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M100 (Performance standards for antimicrobial susceptibility testing), annually updated: CLSI's most popular guideline

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Antimicrobial resistance is a growing threat globally. Published reports show increasing numbers of resistant bacteria, a higher proportion of organisms resistant to multiple antimicrobials, and an expanding number of patients harboring organisms resistant to antimicrobials. Infections due to multidrug resistant bacteria are rising, while colonization rates in patients with these antimicrobial-resistant organisms are high. Antimicrobial-resistant organisms are concerning not only for patient care but also for public health. The Subcommittee on Antimicrobial Susceptibility Testing (AST) of the Clinical and Laboratory Standards Institute (CLSI) plays a large role in combatting antimicrobial resistance and supporting stronger antimicrobial stewardship through development of standards and guidelines for laboratory medicine worldwide.

CLSI and Antimicrobial Stewardship: The Clinical and Laboratory Standards Institute (CLSI) is a membership organization that brings together the global laboratory community for a common cause: to foster excellence in laboratory medicine. The mission of CLSI is to develop clinical and laboratory practices and to promote their use worldwide in an effort to lead to quality practices for better health. CLSI documents encompass all areas of the clinical laboratory including microbiology, hematology, chemistry, and so forth. Historically, CLSI was known as the National Committee on Clinical Laboratory Standards (NCCLS). The organization's name was changed to CLSI in 2005 to better capture its purpose and global reach. There are many CLSI committees which develop standards and documents; the Subcommittee on Antimicrobial Susceptibility Testing (AST) is one of those committees. The AST Subcommittee of CLSI (NCCLS) formed in 1969 and is at present a large group of individuals with diverse representation worldwide. The AST Subcommittee evaluates and develops standards and guidelines that promote accurate antimicrobial susceptibility testing and appropriate reporting. The ultimate purpose of this subcommittee is to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care. The AST Subcommittee focuses on AST for bacteria, excluding mycobacteria. CLSI's M100 document *Performance Standards for Antimicrobial Susceptibility Testing* is under the purview of the AST Subcommittee; however, several other documents are also managed by the AST Subcommittee and are listed in the table below.

No.	CLSI Document
M02	Disk diffusion methods (aerobes)
M07	MIC testing methods (aerobes)
M11	MIC testing methods (anaerobes)
M100	Tables (disk and MIC for aerobes and MIC for anaerobes)

M23*	Guidance for setting breakpoints, setting quality control ranges, making recommendations in AST documents
M39*	Antibiograms
M45*	Fastidious organisms

*Guidelines; MIC = minimum inhibitory concentration

The CLSI Consensus Process: Decisions at CLSI are based on the consensus process (i.e., general agreement), and interests amongst various constituencies are balanced. Three types of healthcare constituencies, or factions, are represented within the AST Subcommittee: 1) industry; 2) government; and 3) professions. Representatives from these groups discuss issues and work together to support the mission of the AST Subcommittee. Industry is represented by manufacturers of *in vitro* diagnostic devices or pharmaceuticals, laboratory or hospital information system vendors, suppliers of devices, and clinical research organizations. Government is represented by public health agencies (e.g., the Centers for Disease Control and Prevention [CDC]), regulatory bodies (e.g., Food and Drug Administration [FDA]), and accrediting organizations. Finally, the Professions group is represented by clinical laboratories, research laboratories, healthcare delivery institutions, professional societies, trade organizations, educational institutions, and standards organizations. The AST Subcommittee attempts to maintain balance between the various types of professions, such as clinical microbiologists, infectious diseases clinicians, and infectious diseases pharmacists, to name a few. The AST Subcommittee meetings are open for anyone to attend, and comments and issues from attendees and all users of the documents are encouraged and addressed. Minutes from past meetings of the AST Subcommittee are available publically on the website. CLSI publishes standards and guidelines; both types of documents are developed through the consensus process. A "standard" is a document which clearly identifies specific, essential requirements for materials, methods or practices. Although its use is voluntary, a standards CLSI document should be used in an unmodified form. The M100 is an example of a standards document developed by the AST Subcommittee. A "guideline" document, on the other hand, describes criteria for general operations and is also voluntary. For example, the M45 guideline document, *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*, provides testing and reporting recommendations for certain bacteria which are not included in the M100.

The M100 Standard Document and the Free "eM100": Most laboratories know the M100 document for its guidance on minimum inhibitory concentration (MIC) and disk diffusion criteria for aerobic bacteria, and MIC criteria for anaerobic bacteria. However, the M100 contains a wealth of information beyond simply provision of clinical breakpoints. A bulleted list of the variety of information is provided below.

- Antimicrobials to test and report (tiered testing recommendations)
- Breakpoints for disk and MIC methods for aerobes; MIC for anaerobes
- Screening and confirmatory testing
- Quality control ranges
- Preparation of MIC panels
- Suggestions for confirmatory testing of unusual susceptibility results
- Intrinsic resistance tables
- Quality control strains
- Anaerobe antibiogram
- Description of antimicrobial classes and subclasses
- Description of antimicrobial routes of administration

The M100 document is constantly under scrutiny and review by the AST Subcommittee. M100 is revised annually, and the updated M100 is available in January of each calendar year. The AST Subcommittee meets face-to-face twice per calendar year – once in January and once in June. The annual revision of the M100 begins with the presentation and consideration of data at the January

CLSI meeting during which issues are discussed and may be incorporated into next year's M100 document. Updates and revisions to the M100 made during the January meeting are then reviewed at the June meeting. Revisions accepted from the June meeting are then added to the draft which is prepared for publication in January of the following year. Other M100 formats beyond the traditional paper copy are available through CLSI. The M100 is now offered free of charge electronically – the "eM100" or Free M100 – on the CLSI website as a read-only web version and is available as a quick reference.

2017 M100 Updates and a Preview of Upcoming 2018 Changes: There are several major changes to the 2017 M100 document which will be reviewed. As usual, a complete summary is included in the M100 introductory pages under "Summary of Changes" (p. xiv-xxi in M100 2017). Major changes are listed below.

- Clarification of the terms "breakpoint," "interpretive category," and epidemiologic cutoff values (ECVs)
- Clarification of testing and reporting for colistin and polymyxin B for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- Addition of ECVs for colistin for Enterobacteriaceae
- Addition of ECVs for azithromycin for *Neisseria gonorrhoeae*
- Description and directions of a new method for detection of carbapenemases in Enterobacteriaceae – the modified Carbapenem Inactivation Method (mCIM)
- Deletion of nalidixic acid breakpoints for *Salmonella* spp.
- Clarification of AST for atypical (poorly growing) *Staphylococcus aureus*
- Revised testing recommendations for coagulase-negative staphylococci and oxacillin
- Deletion of tetracycline as intrinsically resistant in *Morganella morganii*

Highlights of the 2017 M100 updates will be discussed in detail in the presentation. The difference between the criteria for establishment of ECVs versus clinical breakpoints, as well as the differences in their clinical applications, will be discussed. In short, ECVs are established only by examination of the distribution, or spread, of MICs, while establishment of clinical breakpoints requires stricter criteria including MIC distribution, clinical correlation data, and pharmacokinetic/ pharmacodynamic data. Another subject of current interest to laboratories is the change in polymyxin testing recommendations, especially in light of increasing resistance to colistin or polymyxin B in gram-negative bacteria across the globe. Colistin disk diffusion breakpoints were eliminated in 2017 for *P. aeruginosa* – the only organism at the time for which colistin disk diffusion breakpoints still existed – due to poor disk performance. In fact, disk diffusion testing and gradient diffusion tests for the polymyxins do not reliably detect resistance for any organisms and should not be used as a method of testing. Furthermore, colistin and polymyxin B breakpoints for the "Other Non-Enterobacteriaceae" group of gram-negatives in Table 2B-5 were removed, and the "Intermediate" category of colistin in *P. aeruginosa* was also removed. ECVs were also established for azithromycin for *N. gonorrhoeae* due to the need to monitor for emerging resistance. Furthermore, the mCIM test was introduced in the 2017 M100 as a screen for carbapenemases in Enterobacteriaceae for epidemiologic or infection control purposes. This test is believed by some laboratories to be more practical than the Carba NP carbapenemase screening test. Continuing with gram-negative bacteria, nalidixic acid disk testing for *Salmonella* spp. as a surrogate test for

fluoroquinolone resistance was eliminated from M100 given the inaccuracies in testing, and other recommendations for such testing were suggested in its place. For gram-positive bacteria, guidance was provided on testing of atypical *S. aureus* strains which are difficult to grow on routine AST media. Such strains may be cultivated from a variety of patient specimens including infected prosthetic joints. Guidelines for testing of atypical *S. aureus* strains include assessing for penicillin binding protein 2a (PBP2a) using induced growth or testing for *mecA* when such isolates do not grow on media suggested by CLSI for AST of staphylococci.

Upcoming changes to the M100 for 2018 include application of the mCIM test to *P. aeruginosa*, removal of the Modified Hodge test from the document, clarification of acceptable colistin testing methodologies, introduction of ceftazidime-avibactam breakpoints for Enterobacteriaceae and *P. aeruginosa*, and grouping of all ECVs in the document into one area.