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New Consensus Guidelines from the Clinical and Laboratory Standards Institute for Antimicrobial Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria

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The Clinical and Laboratory Standards Institute (CLSI) recently published a new laboratory guideline for antimicrobial susceptibility testing of infrequently encountered or fastidious bacteria not covered in previous CLSI publications. The organisms include *Aeromonas* species, *Bacillus* species, and *Vibrio* species that may cause infections following environmental exposure. Fastidious organisms that may cause endocarditis or medical device infections include *Abiotrophia* and *Granulicatella* species; coryneform bacteria; *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* group gram-negative rods; and the instrinsically vancomycin-resistant gram-positive organisms *Erysipelothrix, Lactobacillus, Leuconostoc,* and *Pediococcus* species. Organisms not previously covered in depth in CLSI guidelines include *Branhamella catarrhalis, Campylobacter jejuni, Campylobacter coli, Listeria* species, and *Pasteurella* species. Clinically important drug resistance has been reported for each of these organisms. The guidelines provide recommendations for when it may be important to test these organisms, how standard methods may be easily adapted for testing, and appropriate interpretive criteria for results. Communication with infectious diseases clinicians prior to performing such testing is emphasized.

Improved management of cases involving immunosuppressed patients, expanded use of various prosthetic devices, and the wide use of intravascular catheters occasionally lead to infections with infrequently encountered bacteria and fungi [1–3]. Infections due to corynebacteria, lactobacilli, *Bacillus* species, *Leuconostoc* species, and *Pediococcus* species can occur in these circumstances. Endocarditis associated with native or prosthetic valves may be caused by species belonging to genera such as *Abiotrophia* or *Granulicatella* or by members of the *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* (HACEK) group of fastidious gram-negative rods [4, 5]. Soft-tissue infections due to *Aeromonas, Plesiomonas,* or *Vibrio* species may occur following exposure to fresh or salt water [6, 7]. Animal bite wound infections due to *Pasteurella* species are not uncommon, and soft-tissue or systemic infections due to *Erysipelothrix rhusiopathiae* can result from fish, poultry, or swine exposures [8, 9]. When these uncommon bacterial pathogens are encountered, it may prompt consultation with an infectious diseases specialist for optimal patient management. Even the most experienced clinician may ask, "What should an infection due to that organism be treated with? Can you provide me susceptibility data on my patient's isolate?" The response from the clinical microbiology laboratory is often, "There are no guidelines for testing that organism." However, resistance to antimicrobial agents that might be selected for therapy has been reported for nearly all of these organisms, emphasizing the need for reliable in vitro susceptibility testing recommendations for these bacteria. The purpose of this review is to provide the rationale for the development of the new Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) guidelines on antimicrobial susceptibility testing of infrequently encountered or fastidious bacteria. A second goal is to emphasize

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the critical importance of communication between clinicians and clinical microbiology laboratories when testing of these organisms is contemplated in individual cases.

THE ROLE OF THE CLSI IN ANTIMICROBIAL SUSCEPTIBILITY TESTING

Laboratories have relied upon the CLSI for many years to provide comprehensive, up-to-date standards and guidelines for antimicrobial susceptibility testing. The CLSI documents provide guidance on the most-relevant drugs to test and report on specific organisms, quality-control ranges to assure accurate and reproducible results, and interpretive criteria or breakpoints to interpret MICs and disk diffusion zone measurements [10–12].

The most widely used CLSI documents include M2 for performance of disk diffusion tests [11] and M7 for performance of MIC tests [10]. These 2 documents are used with a companion document, M100 [12], which contains the supplemental tables with drugs recommended for testing and reporting, interpretive breakpoints, and quality-control ranges. Both M2 [11] and M7 [10] address testing of common, rapidly growing aerobic bacteria, including staphylococci, enterococci, members of the family Enterobacteriaceae, *Pseudomonas* species, *Acinetobacter* species, *Burkholderia cepacia, Stenotrophomonas maltophilia,* and *Vibrio cholerae.* M2 [11] and M7 [10] also include recommendations for testing of *Haemophilus influenzae, Neisseria gonorrhoeae, Streptococcus* species (including *Streptococcus pneumoniae*), and, most recently, *Neisseria meningitidis.* Since 2001, some limited recommendations have been added for susceptibility testing of potential agents of bioterrorism, including *Bacillus anthracis, Brucella* species, *Burkholderia mallei, Burkholderia pseudomallei, Francisella tularensis,* and *Yersinia pestis* [12]. Another CLSI document, M11 [13], describes agar and broth microdilution MIC tests for anaerobic bacteria.

CLSI METHODS FOR ESTABLISHING BREAKPOINTS

To establish MIC interpretive criteria or breakpoints for new antimicrobial agents, to modify existing breakpoints, or to establish breakpoints for organisms for which breakpoints have not previously existed, 4 types of data have been required, as outlined in a CLSI publication [14]. First, an analysis in performed of the MICs of a particular drug with wild-type bacterial isolates that lack known drug-resistance mechanisms, as well as of the MICs of the drug with strains that contain known drug-resistance mechanisms that affect the particular drug class, to assess the impact of that drug-resistance mechanism. Second, the pharmacokinetics of the drug are examined, including levels achieved in various body fluids and tissues in healthy volunteers and in patients with various types of infections.

In recent years, the CLSI has found pharmacodynamic determinations to be a useful third parameter to consider in establishing breakpoints. The importance of the peak serum level of the drug or the area under the drug-concentration curve (AUC), compared with the drug's MICs, has been recognized with aminoglycosides and fluoroquinolones. In addition, the duration of the period in which the drug levels in serum or other fluids are maintained above a proposed MIC breakpoint ($T > MIC$) is useful with β-lactams and glycopeptides [15]. Mathematical modeling of the likelihood of attaining the desired pharmacodynamic parameters with various drug doses has assisted in the selection of safe interpretive breakpoints [16].

The fourth element in the determination of breakpoints involves a careful review of clinical and bacteriological response data usually collected during large clinical trials of a new agent before its approval by the US Food and Drug Administration. It should be noted, however, that these data are often limited by the design of clinical trials to systematically exclude patients whose isolates are thought to be drug resistant on the basis of prior assumptions from the microbiological and pharmacokinetic data. Moreover, data from large clinical trials are generally not available for reassessment of older drugs when new bacterial drug-resistance mechanisms emerge several years after a drug has been introduced into clinical practice. The process of integrating the 4 types of data in determining breakpoints has been outlined in detail in CLSI document M23-A2 [14].

A NEED FOR ADDITIONAL ANTIMICROBIAL SUSCEPTIBILITY TESTING RECOMMENDATIONS

Despite the comprehensive nature of CLSI documents M2, M7, M11, and M100 [10–13], there were several genera of bacteria that were isolated periodically by clinical microbiology laboratories from human infections for which there were no CLSI recommendations. These included various coryneform bacteria, *Bacillus* species (other than *B. anthracis*), *Abiotrophia* and *Granulicatella* species, and several species of fastidious gram-negative bacteria (e.g., HACEK group organisms and *Pasteurella* species). Very limited information was provided in CLSI documents M2 [11] and M7 [10] for testing *Listeria* species, *Campylobacter jejuni,* and *Campylobacter coli.* The lack of test methods or interpretive criteria for these organisms and the lack of guidance regarding the most important drugs for testing made it difficult to assess the susceptibility of isolates from individual patients and difficult for public health authorities to monitor any emerging drug resistance. This realization led CLSI to examine the incidence of drug resistance and to pursue development of guidelines for antimicrobial susceptibility testing of several infrequently encountered or fastidious bacteria that were not addressed in the previous CLSI documents.

SOME RESISTANCE CONCERNS FOR INFREQUENTLY ISOLATED OR FASTIDIOUS BACTERIA

Resistance in uncommon gram-positive cocci and rods. Notable among the *Corynebacterium* species are *Corynebacterium jeikeium* and *Corynebacterium urealyticum,* both of which have been reported to be multidrug resistant (including resistance to penicillins and cephalosporins, macrolides, and aminoglycosides) and both of which may cause medical device–related infections [17]. *Corynebacterium striatum* may be resistant to macrolides, lincosamides, tetracyclines, and fluoroquinolones [17, 18]. The related genera, *Arcanobacterium* and *Arthrobacter,* can be resistant to fluoroquinolones and aminoglycosides [17], *Brevibacterium* species may have reduced β-lactam susceptibility [19], and *Turicella* may be macrolide and clindamycin resistant [19]. It is not widely known that *Microbacterium resistens* is intrinsically vancomycin resistant [20], and *Leifsonia aquatica* strains have diminished vancomycin susceptibility [19]. *Listeria monocytogenes* is predictably susceptible to penicillin, to ampicillin, and to synergy between those agents and gentamicin, but it is intrinsically cephalosporin resistant [21]. However, alternative agents may be needed for patients who are allergic to or intolerant of the drugs of choice [22].

There are numerous species of *Bacillus* that can cause wound or ocular infections resulting from traumatic inoculations with soil or water. *Bacillus cereus* and *Bacillus thuringiensis* produce 1 or more potent broad-spectrum β-lactamases that affect all penicillins, cephalosporins, and carbapenems [23]. However, *Bacillus* species may be susceptible to other drug classes, including vancomycin, macrolides, fluoroquinolones, or aminoglycosides, that could be used for therapy [24].

There are several uncommon, intrinsically vancomycin-resistant, gram-positive cocci and rods that can cause serious human infections. These include *Leuconostoc, Pediococcus, Erysipelothrix rhusiopathiae,* and many—but not all—species of *Lactobacillus.* Some of these bacteria can, at times, be confused with vancomycin-resistant enterococci [25]. Lactobacilli can cause bacteremia and endocarditis that is difficult to treat because of resistance or marginal susceptibility to penicillins, cephalosporins, and aminoglycosides [26]. Some strains may only be susceptible to carbapenems or newer agents directed against drug-resistant gram-positive bacteria [27, 28]. *Leuconostoc* and *Pediococcus* species are infrequently encountered relatives of the streptococci that are resistant to vancomycin but are usually susceptible to β-lactams, chloramphenicol, tetracyclines, and aminoglycosides [27]. However, resistance to cephalosporins and carbapenems has been reported in *Leuconostoc* species [29].

Isolates previously known as nutritionally-deficient or "satelliting" streptococci have now been placed in 2 new genera: *Abiotrophia* and *Granulicatella.* It is difficult for clinical laboratories to separate these 2 genera by standard biochemical tests; they may simply be reported as *Abiotrophia* or *Granulicatella* species. They have been reported to have diminished susceptibility to penicillin, resulting in poorer response to treatment with penicillin in patients with endocarditis [30]. Fluoroquinolone resistance has been reported in an *Abiotrophia* isolate from a neutropenic patient with cancer [31].

Resistance in less-commonly isolated, nonfastidious gram-negative rods. *Aeromonas* species, *Plesiomonas shigelloides,* and noncholera *Vibrio* species represent less frequently isolated gram-negative rods that have lacked CLSI interpretive criteria, even though they are not fastidious and grow well in or on unsupplemented Mueller-Hinton medium. *Aeromonas* species can produce as many as 3 different β-lactamases, including a carbapenemase [32]. Although it is generally recognized that *Aeromonas* species are resistant to ampicillin, they can have variable susceptibility to cephalosporins [33]. *P. shigelloides* has been transferred to the family Enterobacteriaceae but has not specifically been included in the CLSI M2, M7, and M100 publications [10–12]. *P. shigelloides* isolates produce a β-lactamase that may be weakly expressed under standard test conditions, such that susceptibility to ampicillin is greatly affected by the density of the inoculum used in a susceptibility test [34]. Most of the clinically significant *Vibrio* species, including the so-called halophilic species, grow well in standard Mueller-Hinton medium without additional NaCl. The susceptibility of the different species can vary, particularly with respect to the older penicillins, cephalosporins, and the sulfonamides [35].

Resistance in fastidious gram-negative rods. The HACEK group of fastidious gram-negative bacilli have long been recognized as causative agents of infective endocarditis [36]. As part of the normal oropharyngeal flora, these bacteria can be repeatedly exposed to antimicrobial agents during therapy for various types of infections, leading to the development of drug resistance. *Haemophilus aphrophilus* and *Haemophilus paraphrophilus* are the species most often associated with endocarditis or brain abscesses. *Actinobacillus actinomycetemcomitans* may be resistant to penicillins, macrolides, and aminoglycosides [37]. *Eikenella corrodens* is often implicated in bite-wound infections that may be treated empirically with agents that are active against anaerobes and gram-positive bacteria (e.g., clindamycin) but not *E. corrodens. Cardiobacterium hominis, E. corrodens,* and *Kingella* species may produce β-lactamases that are inhibited by clavulanic acid. These β-lactamases can be readily detected by testing of colonies with nitrocefin [38–40].

Pasteurella species are relatively fastidious gram-negative rods that are most often associated with infected cat or dog bites but can cause pneumonia and bacteremia in immunosuppressed in-

dividuals. *Pasteurella* species may be penicillin resistant because of production of a β-lactamase [41], and they are often not susceptible to oral agents that might be used for empiric therapy of bite wound infections [42, 43]. The β-lactamases in *Pasteurella* species can also be detected by testing with nitrocefin [41].

C. jejuni and *C. coli* cause gastrointestinal infections in both developed and developing countries. In some parts of the world, fluoroquinolone and macrolide resistance occurs in those 2 species, and fluoroquinolone and macrolide resistance is increasing in the United States as well [44–46]. Therefore, it is likely that clinical laboratories will be asked to test individual clinical isolates of *Campylobacter* in the future, and public health laboratories will need to perform surveillance of antimicrobial resistance in human and animal isolates. The CLSI previously described testing conditions for *Campylobacter* species but did not define interpretive breakpoints [12].

***Drug resistance in* Moraxella catarrhalis.** *M. catarrhalis* causes a variety of mild-to-moderate respiratory infections that are often treated with oral antimicrobial agents. Approximately 90% of contemporary isolates produce 1 of 2 relatively weak β-lactamases (BRO-1 and BRO-2) that render them resistant to penicillin and amoxicillin, but these β-lactamases are inhibited by clavulanic acid and do not hydrolyze most expanded- or extended-spectrum cephalosporins to a significant extent [47]. However, *M. catarrhalis,* like *Neisseria* species, are intrinsically resistant to trimethoprim, and infrequent resistance to sulfonamides and tetracyclines has been reported [48, 49].

THE NEW CLSI M45-A GUIDELINE

In response to the recognized need for guidance in performing antimicrobial susceptibility testing of the fastidious or uncommon bacteria described above, the CLSI formed a working group in 2003 to develop a new CLSI document. The document, "Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria," was published as an approved guideline (M45-A) in May 2006 [50] and represents a consensus approach to standardized antimicrobial susceptibility testing of 14 genera, species, or organism groups of uncommon or fastidious bacteria. It includes details of the standardized methodology for testing each organism or organism group, gives reasons for testing or not testing the organisms, lists appropriate quality-control measures, and provides specific interpretive breakpoints. There are 14 separate tables that highlight this information and also provide key drug-resistance concerns, references for deriving the interpretive breakpoints, and several additional testing notes.

M45-A TESTING RECOMMENDATIONS

For all organisms included in M45-A [50], the testing media, incubation conditions, and quality-control procedures are the same standardized methods as those recommended for testing commonly encountered bacteria in CLSI M2, M7, and M100 [10–12]; no exotic test media or test formats have been suggested. Broth microdilution MIC tests are described for all of

Table 1. Summary of infrequently isolated or fastidious bacteria included in Clinical and Laboratory Standards Institute document M45-A [50] and the suggested media for testing.

Organism	Broth microdilution MIC test	Disk diffusion test
Gram positive		
Abiotrophia and *Granulicatella* species	CAMHB and 2.5%–5% LHB and 0.001% pyridoxal HCl	NR
Bacillus species (excluding *Bacillus anthracis*)	CAMHB	NR
Corynebacterium species	CAMHB and 2.5%–5% LHB	NR
Erysipelothrix rhusiopathiae	CAMHB and 2.5%–5% LHB	NR
Lactobacillus species	CAMHB and 2.5%–5% LHB	NR
Leuconostoc species	CAMHB and 2.5%–5% LHB	NR
Listeria monocytogenes	CAMHB and 2.5%–5% LHB	NR
Pediococcus species	CAMHB and 2.5%–5% LHB	NR
Gram negative		
Aeromonas hydrophila complex and *Plesiomonas shigelloides*	CAMHB	MHA
Campylobacter jejuni and *Campylobacter coli*	CAMHB and 2.5%–5% LHB	MHA
HACEK group[a]	CAMHB and 2.5%–5% LHB	NR
Moraxella catarrhalis	CAMHB	NR
Pasteurella species	CAMHB and 2.5%–5% LHB	MHA and 5% SB
Vibrio species (excluding *Vibrio cholerae*)	CAMHB	MHA

NOTE. CAMHB, cation-adjusted Mueller-Hinton broth; LHB, lysed horse blood; MHA, Mueller-Hinton agar; NR, not recommended; SB, sheep blood.

[a] HACEK group includes *Haemophilus aphrophilus, Haemophilus paraphrophilus, Haemophilus segnis, Actinobacillus actinomycetemcomitans, Cardiobacterium* species, *Eikenella corrodens,* and *Kingella* species.

the organisms, incorporating either unsupplemented cation-adjusted Mueller-Hinton broth or cation-adjusted Mueller-Hinton broth supplemented with 2.5%–5% lysed horse blood (table 1). The latter is the same medium recommended for testing of *S. pneumoniae* and other streptococci [12]. The only organisms in M45-A [50] for which disk diffusion testing with some drugs is recommended at present are *Aeromonas, Plesiomonas, Campylobacter, Pasteurella,* and *Vibrio* species (table 1). Recommendations for testing *Aeromonas, Plesiomonas,* and *Vibrio* species, including disk diffusion and MIC breakpoints, are the same as those for testing Enterobacteriaceae, described in CLSI M2, M7, and M100 [10–12].

Use of standard quality-control organisms recommended for tests described in CLSI M2, M7, and M100 [10–12], including *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213 and ATCC 25923, *Escherichia coli* ATCC 25922 and ATCC 35218, and *C. jejuni* ATCC 33560, are used as controls for testing the organisms included in M45-A [50].

DEVELOPING M45-A INTERPRETIVE BREAKPOINTS

As mentioned above, CLSI's standard process for developing interpretive breakpoints is very complex and requires data from testing large numbers of organisms and studying outcomes in significant numbers of human infections. Because of the low frequency of infections due to the organisms included in M45-A [50], and because most of the antimicrobial agents of interest have been marketed for a number of years, it was not possible to adhere to all of the rigorous requirements outlined in CLSI document M23-A2 [14] to establish interpretive breakpoints for these "orphan" organisms. The breakpoints listed in M45-A [50] were derived, in most cases, from breakpoints currently listed in CLSI M100 [12] for more-common species that cause similar types of infections at similar body sites. In a few cases, tests were performed to help establish M45-A [50] breakpoints (e.g., coryneform bacteria, *Bacillus* species, *Pasteurella* species, and the *C. jejuni* and *C. coli* disk diffusion breakpoints). Within each of the 14 organism-group tables of interpretive criteria in M45-A [50], the sources used for the breakpoints are indicated. Thus, the methodology employed in M45-A [50] is well standardized, although the interpretive breakpoints proposed in this "guideline" were not derived using the large data bases normally associated with CLSI standards. The appropriateness of the chosen breakpoints for each organism or organism group was assessed by determining the usual distribution of MICs of wild-type strains and MICs of strains with well-characterized drug-resistance mechanisms reported in the published literature and/or determined by tests performed in the laboratories of several of the working group members. The limited number of publications that were available indicating clinical responses in case reports or case series were scoured for MICs of the drugs associated with success or clinical failures. Where no known drug resistance has been described, a susceptible-only breakpoint was assigned.

APPLICATION OF CLSI M45-A IN A CLINICAL MICROBIOLOGY LABORATORY

It is very important to understand that the provision of this new CLSI guideline does not mean that antimicrobial susceptibility testing should be performed on every clinical isolate for the organisms included in M45-A [50]. The numbers of isolates tested will be low for most of the organisms or organism groups. Exceptions will occur for *Bacillus, Corynebacterium, Lactobacillus,* and *Leuconostoc* species that are often considered to be normal flora. As with other organisms that are indigenous to the skin and mucous membranes, it is imperative to be certain, prior to testing, that a particular isolate among these genera is likely to be clinically significant and not representative of contamination or normal flora.

Although *Aeromonas, Plesiomonas, Campylobacter, Erysipelothrix, Listeria, Moraxella, Pasteurella, Pediococcus,* and *Vibrio* species are more likely to be associated with a pathogenic process, susceptibility testing of these organisms is not always necessary. Even cases of infective endocarditis due to *Abiotrophia* or *Granulicatella* or a HACEK gram-negative rod may often be managed by following recommendations in the medical literature without the results of susceptibility testing.

Consequently, antimicrobial susceptibility testing of organisms addressed in M45-A should "only be undertaken in consultation with infectious diseases or other expert clinicians that can assist in determining if susceptibility testing is needed in the management of a specific patient, and in interpretation of any results generated" [50, p. 5]. This statement is included in bold type in the introductory pages of M45-A [50]. Generally, only isolates involved in serious infections would be tested, and additional considerations for testing would include (1) persistent infection, (2) clinical failure, (3) allergy to or intolerance of the drugs of choice, and (4) possible resistance to a drug that might be prescribed. Testing of the organisms described in M45-A [50] should only be performed by laboratories experienced with the recommended broth microdilution MIC procedures.

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