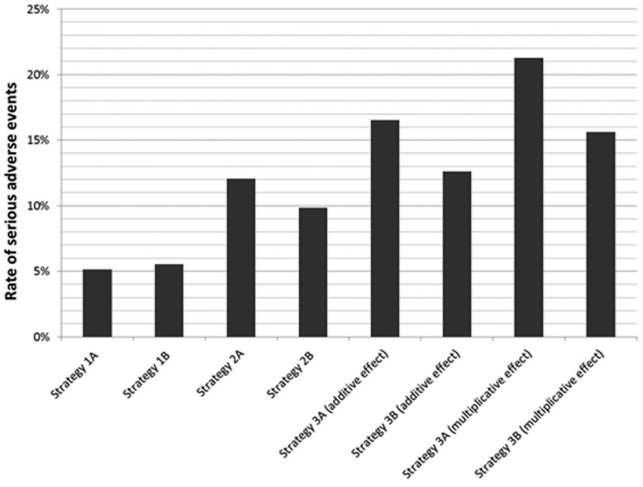
Figure 4: Predicted rates of serious adverse events in six different clinical strategies using both an additive and a multiplicative model to predict outcomes of combination therapy



Legend: Strategy 1 uses voriconazole, Strategy 2 LAmB and strategy 3 both as empiric therapy in case of unknown resistance. The B variants of the strategy are with implementation of PCR for Aspergillus, the A variants without.

Disclosures. **All authors:** No reported disclosures.

969. GRP78 and Integrin β1/α3 Play Disparate Roles in Epithelium Invasion During Mucormycosis

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Background. Mucormycosis is a lethal fungal infection caused by Mucorales. Inhalation is the major route of entry resulting in rhino-orbital or pulmonary infections. Nasal and lung epithelial cells are among the first cells that encounter inhaled spores. We sought to identify the nasal and lung epithelial cell receptors interacting with *Rhizopus* during tissue invasion.

Methods. *R. delemar*-induced nasal (CCL30) or lung epithelial (A549) cell invasion was studied using Uvetix dye, while host cell injury was determined by ^{51}Cr-release assay. Epithelial cell receptors were isolated by affinity purification of biotinylated host cell membrane proteins and then identified by LC-MS. Blocking antibodies were used to confirm the role of the receptor in the invasion/injury assays. For survival studies, ICR mice were immunosuppressed with cyclophosphamide and cortisone acetate on day-2, +3, and +8. Mice were infected with 2.5×10^5 *R. delemar* spores intratracheally, and then treated with a single dose of 100 μg (i.p.) anti-β1 integrin antibody. Placebo mice received 100 μg of isotype-matching IgG.

Results. *R. delemar* invades and damages both cells in a time-dependent manner. Nasal Grp78 and alveolar β1α3 integrin were isolated as putative receptors. Polyclonal antibodies targeting Grp78 or β1 integrin blocked *R. delemar*-mediated endocytosis of nasal and lung cells by ~70%. Also, anti-Grp78 and anti-β1 integrin antibodies blocked *R. delemar*-induced nasal and lung cell injury by ~60% ($P < 0.001$). Elevated glucose, iron, or BHB increased the expression of nasal Grp78 by 2- to 6-fold which resulted in enhanced *R. delemar*-mediated invasion and injury of host cells, while having no effect on β1α3 integrin expression. Finally, β1 antibodies protected mice from mucormycosis with median survival time of 16 days for treated mice versus 11 days for placebo and an overall survival of 30% versus 0% for placebo mice ($P = 0.0006$).

Conclusion. The upregulation of Grp78 on nasal epithelial cells in response to physiological elevated concentrations of glucose, iron, and BHB and subsequent enhanced invasion likely to provide insights into why diabetics in ketoacidosis are infected with the rhino-orbital mucormycosis rather than pulmonary disease. Our studies also provide a foundation for therapeutic interventions against mucormycosis.

Disclosures. **All authors:** No reported disclosures.

970. Emerging Pathogen *Candida auris* Evades Neutrophil Attack

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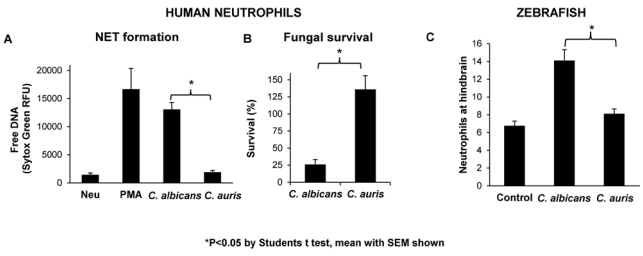
Background. *Candida auris*, an emerging fungal pathogen, causes hospital-associated outbreaks of invasive candidiasis with mortality near 60%. Little is known about the pathogenesis of this species that has newly arisen in the last 10 years, and it is unclear why this species is rapidly spreading worldwide. Neutrophils, critical for control of invasive candidiasis, kill fungi through phagocytosis or the release of neutrophil extracellular traps (NETs), which are structures of DNA, histones, and proteins with antimicrobial activity. The objective of this study was to delineate the neutrophil response to *C. auris*.

Methods. We examined interactions of human neutrophils with *C. auris* and included *C. albicans* for comparison. Neutrophil–*Candida* interactions were visualized by time-lapse fluorescent microscopy and scanning electron microscopy (SEM). We utilized oxidative stress indicator CM-H2DCFDA to measure the generation of reactive oxygen species (ROS) in neutrophils. NET formation was quantified by Sytox Green staining and assessed by SEM and immunofluorescent labeling of NET-associated proteins. Fungal viability was evaluated using microbiological counts and viability stains. We utilized a zebrafish larvae infection model to evaluate neutrophil–*Candida* interactions in vivo.

Results. Imaging revealed the phagocytosis of *C. albicans* by human neutrophils followed by the formation of NETs. In contrast, neutrophils encountering *C. auris* rarely engaged in phagocytosis or produced NETs. By Sytox Green staining, *C. auris* triggered negligible NET release by human neutrophils, with levels 7-fold lower when compared with *C. albicans* (Figure A). *C. auris* did not induce neutrophils to generate ROS, a key signaling mechanism for NET formation. The ineffective neutrophil response to *C. auris* correlated with diminished fungal killing (Figure B). Imaging of neutrophils in a zebrafish model of invasive candidiasis revealed the recruitment of approximately 50% fewer neutrophils in response to *C. auris* when compared with *C. albicans* (Figure C).

Conclusion. *C. auris* evades neutrophils by altering multiple aspects of their usual anti-candidal responses. We propose that this diminished innate immune response may contribute to the unexpected virulence of *C. auris*.



Disclosures. **All authors:** No reported disclosures.

971. Breakthrough Invasive Fungal Infections (IFI) in Acute Leukemia (AL) Patients Receiving Antifungal Prophylaxis

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Background. A major challenge in patients with AL receiving chemotherapy is to decrease the risk of IFI during the prolonged neutropenic period. Even with antifungal prophylaxis, the incidence of breakthrough IFI can be as high as 14%. Our objectives were to determine the incidence of all IFI and breakthrough IFI, to define risk factors associated with IFI, and to assess outcomes.

Methods. Single-center retrospective cohort analysis of all adult patients admitted to the University of Michigan for AL from January 1, 2010 to December 31, 2013. Chart review determined co-morbidities, chemotherapy regimens, antifungal prophylaxis, occurrence of IFI as determined by EORTC/MSG criteria, and outcomes. Chi-square, Fischer's, ANOVA, and binary logistic regression tests were performed when appropriate.

Results. Of 363 patients, all but 4 had acute myeloid leukemia (AML); 124 had a stem cell transplant (SCT). A total of 103 (28%) had proven ($n = 13$), probable ($n = 22$), or possible ($n = 68$) IFI. Considering only those 35 patients who had proven or probable IFI, the only risk factor for development of IFI by logistic regression analysis was IFLAG chemotherapy ($P = .006$). Mold infections occurred in 27 patients: *Aspergillus* (19), Mucorales (5), both *Aspergillus* and Mucorales (1), *Alternaria* (1), and *Scedosporium* (1). Additionally, 5 patients had invasive candidiasis and 3 had *Pneumocystis*. Eighteen of 35 patients (51%) had breakthrough IFI while on posaconazole suspension (6), fluconazole (5), micafungin (5) or voriconazole (2). Factors significantly associated with breakthrough IFI were SCT ($P = .04$), neutrophils <500, ≥10 days at diagnosis ($P = .002$) and prophylaxis with posaconazole suspension ($P = .003$). Twelve-week mortality in proven and probable IFI was 31% (11/35). Nine of 11 deceased patients had breakthrough IFI; 8 of whom (5 with mold IFI and 3 with invasive candidiasis) died of the fungal infection.