Poster Presentations

P708 Baseline antifungal usage patterns and knowledge regarding management of invasive fungal infections as a part of a multidisciplinary antifungal stewardship (APS) program

Jensy Sachdev1, Gagandeep Singh1, Immaculata Kea1, Marish Soney2
1Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India
2Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

Poster session 1, September 21, 2022, 12:10 PM - 1:10 PM

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 (APS) program at a tertiary-care center.

Methods: Data including clinical history, investigations, and antifungal therapy was collected by chart review and review 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 discharged/guideline using the Valero 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, 81 patients had a single IFI. 48 (52.8%) of whom received appropriate antifungal therapy, 17 (20%) received other than the recommended antifungal therapy and 23 (27.1%) received no antifungal. A total of 47 patients had dual IFIs, 19 (46.7%) of whom received other than the recommended antifungal therapy for one or both infections; 1 (2.6%) was treated appropriately for one infection but left untreated for the other; 2 (13.6%) patients were untreated for both infections and 2 (13.6%) were appropriately treated for both infections. The most common types of inappropriate antifungal use were inappropriate antifungal for organism (26 incidents), inadequate dose (11 incidents), inappropriate antifungal for site (6 incidents), inadequate duration (4 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 colonizers, 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 Valero 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 active and penetrations 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 contaminants and left untreated. Many immunocompromised patients with IFIs are ‘undetectable’, i.e., cannot be categorized under existing guidelines. Even for ‘detectable’ patients, there is considerable variability in antifungal treatment guidelines. These are in need for a standardized algorithm-based treatment at institutional level for those groups of patients.

P709 Virulence factors andazole-resistant mechanism of Candida tropicalis isolated from candidemia

Elahe Sasan Sahevedin1, Mohamad Hosssein Yadeger1, Sadegh Khodavansory1, Saeed Rezaie2, Mohammadreza Salehi3, Mahdi Solmaz Gataev3
1Hormogian University of Medical Sciences, Bandar Abbas, Iran
2Tabriz University of Medical Sciences, Tehran, Iran, Tehran, Iran
3Tabriz University of Medical Sciences, Tehran, Iran, Tehran, Iran

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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 EFG1, UPC2, MDR1, and CDR1 genes of 14 (4 flucytosine resistant 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 resistance determinants as follows: coagulase 6 (8.9%), pili pherolipase 3 (11.1%), protease 31 (66.7%), yeast-like cells 31 (70.2%), azole-resistant fungi 45 (100%), and CDR1 40 (100%). All the isolates were susceptible to amphotericin B and showed the highest resistance to voriconazole. There was a significant positive correlation between microorganism minimum inhibitory concentration (MICs) and benzydamine production (p < 0.014). However, we found a negative correlation between fluconazole MICs and benzydamine production (p < 0.038). We observed the high expression of EFG1 and UPC2 genes in fluconazole-resistant C. tropicalis isolates.

Conclusions: Candida tropicalis isolated from candidemia patients commonly express high capacities for biofilm formation, hemolysis, ototoxic activity, and hydrophobicity. In addition, the overexpression of EFG1 and UPC2 genes was considered one of the possible mechanisms of azole resistance.

P860 Comparison of efficacy of innovator molecule of Itraconazole with generic forms of Itraconazole in treatment naive subjects with chronic pulmonary aspergillosis

Indrapal Singh, Keshavamurthi Vinay, Rilesh Agrawal, Shivprakash Rudramath PGIMER, Chandigarh, Chandigarh, India

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Objectives: Itraconazole capsules 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 (≥ 0.5 μg/ml) 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 outcome. We also performed morphometric analysis of different brands of Itraconazole by video densitometry.

Results: A total of 195 (generic) subjects and 195 (innovator) subjects of CPA were enrolled. The median (IQR) age of the study population 44 (10-59) years was 42 (12-52) years. The proportion of subjects who achieved therapeutic trough Itraconazole levels was significantly (P = 0.001) higher with the innovator than the generic brands [72/99 (73%) vs. 27/84 (32%)]. 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] μg/ml). The average trough Itraconazole levels and the trough Itraconazole levels > 1 μg/ml 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 dimer particles.

Conclusions: 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.
Table 1. Outcomes.

| Total (n = 193) | Generic drug, (n = 94) | Innovator molecule (n = 99) | P-value |
|----------------|------------------------|----------------------------|---------|
| Primary outcome |                        |                            |         |
| Proportion of subjects achieving ≥0.5 mg/l at 2 weeks | 99 (51.3) | 27 (28.7) | 72 (72.7) | <.0001 |
| Secondary outcomes |                      |                            |         |
| Itraconazole levels at 14 days, mg/l | 0.5 (0-1) | 0 (0-0.5) | 0.8 (0.5-1.6) | <.0001 |
| Average Itraconazole levels, mg/l | 1.4 (0.7-2.4) | 0.8 (0.4-1.3) | 2.1 (1.2-2.8) | <.0001 |
| Proportion of subjects achieving average itraconazole ≥1 mg/l | 98 (50.8) | 24 (25.5) | 74 (74.7) |         |
| Adverse events, n (%) | 43 (22.3) | 23 (24.5) | 20 (20.2) | .494   |

* A total of 27 subjects with generic drug achieved therapeutic drug levels and were not given the innovator molecule.