Assessment of Anti-fungal Drugs Utilization Pattern Among Patients Attending at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, 2022

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ABSTRACT
<u>Background</u>: the inappropriate use of anti-fungal agents can cause adverse events, toxicity, unnecessary exposure and cost, and increased microbial resistance, which has important implications for morbidity and mortality. With a lack of adequate Information on how drugs are being prescribed and utilized, it is almost impossible to initiate a discussion on rational drug use or improvement on prescription habits and developing practical guidelines. Drug utilization might not necessarily provide answers on its own, but it contributes to rational drug use. <u>Objective</u>: To Assess anti-fungal agent utilization patterns among patients attending Zewditu Memorial Hospital, Addis Ababa, Ethiopia, 2022. <u>Methodology</u>: A Retrospective Cross-sectional study design was used. Data regarding patient characteristics, medications, diagnosis, dose and type of anti-fungal agent used were collected using data abstraction forms by reviewing the patient's medical card and medication charts. The data was entered into the SPSS 21 version for analysis. The analyzed data was interpreted and presented in charts, graphs and tables. <u>Results</u>: 124 anti-fungal agents were prescribed to 75 patients. Female patients received (n=66, 53.23%) of these prescriptions, and Male patients received (n=58, 46.77%).patients who were under 18 years old received (n=100, 80.6%), and patients who were 18 years old and above received (n=24, 19.3%).In this study, prescription of Fluconazole was(n=54, 44.4%) and Ketoconazole (n=55, 43.5%) while Clotrimazole was(n=9, 7.3%) and Terbinafine(n=6, 4.8%).the fungal infection of this patients were tinea capitis (n=48, 64%,) tinea unguium (n=13, 17.3%),tinea corporis(n=6, 8%)tinea pedis(n=7, 9.3%) tinea barbea (n=1, 1.3%). <u>Conclusion</u>: This study finding shows that Fluconazole was the most common anti-fungal drug prescribed orally, similar to elsewhere. However, oral Fluconazole was closely followed by Ketoconazole, which was the most frequently prescribed drug topically. This differed from other studies, meaning Clotrimazole was the most prescribed drug topically anti-fungal in different countries. Lastly, most studies support that Combination therapy of antifungals was more likely than Monotherapy.

Keywords: Anti-fungal, Utilization Pattern, Fungal infection

INTRODUCTION
Background of the Study
Fungal infections could be categorized as superficial, affecting the specificity of the skin, nail, hair, or mucous layer, or systemic. It is most likely occurring in immunocompromised individuals like those with AIDS more frequently (1). Anti-fungal agents are medicines that stop the growth of or kill fungal pathogens that cause infections from a host with minimal

toxicity to the host. Anti-fungal drugs can be classified into three main groups according to their site of action. These are azoles, 5-fluorocytosi, and polyenes (2).

The indiscriminate use of these drugs results in undesirable side effects, drug interactions, ecological disturbances, and difficulties in diagnosis. In addition, problems such as improper storage, distribution, compliance, and selection of drugs constitute the main threat to society (3). Rational use of medicines /drugs is defined as "patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period, and at the lowest cost to them and their community" (4).

In 1997, the World Health Organization (WHO) defined drug utilization as «the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences» (5). Without the optimum data on how drugs are being distributed, prescribed, and use of drugs in society and utilized, it's hard to initiate a discussion on rational drug use or improvement of prescribing habits. Drug utilization might not necessarily provide answers, but it contributes to the practice of rational drug use (6).

Drug utilization also involves differentiating good prescribing practices from bad prescribing practices, encouraging rational prescribing, assisting in solving problems related to drug therapy, providing Information to various authorities about drug-related misdeeds, and assisting in framing a drug or health policy (7).

Statement of the Problem
Fungal infections in humans are considered life-threatening and have unfortunate health consequences (8). Some fungal infections are superficial, affecting the skin, nails, hair, mucous layer, or systemic. Even though systemic infections are found to be more life-threatening, superficial infections are considered essential because their existence is epidemiologically widespread (9).

Each year, over one billion people of all ages are affected by fungal infections across the globe (10). Estimates over 1.6 million deaths and influence undesirable clinical outcomes and fatal outcomes of several diseases (11). This figure is three times higher than the yearly passing from malaria and equivalent to the rate of tuberculosis deaths per year (12).

The incidence of fungal infections is increasing rapidly and becoming a challenge to the healthcare system. The growing population of immunocompromised individuals and the change in medical practice pose contributing factors (13). Human immunodeficiency virus (HIV), cancer, organ transplant, and other diseases are major contributing factors to the increase of this incidence. Approximately there are 38 million (HIV)-infected people across the globe. With a total population of 1.3 billion, Africa accounts for 75% of HIV-positive people in the world (14). In particular, Africa takes up to approximately 50% of all fungal-related passing as a consequence of HIV infections. However, there is a lack of data accuracy (15).

Other contributing factors are the indiscriminate use of broad-spectrum antimicrobials and aggressive treatment of malignant diseases. Moreover, mild to moderate fungal infections, such as superficial and subcutaneous fungal infections affecting the skin, are common in the community, even among people with no known immune deficiency disease (16).

The general occurrence of these medical services-related contaminations, such as candidaemia, has been considered higher in low-income and middle-income countries than in high-income nations, perhaps because of insufficient assets for disease counteraction and control and antimicrobial stewardship (17).

Anti-fungals are more challenging to treat than other antimicrobial infections, and drug interactions are extra problematic (18). As a result, the inappropriate use of anti-fungal agents can cause adverse events, toxicity, unnecessary exposure and cost, increased microbial resistance has important implications for morbidity and mortality (19). Moreover, some challenges in treating fungal infections are due to fungal organisms invading quite slowly and antimicrobial agents poorly penetrating the tissue, where most fungal infections often occur (20).

Knowing the drug utilization pattern is crucial to maximizing treatment outcomes and minimizing antimicrobial irrational use and its consequences, such as developing resistance by previously susceptible organisms (21).

For the last two decades, the study of antimicrobial resistance has focused on antibacterial resistance; as a result, anti-fungal resistance has lingered behind. Even though fungal infections are life-threatening, global health organizations and governments give this issue sufficient attention (22). Accurate data on the incidence and prevalence of these infections is challenging in African countries, particularly in sub-Saharan Africa. Limited Management protocols, evidence-based cases, a small number of diagnostic facilities, and a shortage of appropriate anti-fungal drugs and specialists amplify this problem. This situation results in high and preventable mortality and morbidity.

Ethiopia is one of the most prevalent Infectious diseases in sub-Saharan courtiers, with fatal and predominant diseases such as HIV. Despite the life-threatening nature of many fungal infections, appropriate diagnosis and availability of treatments in developing countries are limited. (23) Studies associated with fungal infections and anti-fungal utilization are limited in Ethiopia. These are an alarm for looking into the pattern of anti-fungal agent utilization for improving rational use of drugs in the country.

Significance of the Study
With a lack of adequate Information on how drugs are being prescribed and utilized, it is almost impossible to initiate a discussion on rational drug use or improvement on prescription habits and developing practical guidelines. Drug utilization might not necessarily provide answers on its own, but it contributes to rational drug use.

The results of this study will positively impact the provision of Information for the health service system on current drug utilization patterns, with the hope of optimizing rational anti-fungal use in the future.

LITERATURE REVIEW
Almost all superficial and subcutaneous fungal infections can be easily treated and controllable. Systemic fungal infections may be related to an invasive or opportunistic organism that causes

disease in immunocompromised individuals. These infections are life-threatening and are linked to increased morbidity and mortality (13).

A study in Oman 2013 aimed to describe the anti-fungal prescription pattern of patients attending a university hospital in Oman. This retrospective cross-sectional study demonstrates that the most commonly prescribed anti-fungal was Fluconazole (52.8%), nystatin (17.2%) and voriconazole (11.2%). Hematology prescriptions account for over 50% of all anti-fungals prescribed, followed by infectious diseases, leukemias, and immunocompromised conditions (respectively) (24).

In Australia, a cross-sectional study done in 2016 implies that the use of most anti-fungal increased from 2005 to 2016, particularly posaconazole, itraconazole, and Fluconazole. At first, the most commonly dispensed systemic anti-fungal was Ketoconazole (46.0%), then it was replaced by Fluconazole (69.8%) (25).

A retrospective study was conducted in India in 2017 on prescribing patterns of anti-fungals aiming to provide help to police makers. Out of 1500 prescriptions, 500 were anti-fungal agents. 40.2% of patients were around 18-35, with males accounting for 59.6% and 40% for females. The study reveals that the most used oral antifungals were Fluconazole, Terbinafine, and Clotrimazole topical antifungals (26). In another similar study in an Indian hospital in 2019, a study also demonstrated that the commonly prescribed anti-fungal agents were the Azole groups. Age group 21-40yrs accounts for more than half (51.8%) males and (48%) females. Topical anti-fungals estimated (64%) of the drug prescribed (27).

In Saudi Arabia, a retrospective study on drug utilization patterns and cost-utility analysis of anti-fungal drugs in 2019. aimed to optimize the prescription pattern of anti-fungal medicines and their economic burden on patients. The study implies that the majority of the patients were age group (31–45) with females accounting for more than 50% of the Population. Clotrimazole was the most used topical anti-fungal, followed by Fluconazole (systemic)   (28).

In 2021, two other studies were conducted in India on drug utilization patterns and analyzing anti-fungal drugs used in dermatology. One of the studies demonstrates that prescribing Combination therapy was more likely than Monotherapy. Their generic name prescribed any of the drugs. Itraconazole (24.21%) and Ketoconazole (13.36%) were the most frequently prescribed anti-fungal agents, with 3.18% being the average number of drugs prescribed per encounter (29). Similarly, in the other study, 218 patients from various departments were incorporated from a hospital, and Ketoconazole and Clotrimazole were indicated for topical use (30).

In 2018, a study was conducted in the northern east of Ethiopia, Prescribing Patterns for Skin Diseases in Dermatology OPD at Borumeda Hospital. The most commonly prescribed drug was ketoconazole shampoo (50.9%) from the anti-fungal anti-fungal (31).

These studies indicate that the antifungal drug utilization pattern is very close, with azoles and Fluconazole being the most commonly prescribed antifungal drugs. However, we also observed that there is limited data and little to no studies conducted on antifungals on this topic.

OBJECTIVES

General Objective
- To assess the utilization pattern of antifungal agents at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, 2022.

Specific Objectives
- To evaluate the utilization pattern of antifungal agents at Zewditu Memorial Hospital.
- To identify the types of antifungal drugs prescribed at Zewditu Memorial Hospital.
- To assess adherence to antifungal drug prescriptions at Zewditu Memorial Hospital.
- To investigate the frequency and underlying reasons for antifungal drug prescriptions at Zewditu Memorial Hospital.

METHODS & MATERIALS

Study Area and Period
The study was conducted at the dermatology clinic of Zewditu Memorial Hospital of Ethiopia. The hospital is located in Addis Ababa, around Mexico, ambassador. It is one of the government-owned hospitals that provides different healthcare services in the community. These services include medical pediatrics, gynecological, ophthalmology, emergency, and outpatient activities. The data collation period was undertaken from May 09, 2022, to May 31, 2022, in the dermatology clinic of Zewditu Memorial Hospital.

Study Design
A retrospective Cross-sectional study design was used to assess anti-fungal agent utilization pattern at Zewditu Memorial Hospital Addis Ababa, Ethiopia, 2022

Population
Target Population:
The target population was all patients who had visited the Zewditu Memorial Hospital.

Source Population:
The sample population was all patients at the dermatology clinic of Zewditu Memorial Hospital.

Sample Population:
The sample population was all Zewditu Memorial Hospital dermatology clinic patients who qualified for the inclusion criteria.

Inclusion and Exclusion Criteria:
- Patient who visited the dermatology clinic of Zewditu Memorial Hospital at the time frame of the six months (September 11, 2020, to March 9, 2021)
- Patients with incomplete medical records were excluded from the study.

Sample Size Determination
The total sample size for the study was determined using the following formula. The sample size was determined using a single proportion population formula as follows.

$$n = \frac{\left(Z_{\frac{a}{2}}\right)^2 P(1-P)}{d^2}$$

Where: n = sample size

- P = estimate of the proportion of prescriptions with an inappropriate prescription pattern, 0.5 since there is no research finding regarding an estimate of anti-fungal drug utilization pattern
- d = margin of sampling error tolerated, 0.05
- Z = the standard normal value at confidence interval of 95% = 1.96

The sample size was:

$$n = (1.96)^2 \times 0.5 \ (1-0.5) \ /0.05^2 = \textbf{384}$$

Sampling Technique/Sampling Procedures

The Data was collected from a sample of 384 medical record charts of patients of both genders and all ages who attended the dermatology clinic of Zewditu Memorial Hospital for a significant period. The 384 samples were selected using a systematic random sampling method from a total card of 1152 over 6 months.

Data Collection Procedures

Data collection was from May 09 to May 31 in Zewditu Memorial Hospital. Data was collected through medical record reviews of patients using a prepared standard checklist with Patients' Information (age, gender, diagnosis) and drugs' Information (name, route of administration, treatment duration).

Study Variables
Independent Variables

- age
- Gender
- Diagnosis

Dependent Variables

- Pattern of anti-fungal used

Data Analysis and Interpretation

Data was analyzed using descriptive statistics. Then, frequencies and percentages were reported for categorical variables, while the mean and standard deviation were used to summarize the data for continuous variables. The Statistical Package for the Social Sciences (SPSS), Version 21, was used to analyze the data.

Data Quality Management

One data collection method was utilized. Data collected from medical record cards was reviewed cautiously and in detail. Any incomplete or unclean recorded medical card was checked and analyzed afterwards.

Operational Definitions
- **Anti-fungal:** medication used to treat fungal infection
- **Drug utilization pattern:** a critical tool to analyze the rational use of medication, particularly on medical, social, and economic consequences in society**.**

Ethical Consideration

Before data collection, an official letter was secured from the Department of Internal Medicine at Zewditu Memorial Hospital and received hospital approval. Verbal informed consent was obtained from each patient after explaining the study's purpose. The confidentiality of information and the privacy of patients were strictly upheld throughout the study.

RESULTS

Socio-demographic Characteristics

Of the total number of 384 patient medical card charts reviewed at the dermatology clinic of Zewditu Memorial Hospital, three were excluded due to incompleteness of data. Of 381 patients, the number of female patients was (n=215, 56.4%), and male patients were (n=166, 43.6%). The +SD mean of patients' age was 11.426 ± 10.9905 while patient under 18yrs old counted (n=295, 77.4%) and (n=86, 22.6%) were 18yrs old and over. (table1)

Table 1: Socio-demographic characteristics of 381 patients at the dermatology clinic of Zewditu Memorial Hospital Addis Ababa, Ethiopia, 2022

Variable	Category	frequency	Percent
Sex	Male	166	43.6%
	Female	215	56.4%
Age	<18	295	77.4%
	≥ 18	86	22.6%
	Mean+SD	11.426 ± 10.9905	

Anti-fungal Drug Utilization Pattern

Three hundred eighty-one medical charts (n=306, 80.3%) were prescribed anti-fungal agents, while (n= 75,19.7%) were prescribed anti-fungal agents for different kinds of superficial fungal infections. Out of these 75 patients (n=42, 56%) were female patients and (n= 33, 44%) were male patients. The +SD mean of patients' age was 12.775 ± 11.7140, from which patients under 18 were (n=54,72%) and (n=21, 28%) were 18 and over. (Table 2)

Table 2: Socio-demographic characteristics of 75 patients receiving anti-fungal medication at the dermatology clinic of Zewditu Memorial Hospital Addis Ababa, Ethiopia, 2022

Total number of patients with anti-fungal exposure (N)		75
Age, years (mean±SD)		12.775 ± 11.7140
Gender	Male	N= 33, 44%
	Female	N= 42, 56%
Treatment duration, days (mean±SD)		19.68±5.580

In this study, for 75 patients, a total of 124 anti-fungal were prescribed, from which Fluconazole was (n=54, 44.4%) and Ketoconazole (n=55, 43.5%) while Clotrimazole was (n=9, 7.3%) and Terbinafine (n=6, 4.8%). (Figure1)
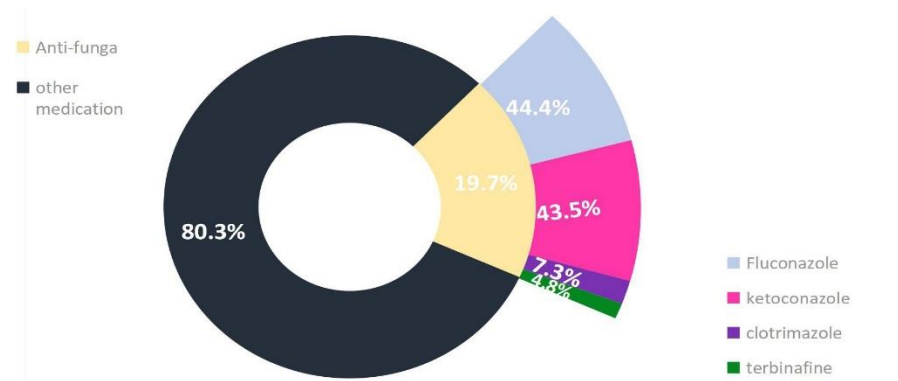

Figure 1: Anti-fungal agent utilization pattern at the Zewditu Memorial Hospital dermatology clinic, Addis Ababa, Ethiopia 2022.

Anti-fungal Drug Prescribing Pattern

In this study, 124 anti-fungal agents were prescribed for 75 patients with superficial fungal infection, from which Female patients received (n=66, 53.23%) of these prescriptions and Male patients received (n=58, 46.77%) Patients who were under 18yrs old received (n=100, 80.6%), and patient who were 18yrs old and above received (n=24, 19.3%). (Table 3)

Table 3: prescribing pattern of (124) anti-fungal drugs to (75) patients at the dermatology clinic of Zewditu Memorial Hospital Addis Ababa, Ethiopia, 2022

Total number of anti-fungal prescription		N=124
N= 75, patients receiving anti-fungal medication	Male	N= 58, 46.77%
	Female	N= 66, 53.23%
	≤ 18 years	N= 100, 80.6%
	>18 years	N= 24, 19.3%

(n=63, 50.8%) These anti-fungal were topical, including Ketoconazole and Clotrimazole, and (n=61, 49.2%) were oral routes, including Fluconazole and Terbinafine. (Table 4**)**

Table 4: Prescribing patterns of anti-fungal drugs according to their dosage, route of administration and strength at the dermatology clinic of Zewditu Memorial Hospital Addis Ababa, Ethiopia, 2022

Type of anti-fungal	Route of administration	Dosage form	number	Percent	Dose/Strength
Ketoconazole	topical	Shampoo	49	90.7%	2%
		Cream	5	9.3%	2%
Fluconazole	oral	Tablet	55	100%	50mg,100mg,150mg 200
Clotrimazole	topical	Cream	9	100%	1%
Terbinafine	oral	Tablet	6	100%	125mg,250mg

In this study, the prescribed anti-fungal agents were for the diagnosis of superficial fungal infections, including tinea capitis (n=48, 64%), tinea unguium (n=13, 17.3%), tinea corporis (n=6, 8%), tinea pedis (n=7, 9.3%), and tinea barber (n=1, 1.3%).

Overall, (n= 28) of patients who were (n=11, 39.3%) males and (n=17, 60.7%) females received a prescription of only one anti-fungal drug. From (n=46) patients, (n=21, 45.7%) males and (n=25, 54.3%) females received prescriptions for two   anti-fungal drugs. Then, (n=1, 100%) male patients received a prescription containing three anti-fungal drugs.

DISCUSSION

Our findings show oral Fluconazole was the most commonly prescribed anti-fungal (44.4%). This result was in line with the studies done in Australia (25) and India (26). This could be because the azole group of anti-fungal agents continues to be the antimycotic agent commonly prescribed in our studies and many others. In addition to this, because of Fluconazole's long half-life, good patient tolerability, and minimal associated toxicity, it has become particularly preferable (32).

Although topical Ketoconazole (43.5%) was the second most prescribed anti-fungal in our study, while Clotrimazole (7.3%) and Terbinafine (4.8%) were the least prescribed, Clotrimazole was the most prescribed topical anti-fungal agent in other studies. Possible explanations for this disparity include differences in the types of fungal infections treated, the location of the infection, and the availability of dosage forms appropriate for the diagnosis.

In this study, most anti-fungal agents were received by female patients (53.2%) compared to male patients who received 46.8% of these medications. In addition, patients under 18 years old received more anti-fungals   (80.6%) than patients who were 18 years old and above (19.4%). However, according to a study conducted in Oman (24), male patients received a higher number of anti-fungals than female patients, and anti-fungal agent prescriptions for patients (> 18 years) were slightly higher than those 18 years. This may be due to their study being done on general fungal infections.

Among these anti-fungal agents, a slightly higher number of anti-fungals was prescribed by the topical route (50.8%) and the oral route (49.2%). This was contrary to a study done in Oman (24). In their findings, the oral route was significantly higher than the topical route. This may be because their study was done on both superficial fungal infections and systemic infections, presumably treated by systemic anti-fungal drugs, unlike ours, which only included superficial infections mainly treated by topical anti-fungals.

Among these anti-fungal agents, a slightly higher proportion (50.8%) were prescribed topically than orally (49.2%). This was in contrast with a study done in Oman (24). In their findings, the oral route was significantly higher than the topical route.

This may be due to the fact that their study was done on both superficial and   fungal infections, which are presumably treated by systemic antifungal drugs. In contrast, our study only included superficial infections, which are mostly treated with topical antifungals.

Moreover, our result implies that the most prevalent fungal infection was tinea capitis (63.2%), followed by tinea unguium (17.1%), tinea corporis (9.2%), and tinea pedis (9.2%), tinea barber (1.3%). However, a study in Saudi Arabia (28) shows that tinea corporis is the most common fungal infection. This result parallels another survey that was conducted in India (27). This difference could be due to the nature of the infection, risk factors associated with the patients' immunity under the study, or various environmental factors in these different countries (33).

STRENGTHS AND LIMITATIONS OF THE STUDY

Strengths
- The collected data were carefully reviewed and checked for completeness, contributing to the quality of the findings.
- This study can be the first stepping stone for further studies in the future.
- The sampling technique was probable sampling so that the result could be generalized.

Limitations
- The study only includes superficial fungal infections , which limits information about systemic fungal infections.
- The data used for this study includes a short period.

CONCLUSION AND RECOMMENDATIONS

Conclusion
The pattern of use of antifungal drugs in our study was comparable to that of other countries. In particular, Fluconazole was the most common antifungal drug prescribed orally. However, Ketoconazole was the most frequently prescribed drug topically, which was different from other studies. This means that Clotrimazole was the most prescribed drug topically antifungal in other countries. Most studies support the idea that combination therapy is more likely than Monotherapy.

Recommendations
- Researchers are recommended to further study this matter with large-scale primary data-based studies to explore the utilization pattern of anti-fungal anti-fungal drugs in detail.
- To the health community to have an understanding of this study of anti-fungal utilization patterns and help in directing future studies and medical practice
- To police makers, this study' s results could contribute to developing local policies for the rational use of anti-fungal drugs.

Acronym and Abbreviations
AIDS, Acquired Immunodeficiency Syndrome
ART, Anti-Retroviral Therapy
HIV, Human Immunodeficiency Virus
ICU, Intensive care unit
SPSS, Statistical package for the social sciences
STG, Standard Treatment Guidelines
WHO, World Health Organization
ZMH, Zewditu Memorial Hospital

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