JAC Antimicrob Resist
doi:10.1093/jacamr/dlab035

JAC-Antimicrobial Resistance

Should ceftriaxone-resistant Enterobacterales be tested for ESBLs? A PRO/CON debate

Maria Virginia Villegas[1]*, German Esparza[2] and Jinnethe Reyes[3]

[1]*Grupo de resistencia antimicrobiana RAEH, Universidad El Bosque, Bogota, Colombia;* [2]*Programa de proeficiencia en microbiología, PROASECAL SAS, Bogota, Colombia;* [3]*Molecular Genetics and Antimicrobial Resistance Unit, International Center for Microbial Genomics, Universidad El Bosque, Bogota, Colombia*

*Corresponding author. E-mail: mariavirginia.villegas@gmail.com

ESBLs are a group of plasmid-mediated, diverse, complex and rapidly evolving enzymes that pose a therapeutic challenge today in hospital- and community-acquired infections. Thirty-six years after the first report, diagnostic and therapeutic approaches for ESBLs are still the subject of controversy. Detection of these enzymes is recommended for epidemiological purposes and facilitates targeted therapy, necessary for antimicrobial stewardship. On the other hand, ESBLs are not confined to specific species, phenotypic detection methods have pitfalls, and concerns exist about the accuracy of antimicrobial susceptibility testing systems to rely on MIC values for cephalosporins and β-lactam combination agents. In this issue, we present a PRO/CON debate on ESBL testing for ceftriaxone-non-susceptible Enterobacterales.

There is no consensus on the precise definition of ESBLs. In a review by Paterson and Bonomo,[1] they cite a general working definition in which these enzymes confer resistance to penicillins, monobactams and cephalosporins except cephamycins (although their degree of hydrolysis may vary greatly), are inhibited *in vitro* by clavulanic acid and tazobactam and remain susceptible to carbapenems. Despite ESBLs having been known for almost 40 years, controversy still exists for diagnostic and therapeutic approaches.[2] CLSI initially recommended ESBL detection for only *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca* and *Proteus mirabilis* that test non-susceptible to third-generation cephalosporins, and reporting rules stated that all cephalosporin results should be interpreted as resistant. In 2010, CLSI updated and lowered the susceptibility breakpoints for ceftizoxime, ceftriaxone and cefotaxime from 8 mg/L to 1 mg/L and for ceftazidime and aztreonam from 8 mg/L to 4 mg/L, detecting ESBL production only for epidemiological purposes while keeping cephalosporin results as tested.[3] Data coming from clinical, pharmacokinetic (PK)/pharmacodynamic (PD) models and MIC distributions were considered in revising the breakpoints, however, there were some limitations as information concerning MIC, concomitant drug treatment, site of infection and cephalosporin dosage regimen was not always available to predict outcomes.[4] Of note, CLSI has no recommendations for testing and reporting ESBLs for β-lactam combination agents like piperacillin/tazobactam. On the other hand, many clinical laboratories are still performing ESBL testing with automated systems (e.g. Vitek 2) not using the current CLSI cephalosporin breakpoints.[5] There are still gaps regarding how to test for co-production of enzymes (e.g. ESBL and AmpC), how accurate the MIC is for predicting the clinical outcome and how carbapenems can be used appropriately. In this issue, we have invited international thought leaders for a PRO/CON debate regarding the impact of testing for ESBL production for ceftriaxone-non-susceptible Enterobacterales.

Tamma and Humphries[6] point out that using ceftriaxone-non-susceptible Enterobacterales as the main diagnostic approach is inaccurate, encourages carbapenem overuse, ignores the potential for ESBL production in other species and promotes the silent epidemic of ESBL transmission.[7]

Conversely, Mathers and Lewis[8] argue that phenotypic testing for Enterobacterales harbouring ESBLs does not add to accurate *in vitro* β-lactam MICs for clinical decision-making and may be problematic because of inaccuracies when multiple classes of β-lactamases are produced by the same organism, thus limiting the testing application to specific species and resistance types.[9,10]

The clinical impact of ESBL-producing bacteria has been clearly linked to poor outcomes when patients are treated with cephalosporins or piperacillin/tazobactam reported as susceptible *in vitro*; also, we have to keep in mind that there is a dramatic rise of MIC for extended-spectrum cephalosporins as the inoculum increases (for example, intra-abdominal abscess and pneumonia or body sites with difficult drug penetration like lung, central nervous system or bone) beyond that used in routine susceptibility tests. The same isolates may test susceptible at the standard inoculum and resistant at a higher inoculum.[11] Clinical failures even when the MIC result are below the breakpoint has been reported. According to IDSA, carbapenems are the preferred drugs for moderate to

severe ESBL infections and they advise against using cefepime and piperacillin/tazobactam. The recommendation for laboratories not performing ESBL phenotypic testing is to use a ceftriaxone MIC $\geq$2 mg/L as a proxy for ESBL production by *E. coli*, *K. pneumoniae*, *K. oxytoca* or *P. mirabilis* and to use caution when interpreting phenotypic ESBL tests.[12] Combining molecular detection and accurate MIC results for cephalosporins and β-lactam/β-lactamase inhibitor combination agents helps in choosing the appropriate therapy as well as implementing epidemiological precautions for ESBL-producing Enterobacterales. As mentioned by the authors in the debate, the accuracy of antimicrobial susceptibility testing to suspect or confirm ESBLs is far from being perfect. Clinical laboratories are not able to implement the standard broth microdilution for routine testing and instead are using commercial antimicrobial susceptibility testing methods with different performances. Furthermore, MIC accuracy depends on inoculum, antibiotic dilutions, enzyme expression and bacterial heterogeneous populations, among others. Henderson *et al.*[13] found poor reliability in susceptibility testing performance for piperacillin/tazobactam results with automated systems and even with disc diffusion using a subset of strains from the MERINO trial. On the other hand, molecular platforms will detect ESBL genes from bacterial colonies or directly from clinical samples like blood or respiratory secretions, which will provide rapid and accurate results for therapeutic and epidemiological decisions. Detection of ESBLs provides valuable information beyond infection prevention and will contribute to antimicrobial stewardship. For example, plasmids harbouring ESBLs may also harbour virulence factors and other antibiotic resistance determinants. Additionally, accurate detection of *K. pneumoniae* carbapenemases (KPCs) may help identify those that give a false positive ESBL test, as well as carbapenemases that escape from MIC screening. Besides, some mutant KPCs may behave like classic ESBL enzymes enforcing the need for molecular detection.[14] Detecting ESBLs has clinical, epidemiological and therapeutic implications, making this decision a complex issue, for which we invite you to read the arguments on both sides of the debate.

Transparency declarations

M.V.V. reports receiving grants and honorarium from Merck, Pfizer and West. G.E. reports receiving speaker honoraria and advisory board from Merck, Pfizer and bioMérieux. J.R. has none to declare.

References

1 Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol Rev* 2005; **18**: 657–86.

2 Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β-lactamase producing Enterobacterales infections: an update. *Infect Dis Clin North Am* 2020; **34**: 677–708.

3 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Thirtieth Edition: M100*. 2020.

4 Dudley MN, Ambrose PG, Bhavnani SM *et al*. Background and rationale for revised clinical and laboratory standards institute interpretive criteria (breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and aztreonam. *Clin Infect Dis* 2013; **56**: 1301–9.

5 McKinnell JA, Bhaurla S, Marquez-Sung P *et al*. Public health efforts can impact adoption of current susceptibility breakpoints, but closer attention from regulatory bodies is needed. *J Clin Microbiol* 2019; **57**: e01488–18.

6 Tamma PD, Humphries RM. PRO: Testing for ESBL production is necessary for ceftriaxone-non-susceptible Enterobacterales: perfect should not be the enemy of progress. *JAC Antimicrob Resist* 2021; **3**: dlab019.

7 Tamma PD, Cosgrove SE, Avdic E *et al*. Reporting extended-spectrum β-lactamase positivity may reduce carbapenem overuse. *Open Forum Infect Dis* 2019; **6**: ofz064.

8 Mathers AJ, Lewis JS. II,. CON: Testing for ESBL production is unnecessary for ceftriaxone-resistant Enterobacterales. *JAC Antimicrob Resist* 2021; **3**: dlab020.

9 Robberts FJ, Kohner PC, Patel R. Unreliable extended-spectrum β-lactamase detection in the presence of plasmid-mediated AmpC in *Escherichia coli* clinical isolates. *J Clin Microbiol* 2009; **47**: 358–61.

10 Poulou A, Grivakou E, Vrioni G *et al*. Modified CLSI extended-spectrum β-lactamase (ESBL) confirmatory test for phenotypic detection of ESBLs among Enterobacteriaceae producing various β-lactamases. *J Clin Microbiol* 2014; **52**: 1483–9.

11 Docobo-Perez F, Lopez-Cerero L, Lopez-Rojas R *et al*. Inoculum effect on the efficacies of amoxicillin-clavulanate, piperacillin-tazobactam, and imipenem against extended-spectrum β-lactamase (ESBL)-producing and non-ESBL-producing *Escherichia coli* in an experimental murine sepsis model. *Antimicrob Agents Chemother* 2013; **57**: 2109–13.

12 Tamma PD, Aitken SL, Bonomo RA *et al*. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). *Clin Infect Dis* 2020; doi: 10.1093/cid/ciaa1478.

13 Henderson A, Paterson DL, Chatfield MD *et al*. Association between minimum inhibitory concentration, β-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. *Clin Infect Dis* 2020; doi:10.1093/cid/ciaa1479.

14 Haidar G, Clancy CJ, Shields RK *et al*. Mutations in *bla* (KPC-3) that confer ceftazidime-avibactam resistance encode novel KPC-3 variants that function as extended-spectrum β-lactamases. *Antimicrob Agents Chemother* 2017; **61**: e02534–16.