Correlation of reference agar dilution MIC values and Kirby-Bauer disk diffusion testing for fosfomycin against Gram-positive and Gram-negative bacteria

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Background: Intravenous ZTI-01 (fosfomycin; FOS) is under US development to treat hospitalized patients with complicated urinary tract infections (cUTI). FOS is an active bactericidal agent that targets early cell wall synthesis inhibition and has *in vitro* activity against Gram-negative (GN) and -positive (GP) bacteria, including MDR organisms. CLSI interpretive criteria, based on the oral formulation, exist only for urinary tract isolates of *Enterococcus faecalis* (EF) and *Escherichia coli* (EC) for agar dilution (AD; 25 µg/mL glucose-6-phosphate [G6P] supplementation) and disk diffusion (DD) methods.

Methods: A total of 938 GN and GP isolates collected in US medical centers were tested against FOS by AD (25 µg/mL [G6P] supplementation) and DD (FOS, 200 µg/50 µg G6P). Interpretive discrepancy rates occurring between disk diffusion results and MIC values were calculated. For analysis purposes, the current CLSI interpretive criteria for EF/EC were applied to all organism groups. No major (ME) or very major (VME) errors occurred when applying interpretive criteria to test results of *Staphylococcus aureus* and coagulase-negative staphylococci. Minor errors (MIE) for coagulase-negative staphylococci were 12.5% in the I+1 to I-1 range; 2.9% MIE overall. For EF, there were no ME/VME and 2.6% MIE (I+1 to I-1); 1.5% MIE overall. ME of 3.9% and 27.5% MIE occurred in the I+1 to I-1 range for *E. faecium*; 3.5 and 24.1% overall. Error rates were high for β-hemolytic streptococci at 23.8% ME and 23.8% MIE overall. The ME rate and MIE rates for Enterobacteriaceae were 10% (1/10) and 30% (3/10) for the I+1 to I-1 range; total error rates were 0.28 and 2.0%, respectively. EC had no ME/VME and only one MIE (0.9%). Error rates were high for *Pseudomonas aeruginosa* (PA) and *Acinetobacter baumannii* (AB).

Conclusions: The current CLSI MIC and DD interpretive criteria for EC and EF performed well in the correlation of MIC and disk zone diameters. Other enterics and the staphylococci also performed well in the correlation when applying CLSI breakpoints for EC/EF. β-hemolytic streptococci, PA and AB did not perform well. The adequacy of breakpoints to be used for FOS, currently being studied at a dose of 6g q 8hr, will need to account for the significantly higher plasma and urine concentrations obtained after IV administration compared to the approved 3g oral dosage with limited bioavailability. Results from the Phase 2/3 cUTI trial including correlation of MIC and DD testing results will be important in determining the appropriateness of the FDA current breakpoints.

Character count: 2129 (2200 allowed)

Key words: fosfomycin, Enterobacteriaceae, disk diffusion

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