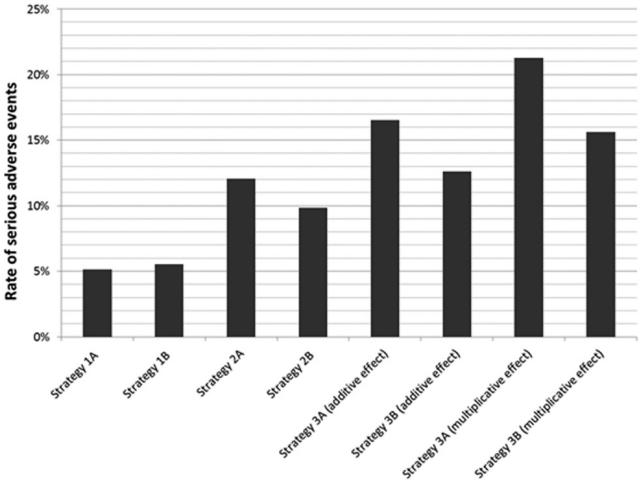
Figure 4: Predicted rates of serious adverse events in six different clinical strategies using both an additive and a multiplicative model to predict outcomes of combination therapy



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.

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

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Session: 125. Fungal Infections
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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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Session: 125. Fungal Infections
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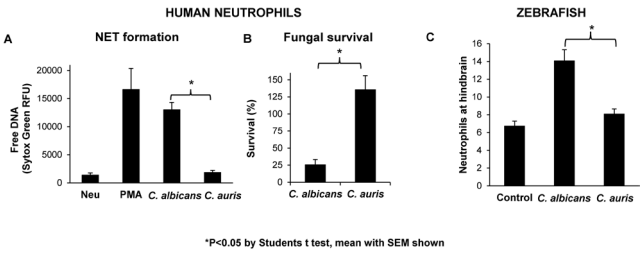
Background. *Candida auris*, an emerging fungal pathogen, causes hospital-associated outbreaks of invasive candidiasis with mortality near 60%. Little is known about the pathogenesis of this species that has newly arisen in the last 10 years, and it is unclear why this species is rapidly spreading worldwide. 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.

Conclusion. Patients receiving chemotherapy for AL remain at risk for IFI despite the the use of antifungal prophylaxis. In our study, prophylaxis with posaconazole suspension was found to be an independent risk factor for breakthrough IFI. Mortality was high among patients with breakthrough IFI.

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

972. Asymptomatic Carriage of *Clostridiodes difficile* and Risk of Subsequent Infection

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Session: 126. Healthcare Epidemiology: The Poop Pager and Other Novel Perspectives on *C. difficile* in the Healthcare Setting

Friday, October 5, 2018: 10:30 AM

Background. *C. difficile* is one of the most common healthcare-associated infections in the United States. Studies of patients with asymptomatic carriage of toxigenic *C. difficile* have reported conflicting results on the risk of subsequent *C. difficile* infection (CDI). Older studies suggest that the risk was low and colonization may be protective. Subsequent studies indicate that asymptomatic carriers have a 6-fold greater risk of developing CDI. The aims of our study were to assess the burden of asymptomatic *C. difficile* carriage and risk of subsequent CDI.

Methods. Adult inpatients at NorthShore University HealthSystem, Illinois hospitals between August 1, 2017 and February 28, 2018 were eligible for the study. Focused admission screening of patients at high risk of *C. difficile* carriage was performed: (1) history of CDI or colonization, (2) prior hospitalization past 2 months, or (3) admission from a long-term care facility. A rectal swab was collected and tested using the cobas® Cdif Test (Roche) real-time PCR. The development of hospital onset CDI (HO-CDI) in colonized patients was monitored prospectively for at least 2 months. HO-CDI testing of colonized patients was performed using the Cepheid GeneXpert RT-PCR. HO-CDI was defined as patients hospitalized for at least 72 hours with 3 or more episodes of diarrhea/24 hours, in the absence of other potential causes of diarrhea. Patient demographics were collected using a standardized form and data analyzed using VassarStats.

Results. There were 6,104 patients enrolled in the study and 528 (8.7%) were positive on admission for toxigenic *C. difficile* carriage. The mean age of colonized patients was 75.5 years (range 24–103) and 56.4% (298 patients) were females. Of 528 colonized patients, 21 (4%) had a positive CDI test. A total of 7 patients (1.3%) developed HO-CDI. Mean time to positive HO-CDI was 46.1 days (range 5–120 days). Of 5,576 patients that were negative for *C difficile* carriage on admission, 14 (0.3%) patients developed HO-CDI. The relative risk of HO-CDI was 5.28 (95% CI: 2.14–13.03, $P = 0.05$).

Conclusion. We found that 8.7% of at-risk admissions were asymptomatic toxigenic *C. difficile* carriers. While only 1.3% developed HO-CDI, asymptomatic carriers had a 5 times higher risk of subsequent CDI compared with non-carriers.

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

973. Inter-facility Patient Sharing and *Clostridium difficile* Incidence in the Ontario Hospital Network: A 13-Year Longitudinal Cohort Study of 116 Hospitals

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Session: 126. Healthcare Epidemiology: The Poop Pager and Other Novel Perspectives on C. difficile in the Healthcare Setting

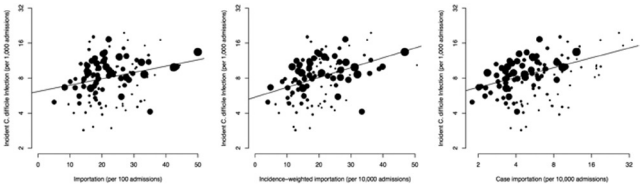
Friday, October 5, 2018: 10:30 AM

Background. Inter-facility patient movement plays an important role in the dissemination of antimicrobial resistance and *C. difficile* infection (CDI) throughout healthcare systems. However, the relative performance of different patient sharing metrics for predicting CDI incidence is not known. We compared 3 different measures of inter-facility patient sharing as they relate to CDI incidence in Ontario facilities.

Methods. A retrospective cohort analysis was used to predict incident CDI (ICD-10 = A04.7 identified from Discharge Abstract Database records) across Ontario hospitals ($N_{hospitals} = 116$) between April 1, 2003 to March 31, 2016. Patients with a stay of <3 days and those with a history of CDI in the prior 90 days were excluded from the risk set but not from patient sharing metrics. Poisson regression models with facility-level random effects were used to predict facility CDI incidence (per 1,000 admissions) and measure the percent change in facility-level variance (PCV). The 3 metrics of inter-facility patient sharing included: (1) "importation"—the rate of patients with a discharge from another distinct facility in prior 90 days, (2) "incidence-weighted importation"—equal to importation weighted by the incidence of CDI in the previous facility, and (3) "case importation"—importation of patients with a history of CDI.

Results. Over the 13-year period, we observed 58,427 cases of healthcare-associated CDI among 12,750,000 admissions. Facility CDI incidence ranged from 2.9 to 19.6 per 1,000 admissions (6.8-fold range). Patient sharing metrics were strongly related to facility CDI incidence (figure). In models adjusting for facility risk factors, all 3 measures still explained an important portion of inter-facility variation in CDI incidence: importation (PCV = 5%, $P = 0.01$), incidence-weighted importation (PCV = 15%, $P < 0.001$), and "case importation" (PCV = 48%, $P < 0.001$).

Conclusion. We observed a substantial variation in facility CDI incidence that was explained by linkages between acute care facilities, especially linkage to other facilities with a high incidence of CDI. Facility infection prevention staff should consider incorporating the facility CDI incidence into risk stratification assessments of patient transfers.



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

974. Impact of Mandatory Infectious Disease (ID) Specialist Approval on Hospital-Onset *Clostridium difficile* (HO-CDI) Testing and Infection Rates: Results of a Pilot Study

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Session: 126. Healthcare Epidemiology: The Poop Pager and Other Novel Perspectives on C. difficile in the Healthcare Setting

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Background. The 2017 IDSA *C. difficile* guidelines recommend the use of nucleic acid amplification testing alone for detection of HO-CDI if appropriate stool specimens are collected (e.g., patients not receiving laxatives and ≥3 unformed stools in 24 hours). The potential role of ID specialists in enforcing appropriate *C. difficile* testing is unclear.

Methods. At a single academic hospital, we performed a pilot study of an ID specialist-led approval process for *C. difficile* testing. During the baseline period (January 2016 and November 2017), HO-CDI testing appropriateness was enforced using a computerized decision support tool that discouraged inappropriate testing based on detected laxative use and stool frequency criteria; however, clinicians frequently ignored the computer alerts. During the intervention period (December 2017 and March 2018), all HO-CDI testing on hospital day 4 or later triggered a computer alert requesting mandatory testing approval by an ID specialist. Approvals were provided via telephone consultation 7 days a week between 8 a.m. and 5 p.m. (in both periods, CDI testing was not performed overnight). We analyzed differences HO-CDI testing and infection rates (defined by CDC's LabID event) per 10,000 patient days using Poisson models. We also analyzed the number of approval pager calls, rates of *C. difficile* testing approval, and time burden.

Results. Two infectious diseases specialists (M.Y.L.; J.S.) primarily answered *C. difficile* pager approval requests; the remainder of approvals were provided by ID specialists already consulted on the patients. During the intervention period, ordering providers made 159 calls to the approval pager; 119 (75%) received approval. HO-CDI testing and infection rates declined between the baseline and intervention periods (figure). There was a mean of 1.3 pager approval requests per day (range, 0–4) with an average of 3 minutes of time spent per request.