targeted antimicrobial-resistant threats.

Recommendations for Supplemental AST of CP-CRE[1]

The footnotes immediately follow the table on the next page. Blank or empty cells means 'not applicable.'

Antimicrobial Class	*Testing Purpose*— Confirmatory testing *Isolate to test*— All CP-CRE received from clinical laboratories	*Testing Purpose*— Define phenotype for other non-targeted and novel CP-CRE *Isolate to test*— All CP-CRE received from clinical laboratories	*Testing Purpose*— Suspected pan-resistant or pan-not susceptible CP-CRE[2] *Isolate to test*— CP-CRE testing R or NS to all antimicrobials tested in "Defining phenotype for other non-targeted and novel CP-CRE" column	*Testing Purpose*— Other agents[3] for treating highly resistant CP-CRE *Isolate to test*— CP-CRE testing R or NS to all antimicrobials in "Suspected pan-resistant or pan-not susceptible CP-CRE" column
Extended-spectrum cephalosporins	Ceftazidime **and** Cefepime **and** Ceftriaxone **or** Cefotaxime	Ceftazidime **and** Cefepime **and** Ceftriaxone **or** Cefotaxime	Ceftazidime **and** Cefepime **and** Ceftriaxone **or** Cefotaxime	
Cephamycins		Cefoxitin **or** Cefotetan	Cefoxitin **and** Cefotetan	
Penicillins + β-lactamase inhibitors		Amoxicillin-clavulanate **or** Ampicillin-sulbactam	Amoxicillin-clavulanate **and** Ampicillin-sulbactam	
Anti-pseudomonal penicillins + β-lactamase inhibitors		Piperacillin-tazobactam **or** Ticarcillin-clavulanate	Piperacillin-tazobactam **and** Ticarcillin-clavulanate	
Carbapenems	Ertapenem **and** Meropenem, Imipenem, **or** Doripenem	Ertapenem **and** Meropenem, Imipenem, **or** Doripenem	Ertapenem, Meropenem, Imipenem, **and** Doripenem	
Monobactams	Aztreonam	Aztreonam	Aztreonam	
Newer β-lactam combination agents				Examples include but are not limited to: Ceftazidime-avibactam, Ceftolozane-tazobactam, Meropenem-vaborbactam, Imipenem-relebactam

Table continued

Antimicrobial Class	*Testing Purpose*— Confirmatory testing *Isolate to test*— All CP-CRE received from clinical laboratories	*Testing Purpose*— Define phenotype for other non-targeted and novel CP-CRE *Isolate to test*— All CP-CRE received from clinical laboratories	*Testing Purpose*— Suspected pan-resistant or pan-not susceptible CP-CRE[2] *Isolate to test*— CP-CRE testing R or NS to all antimicrobials tested in "Defining phenotype for other non-targeted and novel CP-CRE" column	*Testing Purpose*— Other agents[3] for treating highly resistant CP-CRE *Isolate to test*— CP-CRE testing R or NS to all antimicrobials in "Suspected pan-resistant or pan-not susceptible CP-CRE" column
Siderophore				Cefiderocol
Aminoglycosides		Gentamicin **or** Tobramycin, Amikacin	Gentamicin **and** Tobramycin, Amikacin	Plazomicin[4]
Tetracyclines		Tetracycline	Tetracycline, Doxycycline **and** Minocycline	Eravacycline[4], Omadacycline[4]
Glycylcycline			Tigecycline[4]	
Fluoroquinolones		Ciprofloxacin **or** Levofloxacin	Ciprofloxacin	Moxifloxacin[4]
Folate pathway inhibitors		Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole	
Phenicols		Chloramphenicol	Chloramphenicol	
Lipopeptides			Colistin[5], Polymyxin B[6]	
Fosfomycins			Fosfomycin[7,8]	

[1] The antimicrobials presented are for public health and epidemiological purposes. They are not intended to replace the list of antimicrobials used by laboratories to prepare clinical reports or to contribute to therapeutic decision making, but rather to facilitate the detection, notification, and monitoring of targeted antimicrobial-resistant threats. All lists should be adapted as needed to match local formularies. These antimicrobials may not be appropriate for treatment of individual patients and should not be interpreted as such.

[2] Use of a strict "resistant" definition (R category only) vs. "not susceptible" (R category plus Intermediate [I] category) should be determined by country-level authorities.

[3] Antimicrobials that are unavailable for clinical use in the country should not be tested.

[4] Requires use of FDA or EUCAST breakpoints, if applicable.

[5] For colistin, only broth microdilution, Colistin Broth Disk Elution, and Colistin Agar Test MIC methods are acceptable; disk diffusion and gradient methods should not be used.

[6] For polymyxin B, broth microdilution is the only approved method; disk diffusion and gradient methods should not be used.

[7] The only CLSI-approved MIC method for testing is agar dilution using agar media supplemented with 25µg/mL of glucose-6-phosphate. EUCAST offers guidance for gradient diffusion method.

[8] Breakpoints apply only to *E. coli* urinary tract isolates and should not be extrapolated to other species of Enterobacterales.

Appendix B: Explanations for Accessibility for Figure 1 and Figure 2

Footnotes for this appendix immediately follow the figure descriptions.

Figure 1. Suggested Workflow for CP-CRE Identification in Areas of Low Prevalence:

A blue-colored flow chart describing workflow suggestions for testing clinical culture isolates with priority CRE identified. If priority CRE is identified[9], perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test. If results are negative, no additional testing is necessary. If results are positive, alert IPC and perform carbapenemase identification using immunochromatography or real-time PCR. If KPC, NDM, VIM, IMP, or OXA-48-like carbapenemases are identified, alert IPC[10]. If these enzymes or genes are not identified, alert IPC[11] and perform additional testing needed to investigate a potential novel carbapenemase. (return to **Figure 1**)

Figure 2. Suggested Workflow for CP-CRE Identification in Areas of High Prevalence:

A green-colored flow chart describing workflow suggestions for testing clinical culture isolates with priority CRE identified. If priority CRE is identified[9], perform carbapenemase identification using immunochromatography or real-time PCR. If KPC, NDM, VIM, IMP, OXA-48-like carbapenemases are identified, alert IPC[10]. If not, perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test. If results are positive, alert IPC[11] and perform additional testing needed to investigate a potential novel carbapenemase. If results are negative, no additional testing is necessary. (return to **Figure 2**)

[9] Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are non-carbapenemase-producing

[10] Carbapenemases triggering alerts may vary depending on epidemiology within facility.

[11] When alerting IPC about *Enterobacter* spp. that is carbapenemase production positive but negative for carbapenemase genes or enzymes, exclude isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile for *Enterobacter* is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile is indicative of a possible IMI or NMC carbapenemase.

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