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CLSI Subcommittee on Antimicrobial Susceptibility Testing

CLSI AST News Update

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The CLSI **Outreach Working Group (ORWG)** is providing this Newsletter to highlight some recent issues related to antimicrobial susceptibility testing and reporting. We are listing links to some new educational materials and reminding you where you can find information about the CLSI AST Subcommittee proceedings.

Inside This Issue:

CLSI AST Subcommittee Partnerships

Representatives with expertise in antimicrobials from the following organizations attend and participate in CLSI AST Subcommittee meetings and aid in dissemination of information regarding CLSI decisions and AST issues.

American College of Clinical Pharmacy Infectious Diseases Practice and Research Network (ACCP INFD PRN)

American Society for Microbiology (ASM)

Association of Public Health Laboratories (APHL)

ASTM International, formerly known as American Society for Testing and Materials

College of American Pathologists (CAP)

European Union Committee on Antimicrobial Susceptibility Testing (EUCAST)

Infectious Diseases Society of America (IDSA)

Pediatric Infectious Diseases Society (PIDS)

Society for Healthcare Epidemiology of America (SHEA)

Society of Infectious Diseases Pharmacists (SIDP)

Susceptibility Testing Manufacturers Association (STMA)

What does the CLSI AST Subcommittee do?

The first edition of the CLSI AST News Update (Vol 1, Issue 1, Spring 2016) described details about the organization and operation of the CLSI AST Subcommittee.

- You can access that Newsletter **here.**
- To learn more about upcoming or past meetings, click **here.**
- CLSI posts meeting minutes and summaries for public access **here.**
- If you are planning on attending a CLSI AST Subcommittee meeting, check out the Orientation presentation **here.**

Interested in becoming a CLSI volunteer? Learn more here.

Please remember that the CLSI AST Subcommittee welcomes suggestions from you about any aspect of CLSI documents, educational materials, or this Newsletter.

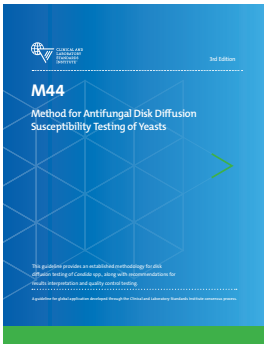
Future CLSI AST Meetings

June 16–18, 2019
Dallas, Texas, USA

January 26–28, 2020
Tempe, Arizona, USA

June 14–16, 2020
Baltimore, Maryland, USA

New/Updated CLSI AST Documents Are Here!



Updated Document December 2018
M44 | Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts, 3rd Edition

- Replaces former document M44-A2
- Describes disk diffusion susceptibility testing method for yeasts

New Recommendations:

- Addition of disk diffusion standards for micafungin
- Explanation of circumstances in which routine antifungal testing may be warranted

Updated Recommendations:

- List of specific *Candida* spp. for which there are zone diameter breakpoints and interpretive categories for certain antifungal agents
- Revised definitions for interpretive categories to align with other CLSI susceptibility testing documents

New Rationale Document February 2019
MR02 | Fluoroquinolone Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa*

CLSI publishes rationale documents that provide the scientific reasons behind the subcommittee's decisions, along with documentation of the standardized data and methods used to determine breakpoints. To access these free rationale documents, click **here.**

Recent publication on revised fluoroquinolone breakpoints

"Don't Get Wound Up: Revised Fluoroquinolone Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa*" authored by Tam T. Van, Emi Minejima, Chiao An Chiu, and Susan M. Butler-Wu. doi:10.1128/JCM.02072-18 (May 2019) PMID 31043468.

Access this publication **here.**

New Information for M100– Daptomycin and *Enterococcus* spp. Testing Recommendations - Second Revision to CLSI Daptomycin Breakpoints

Daptomycin is one of the few treatment options for serious infections caused by vancomycin-resistant enterococci. It has become increasingly evident that daptomycin treatment outcomes are best if doses above the currently FDA-approved 6 mg/kg/day are used for this indication. In order to better understand this, a CLSI *ad hoc* working group was formed to review (and in some cases generate new) data regarding daptomycin activity against the enterococci. Studies on testing issues, murine and human *in vivo* PK/PD, safety of off-label doses and treatment outcomes were included, and are described in detail in a forthcoming rationale document. The end result of this work which was reviewed and approved in June 2018 was publication of revised *Enterococcus* spp. breakpoints for daptomycin in the M100 29th Edition (2019), which included introduction of a new susceptible-dose dependent (SDD) category. The SDD category was based on use of daptomycin doses of at least 8 mg/kg/day, which is above what is currently FDA-approved.

In January 2019, new data were reviewed that demonstrated these new breakpoints cut into the wild type *Enterococcus faecium* daptomycin MIC distribution. As a result, laboratories attempting to validate the breakpoints were facing challenges of obtaining an accurate daptomycin MIC that was reproducible within one interpretive category. Following further discussion, CLSI voted to revise the daptomycin breakpoints a second time, establishing specific breakpoints for *E. faecium* and *Enterococcus* spp. other than *E. faecium*. An update to M100 29th Edition was e-mailed on March 13, 2019 to laboratories that purchased M100 29th Edition and is currently available in the free-of-charge, online version of M100 29th Edition, **M100 Free.**

The full revision memo can be accessed **here.**

The current daptomycin breakpoints and associated comments now recommended by CLSI AST SC for use in clinical laboratories are shown below in an excerpt from the current Table 2D.

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	I	R	S	SDD	I	R	
LIPOPEPTIDES										
B	Daptomycin ***E. faecium*** only	-	-	-	-	-	≤ 4	-	≥ 8	**(11)** Daptomycin should not be reported for isolates from the respiratory tract. **(12)** The breakpoint for SDD is based on a dosage regimen of 8-12 mg/kg administered every 24 h in adults and is intended for serious infections due to ***E. faecium***. Consultation with an infectious diseases specialist is recommended.
B	**Daptomycin *Enterococcus* spp. (other than *E. faecium*)**	**-**	**-**	**-**	**-**	**≤ 2**	**-**	**4**	**≥ 8**	**(13)** The breakpoint for susceptible is based on a dosage regimen of 6 mg/kg administered every 24 h in adults. **See comment (11).**

Webinars

For information on upcoming webinars please go **here.**

Archived and Free On-Demand Webinars:

Recently archived CLSI webinars can be accessed on demand **here.** Archived on-demand webinars are available free of charge for CLSI members six months after the scheduled event. Some recent webinars are listed below:

- *CLSI/SIDP/ACCP Annual Webinar: "Merging Microbiology and Stewardship: Making the Most of 2019 CLSI Updates on Antimicrobial Susceptibility Testing for Gram-positive and Gram-negative bacteria in Your Stewardship Activities"
- CLSI 2019 Antimicrobial Susceptibility Testing Update (February 2019)
- CLSI-CAP Annual Webinar: "Resources for Implementation of Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) in the Clinical Microbiology Laboratory" (FREE, November 2018)
- "Preparation, Presentation, and Promotion of Cumulative Antibiograms To Support Antimicrobial Stewardship Programs" (FREE, October 2018)
- "CLSI Documents for AST: What's Available for You?" (FREE, May 2018)

* This webinar was not hosted by CLSI, but can be purchased on demand **here.**

Upcoming Webinars:

Dates and times will be announced soon **here.**

- Rationale Documents Webinar | Summer 2019
- VET09, Understanding Susceptibility Test Data as a Component of Antimicrobial Stewardship in Veterinary Settings Webinar | Summer 2019
- CLSI-CAP Annual Webinar, Subject TBD | Fall 2019

Archive of Retired Breakpoints

An archive of breakpoints removed from M100 since 2010 together with the rationale for their removal is available **here.**

Similarly, an archive of methods removed from M100 since 2017 is available **here.**

Check It Out! Educational Workshops Held at CLSI Meetings

Nicole Scangarella-Oman, GlaxoSmithKline, Collegeville, PA

To coincide with the January and June CLSI Committees Weeks, the ORWG coordinates a biannual "live" Educational Workshop, typically held on the Saturday evening prior to the start of the AST Subcommittee Working Group meetings.

The January 2019 workshop, held in St. Augustine, Florida, was entitled "Recent Advances in PK/PD and its Use in Setting Breakpoints." This workshop provided an opportunity for various groups to provide perspectives from each susceptibility testing subcommittee, highlight recent advances in PK/PD methodology and application, and discuss remaining challenges regarding the use of PK/PD, especially in setting breakpoints. Presenters included representatives from the Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST), Subcommittee on Antifungal Susceptibility Tests, and the Subcommittee on Antimicrobial Susceptibility Testing (SCAST). A spirited question and answer session following the presentation was moderated by Linda Miller.

The next workshop, entitled "To MIC or Not to MIC, That is the Question: Molecular Characterization of Antimicrobial Resistance (AR) for Healthcare in 2019" will be held on Saturday, June 15, 2019, in Dallas, Texas.

PowerPoint presentations from past workshops can be found by accessing the CLSI webpage **here.** Select the arrow in the dropdown box. The workshop entries are all preceded with the word "Education" in the dropdown window and you can filter by "All Education." Or type the word "Education"in the search field for any education-related workshop materials.

Featured Article

Practical Approach to Evaluating Requests to Test New Antimicrobials

Catherine A. Hogan, Stanford University School of Medicine, Stanford, CA

Many new antimicrobials have recently come to market to address the rising threat of multidrug-resistant (MDR) bacteria. Clinical and public health laboratories are critical participants in the management of patients with MDR infections and must develop a plan for antimicrobial susceptibility testing (AST) of these new agents, either in-house or at a reference laboratory.

Herein, we present an example of a practical approach to this challenge. Let's consider how a laboratory might respond to the scenario of receiving the following request from the institutional antimicrobial stewardship team:

"Can the laboratory start testing carbapenem-resistant *Enterobacteriaceae* (CRE) for ceftazidime-avibactam (CZA; AVYCAZ®) susceptibility?"

1. Consider the clinical need

The Antimicrobial Stewardship Program (ASP) chair has requested all CRE be tested for CZA susceptibility. This request seems simple, but careful consideration should be given to different testing approaches. Some key questions for the laboratory to consider are listed in Table 1.

Table 1. Example of Considerations When Developing a CZA Testing Strategy in the Clinical Laboratory

Question: 1. Should isolates from all patient populations and/or anatomical sites be tested?
Information Review: Drug label[1] shows CZA is FDA-approved for: • Complicated urinary tract infection in adults and children ≥ 3 months old • Complicated intra-abdominal infection in combination with metronidazole in adults and children ≥ 3 months old • Hospital and ventilator-associated bacterial pneumonia in adults
Decision: ASP Chair and Laboratory determine that testing will be done routinely for CRE from: • Blood, urine, and intra-abdominal isolates from children/adults, and • Lower respiratory isolates from adults. Isolates from other sources (eg, wounds, cerebrospinal fluid [CSF]) will not be tested routinely.
Further Discussion: Should all urine isolates be tested? Many CRE from urine were deemed colonizers by ASP upon review of the hospital's data, and not treated. (CRE often colonize the urinary tract, especially among nursing home residents in whom CRE are more common.) Laboratories are not restricted to only performing susceptibility testing on isolates from clinical specimen sites that are FDA-approved. Such testing may provide guidance for off-label use of a drug when there is no FDA-approved alternative, as may be seen with some MDR isolates.

Practical Approach to Evaluating Requests to Test New Antimicrobials (*Continued*)

Table 1. (Continued)

Question: 2. Should reflex testing be done for all *Enterobacteriaceae* with phenotypic resistance to all carbapenems on our panel (eg, ertapenem, imipenem, meropenem), or only if resistant to meropenem and/or imipenem?
Information Review: • Laboratory data on the number of isolates that are R to ≥ 1 carbapenem • Laboratory data on the number of *Enterobacter* isolates that are R to ertapenem but S to imipenem and meropenem; literature review indicates these are mainly AmpC producers[2] • Literature review reveals some carbapenemase-producing CRE (CP-CRE) may be intermediate to imipenem and/or meropenem[3] • CLSI M100 Appendix B indicates *Proteus/Providencia/Morganella* spp. may be I or R to imipenem (but not ertapenem or meropenem), via intrinsic resistance mechanisms
Decision: • Test all *Enterobacteriaceae* that are I or R to meropenem or imipenem • Do not test *Proteus/Providencia/Morganella* that are I or R to imipenem only • Do not test any *Enterobacteriaceae* that are R to ertapenem only
Further Discussion: • Should laboratory test CZA on isolates that are S to one or more agents that might be appropriate for therapy (eg, CRE that are S to a fluoroquinolone or trimethoprim-sulfamethoxazole)? • Should other antimicrobial options be considered for routine testing of CRE (eg, fosfomycin for *E. coli* urinary tract infection)? • The laboratory may initially decide against these options, with the plan to reconsider as needed in the future.
Question: 3. If phenotypic/molecular carbapenemase testing is done, should these results inform the decision to test CZA?
Information Review: • CZA is a novel beta-lactam combination agent composed of ceftazidime and avibactam with activity against class A, C, and D beta-lactamase-producing isolates, including those that express KPC, the most common CRE type in the USA.[4] • CZA has no activity against class B metallo-beta-lactamases (MBL) (eg, NDM-1, IMP, VIM). • Laboratory protocol already includes testing isolates that meet CP-CRE definition (see question 1) by the modified carbapenem inactivation method (mCIM)/EDTA modified carbapenem inactivation method (eCIM) methods for carbapenemase.
Decision: • An isolate positive for both mCIM and eCIM indicates production of an MBL and does not need to be tested since it will be CZA resistant.[4]
Further Discussion: • Should the CZA testing be done in parallel with, or after, the mCIM/eCIM testing? The latter option will result in a delay of result reporting.

Practical Approach to Evaluating Requests to Test New Antimicrobials (*Continued*)

Table 1. (Continued)

Question: 4. Might testing for non-*Enterobacteriaceae* be considered if requested by clinician?
Information: • CZA has no activity against *Acinetobacter* spp., but has activity against *P. aeruginosa.* • Drug labeling demonstrates that indications for use include *P. aeruginosa.* • FDA Susceptibility Test Interpretive Criteria (STIC) website[5] includes CLSI/FDA breakpoints for *P. aeruginosa*
Decision: • *P. aeruginosa* will be included in verification studies, or discussed with reference laboratories that will perform CZA testing.
Further Discussion: • Discuss with ASP if CZA should be tested routinely for *P. aeruginosa* isolates (eg, those "R" to all other antipseudomonal beta-lactams ([aztreonam, ceftazidime, cefepime, piperacillin-tazobactam, meropenem and/or imipenem])

2. Testing in-house or send out?

This question requires consideration of:

- Expected volume of testing, based on the number of carbapenem-resistant *Enterobacteriaceae* from last year's antibiogram
- Availability of testing options and materials
- Capacity to perform testing in-house
- Staffing capacity to perform verification studies, write standard operating procedures (SOPs), etc.
- Impact of testing option(s) on turnaround time to results

A basic cost-analysis of in-house vs send-out testing should be performed, keeping in mind that the results of testing CZA are often critical to patient care. Close collaboration with infectious diseases, critical care physicians, laboratory medicine, and administrative colleagues is essential to ensure an optimal workflow. For the purpose of this exercise, let's assume the laboratory encounters ~100 isolates per year that meet the testing criteria defined in Table 1, and determines testing should be done in-house.

3. How to perform the verification studies?

The essentials of a verification study are presented in Table 2; further guidance is found in references.[6-9]

Table 2. The Essential Components of a Verification Study

Pre-verification Activities	
Determine Need for/ Scope of Verification Study	According to CLIA (§CLIA 493.1253), any new testing introduced in your laboratory requires a verification study. The extent of the verification study is at the discretion of the laboratory director. If CZA is added to an existing FDA-approved AST system already in use in the laboratory, a limited study may be sufficient. Otherwise, a more robust study should be considered.
Selection of AST Method	**Available Methods:** FDA-cleared AST methods for new antimicrobials typically include disks, gradient diffusion strips (including some that may be research use only [RUO]), and manual broth microdilution. Testing for new agents on automated instruments is generally not available for several years post antimicrobial approval; contact the manufacturer for information.
	Literature Review: The laboratory should consult the literature to review AST method performance data. • Example: recent data show gradient diffusion strips perform better than disk for CZA.[10,11] **Note:** please refer to the CLSI workaround for potentially false "R" disk diffusion results below. • When evaluating published studies, carefully review the methods section, to ensure the authors followed CLSI recommendations for AST evaluations.[9]

Practical Approach to Evaluating Requests to Test New Antimicrobials (*Continued*)

Table 2. (Continued)

Pre-verification Activities (Continued)	
Review Breakpoints and Testing Considerations	**CLSI M100 and FDA STIC Website:** Both sources list MIC and disk breakpoints for new antimicrobials. New antimicrobials are sometimes listed on the FDA website earlier than in M100. Either breakpoint is acceptable for use by clinical laboratories; however, manufacturers of commercial AST systems must use the breakpoints listed on the FDA website. **Example:** M100 and FDA list CZA disk (S ≥ 21mm; R ≤ 20mm) and MIC (S≤ 8/4; R≥ 16/4) breakpoints. There is no intermediate breakpoint for CZA. CLSI and FDA recommend disk zones of 18-20 mm should be confirmed by an MIC method, due to the risk of overcalling resistance.[4]
Verification	
Accuracy	**Method:** Compare categorical (MIC and disk) and essential (MIC only) agreement of the AST method with a reference method. Reference/comparator methods are typically disk diffusion or broth microdilution (BMD) performed in-house or by a reference laboratory.
	Select Testing Isolates: • Minimum of 30 isolates recommended by CLSI • Ideally, isolates should span a range of MICs and include diverse species and resistance phenotypes (including ESBL, AmpC, KPC, OXA-48) • Suggest including isolates resistant to CZA, such as those harboring an MBL • Sources include: – In-house collections – Proficiency testing challenges – Colleagues – Antimicrobial pharmaceutical company – CDC & FDA Antibiotic Resistance (AR) Bank (contains challenge isolate panels that include BMD MICs).[12]
	Testing and Data Analysis: • Test isolates by the new AST method and the comparator in parallel – If using the CDC & FDA AR Bank isolates, only test by the new AST method; MIC results posted were generated by reference BMD testing and are acceptable to use for comparator results without additional testing. • A limited number of errors are acceptable. Generally acceptable error rates, with caveats, are below: – Major errors (ME): < 3% of the total susceptible isolates – Very major errors (VME): < 3% of the total resistant isolates – If testing 30 isolates, only one ME and one VME is acceptable.[7] – Given the lack of an intermediate breakpoint for CZA, all errors are MEs or VMEs; the laboratory director may accept a higher error rate and consider follow-up testing if the zone/MIC is near the breakpoint. • Always address discrepancies – Repeat testing for isolates with discrepancies by both methods – If discrepancy is not resolved, send to a reference laboratory for evaluation by a third method. CDC & FDA AR Bank isolates cannot be forwarded to another laboratory. • Proper documentation of the verification study design and results needs to be written and stored for future reference.

Practical Approach to Evaluating Requests to Test New Antimicrobials (*Continued*)

Table 2. (Continued)

Verification (Continued)	
Precision	**Method:** • One option is to evaluate precision through routine testing of QC strains. – For CZA, *Klebsiella pneumoniae* ATCC® 700603 is used. – Note that ceftazidime, or another antimicrobial listed in Table 4A-2 or 5A-2, should also be tested to ensure integrity of this QC strain. – 95% of results must fall within acceptable QC ranges. • During the verification of CZA, daily QC should be performed by the recommended CLSI or manufacturer method.
Post-verification Activities	
Activities	Ongoing QC, training and proficiency documentation for staff, maintenance of software, and correlation of results with clinical findings

4. How to perform QC? Should we consider an IQCP?

CLIA requires the laboratory either performs AST QC daily or develops an Individualized Quality Control Plan (IQCP).[4] In many laboratories, CRE are relatively uncommon and CZA will be tested infrequently (ie, less than once a week). As such, the laboratory may choose to not perform an IQCP, but to do QC each time a patient isolate is tested.

5. What results should I expect? (ie, how often are carbapenem-resistant isolates R to CZA?)

In vitro susceptibility rates of *Enterobacteriaceae* to CZA are very high, with > 99.5% susceptibility overall, and > 97% among class A and D carbapenemase-producing isolates.[13,14] In contrast, as highlighted previously, little to no activity is expected against MBL-producing *Enterobacteriaceae*. If the laboratory encounters a high rate of resistance, this should be investigated to ensure it is not due to technical error.

In summary, broad-spectrum agents such as ceftazidime-avibactam have strongly enhanced the therapeutic arsenal against MDR gram-negative organisms, an important cause of morbidity and mortality in patients in hospitals and long-term care facility settings. Implementing testing and completing a verification study for a new antimicrobial agent such as CZA carry additional workload which may seem daunting to the laboratory. However, accurate and timely microbiological testing is instrumental in identifying effective therapies that may significantly impact patient outcomes and enable effective resource allocation.

References

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Practical Approach to Evaluating Requests to Test New Antimicrobials (*Continued*)

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10 Shields RK, Clancy CJ, Pasculle AW, et al. Verification of ceftazidime-avibactam and ceftolozane-tazobactam susceptibility testing methods against carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. *J Clin Microbiol.* 2018;56(2): pii: e01093-17.

11 Wenzler E, Lee M, Wu TJ, et al. Performance of ceftazidime/avibactam susceptibility testing methods against clinically relevant gram-negative organisms. *J Antimicrob Chemother.* 2019;74(3):633-638.

12 Centers for Disease Control and Prevention & US Food and Drug Administration Antibiotic Resistance (AR) Isolate Bank. 2018; https://www.cdc.gov/drugresistance/resistance-bank/index.html. Accessed April 6, 2019.

13 Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. Ceftazidime/avibactam tested against gram-negative bacteria from intensive care unit (ICU) and non-ICU patients, including those with ventilator-associated pneumonia. *Int J Antimicrob Agents.* 2015;46(1):53-59.

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Practical Tips

Where Can We Find the Latest Resources for *Candida auris*?

The Centers for Disease Control and Prevention (CDC) is concerned about the global emergence of *Candida auris*. Because this fungus is newly emergent, published resources are rare, and our knowledge of this organism is in a constant state of flux. CDC maintains continuously updated web pages with *C. auris* information for the public, laboratory directors, hospital infection control specialists, and clinicians. The links provided below will take you to the most current information on the CDC website.

General information about *C. auris* and launch point

US tracking and case counts

Identification, including algorithms for most typing systems

Antifungal susceptibility testing and interpretation

Treatment and management

Infection control

Fact sheets that can be printed and distributed

Hot Topic

The Antibiotic Resistance Laboratory Network (AR Lab Network) – Bridging the Gap by Offering Expanded Antimicrobial Susceptibility Testing

Paula Snippes Vagnone, AR Lab Network Central Region Lab Coordinator, Minnesota Department of Health, Public Health Laboratory, St. Paul, MN

Infections caused by isolates of carbapenemase-producing *Enterobacteriaceae* that are resistant to nearly all available antimicrobial agents are difficult to treat and a significant cause of morbidity and mortality. In contrast to serine carbapenemase (eg, KPC)-producers, isolates of *Enterobacteriaceae* that produce metallo-β-lactamases (MBL) are the most challenging, as these are resistant to meropenem-vaborbactam and ceftazidime-avibactam, the newest beta-lactam combination agents. However, isolates of *Enterobacteriaceae* with MBLs (eg, NDM, VIM, and IMP) have been shown to be susceptible to a combination of ceftazidime + avibactam + aztreonam. This combination is listed in the Sanford Guide as the primary option for treatment of serious infections caused by MBL-producing *Enterobacteriaceae*.[1] Providing antimicrobial susceptibility testing of an isolate to aztreonam, ceftazidime-avibactam,[2] and aztreonam-avibactam[3] can provide useful information to guide patient treatment. Of note, the beta-lactam combination of aztreonam-avibactam is in Phase III clinical trials.

Most clinical laboratories find it difficult to test some of the newer antimicrobial agents that might warrant consideration for treatment of highly resistant organisms. It can take years before these drugs are available on commercial antimicrobial susceptibility testing systems used in clinical laboratories. The AR Lab Network[4] has introduced a new testing approach to bridge the gap. A pilot program was initiated in 2019 at four of the seven AR Lab Network regional laboratories (Minnesota, New York Wadsworth, Tennessee, and Wisconsin) to provide expanded antimicrobial susceptibility testing (ExAST). This program will be extended in 2020 to the remaining AR Lab Network regional laboratories. However, ExAST is now available to all health care facilities in the United States and it is suggested that you contact your state or local public health laboratory (PHL) to determine which AR Lab Network regional laboratory is currently serving your facility for ExAST. Testing is available free-of-charge for highly resistant isolates that meet specific criteria. An HP D300e Digital Dispenser is used for on-demand production of minimal inhibitory concentration (MIC) panels[5] that are used for CLSI reference broth microdilution (BMD) testing of the newest antimicrobial agents. This testing is CLIA compliant and enables AR Lab Network regional laboratories to perform ExAST with a quick turn-around time.

Based on the current national need, ExAST at the AR Lab Network regional laboratories will offer testing (and reporting as indicated) of MBL-producing isolates of *Enterobacteriaceae* with the following antimicrobials and antimicrobial combinations:

- **Aztreonam** – MIC and interpretation will be reported.
- **Ceftazidime-avibactam** – MIC and interpretation will be reported.
- **Aztreonam-avibactam** – MIC will be reported with no interpretation (agent not FDA-approved and no CLSI or FDA breakpoints are available).

The report sent back to your laboratory will include a comment similar to the following to help explain the results: *"For aztreonam-avibactam, a minimum inhibitory concentration (MIC) is reported without an interpretation because clinical breakpoints for this drug combination have not been established. This drug demonstrates in vitro activity against metallo-β-lactamase (MBL) producing Enterobacteriaceae. Its clinical efficacy is under evaluation in clinical trials. Surveillance data indicate that MICs of MBL-producing isolates of Enterobacteriaceae (n = 580) ranged from ≤ 0.015/4 to 8/4 µg/mL."*

Since this MIC testing has been validated in each of the AR Lab Network regional laboratories performing ExAST, the MIC result with the comment can be reported by the submitting laboratory.

The Antibiotic Resistance Laboratory Network (AR Lab Network) – Bridging the Gap by Offering Expanded Antimicrobial Susceptibility Testing (*Continued*)

What is the purpose of ExAST?

- To provide clinicians, hospital laboratories, and public health laboratories with a resource for testing highly resistant organisms with newer agents not widely available on current antimicrobial susceptibility testing systems.

  Note: CDC through the AR Lab Network plans to expand testing as new or novel antimicrobial treatment options become available for serious infections caused by multi-drug resistant organisms.

What are the required criteria* for submitting an isolate for ExAST?

- Any species of *Enterobacteriaceae* from any specimen source that tests not susceptible to all beta-lactams, including either ceftazidime-avibactam or meropenem-vaborbactam (these isolates may be MBL-producing isolates with few effective treatment options) is acceptable for submission.

  -OR-

- *Enterobacteriaceae* possessing NDM, VIM, or IMP genes confirmed by a molecular test and which are not susceptible to all or the majority of antimicrobial agents already tested.

In addition, please note:

- Unless the isolate is a molecularly-confirmed MBL, testing for ceftazidime-avibactam and meropenem-vaborbactam should be performed before consideration is given to accepting the isolate for ExAST.
- Results for aztreonam from the submitting laboratory will be considered on a case by case basis and in context with all other results available on the isolate.
- The submitting laboratory must include the clinical team in conversations with AR Lab Network regarding ExAST.

*Although these are the basic criteria, exceptions may be made. Suitability for testing will be explored when you contact your AR Lab Network laboratory about a specific isolate/patient.

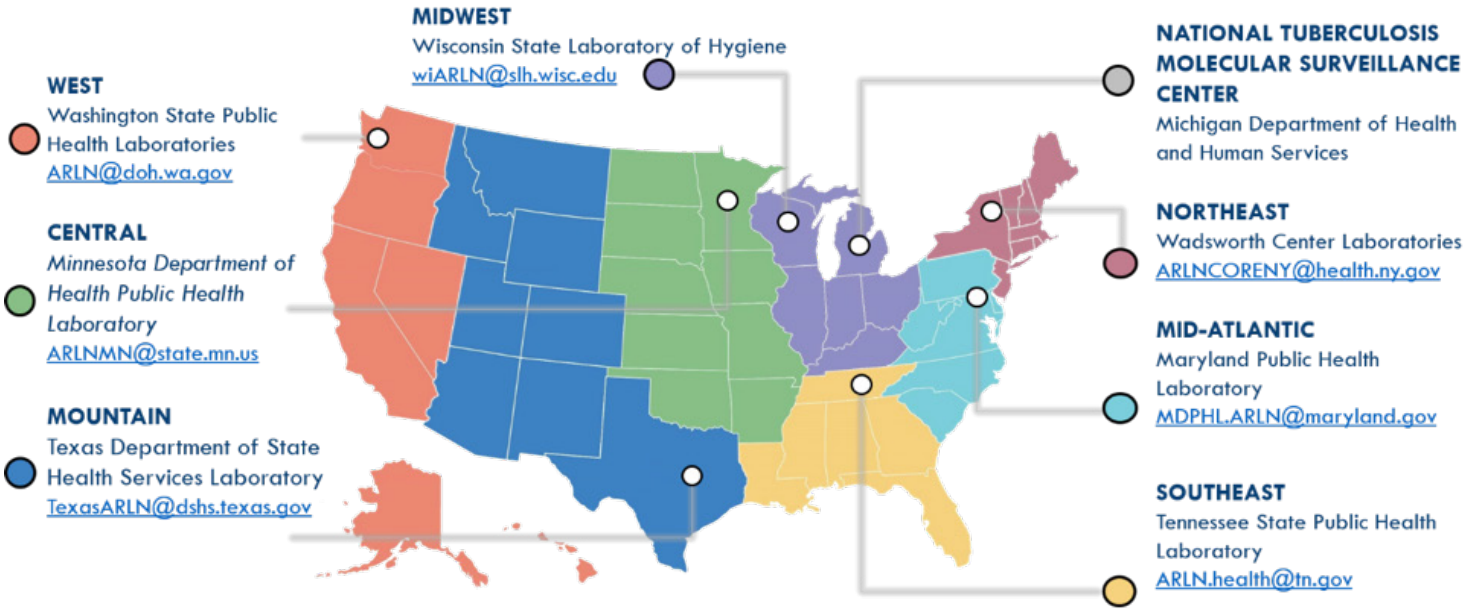
What is the current ExAST process at the AR Lab Network regional laboratory?

- Once received, the isolate is confirmed as an MBL producer by performance of the following tests (even if such testing was performed at the submitting laboratory): BMD, modified carbapenem inactivation method (mCIM), and molecular testing for KPC, NDM, VIM, IMP, OXA.
- An isolate that is confirmed as an MBL producer will be tested for susceptibility to aztreonam, ceftazidime + avibactam, and avibactam + aztreonam. The special MIC testing may be performed on a highly resistant isolate even if it is not confirmed as an MBL (NDM, VIM, IMP) producer if there is suspicion it may produce a novel carbapenemase.
- ExAST turn-around time is three business days from the time the isolate is received.

The Antibiotic Resistance Laboratory Network (AR Lab Network) – Bridging the Gap by Offering Expanded Antimicrobial Susceptibility Testing (*Continued*)

How do I request ExAST?

- Contact the AR Lab Network regional laboratory serving your facility. Staff at the regional laboratory will discuss the requirements for submission (eg, isolate's resistance characteristics) and will provide instructions to you for submitting your isolate.
- You can access the AR Lab Network site for more information about your facility's AR Lab Network regional laboratory and ExAST by clicking **here.**



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In Memoriam

Sydney M. Finegold, MD

Janet A. Hindler, Los Angeles County Department of Health, Los Angeles, CA

Sydney Finegold, MD, a leader in the field of infectious diseases and clinical microbiology, died on September 17, 2018 at the age of 97. Dr. Finegold was a longstanding contributor to CLSI, primarily as related to antimicrobial susceptibility testing of anaerobic bacteria.

For more than 50 years, Dr. Finegold's name has been synonymous with anaerobes and the infections caused by them. No one has had more influence in this area than he. His laboratory pioneered the identification and naming of numerous anaerobes and the part they play in a wide variety of infections. His most recent contributions involved identifying the role of anaerobic bacteria in autism, about which he was extremely passionate.

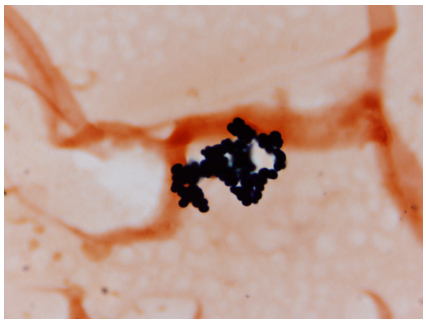
Most of Dr. Finegold's long and highly distinguished career was spent in Los Angeles at the UCLA School of Medicine and the Wadsworth VA Hospital. He became Emeritus Professor of Medicine, Microbiology, Immunology and Molecular Genetics and Staff Physician, Infectious Disease Section, in 2000.

In 1961, Dr. Finegold was part of the group that led to the formation of the Infectious Diseases Society of America (IDSA). He founded the Anaerobe Society of the Americas, the VA Society of Practitioners in Infectious Diseases, and the Society of Microbial Ecology and Disease. He was a fellow in the American Academy of Microbiology, fellow in the IDSA and Master in the American College of Physicians. Dr. Finegold was the recipient of numerous awards for his many contributions including the first Sonnenwirth Memorial Lectureship though the ASM and the IDSA's prestigious Alexander Fleming Award for Lifetime Achievement.

Dr. Finegold authored hundreds of research papers, book chapters and nearly 40 books. Perhaps the most noted of these are the "Wadsworth Anaerobic Bacteriology Manual" and "Anaerobic Infections in Humans." Among the microorganisms characterized in his laboratory are *Bilophila wadsworthia* and *Finegoldia magna*, which was named after him.

Up until his final days, Dr. Finegold was known and admired for his boundless energy and intellectual curiosity. He was always on the lookout for the unexpected. But his most lasting contribution as an inspiring teacher and mentor can be found in the careers and achievements of his many students around the globe.

Sydney M. Finegold, MD



Gram Stain
Finegoldia magna in blood culture

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