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Carbapenemase Mechanism Testing to Support Treatment, Infection Control, and Public Health:

The Role of the Clinical Laboratory

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INTRODUCTION

The 2019 Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistant Threats in the United States*, listed carbapenem-resistant Enterobacterales (CRE) as a top-tier, urgent threat.¹ Approximately 1% to 3% of all Enterobacterales isolates encountered in a clinical setting in the United States are resistant to carbapenems,^{2–4} and between 22% and 59% of these isolates carry a carbapenemase, an enzyme that can inactivate many beta-lactam antibiotics including carbapenems.^{5–7} The mechanism, frequency, and type of carbapenemase-producing CRE (CP-CRE) can vary by geographic location, bacterial species, and health care facility type.^{5,6,8}

The potential spread of CP-CRE within health care facilities is a significant threat to patient and public health, primarily due to the mobile nature of carbapenemase genes that are often located on plasmids.¹ The availability of novel therapeutics and their mechanisms of action for specific carbapenemases, however, has added a new dimension to the diagnosis, treatment, and control of CP-CRE.⁹ Against non-CP-CRE, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam each have a high likelihood of activity if the isolate tests susceptible to the individual compound.¹⁰ The activity of these

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DECLARATION OF ARTIFICIAL INTELLIGENCE AND ARTIFICIAL INTELLIGENCE-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this study, the authors used ChatGPT and Bing! to assist in outline development, as a thesaurus, and to streamline reference identification. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

DISCLOSURE

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compounds in the presence of a carbapenemase, however, may not be accurately reflected in the isolate antimicrobial susceptibility testing (AST),⁹ especially if the beta-lactamase-inhibitor is not effective against the specific carbapenemase present. For example, an oxacillinase (OXA)-48-producing isolate may test susceptible to meropenem-vaborbactam by phenotypic AST but is clinically ineffective due to vaborbactam's inability to neutralize OXA-48.¹¹ Therefore, from the health care perspective, clinical decision-making is informed by knowing both the specific carbapenemase present and the isolate AST results, which is reflected in the Infectious Diseases Society of America (IDSA)'s mechanism-specific treatment approach for infections caused by CRE (Fig. 1).¹²

Although the identification of carbapenemase mechanisms is important for treatment and infection control, many clinical laboratories continue to rely on reference or public health laboratories (PHLs) to perform this testing.⁴ This review aims to outline why clinical microbiology laboratories should consider implementing carbapenemase mechanism testing for CRE isolates and colonization screening. We will review available diagnostic methods, explore barriers to implementation, and propose actions clinical microbiology laboratories can take in both the near term and long term to implement carbapenemase mechanism testing in their facilities.

BACKGROUND

Annually, CDC's National Healthcare Safety Network surveys acute and long-term acute care hospital (LTACH) facilities to understand the landscape of laboratory methods used to detect multidrug-resistant organisms (MDROs). About half of the facilities surveyed in 2015 to 2016 reported performing some type of in-house carbapenemase testing,⁴ but that percentage has not changed over the past decade (CDC, NHSN, 2022, unpublished data).

Alternative approaches, such as surrogate testing (use of expert rules for automated AST systems), cannot fully replace the need for carbapenemase mechanism testing. According to the Clinical and Laboratory Standards Institute, carbapenemase genotype predicts phenotypic carbapenem resistance with an approximate accuracy of 95% to 100%; however, the inverse is not true, which is why mechanism testing is required.¹³ Studies that have attempted to develop predictive antibiograms for carbapenemase production have also been unsuccessful for routine clinical usage.¹⁴ Even the dogma that New Delhi metallo-beta-lactamase (NDM) producers are susceptible to aztreonam, thus suggesting the carbapenemase mechanism present, is no longer as predictive as it once was.¹⁵ NDM does not hydrolyze aztreonam, but many NDM-producing CRE are resistant to aztreonam because of other resistance mechanisms, such as extended-spectrum beta-lactamases.¹⁵ The challenge of mechanism-specific predictive antibiotic susceptibility profiles is compounded by the number and diversity of species in the Enterobacterales, the frequency of different carbapenemases within each species, and the corresponding impact on isolate antimicrobial susceptibility.

Among CP-CRE in the United States, *Klebsiella pneumoniae* carbapenemase (KPC) is the most common carbapenemase mechanism (73.2%), followed by NDM (16.9%), OXA-48-like (4.1%), and other mechanisms.⁵ The newer β -lactamase inhibitor combinations

have been designed to neutralize these specific carbapenemases. In general, ceftazidime-avibactam may have activity against KPC or OXA-48-producing CRE but does not have activity against NDM-producing CRE,^{10,16} while meropenem-vaborbactam and imipenem-relebactam may have activity against KPC-producing CRE but not against OXA-48-like or NDM-producing CRE.^{17,18} Aztreonam-avibactam (ceftazidime-avibactam in combination with aztreonam) or cefiderocol may have activity against infections caused by NDM-producing CRE.^{19,20}

To have the greatest impact on patient therapy decisions, carbapenemase mechanism testing must be available quickly.^{21,22} Clinical laboratories performing in-house carbapenemase mechanism testing have an average turn-around-time (TAT) of 6 days sooner (range 3–14) than when sending isolates to their PHL,²³ illustrating some of the significant hurdles encountered with interfacility isolate transfer.

In addition to aiding in patient therapy decisions, carbapenemase mechanism testing informs infection prevention and control (IPC) activities intended to prevent the spread of CRE to other patients. Some hospital acquired infection (HAI)-prevention activities, such as initiation of Isolation and Contact Precautions for CP-CRE patients in acute care settings, are aided by knowledge of the presence or absence of carbapenemase activity but do not necessarily require carbapenemase mechanism testing. However, knowing the specific carbapenemase mechanism is needed for the more targeted prevention activities outlined in Public Health Strategies to Prevent the Spread of Novel or Targeted Multidrug-resistant Organisms (MDROs)²⁴ and for activities initiated in response to the detection of specific MDROs.²⁵

Per the *Interim Guidance for Public Health to Contain Novel or Targeted Multidrug-Resistant Organisms (MDROs)*, when infected or colonized patients are identified, IPC response/containment activities should be initiated *immediately* to prevent future spread of the identified organism/mechanism.²⁵ One of the recommended activities is colonization screening of epidemiologically linked patients to determine whether transmission has occurred and guide how precautions should be applied to prevent future transmission events.²⁴ Cohorting of colonized or infected patients has been demonstrated to decrease additional CRE transmissions (including CP-CRE), and if cohorting multiple patients together, it should be conducted based on the identified resistance mechanism.^{26,27}

Haverkate and colleagues²⁸ demonstrated that a single patient colonized with KPC led to 0.4 transmission events per LTACH stay; however, 29.3% of patients within the cohort were already colonized, exponentially increasing the potential for a transmission event to occur. In contrast, in a model of CRE colonization screening effectiveness, identifying and placing only 1 out of every 9 colonized persons on contact precautions led to an 8% increase in CRE prevalence over 10 years, but increasing the rate of identifying colonized individuals (to 1 out of every 5) led to a steady decrease in new cases.²⁹

Despite the information colonization screening provides, laboratory capacity for this testing is a major unmet need. One example of this is in colonization assessments within long-term care facilities. The Antimicrobial Resistance Laboratory Network (AR Lab Network) often

performs colonization testing in these facilities, which were home to 1.3 million residents in the United States in 2020.³⁰ Even if all AR Lab Network resources were hypothetically dedicated to this population, the current capacity would only allow 2% of residents to be screened annually. This is only one example of this unmet need.

DISCUSSION

Facility and Patient Challenges

There are several barriers that a clinical laboratory may encounter when implementing carbapenemase mechanism testing. First, facilities must secure administrative buy-in. Facilities may have concerns about public perception (eg, positive findings cause the facility to be identified in the media/news),^{31–33} additional costs (eg, personal protective equipment [PPE] and general laboratory costs), or staffing. Billing/reimbursement may also be a barrier. Carbapenemase mechanism testing on clinical isolates *may* be reimbursed, but this is not guaranteed. Colonization screening is currently not reimbursed for any MDRO (eg, methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant *Enterococcus* [VRE], or CP-CRE), despite the multitude of clinical laboratories performing these screens routinely for infection prevention purposes.³⁴

Though not reimbursed, there are several examples where MDRO colonization screening has been demonstrated effective in decreasing downstream costs, including length of hospital stay.^{35–37} Following the implementation of routine MRSA screening, the Veteran's Affairs hospital system observed a 62% decrease in intensive care unit-related MRSA infections, a decline in health care-associated infections, and a decrease in the overall rate of facility transmission.³⁵ Perencevich and colleagues³⁶ predicted a 39% annual reduction in VRE incidence should colonization screening be implemented. Lastly, the implementation of an active surveillance program for asymptomatic *Clostridioides difficile* resulted in long-term savings associated with a decrease in new infection rates, length of hospital stay, patient isolation, and PPE costs.³⁷ It is important to note that these cost savings go beyond monetary costs and include social costs. Together, these examples highlight the potential value of colonization screening, including long-term cost savings, in the health care setting.

When considering unreimbursed testing, facilities may be tempted to point at the laboratory budget without considering the cost impact on patient isolation or outbreak management. Gill and colleagues²³ evaluated the potential expansion of carbapenemase mechanism testing in the context of carbapenem-resistant *Pseudomonas aeruginosa*. Often this testing is sent to the PHL, but the authors found that bringing carbapenemase mechanism testing in-house was not significantly more expensive than sending to the PHL (US\$46.92 vs US\$40.53), while also offering a significant reduction in TAT (same-day results vs median of 6 days), which directly impacted patient care and treatment decisions.²³

Health care worker and patient buy-in may be another barrier. Because Enterobacterales colonize the gastrointestinal tract, the optimal specimen for assessing colonization is a rectal or perirectal swab.^{38–42} Despite the evidence demonstrating the appropriateness of this specimen type for detection, the collection of rectal/perirectal swabs is fraught with challenges, including health care staff/patient embarrassment^{43,44} or patient discomfort⁴⁴

with collection. Dyakova and colleagues⁴⁵ found that the likelihood of patient rectal swab compliance was strongly influenced by the individual staff member engaging with the patient, indicating that staff education was one method to enhance patient acceptance of rectal sampling.

Clinical Laboratory Challenges

When selecting a carbapenemase mechanism test, requirements for both CRE isolates and colonization screening must be considered. Laboratories must weigh factors such as workflow, cost, accuracy, TAT, hands-on time (HoT), performance, required expertise, and sustainability. Cost per consumable is frequently assumed to be the most powerful decision-making driver; however, this cost should not be considered alone. For example, a lower cost, laboratory-developed test (LDT) may require additional HoT or expertise to develop and implement than a ready-to-use, higher cost test, with little HoT. A more expensive, but faster test may save money elsewhere, such as with patient isolation costs or staff HoT.

Because of the lack of laboratory-specific guidelines, clinical laboratories will need to define which isolates (ie, which organisms with which susceptibility profiles) should be prioritized for carbapenemase mechanism testing. Some recommendations have prioritized testing based on carbapenem breakpoints (eg, intermediate or resistant)⁴⁶ versus using epidemiologic cutoff values.⁴⁷ Also in dispute is *which* carbapenems (eg, ertapenem, imipenem, meropenem, or a combination) should be considered in this definition. While deciding which criteria a laboratory will use, balancing the sensitivity of the definition with capacity is key. Loosening the inclusion criteria increases sensitivity for detecting weaker carbapenemases (ie, carbapenemases with less robust carbapenem hydrolysis, such as OXA-48-like or KPC), but may lower specificity, thus increasing testing burden.

Once the definition of *what* to test is established, laboratories must also determine *how* to test. Carbapenemase testing falls into two main categories: broad carbapenemase production (B-CP) versus mechanism-specific carbapenemase (M-CP) methods. B-CP methods (eg, modified carbapenem inactivation method) determine if a carbapenemase is present (ie, presence/absence) but do not differentiate the specific carbapenemase present (eg, NDM). In contrast, M-CP methods (eg, nucleic acid amplification tests/NAATs or lateral flow assays) identify the specific carbapenemase mechanism present. Looking at the treatment guidelines can help laboratories decide which type of test to pursue.¹² The IDSA treatment guidance makes recommendations based on the *specific* carbapenemase identified¹²; therefore, the test selected should identify carbapenemase mechanisms whenever possible. A review of available diagnostic methods, including pros/cons, is available in Table 1.

As illustrated earlier, B-CP and M-CP methods provide different information. On their own, B-CP methods can help initiate IPC activities while waiting for the identity of the specific carbapenemase(s). When combined with M-CP methods, B-CP methods can screen for carbapenemases not detected by commercial tests. If a laboratory plans to perform only one carbapenemase test, it should select M-CP methods because they provide the most useful information for guiding patient treatment and public health action. IPC activities, including patient cohorting, are also often mechanism-specific, especially in regions where certain carbapenemases are considered endemic and others are considered rare.

Knowledge of the facility-level prevalence and local epidemiology can assist a laboratory in the test selection process. No test can cover every mechanism or variant, and every test has diagnostic limitations. Reviewing the instructions for use (IFU) of potential tests can assist in this decision-making process but is only the starting place. The IFU should list all mechanisms or variants covered by a particular test, but this information may be partially based on in silico prediction. To bolster the laboratory decision-making process, laboratories can also harness real-world performance data from peers and the scientific literature.

Pairing local epidemiology and methodological limitations helps the laboratory make a well-informed decision on the best test for their laboratory. For instance, imipenemase (IMP) detection can be challenging from a variant-coverage design perspective.^{48–52} Facilities concerned about IMP should understand which variants are circulating in their area, and then consider which variants are covered by their proposed assay.^{48–51}

Once a method is selected, laboratories will need to validate/verify the selected assay and develop the corresponding laboratory informatics before initiating patient testing. Laboratories must also consider appropriate reporting to the clinician, pharmacist, infection prevention team, and public health. New test onboarding for the clinical care team should include education regarding how mechanisms inform appropriate treatment. Decision-making cascades should be developed for testing, reporting, and antibiotic stewardship related to the specific carbapenemase mechanism identified. Facilities must also consider whether and how the result, and potentially the isolate, will be sent to public health.

FUTURE CONSIDERATIONS

Despite the challenges, there are feasible actions a clinical laboratory can take toward implementing carbapenemase mechanism testing in the short term and long term. First, the clinical laboratory can begin working alongside the facility's antimicrobial stewardship committee, infection prevention team, clinicians, and the corporate suite to elicit and receive facility-wide support. Clinical laboratories can also begin or increase isolate submissions to their PHL for mechanism testing, working with the PHL to expedite isolate submission, triage, and reporting. Clinical laboratories, or their infection prevention counterparts, can review clinical culture results, follow up on positives with their infection prevention teams, and help coordinate colonization assessments for high-risk contacts.

Next, clinical laboratories can begin investigating available diagnostic platforms for mechanism testing (see Table 1). Once laboratory leadership determines the diagnostic platform and approach they will take, laboratories can procure instrumentation or reagents and begin validation/verification testing. This may be a layered activity but could start with requesting isolates for validation/verification purposes. The CDC and FDA AR Bank (AR Bank; <https://wwwn.cdc.gov/arisolatebank/>) is a ready resource of well-characterized isolates to support these and other testing activities.

A clinical laboratory could reasonably aim to onboard carbapenemase mechanism testing within the next year. Some ways to expedite this process include sharing workflows or validation/verification materials among peers (eg, plans, templates, and developed tools),

reviewing real-world performance data, referencing public health testing guidance, using well-characterized isolates (shared among peers or from the AR Bank), or by working with their manufacturers. Once a laboratory is performing testing on isolates, expansion to colonization screening based on patient or resident risk factors could be the next step.

SUMMARY

For the nation to effectively treat patients with CRE infections and generate actionable IPC data in all facilities, additional carbapenemase mechanism testing capacity is needed. Therefore, it is critical that clinical laboratories implement routine carbapenemase mechanism testing to maintain a high standard of patient care. Once implemented, clinical laboratories should routinely perform carbapenemase mechanism testing on relevant CRE isolates to inform patient treatment and expand their testing menus to perform colonization screening assessments to prevent further transmission of CP-CRE.

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KEY POINTS

- In the United States, carbapenemase mechanism testing for carbapenem-resistant Enterobacterales (CRE) isolates and colonization screening is performed in only about half of clinical laboratories.
- Newer antimicrobial agents are being designed to target specific carbapenemase mechanisms (eg, meropenem/vaborbactam for *Klebsiella pneumoniae* carbapenemases and aztreonam/avibactam for metallo-beta-lactamases); therefore, routine carbapenemase mechanism testing for CRE is essential for informed patient treatment decisions.
- Carbapenemase-producing-CRE (CP-CRE) colonization screening guides infection prevention and control activities, allowing a facility to determine whether transmission of targeted CP-CREs has occurred and advises how precautions should be applied to prevent further transmission.

<u>Antibiotic</u>	<u>CP-CRE Mechanism</u>		
	KPC	OXA-48	NDM ^a
Meropenem-Vaborbactam			
Ceftazidime-Avibactam			
Imipenem-Relebactam			
Cefiderocol			
Ervacycline ^b			
Tigecycline ^b			
Aztreonam-Avibactam			

Fig. 1.

IDSA preferred antibiotics for treatment of CRE, by carbapenemase mechanism present.

^aAnd infections caused by other metallo-beta-lactamase producing isolates, ^bOutside of blood or urinary tract. Dark gray - first line therapy, light gray - alternative therapy.

Table 1
Summary of available diagnostic methods and considerations for carbapenemase mechanism testing

Method Type	Availability	Equipment Required	Cost	Intended Use	Result Type	TAT	HoT	Flexibility	Expertise Required	Ease of Result Interpretation
Molecular (eg, NAAT)	FDA, CE-IVD, RUO, and LDT	Y	\$\$-\$\$\$	Isolates or Specimens	Specific	<2 h	Low to medium	Low	Low to high	Low to high
Lateral flow	FDA, CE-IVD, and RUO	N	\$\$	Isolates or specimens ^a	Specific	<20 min	Low	Low	Low	High
mCIM	LDT	N	\$	Isolates	Broad	Overnight	High	High	Medium	Medium
Colorimetric (eg, CarbaNP)	FDA, CE-IVD, and LDT	N	\$-\$\$	Isolates	Broad	<2 h	Low to medium	High	Medium	Medium
β-lactam inhibitor-based (eg, combined disk test)	CE-IVD, LDT	N	\$\$	Isolates	Narrow	Overnight	High	Medium	Medium	Medium
MALDI-TOF MS	RUO, LDT	Y	\$\$\$	Isolates	Broad	<5 h	Medium	High	High	Low to medium
WGS	LDT	Y	\$\$\$	Isolates	Specific	Days	Medium to high	Medium	High	Low

Abbreviations: CarbaNP, carbapenemase nordmann-poirel; FDA, FDA cleared; HoT, hands-on time; LDT, laboratory developed test; MALDI-TOF MS, matrix-assisted laser desorption/ionization-time of flight mass spectrometry; mCIM, modified carbapenemase inactivation method; NAAT, nucleic acid amplification test; RUO, research use only; TAT, turn-around-time; WGS, whole genome sequencing; \$, lowest cost; \$\$, intermediate cost; \$\$\$, highest cost.

^aEx US only, Flexibility—the flexibility of an assay to detect novel or emerging carbapenemase variants or classes.