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Journal of Infectious Diseases & Travel Medicine
ISSN: 2640-2653

Antifungal Susceptibility Pattern of Fungi Associated with Tinea capitis in School Children of Morogoro Municipality, Tanzania

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Research Article

Volume 5 Issue 2

Received Date: October 25, 2021

Published Date: December 07, 2021

DOI: 10.23880/jidtm-16000155

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Abstract

Introduction: Tinea capitis is one of the common skin diseases affecting school-age children in developing countries. However, the susceptibility of fungi associated with this disease against antifungal agents commonly used has not been fully investigated.

Aim: The aim of this study was to determine the antifungal susceptibility pattern of fungi associated with tinea capitis amongst children sampled from selected schools in Morogoro Municipality, Tanzania.

Methods: A descriptive cross-sectional study was conducted involving 72 school children recruited from 10 primary schools in selected class strata within Morogoro Municipality, Tanzania using a multistage sampling technique. Pure cultures of fungi isolates were obtained from scrappings of head lesions in school children and tested for sensitivity to commonly used antifungal agents using the Kirby Bauer agar disk diffusion method.

Results: The identified fungi were *Trichoderma longibrachiatum, Cytobasidium minutum, Aspergillus spp, Ectophoma multirostrata, Aureobasidium pullulans, Aspergillus flavus, Cladosporium tenuissimum, Pichia terricola, Penicillium flavigenum* and *Fusarium solani.* Out of 10 fungal isolates, 9 (90%) were sensitive to both amphotericin B and nystatin, 4(40%) sensitive to clotrimazole, 1(10%) sensitive to fluconazole and griseofulvin, 3(30%) sensitive to itraconazole, and no isolate showed sensitivity to ketoconazole. Nystatin and amphotericin B showed best antifungal activity against *Trichoderma longibrachiatum, Cytobasidium minutum, Fusarium solani and Aspergillus sp* while clotrimazole and ketoconazole had intermediate fungal growth inhibition and best activity against *Fusarium solani* and *Aspergillus sp* but were resistant to the other antifungal agents. Fluconazole, griseofulvin, and itraconazole were not effective to any of the isolates.

Conclusion: This study revealed that nystatin and amphotericin B were ideal antifungal drugs for the treatment of tinea capitis in the studied population.

Keywords: Tinea capitis; Antifungal Susceptibility Pattern; School Children; Morogoro; Tanzania

Abbreviations: SDA: Sabouraud Dextrose Agar; AMPHO: Amphotericinb; CTRIM: Clotrimazole; FLUCZ: Fluconazole; ITRAC: Itraconazole; GRISE: Griseofulvin; KETOC: Ketoconazole; NYSTA: Nystatin; CLSI: Clinical and Laboratory Standard Institute; HESLB: Higher Education Student Loan Board.

Introduction

Tinea capitis is a superficial fungal infection of the scalp, eyebrows and eyelashes, with a propensity for attacking hair shafts and follicles [1]. Tinea capitis is sometimes known as ringworm of the scalp, it is not really a worm but a fungal

infection whereby the fungus makes circular marks on the scalp and especially flat centers and raised borders. It is the most common dermatophytosis in children aged between six months, prepubertal age and prevalent in adults whose immunity has been suppressed [2-4]. The two most common dermatophytes responsible for tinea capitis infection are *Trichophyton tonsurans* and *Microsporum canis* [5]. Tinea capitis remains a common childhood infection in many parts of the world [6]. The distribution is attributed by factors such as climate, population migration patterns, lifestyle, primary host range, secondary host immunity, presence of immunodeficiency diseases, and patient's attitude to prompt treatment following clinical presentation and standard of living [7]. Tinea capitis is quite common in Africa with prevalence among children ranging between 14 and 86% [7]. In developing countries in Eastern Africa, it is categorized as a disease of poverty due to poor socio economic status, high population densities and poor hygienic conditions these factors are responsible for high prevalence of tinea capitis [8,9]. In Tanzania, large city such as Dar-es-Salaam the prevalence of dermatophytosis was found to be 11% of 420 primary school children [10].

Currently, tinea capitis treatment options include both topical and oral agents including antifungal drugs such as clotrimazole, miconazole, nystatin, terbinafine, itraconazole, griseofulvin and fluconazole [11,12]. Recently, due to increase in the reports of antifungal drug resistance in dermatophytes, it has been suggested by number of studies to perform the antifungal drug susceptibility testing. Antifungal susceptibility testing will help in understanding the epidemiological pattern of drug resistance in a particular region, choosing the most efficacious antifungal agents for standard treatment and the antifungal susceptibility data will help in effective management. Several studies have been conducted in Tanzania to determine the prevalence and burden of fungal infection [13,14]. There is paucity of data regarding antifungal susceptibility of fungi associated with tinea capitis or *invitro* drug resistance to dermatophytes whereas some infections respond well to topical antifungal therapy, others like tinea capitis may require systemic therapy [15]. In some cases, therapy is not effective because of resistance to the drugs by the fungi. Therefore, with the increasing variety of drugs to treat dermatophytes on the market, the need for testing of antifungal susceptibility of dermatophytes has become apparent [16]. To our knowledge, there are few studies on prevalence, antifungal testing and treatment practice of tinea capitis in different parts of Tanzania. There are no reports on epidemiologic studies and antifungal testing on tinea capitis among school children in Morogoro Municipality, Tanzania.

In this study, the agar disk diffusion method which is standardized, simple and reproducible was used to determine the *in vitro* antifungal susceptibility of denmatophytes associated with tinea capitis [17,18]. The findings of this study will allow the clinician to apply the appropriate therapy for the management of infections caused by dermatophytes for school children in Tanzania.

Materials and Methods

Study Design and Setting

The present study was a descriptive cross-sectional study involving primary school children with clinical presentation suggestive of fungal infections of the head, including ring scalp, baldness and alopecia. Swabs and scrapings were taken from the head lesions and placed into sterile containers and transported to the laboratory at Sokoine University of Agriculture (SUA) for isolation and identification.

Sample Collection

A multistage sampling technique was used to select school children from different primary schools and class strata. A total of 72 school children with clinical signs suggestive of tinea capitis infection were recruited from 10 primary schools; namely Misufini, Mafiga, Msamvu, SUA, Kikundi, Chamwino, Mtawala, Bigwa, Mwere and Mbuyuni (Figure 1). School children aged between 6 and 14 years from classes 1, 3, 5 and 7 were enrolled into the study after obtaining a written consent from parents/guardians. Lesions were physically examined in broad daylight and then skin scrapping's were taken from the head lesions using a sterile scalpel blade and placed into a sterile container.

Isolation of Tinea capitis

Sabouraud dextrose agar (SDA) (Sigma Aldrich, St. Louis, USA) was prepared according to the instruction of the manufacturer's. Briefly, cool sterilized medium was mixed with skin scrapping's and poured into 150 mm sterile cell culture dishes (Corning Incorporated, Corning, NY). The dishes were then allowed to solidify and incubated at room temperature (about 25°C) for three days and the ensuing colonies sub-cultured in in 9 mm diameter SDA Petri dishes (MLS, Menen, Belgium). Fungal colonies were passaged four times to obtain pure cultures.

Antifungal Sensitivity Test

Fungi sensitivity to ketoconazole (15 µg), nystatin (50 µg), fluconazole (25 µg), clotrimazole (10 µg), griseofulvin (25 µg) and amphotericin B (10 µg) (Rosco, Taastrup, Denmark) was performed using the agar diffusion method. A total of 32.5 g SDA powder was mixed with 500 ml of distilled water, allowed to dissolve and then autoclaved at 121°C for

15 minutes. The fungi were suspended in 10 ml of warm agar in sterile tubes, homogenized and then poured into petri dishes and allowed to solidify, before placing the antifungal onto the surface of the agar. The plates were then incubated at room temperature for seven days and the diameter of zone of inhibition measured using a mm ruler to appreciate the sensitivity of each fungal isolate to the antifungal agents. Interpretation of antifungal susceptibility (susceptible S, intermediate I and resistant R) was based on CLSI standards [17,19,20] (Table 1).

Antifungal susceptibility of isolates associated with tinea capitis in school children after incubation with antifungal agents including amphotericin B (AMPHO), clotrimazole (CTRIM), fluconazole (FLUCZ), itraconazole (ITRAC), griseofulvin (GRISE), ketoconazole (KETOC) and nystatin (NYSTA). The zone of growth inhibition was measured in mm.

Ethical considerations

The purposes and benefits of the study were explained to the school children, parents/guardians and teachers. Informed written consent from the parents/guardians of the study subjects was sought before recruitment into the study. Ethical clearance was obtained from the National Health Research Committee of the Tanzania National Institute for Medical Research, certificate number NIMR/HQ/R.8a/Vol. IX/1943.

Results

Antifungal Susceptibility

A total of 72 school children were recruited as study subjects, 12 (16.67%) had tinea capitis. Identification of fungal isolates by morphological and molecular techniques in related studies by Macha, *et al*. [21] had indicated the following fungi to be associated with tinea capitis: *Trichoderma longibrachiatum, Cytobasidium minutum. Aspergillus spp, Ectophoma multirostrata, Aureobasidium pullulans, Pichia terricola, Aspergillus flavus, Cladosporium tenuissimum, Penicillium flavigenum and Fusarium solani*. Interpretation of antifungal susceptibility (susceptible S, intermediate I and resistant R) was based on Clinical Laboratory Standard Institute (CLSI) standards (Table 1) and the antifungal susceptibility of these fungi is shown in Table 2.

Antifungal drugs	Potency	Zone diameter in mm		
		Sensitive	Intermediate	Resistant
Amphotericin B	10 µg	>15	10-14	<9
Clotrimazole	10 µg	≥20	19-12	≤11
Fluconazole	25 µg	≥19	15-18	≤14
Griseofulvin	25 µg	≥10	-	No zone
Itraconazole	10 µg	>15	10-14	≤9
Ketoconazole	15 µg	≥30	29-23	≤22
Nystatin	50 µg	≥15	10-14	≤10

Table 1: Criteria of susceptibility and resistance of antifungal disks.

Antifungal sensitivity (Ø in mm)									
Fungal isolate	BLASTn	Accession number	AMPHO	CTRIM	FLUCZ	GRISE	ITRAC	KETOC	NYSTA
MSU03	*Aspergillus sp*	MN700638	21	24	20	0	17	25	32
MSU03	*Ectophoma multirostrata*	MN700639	17	20	0	0	0	0	15
MSU04	*Fusarium solani*	MN700640	17	16	10	0	12	13	24
MSU06	*Pichia terricola*	MN700642	0	0	0	0	0	14	10
KIK02	*Trichoderma longibrachiatum*	MN700636	16	15	0	0	18	18	28
KIK04	*Cytobasidium minutum*	MN700637	20	10	0	0	0	17	25
KIK06	*Cladosporium tenuissimum*	MN700643	18	29	0	20	16	0	20
KIK06	*Aspergillus flavus*	MN700645	16	15	0	0	0	12	13
CHA 03	*Penicillium flavigenum*	MN700644	20	0	0	0	0	0	28
SUA 07	*Aureobasidium pullulans*	MN700641	29	20	0	0	0	20	34

Table 2: Antifungal susceptibility of fungi isolates Macha, *et al*. [21].

Primary schools: KIK= Kikundi, MSU= Msufini, CHA= Chamwino Number 0 representing resistance to the antifungal.

Antifungal agents: Amphotericin B (AMPHO), clotrimazole (CTRIM), fluconazole (FLUCZ), itraconazole (ITRAC), griseofulvin (GRISE), ketoconazole (KETOC) and nystatin (NYSTA).

Antifungal Susceptibility of Fungi Isolated from Tinea capitis

Pure cultures of the fungi were tested for sensitivity to different antifungal agents including: amphotericin B, clotrimazole, fluconazole, griseofulvin, itraconazole, ketoconazole and nystatin. The results are shown in Figure 2 and Table 2.

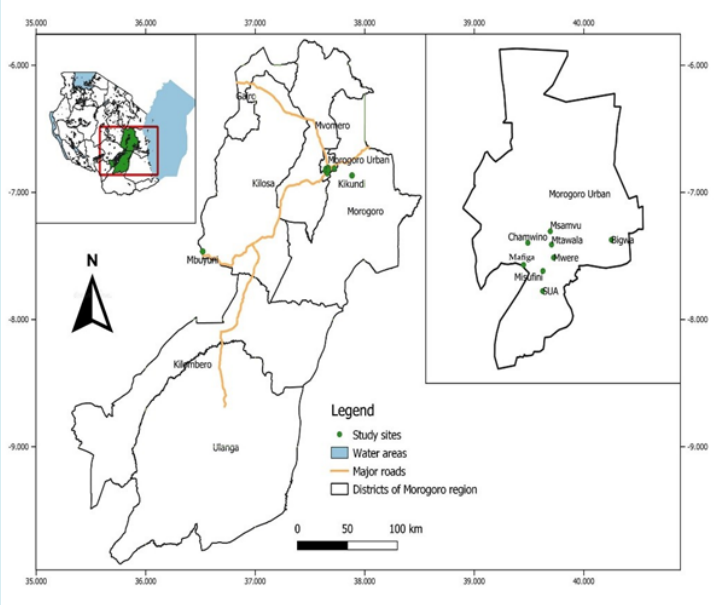

Figure 1: Map showing the study sites (Misufini, Mafiga, Msamvu, SUA, Kikundi, Chamwino, Mtawala, Bigwa, Mwere and Mbuyuni) in Morogoro municipality, Tanzania.

Figure 2: Antifungal susceptibility of fungi isolates associated with tinea capitis from school children. Amphotericin B (AMPHO), clotrimazole (CTRIM), fluconazole (FLUCZ), griseofulvin (GRISE) represented with a "G", itraconazole (ITRAC), ketoconazole (KETOC) and nystatin (NYSTA).

Test results of the susceptibility to antifungal drugs were interpreted as susceptible (S), intermediate (I) or resistant (R) according to CLSI standards (Table 1). Antifungal susceptibility pattern of 10 fungal isolates associated with tinea capitis (Table 3).

Antifungal	Susceptible (S) n (%)	Intermediate (I) n (%)	Resistant (R) n (%)
Amphotericin B	9 (90%)	0 (0%)	1 (10%)
Clotrimazole	4 (40%)	4 (40%)	2 (20%)
Fluconazole	1 (10%)	0 (0%)	9 (90%)
Griseofulvin	1 (10%)	0 (0%)	9 (90%)
Itraconazole	3 (30%)	1(10%)	6 (60%)
Ketoconazole	0 (0%)	1(10%)	9 (90%)
Nystatin	9 (90%)	0 (0%)	1(10%)

Table 3: Test results of the susceptibility to antifungal drugs fungal isolates associated with tinea capitis.

Discussion

Tinea capitis is the commonest childhood infection. Given the growing prevalence of tinea capitis in children and immune-compromised adults, it is now regarded as a public health issue worldwide [22]. It is more than a decade since various antifungal drugs with broad effect against the infection have been introduced [23]. These antifungal drugs have been mentioned to have a limited number of cellular targets. This is due to the fact that the mechanisms of action of these drugs overlap one another, hence contributing to the emergence of multidrug resistant phenotypes [24].

In 2008, antifungal susceptibility testing protocol for dermatophytes was approved for the first time by clinical and laboratory standard institute (CLSI), which was further modified in 2010 [25]. The azoles, allylamines, and polyenes represent the most widely used treatments for infection caused by dermatophytes. The azoles are separated into two distinct classes: the imidazoles (eg. clotrimazole, ketoconazole) and triazoles (eg. fluconazole, itraconazole). The triazoles are used as systemic first-line agents for most severe fungal diseases [26]. Different methods can be used to determine the activity of various antifungal drugs against various fungal genera and species. Barry, *et al*. [27] suggested the standard disk diffusion assay as a good model for antifungal tests in routine laboratory diagnosis and assessment of dermatophyte resistance against antifungal drugs. In this study, the disk diffusion method was used to determine the activities of seven antifungal drugs: Amphotericin B, clotrimazole, fluconazole, griseofulvin, itraconazole, ketoconazole and nystatin against 10 fungi isolates associated with tinea capitis (*Trichoderma longibrachiatum, Cytobasidium minutum, Aspergillus spp, Ectophoma multirostrata, Aureobasidium pullulans, Pichia terricola, Aspergillus flavus, Cladosporium tenuissimum, Penicillium flavigenum,* and *Fusarium solani*).

The fungal isolates studied showed 90% sensitivity to amphotericin B and nystatin, 40% sensitivity to clotrimazole, 10% sensitivity to fluconazole and griseofulvin, 30% sensitivity to itraconazole, and all were resistant to ketoconazole. Fungi isolates associated with tinea capitis were found to be sensitive to nystatin and amphotericin B. Nystatin and amphotericin B had large inhibition zones ≥ 15mm around the disks and the best activity against *Trichoderma longibrachiatum, Cytobasidium minutum, Aspergillus spp, Ectophoma multirostrata, Aureobasidium pullulans, Pichia terricola Aspergillus flavus, Cladosporium tenuissimum, Penicillium flavigenum,* and *Fusarium solani*.

Few studies have been conducted to determine the antifungal susceptibility pattern of agents of tinea capitis. Some authors have reported a 100% susceptibility of candida species to amphotericin B [20]. This is in agreement with the findings of this study which have shown amphotericin B to be 90% effective against fungal isolates associated with tinea capitis. Interestingly, in this study nystatin which is a polyene antifungal that exerts its effect by targeting the fungal cell membrane via ergosterol binding. Thus causing an increase in cell wall permeability was found to be 90% sensitive to the fungal isolates. This is in agreement with the report of Khan, *et al*. [19] that it could be used to treat fungal lesions. Our study indicated that most isolates tested were resistant to fluconazole, griseofulvin and ketoconazole (90%), followed by itraconazole (60%), clotrimazole (20%); the least effective was recorded for amphotericin B and nystatin (10%). Clotrimazole and ketoconazole had an intermediate inhibition zone against *T. longibrachiatum, F. solani* and *A. flavus* but resistant to *C. tenuissimum* and others.

Griseofulvin has been reported as an effective and cost-effective drug in the treatment of tinea capitis by a number of studies [17,28-31]. According to our study, it

was ineffective against 90% of the ten fungal isolates. This is in agreement with Alkeswani, *et al*. [32] that griseofulvin has been falling out of favor due to significant treatment failure, high cost and long duration of treatment. However, this could be due to species specific differences in response to treatment, mutation, such as missense substitution. This kind of mutation was seen in a dermatophyte *T.rubrum* which contributes to cross resistance to antifungals [33-35]. According to a systemic review and a meta-analysis, azoles such as itraconazole and ketoconazole were considered the most effective agents in treating tinea capitis infection caused by *Trichophyton spp* and *Microsporum canis* [36-38]. Despite the fact that they are associated with serious hepatotoxicity and death [39].

They are many studies indicating that fluconazole, itraconazole and ketoconazole has less effect against dermatophytes [31,40-42]. Our findings are in agreement with those reports. This could be due to the fact that triazoles have components that can interfere with the test or it could be the culture medium used that is Sabouraud Dextrose Agar components interfere the test [31]. Recently, it was reported that itraconazole should not be considered as a first line agent for cutaneous fungal infections in children, because data on safety and efficacy are lacking [43] and oral ketoconazole has fallen out of favor in many jurisdictions due to risks of hepatotoxicity [39,44]. Our study, suggests that nystatin and amphotericin B can be used to treating dermatophytosis.

Conclusions and Recommendations

Doctors should be informed on the antifungal drugs that are able to treat dermatophytoses, however optimal regimens for application of antifungal agents need further studies.

Funding

This work was supported by the Government of the United Republic of Tanzania through the Higher Education Student Loan Board (HESLB). The funders had no role in the design of the study, or in the collection, analysis, interpretation of data and writing of the manuscript.

Acknowledgments

This work was supported by the Government of the United Republic of Tanzania through the Higher Education Student Loan Board (HESLB). The authors appreciate the College of Veterinary Medicine and Biomedical Sciences of Sokoine University of Agriculture for granting permission to conduct this research in the Department of Veterinary Microbiology, Parasitology and Biotechnology. The authors are also grateful to individuals who assisted with data collection and critical review of the final drafts of the manuscript.

Author Contributions

M.E.M conceived the study, did the laboratory work, analysed data, and wrote the manuscript. M.R.M helped in laboratory work and G.M supervised M.E.M and critically revised and approved the manuscript.

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