RESEARCH BRIEF

Extended-Spectrum β-Lactamase Producers Reported as Susceptible to Piperacillin-Tazobactam, Cefepime, and Cefuroxime in the Era of Lowered Breakpoints and No Confirmatory Tests

Extended-spectrum β-lactamase (ESBL) production, most commonly among Enterobacteriaceae, is associated with serious infections.[1] Until 2009, the Clinical and Laboratory Standards Institute (CLSI) recommended confirmatory testing for ESBL production.[2] When ESBL producers have been treated with penicillins (including piperacillin-tazobactam), cephalosporins (including cefepime), or aztreonam, despite the fact that the in vitro minimum inhibitory concentration (MIC) was in the susceptible range, outcomes have been unfavorable,[1,3] although data are conflicting.[4,5] In part because of this discrepancy between in vivo efficacy and in vitro MICs in the setting of serious ESBL-producing infections, the CLSI historically recommended that once an isolate has been confirmed as an ESBL producer, all penicillins, cephalosporins, and aztreonam should be reported as being resistant. Although no such recommendation was made for piperacillin-tazobactam and other β-lactam/β-lactamase inhibitors, many institutions, on the basis of expert opinion, reported those agents as resistant.

In 2010, the CLSI lowered the susceptibility breakpoints of some cephalosporins and aztreonam and stated that ESBL detection was no longer necessary.[6] These recommendations were made in an effort to eliminate ESBL screening and confirmation, thus decreasing the workload in clinical microbiology laboratories. The rationale behind these changes in breakpoints and ESBL testing recommendations included (1) the inference that these antimicrobials had pharmacokinetic/pharmacodynamic properties that made them effective against "low MIC" organisms, regardless of ESBL production;[6,7] (2) the occurrence of false-negative ESBL confirmatory tests in the presence of other β-lactamases, such as AmpC-type enzymes;[6,7] and (3) analyses showing that lowering the threshold for these specific drugs would label most ESBL producers as cephalosporin/penicillin resistant, thus eliminating the therapeutic need for ESBL confirmatory tests.[7] Recent publications, however, have reported relatively high rates of ESBL production among isolates that are categorized as susceptible per new CLSI breakpoints.[8]

The MIC breakpoints for some β-lactams (ie, piperacillin-tazobactam, cefepime, and cefuroxime) were not lowered by the CLSI in 2010, despite the fact that treatment failures have occurred with these agents in infections due to ESBL-producing pathogens that displayed in vitro susceptibility to these agents, presumably because of the "inoculum effect." According to a recent Brazilian report, 25% of ESBL-producing isolates (CTX-M type) were susceptible to cefepime.[9] Thus, if the 2010 CLSI recommendations were followed, clinicians would be unaware that a cefepime-susceptible organism was an ESBL producer and that cefepime therapy might be suboptimal.

The aim of this study was to analyze the susceptibility patterns of piperacillin-tazobactam, cefepime, and cefuroxime—the 3 agents for which the CLSI has not lowered the breakpoints—among ESBL-producing organisms and evaluate the impact that new testing guidelines might have on patient therapy.

This study was conducted at Detroit Medical Center, an 8-hospital healthcare system in metropolitan Detroit that has more than 2,200 inpatient beds. For 2009, all unique-patient ESBL-positive cultures of *Escherichia coli* and *Klebsiella pneumoniae* were analyzed. Species identification, susceptibility testing, and ESBL phenotypic tests were conducted by Microscan (Siemens), an automated broth microdilution system, according to 2009 CLSI criteria.[2] Selected isolates were confirmed by the disc diffusion ESBL test.[2] Exemption from approval was granted by the Wayne State University Institutional Review Board. All statistical analyses were performed using SPSS (PASW version 18.0; 2010).

There were 659 *E. coli* and 552 *K. pneumoniae* ESBL-positive organisms identified in unique patients during the study period. Of all isolates, 650 were from urine, 131 were from blood, 136 were respiratory, 6 were from cerebrospinal fluid, and 288 were from wounds or other tissues. Ninety-five percent of ESBL-producing strains of *E. coli* tested susceptible to piperacillin-tazobactam, 18% tested susceptible to cefepime, and 8 (1%) tested susceptible to cefuroxime (Table 1). Among ESBL-producing strains of *K. pneumoniae*, 38% tested susceptible to piperacillin-tazobactam, 18% tested susceptible to cefepime, and 2% tested susceptible to cefuroxime. Even when a lower breakpoint of 16 μg/mL for piperacillin-tazobactam was used, as has been suggested by some investigators, 88% of *E. coli* and 26% of *K. pneumoniae* tested susceptible (Table 1).

Most ESBL-producing *E. coli* and a large portion of ESBL-producing *K. pneumoniae* strains were susceptible to piperacillin-tazobactam in this study, and approximately 20% of ESBL producers demonstrated in vitro susceptibility to cefepime.[6] This is worrisome, since historically piperacillin-tazobactam and cefepime have been shown to be inferior to carbapenems for the treatment of invasive infections due to susceptible ESBL-producing pathogens.[3]

A recent study concluded that β-lactam/β-lactamase inhibitor combinations (including piperacillin-tazobactam) might be a legitimate option for bloodstream infections due to ESBL-producing *E. coli*.[5] There were several limitations of this study.[5] The majority of patients had urinary tract infec-

TABLE 1. Susceptibility Ranges of Extended-Spectrum β-Lactamase–Producing *Escherichia coli* and *Klebsiella pneumoniae* to Piperacillin-Tazobactam, Cefepime, and Cefuroxime, Detroit, Michigan, 2009

	MIC					MIC_{50}, μg/mL	MIC_{90}, μg/mL
	≤8 μg/mL	16 μg/mL	32 μg/mL	64 μg/mL	≥128 μg/mL		
Piperacillin-tazobactam							
E. coli	527 (80)	53 (8)	20 (3)	26 (4)	33 (5)	≤8	≤32
K. pneumoniae	116 (21)	28 (5)	11 (2)	55 (10)	332 (62)	≥128	≥128
	1 μg/mL	4 μg/mL	8 μg/mL	16 μg/mL	32 μg/mL		
Cefepime							
E. coli	13 (2)	99 (15)	7 (1)	26 (4)	513 (78)	≥32	≥32
K. pneumoniae	17 (3)	66 (12)	17 (3)	72 (13)	381 (69)	≥32	≥32
Cefuroxime							
E. coli	6 (1)	1 (0.2)	1 (0.2)	6 (1)	645 (98)	≥32	≥32
K. pneumoniae	7 (1)	0	7 (1)	13 (2)	632 (96)	≥32	≥32

NOTE. Data are no. (%) of organisms, unless otherwise indicated. MIC, minimum inhibitory concentration.

tions. In urinary tract infections, the β-lactamase inhibitor achieves high urinary concentrations, and it might be reasonable to assume that these combination antimicrobials might be effective in treating ESBL-producing infections arising from a urinary source.[10] However, with pneumonia and bacteremia from a nonurinary source, where the β-lactamase inhibitor component achieves lower concentrations, data do not support the superiority of β-lactam/β-lactamase inhibitor combinations over carbapenems.[11]

It is concerning that at hospitals where ESBL testing is no longer performed physicians might provide suboptimal therapy for a life-threatening infection based on misleading in vitro susceptibility reports. In addition, halting testing for the presence of ESBLs would interfere with the routine monitoring of the local and global epidemiological trends of these resistance enzymes. We hope that the CLSI reinstitutes recommendations for ESBL screening and confirmatory testing, particularly in scenarios where testing might impact the interpretation of in vitro susceptibilities to cefepime or piperacillin-tazobactam.

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