Objective: Candida auris is a multidrug-resistant pathogen that presents a serious global threat to human health. The U.S. Centers for Disease Control and Prevention has classified C. auris as an urgent threat to public health due to its clinical and economic impact and future projections of new infections over the next 10 years. Candida auris infections are difficult to treat since many isolates display high levels of resistance to fluconazole and exhibit variable resistance to amphotericin B and echinocandins. In this study, we performed comparative transcriptomics to understand the molecular mechanisms associated withazole resistance in C. auris clinical isolates.

Materials and Methods: Two sets of environmental isolates including azole-resistant (n=2) and azole-susceptible (n=3) isolates were used for RNA-seq analysis. Pair-wise comparisons in DESeq2 were used for comparing the number of differentially expressed genes (DEGs) between the azole susceptible and resistant isolates. GO term enrichment analysis was performed using the ‘rGOseq’ function from the clusterProfiler package. Only GO categories with a p-value <0.05 were considered significant.

Results: Our data show significant enrichment of regulated biofilm genes, drug transport, MAPK pathway, as well as chromatin remodeling genes in azole-resistant strains compared to susceptible isolates. A total of 464 and 564 differentially expressed genes were identified in two azole-resistant isolates compared with the susceptible strain. A large number of mediating transporter genes (CDR1, MDRI, HGT2, HGT7, HGT13, HGT17, and HGT21) were differentially expressed between the two sets of isolates, further the growth inhibition assay using higher MIC values as well as expression of glucose transporter genes was observed in resistant isolates as compared with susceptible strain. Furthermore, resistant strain has two copies of ERG11 while susceptible isolate has only single copy of ERG11. Notably, HGT2 genes involved in the ergosterol biosynthetic pathway were found to be induced in azole-resistant isolates. These include HMT1, EFG1, ERG4, ERG7, ERG8, ERG16, ERG18, and ERG13, and ERG25. Furthermore, other multidrug transporters MDRI and SNQ2 responsible for azole resistance in other Candida species like C. glabrata also showed significant expression changes between the two sets of isolates. Furthermore, HGT7 (glucose transporter) and NTL1, (N-acetyl glucose transporter) genes associated with azole and polynucle resistance were found to be upregulated in the resistant isolates as compared with susceptible strain. Additionally, a Glycosylphosphatidylinositol (GPI)-anchored protein unique for C. auris, PCAS7 was found to be overexpressed in resistant isolate. Importantly, we also identified several secreted asexual proteins (SAP1, SAP2, SAP5, and SAP6) to be downregulated between the two sets.

Conclusion: The present study identifies several gene families that are differentially expressed associated with azole resistant versus suscepti- ble C. auris strains. These findings suggest that azole-resistant C. auris environmental isolates is influenced by changes in cell wall, lipid, and ergosterol biosynthesis. Overall, these data provide a framework for the mechanistic understanding of azole resistance mechanisms in C. auris environmental isolates.

P232
Luliconazole—a novel potent imidazole active against Aspergillus niger and Aspergillus flavus causing stomatitis
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Poster session 1, September 21, 2022, 12:30 PM - 1:30 PM

Background and Objectives: Suppurative otitis media (SOM) is characterized by the inflammation of the middle ear and mastoid, tympanic membrane perforation as well as discharge. The tympanic membrane perforation may result in excessive exposure of the middle ear to pathogens. Aspergillus niger and Aspergillus flavus are the most common causative agents of otomycosis worldwide, where it spreads from the external auditory canal to adjacent anatomical structures, it is classified as Aspergillus otitis externa. Aspergillus otitis treatment is initiated by thorough cleaning of the ear canal, accomplished with suction, and drying with cotton swabs. In developing countries, SOM is a major cause of preventable hearing loss, incidence ranges from 7% to 46% and is common amongst children of lower socioeconomic status. Treatment of SOM does not differ from that seen in the topical treatment of cutaneous disesases. Concomitant topical decongestion and systemic antifungal therapy are needed in cases of otomycosis or Aspergillus otitis externa. Despite this management, treatment failure may result from suboptimal therapeutic management caused by antifungal agent resistance. Luliconazole is currently confirmed for the topical therapy of dermatomycosis. Moreover, it is found that luliconazole has in vitro activity against some molds and yeast species. The aim of the present study was to evaluate the efficacy of luliconazole in comparison to routinely used antifungal on clinical isolates of A. niger and A. flavus.

Methods: The study was carried out in the Department of Microbiology, SMRHIR, Chennai. A total of 55 (29 A. niger and 26 A. flavus) strains of Aspergillus otitis externa obtained from clinical otomycosis cases were confirmed based on macroscopic and microscopic identification by Lacto Phenol Cotton Blue mount and slide culture techniques. Antifungal susceptibility pattern of all the Aspergillus isolates to itraconazole, voriconazole, posaconazole, and luliconazole were determined by broth microdilution method as per Clinical Laboratory Standards Institute (CLSI) M38-A2 guidelines.

Results: The lowest minimum inhibitory concentration (MIC) geometric mean (GM) of all isolates was (0.0059 μg/ml) was attributed to luliconazole followed by posaconazole (0.0149 μg/ml), voriconazole (0.0277 μg/ml) and itraconazole (0.1393 μg/ml). Also, among the azoles tested, luliconazole had the lowest MIC and MIC90 values of 0.0008 μg/ml and 0.0078 μg/ml respectively. Among the triazoles tested posaconazole had a lower MIC10 and MIC90 values of 0.125 μg/ml and 2 μg/ml. The drug of choice for invasive aspergillosis voriconazole had a slightly higher MIC 2 μg/ml and MIC90 value of 3 μg/ml and 2 μg/ml. Luliconazole was found to be more effective even for pan azole-resistant isolates (n = 3) with lower MIC value.

Conclusion: The results of this study showed that luliconazole has an excellent in vitro activity against all Aspergillus isolates with a lower MIC GM, MIC90, and MIC90 values than the triazoles tested. Hence, this novel imidazole antifungal agent can be regarded as appropriate Candida for the treatment of otomycosis caused by A. niger and A. flavus strains. Also, luliconazole had less toxic effects on the human cellular lines, suggesting that it could be a potential antifungal for treating aspergillosis caused by pan azole-resistant isolates.

P233
Evaluation of Beta-D-glucan assay as a tool for antifungal stewardship at a hospital in Mumbai, India
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Objective: Clinical evidence suggests that the Beta-D-glucan (BDG) test is useful as a tool for antifungal stewardship by helping in discontinuing empirical antifungal therapy. This study was hence initiated with the following objectives: (1) to calculate the percentage of echinocandin prescriptions in patients with a subsequent negative BDG test and the compliance to recommendations for stopping echinocandins for the above prescriptions, (2) to study outcomes in patients whose echinocandins were stopped, and (3) to study the total cost savings.

Methods: The study was conducted for a 1-year period from January 2021 to December 2021 in a tertiary care hospital in Mumbai. The antifungal stewardship committee recommended sending a serum sample for BDG along with paired blood culture for all patients before starting empirical antifungal therapy. The choice of empirical antifungal therapy at our hospital is echinocandins (caspofungin, micafungin, and anidulafungin). The BDG test was performed using PentaGlo® assay (Associates of Cape Cod, Massachusetts) that quantitatively measures 1-3-β-D-glucan levels which is run twice a week on Wednesday and Saturday. The cut-offs for a negative, intermediate, and positive result are 60 μg/ml, 67.9 μg/ml, and ≥80 μg/ml respectively. The result of the BDG test and blood cultures were promptly sent to the consultant in charge and recommendations were made to discontinue the echinocandins if both were negative. The compliance with these recommendations was monitored. The patients in whom the echinocandins were stopped were monitored during their hospital stay or on day 28 after stopping the echinocandin whichever was earlier. The total cost savings (indirect Revers (IND) and converted into US Dollars (USD)) were calculated based on an average of 10 days extra therapy with echinocandins.

Results: A total of 317 echinocandins were prescribed to 294 patients and tested during the study period. A total of 17 patients, 17% were discharged against medical advice, 3 patients were discharged and died and 3 were still in hospital at the end of the follow-up period. No deaths could be attributed to invasive fungal infections at 28-day follow-up. Total cost savings were 67944.40 INR, corresponding to 890 USD during the study period.

Conclusion: BDG test-based stewardship strategy helped in reducing the use of echinocandins with cost savings and in reduced risk of invasive fungal infections related to adverse outcomes in patients where echinocandins were discontinued. The universal compliance to recommendations to discontinue could be achieved by constant dialogues between the departments of Clinical Microbiology and Clinical Medicine.

P234
Genetic determinants of antifungal drug resistance in Fusarium solani complex species
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Due to its challenging diagnosis and treatment, fungal keratitis is one of the most serious kinds of corneal infection. The Fusarium species is complex is responsible for nearly half of all fungal keratitis cases. Poorkeratitis is difficult to treat because of the increased antifungal resistance of Fusarium species complex.

Objective: To check the antifungal susceptibility in keratitis-causing isolates of F. solani species complex.

Preliminary study on a few Fusarium species was done using different bioinformatics tools and software (FASTQC, SNAP dikas, OrcaRex, MG/ASUK, etc.). Results: In this study the antifungal drug susceptibility from average MIC were found as fluconazole (312 μg/ml) > itraconazole (25 μg/ml) > amphotericin B (9 μg/ml) > caspofungin (5 μg/ml) > posaconazole (8 μg/ml) > voriconazole (1 μg/ml). Fluconazole had a higher MIC value (152 μg/ml) in all isolates, however, voriconazole was shown to be more sensitive, with a lower MIC range (0.25-4 μg/ml). Glycolaldehyde/Beizmocic resistance protein, nol–mokkog resistance transport, fusicoid acid resistance protein, ophiin antibacterial resistance protein, and copper resistance protein were found by genome-baasal analysis.

Conclusion: As a conclusion of this study, we observed antifungal drug resistance in Fusarium spp., which is often used to treat keratitis in patients, employing Fluconazole, itraconazole, and amphotericin B. Resistance to fluconazole was a gene variant which contributed to antifungal drug resistance. This study using the phenotypic and genotypic characterization of drug resistance patterns will help to combat antifungal drug resistance.