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# O0791 Determination of EUCAST susceptibility breakpoints for voriconazole against Candida krusei using an in vitro PK-PD model

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**Background:** *Candida krusei* is one of the five most common *Candida* species causing invasive candidiasis and is considered intrinsically resistant to fluconazole. Voriconazole exhibits *in vitro* activity against *C. krusei* strains, but whether this *in vitro* activity translates to clinical efficacy is undetermined and whether pharmacodynamics are species specific unknown. We investigated the antifungal activity of voriconazole against *C. krusei* in an *in vitro* pharmacokinetic/pharmacodynamic(PK-PD) model and PK/PD breakpoints were determined.

**Materials/methods:** Three clinical *C. krusei* isolates with EUCAST voriconazole MICs ranging from 0.25 to 1 mg/L were included. Different concentration time profiles of voriconazole were simulated in a previously optimized PK-PD model(Meletiadis et al *AAC* 2012) with *f*Cmax 7, 3.5, 1.75 and 0.8 mg/L and an average $t_{1/2}$ of 6h over 72h. The concentrations of voriconazole were determined with a microbiological assay while fungal load($log_{10}$CFU/mL) was determined by quantitative cultures. The (*f*$AUC_{0-12}$)/MIC ratio was calculated for each voriconazole dose and *C. krusei* isolate. The relationship between *f*$AUC_{0-12}$/MIC ratio and 72h-change in $log_{10}$CFU/mL compared to the respective drug-free control was analyzed using the Emax model. Monte Carlo simulation analysis was performed in order to calculate the probability of target attainment for *C. krusei* isolates with EUCAST MICs 0.125-4 mg/L in patients receiving standard IV voriconazole dosages of 4 mg/kg q12 taking into account the 58% protein binding (Liu et al. *AAC* 2014).

**Results:** The *in vitro* voriconazole pharmacokinetics showed a mean±SD of *f*$C_{max}$ 6.2±0.24 3.8±0.18 1.7±0.1 0.9±0.04mg/L and *f*$AUC_{0-12}$ 44.7±5.7, 29.4±4.8, 11.4±3.5 and 5.9±1.7 mg.h/l, respectively and an average $t_{1/2}$ of 5(2-10)h. The *in vitro f*AUC/MIC–72h$log_{10}$CFU/mL change relationship followed a sigmoid curve ($R^2$ =0.67) for all three strains with a mean (95% CI) $EI_{50}$ of 31(18-52). The proportion of simulated patients attaining the $EI_{50}$ was >99%, 80%, 11% and 0% for isolates with EUCAST MICs≤0.25, 0.5, 1 and ≥2 mg/L, respectively.

**Conclusions:** Adequate target attainment for voriconazole against *C. krusei* was determined at 0.25 mg/L based on 50% maximal in vitro activity. This cut-off is two dilutions lower than the corresponding EUCAST epidemiological cutoff value for *C. krusei* and questions voriconazole use for this indication without significant dose adjustments.