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Dermatophytosis: A Review on Epidemiology, Pathogenesis, Clinical Features, Diagnosis and Treatment Strategies in Nepal

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Authors' contributions

This work was carried out in collaboration among all authors. Author MP wrote the first draft of the manuscript and managed the references. Author BL managed the analyses of the data. Author PG helped in the literature searches, author BC reviewed the manuscript. Author BPM agreed to be responsible for all aspects of the task and accepted the version. All authors read and approved the final manuscript.

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ABSTRACT

Fungal infections of the skin, hair, and nails are the most common clinical conditions caused by dermatophytes. The most common causes of dermatophytic infections are *Trichophyton, Epidermophyton*, and *Microsporum* spp. If left untreated, these infections can lead to increased morbidity and secondary bacterial infections. This review highlights the knowledge on dermatophytes, including their epidemiology, prevalence, pathogenesis, diagnosis, and treatment among Nepalese, based on electronic databases (Google Scholar, NCBI, Pubmed, and Scopus).

Terai region has a higher prevalence of dermatophytosis cases compared to the mountainous areas, primarily due to the hot and humid climate. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the two most common causative agents. In Nepal's tertiary medical facilities, only microscopy and culture techniques are used for diagnosis. However, in community settings, the only diagnostic technique available is clinical observation. In Nepal, topical therapy with azoles or terbinafine is the first-line treatment for cutaneous tinea, while systemic medication with terbinafine is the first line treatment for onychomycosis and tinea capitis. There is a need for further research to develop better prevention and treatment strategies to reduce the burden of these infections.

Keywords: Fungal infection; dermatophytes, epidemiology; pathogenesis; diagnosis; treatment.

1. INTRODUCTION

Fungal infections of the skin, hair, and nail are common clinical conditions that affect a large population worldwide. These infections can result in substantial illness and potentially result in lasting complications if left untreated. Various socio-demographic factors, such as age, gender, occupation, geographic location, personal hygiene, socio-economic status, and lifestyle factors like smoking or alcohol consumption, and immunocompromised state can influence the risk of both communicable and non-communicable fungal infections affecting the skin, hair, and nails [1].

1.1 Dermatophytes

Superficial skin infections in humans are primarily caused by dermatophytes, which affect a significant portion of the world's population, estimated to be around 20-25% [2]. Skin, hair and nail infections are brought on by dermatophytes that infiltrate the stratum corneum or keratinized structures formed from the epidermis [3,4]. Moisture and warm conditions are the most suitable factors to a wide distribution of dermatophytosis in tropical countries [5]. *Trichophyton* genus, which typically affect the skin, hair, and nail, *Epidermophyton* genus, which mainly affect the skin, and *Microsporum* genus, which usually infect the skin and hair are the three genera of dermatophytes.

The hot and humid temperature may contribute to the higher prevalence of dermatophytoses in the Terai region. It creates an ideal environment for dermatophytes to thrive and survive. Furthermore, people in rural areas are unaware of personal cleanliness and lack health-seeking behavior. In the Terai region, agriculture is the most common occupation among the people. Because of the continuous exposure to mud and increased chance of injury dermatophytoses may be seen in higher frequency. Furthermore, men are involved in outdoor activities and the agriculture profession while women are confined to indoor activities which may explain the higher rate of cases among males.

1.2 Epidemiology and Prevalence of Dermatophytes

Tinea is the most frequent skin infection, and the trend has been consistent over the previous 20 years. In a community-based investigation, tinea cases were greater in the terai than in the mountainous zone [6]. A survey of skin illnesses in five villages in the Bara district of rural Nepal revealed a high prevalence of dermatophytoses. They were more common in males than in females [7]. A study was conducted on patients visiting the tertiary hospital from three districts in Nepal's Terai area, and dermatophytosis was shown to be the most common skin ailment. Males were affected more frequently than females [8].

Tinea corporis was found to be the most common infection in a study done between 2008 and 2009 at the College of Medical Science in Chitwan, Nepal. The age range most commonly affected was between 26 and 30 years old, and males (56.5%) were more frequently impacted than females [9]. Likewise, tinea corporis was found to be the most common infection in a study conducted at Kathmandu Medical College between 2017 and 2018. The study also showed that *T. rubrum* (50%) and *T. mentagrophytes* (35%) were the most prevalent dermatophytes [10]. In a study conducted at Grande International Hospital in Kathmandu, tinea corporis was identified as the most frequent infection, and *T. rubrum* (14.2%) was the most commonly detected dermatophyte [11]. The incidence of dermatophytes was reported to be 4.54% in research conducted at the B.P. Koirala Institute of Health Sciences in eastern Nepal, with a M: F ratio of 2.5: 1. The age range from 11 to 20 was the most affected. According to the study, tinea corporis (43%) was found to be the most prevalent clinical type [12]. Nepal is a country where regional differences in the country's climate, socioeconomic standing, religion, and customs are extremely common. In poorer nations, dermatophytosis is significantly caused by factors such as inadequate cleanliness, limited access to water, and overcrowding in addition to hot and humid weather [13].

1.3 Risk Factors

Except for tinea capitis, dermatophytosis generally affects post-pubertal hosts more commonly. The fact that males are more likely to work outside in hot, sweaty settings that favor the growth of dermatophytes, men are typically more affected than women [14]. According to recent studies, direct contacts have a relatively high incidence (72–82%) of dermatophytosis [15].

Dermatophytic infections are more common in rural population. Studies from the early 2000s revealed a rural preponderance that is probably related to the high frequency of outside work, especially agriculture, which makes people likely to perspire more [16]. According to a study by Alolofi and colleagues, those who live in rural areas are more likely to have superficial fungal infections (70.6%) than those who reside in urban areas (29.4%). The environmental and hygienic disparities between urban and rural settings may be accountable for these findings. Additionally, rural residents are poor socio-economic group members who are uninformed of the condition and do not receive any treatments, resulting in multiple sites of lesions [17].

The outbreak of chronic and resistant skin infection may be due to the misuse of combo creams that contain steroids, antifungal, and antibiotics. These creams are easily available in cities and often used without medical advice, leading to a rise in difficult-to-treat cases [18].

According to research, the incidence of dermatophyte infections is 61-67%, with a higher percentage of patients coming from lower socio-economic categories [19]. Lower-middle and medium socio-economic levels come next. Among lower socio-economic groups, poor living conditions, a lack of hygiene, congestion, and inadequate nutrition encourage the formation of dermatophytes, raising the chances of infection, chronicity, and recurrence [20].

Individuals who indulge in outdoor activities in hot, humid climates are more likely to get an infection since these conditions are suitable for dermatophytes. Additionally, recent research has revealed that manual laborers are most frequently impacted [21]. Due to their frequent contact with soil and animals as well as their greater exposure to environmental fungal infections, farmers are at a higher risk [20]. However, more housewives with active infections were discovered in investigations after 2016 [22]. Homemakers are more vulnerable to dermatophytes because of the warm kitchen environment and excessive sweating. In their study, Rudramurthy and the team discovered that homemakers were the most often impacted category (25.1%) [23].

1.4 Pathogenesis and Virulence Factors

The establishment of the fungus in the host tissue, which is necessary for fungal disease, depends on both fungal and host factors [24]. Dermatophytes are spore-producing fungi and are mainly composed of mycelium. Under specific circumstances, they have the ability to infect both human and animals. Depending on the dermatophyte species and the surrounding environment, many forms of conidia are generated. Arthroconidia are infectious fragments of hyphae, although macroconidia, microconidia, and arthroconidia can all develop from asexual spores [25].

The initial stage of a dermatophyte infection involves the attachment and adherence of the infectious components. These elements stick to the surface of keratinized tissue and proceed to the epidermis through the germination of arthroconidia. To facilitate infection, dermatophytes produce a range of virulence factors, including enzymes and non-enzymes. When invading tissue, they secrete enzymes in response to the skin components. Protease, lipase, and cellulose are just a few of the virulence enzymes that dermatophytes secrete, all of which have different substrate preferences. According to their active sites, aspartic, cysteine, glutamic, metallo, serine, and threonine proteases are categorized. A non-enzymatic virulence factor for *Penicillium* and *Aspergillus* infections in humans is also predicted to be Xanthomegnin, a mutagenic mycotoxin known to induce nephropathy and mortality in farm animals exposed to these fungi in food. It is also hypothesized that melanin or melanin-like substances, which are non-enzymatic virulence factors found in dermatophytes, will play a role in the pathogenesis of dermatophytic disorders during infection [26,27]. Within 7 days of infection, arthroconidia are formed, enabling the fungus to travel to new anatomical structures of the original hosts, infect further hosts, and pollute other habitats [25].

1.5 Host Immune Response

When dermatophytes enter keratinized tissue, they trigger an innate immune response in the host tissue through the antigens or metabolites they produce. The main antigens from dermatophytes are the components of their cell walls, including chitin, glucan, and glycopeptides. For the pathogen-host interaction to take place, the fungus must first overcome the host's initial defense mechanisms, which include the skin and mucous membranes [28]. The skin acts not only as a physical barrier but also as an integral part of the innate and adaptive immune systems. When the tissue is under attack by invading pathogens, these immune systems are activated to combat the pathogen and protect the host. After successfully overcoming the host's defense mechanisms, dermatophytes will interact with the epidermal cells, including keratinocytes and Langerhans cells [*29*].

Keratinocytes, which are the most common cells found in the epidermis, play a crucial role in the initial response to dermatophytes or their antigens. They directly participate in defense against the pathogen and activate further immune cells by releasing multiple inflammatory cytokines such as IL-8, IL-6, and TNF-α. Zoophilic species (*Microsporum canis*, *Trichophyton mentagrophytes*, and *Trichophyton verrucosum*) infect animals and humans and induce a stronger immune response. In contrast, anthropophilic species (*Trichophyton rubrum*, *Trichophyton tonsurans*, and *Epidermophyton floccosum*) infect primarily humans. The type of cytokines released by keratinocytes varies depending on the species of dermatophyte. Zoophilic species induce a stronger immune response than anthropophilic species. In addition, natural antimicrobial peptides, such as cathelicidins and defensins, are produced as part of the innate immune defense against dermatophytes. These peptides are expressed by various barrier and secretory epithelial cells in response to infection [30].

1.6 Clinical Features

1.6.1 Cutaneous tinea

Cutaneous tinea is a fungal infection of the skin. It can appear in various forms, including tinea pedis (athlete's foot), tinea corporis (ringworm), tinea cruris (jock itch), tinea barbae, and tinea manuum. Tinea corporis usually manifests as a well-defined, sharply outlined, oval or circular, slightly erythematous, scaly patch or plaque with a raised leading edge. The irritation is typically not severe [31]. When the palmar and interdigital regions of the hand are affected by dermatophytes, it is known as tinea manuum [32]. Tinea cruris is an infection of the groin brought on by dermatophytes. It presents as a pruritic, scaling lesion or plaque in the crease between the scrotum and the leg [33,18]. A fungus infects the skin on the feet, causing tinea pedis, also known as athlete's foot [34]. Scaling and maceration of the interdigital spaces, which often begin on the lateral side and extend to the medial side of the foot, are its defining characteristics. In the plantar and lateral parts of the foot, the infection frequently manifests as a dry pattern and is accompanied by hyperkeratosis. These are the physical manifestations of tinea pedis that are most frequently observed. A less frequent pattern of the infection, however, is when it appears as small vesicles and blisters on a reddish base on the plantar surface of the foot [35]. A dermatophyte fungus infection affects the facial regions of the beard and moustache known as tinea barbae.

1.6.2 Tinea capitis

A fungal condition called tinea capitis affects the scalp and hair. There are two clinical subtypes of tinea capitis: inflammatory and non-inflammatory. While the inflammatory kind can result in painful nodules packed with pus and scarring hair loss, the non-inflammatory variety typically does not. Although it can affect people of any age, it most frequently affects youngsters between the ages of 3 and 14 years. Eyelashes and eyebrows may also be impacted by tinea capitis [36].

1.6.3 Onychomycosis

A fungal nail infection known as onychomycosis can take many different forms, including distal subungual, proximal subungual, endonyx, superficial white, and complete dystrophic. Distal subungual is the most prevalent type, which begins with tinea pedis and results in thick, discolored nails. Similar symptoms are seen in the proximal subungual, endonyx, and superficial white types, whereas total dystrophic onychomycosis destroys the nail [37].

1.7 Diagnosis

Most dermatophyte infections can be diagnosed easily by taking into account the patient's medical history, conducting a physical examination, using a wood's lamp and potassium hydroxide (KOH) microscopy [38]. The gold standard for prescription of systemic therapy for the fungal infections is culture. Colony traits that can be distinguished include color, texture, growth rate, and distinctive morphological elements including spirals, pectinate branches, pedicels, and nodular organs [39]. As conventional methods of dermatophyte detection (KOH microscopy and culture) were found to have delayed diagnostic capability and low accuracy, the development of molecular diagnostic techniques allowed for a more precise and swift diagnosis of dermatophytosis. A prompt and precise laboratory diagnosis is crucial for effective treatment as relying solely on clinical appearance leads to a 50% misdiagnosis rate [40]. This accurate diagnosis enables the timely administration of appropriate antifungal therapy, which avoids non-specific self-medication.

Identification of fungi in dermatological samples using PCR is reliable and provides significantly improved results in comparison with cultures. By utilizing direct DNA isolation and PCR-ELISA technique, dermatophytes can be identified at the species level quickly and accurately, without the need to consider their morphological or biochemical traits [41]. The identification of dermatophytoses involves detecting dermatophyte DNA in patient samples. However the DNA extraction procedure and the fact that molecular taxonomy and species classification don't always agree provide challenges [42]. The methods for diagnosing dermatophytoses are still driven by time, cost, complexity, the variety of species spectrum observed, despite breakthroughs in the molecular field. Consequently, the conditions present and the resources in the laboratory affect several decisions involved in the pursuit of a dermatophytoses diagnosis.

Even tertiary care facilities in Nepal use microscopy and culture methods to identify dermatophytoses cases. This is likely due to the high cost associated with using more advanced molecular techniques like PCR and ELISA.

1.8 Treatment

1.8.1 General measures

As general preventive measures, the patient should be advised to wear loose-fitting cotton clothing that is comfortable. They should also be reminded to change their underpants frequently. They need to be encouraged not to exchange clothing, towels, or bed linens. It is critical to emphasize to patients the importance of constant medication use [43].

1.8.2 Pharmacologic measures

The infection site, etiological agent, and drug penetration potential all have a role in the therapy decision. Antifungal medicines used to treat dermatophytes must be able to penetrate the keratinocytes that make up the stratum corneum since they dwell there. The site of infection and the symptoms are the main factors that affect the duration of treatment. Treatment for skin lesions normally takes two to three weeks, whereas foot inflammation takes four to six weeks [44].

Topical antifungal medications are typically the first choice for treating localized dermatophytoses, with the exception of tinea capitis and onychomycosis. Topical antifungals include drugs such as imidazoles (such as clotrimazole, ketoconazole, and miconazole), triazoles (like fluconazole and itraconazole), and allylamines (such as terbinafine), which work by inhibiting the

formation of cell membranes through the suppression of ergosterol biosynthesis. Miconazole, clotrimazole, and ketoconazole are well-known azole antifungals that have been widely used to treat dermatophytose. Luliconazole and efinaconazole are two more recent azoles to appear; luliconazole is approved for the treatment of tinea corporis, tinea cruris, and tinea pedis, while efinaconazole is approved for the treatment of onychomycosis [45]. However, topical antifungals cannot penetrate the hair shaft, making oral antifungals necessary in cases of tinea capitis (Table 1).

Table 1. Treatment of cutaneous tinea, onychomycosis, and tinea capitis [43,46]

Treatment of cutaneous tinea	
Topical therapy (only treatment required in limited disease)	• Azoles once daily or twice daily for 2-4 weeks • Terbinafine 1% twice daily for 2 weeks
Systemic therapy	1st choice: • Terbinafine 250 mg/day for 2-3 weeks In children: • Weight (Wt) < 20 kg = 62.5 mg/day • Wt (20-40) kg = 125 mg/day • Wt > 40 kg = 250 mg/day 2nd choice: • Itraconazole 100 mg/day for 1-4 weeks
Treatment of onychomycosis	
Systemic therapy (1st line)	1st choice: • Terbinafine – 250 mg/day for 6 weeks (fingernails) and for 12 weeks (toenails) In children: • Wt < 20 kg = 62.5 mg/day • Wt (20-40) kg = 125 mg/day • Wt > 40 kg = 250 mg/day 2nd choice: • Itraconazole- 200 mg twice daily for 1 week every month for 2 cycles (fingernails) and for 3 cycles (toe nails) In children: • Pulse therapy – 5 mg/kg/day for 1 week every month 2 pulses (fingernail) and 3 pulses (toenail)
Topical therapy	Cicroplix 8% once daily Amorolfine 5% once/week
Adjunctive	1. Surgical/chemical nail avulsion 2. Laser 3. Photodynamic therapy (PDT)
Treatment of tinea capitis	
Systemic (1st line)	• Terbinafine 250 mg/day for 2-4 weeks (*Trichophyton* species) - Dosage wt < 20 kg = 62.5 mg/day for 2-4 weeks - Wt (20- 40) kg = 125 mg/day for 2-4 weeks - Wt > 40 kg = 250 mg/day for 2-4 weeks • Griseofulvin – higher efficacy against *Microsporum* species - Dosage wt < 50 kg = 15-20 mg/kg/day for 6-8 weeks - Wt > 50 kg = 1g/day for 6-8 weeks • Itraconazole- effective against both *Trichophyton* and *Microsporum* species - Dose : 50-100 mg/day for 4 weeks
Topical therapy (only to prevent transmission)	• 2% ketoconazole • 1-2.5% selenium sulfide • 2.5% povidone iodine shampoo

Table 2. Characteristics of antifungal agents for the treatment of dermatophyte infections [49]

	Griseofulvin	Ketoconazole	Fluconazole	Itraconazole	Voriconazole	Terbinafine
Keratin binding	Low	Strong	Low	Strong	*	Strong
Excretion by sweat	High	High	High	Moderate	*	Low
Grease affinity	Low	Low	Low	High	*	High
Mechanism of action	Disrupts micotic spindle/microtubules	Inhibits 14- α demethylation of lanosterol	Inhibits 14- α demethylation of lanosterol	Inhibits 14- α demethylation of lanosterol	Inhibits fungal cytochrome P-450 dependent 14- α lanosterol demethylase	Inhibits squalene epoxidation
Fungicidal	No	No	No	No	*	Yes

Unlike other antifungals, griseofulvin (an oral antifungal) works by inhibiting fungal mitosis by targeting microtubules. Griseofulvin is commonly used for tinea capitis due to its safety, effectiveness, and affordability, but it requires a long course of treatment that may impact patient compliance. Itraconazole is another effective option, but it can be expensive. In addition to these treatments, adjuvant therapy with topical 2 percent ketoconazole or selenium sulfide shampoo may also be used to reduce the spread of infection [47]. For onychomycosis, oral antifungal agents (terbinafine, itraconazole, and fluconazole) are used as they are effective against fungal infection of the nail. However, terbinafine is superior in its effectiveness. When oral antifungals are ineffective at treating the disease, surgical avulsion of the nails and chemical nail ablation with potassium iodide are further options [48] (Table 2).

Cost-effectiveness is a key consideration for choosing antifungals in a country like Nepal since many people here have low socio-economic conditions. The easy availability of steroids and antibiotics without a prescription leads to self-treatment of fungal infections, which can contribute to disease chronicity. Furthermore, non-compliance after a few days of utilizing the prescribed drugs is responsible for inadequate therapy and recurring fungal infection. As a result, it is critical to treat the patient by selecting the appropriate treatment based on the organism, the portion of the body affected, the chronic disease conditions, and the patient's socio-economic status. Furthermore, even if the disease is treated after the initial administration of the prescription, the patient should be instructed to continue using the drug for the specified period of time.

Joshi and his team's investigation at Nepal Medical College over the course of a year found that many patients neglect to see a doctor despite having an infection. The majority of patients who were looking for medication did so from their neighborhood community pharmacy [50]. Joshi and his team reported that itraconazole followed by fluconazole and terbinafine are the most commonly used antifungals. In contrast, a study by Khadka found that miconazole, followed by ketoconazole, and clotrimazole is the most effective treatment for dermatophytes [51].

Table 3. Contraindication of antifungal drugs [54,55,43]

Drug	Contraindications
Terbinafine	Hepatic, renal impairment, Depression
Itraconazole	Heart failure, Hepatotoxicity,
Griseofulvin	Hepatic impairment, Lupus erythematous, Porphyria
Fluconazole	Hepatic, renal impairment and QTc prolongation

Antifungal medication abuse has resulted in the establishment of resistant strains that are difficult to cure. Over the past ten years, antifungal drug resistance has surged in Nepal [51]. In a study conducted at the National Medical College and Teaching Hospital, Birgunj, Nepal, it was discovered that itraconazole was the most effective medication while fluconazole was the most resistant [52]. Similar result was seen in a study done by Karn and team at Universal College of Medical Science, Bhairahawa, Nepal [13].

1.9 Contraindication Antifungal Drugs

There are various contraindications to the antifungal drugs. Azoles, terbinafine and

griseofulvin should be avoided or used with great caution in case of hepatic impairment. Itraconazole is contraindicated in left ventricular dysfunction [53]. A summary of some important contraindications to the drugs used against dermatophytes is shown in Table 3.

2. CONCLUSION

Dermatophytosis is a global illness that poses a severe threat to public health, particularly in poor nations such as Nepal. There is an increase in recurrent dermatophyte infections and treatment-resistant cases, leading to morbidity in people. The primary cause is a lack of personal hygiene awareness, as well as the inadvertent use of locally available combination creams including steroids, antibiotics, and antifungals. Another reason for the low accuracy in the diagnosis of dermatophytes and thus the over-the-counter use of anti-fungal drugs can be attributed to the use of conventional methods (clinical observation and microscopy using KOH) for the diagnosis even in most tertiary centers. It is critical to enhance public knowledge about dermatophytosis and the importance of receiving a full treatment regimen from an expert after receiving an accurate diagnosis. Similarly, it is vital to take rigorous policy measures to prohibit the sale of unprescribed drugs at pharmacies. Furthermore, diagnostic techniques should be updated with new diagnostic instruments such as PCR, which have great accuracy and thus aid in the proper diagnosis and treatment of patients.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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