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Onychomycosis: Pathogenesis, Diagnosis, and Management

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INTRODUCTION

Most cutaneous infections are the work of the homogeneous group of keratinophilic fungi known as dermatophytes. The dermatophyte *Trichophyton rubrum* is the major cause of tinea pedis and onychomycosis (8). After originating in West Africa, Southeast Asia, Indonesia, and Northern Australia, *T. rubrum* spread to Europe and North and South America in the late 19th and early 20th centuries, where it found a niche within a

recently shod populace (8). Subsequent 20th century developments including wars, the modern health movement and the associated use of occlusive footwear and locker rooms, and migration of people since the invention of the jumbo jet, promoted an increased incidence of tinea pedis and onychomycosis (8).

Dermatophytoses of the fingernails and toenails, in contrast to those at other body sites, are particularly difficult to eradicate with drug treatment. This is the consequence of factors intrinsic to the nail—the hard, protective nail plate, sequestration of pathogens between the nail bed and plate, and slow growth of the nail—as well as of the relatively poor efficacy of

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new generation of antifungal drugs that produce impressive, long-lasting cure rates with shorter treatment times and better safety profiles than ketoconazole and griseofulvin. In this paper, current knowledge of the pathogenesis, diagnosis, and management of onychomycosis with these new agents is reviewed and evaluated.

ONYCHOMYCOSIS

Definition and Clinical Impact

"Onychomycosis" traditionally referred to a nondermatophytic infection of the nail but is now used as a general term to denote any fungal nail infection (63) (tinea unguium specifically describes a dermatophytic invasion of the nail plate). In spite of the clearly diseased appearance associated with this condition, onychomycosis is all too often regarded as merely a cosmetic problem of relatively minor importance that is hardly worth the effort to resolve. This belief may have been supported by the adverse effects and long dosing courses associated with some of the earlier antifungal agents.

In fact, onychomycosis can have significant negative effects on patients' emotional, social, and occupational functioning and can, in addition, consume a sizable proportion of health care dollars. Affected patients may experience embarrassment in social and work situations, where they feel blighted or unclean, unwilling to allow their hands or feet to be seen. Patients may fear that they will transmit their infection to family members, friends, or coworkers, fears that can lead to diminished self-esteem and the avoidance of close relationships (55). Employment suffers if employers are reluctant to hire individuals with abnormal nails, particularly for jobs such as food handling or modelling or where interaction with the public is required. A more tangible barrier to work success is the discomfort some patients experience that prevents them from carrying out work-related tasks such as prolonged standing, writing, or typing. Finally, onychomycosis can compel workers to take periodic sick leave, a problem even for treated patients if therapy is ineffective and/or long-lasting (55). This lack of success, in turn, can cause patients to feel discouraged or even to stop treatment, resigning themselves to permanent disfigurement and discomfort.

Onychomycosis in immunocompromised patients, such as those infected with human immunodeficiency virus (HIV), can pose a more serious health problem (55). Not only does the difficult-to-treat infection serve as a constant reminder to the patient of his or her own deteriorated condition, but the possibility exists of transfer of a very high titer of fungal pathogens to another person (55).

Epidemiology and Risk Factors

Dermatophytoses of the stratum corneum, hair, and nails are common, whereas infection of the dermis and subcutaneous tissue by these agents is rare (64). Although dermatophytic infections are rarely life-threatening, their high incidence and prevalence and the associated morbidity (64) make them an important public health problem (1).

Reports concerning the prevalence of onychomycosis are conflicting, with estimates ranging from 2 to 3% of the general U.S. population (27) to 13% of the male Finnish population (40). In a recent outpatient-based, cross-sectional survey of 1,038 patients in a dermatology clinic waiting room in Cleveland, Ohio, culture-confirmed dermatophyte onychomycosis was identified in 8.7% of the total population and in 6.5 and

who presented for onychomycosis were excluded) (27). These figures are comparable to those for the general Finnish population (8.4%) (40). Several studies have shown that the prevalence of onychomycosis increases with age. For example, none of the 200 Finnish subjects who were younger than 20 years had onychomycosis but almost 24% of those aged 70 years or older had the disorder. Similarly, 28.1% of the members of the Ohio cohort aged 60 years or older were culture positive for onychomycosis, versus 1.1 and 2.9% for those aged 10 to 18 years and 19 to 30 years, respectively (27). Reasons for the age-related increase in onychomycosis may include poor peripheral circulation, diabetes, repeated nail trauma, longer exposure to pathogenic fungi, suboptimal immune function, inactivity, or the inability to cut the toenails or maintain good foot care (22, 27, 55).

As is the case among adults, prevalence rates for onychomycosis among children are quite variable: a recent review of studies of the subject in several countries outside North America lists prevalence rates varying from 0% (United States, Wales, and Finland) to 2.6% (Guatemala) (38). To learn more about the prevalence of onychomycosis among children in North America, a prospective survey was conducted of 2,500 young (≤ 18 years) patients and family members in Canada and the United States. Subjects' nails were examined for signs of onychomycosis and sampled for direct microscopy and culture. Onychomycosis was diagnosed in 11 children (10 with affected toenails, and 1 with affected fingernails), indicating a prevalence of 0.44%; however, 7 of these children had been referred for treatment of onychomycosis or tinea pedis. Thus, the prevalence of onychomycosis in children with primary diagnoses other than onychomycosis or tinea pedis was 4 of 2,500, or 0.16% (37). The reasons for this 30-fold decrease in the prevalence of onychomycosis in children relative to adults may include reduced exposure to fungus because less time is spent in environments containing pathogens; faster nail growth; smaller nail surface for invasion; and lower prevalence of tinea pedis (37).

Contact with the source of the infection constitutes a risk factor; for example, *Trichophyton verrucosum* commonly infects the faces of farmers who lean against their cows as they milk them (64). There is no doubt that several factors unique to modern life have resulted in an increased prevalence of onychomycosis. These include the wearing of shoes, particularly fashionably tight, high-heeled shoes; the increased use by large numbers of people of damp spaces such as locker rooms and gymnasiums; the declining health of the aging American population, and the increased number of immunocompromised patients through disease (e.g., HIV infection) or therapeutic agents (e.g., immunosuppressive therapies associated with cancer or posttransplantation care, and the extensive use of broad-spectrum antibiotics) (25). Other factors that increase the risk of onychomycosis are direct trauma to the nail, including that resulting from certain tic disorders (e.g., nail biting).

DERMATOPHYTES AND ONYCHOMYCOSIS

The term "dermatophytosis" is used to describe infection by members of the genera *Microsporium*, *Trichophyton*, and *Epidermophyton*. The species that most often cause onychomycosis in North America and parts of Europe are *T. rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*; the first two species are much more often implicated than *E. floccosum* (58). Infections of the skin, nail, and hair by nondermatophytic molds such as *Scytalidium* and *Scopulariopsis* are termed "dermatomycoses." Dermatophytes account for most (90%) cases

infections (31). Both dermatophytes and nondermatophytes, especially *Candida albicans*, have been identified as sole etiologic agents of onychomycosis; however, the incidence of true mixed infections (caused by dermatophytes plus nondermatophytes) is difficult to determine accurately (58) and is discussed in detail below.

The dermatophytes are hyaline septated molds. The hyphae of these mycelial organisms penetrate the stratum corneum of the skin and nails. The fungal cells manufacture keratinolytic proteases, which provide a means of entry into living cells (39). Some dermatophytic species, which are basically soil saprophytes that have acquired the ability to digest keratinous debris in soil, have evolved to be capable of parasitizing keratinous tissues of animals (1).

The families that include many of the known keratinolytic fungi are the *Arthrodermataceae* and *Onygenaceae* in the phylum *Ascomycota* (52). Members of these families are homogeneous with respect to appearance, physiology, taxonomy, antigenicity, basic growth requirements, infectivity, and the diseases they cause (52). Some, such as *Microsporium canis* and *T. mentagrophytes*, have affinity for the keratin of animals and humans, whereas others are more specialized for a particular animal host (1).

Variability with respect to the causative microorganism is both geographic and, within a given region, temporal. Because organisms that cause clinically apparent disease tend to receive the most attention, pathogens whose invasion leads to hard-to-detect disease may be present in a region but are less likely to be identified (1). By contrast, pathogens that cause readily apparent signs and symptoms are likely to be identified and their prevalence is likely to be noted. Thus, because reports during the 1970s focused primarily on scalp infections, *T. violaceum* was the most frequently isolated dermatophyte during that decade in Europe (1) although *T. tonsurans* is the principal agent of tinea capitis in the United States and is emerging in Europe.

Changes over time within a region in the prevalence of particular dermatophyte species also are common: although *M. audouinii* and *M. canis* were the most common causes of scalp infection in Western and Mediterranean Europe 50 to 100 years ago, tinea capitis has declined in incidence in Western Europe and, when present, is caused primarily by *M. canis* (1) or *T. violaceum* (1). Similarly, *M. audouinii* and *M. canis* were the main causes of tinea capitis in the United States earlier in this century; this role has been taken over by *T. tonsurans* (1). Another change that has occurred in recent years is the growing prevalence of dermatophytoses of the foot (tinea pedis) and nails (tinea unguium) and decline in the prevalence of scalp infections (1).

CLINICAL TERMINOLOGY

As in many areas of medicine, the clinical terminology used to describe dermatophytic infections evolved in advance of accurate knowledge about causation or pathophysiology. Tinea ("a gnawing worm") or "ringworm," a term derived from the appearance of the characteristic skin lesions in this common dermatophytosis (64), affects the scalp (tinea capitis), glabrous skin (tinea corporis), groin (tinea cruris), nail (tinea unguium), feet (tinea pedis), beard (tinea barbae), and hand (tinea manuum). Other dermatophytoses are named for their appearance, such as tinea favosa (favus, or honeycomb-like due to *T. schoenleinii*) or tinea imbricata ("composed of overlapping

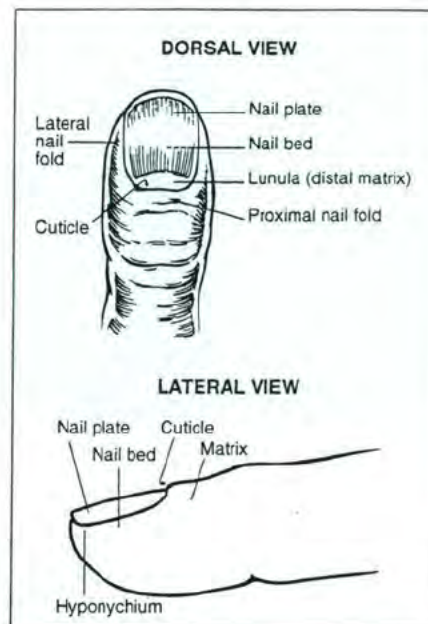


FIG. 1. The nail unit. Reprinted from reference 11 with permission of the publisher.

ANATOMY OF THE NAIL

A review of the anatomy of the nail unit and the process of nail growth may be helpful in understanding the pathogenesis of dermatophytic fungi in the nail unit. A diagram of the nail unit is presented in Figure 1 (11). It consists of the following structures: proximal and lateral folds, cuticle, matrix, nail plate (commonly called the nail), nail bed, and hyponychium. The cuticle is the horny layer of the proximal nail fold; it consists of modified stratum corneum and protects the nail matrix from infection (12). The nail matrix is the growth center of the nail. As the nail grows, cells of the nail matrix divide, differentiate, and keratinize and are incorporated into the nail plate. The distal, visible part of the matrix looks like a "half moon" and is called the lunula. The matrix extends approximately 5 mm proximally beneath the proximal nail fold (12). The nail plate is the largest structure of the nail unit and grows by sliding forward over the nail bed, whereupon the distal end becomes free of the nail bed (44). The hyponychium, the most distal component in the nail bed, is composed of epidermis that includes a granular layer similar to that seen in plantar and volar surfaces (12). Fingernails grow at a rate of 2 to 3 mm per month, and toenails grow at a rate of 1 mm per month. Therefore, it takes about 6 months to replace a fingernail and between 12 and 18 months to replace a toenail (12). This rate of growth is often decreased in the presence of peripheral vascular disease and onychomycosis and in the elderly (12).

CLASSIFICATION OF ONYCHOMYCOSIS

Four types of onychomycosis, characterized according to clinical presentation and the route of invasion, are recognized.

Distal Subungual Onychomycosis

Distal subungual onychomycosis (DSO) is the most common form of onychomycosis. It is characterized by invasion of the nail bed and underside of the nail plate beginning at the hy-

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