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# Opportunistic Dermatophyte Infections in Immunocompromised Patients With Rheumatoid Arthritis: A Review Article

Dhuha A. Athouf
Department of Pathological Analysis, College of Science, University of Thi-Qar, Nasiriyah, Iraq

Email: dhuha.abdulaama@sci.utq.edu.iq

**Abstract.** Background: Opportunistic dermatophyte infections pose an increasing issue in immunocompromised individuals, especially those with rheumatoid arthritis (RA). Rheumatoid arthritis patients frequently get immunosuppressive treatment, such as corticosteroids and biologics, rendering them susceptible to fungal infections. Dermatophytes, a category of keratinophilic fungus, can induce severe and unusual infections in these patients, frequently resulting in chronic, treatment-resistant diseases. This review examines the epidemiology, risk factors, clinical symptoms, and diagnostic difficulties associated with opportunistic dermatophyte infections in individuals with rheumatoid arthritis. Additionally, it emphasizes contemporary therapeutic methods and preventive measures to reduce the risk of infection in this at-risk population. Timely diagnosis and customized antifungal therapy are essential for enhancing patient outcomes. Objectives: This study seeks to examine opportunistic dermatophyte infections in immunocompromised individuals with rheumatoid arthritis (RA), especially those receiving immunosuppressive treatment. Conclusion: The interaction between compromised immune responses and heightened vulnerability to fungal infections requires proactive prevention and early intervention techniques. By maintaining good hygiene, wearing suitable footwear, employing antifungal treatments, and obtaining prompt medical consultation, patients can significantly reduce the dangers associated with dermatophyte infections.

**Highlights:**

1. High Risk in RA Patients, Immunosuppressive drugs increase susceptibility to dermatophyte infections.
2. Difficult to Diagnose and Treat, Infections can become chronic and drug-resistant, requiring timely and tailored antifungal therapy.
3. Prevention Is Essential, Good hygiene, proper footwear, and early medical attention help reduce infection risk.

**Keywords:** Dermatophyte, Fungi, Immunocompromised, Rheumatoid Arthritis, Opportunistic

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# Introduction

"Dermatophytes represent the most prevalent pathogenic filamentous fungus, exhibiting an infection incidence of up to 20%-25% globally [1]". "Dermatophytes typically infect the nails, skin, and hair, resulting in various superficial dermatophytoses, including Tinea capitis, Onychomycosis, Tinea corporis, and Tinea pedis. Dermatophytes may seldom penetrate skin tissue and deep organs, especially in immunocompromised individuals with congenital or acquired immunodeficiency, leading to potentially life-threatening illnesses if not treated appropriately [2]".

"Dermatophytes are keratinophilic fungi that cause benign and prevalent infections globally. Nonetheless, they may result in infrequent and serious illnesses in immunocompromised individuals. "Severe manifestations encompass severe and/or invasive dermatophytosis, specifically deep dermatophytosis and Majocchi's granuloma [3]". "In humans, dermatophytes are primarily restricted to the stratum corneum, nails, and hair, and do not aggressively infiltrate beyond the basal layer [4]".

"Dermatophytes are extensively prevalent in the environment, affecting an estimated 20–25% of the global population annually". "These fungi are keratinophilic and keratinolytic, leading to infections of keratin-rich structures, including skin, hair, and nails."The manifestation of this infectious disease ranges from asymptomatic persons to those exhibiting acute inflammatory or non-inflammatory, persistent, invasive, and sometimes life-threatening symptoms [5]".

"Dermatophytes are the causal agents of dermatophytosis, commonly known as ringworm or tinea, which are the most widespread fungal infections impacting the skin and its appendages in both immunocompetent and immunocompromised persons [6]". "The condition impacts areas of the human body abundant in keratin, including the skin, hair, and nails. Only Trichophyton can influence all three structures, whereas Microsporum specifically targets skin and hair, and Epidermophyton focuses on skin and nails, depending on their affinity for distinct classes of keratin [7]".

"Fungi have often induced diseases in immunocompromised individuals, including those with HIV, cancer, diabetes, and those undergoing immunosuppressive therapy [8] [9]". "Healthy persons with immune system deficiencies due to age (children and

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elderly), antibiotic therapy, or pregnancy are classified in a distinct group [10]. Besides prevalent diseases, fungus can induce severe, life-threatening infections [11] [12]".

"Various risk factors may exacerbate the likelihood of dermatophyte infection, including type 2 diabetes, sedentary lifestyle, vascular illness, anemia, immunosuppression resulting from leukemia, organ transplantation, acquired immunodeficiency syndrome (AIDS), and the administration of immunosuppressants [13]". "The increased prevalence of dermatophyte infections, particularly chronic and recurring dermatophytosis, significantly affects patients' quality of life and frequently necessitates prolonged therapies, resulting in psychological and economic strain [14] [15]".

"Immunosuppressed patients exhibit a greater prevalence of superficial dermatophytosis, are more susceptible to recurring and chronic infections, and have an increased likelihood of developing invasive diseases compared to immunocompetent patients". "Marconi et al. examined instances of invasive dermatophyte infections and demonstrated that almost fifty percent of patients with profound dermatophytosis were immunosuppressed [16]".

This study aims to investigate opportunistic dermatophyte infections in immunocompromised patients with rheumatoid arthritis (RA), particularly those on immunosuppressive therapy. The specific objectives are: to assess the prevalence of opportunistic dermatophyte infections in immunocompromised patients with rheumatoid arthritis and identify the predominant dermatophyte species; to investigate the clinical manifestations and diagnostic challenges associated with these infections in this population; and to evaluate and propose effective prevention strategies to mitigate the risk of dermatophyte infections in rheumatoid arthritis patients.

# Literatures Review

## A. Molecular Characterization of Dermatophytes

Molecular techniques have been utilized for the categorization and epidemiological investigation of dermatophytes. Dermatophyte genomes vary from 2.25 Mb to 24.1 Mb, with the whole genomes of multiple species, such as Microsporum canis, having been annotated [17]. "Dermatophyte genomes are

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haploid and possess a limited amount of repetitive DNA [18]. "Conidia (spores) possess a singular nucleus, whereas hyphae are typically multinucleated cells containing genetically distinct nuclei [19]". The genomes of dermatophyte species exhibit considerable conservation, with more than 6000 orthologs common to anthropophiles, zoophiles, and geophiles". "M. canis possesses 943 distinct genes, representing the highest level of heterogeneity documented among dermatophytes [17]". "Baert et al. recently suggested a novel categorization strategy for dermatophyte species utilizing a phylogenetic approach based on two gene regions: the internal transcriber spacer region (ITS) and partial β-tubulin [20]".

"Besides the taxonomy of genus and species, epidemiological studies have been undertaken to delineate genetic variants in dermatophytes, analyzing mitochondrial DNA sequences, random amplified polymorphic DNA, microsatellites, and RNA sequencing". "Microsatellite DNA polymorphisms have been detected in dermatophytes, presenting a cost-effective methodology for the fast characterization of strain variation and facilitating genotypic comparisons across extensive sample collections. Numerous studies have employed this methodology for M. canis sample collections from diverse global areas, revealing intraspecies genetic variations [21] [22]". "Moskaluk et al.(2022). The genetic understanding of dermatophytes has significantly advanced in recent years, facilitating a deeper comprehension of fundamental dermatophyte processes, including the initiation of infections [22]".

## B. Taxonomy of Dermatophytes

Dermatophytes have traditionally been classified within the class Deuteromycetes, sometimes referred to as "Imperfect Fungi". The sexual stage of dermatophytes is beneficial for epidemiological studies and for species identification. "Consequently, dermatophyte species can be classified into three genera based on differences in conidial morphology: Microsporum, Epidermophyton, and Trichophyton [23]".

### 1. Epidermophyton

"This genus is characterized by large, multicellular, club-shaped, thin-walled macroconidia that are clustered together; microconidia are absent". "The

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characteristics of the genus are taken from E. floccosum. Two species of Epidermophyton are classified based on anamorph morphology: E. floccosum and E. stockdaleae. E. floccosum is the sole pathogenic "anthropophilic" species in this genus, globally accountable for the bulk of Tinea cruris infections [24]".

2. Microsporum

"This genus contains microconidia and macroconidia. Macroconidia are spindle-shaped, multi-septate structures with either a thin or thick echinulate cell wall. "They may be either plentiful or scarce". "The echinulations on the macroconidial cell wall constitute the defining trait that distinguishes this genus. "Pyriform microconidia have a diameter of approximately 2-3 µm. M. audouinii is the designated type species. Based on anamorph morphology, there are roughly 18 species of Microsporum. Tinea corporis and Tinea capitis in the Mediterranean region are predominantly attributed to M. canis [25]".

3. Trichophyton

"This genus generates microconidia measuring 2-3 µm and exhibiting a pear form, as well as macroconidia that are cigar-shaped and with smooth walls". Trichophyton is classified into 25 species based on its anamorphic morphology, with T. tonsurans serving as the type species [25] [26]. "In Central and Northern Europe, T. rubrum has been the predominant dermatophyte for the last 20 to 30 years. "Reports indicate that in the United States and Canada, the predominant organism responsible for tinea capitis in children is Trichophyton tonsurans, whereas T. mentagrophytes var. interdigitale, a variant of T. mentagrophytes, is the primary organism isolated in cases of Tinea pedis and Tinea cruris [27]".

## C. Clinical Manifestation of Dermatophytes

Traditionally, dermatophytosis has been designated by appending the Latin name for the affected anatomical place to the term Tinea [28].

1. Tinea Corporis (glabrous skin)

It frequently impacts the shoulders, limbs, or trunk; the face is also occasionally involved. "The infection may present as moderate or severe, often characterized by annular, scaly lesions or plaques featuring central clearing and

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a raised, scaling margin". "Chronic infections caused by zoophilic dermatophytes may present as papules and vesicles accompanied by cutaneous infiltrates (26)". "The spread and etiological agent of Tinea corporis varies by geography and the origin of the infection. T. rubrum, originating from individuals with Tinea pedis, is certainly the most prevalent global cause. T. tonsurans, the predominant cause of Tinea capitis, is also responsible for Tinea corporis in areas where Tinea capitis is prevalent. If the transmission comes from a pet, M. canis is usually the responsible agent. T. verrucosum, E. floccosum, T. mentagrophytes, and M. audouinii are additional dermatophytes that induce complications [26]".

2. Tinea Barbae (facial hair)

"Tinea affecting the chin and upper lip is termed Tinea faciei. There are three types of lesions: deep inflammatory plaques, noninflammatory superficial regions, and severe pustular eruptions. "The invasion of Endothrix in the affected region may lead to fragile, dull hair [29]". "The potential outcome may involve considerable scarring and irreversible hair loss, with T. verrucosum and T. mentagrophytes var. granulosum being more commonly implicated as causal agents. Diseases are transmitted through contact with cattle, dogs, and other animals; hence, dairy farmers and cattle ranchers are frequently impacted". "Transmission between individuals may occur in barbershops without antiseptic practices. Omran et al. (2008) indicated that T. mentagrophytes was the most abundant agent in positive cultures of Tinea barbae [30]".

3. Tinea Cruris (Jock Itch) (inguinal region)

It is typically more prevalent among young adults. However, post-pubertal females who are overweight or habitually don tight pants are more susceptible to being affected. "The clinical manifestation of Tinea cruris is variable; nevertheless, the underlying rash typically appears red to reddish-brown, and acute rashes may exhibit a burning sensation" [31].

4. Tinea Capitis (eyelashes, eyebrows, and scalp)

It is among the most prevalent types of dermatomycosis. In the USA, fewer than 5% of Tinea capitis infections are caused by Microsporum species, whereas over 90% are attributed to T. tonsurans [32]". "These two species infiltrate hair

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shafts and surpass superficial irritation. "The infection may be moderate, nearly asymptomatic, characterized by patchy scaling and pale gray hair stumps accompanied by mild erythema, or it may be severe, leading to kerion and folliculitis formation". "Three terms that describe a hair infection are favus, endothrix, and ectothrix, which denote the presence of arthroconidia within the hair shaft and outside the hair shaft, respectively. Additionally, a black dot is observed when infected hairs abruptly fracture at the follicular opening [32]".

5. Tinea Pedis (Athlete's Foot)

Men are more predisposed than women to get this fungal illness, predominantly affecting those aged 20 to 40". "This infection typically begins in the interdigital clefts and subsequently disseminates throughout the ankles, dorsum, soles, legs, and toenails, a condition referred to as Tinea unguium. Individuals with diabetes are believed to possess a 50% heightened probability of acquiring a fungal illness, such as tinea pedis [33]". "Tinea pedis is classified into interdigital, squamous-hyperkeratotic, and vesicular-dyshidrotic types. The predominant clinical manifestation is interdigital, mostly affecting the spaces between the fourth and fifth toes, presenting as maceration, fissuring, and desquamation. Squamous-hyperkeratotic type (hyperkeratosis and acanthosis) characterized by pinkish skin on the heels, sides, and soles of the foot, which is adorned with little silvery scales (moccasin foot), and vesicular-dyshidrotic type. The etiology of the complicated illness, characterized by a combination of dermatophyte and bacterial pathogens, is a polymicrobial infection and is clinically more severe [34]". "Melikoğlu et al. (2023) identified the dermatophytes responsible for Tinea pedis as T. rubrum, T. mentagrophytes, M. canis, E. floccosum, T. verrucosum, and T. violaceum, listed in order of decreasing incidence [35]".

6. Tinea Unguium

Approximately 20 percent of nail disorders are attributable to onychomycosis. Primarily, 80–90% of Tinea unguium cases are attributed to T. rubrum and T. mentagrophytes var. interdigitale. "Children's nails grow more rapidly and possess smaller surfaces compared to adults, resulting in infection rates in

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children being thirty times lower than those in adults [36]". "Vestergaard-Jensen et al. (2022) identified the prevalent dermatophyte species isolated from the toenails of 1,305 children aged 3 to 15 across 17 schools as T. tonsurans, T. rubrum, and T. mentagrophytes [37]".

7. Tinea Versicolor

Pityriasis versicolor is caused by lipophilic dimorphic fungi belonging to the Malassezia genus (Pityrosporum ovale or Pityrosporuni orbiculare), which are part of the natural skin flora. "Typically, it manifests as small to medium-sized erythematous, hyper- or hypopigmented macules that are either round or oval in appearance. "Typically, fine desquamation affects the upper trunk, especially the shoulders, neck, and occasionally the face". "Fungal proliferation may arise in filamentous and yeast forms due to many factors, including the application of greasy lotions, elevated humidity, corticosteroid misuse, or genetic predispositions [38]".

8. Tinea Manuum

T. rubrum is the predominant dermatophyte responsible for ringworm on the palms. "Diffuse dry scaling lesions that accentuate the flexural creases of the palms frequently represent the clinical manifestation of Tinea manuum. When supplementary dermatophytes are involved, inflammatory lesions are infrequent but may nevertheless lead to a sustained reaction [39]".

## D. Factors Associated With Dermatophytes Infection

In addition to enzymes, certain additional factors have been linked to a heightened occurrence of dermatophytosis [40]. "This encompasses increased temperatures and humidity in tropical and subtropical countries, together with geographical factors, indicating a greater incidence of the infection in rural areas relative to metropolitan locales [40]. Patients afflicted with diabetes exemplify how chronic conditions can potentially enhance the transmission of infectious diseases". "The prevalence of Tinea infections is markedly elevated in developed nations due to the use of immunosuppressive medications and the increased occurrence of conditions like Acquired Immune Deficiency Syndrome (AIDS), in contrast to infections among individuals in impoverished socioeconomic environments [41]".

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The incubation time for dermatophytosis in humans typically ranges from 1 to 2 weeks prior to the manifestation of symptoms. The humid and warm conditions characteristic of tropical regions are conducive to the proliferation of the disease [42]. "Dermatophyte infections are linked to various risk factors, such as inadequate hygiene and perspiration due to vigorous outdoor activities in high temperatures". "Dermatophytes represent a group of fungi capable of causing skin diseases". The epidemiology of dermatophytosis is influenced by several factors, including travel, socioeconomic status, antifungal medication use, and immunosuppressive conditions [43]".

## E. Pathogenesis of Dermatophytes

The pathogenesis of dermatophytic infections encompasses three primary factors, and understanding their interplay is crucial in the context of persistent dermatophyte infections [44]."The factors encompass fungi, intrinsic host characteristics such as skin barrier function, and the immune response elicited against the fungus. The type of fungi and the host's immune response are significant factors that contribute to recalcitrance and relapses [44]".

"The pathogenesis of dermatophytes involves a specific fungus–host relationship, as these fungi induce diseases in immunocompetent individuals while exclusively targeting superficial keratin structures". "The clinical manifestation of dermatophytoses is contingent upon the attributes of the causative fungi as well as the characteristics of the host [45]". "Geophilic and zoophilic species of dermatophytes primarily induce acute infections, which are marked by the swift eradication of the causative agent when appropriate therapy is employed alongside robust innate and acquired immune responses". "Anthropophilic species typically induce chronic infections that are often asymptomatic or exhibit minimal symptoms, resulting in prolonged and sometimes uncertain therapeutic outcomes, along with diminished immune responses [45]". The initiation of a disease is influenced by the interaction among the pathogen, the host, the environment, and the host skin microbiome (Figure 1).

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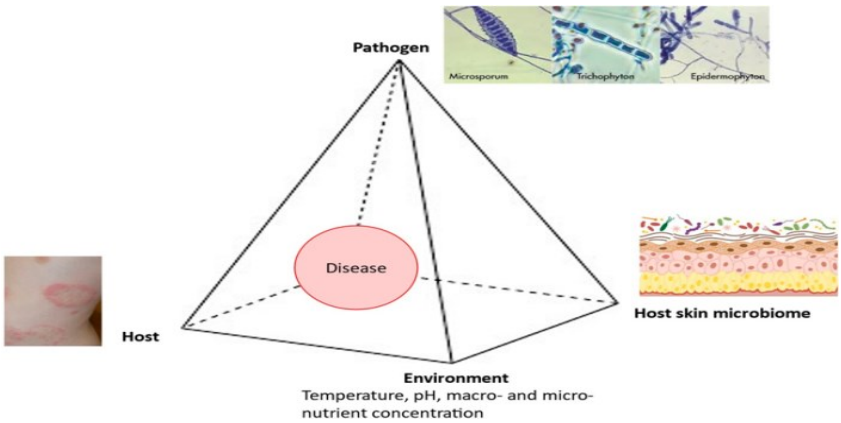


**Figure 1.** Disease pyramid in dermatophytosis

## F. Dermatophytosis

Dermatophytosis is a prevalent superficial infection induced by dermatophytes, a category of pathogenic keratinophilic fungus. "In addition to breaching the epidermal barrier, host immune responses to dermatophytes may also result in pathological inflammation and tissue damage to a certain degree". "Consequently, comprehending the pathophysiology of dermatophytes, encompassing fungal virulence facrs and anti-pathogen immune responses, is highly beneficial [46]".

Dermatophytosis, a condition caused by aerobic fungal organisms that impact keratinized tissues like the epidermis, hair, and nails, has widely afflicted tropical regions. "The clinical manifestation of these fungal infections can be verified by their appearance and the lesions affecting various sites of the host [47]". "Trichophyton rubrum is the predominant fungus responsible for dermatophytosis. Molecular diagnosis is the most effective and precise technique for fungal identification. Notable genetic variation exists between local and global fungal isolates [48]".

## G. Methods for Diagnosing Dermatophytosis

An accurate diagnosis of dermatophytosis is essential for facilitating early treatment and minimizing transmission to other humans or animals [49]. "Previous treatment may compromise various diagnostic assays, resulting in erroneous outcomes [49]". "The clinical sample type collected from the patient influences the diagnostic approaches available, as the sensitivity and specificity of assays may vary based on the sample type".

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"Immunocompromised patients may develop non-dermatophyte mold infections of the skin characterized by the presence of hyphae, including aspergillosis, mucormycosis, fusariosis, and phaeohyphomycosis". "Culture is essential for confirming the diagnosis of deep dermatophytosis and for identifying the pathogen [3]". "In the absence of positive culture, immunohistochemistry utilizing specific antibodies against species such as T. rubrum may be conducted, or specific molecular diagnostic tools for dermatophytes may be applied to tissue samples to aid in confirming the diagnosis [3]".

1. Microscopic examination dependent techniques

a. Bright-field Light Microscope

"Microscopic examination for diagnosing dermatophyte infections has been employed using several diagnostic approaches. "Direct microscopic inspection of skin scrapings, hair, scales, and nails with a clarifying agent under 40x magnification of a bright field microscope, or histological and immunohistochemical analysis of biopsied tissue from infected lesions [50]". "Numerous investigations and experiments have been conducted on various clarifying agents during wet slide preparation to get improved microscopic clarity and reduced time in slide preparation and examination. Potassium hydroxide (KOH), sodium hydroxide (NaOH), calcofluor white, Chicago sky blue, lactophenol cotton blue (LPCB), and a combination of dimethyl sulfoxide (DMSO) and glycerin with NaOH or KOH [50]".

b. Fluorescence Microscope

"The integration of fluorescence techniques in the swift diagnosis of dermatophytosis is predicated on the observation that tissues infected by specific dermatophyte species exhibit fluorescence when stained with hematoxylin/eosin (H and E) or subjected to UV light within the wavelength range of 320 to 400 nm. "The primary challenge confronting the natural fluorescence-based dermatophyte methodology is its inherent limitation to a select few species, resulting in a general reliance on this method for dermatophyte diagnosis. Conversely, the use of a fluorescent dye, specifically calcofluor white, demonstrated considerable improvements over traditional

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KOH wet mount techniques [50]". "Additional infections and dermatological conditions, including bacterial infections, yeast infections, and pigmentary disorders, may also glow under Wood's light, potentially resulting in false positives for dermatophytosis [51]".

2. Modified rapid culturing techniques

a. Dermatophyte Test Medium (DTM)

The isolation and identification of dermatophytes from clinical samples cultured in vitro is regarded as the definitive method for diagnosing dermatophytosis [52]. "In addition to the standard isolation of dermatophytes on mycological specific media, modified culturing media can facilitate a relatively rapid (2 weeks) presumptive identification of dermatophytes compared to conventional culturing methods [53]". "Dermatophytes test medium (DTM) is one of the earliest media developed for the rapid presumptive identification of dermatophytes [54]. DTM is typically used in conjunction with Sabouraud dextrose agar (SDA) medium, as the latter is less discriminatory and has a reduced impact on colony morphology compared to DTM [55]".

"False negatives may arise from the overgrowth of non-dermatophytic fungi, inadequate clinical material, or improper inoculation of clinical samples in cultures, especially in the case of toothbrush samples [49] [56]". "False positives may arise when samples are obtained from patients in contaminated environments [56]". In clinical practice and reference laboratories, cultures are typically cultivated in complete darkness [57].

b. Protocol Dependent on Multi-Chromogenic Media

"A two-day strategy is established for the swift and straightforward differentiation of two closely related dermatophyte species [58]". "The established protocol was formulated as follows: primary isolates aged 2 to 20 days were sub-cultured on four distinct commercially available chromogenic media at varying temperatures of 4, 20, 25, and 30°C, ensuring that the maximum temperature did not exceed 37°C, as temperatures above 37°C are generally detrimental to the growth of most dermatophyte species". "The

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reading protocol for the infected material involved routine inspection from 2 hours to 7 days following incubation". "This study [58] shown that Candiselect™ is a good candidate for the rapid and precise distinction between the two dermatophyte species examined (within a few hours)". Notwithstanding the encouraging outcomes, this technique is limited to differentiating solely between the aforementioned two dermatophytes. If an alternative dermatophyte is identified, it requires additional diagnosis, potentially extending the timeframe beyond that of conventional culture methods".

3. DNA-Dependent Assays

Polymerase chain reaction (PCR) has become increasingly utilized as a diagnostic assay for the detection of dermatophytes. "PCR demonstrates greater sensitivity compared to culture, as it is capable of detecting fungal DNA even in instances where the culture yields negative results [59]". "Nonetheless, akin to microscopy, it is unable to differentiate between living and dead fungal cells [49]. "False negatives may arise from inadequate sampling techniques, whereas false positives can result from the presence of nonviable fungus on the host [49]". "The accuracy of PCR is significantly influenced by the DNA extraction method utilized. For fungal detection, distinct extraction protocols are necessary to effectively digest the fungal cell, in contrast to those used for bacteria or viruses [60]". "Additional procedures may include freeze/thaw cycles, heat application, or mechanical and chemical disruptions, such as the use of beads or supplementary lysis buffers [61]".

"Qualitative (conventional) PCRs for the detection and identification of dermatophytes typically target the Internal Transcribed Spacer (ITS) and 28S ribosomal DNA, which are the most commonly used primers for pan dermatophytes [62]". "Primers have been designed to target conserved regions of the ITS specific to dermatophytes, facilitating the identification of dermatophyte-positive samples [63]". "Quantitative PCRs, specifically real-time PCR (RT-PCR), have been established for the identification of dermatophytes in clinical samples. RT-PCRs utilizing ITS primers specific to dermatophytes have

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successfully differentiated between dermatophyte species identified in clinical samples, including hair, skin, and nail specimens [63]".

4. Assays Utilizing Antibodies

The enzyme-linked immunosorbent assay (ELISA) is a prevalent antibody-antigen-based assay utilized for the detection of numerous diseases. Direct, indirect, sandwich, and competitive/inhibition ELISA methodologies present distinct advantages and disadvantages [64]. "The sensitivity of a low signal can be enhanced by optimizing reagents with greater affinity for the target, altering the type of ELISA conducted, extending incubation durations, or modifying incubation temperatures [64]". "ELISAs have been established to identify dermatophytes through serum samples from clinical patients and the assessment of antibody affinity to isolated M. canis antigen [65]". "The M. canis-specific IgG antibody in felines and canines has been identified using ELISA, exhibiting comparable sensitivity to fungal cultures [65]". "Due to the persistence of antibodies following the resolution of an infection, false positives may arise with this assay [65]". This assay necessitates serum, rendering sample collection more intrusive than alternative diagnostic methods.

## H. Opportunistic Infections

An opportunistic infection generally occurs when the impairment of established innate or adaptive immune responses allows non-strictly pathogenic organisms to infect a host [66]. "Infections significantly contribute to morbidity and mortality in immunocompromised populations. The nature and severity of the immune deficiency influence the characteristics of the possible aetiological agent and the associated opportunistic infection [66]". "Considering the infectious characteristics of NTM and significant fungal pathogens, alongside the previously stated definition of OPIs, two distinct perspectives emerge [67]". Certain fungal species are constituents of the human microbiome, while others serve as environmental pathogens. Candida albicans colonizes more than 50% of the population asymptomatically. It may be found in the skin, oral cavity, intestine, upper respiratory tract, and female reproductive tract [68]. "Under optimal conditions, this yeast can transition from a benign commensal to a pathogenic organism capable of causing infections that are difficult to treat [69]".

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"Airborne microorganisms, including filamentous fungi (Aspergillus, Rhizopus, Mucor) and previously mentioned environmental pathogens (H. capsulatum, C. neoformans), colonize the host through the upper respiratory tract [9]".

## I. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a multifaceted autoimmune disorder marked by persistent joint inflammation resulting from the immune system erroneously attacking synovial cells within the joints [70] and "Rheumatoid arthritis (RA) is a chronic, disabling inflammatory disorder induced by a confluence of environmental and genetic variables. This process frequently transpires years before to the manifestation of joint-related symptoms that are characteristic of rheumatoid arthritis (RA) [70]". "The distinguishing feature of rheumatoid arthritis is symptoms associated with the joints, such as swelling and stiffness. It is important to remember that rheumatoid arthritis (RA) extends beyond joint complications; it can induce systemic inflammation impacting multiple bodily systems [70]". "This systemic inflammation may elevate the risk of further illnesses, including stroke, heart disease, diabetes, and osteoporosis [70]".

"Most epidemiological research suggests that the prevalence of rheumatoid arthritis (RA) ranges from 0.5% to 1.0%. Seventy to eighty percent of individuals with rheumatoid arthritis (RA) possess autoantibodies, including rheumatoid factor and anti-citrullinated protein antibodies (ACPA), indicating that RA is an autoimmune disorder [71]". "Rheumatoid arthritis impacts the tiny joints of the hands, as well as the wrists, elbows, shoulders, feet, ankles, spine, knees, and mouth. RA encompasses supplementary features, as indicated in reference [72]".

The precise etiology of rheumatoid arthritis (RA) is unknown; however it is thought to result from interplay of hereditary and environmental influences. "Rheumatoid arthritis exhibits a greater incidence in women than in males, a trend commonly seen in other inflammatory disorders. This indicates that hormonal influences [73] and gender-specific genetic factors [74] probably have a role in the start of the disease. Moreover, rheumatoid arthritis is more prevalent in older adults, highlighting the influence of aging on its onset [75]".

Rheumatic diseases predominantly exhibit complex traits characterized by the interaction of multiple genetic and environmental factors. Twin studies estimate the

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heritability of rheumatoid arthritis (RA) to be approximately 60% [76]. Currently, over 100 genetic loci have been linked to rheumatoid arthritis (RA) [77]. "The relationship between these loci and the disease has yet to be clarified. The genetic factor exhibits a clear causal relationship to rheumatoid arthritis (RA), necessitating an understanding of the pathological process from a genomic perspective. Recent research on complex trait diseases has shown that numerous disease susceptibility variants influence the expression levels of various genes that operate in a cell-specific context [78]".

Genetic variables are deemed significant in the development of rheumatoid arthritis (RA). The human leukocyte antigen (HLA)-DRB1 gene is linked to the synthesis of rheumatoid factor (RF), an antibody produced during an autoimmune reaction [79]. "Moreover, the aberrant function of peptidyl arginine deiminase (PAD) enzymes can trigger a process known as citrullination, leading to the formation of cyclic citrullinated peptides (CCP). CCPs may serve as autoantigens, provoking an immunological response and the production of anti-(cyclic) citrullinated protein antibodies (ACPAs) (Figure 2) [80]".

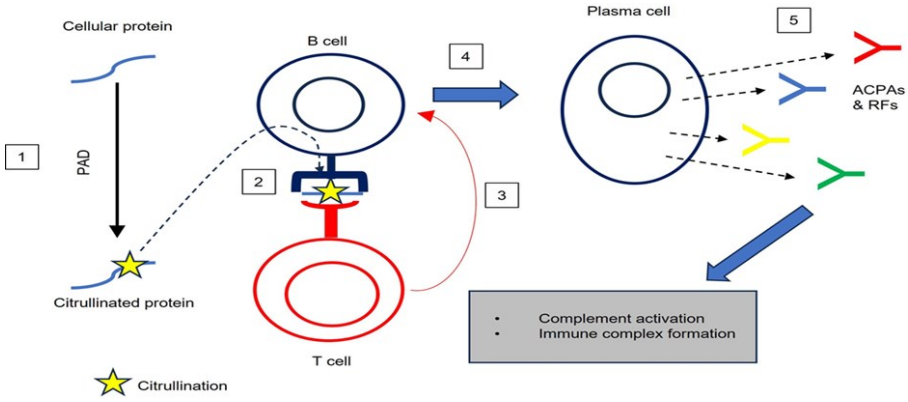


**Figure 2.** Hypersensitivity dependent on B cells. 1. Citrullination of cellular proteins; 2. Processing and presentation of citrullinated proteins; 3. Activation of B cells by T cells; 4. Differentiation of naive B cells into plasma cells; 5. Production of ACPAs and RFs. Anti-(cyclic) citrullinated protein antibodies (ACPAs); peptidyl arginine deiminase (PAD); rheumatoid factors (RFs).

## J. RA's Diagnostic, Prognostic, and Predictive Biomarkers

"The identification and optimization of biomarker panels serve as a valuable medical tool, given their roles in diagnosis, prognosis, prediction, and therapy. The

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ACR 1987 criteria included solely rheumatoid factor as a biomarker. The most recent classification comprises four biomarkers (RF, ACPA, ESR, CRP), each possessing specific limitations [81]". Recent studies have identified additional diagnostic proteins relevant to the early diagnosis of rheumatoid arthritis (RA): antibodies against mutated citrullinated vimentin (anti-MCV), antibodies against carbamylated proteins (anti-CarP), and the 14-3-3 eta protein. "A systematic review of studies assessing the diagnostic potential of biomarkers found no significant difference between cyclic ACPA and anti-MCV. This can serve as a diagnostic tool when RA and ACPA results are negative [82]". "Furthermore, experimental studies have assessed the diagnostic accuracy of the 14-3-3 eta protein, revealing that it was positive in all RA patients who tested negative for RF and ACPA [83]". "Anti-CarP was identified in the serum of RA patients, and multiple studies have indicated that its presence correlates with pre-symptomatic phases, potentially serving as a prognostic tool [84]".

Recent investigations have shown that gene profiles can serve as significant diagnostic instruments. By contrasting FLS from healthy persons with FLS-RA Statistically significant changes have been shown to exist in the genes of heat-shock protein family A members, matrix metalloproteinase 1 (MMP1), matrix metalloproteinase 13 (MMP13), and tumor necrosis factor ligand superfamily member 10 (TNFSF10) [85]. "Moreover, advancements in proteomics facilitate the identification of protein panels, which play a crucial role in early diagnosis. A study employed label-free quantitative proteomics to identify proteins with diagnostic potential, particularly for seronegative rheumatoid arthritis patients. Serum amyloid A-4 protein (SAA4), retinol-binding protein-4 (RBP4), angiotensinogen (AGT), and vitamin D-binding protein (VDBP) have been shown to be sufficiently precise for diagnostic applications [86]". "Glycoprotein YKL-40 serves as a diagnostic biomarker due to its encouraging results [87]". "Several biomarkers (anti-MCV, RF, 14-3-3 eta protein, ACPA) serve as prognostic indicators due to their correlation with severe stages of RA [88]". Additional research is required to find novel possible prognostic biomarkers.

"Predictive biomarkers play a crucial role in the therapeutic management of rheumatoid arthritis, as they are utilized to determine an effective treatment that is likely to elicit a response in all patients. "Multiple studies have indicated that anti-CCP,

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anti-MCV, 14-3-3 eta, cartilage oligomeric matrix protein (COMP), survivin, and calprotectin are associated with a reliable prediction of treatment response [88]".

## K. Therapeutic Approaches for Dermatophytosis

### 1. Localized Management of Dermatophytosis

"Topical antifungals are considered the primary treatment for superficial dermatomycoses due to their high efficacy and reduced systemic side effects. These drugs are formulated into numerous types of vehicles, including creams, sprays, lotions, and gels [88]". "Their effectiveness and penetration capacity are contingent upon the specific site of involvement. Upon application to the skin's surface, these agents can easily penetrate the stratum corneum and either inhibit fungal growth or eliminate the fungi. Topical antifungal agents are classified into three primary categories: benzylamines, azoles, and allylamines [88]". "Various topical creams have been utilized for the treatment of cutaneous Tinea. Rotta et al. conducted a meta-analysis and found that butenafine and terbinafine exhibit superior efficacy compared to clotrimazole, oxiconazole, and sertaconazole [89]".

### 2. Systemic Therapy

"Systemic antifungal treatment may be necessary for certain infections, such as Tinea capitis, chronic dry forms of Tinea cruris, Tinea pedis, Tinea corporis, and extensive disease lesions, or when topical agents fail to provide effective treatment [90]". "Systemic therapy typically employs itraconazole and terbinafine. Griseofulvin and fluconazole have demonstrated systemic efficacy [90]".

### 3. Oral Pharmacotherapy

"Griseofulvin is approved for the treatment of tinea infection of the nails; however, its low affinity for keratin necessitates prolonged therapy [91]. The effectiveness of treating onychomycosis remains limited, with newer azole and allylamine agent's largely supplanting griseofulvin for this purpose [91]". "Ketoconazole is not advised for the treatment of onychomycosis because of the risk of hepatotoxicity, which occurs due to the inhibition of human CYP-dependent demethylation of ergosterol at elevated concentrations, as well as the

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existence of alternative oral therapies [91]. Fluconazole demonstrates high efficacy, low relapse rates, and effectiveness in cases of yeast coinfection; however, research on this treatment approach remains limited [92]".

"The oral therapy regimens for onychomycosis include terbinafine at a dosage of 250 mg per day for 12 weeks for toenails or 6 weeks for fingernails. Alternatively, itraconazole can be administered at 200 mg twice daily as pulse therapy, consisting of one week of itraconazole followed by three weeks without it, with 2–3 pulses recommended (two pulses for fingernails and three for toenails) [93]".

"In nations where fluconazole is authorized for onychomycosis treatment, the predominant regimen involves administering fluconazole 150–300 mg weekly until the affected nail has fully regrown (fingernails: approximately 3–6 months; toenails: approximately 9–12 months) [91]". "The implementation of pulsed terbinafine regimens has been proposed to enhance the safety profile of oral terbinafine; however, in contrast to itraconazole, the efficacy of pulsed terbinafine has not been definitively demonstrated when compared to continuous regimens [94]".

## L. Therapeutic Strategies in Rheumatoid Arthritis

"Various therapeutic options have been employed over time to enhance patients' quality of life, mitigate the risk of adverse events, and assess the safety and efficacy profiles of novel active compounds. The principle defined by the ACR is "Treat to target," which pertains to selecting an effective treatment to attain remission or, alternatively, to minimize disease activity. "Therapeutic action must be swift and assertive, as pre-existing erosions are irreversible [95]". "The therapy protocol commences with a precise diagnosis and encompasses preventive measures, as well as non-pharmacological and pharmacological interventions, to achieve prompt outcomes. "The 2021 ACR guideline for rheumatoid arthritis treatment revised the pharmaceutical treatments, including seven strong recommendations and 37 conditional ones [72]".

### 1. Non-pharmacological Approaches for Rheumatoid Arthritis

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"The identification of risk factors offers strategies for preventing rheumatoid arthritis. Emphasizing prevention may be a crucial component of the overall care of rheumatoid arthritis (RA). Four levels of prophylaxis (primary, secondary, tertiary, and clinical) have been demonstrated. "Primary prevention aims to avoid the initiation of pathological processes, secondary prevention addresses risk factors to identify and mitigate them, and tertiary prevention focuses on methods to minimize harm. Clinical prevention includes mitigating problems and preventing relapses [95]". "Screening measures for individuals at risk of developing rheumatoid arthritis may lead to reduced incidence and prevalence rates. Blood relatives, twins of rheumatoid arthritis patients, and seropositive individuals require vigilant monitoring due to their risk status [96]".

"The objectives of non-pharmacological approaches include alleviating anxiety and depression, minimizing pain, and enhancing mobility. Polyunsaturated fatty acids (PUFAs) have garnered increased interest due to their associations with various brain disorders, such as anxiety and depression. The polyunsaturated fatty acids (PUFAs) encompass docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are part of the omega-3 fatty acid series [97]". "A meta-analysis of 26 double-blind randomized placebo-controlled trials was conducted to assess the efficacy of PUFAs, specifically DHA and EPA, in the treatment of depression. The findings indicated that omega-3 PUFAs significantly enhanced depression outcomes [98]".

## 2. Pharmacological Interventions in Rheumatoid Arthritis

Ongoing enhancements in drug design methodologies have resulted in significant advancements in pharmacological tactics aimed at discovering a remedy for rheumatoid arthritis (RA). "The novel therapy choices have successfully diminished symptoms, decelerated development, and averted consequences [72] [99]". "Current therapy modalities for rheumatoid arthritis, as per ACR and EULAR guidelines, encompass two approaches: symptomatic management (NSAIDs and glucocorticoids) and disease-modifying management (DMARDs), [72] [99]".

"The symptomatic treatment of rheumatoid arthritis largely involves nonsteroidal anti-inflammatory drugs and glucocorticoids, however mild opioid analgesics may be explored for short-term pain management following a thorough

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evaluation of the benefit-risk ratio [100]". "Nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, ibuprofen, and coxibs, are utilized during the acute phase response to alleviate pain by mitigating inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their pharmacological effects by inhibiting cyclooxygenase (COX), particularly COX-2, which is elevated during inflammation". Nonetheless, the potential for injury must be acknowledged, as the suppression of prostaglandins may result in severe adverse effects, including hemorrhage, gastrointestinal ulcers, renal failure, cardiac failure, dermal rashes, vertigo, cognitive disorientation, and convulsions. Certain negative effects may be mitigated by utilizing COX-2-selective NSAIDs (celecoxib, rofecoxib, valdecoxib) [100]".

"The efficacy of NSAIDs in rheumatoid arthritis has been established in placebo-controlled trials with patients not receiving glucocorticoid treatment [101]". "Glucocorticoids (prednisone, hydrocortisone, prednisolone, dexamethasone) exhibit superior potency and efficacy compared to nonsteroidal anti-inflammatory drugs (NSAIDs), attributable to their intricate mechanisms of anti-inflammatory and immunosuppressive action; yet, NSAIDs possess a marginally more favorable safety profile [70]".

"The long-term negative effects of glucocorticoids include weight gain, fluid retention, muscular weakness, diabetes, and osteoporosis". Consequently, they possess a transient application and can be delivered orally, intravenously, intramuscularly, and intra-articularly [102]". "Glucocorticoids (GCs) serve two primary functions in the management of rheumatoid arthritis (RA): as a bridging therapy for disease-modifying antirheumatic drugs (DMARDs) until their effects manifest, and as supplementary therapy for persistent active RA despite DMARD administration. It is essential to avoid the abrupt cessation of corticosteroid therapy due to adverse feedback on the control of hypothalamic–pituitary–adrenal (HPA) axis pulsatility [70]". DMARDs are pharmacological medications utilized to induce remission by inhibiting autoimmune activity and delaying or preventing joint deterioration.

"Initiating treatment promptly is essential, as early implementation correlates with improved outcomes". "This is particularly important considering that DMARDs

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are slow-acting medications, exhibiting a delayed onset ranging from 6 weeks to 6 months. DMARDs are categorized into three types: conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [103]".

# Conclusions

Opportunistic dermatophyte infections present a considerable threat to immunocompromised individuals with rheumatoid arthritis, especially those receiving immunosuppressive treatment. Dermatophytes are common fungal pathogens primarily associated with superficial infections of the skin, nails, and hair. In immunocompromised patients, atypical infections may occur, characterized by large lesions or skin invasion. The interaction between compromised immune responses and heighttened vulnerability to fungal infections requires proactive prevention and early intervention techniques. By maintaining good hygiene, wearing suitable footwear, employing antifungal treatments, and obtaining prompt medical consultation, patients can significantly reduce the dangers associated with dermatophyte infections. Moreover, routine dermatological examinations and patient education are essential in diminishing infection rates. Achieving equilibrium between immunosuppressive therapy and infection prophylaxis is crucial for safeguarding the overall health and welfare of rheumatoid arthritis patients. Additional research is required to enhance care options and elevate patient outcomes in this at-risk demographic. Future research on the prevalence and characteristics of this entity among various immunosuppressed patient populations will enhance our comprehension of dermatophytosis pathophysiology and facilitate the development of novel therapeutic strategies. The timely and appropriate management of superficial dermatophytosis upon initiating immunosuppressive therapy is crucial in averting the progression to more serious disease manifestations.

Compared to previous studies, the study of [104]"showed that a slightly higher prevalence of dermatophytosis in the RA population than in a control group and conclude that further studies conducted in larger series are needed to draw definite conclusions".

## Prevention and Recommendations

### Strategies to Reduce Opportunistic Dermatophyte Infections

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Individuals with rheumatoid arthritis (RA) who are immunocompromised as a result of disease-modifying antirheumatic medications (DMARDs) or corticosteroids face a heightened risk of opportunistic dermatophyte infections. Implementing preventive measures is essential to reduce infection risk. The subsequent actions may mitigate the probability of fungal infections:

1. Upholding Adequate Hygiene: Consistent cleansing of hands and feet with gentle soap and meticulous drying, particularly between the toes, can inhibit fungal proliferation.
2. Selecting Breathable Footwear: Opting for shoes constructed from breathable materials, such as leather or mesh, minimizes moisture buildup, hence fostering an atmosphere favorable to fungal growth.
3. Employing Antifungal Powders or Sprays: The application of antifungal powders or sprays to the foot and the interior of shoes can aid in the prevention of fungal colonization.
4. Avoid walking barefoot in public areas: Fungal infections are frequently transferred in community spaces such as swimming pools, gyms, and locker rooms. It is recommended to wear protective footwear in these regions.
5. Consistent Nail and Skin Maintenance: Maintaining clipped nails and preventing nail stress helps diminish the likelihood of fungal infections. Hydrating the skin while preventing excessive moisture accumulation is advantageous.
6. Refraining from Sharing Personal Items: Patients should avoid sharing towels, socks, or shoes to prevent cross-contamination.
7. Early Infection Surveillance: Routine self-assessment for indicators of fungal infections, including pruritus, erythema, desquamation, or nail pigmentation changes, can facilitate prompt identification and intervention.

## Guidelines for Individuals with Rheumatoid Arthritis

Individuals with rheumatoid arthritis should adhere to particular guidelines to reduce the likelihood of opportunistic dermatophyte infections.

1. Routine Dermatological Check-ups: Regular consultations with a dermatologist facilitate early detection and management of infections.

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2. Consultation with a Physician Prior to Initiating Immunosuppressive Therapy: Patients should engage in discussions regarding infection risks with their healthcare provider before starting or altering immunosuppressive treatment.
3. Prompt treatment of fungal infections through early intervention with topical or systemic antifungals is essential to prevent complications.
4. Maintaining a Balanced Diet and Health Practices: A balanced diet and effective health practices, such as adequate hydration and vitamin supplementation, contribute to the strengthening of the immune system.
5. Educating Patients on Infection Risks: Patients must recognize their heightened vulnerability to infections and implement proactive strategies to minimize exposure.

Incorporating preventive strategies and recommendations allows patients with RA to significantly reduce their risk of opportunistic dermatophyte infections while safely maintaining their immunosuppressive therapy.

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