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A new method for determination of ECOFFs of antifungal drugs and Candida species with EUCAST methodology

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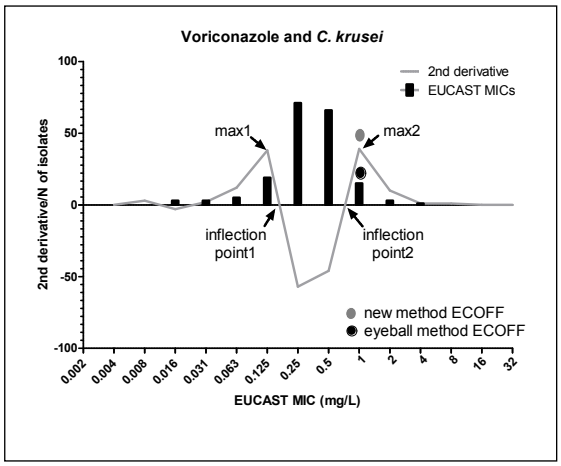
Background: Epidemiological cutoff (ECOFF) values are commonly used to define wild-type populations and to detect strains with MICs outside the wild-type distribution that may reflect strains with reduced susceptibility. Determination of an ECOFF is quite challenging since it requires complex statistical analysis and so far there is no clear consensus as to what the best method is. EUCAST utilized a nonstatistical approach namely the “eyeball method” where ECOFFs are determined by visual inspection of the MIC distribution as the MIC at the beginning of left (right?) tail. Although this approach does not assume a specific shape of MIC distribution, it is subjective and difficult for non-symmetrical distributions and MIC distributions with a high kurtosis. We therefore develop a new and simple method for ECOFF determinations based on the derivatization of MIC distributions.

Material/methods: Thirty-five MIC distributions were extracted from the EUCAST website for 7 drugs (amphotericin B, fluconazole, voriconazole, posaconazole, itraconazole, anidulafungin and micafungin) and 5 yeast species (*Candida albicans*, *Candida parapsilosis*, *Candida krusei*, *Candida glabrata*, *Candida tropicalis*). The new ECOFF (dECOFF) was determined for each MIC distribution by calculating the numerical second derivative at each MIC of the MIC distribution (GraphPad Prim 4.0, San Diego, CA). The second derivative describes the change of the steepness of the MIC distribution function at each MIC. It becomes zero at inflection points where the curve changes from being

concave to convex or vice versa (1SD away from the mean of a normal distribution), minimum at the point with the greatest concavity (center of a unimodal distribution) and maximum at the points with the greatest convexity (>2SD away from the mean) (see Figure).

The absolute (0 two-fold dilution difference) and essential (1 two-fold dilution difference) agreement between eyeball ECOFF and dECOFFs were then calculated for all drug-species combinations. The differences and correlation between the two methods were assessed with Pearson and paired t test analysis, respectively after log transformation.



Results: Of 35 comparisons (5 species x 7 drugs), the dECOFF was the same in 16/35 (46%), one dilution different in 17/35 (49%) (8 were higher, 9 lower) and 2 dilutions lower in 2/35 (5%) (voriconazole with *C. albicans* and *C. parapsilosis*) than the eyeball ECOFF. For the latter two species and all azoles, the dECOFFs were lower than the eyeball ECOFF. The two methods were highly correlated (r_s 0.9925, $p<0.0001$) and differences were not statistically significant ($p=0.83$).

Conclusions: The new method of ECOFF determination gave similar results (95% agreement within 1 dilution) with the “eyeball” method. It is simple, mathematically solid and more objective than the “eyeball” method. The new method can easily be used to determine ECOFFs by clinical microbiology laboratories and detect isolates with reduced susceptibility to antifungal drugs.