Disclosures. All authors: No reported disclosures.

145. Assessment of Candida auris Response to Antifungal Drugs Using Time–Kill Assays and an Animal Model

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Background. Candida auris is an emerging nosocomial pathogen that is resistant to Fluconazole and variably susceptible to other systemic drug classes. Treatment with echinocandins has been recommended based on MICs in the susceptible range, but supporting in vivo data is lacking.

Methods. We tested the MIC of C. auris strains (n = 12) to fluconazole, voriconazole, posaconazole, anidulafunig, amphotericin B and flucytosine. Representative C. auris strains from Israel and South Africa, and a reference C. albicans strain were analysed using time–kill curve assays. Fungicidal activity was defined as reduction of ≥3 log from baseline CFU/mL to −0.9 for caspofungin (MIC ×16), consistent with fungicidal activity of amphotericin B and weak fungistatic activity of caspofungin. In the mouse model, survival rate was similar with sham treatment (33%) and treatment with caspofungin 1 mg/kg/day (44%) and 5 mg/kg/day (22%), P = 0.7.

Conclusion. Despite generally low MIC, caspofungin has only mild fungistatic activity on C. auris and no effect on survival in a mouse infection model. Amphotericin B has fungicidal activity against C. auris.

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146. Pharmacodynamic Optimization for the Treatment of Invasive Candida auris Infection

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Background. Candida auris is an emerging, nosocomial multidrug-resistant threat with high treatment failure rate and mortality. The optimal antifungal agent to use and susceptibility breakpoints are based on limited clinical data.

Methods. Nine clinical C. auris strains were MICs were determined by CLSI standards. Drug treatment studies consisted of fluconazole (FLC) dose range 0.78–200 mg/kg/12 h, micafungin (MFG) dose range 0.3125–80 mg/kg/24 h, or amphotericin B deoxylcholate (AMB) dose range 0.78–20 mg/kg/24 hours. Plasma PK was previously determined in the murine model for all three drugs. A 96 h neutropenic murine model of invasive candidiasis (IC) was used for all studies. The Emul Hf equiva- lence was used to model the dose–response data to PK/PD index AUC/MIC (FLC and MFG) and Cmax/MIC (AMB). The static and 1 log kill doses (when achieved) and the associated PK/PD targets (AUC/MIC or Cmax/MIC) were determined and compared with previous murine IC studies with C. albicans, C. glabrata, and C. parapsilosis.

Results. MIC range: FLC 2–256 mg/L, MFG 0.125–4 mg/L, and AMB 0.38–6 mg/L. Dose-dependent activity was observed with all three drugs. Net stasis was achieved against seven strains for FLC, eight strains for MFG, and eight strains for AMB. However, MFG performed significantly better than comparators for cidal endpoints. A 1 log kill endpoint was achieved in eight strains for MFG, whereas this endpoint was only achieved in one strain for FLC and three strains for AMB. PK/PD analyses demonstrated a strong relationship between AUC/MIC and treatment outcome for FLC (R² 0.61) and MFG (R² 0.77); and Cmax/MIC and treatment outcome for AMB (R² 0.64). The median static dose and 1 log kill dose (MFG only) and associated AUC/MIC or Cmax/MIC values are shown (Table).

Table

| Drug       | Dose (mg/kg/24 hours) | AUC/MIC | Cmax/MIC | Dose (mg/kg/24 hours) | AUC/MIC |
|------------|-----------------------|---------|----------|-----------------------|---------|
| FLC        | 107                   | 26.3    | 0.4      | 3.86                  | 0.87    |
| MFG        | 1.25                  | 53.7    | 1.25     | 3.86                  | 0.87    |
| AMB        | 1                   | 130     | 1        | 130                   | 1       |

Conclusion. MFG was the most potent drug over the dose range achieving up to 2 log kill against eight of nine strains. PK/PD targets for C. auris against FLC and AMB were similar to other Candida species; however, MFG targets were ≥20-fold lower than C. albicans, C. glabrata, and C. parapsilosis. Using the median stasis targets and human PK for each drug, resistance thresholds could be 16 mg/L for FLC, 2–4 mg/L for MFG, and 1–2 mg/L for AMB.

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147. Risk Predictive Model for 90-Day Mortality in Candida bloodstream infections

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Background. Candida bloodstream infections (CBSI) continue to be associated with high mortality, despite changes in antifungal treatment and diagnostics.

Methods. All patients age 18 or greater with a first episode of CBSI by blood culture from 1/2002 to 1/2015, admitted to Barnes-Jewish Hospital, a tertiary referral hospital in St. Louis, MO, were included. We collected data on demographics, comorbidities, laboratory values, vital signs, i ndwelling devices, and medical treatments of interest from the electronic medical record. We analyzed the potential predictor variables using univariate logistic regression. Variables associated with mortality were considered for model inclusion. The final model was built using multivariable binary logistic regression. A predictive equation was created, and a receiver–operator curve (ROC) was calculated to determine the appropriate cut-off points and c–statistic.

Results. Of the 1873 episodes of CBSI identified, 789 (42%) resulted in death in 90 days. The variables included in this model were age (40–49: 0.463, 95% CI 0.291–0.736; 50–59: 0.542, 0.342–0.860; ≥70: 0.560, 0.400–0.785); history of CAD (1.616, 1.171–2.230), chronic liver disease (1.563, 1.178–2.073), the presence of ventilator (1.847, 1.248–2.682), and urinary catheter (1.365, 1.088–1.648), two or more central lines (1.658, 1.020–2.694); removal of lines after positive culture (0.259, 0.181–0.370); ophthalmology consult during admission (0.441, 0.329–0.592); thoracacetis/chest tube (3.827, 1.550–9.448); diagnosis of secondary malignancy (2.131, 1.488–3.053); whether antimetabolites (2.119, 1.353–3.318), dapsone (4.507, 1.450–14.012), linezolid (1.605, 1.059–2.435), quinolones (1.384, 0.988–1.920) were ordered 90 days before positive culture. An ROC curve was calculated with an internal c–statistic of 0.806.

Conclusion. We created a risk predictive model for 90-day mortality in patients with CBSI, with 81% probability of predicting mortality. This model can lead to development of point-of-care applications to aid decision-making regarding escalation/de-escalation of care.

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148. Time Trends in the Burden of Hospitalizations with Invasive Aspergillosis in the United States, 2004–2013

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149. β-1,3-D Glucan Testing Is Overused in Patients Without Solid Organ/Stem Cell Transplant or Hematologic Malignancies
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Background. β-glucan (BDG) assay aids in diagnosis of some invasive fungal infections (IFI) in at-risk patients. Due to an increase in the number of BDG tests ordered at Johns Hopkins Hospital in patients not at high-risk for IFI, we evaluated the appropriateness of testing and conducted a survey to understand providers’ knowledge about the test.

Methods. From December 2015 to July 2016, we identified inpatients >17 years capable of having at least one BDG test. We did not evaluate patients with solid organ/stem cell transplant or hematologic malignancies as they generally have indications for BDG testing. Using a standard data collection form, one infectious disease (ID) physician reviewed all test for appropriateness; 20% of cases were reviewed by an additional ID physician. Students, housestaff and allied staff from departments of medicine and surgery were surveyed regarding their knowledge of BDG test characteristics including indications and causes of false-positive results.

Results. 355 patients with at least one BDG were included. 33% (n = 116) had a risk factor for IFI (e.g., AIDs, immunosuppressing medication, malignancy, total parenteral nutrition, and prolonged ICU stay) although only 13% (n = 48) of these had proved or possible IFI. 49% (n = 173) had no indication for testing. Of these, 4% (n = 8) had inappropriate antigens started based on BDG results. Being at an intensive care unit or having cirrhosis was associated with inappropriate BDG use (P = 0.03). Most of the 47 clinicians surveyed recognized the utility of BDG in the diagnosis of candidiasis (63%) and Aspergillus (78%) but only 49% recognized its utility in diagnosis of Pneumocystis. Fifty-two percent identified its lack of utility for diagnosis of Cryptococcus infection but only 44% recognized lack of utility for diagnosing Zygomycetes. The majority of those surveyed were unable to identify causes of false-positive results of the assay.

Conclusion. In patients without solid organ/stem cell transplant or hematologic malignancy, clinicians ordered the BDG test in absence of clinically strong evidence of IFI in almost 50% of patients. Survey results suggest an incomplete understanding of organisms associated with positive BDG tests. Clinicians must be educated about the correct patient population in which a new test should be used.

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