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Baseline antifungal usage patterns and knowledge regarding management of invasive fungal infections as a part of a multidisciplinary antifungal stewardship (AFS) program

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Objectives: To establish a baseline of antifungal usage patterns (indication, duration, toxicity, and cost) and physician's knowledge of management of invasive fungal infections, as a basis for implementation of a multidisciplinary antifungal stewardship (AFS) program at a tertiary care center.

Methods: Data including clinical history, investigations, and antifungal therapy was collected by chart review and bedside rounds from 100 patients with laboratory-confirmed invasive fungal infections (IFIs). Requirement and adequacy of antifungal therapy were assessed in comparison with IDSA and EORTC/MSG guidelines and scored at discharge/death using the Valerio system. This system assigns points to six parameters: indication, optimal selection of antifungal agent, dosage according to individual characteristics, loading and maintenance dose, therapy adjustment after microbiological results, route of administration, and length of therapy. The maximum score (10) indicates appropriate therapy. Any score of < 10 is classified as inappropriate.

Results: Out of 100 patients who met the criteria for IFI, 85 patients had a single IFI, 45 (52.9%) of whom received appropriate antifungal therapy, 17 (20%) received other than the recommended antifungal therapy and 23 (27.1%) received no antifungals. A total of 15 patients had dual IFIs, 10 (66.7%) of whom received other than the recommended antifungal therapy for one or both infections, 1 (6.7%) was treated appropriately for one infection but left untreated for the other, 2 (13.4%) patients were untreated for both infections and 2 (13.4%) were appropriately treated for both infections. The most common types of inappropriate antifungal use were inappropriate antifungal for organism (16 incidents), inadequate dosage (11 incidents), inappropriate antifungal for site (6 incidents), inadequate duration (6 incidents), and failure to adjust antifungal therapy based on microbiological test results (6 incidents). Common reasons observed for inappropriate antifungal use were delay in starting antifungal therapy or in ordering appropriate tests for establishing diagnosis, uncertainty in distinguishing fungal pathogens from colonisers, lack of rigorous antifungal charting, unavailability of first-line drug, and attempts to use a single antifungal to cover dual IFIs.

Conclusions: There are several inadequacies in Valerio scoring system, i.e., no weightage given to timely initiation of treatment, no deductions for delay in starting treatment once reports have been received, or for use of unnecessary antifungals in addition to recommended ones. Antifungals are often chosen by organism only while ignoring site-specific action and penetration of the drug. There is no comprehensive system for recording antifungal use, making it difficult to ascertain cumulative antifungal use over time. Direct association could not be made between inappropriate antifungal use and outcome as most patients had multiple comorbidities apart from fungal infection. Where fungal infection occurs along with TB, fungi are often considered commensals and left untreated. Many immunocompetent patients with IFIs are 'unclassifiable', ie, cannot be categorized under existing guidelines. Even for 'classifiable' patients, there is considerable subjectivity in antifungal treatment guidelines. There is a need for a standardized algorithm-based treatment at institutional level for these groups of patients.

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Virulence factors and azole-resistant mechanism of *Candida tropicalis* isolated from candidemia

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Background: Limited knowledge exists on the virulence factors of *Candida tropicalis* and the mechanisms of azole resistance that lead to an intensified pathogenicity and treatment failure. We aimed to evaluate the virulence factors and molecular mechanisms of azole resistance among *C. tropicalis* isolated from patients with candidemia.

Materials and Methods: Several virulence factors, including extracellular enzymatic activities, cell surface hydrophobicity (CSH), and biofilm formation were evaluated. Antifungal susceptibility pattern and expression level of ERG11, UPC2, MDR1, and CDR1 genes of 8 (4 fluconazole resistance and 4 fluconazole susceptible) clinical *C. tropicalis* isolates were assessed. The correlation between the virulence factors and antifungal susceptibility patterns was analyzed.

Results: During a 4-year study, 45 *C. tropicalis* isolates were recovered from candidemia patients. The isolates expressed different frequencies of virulence determinants as follows: coagulase 4 (8.9%), phospholipase 5 (11.1%), proteinase 31 (68.9%), esterase 43 (95.6%), hemolysin 44 (97.8%), biofilm formation 45 (100%), and CSH 45(100%). All the isolates were susceptible to amphotericin B and showed the highest resistance to voriconazole. There was a significant positive correlation between micafungin minimum inhibitory concentrations (MICs) and hemolysin production ($rs = 0.316$). However, we found a negative correlation between fluconazole MICs and esterase production ($rs = -0.383$). We observed the high expression of ERG11 and UPC2 genes in fluconazole-resistant *C. tropicalis* isolates.

Conclusion: *Candida tropicalis* isolated from candidemia patients extensively displayed capacities for biofilm formation, hemolysis, esterase activity, and hydrophobicity. In addition, the overexpression of ERG11 and UPC2 genes was considered one of the possible mechanisms of azole resistance.

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Comparison of efficacy of innovator molecule of itraconazole with generic forms of itraconazole in treatment naïve subjects with chronic pulmonary aspergillosis

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Objective: Itraconazole capsule has a variable and unpredictable bioavailability. Whether generic brands of itraconazole are as effective as the innovator molecule in the treatment of subjects with chronic pulmonary aspergillosis (CPA) is unclear. We compared the proportion of subjects who achieved therapeutic drug levels with the generic and the innovator itraconazole at 2 weeks after treatment initiation.

Methods: In this retrospective study, we compared the proportion of subjects with CPA achieving therapeutic drug levels ($\geq$ 0.5 mg/l) with the generic and the innovator itraconazole at 2 weeks after treatment initiation. We performed a multivariate logistic regression analysis to ascertain if the trough itraconazole levels affected the treatment outcomes. We also performed morphometric analysis of different brands of itraconazole by video dermoscopy.

Results: A total of 193 [generic brands ($n = 94$) and innovator itraconazole ($n = 99$)] subjects of CPA were enrolled. The median (IQR) age of the study population [54% (105/194) men] was 42 (32-55) years. The proportion of subjects who achieved therapeutic trough itraconazole levels was significantly ($P < .0001$) higher with the innovator than the generic brands [72/99 (73%) vs. 27/94 (29%)]. The median trough itraconazole level at 2-weeks was also higher with the innovator brand than the generic brands [0.8 (0.5-1.6) vs. 0 (0.0.5) mg/l]. The average trough itraconazole levels and the trough itraconazole levels >1 mg/l independently predicted favorable treatment response after adjusting for age, gender, and CPA severity. The generic brands had a variable number, size, and a larger pellet size on the morphometric analysis. Two brands had dummy particles.

Conclusion: Significantly higher proportion of subjects achieved therapeutic drug levels with the innovator brand of itraconazole than the generic brands. Importantly, the serum itraconazole levels independently predicted a favorable response to treatment in CPA.