CLSI Changes for Cephalosporin / *Enterobactericaeae* breakpoints

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By Paul C. Schreckenberger, Ph.D., D(ABMM), F(AMM)

**Changing MIC Breakpoints: Do Mechanisms Count?**

It is argued that treatment outcomes, e.g. for ESBL producers, can be predicted solely from MICs, irrespective of the resistance mechanism. Proponents of this view contend that it is unnecessary for clinical microbiology laboratories to edit susceptibility data on the basis of resistance mechanisms and that these should only be sought, if at all, for purposes of epidemiological surveillance. (1) The inherent danger in this approach is that some resistant pathogens may not be recognized because they are falsely susceptible in routine tests and this can lead to patients receiving ineffective antibiotics resulting in adverse clinical outcomes. Because susceptibility tests may be unreliable, special tests are required to detect the resistance mechanisms involved so that susceptibility reports can be modified for patient safety (2). In January 2010, the CLSI published new breakpoints for some (but not all) of the cephalosporin class of antibiotics. (1) The CLSI Antibiotic Subcommittee recommends that when using the new breakpoints, treatment decisions can be based solely on MICs alone and published the following statement: “When using the new interpretive criteria, routine ESBL testing is no longer necessary before reporting results (e.g. It is no longer necessary to edit results for cepahoporins, aztreonam, or penicillins from susceptible to resistant.” (1). There are several problems inherent with this approach.

1. **Clinical studies show patients with “susceptible” MICs plus ESBL fail therapy.**

   No randomized controlled trials have ever been performed that evaluated the use of various comparator antibiotics in treatment of serious infections due to ESBL-producing organisms. It is unlikely that such studies will ever be performed. Existing data come only from retrospective studies. One such study was reported by Paterson et al. in 2001 and showed that when treatment of ESBL positive organism with a cephalosporin that the laboratory reported as susceptible, 4 of 4 patients failed therapy when the MIC was 8 μg/mL, 2 of 3 failed therapy when the MIC was 4, 1 of 3 failed therapy when the MIC was 2 and 3 of 11 failed therapy when the MIC was ≤ 1. (3) Similar treatment failures were reported by Kim et al in 2002. (4) Karas and colleagues reported treatment failure in a patient with sepsis and pneumonia caused by an ESBL-positive *K. pneumoniae* who was treated with IV cefotaxime based on the laboratory report of susceptible by disk diffusion testing. After two days treatment the patient’s condition deteriorated and an Etest was set up that revealed a cefotaxime MIC of 0.75 μg/mL, which, is below the new CLSI susceptible breakpoint. Therapy with cefotaxime was stopped and the patient was switched to ciprofloxacin. Clinical improvement was noted the next day. The authors’ noted that removal of the central venous catheter did not contribute to resolution of the infection and the patient only improved when cefotaxime was replaced with ciprofloxacin. The authors’ postulated that if an infectious site in a patient has a high concentration of ESBL producing organism (i.e. >10^7 cfu/ml), cephalosporin failure is likely. (5)
2. Inoculum used in broth microdilution (BMD) test (5 x 10^5 cfu/ml) is too low and may dilute out resistant populations giving false susceptible results. Studies by Thomson and Moland showed that when a known ESBL (SHV-3) producing strain of C. freundii was tested by BMD using an inoculum density of 5 x 10^5 cfu/ml the following MICs were obtained: cefotaxime 2, ceftaxidime 1, aztreonam 0.5 and cefepime 0.5 (All Susceptible). When the test was repeated using an inoculum density of 5 x 10^7 cfu/ml the following MICs were obtained: cefotaxime 256, ceftazidime 32, aztreonam 32, and cefepime >1024 (All Resistant). (6) Paterson et al. reported that in two patient that died after receiving cephalosporin monotherapy based on laboratory report of susceptible, the in vitro MICs increased dramatically when a 10-fold increase in inoculum was used. Ceftriaxone MICs went from 8 to >256 μg/ml and cefepime MICs went from 0.5 to 8 μg/ml. (7).

3. Animal studies have also demonstrated an inoculum effect and adverse outcomes when cephalosporins are used to treat ESBL-producing organism with MICs of cephalosporins in the susceptible range. Using the rat intra-abdominal abscess model Rice and colleagues showed that extended spectrum cephalosporins may be less effective in treating serious infections due to ESBL producing bacteria than standard susceptibility tests would imply. Their in vitro studies showed that the activity of these agents against an ESBL producing strain of K. pneumoniae was highly inoculum dependent. They recommended avoiding use of extended spectrum cephalosporins as single agents when treating serious infections with ESBL-producing organisms. (8)

4. Different susceptibility testing methods give varying results. In the 2007 CAP survey D-C 2007 D-19, laboratories were asked to perform susceptibility testing on a C. freundii strain containing a PER-1 ESBL with a reference MIC of 16 μg/ml to cefepime which is considered non-susceptible. Fifteen percent of 311 MicroScan users reported cefepime susceptible (modal MIC >16), 97% of 244 Vitek Legacy users reported cefepime susceptible (modal MIC ≤ 4), 86% of 230 Vitek 2 users reported cefepime susceptible (modal MIC 2), and 34% of 74 disk diffusion users reported cefepime susceptible. (9) These proficiency survey results show that the same isolate tested in various laboratories using different methods can lead to widely disparate results, thus calling to question the reliance on standard susceptibility testing alone as the sole criteria for determining accurate antibiotic susceptibility results.

5. MIC results are not reproducible and can vary up to >3 dilutions upon repeat testing. The published CLSI Table entitled: “Acceptable limits of QC strains used to monitor accuracy of standard susceptibility tests” allows between a 3 and 8 two-fold dilution range when performing QC testing with a defined control organism E. coli ATCC 25922. Results within this 3-8 dilution range are considered to be “in control” when using standardized susceptibility test systems. (CLSI M-100 S20 Table 4) (1) In this imperfect reality an ESBL producer with a cefotaxime MIC of 1 μg/ml (probably responsive to cefotaxime in vivo) cannot be reliably distinguished from one with an MIC of 4 μg/ml (probably not responsive). It is therefore simpler and safer to follow the precautionary approach of screening for ESBLs and if found, reporting the isolate as resistant. (10).

6. Some cephalosporin breakpoints were not lowered enough and others not lowered at all. The breakpoints for 4 antibiotics: cefazolin, cefotaxime, ceftizoxime, and ceftriaxone were lowered by 3 doubling dilutions from ≤ 8 to ≤ 1 μg/ml. Ceftazidime and
Aztreonam were lowered by only one doubling dilution from \( \leq 8 \) to \( \leq 4 \) \( \mu g/ml \), and the breakpoints for 4 antibiotics were not revised: cefuroxime, cefepime, cefotetan and cefoxitin. As a result some ESBL-producing isolates will test resistant to all extended-spectrum cephalosporins, some will test non-susceptible to some (those whose breakpoints were lowered to \( \leq 1 \) \( \mu g/ml \)) and susceptible to others (those whose breakpoints were not changed or changed only by a single dilution). Note that the epidemiologic cut-off values for the wild type strains of Enterobacteriaceae are \( \leq 0.5 \) for most species with the cephalosporin antibiotics. That means that strains with extended spectrum cephalosporin MICs >1 have acquired some mechanism of antibiotic resistance. It would have made more sense to lower the susceptible breakpoints to \( \leq 1 \) for ceftazidime, aztreonam and cefepime so that organism’s possessing ESBLs would test non-susceptible to these drugs as well. This is the approach that was taken by EUCAST (European Committee for Antimicrobial Susceptibility Testing) and would truly have nearly eliminated the confusion of reporting some cephalosporins susceptible and others non-susceptible.

ESBL enzymes have preferred substrates and laboratories may miss ESBL resistance if they are not testing the preferred antibiotic substrate and are not performing ESBL confirmatory testing. CTX-M ESBLs are rapidly becoming the predominant ESBL in the United States. These ESBLs preferentially hydrolyze cefotaxime and spare ceftazidime. Laboratories that do not routinely test cefotaxime and discontinue ESBL confirmatory testing will fail to recognize CTX-M ESBLs and this may lead spread of this resistance gene to other organisms and other patients.

In conclusion, I urge all laboratories to continue testing and confirming ESBLs in all species of Enterobacteriaceae. When ESBLs are confirmed all penicillins, cephalosporins and aztreonam should be reported as resistant. Combining the use of the lower MIC breakpoints with ESBL confirmation testing gives the laboratory the best chance of getting the result right for the patient. There is no compelling reason to tell any laboratory that it is better to stop performing ESBL testing. As a laboratory director I am bound by law to implement methods of testing that assure the quality of every result that leaves the laboratory. In this regard the best way to do that is to combine the use of lower breakpoints with ESBL confirmatory testing and when ESBL are confirmed, change all cephalosporin antibiotics to resistant.

References


