Natural History of Disease

According to Dorland’s Illustrated Medical Dictionary, epidemiology is “the study of the relationships of the various factors determining the frequency and distribution of diseases in a human community.” A second definition relates to the determination of causes of outbreaks. Simply speaking, every disease has a natural history and agent, host, and environmental causes that precede the development of signs and symptoms in the host. In wellness or before pathogenesis, the human host is in equilibrium with its environment and potential disease-associated agents. When the environment or agent overwhelms the host or upsets this equilibrium, a period of pathogenesis or a state of disease results.

Characteristics inherent in the particular human host determine whether the environment and disease-causing agents are able to upset the equilibrium and result in a state referred to as “disease.” In infectious diseases such as fungal conditions, characteristics that can lower the barriers to disease include fissures in the skin and defects in the immune system. Individuals who have such characteristics are regarded as “susceptible” or “at risk.” The profiling of susceptible populations is sometimes couched as the study of risk factors. In the case of infectious diseases, such as fungal infections, the most obvious factor leading to increased susceptibility is some form of immunodeficiency.

The disease state is a dynamic process, starting when the disease has no discernible signs or symptoms and no associated morbidity. If physicians fail to diagnose and treat the pathologic process, the disease, not having been interrupted or delayed, follows its natural course and causes further changes. In fungal disease, these may be changes in morphology, which can lead to increased morbidity, amputation, disability, or even death. The goal of epidemiology is to identify agent, host, and environmental factors associated with diseases so as to maintain health or, when this is not possible, interrupt or delay the natural progression of disease processes at the earliest possible time. This requires some understanding of the natural history of the disease.

Natural History of Onychomycosis

Like every disease state, onychomycosis has a natural history with multiple factors involving agent, host, and environment. For example, when clinicians observe the friable, thickened, and discolored nail of
classic onychomycosis, they are seeing only one part of the natural course of the disease process. This classic presentation is a manifestation of a relatively late stage in the natural history of onychomycosis. Detection of a nail abnormality is preceded by weeks or months of interaction among the environment, the agent, and the human host. The natural history of the disease does not end when the deformed nail is examined by the physician. The disease process may continue, and subungual and surrounding periungual tissue and adjacent skin may become affected. This can precipitate damage to the integrity of the skin, allowing secondary pathogenic organisms to enter. The end result may be bacterial infection or the accumulation of subungual debris leading to nail-bed ulceration.

The impact of onychomycosis on a particular patient may be significant. For example, if the natural course of this process continues in a diabetic patient, cellulitis or osteomyelitis can occur, followed by necrosis. Ultimately, major lower-limb amputation may be necessary (Fig. 1).

Agent, Host, and Environmental Factors

According to a study by the National Center for Health Statistics, fungal infections are the most common skin diseases in people of all ages. Onychomycosis occurs worldwide, and its incidence has been steadily increasing. Up to 50% of all nail disorders are caused by fungal infection, and approximately 30% of patients with cutaneous fungal infection also have fungal nail disease. A survey in the United Kingdom found the prevalence of onychomycosis to be 2.8% in men and 2.6% in women. The study suggests that 1.2 million people in the UK have fungal nail infection. According to a US survey, the prevalence of onychomycosis is approximately 3.0% in males and 1.4% in females.

But the overall prevalence does not present the whole story. Many host and environmental factors contribute to the growing incidence of fungal nail infections, including an aging population, a growing prevalence of diabetes, an increasing number of people who have AIDS and HIV infection or who are immunocompromised for other reasons, the use of broad-spectrum antibiotics and chemotherapeutic agents, hereditary factors, life-style changes, and growing participation in physical-fitness activities. Onychomycosis also has been found more commonly among postmenopausal women than among those who are premenopausal. These factors account for a higher prevalence of onychomycosis in some populations than in others (Table 1).

Onychomycosis in HIV-Infected Patients

In patients with HIV infection, onychomycosis is one of the earliest fungal infections to emerge, often appearing when the CD4-lymphocyte count drops to approximately 450 cells/mm³ (normal range, 1,200 to 1,400). The condition becomes more common as the CD4-lymphocyte count falls lower. Onychomycosis has been reported to occur in 11% to 67% of AIDS patients with relatively serious disease (symptomatic or CDC stage IV). Toenails are more frequently involved than fingernails. In contrast to the distal site of onset for onychomycosis in nonimmunocompromised patients, the infection often starts as proximal white subungual onychomycosis.
in HIV-infected patients. In this presentation, the infection starts under the proximal nail fold, becomes established in the nail fold and nail bed, invades the nail plate ventrally, and then moves distally through the nail. The nail plate may be smooth and intact or plaster-like and crumbly. In patients with HIV, the infection spreads rapidly to the other nails of both fingers and toes. Later in the natural history, subungual keratosis may become marked and the periungual region may become involved.

The most common pathogens are dermatophytes, just as in nonimmunocompromised patients. A chalky white involvement of the outer nail plate (superficial white onychomycosis), which is rare in normal individuals (but when found is usually caused by *Trichophyton mentagrophytes*), is common and generally caused by *Trichophyton rubrum* in HIV-infected patients. Because severe nail involvement is unusual in healthy people in their twenties, patients who present with extensive involvement of all toenails and subungual keratosis should be referred for HIV testing.

### Table 1. Risk Factors for Onychomycosis

<table>
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<tr>
<th>Risk Factor</th>
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<td>HIV infection</td>
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<td>Trauma to the nails</td>
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<tr>
<td>Atopy</td>
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<tr>
<td>Immunosuppression (e.g., that induced by corticosteroids or immunosuppressant therapy)</td>
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<td>Older age</td>
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<td>Hyperhidrosis</td>
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### Onychomycosis in Patients with Diabetes

Fungal nail infections in patients with diabetes have been reported to contribute to the severity of their foot problems, but whether the infections are more common in this patient population is not known. Since onychomycosis is often associated with tinea pedis, fissures can form that are a portal of entry for bacteria which, especially in the patient with diabetes, could result in deep infections and serious consequences. Curing the fungal infection is therefore an appropriate goal in the treatment of these patients.

### Other Diseases That Increase Susceptibility

As might be expected, onychomycosis has been reported with other types of immunosuppression in addition to HIV infection. The immunosuppression required for organ transplantation may increase susceptibility to dermatophyte infection. The unusual proximal white subungual onychomycosis seen in AIDS patients has also been reported in cases of immunodeficiency caused by systemic corticosteroid therapy and, as in AIDS patients, was associated with *T. rubrum* infection. A study of 180 patients suggested that atopy or decreased cell-mediated immune response was associated with chronic dermatophytosis, indicating that inherited immunologic predisposition also influences susceptibility to such diseases.

Onychomycosis may also be associated with trauma to the nail, hyperhidrosis, tinea pedis, and systemic

![Figure 2. Fungi cultured from HIV-positive patients with onychomycosis.](image-url)
disease. The association with hyperhidrosis may simply indicate a host factor that provides a warm, moist environment supporting the fungal agent.

**Association of Onychomycosis with Aging**

Onychomycosis is often considered an age-related infection. The condition is estimated to affect from 2% to 13% of the US population as a whole, and well under 0.5% of people under the age of 18. However, as many as 15% to 20% of people between 40 and 60 years of age may be affected, with the figure rising to 30% by age 60. Changes in immune competence are known to occur with age, making the elderly more susceptible to eukaryotic pathogens. The cause may be reduced efficiency of T-cell and phagocytic cell activity, though it is not known whether this accounts for the increase of onychomycosis in the elderly. One could speculate that changes in the skin and the greater prevalence of vascular embarrassment might play a role as well.

Rosenbach and Schneider conducted a study to evaluate the overall cost of onychomycosis in a Medicare population (ie, persons 65 years of age and older). The results revealed that during 1989, a total of 662,000 of these older patients made 1.3 million visits to a physician because of a primary complaint of onychomycosis. That same year, the costs associated with such visits exceeded $43 million. Today these costs would undoubtedly be higher.

**Causative Pathogens**

Attempts have been made to induce tinea infection by repeatedly exposing uninfected volunteers to fungal spores, but these attempts have been unsuccessful. This emphasizes the importance of host susceptibility and environmental factors in initiating infection.

Dermatophytes, which are ubiquitous in the environment, are by far the most common nail pathogens and account for 80% to 90% of all infections. Toenails are affected approximately four times more frequently than fingernails. In toenails, dermatophytes are the predominant group of organisms responsible for onychomycosis. In fact, no yeasts were isolated in a study in which samples from 139 toenails were cultured. Studies from the UK found Candida species in less than 1% of the isolates from toenails. The vast majority of superficial fungal infections have been shown to be caused by dermatophytes, with *T. rubrum* the organism most commonly isolated. Although molds are also common outdoors and in household environments, in temperate zones nail disease caused by molds (eg, *Scopulariopsis*, *Acremonium*, *Fusarium*, *Aspergillus*) accounted for less than 3% of fungal nail infections.

**Summary**

Clean, healthy-looking nails are important in our society. Dystrophic nails can be a social impediment by causing significant embarrassment and affecting a patient’s self-esteem. In some people, onychomycosis can be a source of anxiety or even contribute to depression. Insecurity about nail disfigurement may lead a patient to avoid intimate situations, restricting the ability to form close relationships. Especially in populations that are already stigmatized, such as HIV-infected patients, clearing fungal infections can have a positive impact on self-esteem.

In the elderly, the disease can exacerbate preexisting foot problems and decrease the patient’s mobility and independence. In addition, thickened nails can be painful and difficult to cut and can interfere with the function of the nail unit, causing pain when the patient wears a shoe or walks. Therefore, health-care professionals should be alert to the possibility of onychomycosis, particularly in high-risk populations, so that the condition can be diagnosed and appropriately treated.

**References**


