

# Prescribing Pattern of Antifungal Medications at a Tertiary Care Hospital in Oman

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## ABSTRACT

**Introduction:** Inappropriate use of antifungal agents is implicated in the global burden of antifungal resistance, adverse outcomes like persistent infections, unnecessary exposure and increased cost. Data collection from time to time is to be done in order to have a check on the resistance/sensitivity pattern of the commonly prescribed antifungal drugs.

**Aim:** To describe the pattern of antifungal drug prescription and administration to patients attending a university hospital in Oman.

**Materials and Methods:** This was a descriptive, retrospective cross-sectional study conducted at Sultan Qaboos University Hospital (SQUH), a university hospital in Oman that covered the electronic patient's data for a period of one year (January 2013 to December 2013). The study included inpatients and outpatients of all ages and both genders attending SQUH and receiving antifungal medications at the study period. Frequencies and percentages were reported for categorical variables, while the

mean and standard deviation were used to summarize the data for continuous variables.

**Results:** A total of 1353 antifungal drug prescriptions were prescribed for 244 patients. More than half of all antifungal drug prescriptions were prescribed by haematology, infectious disease and family medicine departments. The majority of patients to whom these drugs were prescribed were diagnosed to have infectious diseases followed by prophylactic use in leukaemias and immunocompromised conditions. Fluconazole was the most commonly prescribed antifungal drug (n=715, 52.8%) followed by nystatin and voriconazole (n=233; 17.2% and n=152; 11.2%, respectively).

**Conclusion:** This study will help in understanding antifungal prescription practices and help in directing future studies and also in developing local policies for appropriate use of antifungal drugs.

**Keywords:** Amphotericin B, Fungal infections, Tinea pedis

## INTRODUCTION

Fungal infections constitute a serious threat to human health and life [1]. These infections range from superficial, cutaneous and subcutaneous infections to systemic fungal infections. In recent years, advances in medical technology such as total parenteral nutrition, invasive monitoring devices and broad-spectrum antibiotics has led to an increase in the incidence of these infections [2,3]. The incidence has increased particularly in immunocompromised patients such as those with cancer, Acquired Immunodeficiency Syndrome (AIDS) and organ transplants and there are a growing number of fungal infections in sepsis cases [2-4]. The mainstay therapy for these infections is antifungal agents, which can be given by different routes. Several antifungal agents were developed over the past years in response to the increased incidence and the high mortality rates associated with these infections [1,5].

Inappropriate use of antifungal agents is implicated in the development of antifungal resistance and can lead to adverse outcomes like persistent infections, unnecessary exposure and increased cost [6,7]. However, data on antifungal consumption in high-risk areas are scarce. Such data are essential to address public health problems related to the effectiveness of antifungal medications [8]. This problem is of particular concern for developing countries as they do not have well established antifungal management protocols or/and programs. In addition to this, there is also limited data on the incidence or/and prevalence of inappropriate antifungal use and the risk factors associated with it in these countries [6]. In Oman, there are no reports on the utilization pattern of the use of antifungal

agents. There are mainly few case reports that are published on specific types of fungal infections and their management [9-15]. Therefore, this study describes the patterns of antifungal drugs prescribing and administration to patients who attended Sultan Qaboos University Hospital (SQUH), Oman.

## MATERIALS AND METHODS

The study was a descriptive, retrospective cross-sectional in nature conducted at SQUH, an academic tertiary care hospital in Oman. It covered one year (January 2013 to December 2013) and data outside this period were excluded. Inpatients and outpatients of all ages and both genders attending SQUH and receiving antifungal medications during the study period were included. Patients' information (age, gender, body mass index, status, diagnosis and treating department) and drugs information (name, route of administration, treatment duration) were collected from computerized hospital database and analysed thereafter. The study was approved by the Medical Ethics Committee of SQUH.

## STATISTICAL ANALYSIS

Data was analysed using descriptive statistics. Frequencies and percentages were reported for categorical variables, while the mean and standard deviation (or median and interquartile range, wherever appropriate) were used to summarize the data for continuous variables. The Statistical Package for the Social Sciences (SPSS), Version 19.0 (IBM Corp., Chicago, Illinois, USA) was used to analyse the data.

## RESULTS

### Demographic characteristics of the study group

The study included 244 patients (56.1% males and 43.9% females). The average age of the patients was 37.5±20.2 years (ranged from 0.1 to 97 years). A total of 1353 antifungal drug were prescribed for the 244 patients. Of these, 40.5% were for inpatients and 59.5 % were for outpatients. The range of episodes per patient was 1 to 37. The baseline characteristics of the patients are shown in [Table/ Fig-1].

More than half of all antifungal drug prescriptions were prescribed by haematology, infectious disease and family medicine departments [Table/Fig-2]. The majority of patients prescribed these drugs were diagnosed to have infectious diseases followed by prophylactic use in leukaemia and immunocompromised conditions [Table/Fig-3].

### Antifungal drug utilization pattern

The average number of antifungal drugs prescribed per patient was 5.6 with male patients receiving higher average number of prescriptions compared to the female patients (6.1 vs. 5.1,  $p=0.175$ ). There was no significant difference in the average number of prescriptions between adults (>18 years) compared to children (≤ 18 years) (5.7 vs. 5.4,  $p=0.929$ ).

Total number of antifungal drug prescriptions (N)	1353
Age, years (mean±SD)	37.5±20.2
Gender (n, %)	
Male	137, 56.1%
Female	107, 43.9%
Body Mass Index* (mean±SD)	22.9±16.7
Patient's status (n, %) (per prescription):	
Inpatient	(548, 40.5%)
Outpatient	(805, 59.5%)
Treatment duration, days (mean±SD)	14.8±18.8
Total number of drugs prescribed per patient [mean, median (IQR)]	5.6, 4.0 (6.0)
Male	6.1, 4.0 (7.0)
Female	5.1, 3.0 (5.0)
≤ 18 years	5.4, 4.0 (8.0)
>18 years	5.7, 4.0 (6.0)

**[Table/Fig-1]:** Demographic characteristics of 244 patients receiving antifungal medication at Sultan Qaboos University Hospital in 2013.  
\*132 missing values in the electronic records, SD: standard deviation

The majority of drugs were administered by the oral route (n=992; 73.4%) followed by the parenteral route (n=320; 23.7%), topical route (n=27; 2.0%), and then vaginal route (n=13; 1.0%).

Fluconazole was the most commonly prescribed antifungal drug (n=715, 52.8%) followed by nystatin and voriconazole (n=233; 17.2% and n=152; 11.2%, respectively) [Table/Fig-4]. Fluconazole was the most common antifungal drug prescribed in adult patients irrespective to their gender or inpatients and outpatients status. It was the most common drug prescribed by the majority of the departments [Table/Fig-2] and across different diagnosis except solid tumours [Table/Fig-3]. However, amphotericin was the most common prescribed drug in patients ≤ 18 years of age (36.3%) [Table/ Fig-4]. It was the most common (61.2%) antifungal drug prescribed in paediatric department [Table/Fig-2]. Several departments prescribed antifungal drugs for different diagnoses [Table/Fig-2,3]. Fluconazole was the most commonly prescribed antifungal agent prescribed by haematology, infectious disease and family medicine departments while nystatin was the most commonly prescribed antifungal agent by oncology department [Table/Fig-2].

## DISCUSSION

Superficial fungal infections (e.g., tinea pedis, sporotrichosis, vulvovaginal candidiasis) are the common form of fungal infections [4,5]. However, the last three decades showed an increase in the incidence and mortality of invasive fungal infections (e.g., aspergillosis, candidiasis, histoplasmosis, cryptococcosis) especially in patients with impaired immunity [2,3,7]. Contrary to superficial infections which are easily treatable, systemic fungal infections are a clinical challenge [2,3]. They often occur in patients with impaired immunity and with several comorbidities and it is uncommon for their causative species to show resistance to several antifungal agents [2,3]. This has led to the development of many antifungal drugs to combat these infections and to provide more options for physicians by using drugs with better toxicity profiles. For example, conventional amphotericin B was the standard treatment for invasive fungal infection for about four decades since its initial approval in 1958 [16]. However, its liposomal formulation and newer drugs such as echinocandins (e.g., anidulafungin, caspofungin) and voriconazole became available alternatives to conventional amphotericin [16].

Limited pharmacoeconomic analyses exist in the antifungal therapeutic area. One study reported that, in 2004, two billion US \$

Department/specialty	Patient*		Prescriptions*		Antifungal Drug						
	N	%	N	%	Fluconazole	Nystatin	Voriconazole	Amphotericin	Anidulafungin	Clotrimazole	Ketoconazole
Haematology	74	30.3	726	53.7	56.7	15.0	18.7	5.2	4.3	-	-
Infectious disease	31	12.7	158	11.7	77.2	1.9	3.2	12.7	5.1	-	-
Family medicine	25	10.2	55	4.1	56.4	1.8	-	-	-	36.4	5.5
Oncology	24	9.8	144	10.6	33.3	48.6	2.8	0.7	14.6	-	-
Paediatric	19	7.8	85	6.3	7.1	24.7	5.9	61.2	-	-	1.2
Emergency	13	5.3	36	2.7	58.3	-	-	22.2	11.1	-	8.3
Obstetrics	13	5.3	16	1.2	100	-	-	-	-	-	-
Medicine	7	2.9	17	1.3	70.6	17.6	-	-	11.8	-	-
Gastroenterology	6	2.5	24	1.8	54.2	12.5	-	-	33.3	-	-
Surgery	6	2.5	17	1.3	23.5	23.5	-	-	52.9	-	-
Urology	5	2.0	10	0.7	80.0	20.0	-	-	-	-	-
Pulmonology	4	1.6	13	1.0	23.1	-	7.7	7.7	61.5	-	-
Ophthalmology	4	1.6	13	1.0	53.8	46.2	-	-	-	-	-
Neurology	3	1.2	7	0.5	42.9	57.1	-	-	-	-	-
Nephrology	3	1.2	16	1.2	56.3	43.8	-	-	-	-	-
Others	5	2.0	14	1.0	-	-	-	-	-	-	-

**[Table/Fig-2]:** Distribution of patients (N=244) and antifungal drugs among departments/specialties (N=1353 prescriptions).

\*Two missing data both patients and prescriptions

Diagnosis	Patients*		Prescriptions*		Antifungal Drug						
	N	%	N	%	Fluconazole	Nystatin	Voriconazole	Amphotericin	Anidulafungin	Clotrimazole	Ketoconazole
Leukaemias	69	28.3	638	47.2	55.0	18.3	17.7	4.4	4.4	-	-
Infections	86	35.2	277	20.5	49.8	13.4	2.2	12.6	13.7	7.2	-
Solid tumours	24	9.8	139	10.3	0.4	36.7	2.9	0.7	9.7	-	-
Immunocompromised	29	11.9	124	8.5	83.1	4.8	1.6	8.1	-	-	2.4
Hematological diseases	13	5.3	97	7.2	34.0	6.2	26.8	24.7	8.2	-	-
Central nervous diseases	5	2.0	16	1.2	12.5	25.0	6.3	43.8	12.5	-	-
Others	16	6.6	58	4.3	-	-	-	-	-	-	-

**[Table/Fig-3]:** Distribution of patients (N=244) and antifungal drugs as per diagnosis (N=1353 prescriptions).

\*Two patients' diagnoses are missing, four prescriptions data missing

Drug	Prescription (N=1353)		Age (years)				Gender				Patient status*			
			≤ 18 (n=199)		> 18 (n=1154)		Male (n=830)		Female (n=523)		Inpatient (n=548)		Outpatient (n=804)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Fluconazole	715	52.8	49	24.6	666	57.7	456	54.9	259	49.5	154	28.1	561	69.8
Nystatin	233	17.2	36	18.1	258	15.8	152	18.3	81	15.5	111	20.3	121	15
Voriconazole	152	11.2	34	17.1	118	10.2	83	10	69	13.2	97	17.7	55	6.8
Amphotericin	130	6.9	72	36.3	58	5.0	94	11.3	36	6.9	102	18.6	28	3.5
Anidulafungin	96	7.1	7	3.5	89	7.7	41	4.9	55	10.5	83	15.1	13	1.6
Clotrimazole	20	1.5	-	-	20	1.7	1	0.1	19	3.6	-	-	20	2.5
Ketoconazole	7	0.5	1	0.5	6	0.5	3	0.4	4	0.8	1	0.2	20	2.5

**[Table/Fig-4]:** Distribution of antifungal drugs prescribed according to age, gender and patient's status.

\*one patient data is missing

in annual hospital costs in the United States could be attributable to invasive fungal infections [17]. In terms of the total cost of treatment, more expensive antifungal agents may be more cost-effective than lower-cost agents that are less effective and/or more toxic [18]. Pharmaco-epidemiological studies from developing countries detailing antifungal drug prescribing patterns of physicians are very few.

In this study, only 35.2% (n=86) of the patients prescribed with antifungal agents were diagnosed with fungal infections. These infections ranged from superficial to systemic infections including Tinea unguis, Tinea corporis, Tinea pedis, recurrent candidiasis, vaginitis and mucormycosis. The clinical diagnosis was not being able to trace in the electronic system for many cases of the study cohort and most of the patients with multiple prescriptions were prescribed the drugs consecutively on different visits despite the lack of a definite diagnosis. The reason that they have been receiving antifungal therapy could be as prophylaxis or empiric therapy for their underlying conditions which makes them susceptible to invasive fungal infections. These conditions included leukaemias (28.3%, n=69) and immunocompromised status (11.9%, n=29) [Table/Fig-3]. Most of the patients were treated in haematology department (30.3%, n=74) [Table/Fig-2] followed by infectious disease and family medicine departments (12.7%, n=31 and 10.2%, n=25, respectively). In one study, the most common underlying condition was malignancy (42%), followed by hematologic/immunologic deficiency (16%), and cardiovascular condition (15%) [19]. The high rate of antifungal drugs use in haematology department is understandable as it is known that fungal infections are a major cause of death in many hospitalization wards [20].

While *Aspergillus*, *Candida* and *Cryptococcus* species account for the majority of infections, recent epidemiological trends indicate a shift towards *Aspergillus* and non-*albicans* *Candida* species that often have diminished susceptibility to current antifungal agents such as fluconazole [21]. Clinically, candidiasis and aspergillosis account for between 80% and 90% of systemic fungal infections in immunocompromised patients [19]. In this study, it was not possible

to retrieve data about the isolated species that caused the infections due to unavailability in the records.

A large retrospective cohort study in paediatric inpatients showed that fluconazole was the most commonly prescribed antifungal agent (76%) [16]. The same study showed an increase in the utilization of both voriconazole and the echinocandins between 2000-2006, while there was a significant decrease in the utilization of conventional amphotericin, itraconazole and flucytosine. Another study showed that fluconazole was the most commonly prescribed antifungal drug in 13 intensive care units in Germany [22]. Fluconazole is a widely used azole because of its long half-life, good patient tolerability and minimal associated toxicity. It is commonly used for the treatment of oropharyngeal and oesophageal candidiasis and as prophylactic agent in patients undergoing bone marrow transplantation or on cytotoxic chemotherapy [20].

Amphotericin B is very effective agent in treatment of several systemic fungal infections such as *Cryptococcus*, *Aspergillus* and *Candida*. It is also used as prophylaxis in suspected fungal infections in patients with febrile neutropenia. However, it is associated with several side effects limiting its use especially nephrotoxicity even with liposomal formulations [1,4,5]. In paediatrics, amphotericin is commonly used in treatment of candidemia and cryptococcal meningitis mainly in patients with immunocompromised status. Similar to previous studies amphotericin B in our cohort was mainly used for paediatrics. We also noticed that some of amphotericin prescription originated from Emergency department and almost one third were for outpatients. This observation require further exploration as this drug should have limited prescriber and patients on this drug should be monitored closely for possible nephrotoxicity.

Nystatin is a widely used antifungal medication for superficial fungal infections and of bacterial origin [23]. Cutaneous, vaginal, mucosal, and oesophageal *Candida* are sensitive to nystatin [24]. Voriconazole, a second-generation azole, is a broad-spectrum antifungal drug that has activity against some filamentous fungi (e.g. *Aspergillus* spp.) and also against *Fusarium* and *Scedosporium* species [5,7,24]. It is used commonly in clinical practice. However, it has many drug-drug

interactions such as with digoxin and prednisolone [5,7,24]. The new agents, echinocandins, are active against some amphotericin B-resistant fungi, may have a role in the management of febrile neutropenia and exciting good option for combination antifungal therapy [5,24]. In our study, anidulafungin was prescribed in 7.1% of the patients [Table/Fig-4] majority of which are adult inpatients. Pulmonology specialty and surgery department were the most common departments/specialties prescribing this drug (61.5% and 52.9%, respectively) [Table/Fig-2]. This could be due to its efficacy against invasive aspergillosis, oesophageal candidiasis and peritonitis and intraabdominal abscess caused by candida species. Ketoconazole and clotrimazole were the least used antifungal agents in our study (0.5% and 1.5%, respectively). As elsewhere these two agents are mainly indicated for topical applications [1].

## LIMITATION

SQUH is a referral hospital in Oman and the results might not be generalizable to the whole country. It is possible that the results in other hospitals might be different. Data of this study were obtained from the electronic records and this limited our ability to gather information about the nature of the isolated microorganisms, the prevalence of antifungal resistance and patient's clinical outcome.

## CONCLUSION

The pattern of use of antifungal drugs in our study cohort was similar to the trend elsewhere in the world. Fluconazole was the most common antifungal drug prescribed in our study cohort. The use of newer antifungal agents is also increasing. Due to limited data in our region, the results of this study will help in understanding antifungal prescription practices and help in directing future studies and in developing local policies for appropriate use of antifungal drugs. Such policies will have an impact on many economic parameters such as length of stay and costs of hospitalization.

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