Background: A recent randomized clinical trial showed that voriconazole-anidulafungin combination therapy may improve outcome of voriconazole monotherapy against invasive aspergillosis when drugs were combined at standard dosages (Marr et al Ann Intern Med. 2015). Whether alternative dosages can maximize efficacy of combination therapy particularly against azole-resistant isolates is unknown. We therefore investigated the activity of voriconazole-anidulafungin combination against voriconazole-susceptible and -resistant *Aspergillus fumigatus* using different doses of anidulafungin in an *in vitro* pharmacokinetic-pharmacodynamic model.

Material/Methods: Four clinical *A. fumigatus* isolates with anidulafungin CLSI MEC 0.008 mg/L and voriconazole CLSI MICs 0.12-2 mg/L were tested in a pharmacokinetic-pharmacodynamic model (Siopi AAC 2015). Free human serum drug concentration-time profiles were simulated for nine combination regimens of voriconazole (*f*$_{C_{\text{max}}}$ 3/1.5/0.3 mg/L, *t$_{1/2}$* 6h dosed q12) and anidulafungin (*f*$_{C_{\text{max}}}$ 0.16/0.08/0.01 mg/L, *t$_{1/2}$* 24h dosed q24) (Liu AAC 2014). Drug levels were determined by microbiological diffusion assays and fungal growth by measuring galactomannan production using a commercially available sandwich-ELISA. *In vitro* interactions were assessed with Bliss independence model and response surface was modeled using the canonical-mixture nonlinear global response-surface $E_{\text{max}}$-based model (Meletiadis AAC 2007). The % of patients attained the pharmacodynamic target associated with 50% of maximal efficacy ($E_{50}$) was calculated for 10,000 simulated patients treated with 4 mg/kg of voriconazole alone and together with 100, 50 and 25 mg of anidulafungin as a combination therapy and for isolates with different voriconazole MICs. The optimal total target serum levels were determined taking into account the protein binding of each drug.

Results: The combination was mostly independent against voriconazole-susceptible isolates at intermediate and high drug exposures, whereas synergistic interactions (8-16%) were found at low drug concentrations. Stronger synergy (20-80%) was observed for isolates with high voriconazole
MICs at intermediate and low drug exposures, while at higher drug concentrations independence was found. At the highest anidulafungin exposure ($f_{C_{max}}=0.16 \text{ mg/L}$), antagonistic effects (-5 to -12%) were observed. The $E_{100}$ attainment rates for isolates with voriconazole MICs 0.5, 1, 2 and 4 mg/L were 97%, 72%, 9% and 0% for voriconazole monotherapy and increased to 100%, 86%, 34% and 2% for combination therapy with 100mg anidulafungin, respectively. The highest $E_{100}$ attainment rates were found for combination therapy with 25 mg of anidulafungin (100%, 99%, 79% and 16%, respectively). The serum target levels required to attain the $E_{100}$ were two-fold reduced from $3 \frac{t_{C_{min}}}{MIC}$ in voriconazole monotherapy to $1.5 \frac{t_{C_{min}}}{MIC}$ in combination therapy providing that anidulafungin $t_{C_{max}}$ will be between 6 and 10 mg/L.

**Conclusions:** The combination of voriconazole-anidulafungin is beneficial particularly for patients with sub-therapeutic serum concentrations infected with voriconazole-resistant *A. fumigatus* isolates. The lower dose of 25 mg of anidulafungin may increase efficacy of combination therapy.