CME Information

CME Released: 05/30/2003; Valid for credit through 05/30/2004

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Target Audience

This educational activity is intended for dermatologists, podiatrists, and primary care physicians.

Goal

The goal of this activity is to update clinicians on the recognition and treatment of onychomycosis.

Learning Objectives

1. Describe the pathophysiologic features and epidemiologic aspects of onychomycosis.
2. Identify susceptible patients.
3. List the consequences of onychomycosis and explain the rationale for preventive therapy in susceptible patients.
4. Select appropriate diagnostic procedures.
5. Recommend effective treatment modalities.

Credits Available

Physicians - maximum of 2 *AMA PRA Category 1 Credit(s)*™

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Progression and Recurrence of Onychomycosis

Faculty: Richard K. Scher, MD, FACP, Course Director; Warren Joseph, DPM; Jeffrey Robbins, DPM

Posted: 04/21/2003

Progression and Recurrence of Onychomycosis , Presented by Richard K. Scher, MD, FACP; Warren Joseph, DPM; Jeffrey Robbins, DPM

Introduction

Onychomycosis is a progressive, recurring fungal infection that begins in the nail bed and progresses to the nail plate. Although superficial, fungal nail infections should be taken seriously because they can cause significant health problems: they are contagious -- a reservoir of fungal microorganisms is created that can be transmitted through shoes and direct contact.[1] Consequently, infection can spread from the feet (in toenail onychomycosis) to other areas of the body within an individual patient.[2] Infection can also be transmitted between susceptible individuals.[3]

Fungal nail infections increase the susceptibility of patients to other serious complications. In diabetic patients, onychomycosis can open the door to secondary bacterial infections promoting foot ulcers and gangrene.[1,4] Onychomycosis can also trigger recurrent cellulitis and thrombophlebitis.[1,5] In addition to these significant health problems, the substantial psychosocial consequences of onychomycosis alone justify serious management.

Observations from a recent survey found that 92% of patients with onychomycosis reported experiencing negative psychosocial and/or physical effects.[6] Patient self-assessment surveys and observational studies indicate that 67% to 74% of patients are embarrassed by the condition of their nails as a result of onychomycosis.[7,8] A significant proportion of patients also experience pain (36% to 48%) or limited mobility (41%) resulting from onychomycosis.[7-9] This disease may also reduce self-image and self-esteem.[6,9] Importantly, quality-of-life scores have been shown to correlate significantly with the duration and severity of mycosis and the number of nails involved, observations that support early and aggressive management.[10] In summary, onychomycosis has a negative impact on quality of life.

Some physicians decline to treat onychomycosis, despite the negative consequences of this infection on patient health and quality of life. Physicians who feel it unnecessary to treat onychomycosis may regard the disease as a cosmetic problem rather than a health problem.[11] Physicians may also be concerned that the risk of systemic therapy may outweigh the benefits. Attitudes toward onychomycosis need reexamination because the number of patients who are susceptible to this disease is substantially increasing. To manage these patients effectively, physicians will need to understand the characteristics of the disease and adopt appropriate diagnostic, treatment, and preventive strategies.

Fungal Nail Infections: Magnitude of the Problem

Prevalence and High-risk Patient Populations

Onychomycosis is not an uncommon disease. This type of infection has been estimated to be responsible for up to 50% of all nail diseases, and the incidence of onychomycosis is increasing.[9] Recent large scale studies indicate that the prevalence of onychomycosis is approximately 6.5% in Canada and nearly 14% in North America.[12,13] Individuals with certain conditions are more susceptible to fungal nail infections and, therefore, may have a higher prevalence of the disease than the general population. Predisposing characteristics to onychomycosis include the following:

- Increasing age
- Male gender
- Genetic susceptibility
- Poor peripheral circulation
- Diabetes mellitus
- Immunosuppression (eg, HIV infection)
- Nail trauma

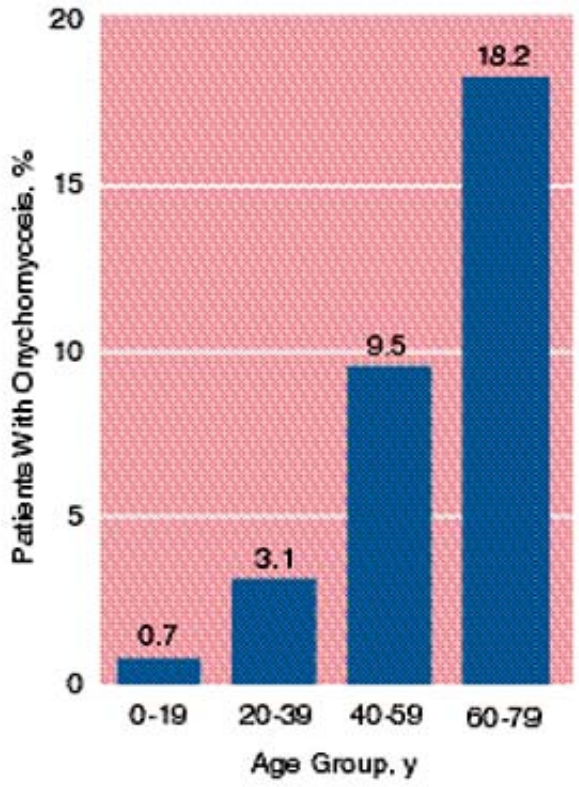

Figure 1.

Correlation Between Age and Prevalence of Onychomycosis (Data From Gupta et al, 2000)[12]

A recent epidemiologic study of onychomycosis in patients visiting physicians' offices found that the prevalence of onychomycosis substantially increased with age (Figure 1). [12] For example, the prevalence of fungal nail infections was 0.7% in patients younger than 19 years of age, compared with 18.2% in patients 60- to 79-years of age.[12] Several studies have also observed that men are more prone to onychomycosis than women; men are 1.7 to 3.0 times more likely to have a fungal nail infection.[12,14] The reasons for this gender difference are not clear but may involve social and/or genetic factors.

Individuals may also have a genetic predisposition to infection with *Trichophyton rubrum*, a dermatophyte that often causes onychomycosis. Serologic and genetic analyses of Human leukocyte antigens (HLA) Class I in a homogeneous population found that people who lacked the HLA-DR53 phenotype were at increased risk for onychomycosis caused by *T rubrum*.[15] Therefore, HLA-DR53 may play a key role in the immune response of T cells to fungal peptides during onychomycosis.

Poor peripheral circulation and diabetes can also increase an individual's risk of developing onychomycosis. The prevalence of onychomycosis in patients with chronic venous insufficiency has been reported to be 36.1%,[16] and patients with peripheral arterial disease are more likely to have onychomycosis than individuals without arterial disease.

Figure 2.

Onychomycosis of the Toenail in a Diabetic Patient

Recent epidemiologic analyses indicate that diabetic patients are 2.8 times more likely to have onychomycosis than nondiabetic patients.[14] Patients with diabetes are particularly susceptible to fungal nail infections because they often experience impaired sensation; lack of pain sensation can make them less aware of trauma to their feet, such as nail changes that develop during onychomycosis.[17] Thickened mycotic nails can cause pressure necrosis of the nail bed in diabetic patients, and sharp infected nails can pierce the skin. These minor ulcerations are serious in patients with diabetes because they are often unrecognized and can lead to serious diabetic foot infections.[17] The potential impact of fungal nail infections in these patients was illustrated by the observations of a recent retrospective database analysis.[4] This study found that onychomycosis was a significant risk factor for gangrene and foot ulcers in diabetic patients; 16% of cases of gangrene and 10% of foot ulcers were attributed to onychomycosis.[4]

Fungal infections are frequently encountered and are a major cause of morbidity and mortality in individuals infected with HIV.[18] These individuals are particularly susceptible to proximal subungual onychomycosis. The prevalence of onychomycosis in HIV-infected patients has been reported to be 30%, and may be directly related to the degree of immunosuppression.[19] Multiple fungal species are frequently cultured from these patients, which may also be a reflection of their immunocompromised state.[19]

The development of onychomycosis sometimes follows a traumatic event to the nail.[2] The nail on the longest toe of the foot is particularly susceptible to fungal infection because it accepts the burden of pressure and trauma from footwear.

Recurrence

Patients who have a genetic predisposition to onychomycosis or who belong to a susceptible population (ie, elderly, diabetic, etc) are likely to experience repetition of the disease. In these cases, onychomycosis is a progressive and recurring condition that should be viewed as a controllable rather than a curable disease. Patients prone to onychomycosis are often not permanently cured with therapy.[20,21]

Pathophysiology of Onychomycosis

Nail Structure

The main structural components of the nail include the proximal and lateral folds, cuticle, matrix, plate, bed, and

hyponychium (Figure 3).[22] The *proximal nail* fold is located at the proximal end of the visible nail plate where the skin folds over itself. The horny layer of the proximal nail fold is called the cuticle.

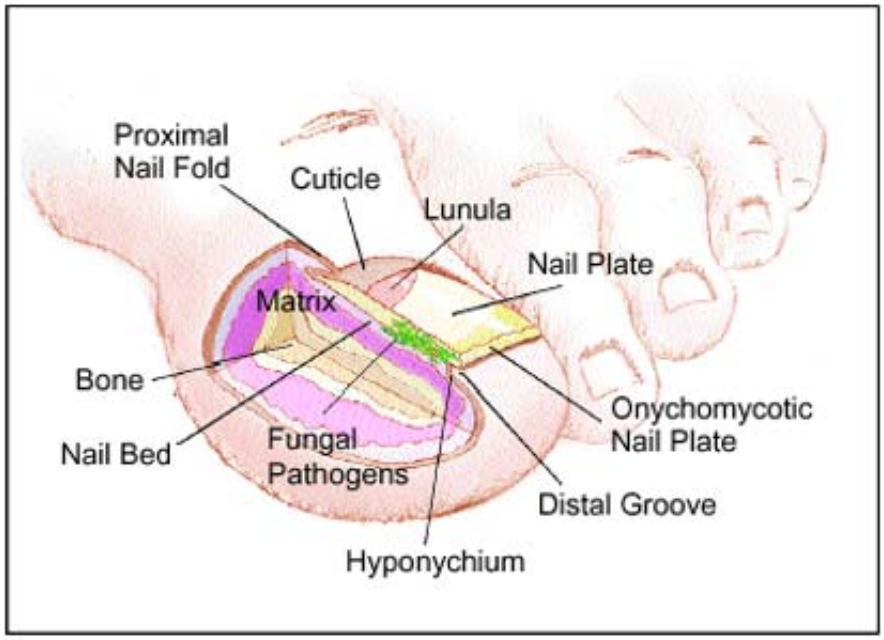

Figure 3.

Structure of the Nail

The *cuticle* consists of modified stratum corneum that originates at the junction of the dorsal and ventral epithelial surfaces and proceeds along the nail surface. The cuticle protects the matrix from exposure to foreign material, including infection from microorganisms. The *matrix* is the growth center of the nail and is located at the proximal end under the cuticle. This site contains basal cells that migrate into the nail plate, where they divide and differentiate, forming the hard, keratinized component of the nail plate.

The *nail plate* is the largest structure of the nail unit and is attached to the top of the nail bed. This transparent structure is gradually replaced as it grows out. The structure is completely renewed every 6 months on fingers and every 10- to 18- months on toes. The nail plate grows faster on longer digits, digits that are used most often, and on traumatized nails. The *nail bed* is located under the nail plate and consists of epidermal grooves and ridges that contain small blood vessels. The dermis of the nail borders bone (the phalanx) rather than subcutaneous tissue. Consequently, a bacterial infection of the nail bed can proceed from the epidermis through the dermis to the bone, increasing the chances of developing osteomyelitis. The location where the nail plate distally detaches from the nail bed is called the *hyponychium*, which extends from the nail bed to the distal groove.

Progression of Fungal Infection

Onychomycosis of the toe is often associated with tinea pedis, a superficial fungal infection of the foot, suggesting that the skin is the main source of fungal organisms that infect the nail.[7,23,24] Initially, fungal organisms usually invade the nail (between the nail plate and nail bed) through an opening in the subungual space of the hyponychium, near the distal groove. The infection starts distally, then progresses proximally. However, trauma to the cuticle may also permit entry of fungal organisms. Onychomycosis is considered a superficial infection because the growth of fungal hyphae occurs on the nail bed just below the nail plate (Figure 3 and Figure 4). In white superficial onychomycosis, the fungal organisms initially grow on top of the nail plate.

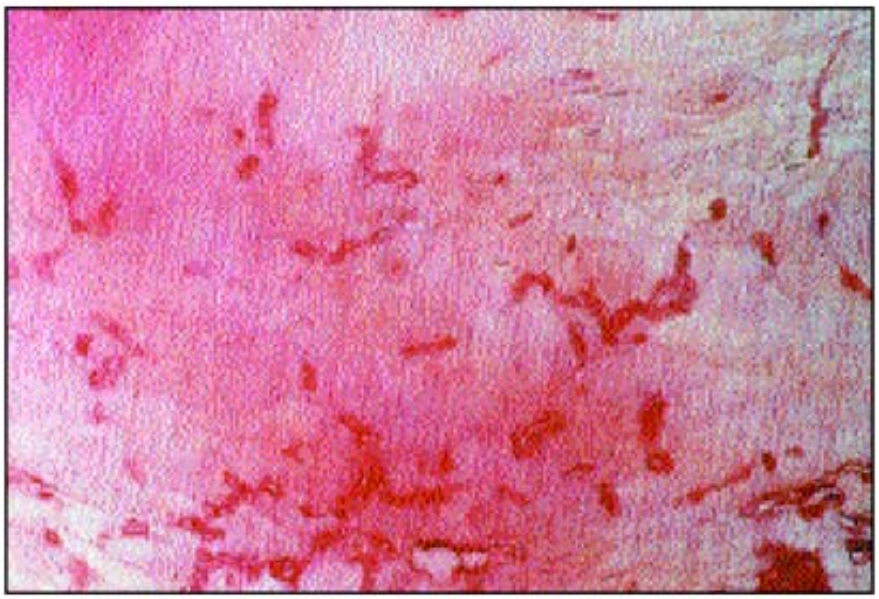

Figure 4.

Nail Clip Biopsy Showing Fungal Hyphae Within Nail Plate (Photo Courtesy of Dr Myron Bodman)

The types of microorganisms that cause onychomycosis can be broadly classified into 2 groups: dermatophytes and nondermatophytes. Dermatophytes are fungi that infect keratinous tissue. Nondermatophytes that can cause onychomycosis are either yeasts or molds. Dermatophytes are the most common causative pathogens of onychomycosis.[12,13,23] *T rubrum* and *T mentagrophytes* are the common dermatophytes isolated from patients with onychomycosis.[13,23] *Candida parapsilosis* and *C albicans* are the common yeasts that are isolated, while *Acremonium* sp, *Aspergillus sydowii*, and *Scopulariopsis brevicaulis* are the common molds.[12,13,25] Multiple fungi are sometimes isolated from immunocompromised patients.[19]

Types of Onychomycosis

Several clinical variations of onychomycosis can develop: distal subungual, proximal subungual, white superficial, and endonyx. *Distal subungual onychomycosis* (DSO) is the most prevalent type of fungal nail infection, occurring in 75% to 85% of cases.[12] This variation of onychomycosis occurs between the distal underside of the nail plate and the nail bed, and is most often caused by the dermatophyte *T rubrum*.[12] Fungal pathogens enter the distal nail bed epidermis from the sole of the foot and toe webs through the hyponychium or the lateral nail fold.[26] In fact, most cases of onychomycosis are associated with dermatophyte infection of the feet (tinea pedis).[27]

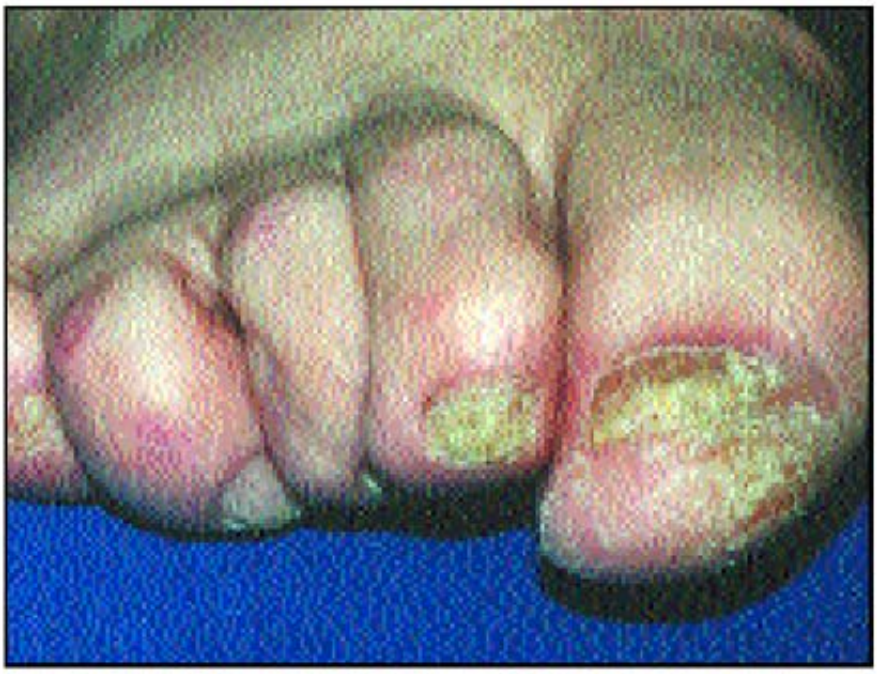

Figure 5A.

Various Types of Onychomycosis of the Toenail: Distal Subungual Onychomycosis

The nail plate appears normal during the early stages of infection, then the horny layers thicken and develop subungual hyperkeratosis. The nail plate -- nail bed attachment eventually becomes disrupted, and the nail plate often develops a yellow-brown discoloration (Figure 5A). As the infection progresses, the fungi advance proximally on the stratum corneum, invading the undersurface of the nail plate.[26] With time, the infection may involve the nail matrix.

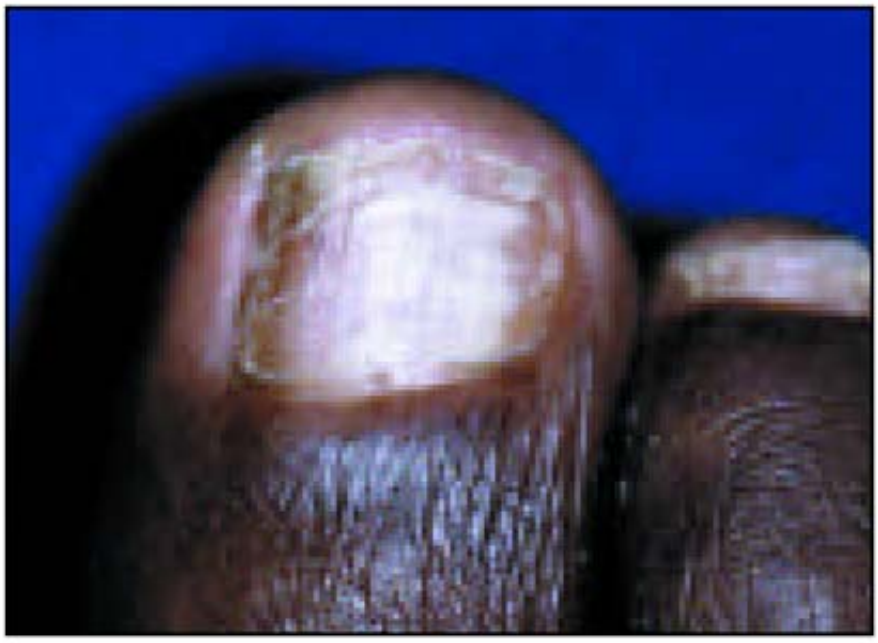

Figure 5B.

Proximal Subungual Onychomycosis: Infection Begins in the Cuticle Area and Migrates Distally

Proximal subungual onychomycosis (PSO) is an uncommon fungal nail infection that occurs at the proximal end of the nail at the matrix, nail bed, and nail plate (Figure 5B). This type of onychomycosis is rare in the general population but

is more common in HIV-infected patients.[12,28] The common pathogens reported to cause PSO include *T rubrum, T megninii, T mentagrophytes, T schoenleinii, T tonsurans*, and *Epidermophyton floccosum*.[26,28] These pathogens initially enter the nail through the proximal nail fold, then advance into the deeper portions of the nail plate.[26] The clinical appearance of PSO consists of white areas extending distally from under the proximal nail fold within the area of the lunula. The surface of the nail plate remains smooth and intact. Unlike DSO, PSO is not usually concurrent with tinea pedis.[28]

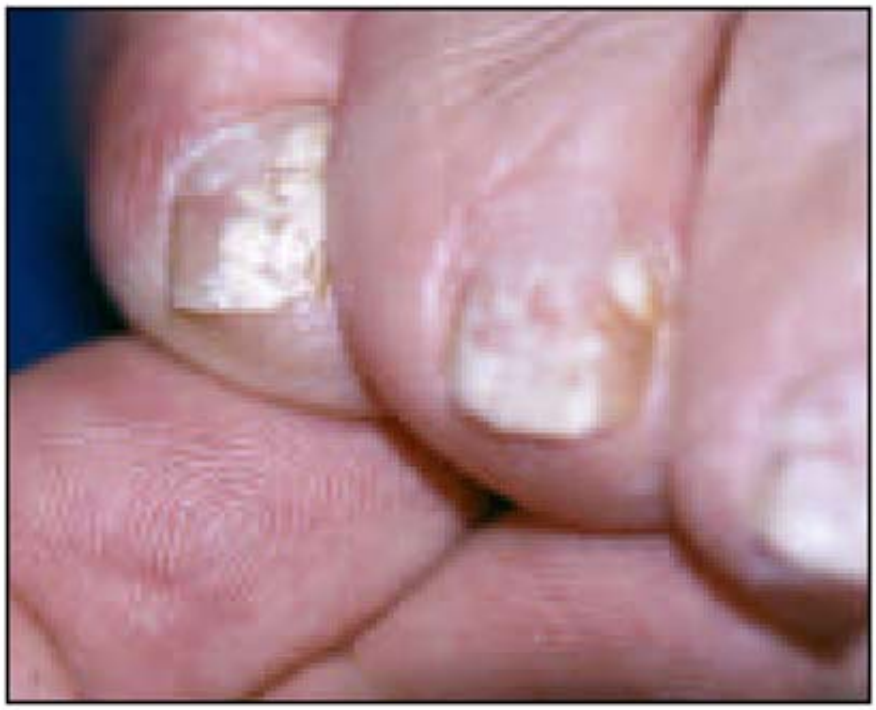

Figure 5C.

White Superficial Onychomycosis

White superficial onychomycosis (WSO) is another type of fungal nail infection that is common in the general population but also develops in HIV-infected patients.[12,29] Pathogens most often found to cause this infection include *T mentagrophytes*, along with *T rubrum* and *Acremonium sp*.[29,30] The infection develops on the surface of the nail plate, almost exclusively on the toenails. Infected nails contain opaque white islands on the surface of the nail plate (Figure 5C). The infection can progress to involve the whole nail plate, which becomes frail and crumbly.

In *endonyx onychomycosis*, fungal organisms invade the nail plate but do not cause nail bed hyperkeratosis, onycholysis, or nail bed inflammatory changes.[31] This type of onychomycosis is mainly confined to the lower layers of the nail plate and is characterized by a diffuse milky-white discoloration of the affected nail. The nail plate surface and nail thickness are normal.

Onychomycosis and Managed Care

Clinical observations clearly indicate that the risk of developing onychomycosis increases substantially with age.[12] This correlation deserves considerable attention by physicians who practice in managed care settings, because the managed care population contains a disproportionate number of geriatric patients, who have a high risk of developing chronic degenerative diseases (ie, diabetes and peripheral vascular disease) that predispose them to fungal nail infections.[14,16,32-34]

US veterans can be considered to be an example of a managed care population with a high risk of onychomycosis. Although the total number of US veterans decreased by 4% during the period from 1990 to 2000, the number of

veterans over the age of 65 years increased from 7.2 million in 1990 to 9.9 million in 2001.[35,36] Similarly, the number of veterans over the age of 85 years increased from 154,000 in 1990 to 590,000 in 2001.[35,36] The growing number of geriatric veterans is reflected in the general US population. For example, the number of individuals over the age of 65 years has increased 12% during the period from 1990 to 2000 in the United States.[37] During this same time period, the number of individuals over the age of 85 years has increased 37%.[37] As the number of geriatric patients rises, physicians can expect to treat more patients with conditions that predispose them to fungal nail infections, such as diabetes and peripheral vascular disease. Indeed, a recent study by the Centers for Disease Control and Prevention found that the prevalence of diabetes increased from 4.9% in 1990 to 6.5% in 1998 -- an increase of 33%.[38]

Since the geriatric population is steadily increasing in managed care, and in the United States as a whole, the prevalence of onychomycosis in these populations is also likely to increase. This is an important consideration for physicians because fungal nail infections in older patients who are ill can cause limb-threatening complications, such as pressure necrosis of the nail bed and secondary bacterial infections.[17]

Onychomycosis: A Stubborn, Recurring Disease

The frequency of recurrence of onychomycosis varies among patients, probably because of varying levels of susceptibility. Although the overall rate of recurrence is not known, recurrence rates between 6.5% and 53% have been reported, despite successful treatment with oral antifungal drugs.[20,21,39] However, the actual recurrence rate of fungal nail infections may be more than 10% higher because clinical trial populations are usually not representative of those encountered in clinical practice.[40] Therefore, when managing onychomycosis, physicians need to include preventive strategies to reduce the frequency and severity of recurring episodes.

Onychomycosis in many patients should be considered a controllable disease rather than a permanently curable disease. Controlling the recurrence of onychomycosis involves pharmacologic treatment and patient education. Patients will usually require follow-up treatment with a topical antifungal agent after the initial episode has been successfully cleared. Since treatment will be administered indefinitely, physicians should take into account potential long-term adverse effects and drug-drug interactions of the available oral medications when designing a preventive treatment strategy. In addition, patients presenting with both onychomycosis and tinea pedis will also require an antifungal medication to resolve the tinea pedis. Treating tinea pedis is important for preventing recurrence of onychomycosis, because the fungal pathogens infecting the skin may act as a reservoir for reinfection of the nail.

Patient education is just as important as pharmacologic therapy for controlling the recurrence of onychomycosis. Physicians need to explain to their patients about the chronic, infectious, and serious nature of the disease. Patients must also understand that they will need to take an active role in preventing future episodes of infection. Simple and effective patient strategies to prevent reinfection are listed below. Patients should be encouraged by their health care professional to follow these strategies.

- Discard old footwear and purchase multiple pairs of new shoes: Infectious fungi can persist in old footwear. Therefore, discarding old footwear eliminates a fungal reservoir that can cause reinfection.
- Replace insoles of shoes if discarding footwear is impractical.
- Alternate wearing shoes: Patients can reduce the fungal reservoir that develops within footwear if they do not wear the same pair of shoes on consecutive days.
- Disinfect footwear: Applying antifungal powder or a disinfectant to footwear will reduce the fungal reservoir that develops.
- Keep feet clean and dry: Patients should clean their feet daily to reduce the growth of fungal pathogens on the skin. Patients should be sure to dry their feet after cleaning them because fungi thrive under wet conditions.
- Contact physician at first signs of recurrence: As with any disease, the likelihood of resolution improves when the condition is detected and treated early. The severity of a recurring infection may be reduced if a patient receives a full regimen of pharmacologic treatment during the early stages of infection. Physicians should describe to their patients what the early signs of onychomycosis look like.

Diagnosing Onychomycosis

The clinical diagnosis of onychomycosis is quite accurate, but laboratory confirmation is always needed to avoid incorrect diagnosis, as well as unnecessary exposure to antifungal medication. Laboratory confirmation is often required to receive reimbursement from managed care organizations. Although the presence of dystrophic nails with yellow to brown discoloration, onycholysis, and subungual hyperkeratosis makes onychomycosis the probable cause, physicians should resist the temptation to begin treatment empirically because psoriatic nail disease, eczematous dermatitis, and lichen planus can cause nail abnormalities that resemble onychomycosis.

Methods of Confirming Diagnosis

Several laboratory techniques are available to physicians for confirming the clinical diagnosis of onychomycosis. These methods include potassium hydroxide (KOH) wet mount, fungal culture, and nail histopathology.

Specimen collection. Proper technique for specimen collection is critical for successful diagnosis. The specimen should be collected from the affected portion of the nail bed. Nails should be scraped or clipped near the bed, where new growth of the fungus is most likely to occur (Figure 6).

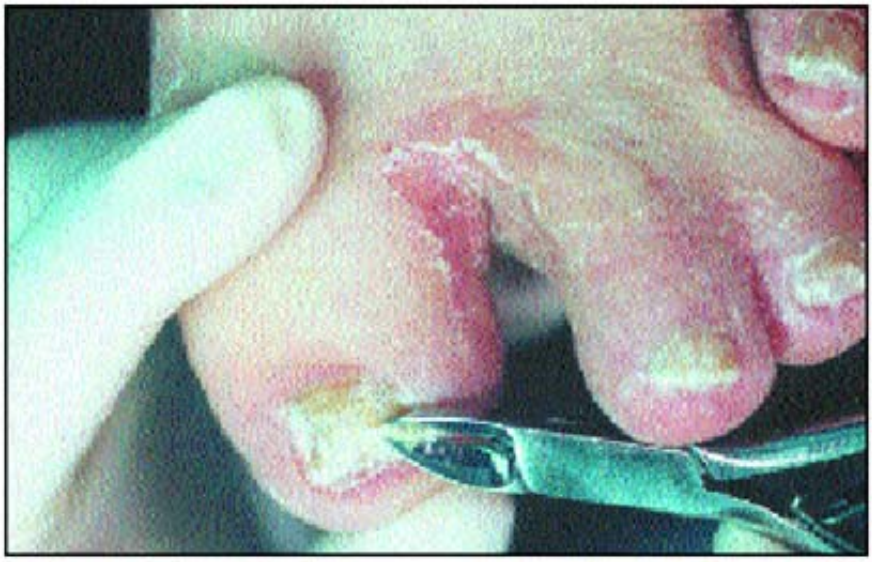

Figure 6.

Obtaining a Nail-Clip Specimen Using 5-Inch Straight Nail Nipper (Photo Courtesy of Dr Myron Bodman)

The nail should be swabbed liberally with alcohol before obtaining the specimen, and nail debris for the KOH preparation and culture should be collected simultaneously. This will eliminate bacteria that can interfere with the growth of fungi. Whole nail clippings should be ground thoroughly with a nail micronizer before being placed on fungal culture medium.[41] Skin scrapings should also be taken from the active borders of the lesions in several locations to increase the probability of obtaining positive material. Specimens should be kept in sterile containers or planted directly on culture tubes. The sampling approach should be tailored to the type of onychomycosis[42,43]:

- Distal subungual onychomycosis.

  Material should be taken from the most proximal area because mycelia from the distal area are often not viable. A large amount of nail plate is removed with a nail nipper; hyperkeratotic debris from the nail bed and from the underside of the nail plate is then obtained using a curette.
- Proximal subungual onychomycosis.

The overlying intact proximal nail plate may be burred thin and then penetrated so that the curette can scoop up subungual debris from the nail bed.

- White superficial onychomycosis.

  The surface of the nail plate is scraped with a curette.

KOH wet mount preparation. The first step in making a diagnosis of onychomycosis is usually the direct microscopic examination of scraping from the nail bed and nail plate for the presence of fungal organisms. This procedure is termed a KOH wet mount test preparation because material obtained from the nails is mixed with potassium hydroxide solution before microscopic visualization. The KOH preparation is time consuming and requires experience and expertise. Although this method detects the presence of infection, it does not identify the specific pathogen.

Procedure for KOH wet mount.

- Obtain nail debris and deposit it on a glass microscope slide.
- Place a cover slip over the specimen on the slide.
- Apply 1 to 3 drops of KOH to the side of the coverslip with an eyedropper; the solution will be drawn over the sample by capillary action.
- Gently warm the slide over a methanol burner, taking care not to boil the specimen.
- Visualize with a microscope.

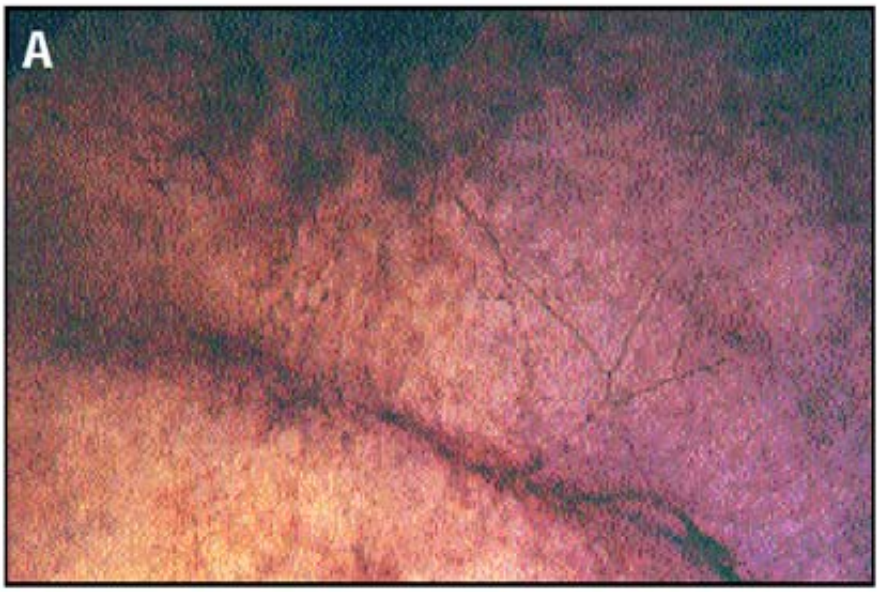

Figure 7A.

Microscopic Visualization of Fungal Hyphae From Nail Samples: Positive KOH and Chlorazol Black E Fungal Stain Using 10 x Objective of a Light Microscope

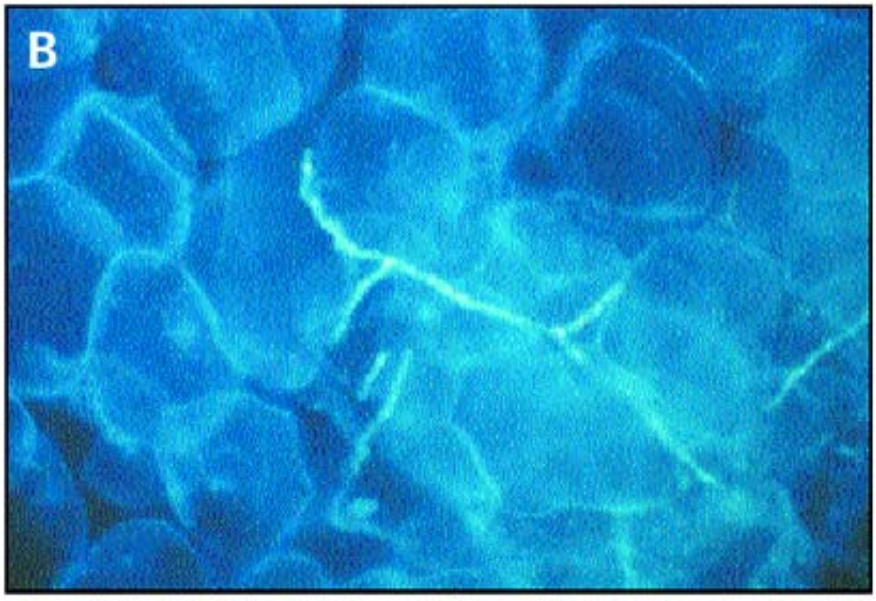

Figure 7B.

High-Power, Phase-Contrast, Positive KOH and Counterstain of *Trichophyton Rubrum* (Photo Courtesy of Sensitivity of Dr Myron Bodman)

Under low power (10x), fungal hyphae appear as dark branching tubes (Figure 7A). Look for segmented branching hyphae among smooth circular cell membranes using high power (Figure 7B).

Issues in interpretation. Multiple negative KOH preparations must be obtained before the suspected nail is considered not to be mycotic.[44] A negative KOH does not in any way rule out onychomycosis but only prompts further testing (ie, culture or biopsy). Poor sampling, poor microscopy techniques, and examiner bias can cause false-negative results. Therefore, a KOH preparation is best conducted by a physician trained in specimen collection and fungal microscopy.

Fungal culture. A fungal culture detects infection and identifies the genus and species of the causative organism. This method is relatively inexpensive, but it takes 7- to 14- days for a result.

Commonly used media for fungal culture. Cycloheximide can be added to culture media to suppress the growth of nondermatophyte fungi, and the addition of antibiotics (eg, chloramphenicol) suppresses the growth of bacteria that can overrun the culture. Samples should be cultured with and without cycloheximide to ensure that any nondermatophytes present can grow.

- Sabouraud dextrose agar (without antibiotics)
- Modified Sabouraud medium (contains chloramphenicol and cycloheximide)
- Dermatophyte test medium (contains antibiotics, cycloheximide, and phenol red)

Procedure for fungal culture.

- Obtain nail specimen, swab liberally with alcohol, pulverize, and place on medium, taking care not to close the cap tightly.
- Incubate culture at room temperature.
- Monitor weekly for fungal growth.

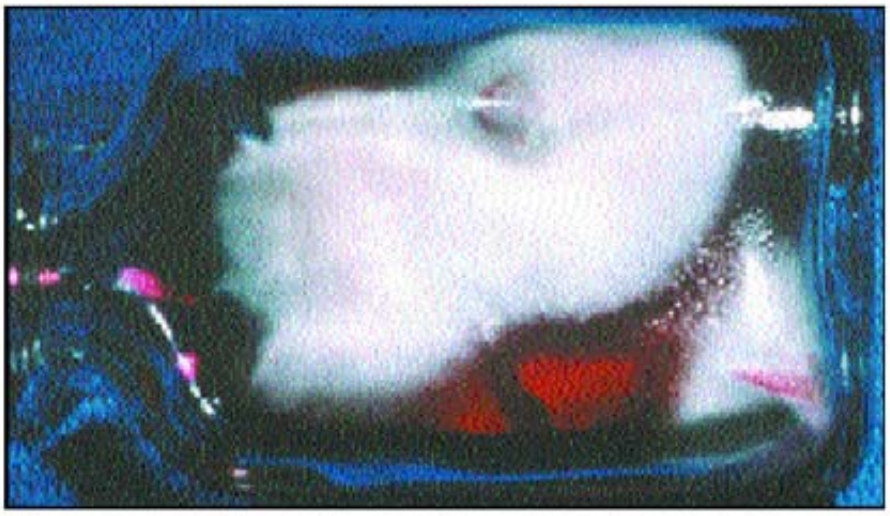

Figure 8.

Dermatophyte Test Medium Positive With Growth of White Fluffy Colonies of *Trichophyton Rubrum* (Photo Courtesy of Dr Myron Bodman)

Dermatophytes generally appear as fluffy or powdery white-to-brown colonies on culture medium (Figure 8). Fungal cultures may be incubated for 4- to 6- weeks before they are interpreted as negative.

Issues in interpretation. Approximately 30% of cultures are false-negative, which can be caused by several factors.[43] For example, fungi may be present, but not viable. If the fungi were alive in the tissue, they may have died during sample processing or culture. Cycloheximide and coexisting microbes can sometimes inhibit the growth of fungi.[43] A fungal culture should be repeated when a negative culture is observed and a KOH preparation is positive. Ideally, several cultures can be inoculated simultaneously to increase the yield.

Nail histopathology. When onychomycosis is strongly suspected but multiple KOH preparations and fungal cultures fail to confirm the diagnosis, large nail plate fragments (at least 3 mm) should be placed in buffered 4% formalin for histologic analysis by a pathologist. Using periodic acid-Schiff (PAS) stain, the pathologist may visualize pathogens (Figure 9). The reported diagnostic sensitivity of this method is nearly 100%,[42] but histopathology cannot identify the specific pathogen. Nevertheless, histologic examination of the nail has the advantage of ruling out other conditions, such as nail psoriasis.

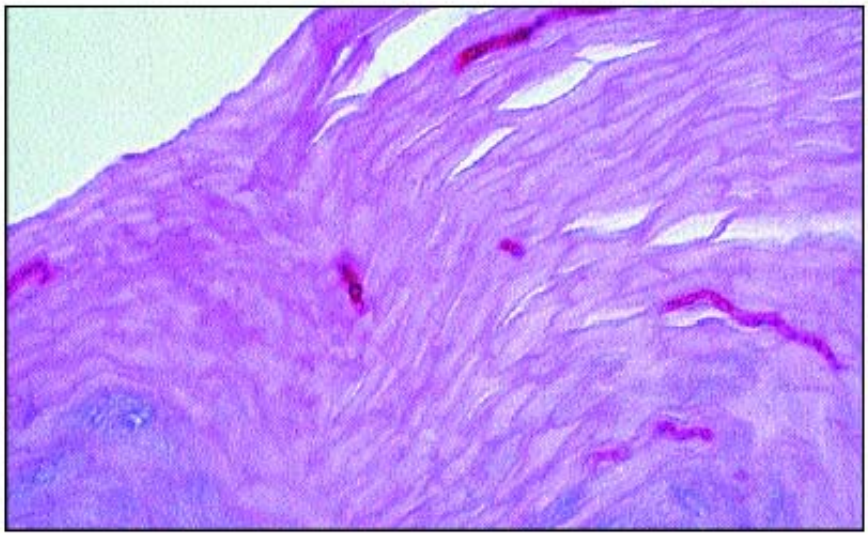

Figure 9.

PAS-Positive Fungal Hyphae Within the Stratum Corneum of the Infected Nail Bed. PAS Indicates Periodic Acid-Schiff Stain.

Treating Onychomycosis

Fungal nail infections are among the most difficult superficial mycotic infections to treat effectively. Therapeutic strategies for onychomycosis vary among patients and are influenced by the severity of the disease.[27] Treatment approaches can be categorized into 4 groups: mechanical debridement, removal of the affected nail (nail avulsion), oral antifungal therapy, and topical antifungal therapy. The likelihood of recurrence is significant with any single approach; combining 2 or more approaches has the potential to maximize therapeutic efficacy and reduce recurrence.

Mechanical Debridement

Mechanical debridement is a traditional podiatric approach to onychomycosis that requires time, specialized instruments, and experience. The goal of this approach is to reduce pressure and fungal load by mechanically reducing nail thickness. Since mechanical debridement removes a large portion of onychomycotic material, it has the potential to enhance the effectiveness of other therapies, especially those involving antifungal medication. However, this approach does have limitations. For example, it does not eradicate the infectious pathogens, and it must be repeated as the nail grows until the infection has been resolved.

Removal of the Nail

Nail avulsion involves removal of the affected nail plate, which can be performed either surgically or chemically using 40% urea, 30% salicylic acid, or 50% potassium iodide. This approach allows growth of a new nail but can traumatize the nail bed, which may affect the appearance of the new nail. Also, total nail avulsion causes discomfort to the patient, and therefore is discouraged.

Oral Antifungal Therapy

Oral antifungal medications are often prescribed as first-line treatments for onychomycosis. These systemic drugs, terbinafine, itraconazole, and fluconazole (not FDA approved for nails), reach the infected nail via the peripheral circulation. The latest generation of oral antifungal medications have been shown to be effective in clinical studies.[45,46] For some of these newer oral antifungals, treatment periods have been reduced and intermittent or pulse dosing regimens have been prescribed to minimize adverse effects and cost. The reason for reducing the treatment period is that the newer drugs can remain in the nails for up to 6 months after treatment has ended.[47] However, it is important that physicians not underestimate the chronic nature of the disease. Despite the fact that oral antifungal medications have greatly improved over the past 10 years, it has been suggested that as many as 25% to 40% of onychomycosis cases are classified as treatment failures in clinical practice.[40]

Before prescribing oral antifungal medications, physicians should consider the potential for adverse effects with each patient. Certain oral antifungal drugs may affect liver function, cause neutropenia and transient taste disturbances, and can be involved in drug-drug interactions.[48,49,55] Therefore, liver function and white cell counts should be assessed at baseline and periodically during treatment. In addition, the financial impact of therapy should be considered with each patient, since the newer oral antifungal drugs are expensive.[50]

Topical Antifungal Therapy

Clinical observations indicate that topical antifungal therapy is effective for the treatment of onychomycosis in some cases.[51] This approach involves the direct application of an antifungal drug to the infected nail. These drugs are thought to diffuse through the nail plate to reach the site of infection, where they then eradicate the fungal organisms.[52] Topical antifungal therapy is generally considered safe, with adverse reactions being mild and localized to the site of application. Adverse events reported include primarily erythema and, less frequently, swelling or a burning/tingling sensation at the application site.[51] Minimizing the treatment period of topical antifungal agents has not been a major

concern in patients with onychomycosis because these drugs may not be as expensive as oral antifungals[50] and have few adverse effects.

When to Stop Treatment With Antifungal Drugs

The treatment periods for antifungal drugs vary from 3 months for oral and up to 12 months for topical. However, these times may vary depending upon the type and extent of infections .[51] In addition, the effectiveness of treatment is sometimes not visibly apparent for several weeks or months into therapy. As a consequence, it may be difficult for a physician to determine whether a particular antifungal treatment is efficacious. A physician may wish to consider waiting 2 months after the end of therapy. If clearing slows during this period, administration of another regimen of therapy is warranted. However, the diagnosis and the prescribed treatment should be re-evaluated if no clearing is apparent after 3 or 4 months of therapy.

Combination Therapy

Given the resilient nature of the pathogens in onychomycosis, physicians should consider combining more than one therapeutic approach for managing fungal nail infections, though combination therapy is not specifically approved in any product's labeling. For example, combining oral and topical antifungal medications may allow complementary drug penetration at the infection site (Figure 10).

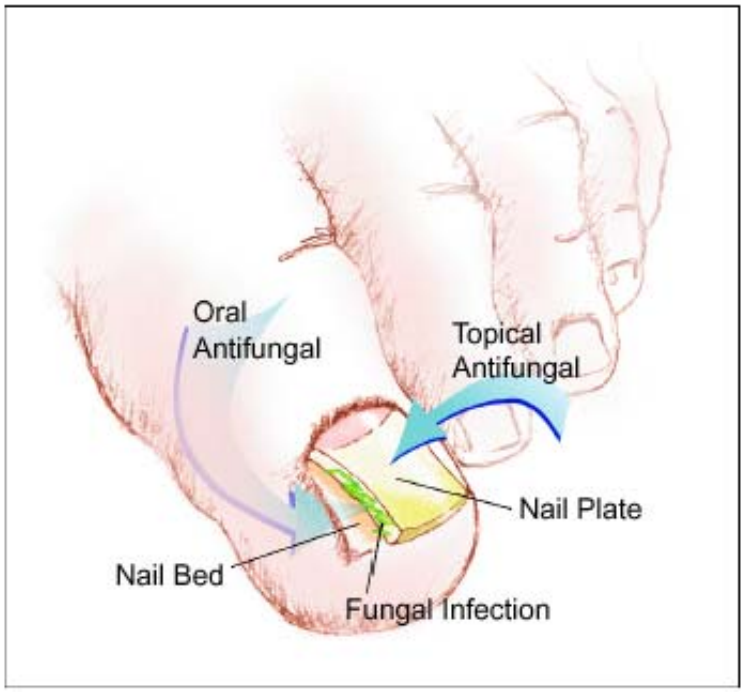

Figure 10.

Pharmacologic Approaches in the Treatment of Onychomycosis

Penetration of the topical antifungal agent through the nail plate from the surface of the nail and diffusion of the systemic antifungal drug through the nail bed may increase the total amount of antifungal activity at the site of infection. Results from an initial study in patients with onychomycosis suggest that this approach can enhance the overall efficacy of therapy.[53] Using a combination of antifungal drugs in this manner may potentially reduce the duration of therapy and allow a reduction in dose of the oral agent, which may reduce systemic adverse effects. Furthermore, using oral and topical antifungal agents consecutively may help reduce recurrence of the disease after the initial episode has been resolved. Once the fungal nail infection has been successfully treated with an oral antifungal drug, continuous treatment with a topical antifungal medication may reduce the frequency and severity of recurrence.

This approach is practical, given the good safety profile of topical antifungals.

Physicians may also consider combining topical antifungal therapy with topical urea. Urea degrades protein, including keratin -- a major component of the nail plate.[22] Potentially, urea can soften the nail plate, making it more porous and penetrable to topical antifungal drugs. This methodology has been successfully used to increase the delivery of topical antifungal agents into the skin. Clinical studies in patients with onychomycosis are needed to examine the safety and efficacy of this type of combination therapy.

Combining mechanical debridement with drug therapy can be successful and should also be considered. Mechanical debridement of the nail plate is recommended before the application of topical antifungals, but it may also be useful during oral antifungal use. Removing onychomycotic material reduces fungal load and may improve the penetration of both topical and oral antifungal agents.

Summary

Physicians today are faced with a rising number of patients who are susceptible to onychomycosis. For example, the number of individuals over the age of 65 years and the number of individuals with diabetes are steadily increasing. In addition, the number of persons living with acquired immunodeficiency syndrome has increased as deaths have declined over the past decade.[54] As these specific patient populations increase, the incidence of fungal nail infections is likely to rise as well. Therefore, physicians should consider preparing effective diagnostic, treatment, and preventive strategies that would efficiently manage onychomycosis for a growing patient cohort.

The successful management of onychomycosis begins with an appreciation of its characteristics. Physicians must understand that onychomycosis is a potentially serious, superficial, and progressive infection. This involves adopting a specific viewpoint: fungal nail infections are a recurring medical problem that should be treated. Once this is accepted, the best approach to management includes ongoing pharmacologic treatment and patient awareness. Preventive medication is necessary to control the disease after the initial episode is resolved. A drug with few adverse effects is preferred, such as a topical antifungal agent, since the medication may need to be taken indefinitely. In addition, it is vital that physicians also treat tinea pedis at the initial onset of onychomycosis and continuously thereafter, because the skin is the likely source of the pathogens that infect the nail.

Patient education is another key component to reducing the frequency and severity of fungal nail infections. Physicians need to communicate the potentially serious and recurring nature of the disease to patients -- that onychomycosis is an infection and that preventive strategies on the part of the patient are necessary to reduce recurrence. A strategic plan involving aggressive treatment, patient education, and continuous preventive medication for fungal nail and skin infections will provide patients with the best chance of successful disease control.

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