Objective: Candida auris is a multidrug-resistant pathogen that presents a serious global threat to human health. The US Centers for Disease Control and Prevention has classified C. auris as an emerging 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 transcriptome to understand the molecular mechanisms associated with azole-resistance in C. auris environmental isolates.

Materials and Methods: Two sets of environmental isolates including azole-resistant (n = 2) and azole-susceptible (n = 2) isolates were used for RNA-Seq analysis. Pair-wise comparisons in cuffdiff 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 “enrichGO” function from the cluster Profiler package. Only GO categories with a p-value < 0.05 were considered significant.

Results: Our data show significant enrichment of organismal biosynthesis genes, drug transport, MAPK pathway as well as chromatin remodeling genes in azole-resistant strains compared to susceptible isolates. A total of 468 and 544 differentially expressed genes were identified in two azole-resistant isolates compared with the susceptible strain. A large number of metabolism transporter genes (CDB1, MDR1, HGT2, HGT3, HGT13, HGT1, and HGT21) were differentially expressed between the two sets of azole-resistant strains. The growth of lower MIC2 and higher resistance strain and CIRG (a drug transporter) was observed in resistant isolates as compared with susceptible strain. Furthermore, resistance strain has two copies of ERG11 while susceptible isolates have single copy of ERG11. Notably, HGT2 genes involved in the ergosterol biosynthesis pathway were found to be induced in azole-resistant isolates. These include HGT1, HGT2, and HGT6, which confer resistance to azoles.

Conclusion: This study identifies several gene families that are differentially expressed in azole-resistant 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.

Keywords: Candida auris, azole-resistant, transcriptome, gene expression, fungal resistance

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Evaluation of Beta-1,3-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-1,3-glucan test is useful as a tool for antifungal stewardship in detecting unnecessary 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 BD 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 recommends 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 echinocandin (caspofungin, micafungin, and anidulafungin). The BDG test was performed using Fungitell® assay (Associates of Cape Cod, Massachusetts) that quantitatively measures 1, 3-D-glucan levels which is run twice a week on Wednesday and Saturday. The cut-off for a negative, indeterminate and positive result were 0.06 μg/ml, 0.08 μg/ml and > 0.10 μg/ml respectively. The result of the BDG test and blood cultures was promptly shared 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 echinocandins whichever was earlier. The total cost savings (in Indian Rupees (INR) and converted into US Dollars (USD)) were calculated based on an average of 10 days extra therapy with echinocandins.

Results: A total of 217 echinocandin-treated patients were prescribed in 294 patients treated during the study period, and the BDG levels (170, 15.0%) was the most commonly prescribed echinocandin following caspofungin (131, 19%), and micafungin (54, 11%). The BDG test as well as blood fungal cultures were negative for 65 prescriptions in 99 patients (35.7%). The compliance to recommendations for stopping echinocandins in these prescriptions was 100% (95.5%). None of those 99 patients had a true culture positive for Candida during the follow-up period. A total of 17 patients died, 1 was discharged against medical advice, 19 were discharged and 12 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 611,674 INR, corresponding to 89,040 USD during the study period.

Conclusion: BDG test-based stewardship strategy helped in reducing the use of echinocandins with cost savings and no increased risk of invasive fungal infections related to adverse outcomes in patients where echinocandins were discontinued. The universal compliance to recommendations to discontinue should be achieved by constant dialogues between the departments of Clinical Microbiology and Clinical Medicine.

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Genetic determinants of antifungal drug resistance in Fusarium solani species complex

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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 complex is responsible for nearly half of all fungal keratitis cases. Fungal keratitis is difficult to treat because of the increased antifungal resistance of Fusarium species.

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

To find the genetic determinants of resistance using whole genome sequencing.

Methodology: Prior to ASTP and according to CLSI, clinical isolates of Fusarium species (n = 5) were cultured on potato dextrose agar for 7 days at room temperature. Fungal species were harvested using 0.5% NaCl and antifungal drug susceptibility testing of 6 different antifungal drugs were tested using CLSI standards both microdilution method and minimum inhibitory concentrations were obtained. After 24 and 48 h, broth microdilution plates were manually examined. The MIC values were obtained using the CLSI standards.

Results: In this study the antifungal drug susceptibility from average MIC value were found as fluconazole (312 μg/ml) > itraconazole (32 μg/ml) > amphotericin B (8 μg/ml) > nystatin (16 μg/ml) > posaconazole (2 μg/ml) > voriconazole (1 μg/ml). Fluconazole had a higher MIC value (128 μg/ml) in all isolates, however, voriconazole was shown to be more sensitive, with a lower MIC range (0.25-4 μg/ml). Glycosyl/Phosphatidylinositol resistance protein, ndh—multidrug resistance transport, fusaric acid resistance protein, oxygen buffer protein resistance protein, and copper resistance protein were found by genome-blast analysis.

Conclusion: As a conclusion of this study, we observed antifungal drug resistance in Fusarium spp., which is often used to treat keratitis patients, employing fluconazole, itraconazole, and amphotericin B. Resistance to fluconazole was the 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.
A study on candiduria in neonates and infants from a tertiary care center, North India.

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Objective: Candida albicans is the major cause of fungal UTI in neonates and infants but nowadays incidence of other species of Candida is also increasing, and these are mostly multidrug resistant. It is, therefore, important to determine the causative Candida species in fungal UTI for appropriate management. This study was undertaken to determine the Candida species distribution in UTI along with susceptibility patterns and outcomes in infant and neonates admitted to various wards and intensive care units (ICUs) of our hospital. The incidence rate of candiduria in ICUs was also assessed.

Method: Urine samples were collected from infants and neonates presented in pediatric and neonatal ICUs and clinical wards with a clinical suspicion of candiduria. Infants at risk of invasive candidiasis were also included in this study. Identification of Candida species was done by Gram’s staining, germ tube test, chlamydospore formation on corn meal agar, color of colonies on CHROMagar, and confirmed by Matrix Assisted Laser Desorption-Time of Flight (MALDI-TOF). Antifungal susceptibility was performed by using the Broth microdilution method as per the latest CLSI guidelines (M38-A3M38-A3).

Result: Urine samples were received from 219 infants, and Candida was isolated from samples from 82 infants (isolation rate 23.7%), of which 30 were admitted to pediatric or neonatal ICU and 22 in the wards. The incidence rate of candiduria in ICU was 3.28%, Candida albicans was the most frequently isolated species from the samples of infants in the wards (13/22 i.e., 59%), while Candida tropicalis was most frequently isolated from samples of infants in the ICUs (13/30 i.e., 43.34%). Candida glabrata was the least commonly isolated species and was only encountered in the ICU. The species distribution of isolates is given in Table 1. There was no discrepancy between the results of conventional methods of identification and MALDI-TOF.

Antifungal susceptibility was performed for 30 randomly selected isolates. All were found to be susceptible to caspofungin, micafungin, itraconazole, voriconazole, fluconazole, and amphotericin B. MIC distribution for various isolates is given in Table 2.

Conclusion: High index of suspicion of candidiasis is necessary for early diagnosis of fungal UTI and initiation of antifungal treatment, especially in critically ill infants requiring intensive care. Species other than C. albicans are also encountered more frequently nowadays and these species often have higher MICs for commonly used antifungal drugs, which may lead to delayed or false response to routine antifungal therapy and inaccurate prolonged use and/or higher doses of antifungal. Identification of Candida isolates at species level along with analysis of the susceptibility patterns is therefore important for successful outcomes in candiduria in neonates and infants.