MSSA and Ceftriaxone Etest issue: CLSI & ASM White Paper

- A recent paper (Pickering, et. al.) published in CID stating that MSSA isolates were 60% resistant to ceftriaxone HAS BEEN RETRACTED with little explanation
- The ceftriaxone Etest is not FDA-cleared for testing against staphylococci, and will overcall resistance in MSSA if used
- There is a need for reference confirmatory testing of any new resistance seen before it is published
- Current CLSI M100 guidance stating that oxacillin (cefoxitin) testing can be used for predicting the susceptibility of staphylococci to ceftriaxone can and should be used

A recent paper by Pickering, *et al*[1], published electronically ahead of print by Clinical Infectious Diseases has been RETRACTED. The paper, entitled "Common Occurrence of Ceftriaxone-Resistant, Methicillin-Sensitive *Staphylococcus aureus* at a Community Teaching Hospital," reported that although the rate of ceftriaxone resistance in methicillin-susceptible *S.aureus* (MSSA) in the literature is ~3%, approximately 60% of MSSA isolates at their institution tested non-susceptible to ceftriaxone. The authors went on to state that ceftriaxone susceptibility cannot be predicted by testing oxacillin (cefoxitin) as recommended in the CLSI M100-S23 document[2], stating that all of their study isolates demonstrated MICs to oxacillin of ≤0.5μg/mL. They concluded that MSSA isolates should be tested for susceptibility to ceftriaxone before this agent is used for treatment of serious infections with MSSA.

The data presented in that study were obtained using Etest Ceftriaxone strips, which are not FDA-cleared for testing of staphylococci. Furthermore, the ceftriaxone MIC values obtained by Etest were not confirmed with a reference method. Therefore, additional studies were conducted to investigate the findings in the Pickering, *et al*.[1] report.

The Centers for Disease Control and Prevention (CDC) acquired 16 MSSA isolates from the Pickering study representing eight pairs of PFGE-indistinguishable but ceftriaxone discordant MSSA. These isolates were tested at CDC using reference broth microdilution (BMD) and disk diffusion, and also with two different Etests with ceftriaxone concentrations from 0.002–32μg/mL and from 0.06–256μg/mL. Although there are no current CLSI interpretive criteria for ceftriaxone with the staphylococci, the 2012 CLSI M100 breakpoint for susceptible was ≤8μg/mL[3] and the FDA susceptible breakpoint for ceftriaxone with staphylococci is ≤4μg/mL (ref).

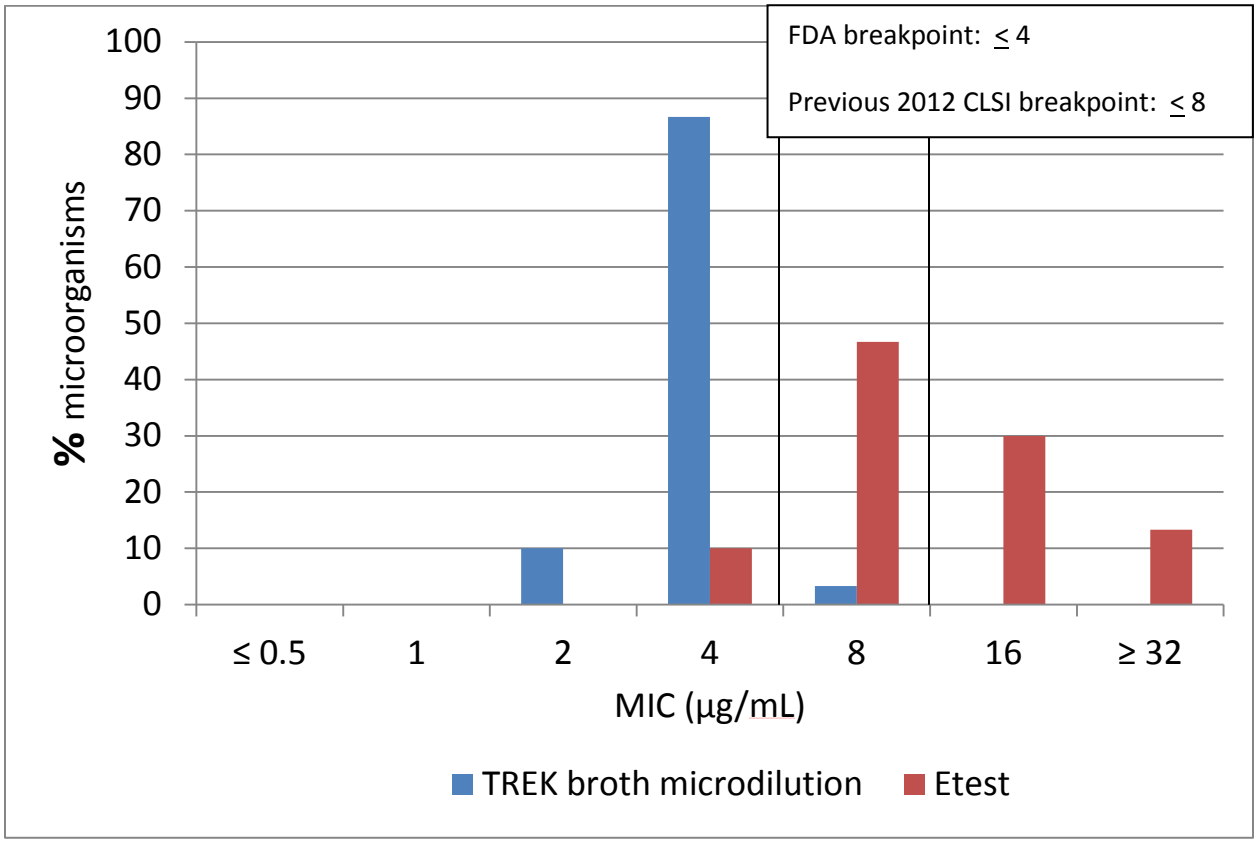
All of the isolates tested ceftriaxone susceptible by both BMD (MIC range 2–4μg/mL) and disk diffusion (DD) (zone range 22–27mm). Ceftriaxone MICs obtained with Etest were generally higher than those obtained with BMD, and the Etest with lower range of ceftriaxone concentrations yielded an MIC of 12μg/mL (Intermediate) for one isolate.

In addition, the microbiology laboratory at Massachusetts General Hospital (MGH) did additional studies with 30 unique, consecutive MSSA recovered from blood stream infections in their patient population (personal communication, Virginia M. Pierce and Mary Jane Ferraro, MGH Microbiology Laboratory). These MSSA isolates were tested against ceftriaxone by Vitek 2, Etest and Trek BMD,

and were also tested by cefoxitin DD, and oxacillin and cefazolin BMD. All 30 isolates were confirmed as MSSA by cefoxitin, and oxacillin, all tested cefazolin susceptible using 2012 CLSI breakpoints[3]. Ceftriaxone testing showed all isolates to have MICs of either 2 (3 isolates), 4 (26 isolates), or 8µg/ml (1 isolate) when tested by BMD; however, when tested by Etest these isolates had MICs of 4 (3 isolates), 8 (14 isolates), 16 (9 isolates) or ≥32µg/ml (4 isolates) (Figure 1). In addition, all isolates were susceptible to ceftriaxone by DD using the 2012 CLSI M100 guidelines[3].

Thus, the Etest showed many major errors as compared to BMD testing and should not be used to test staphylococci to ceftriaxone. It should be pointed out again that the ceftriaxone Etest is not FDA-cleared for testing against *Staphylococcus* isolates in the United States.

Figure 1



Legend: Ceftriaxone MIC testing results for BMD and Etest against MSSA isolates.

References

1. "Common Occurrence of Ceftriaxone-Resistant, Methicillin-Sensitive *Staphylococcus aureus* at a Community Teaching Hospital" by Aaron J. Pickering, Rahman Hariri, Lee H. Harrison, Jane W. Marsh, Amatullah Tasneem, Henry Freedy, Laura Wilson, and Hector Bonilla. [Clin Infect Dis. (2014), doi:10.1093/cid/ciu149]. **Due to an honest error in the interpretation of a key lab test by the study microbiologist, with approval of all authors cited above, the authors are retracting this article from Clinical Infectious Diseases.** http://cid.oxfordjournals.org/content/early/2014/05/14/cid.ciu149.full.pdf+html?sid=72ba99b7-bc90-44e8-9bfb-47e001abc409
2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical and Laboratory Standard Institute; 2013.
3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-second Informational Supplement. CLSI document M100-S22. Wayne, PA: Clinical and Laboratory Standard Institute; 2012.