HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2017 December 18.

Published in final edited form as:

Clin Infect Dis. 2015 January 01; 60(1): 162–163. doi:10.1093/cid/ciu743.

Elevated Staphylococcus Ceftriaxone MICs are an Etest Artifact

Brandi M. Limbago[1], **Virginia M. Pierce**[2], **David R. Lonsway**[1], and **Mary Jane Ferraro**[2]

[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

[2]Massachusetts General Hospital and Harvard Medical School, Boston

To the Editor

The recent publication by Pickering et al [1] described a collection of methicillin-susceptible *Staphylococcus aureus* (MSSA) that displayed elevated ceftriaxone minimum inhibitory concentrations (MICs) when tested by Etest (bioMerieux, Durham, North Carolina) gradient diffusion and would have been called “Resistant” to ceftriaxone based on previous Clinical and Laboratory Standards Institute (CLSI) interpretive guidance. The authors reported that approximately 60% of MSSA tested at their institution would have been misclassified based on the current CLSI guidance, which recommends testing staphylococci only against penicillin and oxacillin or cefoxitin in order to infer susceptibility or resistance to other β-lactam agents. This article was available electronically ahead of print for several months. Although it was subsequently retracted as “an honest error in interpretation,” we believe a fuller explanation of the findings could improve understanding among *Clinical Infectious Diseases* readership.

We investigated the accuracy of the initial report by performing reference broth microdilution (BMD), disk diffusion, and Etest [both low (0.002–32 μg/mL) and high (0.016–256 μg/mL) range ceftriaxone Etest products] antimicrobial susceptibility testing on 8 pulsed field gel electrophoresis (PFGE)-matched pairs of MSSA from the Pickering study [1] reported to have mismatched ceftriaxone susceptibility. All 16 isolates were confirmed as oxacillin, cefoxitin, and ceftriaxone susceptible [2, 3] with BMD and disk methods. Ceftriaxone MICs obtained by both Etest products were typically higher than those obtained with BMD but were still in the susceptible range for 100% of isolates using the high concentration ceftriaxone Etest, and for 93.8% of isolates using the low concentration ceftriaxone Etest (1 isolate tested as intermediate). In addition, 30 consecutive, unique MSSA isolated from blood cultures during 2 months at a single hospital were tested against ceftriaxone byBMD, disk diffusion, and Etest using a single 0.5 McFarland inoculum. All isolates tested ceftriaxone susceptible by disk diffusion and BMD; 13 (43%) isolates tested

Correspondence: Brandi M. Limbago, PhD, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS C-16, Atlanta, GA 30329 (BBL7@cdc.gov).

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Potential conflicts of interest. All other authors report no potential conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

nonsusceptible with Etest (Table 1). We also note that the Etest ceftriaxone package inserts do not list staphylococci as an organism group for which testing has been cleared [4, 5].

In summary, it appears that the ceftriaxone resistance reported in error by Pickering et al is an artifact of inappropriate testing rather than an error in interpretation, which was apparent when reference methods were used to confirm the original findings. This report created considerable angst among the infectious disease community and will require ongoing education to dispel its conclusions. This should serve as a reminder that reports of novel antimicrobial resistance should be confirmed by a reference method prior to publication, and that antimicrobial susceptibility testing should only be performed with validated methods.

Acknowledgments

The authors thank Dr Rahman Hariri, University of Pittsburgh Medical Center Mercy for kindly providing 16 isolates for testing.

B. L. has received institutional funding for travel to meetings from CLSI.

References

1. Pickering AJ, Hariri R, Harrison LH, et al. Common occurrence of ceftriaxone-resistant, methicillin-sensitive *Staphylococcus aureus* at a community teaching hospital. Clin Infect Dis. 2014; 59:e72.
2. Clinical and Laboratory Standards Institute. M100-S22. Performance Standards for Antimicrobial Susceptibility Testing. Wayne, PA: Twenty-second Informational Supplement Clinical and Laboratory Standards Institute; 2012.
3. Clinical and Laboratory Standards Institute. M100-S24. Performance Standards for Antimicrobial Susceptibility Testing. Wayne, PA: Twenty-fourth Informational Supplement. Clinical and Laboratory Standards Institute; 2014.
4. BioMerieux. Antimicrobial agents and indications for use. Durham, NC: bioMerieux; 2011.
5. BioMerieux. Etest Ceftriaxone package insert. Durham, NC: bioMerieux; 2010.

Table 1

Ceftriaxone MIC of 30 Methicillin-susceptible *S. aureus* Tested by Broth Microdilution (BMD) or Etest

	Ceftriaxone MIC Obtained	
	BMD	**Etest**
N (%) susceptible	30 (100)	17 (53)
Mode MIC (μg/mL)	4	8
Median MIC (μg/mL)	4	8
MIC_{50} (μg/mL)	4	8
MIC_{90} (μg/mL)	4	16

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration; *S. aureus, Staphylococcus aureus*.