Research Article

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Prescription Audit of Anti-fungal Treatment of Dermatophytoses in the Dermatology Out Patient Department of a Tertiary Care Hospital

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Abstract

Aims: To study the prescriptions of clinically diagnosed cases of dermatophytoses, to evaluate medical treatment of clinical failure cases, any rise in serum ALT (Alanine aminotransferase) levels associated with usage of oral anti-fungal drugs, availability of drugs in the hospital pharmacy and cost minimization of different oral treatment regimens with Griseofulvin, Fluconazole, Itraconazole and Terbinafine.

Settings and design: Dermatology Out Patient Department (OPD) of a tertiary care hospital, single centre prospective cohort observational study.

Materials and Methods: 370 patients from the Dermatology Out Patient Department (OPD) diagnosed of dermatophytoses were enrolled. Follow-up was done 3±1 weeks apart, twice for newly diagnosed patients and once for patients on ongoing therapy. Two separate blood samples were collected 3±1 weeks apart for estimation of serum ALT. The prime lesion in each patient was graded as mild, moderate and severe. Patients were categorized as clinically cured, clinically improved, or as clinical failure following treatment.

Statistical analysis used: Descriptive statistics, Fischer's exact test and Wilcoxon's signed rank test.

Results: Azoles were the most commonly prescribed antifungals. Clinical status of patients was independent of the oral antifungal drug received (p > 0.05). A statistically significant difference in clinical status between compliant and non-compliant patients was seen (p < 0.05). A statistically significant increase in serum ALT levels was seen (p < 0.05) however, it was not clinically significant. 55.52% of drugs were unavailable in the hospital formulary. The average expenses per prescription was approximately INR 1123.55. Itraconazole was the most expensive treatment regimen followed by terbinafine and fluconazole.

Conclusions: There exists a non-uniformity in the management of dermatophytoses due to lack of adequate guidance and non-availability of drugs and clinical cure of patients depends upon compliance to therapy.

Keywords: Tinea Corporis, Tinea Cruris, Prescription Audit, Cost-Minimization

Key messages: Rational use of drugs is key in treatment of dermatophytoses and is the collective responsibility of physicians and patients if at all a future emergence of antifungal resistance is to be prevented.

Introduction

Dermatophytoses, also commonly known as tinea or ring worm is a superficial fungal infection of keratinised structures such as skin, hair and nails. About 25% of the world population is affected by the disease and an individual person is likely to have a 10 to 20% life-time risk of acquiring dermatophytoses. It is also estimated that 30 to 70% of adults remain as asymptomatic carriers [1].

Clinical patterns of dermatophytoses have undergone a significant change in the past few years and the standard treatment recommendations which were earlier being followed, no longer holds valid today [2].

Dermatophytoses is a condition that has always been trivialized, due to its un-relatedness to mortality. Despite majority of the world's population having suffered this fungal infection either acutely or chronically, there has not been enough research carried out on dermatophytes, when compared to other fungal infections which are

potentially life threatening [3]. Moreover, abundant literature exists for specific clinical types of dermatophytoses such as tinea capitis and onychomycosis, however, relatively fewer studies have been reported on other clinical forms such as tinea corporis and cruris [2].

Hence, the present study was carried out to determine the clinical scenario of dermatophytoses in our hospital, along with the current prescribing practices and any derangement of liver function tests in these patients. Additionally, as public hospitals such as ours mainly cater to the lower socioeconomic strata of the population, it was of interest to ascertain if drugs were actually being prescribed from the hospital formulary and if yes, whether the drugs were available in the formulary throughout the year. If not, to determine the out-of-pocket expenses borne by the patients' due to their unavailability.

Objectives
Our primary objective was to study the prescriptions of clinically diagnosed cases of dermatophytoses. Our secondary objectives included evaluation of medical treatment of clinical failure cases, any rise in serum ALT (Alanine aminotransferase) levels associated with usage of oral anti-fungal drugs, availability of drugs in the hospital pharmacy and cost minimization of different oral treatment regimens with Griseofulvin, Fluconazole, Itraconazole and Terbinafine.

Materials and Methods
The study was initiated after obtaining approval from the Institutional Ethics Committee (IEC). This was a single centre prospective cohort observational study, conducted in the Dermatology Out Patient Department (OPD) of our tertiary care hospital, between January 2016 and September 2017. No formal sample size was calculated and patients were recruited based on a duration specific convenience sampling.

Patients belonging to either gender, between the age group of 12 and 65 years and willing to give written informed consent or assent were included. These patients were either newly diagnosed or follow-up patients of dermatophytoses. Patients diagnosed with tinea unguium, tinea capitis and Majocchi's granuloma, any concomitant skin diseases such as eczema and superficial bacterial infections etc and concomitant systemic diseases, treated with drugs that are known to cause potential drug-drug interactions, for example, anti-retro viral drugs, warfarin, phenobarbitone, phenytoin, rifampicin, steroids were excluded from the study.

After enrolment, follow-up was done 3±1 weeks apart. Newly diagnosed patients (New cases) were followed up twice and patients already on ongoing therapy (Old cases) were followed-up once. On each follow-up visit, self-reported compliance, side effects, clinical status and prescriptions given by dermatologists, were noted. Prescriptions were analysed for completeness in terms of drug name, formulation, dose, frequency and duration. Blood samples for serum ALT levels, were collected twice on two separate occasions. For a 'New' patient, this was done on the second and third visit. For 'Old' cases, blood samples were collected once on the day of recruitment and once on their subsequent follow-up visit.

Each patient was subjectively assessed by the investigator based on three cardinal features viz. erythema, pruritus, and desquamation [4]. The prime lesion in each patient was graded based on their severity as mild, moderate and severe. A four-point scoring for each patient was done as follows: Nil symptoms=0, Mild symptoms=1,

Moderate symptoms=2, Severe symptoms=3 [5]. The minimum score that could be achieved was 0, implying complete disappearance of all symptoms. The maximum score that could be achieved was 9 implying a severe disease.

Response to treatment was assessed during each visit. Depending upon the score given at clinical assessment, patients were grouped into three categories as:
Clinically cured: a complete disappearance of presenting signs and symptoms withscore < 3 (i.e. score=0, 1 or 2)

Clinical improvement: partial relief with lowering of score but total score remaining ≥ 3

Clinical failure: no appreciable change in their signs and symptoms and a total score ≥ 3 but had either the same or a higher score in comparison to their previous score [6-8].

A patient was considered to have completed the study if two separate blood samples could be collected twice, 3±1 weeks apart. Patients who failed to follow-up within 1 week of their scheduled follow-up visit, were considered as lost to follow-up and were followed-up telephonically.

Availability of drugs in hospital pharmacy was checked once a month. Cost minimization analysis was done for the oral antifungal drugs and the cheapest regimen for a similar duration of treatment was evaluated.

Results
A total of 385 patients were screened and a total of 370 patients were enrolled. The median age of patients was 33.5 years (range 13-64 years) with a mean ± SD of 33.83 ± 12.35. The maximum number of 103 (27.83 %) cases belonged to the age group of 31-40 years. Age wise distribution of patients is shown in figure 1.
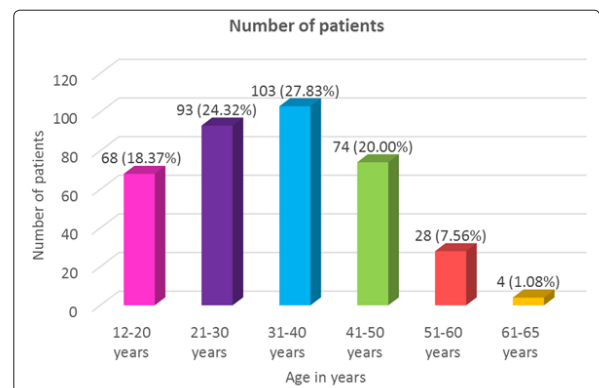

Figure 1: Age-wise distribution (n=370)

Males and females constituted 169 (46%) and 201 (54%) of the sample size, respectively. The largest group of patients consisted of 129 (34.86%) homemakers and 69 (18.64%) students. Out of 370 patients, 296 (80%) were 'New' cases and 74 (20%) were 'Old' cases. A total of 93 patients eventually completed the study.

Tinea corporis constituted the highest number of cases (50.27%) followed by a combination of tinea corporis and tinea cruris (28.37%). The number of patients with various diagnosis are shown in figure 2.
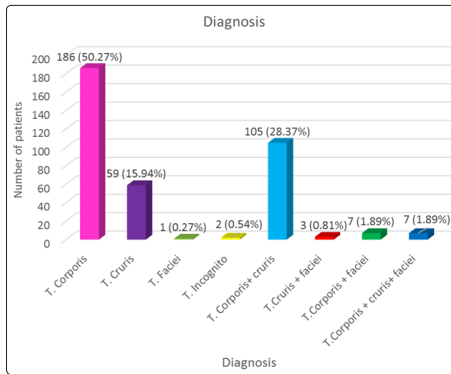
Figure 2: Diagnosis of patients

The percentage of patients with a history of illness < 6 months and > 6 months were 73.24 % and 26.75 % respectively. However, an acute history, with < 1 month duration of illness constituted the highest number of cases (24.86 %) in this study.

A total of 506 prescriptions were analysed, of which, 96% were found to be complete. However, 4% of the prescriptions were found to be incomplete due to missing information regarding the dose (1%), frequency (2%) and duration (1%). The prescribed drugs included anti-fungal agents and antihistaminic (antipruritic) agents. The average number of drugs prescribed per prescription was found to be 3.75 ± 1.08. The average number of antifungal drugs prescribed per prescription was 2.84±0.94. A total of 1882 drugs were found in our prescriptions. Generic name was used for 201 (10.68%) drugs and brand name was used for 1681 (89.31%) drugs.

The commonest class of oral antifungal drug prescribed was Azoles, which was found in 378 (69.87%) prescriptions. Itraconazole was the most commonly prescribed drug, in 299 (61.52%) prescriptions, followed by terbinafine in 129 (26.54%) and fluconazole in 3 (0.61%) prescriptions. None of the patients were prescribed griseofulvin.

A total of 476 (94.07%) out of 506 prescriptions analysed, contained topical antifungal creams and lotions. Azoles, constituted the most commonly prescribed class. Miconazole 2% cream was the most commonly prescribed drug and constituted 48.58% of all topical creams and lotions. This was followed by Sertaconazole 2% (17.81%) and Eberconazole 1% (10.12%) creams. An FDC (fixed dose combination) Beclomethasone 0.025% + Clotrimazole 1% was prescribed in 3 (0.60%) of prescriptions.

A total of 242 (47.82%) out of 506 prescriptions analysed, contained antifungal powders. The most commonly prescribed class (99.57%) was found to be Azoles. This was followed by terbinafine 2 % powder in 0.41% prescriptions. A total of 146 (28.85%) out of 506 prescriptions analysed, contained antifungal soaps. All the soaps prescribed belonged to the class of Azoles (100%). FDCs of Ketoconazole 2% + Cetrimide 0.5% constituted 0.68% of all antifungal soaps prescribed. A total of 453 (89.52%) out of 506 prescriptions contained oral antihistaminic or antipruritic drugs. Levocetirizine was found to be the most commonly (74.57%) prescribed antipruritic drug. A wide variation in dosage schedule of each drug was noted. Most drugs were prescribed in a twice daily dosage for a duration of 3 weeks.

Out of the 93 patients who completed the study, 70 (75.26%) patients were found to be clinically cured and 23 (24.73%) had not achieved

clinical cure until the end of the study. The clinical status based on clinical scores of these patients, who completed the study is shown in table 1.

Table 1: Overall clinical status at completion of study (n=93)

Overall clinical status	Total number of patients	Percentage of patients
Clinical cure	70	75.26%
Clinical improvement	18	19.35%
Clinical failure	5	5.37%
Total	93	100%

Table 2 shows the overall clinical status of patients at completion of study, based on the systemic antifungal agent prescribed on the day of recruitment. There was no statistical significance found across the groups, implying that clinical status of patients was independent of the oral antifungal drug received.

Table 2: Clinical status at completion of study based on systemic antifungal agent prescribed on day of enrolment (n=93)

Oral antifungal agent prescribed on visit 1	Clinical status at completion of study		
	Clinical cure	Clinical improvement	Clinical failure
Fluconazole (n=1)	1 (100%)	0 (0%)	0 (0%)
Itraconazole (n=59)	44 (74.57%)	11 (18.64%)	4 (6.77%)
Terbinafine (n=19)	16 (84.12%)	3 (15.78%)	0 (0%)
Fluconazole & Itraconazole (n=6)	3 (50%)	3 (50%)	0 (0%)
Fluconazole & Terbinafine (n=5)	4 (80%)	1 (20%)	0 (0%)
Itraconazole & Terbinafine (n=3)	2 (66.66%)	0 (0%)	1 (33.33%)
Total (n=93)	70 (75.26%)	18 (19.35%)	5 (5.37%)

Fisher's exact test: (p > 0.05) Considered statistically not significant

Out of the 105 patients who were followed-up on visit 2, 11 (10.47%) patients were categorized into the clinical failure group. The oral antifungal drug that was subsequently prescribed to these patients are shown in table 3.

Table 3: Oral antifungal drugs prescribed to clinical failure cases at visit 2

Oral antifungal drug prescribed on visit 1	Total number clinical failure cases at visit 2	Oral antifungal drugs prescribed at visit 2	Number of patients
Fluconazole	1	Changed to terbinafine	1 (100%)
Itraconazole	5	Continued on same treatment	5 (100%)
Terbinafine	4	Continued on same treatment	2 (50%)
		Changed to itraconazole	2 (50%)
Terbinafine & Itraconazole	1	Continued on same treatment	1 (100%)

Out of the 31 patients who followed up for the third and final visit only one patient (3.22%), was found to be a clinical failure case. This patient was initially prescribed itraconazole however, due to a lack of response, the treatment was changed to a combination of oral itraconazole and fluconazole.

The self-reported compliance of patients who completed the study (n=93) at visit 2 is given in table 4. There was a statistically significant difference in clinical status between compliant and non-compliant patients, which implies that clinical outcome depends on compliance to therapy.

Table 4: Self-reported compliance at visit 2 of patients who completed the study (n=93)

Self-reported compliance at visit 2	Clinical status at visit 2			Total
	Clinical cure	Clinical improvement	Clinical failure	
Compliant	55	5	2	62
Non-compliant	0	24	7	31
Total	55	29	9	93

Fisher's exact test: ($p < 0.05$) Considered statistically significant.

During visit 3, 28 out of 31 patients were clinically cured and 100% reported compliance to the antifungal therapy. Out of the remaining 3 patients who did not achieve clinical cure, 2 reported non-compliance and 1 reported compliance to the therapy.

There was a statistically significant rise in serum ALT levels between baseline and after treatment in patients. A reference serum ALT level of ≤ 40 IU/L was considered as normal. The number of patients who showed normal and elevated serum ALT levels is shown in table 5.

Table 5: Serum ALT levels of patients who completed the study (n=93)

Serum ALT levels (n=93)	Mean±SD*	Total number of patients	
		Normal	Raised
Baseline serum ALT	23.39±10.99	88 (94.62%)	5 (5.37%)
Serum ALT after treatment	24.48±11.87	87 (93.54%)	6 (6.45%)

*Wilcoxon signed-ranks test: ($p < 0.05$) Considered statistically significant.

Out of a total of 1882 drugs prescribed in 506 prescriptions, 1045 (55.52%) of drugs were unavailable in the hospital formulary, during the whole course of the study. The overall expenditure on non-available drugs, borne by patients during the course of the study was approximately INR 3,34,310.41. The average expenses per prescription was approximately INR 1123.55. For a treatment duration of 3 weeks, the average cost borne by a patient per prescription was highest for itraconazole (INR 684.60) followed by terbinafine (INR 645.96) and fluconazole (INR 59.40).

Discussion

There has been growing concerns regarding, the recent changes in epidemiological patterns of dermatophytoses [2]. Moreover, rampant use of over-the-counter medications in India for dermatophytoses has led to a fear of an impending epidemic and emergence of antifungal resistance. A tendency of non-compliance of patients to a treatment regimen has also been incriminated in the possible emergence of resistant strains [9].

Hence, it was only time that we investigated the current epidemiological pattern and prescribing practices for the treatment of dermatophytoses in our tertiary care hospital. Our primary aim was to conduct a prescription audit and follow the patients until completion of treatment and in the process, identify lapses if any and contribute to the existing evidence so as to bring about necessary changes, for better health of the community.

Most of our patients belonged to the age group of 31-40 years. This finding was similar to an earlier study conducted by Maulingkar et al. (2014) [10]. This indicates that adults are most susceptible in their 3rd and 4th decade of life which represents the most active population in the community.

A female predominance over males was seen in our study. This was in contrast to those reported by several other studies such as Sudha et al. (2016) [11]. The reason for female predominance in our study could be attributed to a better education of these women in an urban set-up and greater awareness in general about the disease and the importance of treatment.

The most common diagnosis in our study was tinea corporis followed by a mixed clinical pattern of tinea corporis and tinea cruris. A similar finding was reported by Agarwal et al. (2014) with tinea corporis comprising the most common clinical diagnosis (37.3%) followed by a mixed clinical pattern in 14.7% of their patients [12].

The most preferred oral antifungal drug in our study was Itraconazole. This may be supported by the fact that, in general, itraconazole and terbinafine are the most common treatments used for dermatophytoses. Griseofulvin and fluconazole are also effective but may require longer courses of therapy [13]. A study by Kamerkar et al. (2016) reported that fluconazole and clotrimazole were the most common oral and topical antifungal drugs prescribed respectively in their study [14]. In addition, the use of itraconazole in our study, despite unavailability in hospital pharmacy, may have been influenced by reports of recent changes in epidemiological patterns of the disease at other centres, along with experience derived through clinical practice in our set-up.

Topical miconazole was the most commonly prescribed drug followed by sertaconazole and eberconazole. A similar study by Giri VP et al. (2015) reported that terbinafine was the most commonly prescribed topical antifungal (22.79%), followed by sertaconazole (20.25 %) and ketoconazole (9.49 %) [15]. The use of topical azoles in our study is supported by previous studies that have reported a similar efficacy between topical allylamines and topical azoles [13]. Further, miconazole may have been prescribed most commonly as it was the only topical antifungal formulation available in the hospital formulary.

The percentage of drugs prescribed by their generic names in our study was much lower than the 54.33%reported by Vegada et al. (2015) [16]. This pattern of prescribing could be attributed to the fact that, drugs which were considered to be most beneficial to the patient, at this point in time owing to the changing trends, were unavailable in the hospital formulary.

Our prescriptions also found the use of topical FDC of Beclomethasone 0.025% + Clotrimazole 1%. However, the use of this FDC was found to be irrational as corticosteroid therapy is not required for achieving cure [13].

An inconsistency in dosage regimens was also observed in our study. The most common duration of treatment, irrespective of the severity of the disease, was 3 weeks. Non-resolution of symptoms, warrants prolongation of treatment in dermatophytoses. Thus, such a deviation must have been essential and obligatory for complete cure of patients.

It was found that at completion of the study a higher number patients on terbinafine were clinically cured in comparison to itraconazole. A comparative study by Amit et al (2013) found that terbinafine showed slightly better results than fluconazole in tinea corporis [17]. Terbinafine was reported to have 91% cure rate in tinea corporis and cruris patients, by a study conducted by Shivakumar et al. (2011) Nevertheless, the finding in our study does not imply that itraconazole is less efficacious than terbinafine [18]. Such a finding could be ascribed to the fact that patients often could not afford itraconazole and hence discontinued the medications without clinician's opinion. On the other hand, the full course of terbinafine received by the patient, free of cost may have contributed to greater compliance and hence a better response.

Patients who did not respond to therapy were either continued on the same drug or changed to a different drug or given a combination of two drugs. This implies that there is an inconsistency of treatment of failure cases due to lack of adequate guidelines.

Elevated serum ALT was found in patients receiving either oral itraconazole or terbinafine with a slightly greater frequency with itraconazole. This is in line with cohort study reported by Rodriguez et al. (1999) which found azoles to have greater potential for hepatotoxicity than terbinafine [19]. Elevated serum ALT levels in 'New' patients of our study cannot be fully attributed to the drug prescribed, as any prior history of misuse of drug could not be ruled out. Also, 'Old' patients with elevated serum ALT levels cannot be attributed to the drug alone, as the baseline status of serum ALT before onset of therapy was unknown. Even if there was a statistically significant increase in serum ALT levels from baseline to end of treatment, it was not clinically significant.

Government set-up such as ours, which caters to the lower socio-economic population, is obliged to provide drugs within a limited health budget. Hence, the cheapest oral antifungal drugs like fluconazole and terbinafine and topical miconazole are made available in the formulary. Soaps and powders were generally prescribed to those patients who had moderate to severe symptoms and signs and with extensive disease. However, due to unavailability, the costs of these drugs were borne by the patients.

A pilot study conducted by Kamerkar S (2016) in a tertiary care teaching hospital, in Mumbai, reported that selection of brand of drug can significantly influence the cost of therapy. Their average cost per prescription was INR 78.00 for the treatment of tinea infections [14]. However, we found that, on an average, our patients spend INR 1123.55 per prescription, which is much higher than those reported previously. This value reflects the amount spent on the various formulations of the most expensive class of oral antifungals, Azoles.

For an identical duration of treatment with a twice daily dosing and outcome of clinical cure, cost minimization analysis proved that a treatment regimen with itraconazole costs higher than terbinafine, which in turn costs higher than fluconazole. A similar study by Kamerkar (2016) reported that fluconazole based therapy was cheaper when compared to terbinafine based therapy [14].

This study may be associated with a few limitations. Being a collaborative study between the Department of Pharmacology and the Department of Dermatology, a possibility of change in the prescribing behaviour due to awareness by prescribers, was quite inevitable as it was carried out in an OPD set-up. Further, prior antifungal therapy status was unknownand compliance with lifestyle changes was not studied.

In conclusion, it can be stated that there exists a non-uniformity in the management of dermatophytoses due to lack of adequate guidance and non-availability of drugs and clinical cure of patients depends upon compliance to therapy. The use of combination of two or more oral antifungal drugs was found to be irrational, as the improvement in clinical status of patients at the end of course of treatment was independent of the number of drugs used or the concomitant use of expensive antifungal powders.

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