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Drug Utilization Evaluation of Systemic Antifungals in a Tertiary Care Hospital

Sherin Mathew[1], Cristy Anne Kuriakose[1], Sandra Shaji[1], Binu Upendran[2], Lakshmi R[3*]

[1]Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala-688524, Kerala, India
[2]Department of Nephrology, Lourdes Hospital, Post Graduate Institute of Medical Science and Research, Kochi-682012, Kerala, India
[3]Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala-688524, Kerala, India

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***Corresponding author:** Lakshmi R
Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala-688524, Kerala, India

Abstract

Introduction: The incidence of Invasive Fungal Infection has increased, and it constitutes a serious threat to human health and life, especially in immunocompromised and critically ill patients. We aimed to evaluate the appropriateness of antifungal agents along with their risk factors and sensitivity pattern. ***Methods:*** It is a retrospective, cross-sectional study, which includes details of patients prescribed with systemic antifungal agents during a period of five years (01-06-2016 to 31-05-2021). Collected details were compared with Infectious Diseases Society of America (IDSA) guidelines and mycological results to determine the overall appropriateness. ***Results:*** A total of 102 patients prescribed with systemic antifungals were selected for the study. The majority of the drugs were prescribed as Definitive (59.19%) and T Fluconazole (39.4%) was the most common drug given. The most common indication for antifungal prescriptions was found to be Respiratory tract infection. Appropriateness of antifungal use was assessed on indication, dosage, contraindication, and drug-drug interaction. Overall assessment of antifungal agents and treatment strategy demonstrated that antifungal treatment was appropriate in 41.6% cases, debatable in 36% cases and inappropriate in 22.4% of cases. The most common culture specimen collected was urine and Candida tropicalis (42.86%) was the frequently separated organism from it. Sepsis (21.4%) was the most common risk factor associated with invasive fungal infection. ***Conclusion:*** By implementing an effective antifungal stewardship program, we could improve the rational use of systemic antifungals and thereby prevent the future resistance and improve clinical outcome.

Keywords: Invasive fungal infections, Risk factors, Antifungal agents, Antifungal stewardship, cross-sectional study, causative organisms.

INTRODUCTION

Antifungals agents are used to prevent and treat fungal infections like candidiasis, asperigillosis, cryptococcal meningitis and others. Invasive fungal infections (IFI) are common in immune compromised patients as reflected by their chemotherapy, acquired immune deficiency syndrome and organ transplantation [1]. To treat fungal infections mainly four categories of antifungal agents are preferred they are; polyenes (amphotericin B, nystatin, candicidin, pimaricin, methyl partricin, trichomycin), azoles (Fluconazole, itraconazole, ketoconazole, miconazole, clotrimazole, voriconazole, posaconazole, ravuconazole), echinocandins (caspofungins, micafungin and anidulafungin) and flucytosine (5-fluorocytosine) [2]. The occurance of antifungal resistance is complex and based on multiple hosts and microbial factors. Patients with severe immunodeficiency are more likely to fail therapy because the antifungal drug must fight infection without the benefit of an immune response [3]. The presence of endowing catheters, artificial heart valves and other surgical instruments may also cause refractory infections, as infected organisms attach to these materials and form biofilms that inhibit drug action [4]. One of the key factors in enhancing antifungal drug resistance is the improper use of antifungals. Therefore, effective antifungal therapy should be used to mitigate the enhancement of drug resistance. In addition, the dosage and spectrum of action of antimicrobial agents have significant implications for their effect on the human micro biome [5]. The incidence of the disease and the people most at risk were learned from active surveillance for fungal infections. The growing usage of antifungal

medications in recent years has led to the emergence of drug resistance to these drugs [6].

Management of Invasive Candidiasis supports a prophylactic approach to prevent disease in high-risk patients. Infectious Diseases Society of America (IDSA) guidelines recommend administering prophylactic Fluconazole therapy only to those patients with a 10% or higher risk of infection as determined by a risk prediction score. A patient wouldn't receive drugs as part of an empiric therapy, unless they showed signs and symptoms of infection. If a definitive diagnosis is not made based on culture results once empiric therapy has begun, it may be difficult to determine when to stop the treatment. Pre-emptive therapy may be a better approach to managing Invasive Fungal Infections, especially in Intensive care unit (ICU) patients. In this approach, high-risk patients are screened utilizing diagnostic indicators either before or just as symptoms begins to develop [7]. Treatment for acute illnesses should continue until a baseline level of normal functions has been achieved. The management strategy can be changed, and the treatment should be properly evaluated if they are unable to make significant progress with it. For chronic conditions, the duration of treatment is determined by the severity of the condition and the patient's response [8]. Antifungal susceptibility testing is a very dynamic region of clinical mycology. Based totally on the mounted minimum inhibitory concentration (MIC) breakpoints, it is now viable to decide the susceptibilities of fungal traces to Fluconazole, itraconazole, voriconazole and flucytosine [9].

Several researches have recognized common risk elements for patients developing fungal infection. The most common recognized factors are colonization, broad spectrum antibiotics, indwelling catheter, total parenteral nutrition, surgery, sepsis, diabetes mellitus, mechanical ventilation, renal replacement therapy and neutropenia. It is essential for the clinician to realize and discover the risk factors to have an excessive index of suspicion in critically ill patients [10]. The term "antifungal stewardship" refers to coordinated efforts to monitor and guide the appropriate use of antifungal agents in order to maximise clinical outcomes and reduce side effects. The major objectives of antifungal stewardship are improved treatment, de-escalation or discontinuation of antifungal therapy when necessary, cost savings, and decreased fungal resistance, with no adverse effects on morbidity or mortality. It involves an experienced and qualified multidisciplinary team, based on education, bedside interventions and daily cooperation with the microbiology and pharmacy team [11].

METHODS

Study design

The retrospective cross-sectional study was conducted by taking details of patients from the medical records and the Mediware system available in a tertiarycare hospital for a period of five years (01-06-2016 to 31-05-2021). Patients were selected based on inclusion and exclusion criteria. Inclusion criteria for the study were Patients ≥ 18 years of age, patients prescribed with at least one systemic antifungal therapy and the exclusion criteria include patients who got discharged against medical advice and patients whose medical records were incomplete.

Data collection

The data were collected using specially designed data collection form. Retrospective patient demographic details, pertinent laboratory as well as treatment details were extracted from medical records and hospital's mediware system.

Antifungal therapy appropriateness assessment criteria

Appropriateness is evaluated based on indication, dosage and presence of drug interactions or contraindications (Table 1) [12]. Antifungal therapy, is considered appropriate if all four evaluation criteria (indication, dosage and drug interactions or contraindications) are considered appropriate; debatable if there is at least one debatable characteristic but no inappropriate assessment. Inappropriate, if there is at least one inappropriate evaluation criterion. Indication and dosage are categorized based on the recommendations made by the IDSAguidelines for the diagnosis and management of aspergillosis and candidiasis. The antifungal–drug interactions were assessed using uptodate.com. Finally, the contraindications where estimated from the Summary product characteristics (SPC) of each drug.

Table 1: Criteria for the Appropriateness of Antifungal Therapy

Classification	Indication	Dose	Drug-drug interactions	Contraindication
Appropriate	In accordance with SPC and /or with guidelines And adapted to mycological data	Appropriate dose or under or deviation of 10 %	There is no concurrent drug that has the potential to cause clinically relevant drug-drug interaction involving X and D categories.	No contraindication according to SPC
Debatable	Choice of antifungal not recommended by SPC or guidelines, but based on published clinical data,	>10 - ≤ 25% deviation from the appropriate	The concurrent drug that has the potential to cause clinically relevant drug-drug interactions involving D category only	-

Classification	Indication	Dose	Drug-drug interactions	Contraindication
	evolving clinical experience or absence of appropriate alternative	dose		
Inappropriate	Inappropriate choice based on SPC, guidelines or mycological results with existence of an appropriate alternative	>25 % deviation from the appropriate dose	The concurrent drug that has the potential to cause clinically relevant drug-drug interactions involving X category	Contraindication according to SPC

X Category- Avoid combination, drugs may interact with each other in a clinically significant manner. The risk usually outweighs the potential benefit. These agents are generally contraindicated. D Category- Consider therapy modification, drugs may interact with each other in a clinically significant manner. Patient specific assessments such as aggressive monitoring, empiric dosage changes or choosing alternative agents must be conducted to determine whether the potential benefit outweighs risk. SPC – Summary product characteristics.

Sample size estimation

Earlier research revealed that 44.7% of people used antifungal medications appropriately [12]. Thus, a margin of error of 10% and a confidence interval of 95% were utilized for a sample size of 95 patients. To account for any missing data, the sample size was further raised to 102.

Data analyses

The collected data were compiled using Microsoft Excel, SPSS and were presented using tables and graphs. Statistical calculations were done using; frequencies, mean, Standard deviation (SD), chi square test and cross tabulation. The data were tabulated, analyzed and compared with relevant studies. Analyses were carried out at 10% level of statistical significance.

RESULTS

Patient's characteristics

A total of 102 patients prescribed with systemic antifungal were selected for the study. More patients were in the age group of 58–67 in both populations (Male and Female). Out of 102 patients, more than half of the patients were males, 53.9% (n=55) compared to females, 46.1% (n=47). The minimum age observed was 19 years and the maximum age observed was 93 years. The mean age ± SD was found to be 62.03±13.004. A considerable number of patients prescribed with systemic antifungal drugs were in the age group of 58–67. The comorbidities were sorted into the following categories: the number of patients with one comorbidity, two comorbidities and the number of patients with more than two comorbidities. Most patients with one comorbidity (n=7) were in the age category 48-57, two comorbidities (n=5) were in the age group 58-67 years and more than two comorbidities were in the age group 58-67 (n=22). Commonly observed comorbidities were Diabetes mellitus (n=52), Hypertension (n=35), Lower respiratory tract infection (LRTI) (n=26), Cancer (n=18) and Coronary artery disease (CAD) (n=14). In our study population most of the cases were from General Medicine (48.06%), followed by Nephrology (19.62%) and Oncology (12.76%)) (Table 2).55.9% (n=57) of patients were admitted to ICU and 44.1% (n=45) were admitted to the ward. The majority of patients were admitted for a period of 10 to 19 days. Significantly higher number of patients survived 86.3% (n=88) compared to those that died during treatment 13.7% (n=14).

Table 2: Baseline characteristics of patients prescribed with systemic antifungal agents

Characteristics						
Age	**Number of patients**	**Sex**		**Number of comorbidities**		
		Female	**Male**	**1**	**2**	**More than 2**
18-27	1 (1.0%)	0	1 (1.0%)	0	1	0
28-37	5 (4.9%)	3 (2.9%)	2 (2.0%)	4	0	1
38-47	7 (6.9%)	5 (4.9%)	2 (2.0%)	3	1	3
48-57	20 (19.6%)	10 (9.8%)	10 (9.8%)	7	2	11
58-67	33 (32.4%)	14 (13.7%)	19 (18.6%)	6	5	22
68-77	27 (26.5%)	12 (11.8%)	15 (14.7%)	6	3	18
78-87	8 (7.8%)	2(2.0%)	6 (5.9%)	2	1	5
88-97	1 (1.0%)	1 (1.0%)	0%	0	1	0
Total (%)	102	47	55	28	14	60

	Number of patients	Percentage
Departments		
Cardiology	5	4.91 %
Dermatology	1	0.98 %
General Surgery	2	1.96 %
General Medicine	48	47.06 %
Nephrology	19	18.62 %
Neurology	8	7.84 %
Oncology	12	11.77 %
Orthopaedics	1	0.98 %
Psychiatry	2	1.96 %
Pulmonology	2	1.96 %
Urology	2	1.96 %
Duration of Hospital Stay (days)		
1−9	41	40.2 %
10-19	42	41.2 %
20-29	13	12.7 %
30-39	3	2.9 %
40-49	3	2.9 %

Prescribing pattern of antifungal agents

Taking the same class of antifungals, both parenteral and oral, together, a total of 117 antifungals agents were given to the whole patients. Interpretation of the results shows that, the majority of the patients were prescribed with one antifungal agent (n=91) and the average number of antifungal prescribed per patient was 1.15 (SD: ±0.475, range: 1-4). The mean duration of antifungal treatment was 8.86 days (SD ±6.118 Range 1 - 48). The conversion of parenteral to oral therapy was possible only in 18% of the patients. A total of 7 systemically used antifungal agents were identified from the whole case and they were Amphotericin B (5.13%), Fluconazole (52.99%), Voriconazole (17.95%), Itraconazole (11.11%), Micafungin (1.71%), Caspofungin (0.85%), Terbinafine (9.4%), and Posaconazole (0.86%) (Figure: 1). A total of 125 drugs including parenteral and oral were prescribed during the course in hospital and discharge for indications which mainly includes RTI (31.4%), Sepsis (21.6%),UTI(17.6%), Prophylaxis in Cancer patients (9.85), Cutaneous fungal infection(7.8%), CKD (4.9%) etc. The most commonly prescribed drug for RTI was Inj. voriconazole (27.5%), for Sepsis UTI and CKD, the drug prescribed was T Fluconazole (41.4%, 70%, 50% respectively). Cutaneous fungal infection was treated with T Terbinafine (100%), and Cancer was treated with 50% oral and 50% parenteral Fluconazole. Prophylactic treatment was given for cancer patients 100% (n=10%).Majority of the Empirical therapy was given to patients diagnosed with RTI 33.3% (n=9) followed by cutaneous fungal infection 29.6% (n=8).Most common indication for which the definitive treatment started was for RTI 32.7% (n=18) followed by Sepsis 30.9% (n=17).In 10 patients the treatment started as empirical and later, continued according to the mycological results, the most common disease for which this pattern followed was also RTI 50% (n=5).The most followed treatment pattern in study population was Definitive treatment 53.9 % (n=55) and the least followed pattern was prophylactic and empirical to definitive treatment pattern 9.8% (n=10).

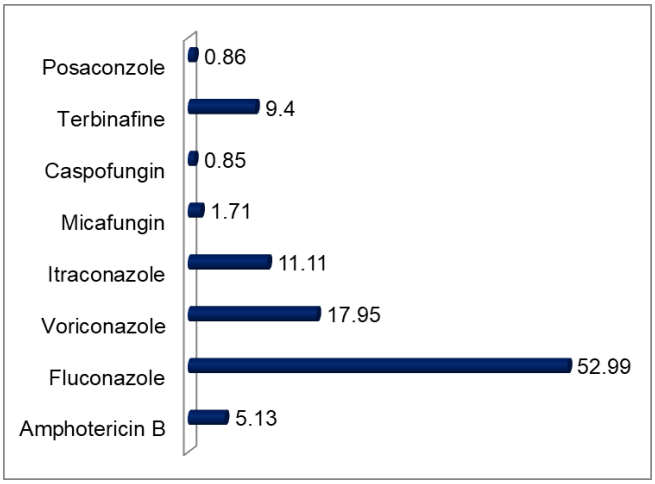

Figure 1: Frequency of Systemic Antifungal treatment used in the study patients

Majority of the drug were prescribed as Definitive 59.19% (n=34) and T. Fluconazole 39.4% (n=28) was the common drug given. Inempirical therapy 28.34% (n=34). T. Terbinafine 32.4% (n=11) was prescribed most. Both oral and parenteral Fluconazole (50%, n=5) was the drug of choice in prophylactic treatment 8.34 %(n=10).The drug that was started as empirical and continued the same after the report of mycological result is categorized under empirical to definitive 4.15% (n=5) and T. Fluconazole 60% (n=3) was the most prescribed drug in this treatment pattern.

Assessment of appropriateness of antifungal therapy

Appropriateness of antifungal drugs areassessed based on the criteria summarized in table. Of 125 drugs prescribed, which include both prescribed during hospital stay and discharge, 96% (n=120) drugs have appropriate indication, 4% (n=5) have debatable indication. The dose was appropriate in 55.2% (n=69), debatable in 34.4% (n=43) cases, and inappropriate in 10.4% (n=13) cases. Contraindication based on SPC was appropriate in 97.6% (n=122) cases and inappropriate in 2.4% (n=3).Finally drug-drug interaction was appropriate in 68.8% (n=86) cases, debatable in 16% (n=20) cases and inappropriate in 15.2% (n=19) cases. Appropriateness of indication was higher (100%) in Inj Amphotericin b, Inj. Caspofungin, Inj. voriconazole, T. Terbinafine, and Syp. Posaconazole, in case of dose, appropriateness was more (100%) in Inj. Caspofungin, Inj. Micafungin, Inj.voriconazole, T. Terbinafine, and Syp. Posaconazole. Contraindication was 100% appropriate in Inj. Caspofungin, Inj. Micafungin, T. Terbinafine, and Syp. Posaconazole and drug–drug interaction was mostly appropriate (100%) in Inj. Amphotericin b, Inj. Caspofungin, T. Terbinafine, and Syp. Posaconazole. Overall assessment of antifungal agent and treatment strategy demonstrated that antfungal treatment was appropriate in 41.6% cases, debatable in 36% cases and inappropriate in 22.4% of cases.The chi square value ($\chi 2$) 76.7683 shows *p-value < 0.001*, hence significant association between Antifungal agents and treatment strategy.The most common antifungal drug administered was T. Fluconazole with 8.9% (n=4) appropriate cases, 73.3% (n=33) debatable cases and 17.8% (n=8) inappropriate cases. The most appropriate drug prescribed was Inj. Fluconazole 25%, debatable was T. Fluconazole 73.33% and inappropriate was also T. Fluconazole (Table 3).

Table 3: Overall appropriateness of Antifungal agent and treatment strategy of the study population

Antifungal Agents	Treatment Strategy		
	Appropriate	Debatable	Inappropriat
Inj.Amphotericin B	2	0	4
Inj.Caspofungin	1	0	0
Inj.Micafungin	1	1	0
Inj.Fluconazole	13	5	4
Inj.Voriconazole	6	2	4
T.Fluconazole	4	33	8
T.Itraconazole	3	3	7
T.Terbinafine	11	0	0
T.Voriconazole	10	1	1
Syp.Posaconazole	1	0	0
Total	52	45	28
$\chi 2 = 76.7683$ df = 18 *p-value < 0.001*			

The chi-square value ($\chi 2$) 76.7683 shows a p-value < 0.001, hence a statistically significant association between Antifungal agents and treatment strategy.

The 120 antifungal agents prescribed during hospital stay was assessed for appropriateness in its treatment pattern and found out that in drugs given as empiricaly or prophylactically high proportion of treatment strategy was appropriate, 55.8% (n=19) and 50% (n=5)respectively.In definitive treatment with antifungal agents a substantial amount of drugs were in debatable 39.4%(n=28) category and in Empirical To Definitive treatment a considerable amount of drugs were in inappropriate category 60% (n=3). The most appropriate treatment pattern was definitive therapy (n=25).There was no significant association between treatment pattern of Antifungal agents and treatment strategy of the study population (Figure 2).

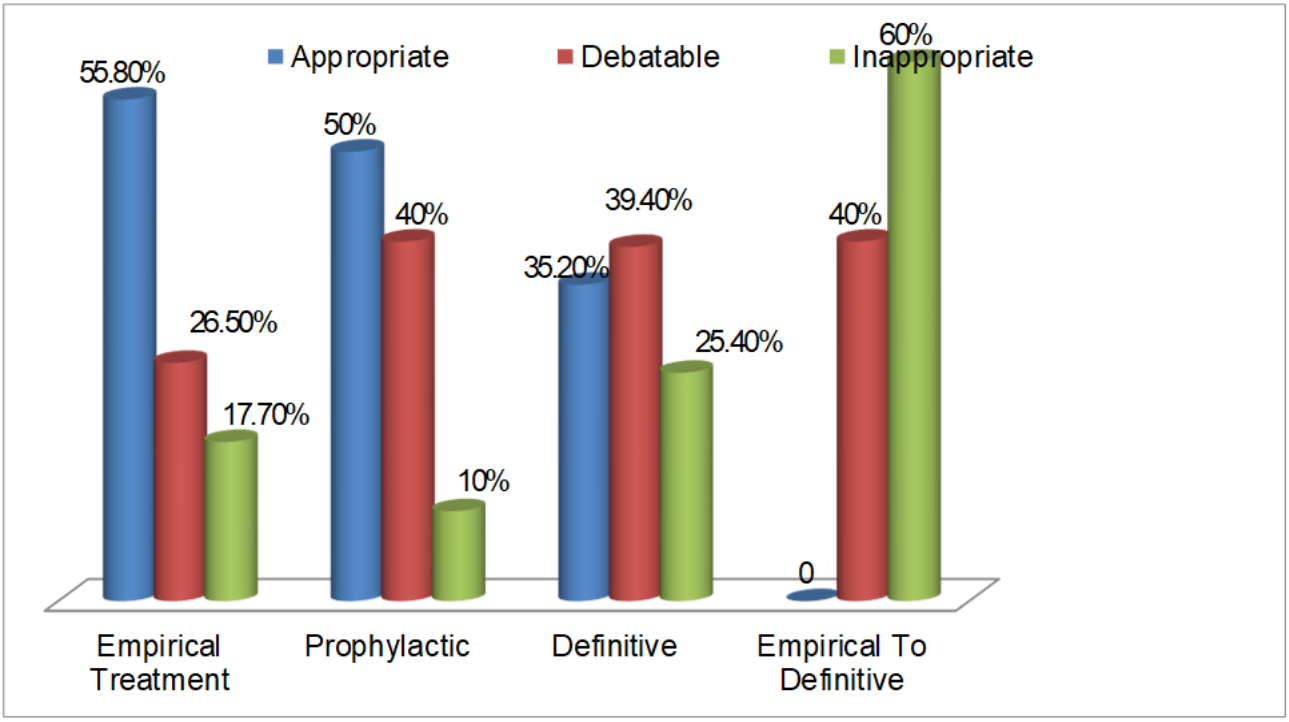

Figure 2: Overall appropriateness of treatment pattern of Antifungal agents and treatment strategy of the study population

The risk factors associated with invasive fungal infections

Our study looked at 10 different risk variables linked to IFD, with sepsis n=64(22.06%) being the most common, followed by catheterizcation n=57(19.65%). In our study, catheterization (72.2%) was revealed to be the most common risk factor for IFD in ICU patients, followed by diabetes mellitus (51.8%) (Table 4). The most number of patients with one risk factor (n=7) were in the age group 58-67 and two risk factor (n=6) were in the age group 48 -57 years and most number of patients with more than two risk factor were in the age group 58-67 (n=21). The occurrence of male dominance was predominant in case of one risk factor (n=1)25.5%and more than two risk factors (n=33)60.0% than females. In the incidence of two risk factors, it demonstrates a female dominance of (n=11)23.4%) over males.

Table 4: Risk Factors Associated with Invasive Fungal Infections in Patients Admitted in Ward and ICU

Risk Factors	No of patients	Percentage	No. of patients in ICU	Percentage
Catheterization	57	19.06	42	21.11
Surgery	17	5.69	9	4.52
Total Parenteral Nutrition	4	1.34	2	1.01
Sepsis	64	21.40	40	20.1
Fungal Colonisation	18	6.02	12	6.03
Diabetes Mellitus	52	17.39	29	14.57
Renal Replacement Therapy	29	9.70	20	10.05
Mechanical Ventilation	25	8.36	23	11.56
Chronic Antibiotic Use	18	6.02	16	8.04
Neutropenia	15	5.02	6	3.02

ICU –Intensive Care Unit

Causative agents and sensitivity pattern of isolated organisms

In 66 patients, specimens were collected for initiating Antifungal therapy in which n=64 (97%) has positive culture data and n=2 (3%) shows no fungal growth .From the positive culture obtained, n= 49 (76.56%) of the culture shows the growth of yeast and remaining n=15 (23.43%) shows the growth of mould. The isolated mould in the study was Aspergillus species and yeast was candida species.Out of 49 (76.56%) Candida species in our study, 30 (61%) were non-Candida albicans, 11 (23%) were candida albicans, and the remaining 8 (16%) were mentioned as other candida species. The non-Candida albicans include *Candida galbrata* 2 (7%), *Candida krusei* 1 (3%), Candida parapsilosis (72.3%), Candia tropicalis 20 (67%). The majority of the specimen collected was urine and the most common organism was Candida tropicalis 42.86%

(n=18) followed by specimen sputum and the isolated organism was *A*sperigillus species 100% (n=12). Candida isolates have been included in the susceptibility study.The susceptibility pattern of Candida isolates is illustrated in table 5. The overall sensitivity of candida species was found to be 100 % in Amphotericin B, Caspofungin and Micafungin, 96.96 % in Voriconazole and 95% in Fluconazole.

Table 5: Susceptibility pattern isolated of candida species (n=49) in the study population

	Candida Albicans	***Candida Glabrata***	***Candida Krusei***	***Candida Parapsilosis***	***Candida Tropicalis***	**Other Candida species**
Total number of isolates	11	2	1	7	20	8
Percentage susceptibility (number of isolates susceptible /Total number of isolates tested)						
Amphotericin B	100 (10/10)	100 (2/2)	0 (0/1)	100 (7/7)	100 (20/20)	100 (3/3)
Caspofungin	100 (4/4)	100 (1/1)	-	100 (5/5)	100 (13/13)	100 (1/1)
Micafungin	100 (4/4)	100 (1/1)	-	100 (5/5)	100 (13/13)	100 (2/2)
Fluconazole	100 (9/9)	-	0 (0/1)	100 (7/7)	100 (20/20)	66 (2/3)
voriconazole	100 (7/7)	100 (1/1)	100 (1/1)	100 (5/5)	94.1 (16/17)	100 (2/2)

DISCUSSION

An increasing number of people, including, burn victims, recipients of organ transplant, those on chemotherapy and Autoimmune disease (AIDS) patients, are liable to fungal infections [13]. Delay in treatment may be due to challenges in diagnosing Invasive Fungal Infection [14]. In our study, we found that aged population are more prone to fungal infection and are prescribed with systemic antifungal agents with a male dominance observed. In our study population, 7 different antifungal drugs were prescribed, with Fluconazole being the most common. Maricela Valerio et.al conducted a stewardship program on the Evaluation of antifungal use in a tertiary care institution. In their study the most frequently used antifungal agent was Fluconazole (58.3%) and the least was Posaconazole (3.9%) which is similar to our study [15]. The most common indication for antifungal prescriptions was found to be Respiratory Tract Infection (RTI). Delay in initiating appropriate antifungal therapy negatively affects survival in critically ill patients with Invasive Fungal Infections. Several challenges exist in confirming a definitive diagnosis of these infections and in identifying high-risk patients and also in preventing these infections [16]. The Treatment pattern was divided into 4 categories: Prophylactic, Empirical, Definitive and Empirical to Definitive. Majority of the drugs were prescribed as Definitive. Despite the availability of new drugs, Fluconazole has been observed to be frequently used. This could be attributed to Fluconazole's effectiveness in treating Candidaemia, which is comparable to that of relatively newer medications like amphotericin B. The mean duration of antifungal treatment was found to be 8.86 days. The appropriateness of antifungal use was based on indication, dosage, contraindication and drug-drug interaction, in accordance to Clinical Practice Guideline for the management of candidiasis and aspergillosis update by The Infectious Diseases Society of America and the summary product characteristics of each drug. The drug interaction of each antifungal with other co administrated agents was focused and drugs showing X and D category interactions are further analyzed for determining the appropriateness of antifungal agents. In our study, it is evident that all the parameters (indication, dosage, contraindication and drug-drug interaction) were appropriate with high percentage when compared with debatable and inappropriate category. Contra indication was more appropriate when compared with other categories. In a similar study, the indication, dose, contraindication and drug-drug interaction were found to be appropriate in 70.5%, 85.8%, 72.6%, 62.6% cases respectively [12]. Percentage of appropriateness is high in both the cases when compared to debatable and inappropriate in antifungal treatment.

The overall appropriateness of antifungal treatment was figured out by comparing the treatment strategy (appropriate, debatable or inappropriate) with antifungal agents and the treatment pattern opted. Antifungal therapy is considered appropriate if all four evaluation criteria (indication, dosage and presence of drug interactions or contraindications) are considered appropriate; debatable if there is at least one debatable characteristic, but no inappropriate assessment and inappropriate, if there is at least one inappropriate evaluation criterion. Overall assessment of antifungal agents and treatment strategy depicted that antifungal agents was mostly appropriate in comparison with other strategies when each of them considered individually, but the appropriateness does not meet the average. The most appropriate antifungal drug administered was Inj. Fluconazole. The consequences of inappropriate antifungal use due to inadequate dose, indication, occurrence of contraindication and drug interactions often leads to inadequate fungal treatment. Antifungal

agents administered by the patients when they were in hospital are considered to find out the overall appropriateness of treatment pattern. Even though most of the drugs prescribed as empirical and prophylactic were appropriate, when considering all 3 treatment pattern definitive pattern showed more appropriateness than others. The results of this study highlighted that, the increased incidences of appropriateness ameliorated patient's conditions and gave more positive outcomes.

Culture and sensitivity testing should always be used as a guide, when using antifungal agents. Positive cultures are recommended in order to begin antifungal therapy because results have demonstrated to be successful after definite treatment is started [17]. The culture shows the growth of yeast and the growth of mould. The isolated mould in the study was found to be Aspergillus species and yeast was candida species [18]. The most common culture specimen collected was urine and Candida tropicalis was the frequently isolated organism from it. Candida isolates have been included in the susceptibility study. In a similar study sensitivity of Candida species to Fluconazole was found to be ranging from 63.3% to 95%. Also the sensitivity to Voriconazole as recorded by these authors was in the range of 76.6% to 100% which was similar to our study [19, 20]. Although the culture of Aspergillus species has been performed, susceptibility pattern has not been recorded in the patient's culture report.

It is essential for the clinician to realize and discover the risk factors to have an excessive index of suspicion in critically ill patients. The most common recognized factors are colonization, broad spectrum antibiotics, indwelling catheter, total parenteral nutrition, surgery, sepsis, diabetes mellitus, mechanical ventilation, renal replacement therapy and neutropenia [10]. Out of 10 different risk factors analyzed in our study population, sepsis was the most common risk factor associated with invasive fungal infection. Gurmeet Singh et al. conducted a prospective study on risk factors for early invasive fungal disease in critically ill patients and discovered that sepsis was the most common risk factor linked with IFI, accounting for 97.3%(n= 72) [21]. In both study the most common risk factor was found to be Sepsis. Our study should be viewed in the light of certain limitations. As our study is retrospective, many incidences might have happened in real time clinical setting that might not be properly documented or simply ignored due to its trivial nature and therefore impossible to assess. Limited parenteral to oral conversion was analyzed during the study. Spectrum of activity towards Itraconazole was not recorded, therefore impossible to treat presumptively. Sensitivity pattern of Aspergillus species was not recorded therefore difficult to treat according to the mycological data. More number of azoles was investigated in our study than other antifungal agents.

CONCLUSION

When analysed retrospectively 41.6% of systemic antifungals were prescribed appropriately. Clinical pharmacist can play an important role in minimizing drug related problems by monitoring, evaluating and suggesting modifications to practitioners' prescribing habits so as to make rational, safe and effective pharmaceutical care and thereby improving the rational use of systemic antifungal agents. By implementing an effective antifungal stewardship program we could improve the rational use of systemic antifungals and thereby prevent the future resistance and improve clinical outcome

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