

Contemporary doxycycline and tetracycline susceptibility testing using CLSI and EUCAST criteria for Gram-positive pathogens: results from SENTRY programme

R. Jones*, M. Stilwell (North Liberty, US)

Objectives: To assess the potency and intermethod agreement for doxycycline (DOXY) and tetracycline (TETRA) susceptibility (S) testing breakpoints when tested against SENTRY Antimicrobial Surveillance Program isolates of Gram-positive species (13,188 isolates) collected worldwide. **Methods:** All organisms were cultured in 2010 with S testing by CLSI M07-A9 (2009) methods and results interpreted by CLSI M100-S11 (2011) and EUCAST (2011) criteria for TETRA and DOXY. A total of 9,012 *S. aureus* (SA; 44.9% MRSA); 2,325 *S. pneumoniae* (SPN); and 1,851 beta-haemolytic streptococci (BHS; 42.8% *S. pyogenes* [SPYO]) were analyzed for S and cross-S rates by the two international breakpoint sets. The tetracycline's S breakpoint MIC (mg/L) criteria differ (CLSI/EUCAST, respectively) as follows: for SA ($\leq 4/\leq 1$), for SPN ($\leq 2/\leq 1$) and for BHS ($\leq 2/\leq 1$). All quality control tests were within published CLSI ranges. **Results:** S rates for DOXY were consistently greater than TETRA for each interpretive criteria used and for each pathogen group analyzed. The CLSI DOXY/TETRA S rates (EUCAST rates) were as follows: 99.2/94.2(96.7/93.2)% for MSSA; 96.2/91.2(93.5/88.1)% for MRSA; 75.3/73.2(73.8/73.0)% for SPN; 81.2/80.3(80.2/79.6)% for SPYO; and 15.7/14.6(15.4/14.6)% for *S. agalactiae* (SAGA). DOXY (MIC₉₀, 0.5 mg/L) was generally 2- to 4-fold more potent than TETRA (MIC₉₀, 2 mg/L) versus MRSA. Use of TETRA-S results to predict DOXY-S was excellent (>99.9 - 100.0%) for SA regardless of breakpoints used, as were predicted for SPN (99.8-100.0%), SPYO (99.6-99.9%) and SAGA (100.0%); errors usually higher applying the lower EUCAST breakpoints. Concerns persist that strains of staphylococci and streptococci having TET-R mechanisms could be categorized by CLSI as S (MICs at 2 or 4 mg/L) by current breakpoints e.g. 2.7% of MRSA tested against DOXY. **Conclusions:** CLSI and EUCAST interpretive criteria for tetracyclines (TETRA and DOXY) remain discordant, but each determines DOXY to have wider spectrum against four Gram-positive pathogen species and that TETRA-S can accurately predict DOXY-S (99.93-99.86% across 13,188 isolates). Moreover, molecular test-confirmed mechanisms appear highly probably among CLSI-susceptible (MICs, 2 or 4 mg/L) strains requiring international harmonization, to also include other tetracycline or-like agents and systematically applying pharmacodynamic principles.

Table. Categorical comparisons between doxycycline and tetracycline using the breakpoint criteria of the CLSI (2011) and EUCAST (2011) for over 9,000 *S. aureus* isolated in 2010.

| Organism/Antimicrobial (no. tested) | Tetracycline (no. isolates) | | | | | |
|--|-----------------------------|--------------|-----------|------------------------------|--------------|-----------|
| | CLSI category ^a | | | EUCAST category ^b | | |
| | Susceptible | Intermediate | Resistant | Susceptible | Intermediate | Resistant |
| Doxycycline | | | | | | |
| MSSA (4,966) | | | | | | |
| Susceptible | 4,677 | 41 | 208 | 4,630 | 18 | 155 |
| Intermediate | 0 | 0 | 33 | 1 | 1 | 84 |
| Resistant | 0 | 0 | 7 | 0 | 0 | 77 |
| MRSA (4,046) | | | | | | |
| Susceptible | 3,689 | 32 | 172 | 3,564 | 117 | 103 |
| Intermediate | 0 | 0 | 128 | 0 | 1 | 38 |
| Resistant | 0 | 0 | 25 | 1 | 0 | 222 |

a. CLSI (2011) criteria for tetracyclines: susceptible at ≤ 4 mg/L and resistant at ≥ 16 mg/L. b. EUCAST (2011) criteria for tetracyclines: susceptible at ≤ 1 mg/L and resistant at >2 (≥ 4) mg/L.