Assumed versus Approved Breakpoints

In our opinion, recent articles by Jacobs et al. (1) and Zhanel et al. (4) disseminated misleading information. Our first objection is that the authors failed to abide by the journal’s policy of not assigning interpretive MIC breakpoints in the absence of approved breakpoints. The Instructions to Authors are explicit on this point:

“The percentage of strains susceptible and/or resistant to an antibiotic at its breakpoint concentration may be given only if an appropriate breakpoint has been approved, as by the National Committee for Clinical Laboratory Standards, 940 W. Valley Rd., Suite 1400, Wayne, PA 19087-1898. In the absence of approved breakpoints, authors cannot assign breakpoints, use breakpoints from related antibiotics, or use a range of concentrations to report a cumulative display of percent susceptible/resistant strains.”

Jacobs et al. and Zhanel et al. reported percent susceptibility of *Streptococcus pneumoniae* to cefaclor using assumed breakpoints. Zhanel et al. assumed breakpoints that are approved for cefoxime, and Jacobs et al. used breakpoints derived by application of pharmacodynamic (PD) principles. The use of an assigned breakpoint for susceptibility (≤0.5 μg/ml) resulted in fewer than a quarter and just over half of the penicillin-susceptible *S. pneumoniae* (PSSP) strains being classified as susceptible to cefaclor, respectively, in the two papers. Those findings are inconsistent with long-standing clinical experience and with NCCLS recommendations. Since its registration, cefaclor has proven itself, time and time again, effective in treatment of infections caused by PSSP. Since the early 1990s, NCCLS has recommended using PSSP strains as susceptible to cefaclor (2). That recommendation remains in the most recent iteration of NCCLS interpretive standards (3), which also includes the recently adopted cefaclor-specific pneumococcal MIC breakpoint for susceptibility, ≤1 μg/ml.

Our second objection concerns the lack of attention to detail that Jacobs et al. used in abstracting their manuscript. Within the body of the article, they compared their PD breakpoint with the NCCLS established breakpoint for *Haemophilus influenzae*. Even though there is considerable explanation of this comparison within the text, this information was not included in the abstract. Unfortunately, the abstract includes only the susceptibility rate (2%) derived using the PD breakpoint, without mentioning the result determined using the NCCLS breakpoint (79%). It is well accepted that the majority of individuals screening articles, through either literature searches or personal reading, review only the abstracts of published manuscripts. Therefore, neglecting to include the percent susceptible by the NCCLS breakpoint only serves to allow the casual reader to misinterpret the published work.

We are troubled by these irregularities since they represent both a disregard for your journal’s Instructions to Authors and a breakdown in the refereeing process that was designed to ensure the scientific rigor of the journal. Occurrences such as these only serve to misinform the reader and to tarnish the reputation of this journal in the eyes of the scientific community.

REFERENCES


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Authors’ Reply

Our first responsibility as physicians and scientists in publishing in vitro susceptibility data is patient welfare. Results must be clinically relevant, based on and predictive of patient outcome, and applicable to patient management. The fact that the concentration of an antimicrobial agent had to exceed the in vitro inhibitory or lethal concentration of the agent to be effective was first documented by Eagle and colleagues almost 50 years ago (7), and the dynamics of this relationship was first demonstrated in animal models by Vogelman et al. in 1988 (15). It has come to the attention of many workers in the field of oral antimicrobial agents and bacterial respiratory tract infections that many of the breakpoints used to classify the susceptibilities of *S. pneumoniae* and *H. influenzae* to oral agents do not correspond with clinical and bacteriological outcomes of infections such as otitis media, sinusitis, and acute exacerbations of chronic bronchitis (1–4, 9). Many of these breakpoints are actually higher than peak concentrations of the agents in serum and tissue, so that clinically achievable concentrations can never reach, let alone exceed, the concentrations needed to inhibit organisms for which the MICs are close to the susceptibility breakpoint values.

To specifically address the points made by Preston and Turnak, firstly the fact that *Antimicrobial Agents and Chemotherapy* published our papers speaks to the validity of our argument that many current breakpoints need to be revised. Nevertheless, all available NCCLS breakpoints at the time the manuscripts were submitted were used. However, many of the breakpoints had been set some time ago, and, due to the nature of the process required to modify them, may not be current. *Antimicrobial Agents and Chemotherapy* is not the only reputable peer-reviewed journal recently allowing use of alternative breakpoints under these circumstances. Doern et al. used an *S. pneumoniae* susceptibility breakpoint of ≤0.5 μg/ml for cefadroxil, cefaclor, cefixime, and cefpodoxime in a paper published in 1998 in *Clinical Infectious Diseases* (5). Pharmacodynamic breakpoints were also used by Mason et al. in a study just published in the *Journal of Antimicrobial Chemotherapy* reporting in vitro susceptibility and pharmacodynamic analysis of *S. pneumoniae* in the United States (10). Additionally, pharmacodynamic breakpoints have recently been used to develop new guidelines for the treatment of otitis media (6)
and sinusitis (14). We also point out that, at the time of submission of our manuscripts, the new NCCLS breakpoints for \textit{S. pneumoniae} had not been finalized, and we were not allowed to use or even mention the new or proposed breakpoints until pneumoniae had not been finalized, and we were not allowed to \textit{S. mission of our manuscripts, the new NCCLS breakpoints for and sinusitis (14). We also point out that, at the time of sub-

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Editorial Comment

Interpretive breakpoints for susceptibility testing that are developed by organizations such as the NCCLS (National Committee for Clinical Laboratory Standards), BSAC (British Society of Antimicrobial Chemotherapy), DIN (Deutsche Industrie Norm-Medizinsche Mikrobiologie), SFM (Societe Francaise de Microbiologie), and others are known to vary for many antimicrobial-organism combinations (1, 2). The scientific rationales for these differences are often not apparent. *Antimicrobial Agents and Chemotherapy* (AAC) is interested in new scientific approaches for establishing interpretive breakpoints. However, we have given and will continue to give preference to published NCCLS breakpoints and guidelines. Although cefaclor did not have established interpretive breakpoints for *S. pneumoniae* when the two articles were published, NCCLS documents did state that penicillin susceptibility results could be applied to cefaclor for this organism. The distributions of penicillin-susceptible, -intermediate, and -resistant organisms were included in both articles. The scientific basis for any proposed breakpoints in manuscripts submitted to AAC must be clearly described (e.g., pharmacodynamic, pharmacokinetic, or species-related criteria, etc.), and the proposed breakpoints must be compared with published NCCLS interpretive breakpoints and guidelines.

REFERENCES


William Craig

Editor