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Prognostic factors of varying treatment outcomes for onychomycosis (nail fungal infection) patients

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ABSTRACT

Prognostic Factors of Varying Treatment Outcomes for Onychomycosis (Nail Fungal Infection) Patients

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M.S., Harvard University, 1992
M.P.H., Boston University, 1989
M.D., Tongji Medical University, 1982

Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy
Public Health

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ABSTRACT

Prevalence of onychomycosis, as high as 26.9% in the general population, can be reduced by improving current antifungal treatment. This could be accomplished by understanding prognostic factors, especially healthy nail growth, associated with achieving complete cure. This population-based study aimed to evaluate if healthy nail length or percentage of total full nail length as healthy can be early indictors for complete cure. Logistics regression analyses were performed by comparing variables between a population who achieved the complete cure and a population who failed after both populations received the same antifungal treatment in two large randomized double-blinded clinical trials that assessed drug efficacy. Results showed that the largest odds ratios for healthy nail length (mm) and percent of total nail grown as healthy (%) were achieved at Week 12 with 1.63 and 1.07, respectively. Mean healthy nail length at Week 12 was 3.56 mm among cured patients and 1.90 mm among failed patients. Other significant baseline factors for the cure were: younger in age; naïve to antifungal treatment; and having less severe disease. Growth of healthy nail during the treatment period is significantly associated with achievement of complete cure. Treatment success might be improved by monitoring the healthy nail growth. This study bears public health importance and can foster positive social changes because better managed disease can improve patient's quality of life and reduce financial burdens to the healthcare system. It could also be a tool for researchers to filter out better drug candidates and reduce research costs therefore cheaper treatments.

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DEDICATION

I would like to dedicate this to my late parents, my wife Shihong, and my sons Cadmus and Delbert.

ACKNOWLEDGMENTS

I started my study about 4 months after my second son was born. It would have been impossible to complete this challenging journey without help from my mother-in-law, who has been cooking and taking care of my children for us over the last 3 ½ years. Big thanks go to her!

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I would like to thank my children Cadmus and Delbert for giving me reason to complete this study. They have been my inspiration to complete this journey. I would like to show them that learning is a lifelong practice.

Most of all, I would like to thank my wife Shihong for her unrelenting support. This degree is as much hers as mine. Without her standing beside me, I might never have taken this journey and reached this milestone.

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CHAPTER 1:

INTRODUCTION TO THE STUDY

Background of the Study

Onychomycosis is a fungal infection of the nail unit and occurs worldwide. The disease accounts for 30% of all superficial fungal infections and about 50% of all nail disorders (Jain & Sehgal, 2000). According to population-based studies, the prevalence of onychomycosis in the general population is between 2 to 8%, which may be an underestimate due to the low level of diagnosis or underreporting (Haneke & Roseeuw, 1999). The estimated prevalence in North America is 6.5 to 13% (Gupta, Taborda, et al., 2000). The prevalence of onychomycosis in Europe is estimated at 26.9% (Haneke & Roseeuw).

Studies (Haneke & Roseeuw, 1999; Jain & Sehgal, 2000) showed an increase in onychomycosis in recent decades, probably due to several factors, including an aging population, changes in lifestyle such as wearing unfit shoes or participating in sporting events, an expanding immunosuppressed population, increased vigilance in detecting the disease, increased use of communal locker rooms, and professional hazards.

Toenails are involved in the majority of onychomycosis cases. The ratio of fingernail to toenail onychomycosis was found to be 1:4 in Spain and 1:19 in Canada. This may be partly because the toenails grow 50-66% more slowly than the fingernails. It takes 12-18 months to grow a big toenail anatomically but only 6 months to replace a fingernail. Slow growth may make it easier for the fungus to establish the infection (Haneke & Roseeuw, 1999).

Onychomycosis affects the lives of individuals with the disease. Once infected, the nail corrodes from the inside out and results in onycholysis (i.e., separation of the nail from the nail bed) and discoloration. Patients report pain and discomfort (Gupta, Taborda, et al., 2000). They often present with a disfigured, especially thickened nail plate. The thickening can cause a problem with toenail cutting and requires some patients to use padding or special shoes to accommodate the thickened toenails. Distorted nails, sometimes with sharp edges, could abrade adjacent skin and cause compensatory changes in adjacent hard and soft tissues such as subungual corns, calluses, and ulcers. Patients with diabetes or peripheral vascular diseases are particularly at risk of the complications of adjacent skin changes because of poor circulation, which will prolong the wound healing time and leave the patients vulnerable for developing cellulitis or even septicemia. Many patients may also have negative self-images (Gupta, Taborda, et al.; Turner & Testa, 2000). Shame may preclude patients from acting in social and occupational circumstances where they feel unwilling to show their hands or feet. Therefore, even if considering it as a cosmetic problem, this infection is often worth the treatment.

Treatment of onychomycosis is a challenging task because the nail fungus often does not live on the nail surface but in the nail bed where there is a rich blood supply, which encourages growth. Treatment is also challenging because the nail bed uses the nail as a protective shield so that many topical medicines do not reach the affected area. In addition, some of the systemic drugs show poor affinity to the nail bed tissues. Even with currently available treatments, the rate of complete elimination of the disease is

unsatisfactory, with a rate ranging between 20 and 50% (Baran & Kaoukhov, 2005; de Berker, 2004).

The terbinafine oral tablet is considered the gold standard treatment of dermatophyte onychomycosis (Crawford et al., 2002; Darkes, Scott, & Goa, 2003; Gupta, Ryder, & Johnson, 2004; Loo, 2006; Roberts, Taylor, & Boyle, 2003). The complete course of treatment for toenail onychomycosis is a 12-week daily dosing with oral terbinafine 250 mg tablets. The product leaflet indicates a 38% complete cure rate (Novartis Pharmaceutical Corporation, 2005). The meta-analysis of published data indicates a 35% to 50% disease-free nail after a standard course of the treatment (Epstein, 1998). Both researchers and physicians feel this rate could be improved (Gupta & Ryder, 2003, Gupta & Tu, 2006). Some researchers have recommended introducing a shorter course of oral dose as a booster treatment during the follow-up period, combining oral dosing with a topical medicine or debridement procedure (Baran & Kaoukhov, 2005; Gupta & Ryder; Gupta & Tu), or increasing the standard treatment duration (Heikkila & Stubb, 2002). Other researchers opted to wait 72 weeks longer before repeating the antifungal medication (De Cuyper & Hindryckx, 1999; Sigurgeirsson, Olafsson, et al., 2002). Practice is inconsistent across medical fields and strategies often are in principal only, without providing clear guidelines on when and how additional therapies should be used. Also, the true benefit of additional medication has not yet been fully reported. Therefore, there is a clear benefit for both the research and medical communites to have a better and more precise way to predict treatment outcome, including indicators for

treatment success, identified in the early stages of treatment as well as for any additional booster treatments.

Problem Statement

Success of antifungal treatment is assessed by whether or not a patient has achieved a complete cure. Complete cure, a dichotomous variable, is defined as completely healthy big toenail regrowth (i.e., clinical cure) and negative mycological culture and microscopy results (i.e., mycological cure) about 36 weeks after conclusion of a standard 12-week daily dosing of systemic treatment. Though total healthy nail growth is one of the criteria for a complete cure assessment, the effect of healthy nail growth during the treatment and posttreatment period on treatment success has only been assessed in a study with 35 patients (Sommer et al., 2003). The results from the study were inconclusive due to lack of sufficient power. Therefore, the associations of healthy nail growth--alone or in combination with other factors--and achievement of a complete cure are still uncertain. These associations will be studied here.

Purpose of the Study

This population-based study was aimed at examining the relationship between healthy nail growth during the treatment and posttreatment periods and achievement of a complete cure. It was intended to identify the best point in time and the best prognostic variables for predicting the achievement of a complete cure. It also assessed the effect of some baseline factors and mycological results on the treatment outcome.

Nature of the Study

This is a prospective study with repeated measurements taken from patients treated with a standard course of terbinafine oral tablets in two identically designed clinical trials conducted by Novartis Pharmaceutical Corporation. The study compared a set of factors between patients who achieved complete cure and patients who failed to achieve complete cure in an effort to identify significant factors associated with treatment success.

Research Questions and Hypotheses

Healthy nail growth is a key surrogate marker for the disease's progression and for assessment of treatment outcome. Since healthy nail growth can be measured as actual length grown or expressed as a percentage of the total full nail length grown as healthy, this population-based study assessed how each variable was associated with a successful outcome. Specifically, this study examined hypotheses associated with the following two questions.

Question 1: What is the link between achievement of a complete cure and the speed of healthy nail growth as measured by the length of healthy nail during the trial period?

Null Hypothesis: There is no association between the achievement of a complete cure and the change in the length of healthy nail growth at any point in time during the 48-week period.

Alternative Hypothesis: There is an association between the achievement of a complete cure and the change in the length of healthy nail growth during the 48-week period.

Question 2: What is the association between the achievement of a complete cure and the proportion of total nail regrown as healthy over the trial period?

Null Hypothesis: There is no association between the achievement of a complete cure and the change in the percentage of total full nail length grown as healthy at any point in time during the 48-week period.

Alternative Hypothesis: There is an association between the achievement of a complete cure and the change in the percentage of total full nail length grown as healthy during the 48-week period.

To test these hypotheses, a determination of whether complete cure was or wasn't achieved was based on mycological results and healthy nail growth status by the Week 48 assessment, since complete big toenail growth takes up to 12-18 months. Healthy nail growth was measured by (a) length (in millimeters) between the nail proximal fold and the lowest point of the disease and healthy nail border, and (b) nail growth as a percentage of total full nail length. These measurements were taken at Weeks 4, 8, 12, 16, 24, and 36 after starting treatment. Other factors included age, sex, disease severity (measured by percentage of infected nail) prior to starting treatment, antifungal treatment history, and clinical signs. The analysis was done to assess if the nail growth pattern alone or combined with these factors could predict the treatment outcome.

Theoretical Base

Failure of antifungal treatment can only be known after a long follow-up period. If treatment failure can be predicted earlier, the probability of success can be improved by other means (Sommer et al., 2003). However, identifying these prognostic factors has been a slow process. Only limited literature has reported the factors associated with treatment success. Since healthy nail growth is a reflection of the effectiveness of treatment and ability of the nail to grow, monitoring healthy nail growth can be the best indicator for treatment success.

This study used archived data prospectively collected from two large clinical trials. It was possible to not only assess the change in healthy nail growth over time, but also to compare such changes between patients who achieved a complete cure and those who failed at certain points in time. Limiting the study to patients who received the same duration of the same drug treatment minimized the impact of underdosing, overdosing, or treating with a different drug. Though nail growth can be affected by factors such as age and gender, the researcher adjusted for these potential confounders when evaluating the association between nail growth and treatment success. Therefore, the study results have high validity.

Though it is especially challenging to monitor nail growth over a long period of time in a large sample, this study provides much-needed information to both physicians and researchers.

Definition of Terms

Definitions for the terms used in this report are provided in this section.

Clinical cure: Completely healthy, 0% residual involvement of the target toenail.

Complete cure: A complete growth of healthy nail and negative microscopy and negative culture from nail sample.

Debridement: A procedure to remove diseased nail using scalpel or nail file.

Dermatophytes: A term that embraces the imperfect fungi of the genera *Epidermophyton*, *Microsporum*, and *Trichophyton*. It causes infections of the skin, hair, and nails because of their ability to obtain nutrients from keratinized material in the skin, hair, and nail.

Dermatophytoma: A dense white linear or round area under an onycholytic nail plate, which consists of a densely packed clump of often thick-walled dermatophyte haphae.

Eponychium: Also called the cuticle, it is situated between the skin of the finger or toe and the nail plate, fusing these structures together and providing a waterproof barrier.

Hyperkeratosis: Hypertrophy of the skin/nail.

Hyponychium: The area between the nail plate and the fingertip, it is the junction between the free edge of the nail and the skin of the fingertip, providing a waterproof barrier.

Lunula: Visible part of the nail matrix; often called *half moon.*

KOH test: The nail sample is treated with potassium hydroxide (KOH), and then examined directly under the microscope for hyphae. The test is positive if hyphae are found.

Macroconidia: Two- or more-celled, smooth-, thin- or thick-walled, and cigar shaped.

Microconidia: One-celled and round or pyriform in shape.

Microscope: See *KOH test*.

Mold: Includes all species of microscopic fungi that grow in the form of multicellular filaments, called hyphae. *Scopulariopsis brevicaulis* is a common mold cause of onychomycosis.

Mycological culture: A process to grow fungus on the medium for the identification of fungus species.

Mycological cure: Culture negative for dermatophytes and negative KOH microscopy from the nail sample.

Nail matrix: The area approximately 5 mm beneath the proximal fold, where the nail is made.

Nail plate: A term for the actual nail, the nail plate is made of translucent keratin. The pink appearance of the nail comes from the blood vessels underneath the nail. The underneath surface of the nail plate has grooves along the length of the nail that help anchor it to the nail bed.

Onycholysis: Separation of the nail from nail bed along the lateral margins

Onychomycosis: Nail is infected by fungal, mainly dermatophytes such as *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermatophyton floccosum*, and so on.

Paronychial inflammation: Inflammation due to infection of the skin folds surrounding the nail plate.

Perionychium: The skin that overlays the nail plate on its sides. It is also known as the paronychial edge.

Relapse: Patients with complete cure prior to Week 48 who tested positive again by mycological culture or positive KOH microscopy and clinical assessment.

Ratio of estimated prevalence (REP) = (Onychomycosis per decade of age × total population) / (100 × citizen in defined period of age)

Tinea pedis: Fungal infection of foot skin.

Assumptions

The study was conducted under two assumptions. The first assumption was that new nail will grow out healthy and evenly push through the nail bed after the fungi that cause onychomycosis have been killed. The second assumption was that the change in healthy nail length will reflect the time needed to grow a completely healthy new nail. The shortest distance between the proximal nail fold and healthy-disease boarder would require the longest time to replace the diseased nail and should be a good predictor of the final treatment outcome.

Limitations

The original clinical trials by Novartis Pharmaceutical Corporation were designed to assess the efficacy of continuous dosing of 250 mg terbinafine oral tablets versus intermittent dosing of 350 mg terbinafine oral capsules. The trials were completed in November 2003. This study was limited to the data collected from these trials.

Nail growth at each trial visit was captured by photographing each patient. Measurements of healthy nail length at baseline and the end of the trial were available from the archived database. The healthy nail length from other points in time needed to be measured from the photographs by this researcher. Therefore, the quality of the photographs might have affected some assessments and disqualified some patients from participation in this study.

Though infection of the nail matrix and nail thickness have been shown to be associated with treatment success, they were not assessed in this study because the data were not collected in the original trials. The interaction with healthy nail growth will need to be assessed in future studies.

Significance of the Study

Because of the disease's high prevalence, it is important to treat patients successfully. However, fungal infections of the nail are very difficult to treat because the fungus commonly lives beneath the nail where it is hard for medicine to reach. The appearance of infected nails may affect patients' social life as well as self-confidence (Elewski, 2000; Gupta, Taborda, et al.; Turner & Testa, 2000). The patients may be embarrassed to wear sandals or open-toed shoes. They may not swim in public. Their partners may be impacted by the presence or appearance of the infection, which may cause a strain in personal relationships.

Left untreated, the nails may also cause medical problems. Infected nails could be reservoirs that spread the fungus to other body areas (Szepietowski, Reich, Garlowska, Kulig, & Baran, 2006), especially when immunity is compromised. For patients with

diabetes or peripheral vascular disease, untreated onychomycosis may decrease their mobility (Jones, 2003). Therefore, prompt treatment is required. However, the current success rate is not optimal and treatment outcome is only known after a long waiting period. This causes both medical and emotional burdens for the patients. If treatment outcome could be predicted at an early stage of the treatment, physicians could be guided to provide appropriate adjuvant treatment to boost the treatment success rate. This may increase patient treatment compliance. It could also reduce financial as well as emotional burdens by avoiding unnecessary second full courses of treatment and by shortening the waiting period for results. Therefore, it can improve the quality of life for sufferers.

If treatment outcome could be predicted at an early stage of the treatment, it could also help researchers to filter out better antifungal candidate compounds for further development. DiMasi, Hansen, and Grabowski (2003) reported that current drug development processes take an average 90.3 months and $802 million to move a drug from the start of the first clinical trial to marketing approval. The cost includes compensation for drug failures during the development phases. The cost is generally higher at the later phases of development. Mean out-of-pocket costs for market approved drugs were US$15 million in Phase I and $115.2 million in Phase III (DiMasi, Hansen, & Grabowski, 2003). One of the approaches to consider mitigating rapidly rising research and development costs is to aggressively identify likely drug failures earlier in the development process. Thus, positive findings from this study could help to reduce the development cost and shorten the development time.

In summary, the public health importance this study bears is that it could (a) curb the spread of the disease, (b) alleviate the patient's financial and emotional burdens by improving the monitoring of treatment progress and boosting the treatment efficacy appropriately, and (c) help the pharmaceutical industry to develop antifungal drugs more efficiently and with less cost so that the new drug will have a higher efficacy and be less expensive for the patients.

Summary and Transition

This chapter articulates the rationale and purpose of the study, provides research questions, assumptions, and interprets study significance. Using a large sample size and high quality data prospectively collected in well-controlled clinical trials provides a unique opportunity to assess the factors associated with achieving a complete cure after a standard course of terbinafine oral tablets. This will help fill the gap in the existing literature about healthy nail growth and its relationship to treatment success.

The literature review in the following chapter presents the anatomy of the nail, causative agents, clinical presentations, diagnoses, epidemiology, and treatment options. These data help us to better understand the challenge antifungal treatments face and therefore enhance the importance of this study. Chapter 3 describes the research methods utilized, including study design, data sources and statistical analyses. Chapter 4 presents study findings. Chapter 5 discusses the results, their implications, recommendations for future studies, and the conclusion.

CHAPTER 2:

LITERATURE REVIEW

Onychomycosis has been the subject of various studies and clinical trials whose purpose has been to show the effectiveness of several treatment options. To better understand the disease and its treatment, this chapter will first describe nail anatomy, fungi that cause the disease, clinical presentation of the disease, and risk factors associated with the infection. It will also summarize treatment options and strategy along with presenting research on prognostic factors.

The literature was identified mainly by extensive searching of various large online databases such as Academic Search Premier, CINAHL Plus, PubMed, and Medline. Some articles were the result of using a search engine such as Google Scholar or Yahoo. Additional articles were identified by reference lists from journal articles and books or were obtained from professional journals available at local libraries. Search terms used alone or in combination included *onychomycosis, dermatophytosis, fungal infection, terbinafine, lamisil, nail anatomy, nail disease, prediction,* and *epidemiology*. With few exceptions, the majority of articles was published in peer-reviewed journals within the last 10 years, and thus reflected the most up-to-date understanding of the disease and available antifungal treatment.

Anatomy of the Nail

The nail (medically referred as the ungual plate) consists of a nail plate and nail bed (Elewski, 1998; Nathan, 2006), as shown in Figure 1. The nail plate is rectangular or quadrilateral in shape and is located on the distal end of each toe and finger. A nail

plate’s internal face is seated on the nail bed. Its proximal part is yellow or white in color and the quarter-moon-shaped lunula (also called half moon) is often seen in the center. The skin between the nail plate and the distal joint in the finger or toe is called the proximal fold. The area approximately 5 mm beneath the proximal fold is called the matrix and part of it is visible through the lunula. The proximal and lateral folds of the skin surrounding the nail form the cuticle and lateral grooves respectively. The end of the nail that is no longer attached to the nail bed is called the free edge. Exposure to air brings a subtle chemical reaction in the free edge and changes the nail plate to an opaque white. The tough skin that curves downward from the plate at the free edge is called hyponychium. The tiny crevice between the free edge and the hyponychium is called the distal groove (Elewski; Nathan).

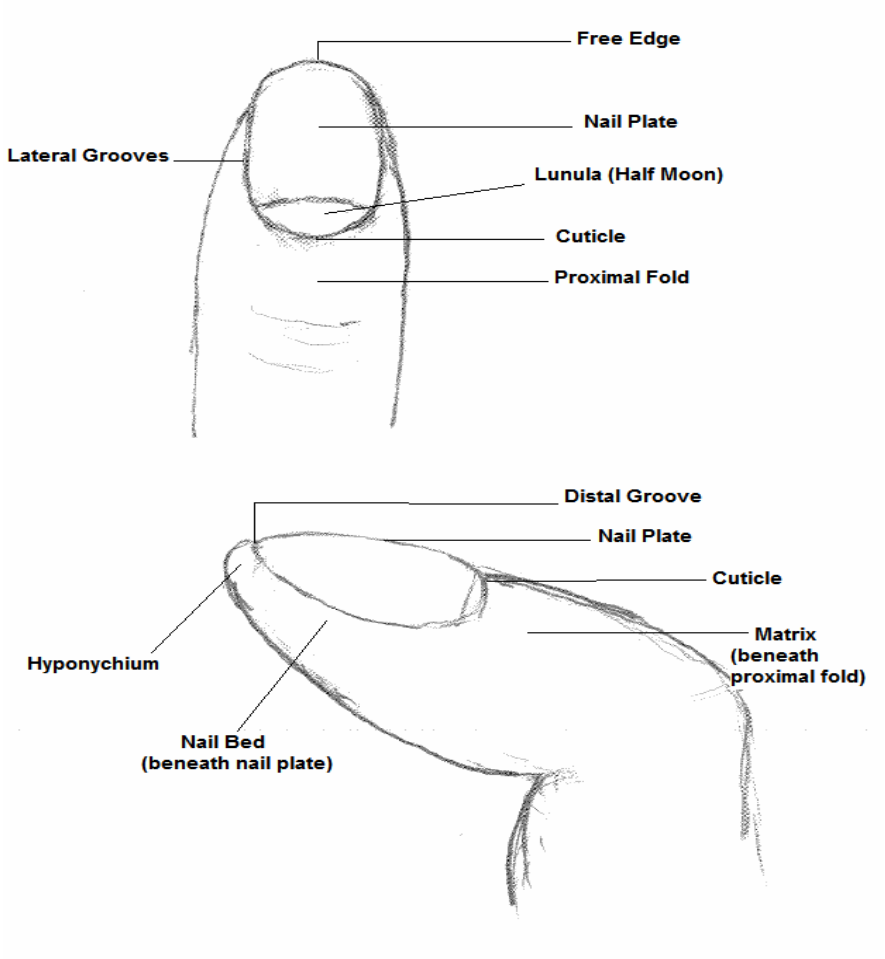

Figure 1. Nail anatomy as shown from dorsal (top) and lateral (bottom) views.

The nail plate is hard but flexible, with a convex external surface. It is created by a group of highly specialized cells, called onychocytes, in the matrix. The onychocytes constantly divide and produce keratin, then undergo a terminal transformation to lose their nuclei and form extremely tight bonds with each other as a nail plate. A new nail plate pushes the old one further away from the matrix and covers the nail bed (Elewski, 1998; Nathan, 2006).

By adhering tightly to the nail plate, the cuticle functions as a protective seal to the nail matrix. Similarly, hyponychium, distal, and lateral grooves serve to seal off the

nail unit from pathogens and toxins. The integrity of this structure is essential in preventing any fungal invasion because well-aged keratin is the ideal target for fungus, especially dermatophytes like *Trichophyton rubrum* (Elewski, 1998; Nathan, 2006). However, the nail becomes more fragile with age. The structure can also be altered by injury, certain medical conditions, or long-term exposure to dampness. The altered nail integrity provides the opportunity for fungal infection.

The nail is grown from the matrix and then pushed toward the nail free edge (Elewski, 1998). The rate of mitosis in matrix cells determines the nail growth rate. The rate can also be influenced by age, health, nail length, and nutritional status (Nathan, 2006). The average toenail grows 1 mm per month and the average fingernail 2 to 3 mm per month (Geyer, Onumah, Uyttendaele, & Scher, 2004). It can take 12 to 18 months to grow a complete new great toenail and about 6 months to replace a fingernail.

Causative Agents

Nail fungal infections are mainly due to dermatophyte, yeast, or nondermatophyte molds (Effendy, Lecha, Chauvin, Chiacchio, & Baran, 2005). They may occur as primary diseases caused by pathogens invading the healthy nail plate, or as secondary infections of nails with a preexisting disease.

Dermatophytes belong to “a homogeneous group of keratophilic fungi” (Effendy et al., 2005, p. 9). They have the ability to utilize keratin as a nutrient source because they possess several enzymes, such as acid proteinases, elastase, keratinases, and other proteinases (Torres-Rodríguez & López-Jodra, 2000). They have developed a dependency on human or animal infection for the survival and dissemination of their

species. The most frequently isolated pathogen from toe onychomycosis is *Trichophyton rubrum*, followed by *Trichophyton mentagrophytes* and *Epidermatophyton floccosum.* They are responsible for over 70% of all cases (Faergemann & Baran, 2003; Foster, Ghannoum, & Elewski, 2004; Haneke & Roseeuw, 1999; Romano, Gianni, & Difonzo, 2005). Under the microscope, the most reliable identification characters for dermatophyte are the microconidia (one-celled and round or pyriform in shape) and/or macroconidia (two- or more-celled, smooth-, thin- or thick-walled, and cigar shaped; Suhonen, Dawber, & Ellis, 1999, pp 3-18). The growth rate of *Trichophyton* colonies is slow to moderately rapid.

Humans, especially in the toe web spaces, are the major reservoir for these fungi (Buchanan, 2006; Tosti, Hay, & Arenas-Guzman, 2005). Infections by dermatophytes are usually caused by the shedding of skin containing viable infectious hyphal elements of the fungus. Desquamated skin may remain infectious in the environment for months or years. Therefore, transmission may take place by indirect contact long after the infective debris has been shed. Substrates like carpet and matting that hold desquamated skin make excellent vectors. Thus, transmission of dermatophytes is usually via the feet through damp floor surfaces and less frequently via direct person-to-person contact (Buchanan; Tosti, Hay, & Arenas-Guzman). Infections of toenail are often chronic and may remain subclinical for many years, only to become apparent when spread to another site, usually the groin or skin.

Yeasts “are true fungi that lack hyphae and account for 5.6% of cases” (Effendy et al., 2005, p. 2). Pathogens are mainly *Candida* species with *Candida albicans* as the

most common isolate. *Candida* is a member of normal flora of skin, mouth, vagina, and stool. Being a pathogen and a colonizer, *Candida albicans* is also found in the environment, particularly on leaves, flowers, water, and soil. Under the microscope, it is characterized by globs to elongate yeast-like cells (Suhonen et al., 1999, p. 18). Yeasts infect more fingernails than toenails. Surveillance data from the United States between 1999 and 2002 showed that *Candida* species counted for over 70% of fingernail onychomycosis but only less than 7% of toenail onychomycosis (Foster et al., 2004). The rate of onychomycosis caused by yeasts was 11% in a European study (Haneke & Roseeuw, 1999).

Molds (nondermatophytic fungi) account for 2.3% to 11% of onychomycosis cases (Buchanan, 2006; Foster et al., 2004; Haneke & Roseeuw, 1999). One of the most commonly isolated molds is *Scopulariopsis brevicaulis* (Effendy et al., 2005), which is a weakly keratinolytic filamentous (a hyaline) fungus that inhabits soil, plant material, feathers, and insects. Molds are distributed worldwide. While they are commonly considered contaminants, they also cause infections in immunocompromised patients and in the elderly with damaged nail integrity (Effendy et al.).

Yeasts and molds can be transmitted through direct contact with infected people, animals, soil, or surfaces. Superficial infections, particularly of the toenails and the feet, also act as reservoirs of the organisms and can spread to other areas of the body and other individuals simply by sharing a nail file or clippers. The prevalence of different pathogens also depends on factors such as climate, geography, migration, and nail care (Buchanan, 2006). Though a single pathogen has caused the majority of onychomycosis

cases, the infections of mixed pathogens has been reported as high as 16% (Koussidou et al., 2000).

Clinical Aspects of Disease

When fungi invade a nail, the nail becomes a safe place for the fungi and protects them while they grow in the nail bed and the nail plate. The fungi eat keratin and cause the nail to become thickened and yellow. The organic waste materials build up under the nail, thus forcing the nail to rise up from the nail bed. Therefore, "onychomycosis is characterized by hyperkeratosis (hypertrophy of the skin/nail) of the nail bed, yellow to brownish discoloration of the nail plate, onycholysis (separation of the nail from nail bed along the lateral margins), and paronychial inflammation" (Werschler, Bondar & Armstrong, 2004, p. 146).

There are five clinical presentations of onychomycosis (Baran & Kaoukhov, 2005), according to the site and the route of the infection (Hay, 2005):

1. Distal lateral subungual onychomycosis (DLSO): Stemming from the nail free edge hyponychium, the fungus affects the nail bed and the nail plate up to the lateral margins of the nail. The infection can gradually reach the matrix. As the disease progresses, the nail plate undergoes clinical changes such as thickening and lifting of the nail bed, which results in onycholysis and a yellowish discoloration (Baran & Kaoukhov, 2005; Nathan, 2006, Seebacher et al., 2007).

2. Endonyx onychomycosis (EO): Stemming from the trimmed nail edge, the fungus directly invades the core of nail plate. Both superficial and deep layers of the nail plate are infected. The infected nail appears to have a white creamy discoloration and

may produce a longitudinal splitting of the nail plate. *T. soudanense* and *T. violaceum* are the common causative organisms. This is a relatively new category from a more comprehensive classification scheme (Baran & Kaoukhov, 2005; Gupta, 2000). Previously, DLSO and EO were considered as one category under the distal subungual infection (Faergemann & Baran, 2003).

3. Proximal subungual onychomycosis (PSO): Stemming from the cuticle, the fungus, usually *Trichophyton rubrum*, attacks the proximal nail bed, nail plate, and then enters the newly formed nail (Nathan, 2006). Yellow or white patches appear around the nail lunula (Hay, 2005). This type of disease is common in immunocompromised persons including those with HIV/AIDS. It may, in fact, serve as an indicator of HIV infection (Faergemann & Baran, 2003; Ravnborg, Baastrup, & Svejgaard, 1998). Paronychia may be associated with secondary PSO, which is due to some molds or *Candida*.

4. White superficial onychomycosis (WSO): The fungus directly targets the upper layers of the nail plate and produces chalky white or brown patches on the nail surface. Eventually, the nail becomes soft and crumby (Baran & Kaoukhov, 2005; Nathan, 2006).

5. Total dystrophic onychomycosis (TDO). The entire nail plate, even the matrix, is infected and results in complete destruction of the nail apparatus. According to some researchers, TDO can be “considered as a combination of all infections” (Faergemann & Baran, 2003, p. 2). There are two types of TDO: primary and secondary. Primary TDO represents simultaneous involvement of all tissues of the nail apparatus. Secondary TDO is the result of other destructive nail dystrophy (i.e., DLSO, PSO, WSO or EO). Both primary and secondary total dystrophic onychomycosis are difficult to treat and often

require combination therapy. Surgical removal of the nail might be considered as a last option (Buchannan, 2006).

The most common type of fungal nail infections is DLSO. PSO is the least common form of onychomycosis and is 10 times more frequent in toenails than fingernails (Nathan, 2006). WSO, representing about 10% of all cases (Baran & Kaoukhov, 2005), is also primarily seen in the toenail.

It should be noted that two or more nails are commonly affected at the same time. On average, 5.5 fingernails or 4.5 toenails were affected according to an Icelandic study (Sigurgeirsson, Steingrimsson, & Sveinsdottir, 2002).

Diagnosis

Clinical examination and mycological testing play the most important roles in detecting onychomycosis. Medical history of the fungal infection and clinical signs are important parts of the diagnosis. The most common clinical signs found among 37,397 clinically diagnosed patients in Europe and East Asia were discoloration and hyperkeratosis. The prevalence for each sign was about 54% (Haneke & Roseeuw, 1999). The important medical histories from a survey of 209 patients were tinea pedis in previous year and scaling on the soles or palms (Fletcher, Hay, & Smeeton, 2004).

However, mycological results from both microscopy and culture are required for disease confirmation (Elewski, 1998; Jaffe, 1998; Seebacher et al., 2007). Since many conditions may mimic the clinical appearance of fungal infection, the clinical examination must differentiate the signs of onychomycosis from possible nonfungal underlying causes such as repeated trauma, psoriasis, lichen planus, local tumors,

vascular disorders, inflammatory diseases, and other disorders (Jaffe; Gupta, & Tu, 2006). It is also essential to determine existence of fungi infection by fungal culture before starting an antifungal treatment (Gupta & Tu). The culture needs to identify both genus and species of the pathogens because different species respond differently to a given antifungal agent (Buchanan, 2006; Scher & Baran, 2003).

Accuracy of mycological results is closely related to the quality of the nail sample (Chauvin, 2005; Elewski, 1998). To obtain a good sample for mycological testing, the nail should be disinfected, then scraped from under the surface or clipped at the infected area so that the entire nail thickness is sampled. The sample site should be selected according to clinical presentation. The most viable hyphae may be found in a hard to reach place. Fungus samples collected from the distal portion may be older and nonviable. A comparison of 194 samples from different types of onychomycosis using the curettage technique showed that the samples from the most proximal parts of affected nail had higher culture sensitivity and detected more types of pathogens (Shemer, Trau, Davidovici, Grunwald, & Amichai, 2007).

The amount of the nail sample should be large enough for both microscopy examination and culture. The sample for microscopy is treated with potassium hydroxide (KOH) to separate the hyphae from keratinocytes as well as kill nonfungal agents, and is then examined directly under the microscope within 20 to 30 minutes of sample collection (Chauvin, 2005). This process is called the KOH test. If hyphal fragments are detected, a fungal culture of the nail sample will be performed to determine the viability of the fungus and identify the fungal species.

Microscopy and culture may have as high as a 30% false negative result (Scher & Baran, 2003) mainly because of poor nail sample collection. New fungi stains and calcofluor floresces have been used by some to increase microscopy sensitivity (Hay, 2005). Histological analysis and polymerase chain reaction have been evaluated as diagnostic tools (Gianni et al., 2001). However, "mycological examination remains the gold standard technique as it provides the most information at reasonable costs with little inconvenience to the patient" (Chauvin, 2005, p. 20).

Epidemiology

Prevalence of onychomycosis varied according to study designs. The United States Health and Nutrition Examination Survey of 20,749 individuals between 1971 and 1974 showed a prevalence of nail mycosis of 2.18% (Johnson & Roberts, 1977). About 8.7% of participants who visited a dermatology clinic in Cleveland, Ohio in 1997 were confirmed with onychomycosis (Elewski & Charif, 1997). The prevalence in the United Kingdom in early 1990 was about 2.7 % (Roberts, 1992). However, the first large survey in Europe between 1997 and 1998 reported the prevalence rate of onychomycosis at over 26%, much higher than expected (Haneke & Roseeuw, 1999). The incidence of onychomycosis, mainly from *T. rubrum,* increased from 55.2% in 1999 to 78.8% in 2002 when analyzing 15,381 specimens collected between 1999 and 2002 across the United States by a mycology laboratory in Cleveland, Ohio (Foster et al., 2004). Some researchers attributed the upward trend to factors such as climate, migration, age, gender, obesity, sports, swimming, religious practices, certain professions, overseas travel, genetic disposition, concomitant disease, and even fashions (Effendy et al., 2005;

Elewski, 2000; Gupta, Cooper, et al., 2004; Pierard, Arrese, Pierard-Franchimont, & Quatresooz, 2006). Increasing vigilance among health care workers and patients may also play a role in the reporting of a higher prevalence.

Certain populations might be more susceptible to fungal infections because of some predisposing factors. Identified high risk populations were the elderly, patients with peripheral arterial disease, diabetes mellitus, immunodeficiency diseases, immunocompromised patients, and psoriasis suffers (Baran & Kaoukhov, 2005; Buchanan, 2006; Dahdah & Scher, 2006; Gupta, Cooper, et al., 2004; Haneke & Roseeuw, 1999, Jaffe, 1998; Tosti et al., 2005).

Age

Onychomycosis does not affect all age groups equally. Prevalence and risk of onychomycosis increase with advancing age (Haneke & Roseeuw, 1999; Roberts, 1992; Svejgaard & Nilsson, 2004). In a North American study, the prevalence of onychomycosis steadily increased with each decade of age: 0% for age group 0 to 10 years, 0.7% for > 10 to 20 years, 3.6% for > 20 to 30 years, 5.6% for > 30 to 40 years, 9.8% for > 40 to 50 years, 13.7% for > 50 to 60 years, 14.1% for > 60 to 70 years, 21.7% for > 70 to 80 years, and 26.9% for those greater than 80 years old (Gupta, 2000). European and East Asian surveys revealed that more than 50% of patients who were 65 years old or older and had suspected foot disease were diagnosed as having onychomycosis (Haneke & Roseeuw). The odds of having onychomycosis among individuals 50 years old or older were 2.71 times that of the younger age group (Sigurgeirsson & Steingrimsson, 2004).

However, a few studies showed that the peak prevalence was in the less-than-60-years-old age group: the highest rate of 25% between age 30 and 40 in Hong Kong (Kam, Au, Wong, & Cheung, 1997), the highest rates in the 50-years-old age group for both males and females in Greece (Koussidou et al., 2002), and a peak in 45 to 55-years-old age group in Italy (Romano et al., 2005). These studies were conducted with patients who sought medical help for suspected fungal infections. The results might not represent the true prevalence in the general population because of potential selection bias. Some onychomycosis patients, especially among the elderly, might be less likely to seek medical help. The ratio of estimated prevalence (REP) has been recommended to present the results because it uses the general population as a reference. Using REP, the pattern of a peak seen in younger age groups was transformed to show an obvious increasing trend with aging for any type of onychomycosis, particularly after the age of 70 (Pierard et al., 2006). REP = (Onychomycosis per decade of age × total population)/(100 × citizen in a defined period of age).

Children have a lower percentage of onychomycosis. The prevalence of onychomycosis in children has been reported between 0% and 2.6%, with a mean of 0.3%, from different parts of the world (Gupta et al., 1997). However, among 500 children and adolescents who sought medical help with superficial mycosis in Poland, nearly 20% of the cases were confirmed to have onychomycosis (Lange, Roszkiewicz, Szczerkowska-Dobosz, Jasie-Walikowska, & Bykowska, 2006). An even higher rate (30.7%) of confirmed onychomycosis was reported among children less than 17 years old who had nail diseases and provided nail samples to dermatologists between January 1,

1990 and December 31, 1999 in Brussels, Belgium (Lateur, Mortaki, & Andre, 2003). The youngest child was only 6 weeks old. The toenail was twice as likely to be infected as the fingernail among children less than 7 years old. Again these results may not represent the prevalence in the general population.

Individuals with Down syndrome were also more likely to have fungal nail infections (Barankin & Guenther, as cited in Gupta & Skinner, 2004). The prevalence of onychomycosis has also been found to be greater in human immunodeficiency virus (HIV)-infected children (Pros, as cited in Gupta & Skinner). However, no actual data were provided by Gupta and Skinner.

Reasons for onychomycosis to occur more frequently in the older age groups may include the following, according to Gupta (2000), Jain and Sehgal (2000), Lateur et al. (2003), and Tosti et al. (2005):

Adults have a slower nail growth rate and larger areas of nail unit conducive for a fungal invasion. Cumulative nail traumas experienced during adulthood may also increase the risk of fungal infection. For example, ill-fitting shoes or sporting activities may damage the physiological seal at the hyponychium. Older individuals become more susceptible to fungal infections because of reduced immune competence with aging, increased fragility in the nail structure, the presence of peripheral vascular disease, and occurrence of multiple episodes of the tinea pedis. Tinea pedis has been observed to precede the development of onychomycosis in many instances.

Goulden and Goodfield (1997) cited that nail growth decreases by 0.5% per year. However, they did not find slow growth to be a predisposing factor for onychomycosis when they compared nail growth rates between 36 patients and 22 controls.

Sex

There was no uniform report on prevalence of the disease between the sexes for onychomycosis. Though men are considered to have a higher risk for onychomycosis than women (Gupta, Gupta, et al., 2000; Sigurgeirsson & Steingrimsson, 2004), the results varied according to study designs, methods of data collection, and size of the study. Effendy et al. (2005) reported that only 45.2% of patients were men in a survey of 44,972 onychomycosis patients from 16 different countries. The prevalence of 1.8% in women and 0.8% in men was cited by Jain and Sehgal (2000). A survey of 43,914 participants in East Asia showed that more women suffered from onychomycosis (43%) than men (39%) (Haneke & Roseeuw, 1999), while a higher prevalence of clinically diagnosed onychomycosis in men than women were seen from the European study of 13,695 participants and the European survey of 22,760 participants in the same project (Haneke & Roseeuw). The reported prevalence rates from the study and the survey were 26% and 27% for men versus 21% and 25% for women, respectively.

Race

Onychomycosis affects persons of all races (Blumgerg, 2005). Epidemiological studies have been conducted in various parts of the world, though no study was conducted to directly assess race as a risk factor. All races are considered susceptible to the disease. Because the disease has a multifactorial etiology (Sigurgeirsson &

Steingrimsson, 2004), other factors could confound any differences seen between races or between studies done in different parts of the world.

Diabetes

Diabetes mellitus is a significant risk factor for onychomycosis because of its effects on microcirculation. Gupta et al. (1998) evaluated 550 diabetic patients from Canada and the United States and found that mycologically confirmed toenail onychomycosis was present in 26% of study participants. The occurrence of onychomycosis was significantly related to aging and the male gender (both $p < 0.0001$). The odds of having toenail onychomycosis among diabetics were 2.77 times higher than normal individuals after controlling for age and sex. The 95% confidence interval (CI) for the odds ratio (OR) is between 2.15 and 3.57. The study also identified that family history of onychomycosis ($p = 0.0001$), concurrent intake of immunosuppressive therapy ($p = 0.035$), and some of peripheral vascular diseases ($p < 0.023$) were significant predictors for onychomycosis in the diabetic population.

Psoriasis

Psoriasis commonly involves nails. Larsen, Haedersdal and Svejgaard (2003) investigated the occurrence of onychomycosis among 79 patients with psoriasis versus 142 patients with other skin diseases in a 15-month period and found that psoriasis patients had a significantly higher incidence of nail abnormality than nonpsoriatics (82.3% vs. 37.3%, $p < 0.01$). After microscopy and culture of the scrapings from clinically abnormal nails (both fingernails and toenails). 21.5% (17 / 79) of psoriasis patients were confirmed to have onychomycosis as compared to 12.7% (18 / 142) of

nonpsoriasis patients. However, the difference was not significant ($p = 0.18$). Psoriasis patients also had significantly more severe toenail infection than patients with other skin diseases ($p < 0.01$).

Sigurgeirsson and Steingrimsson (2004) reported an odds ratio of 2.44 (95% CI: 1.61–3.72) for psoriasis patients compared to nonpsoriasis patients.

Clinical signs of psoriasis and onychomycosis often overlap and present difficulty in distinguishing between them. Both diseases may coexist in some psoriatic patients. Though it has yet to be confirmed, some researchers suggest that "dystrophy nails in psoriatic patients lose their natural preventing barrier and therefore are more predisposed to fungal infection" (Szepietowski & Salomon, 2007, p. 438).

HIV Infection

HIV infection is another major factor in contracting fungal nail infections. In a controlled study, more than 30% of patients infected with HIV were found to have onychomycosis, compared with 12.6% of controls (Cribier, as cited in Cribier & Bakshi, 2004). The overall prevalence of onychomycosis among 400 Canadians and 100 Brazilians infected with HIV was 23.2% (Gupta, Taborda, et al., 2000). More specifically, the prevalence rates in Canadians and Brazilians were 24% and 20%, respectively. The predominant causative organisms were dematophytes. The predisposing factors include a CD4 count of approximately 370, a positive family history of onychomycosis, a history of tinea pedis, and walking barefoot around pools.

In a survey of 250 HIV patients in India (Surjushe et al., 2007), 60 (24%) had untreated onychomycosis. Among them, 38 (63.33%) had toenail onychomycosis, 12

(20%) had fingernail onychomycosis while 10 (16.66%) had involvement in both the toe and finger. Nondermatophyte molds were isolated in 19 (31.66%) patients while dermatophytes were only isolated in 13 (21.66%) patients. Eleven of 13 dermatophytes were identified as *Trichophyton rubrum.* Others identified included *Trichophyton mentagrophytes*. Most isolates for nondermatophytes were *Candida* (*n* = 12) and *Aspergillus niger* (*n* = 3). The most common clinical type was total dystrophic onychomycosis. Though the survey did not include a comparison group, the overall rate is similar to that found by Gupta, Taborda, et al. (2000).

Transplant Patients

Since transplant patients require long-term immunosuppressant use, they are also at risk for onychomycosis. Virgili, Zampino, and Mantovani (2002) cited a prevalence of 12.3% among transplant patients. They also stated that the frequency and severity of clinical findings increased as the duration of immunosuppression use increased. The most common type of clinical presentation is proximal subungual onychomycosis (PSO). Similar to HIV infection, PSO is a clinical marker for immunosuppresion.

Geography

Onychomycosis exists worldwide. Reported prevalence rates vary from country to country. The difference may stem from study design or from data quality. However, Kam et al. (1997) considered that climatic conditions may also affect the growth and spread of fungi, due to an observed seasonal variation of the occurrence of dermytophytes and yeasts as well as a seasonal pattern ascribed to the cases studied in the subtropical climate of Hong Kong.

Using a self-administered questionnaire and self-diagnosis from a set of photographs that depict different severities of onychomycosis, a survey of 9,332 people in England in the early part of 1990 found a prevalence of 2.73% (Roberts, 1992). The same method was used to interview 10,007 people in Spain by telephone after sample photographs had been mailed to the potential study participants between 1992 and 1993 (Sais, Juegla, & Peyri., 1995). The survey reported a prevalence of 2.6%. Another survey of 1,000 healthy volunteers aged 15 or older between April 1997 and December 1997 in Madrid produced a prevalence of 3.1% confirmed onychomycosis (95% CI: 2.12–4.38) (Palacio, Cuetara, Garau, & Perea, 2006). A study of 1,832 volunteers who visited 12 primary care doctor offices in North America between June 1997 and May 1998 found that 13.8% of the volunteers either had positive mycology, positive culture, or both (Ghannoum et al., 2000). A Finnish study reported a prevalence of 8.4% among study participants examined by a dermatologist (Heikkila & Stubb, 1995).

Population studies conducted by Sigurgeirsson, Steingrimsson and Sveinsdottir (2002) estimated that the prevalence of positive mycology in the Icelandic population was 11.1%.

The prevalence of onychomycosis in Denmark was estimated at 16.5%. Among those studied, 52% were males and 48% were females (Svegjaard & Nilsson, 2004).

The signs of onychomycosis were seen in 2 out of 10 European patients who had visited doctors' offices. It increased to 4 out of 10 among patients with reported foot pathology by the physicians. The prevalence of onychomycosis was similar between

European and East Asian populations, with 23% and 22% of the total population, respectively (Haneke & Roseeuw, 1999).

Genetic Factors

Faergemann, Correia, Nowicki, and Ro (2005) stated that “onychomycosis seems to be more common in some families (children and spouses) than others” (p. 17). Though this may be the result of intrafamilial transmission, a genetic role can not be totally excluded from the reason for a clustered distribution because of the prevalence of *Trichophyton rubrum* infection among parents and children is higher than the prevalence among spouses. This may indicate that *T. rubrum* may prefer certain individuals. A pedigree constructed by Zaias (as cited in Faergemann et al., 2005) showed that all affected children had at least one parent with distal subungual onychomycosis, which is consistent with an autosomal-dominant mode of transmission.

Faergemann et al. (2005) also cited a study of human leukocyte antigens (HLA) among *T. rubrum* onychomycosis patients in a Jewish population. It found that HLA–DR52 only existed in all onychomycosis patients, whereas HLA–DR53 only presented in all controls. This may suggest that HLA–DR53 plays a key role in protecting against *T. rubrum* onychomycosis in this population. Of course, more studies would be needed to confirm the finding.

Sigurgeirsson and Steingrimsson (2004) found a more than doubled risk for the disease if parents had onychomycosis (OR = 2.59; 95% CI: 1.89–3.53), or children had onychomycosis (OR = 3.48; 95% CI: 2.05–5.88). However, the risk of onychomycosis

was the same between those having spouse (OR = 2.53; 95% CI: 1.72–3.72) and having parent as a cosufferer.

Swimming

Swimming has been found to favor the occurrence of foot mycoses. Onychomycosis of the toenail is at least three times more prevalent in swimmers than in the rest of the population in Iceland (Sigurgerisson & Steingrimsson, 2004).

Other Risk Factors

Development of onychomycosis is also affected by other factors. Gupta, Gupta, et al. (2000) reported that the number of cigarettes consumed per day was an independent predictor of the disease. More patients in the heavy smoker group had onychomycosis than the lighter smokers. The odds ratio was 1.87 (95% CI: 1.1–1.3) after adjusting for age, sex, and peripheral artery disease. The study also found that peripheral artery disease was another independent predictor. Patients with peripheral artery disease (as measured by ankle-brachial index) were more likely to have onychomycosis (OR = 3.3, 95% CI: 1.0–6.5). The odds ratio increased to 4.8 after controlling for smoking status. There appears to be an interaction between these two risk factors since the crude OR differs from adjusted OR by 30%. However, the authors did not explore it further.

A history of cancer, tinea pedis interdigitalis, and the moccasin form of tinea pedis have also been linked to an increased risk of onychomycosis, with odds ratios of 3.44, 3.93, and 4.26, respectively (Sigurgerisson & Steingrimsson, 2004).

Torres-Rodríguez and López-Jodra (2000) also presented some risk factors related to physical and chemical aggressions. The integrity of the nail and surrounding skin can

be damaged by physical or chemical factors and thus facilitate the penetration of different fungi. The infection may occur as a result of occupation, personal habits, and other considerations. The risk of onychomycosis may be higher for agricultural, construction, or iron workers, as well as for bar and restaurant staff, as people in these occupations are constantly exposed to microtraumas or moist environments. The risk may also be increased for cleaning employees who do not use adequate gloves and have their hands wet for long periods of time. Maceration of their skin and nails may be further worsened by the use of detergents and caustic substances. Fashion may affect the risk of fungal infection as well; nail structure can be compromised with improper footwear. This may occur when people wear shoes with sharply pointed toes, shoes that are excessively closed, or high heels that displace the body weight toward the toes. Extreme “care of the nails” through manicure can also expose a person to a higher risk of the proximal fungal infection because of elimination of the cuticle and microtraumas caused by the instruments. Personal habits such nail biting or finger sucking also could expose people to fungal infection.

Sigurgeirsson and Steingrimsson (2004) suggested that patients with asthma, urticaria, and angioedema were more likely to have onychomycosis. However, it is not entirely clear how they are related. Fungal infection may cause an allergic reaction. On the other hand, patients with these allergic disorders may be more prone to onychomycosis.

Jain and Sehgal **(**2000) also found a relationship between different religions to occurrence of infection. For example, *Candida* infection usually involves the fingernails.

However, it occurs more on the toenails in Muslims. One possible explanation is that fixed rituals requiring Muslims to wash their feet five times a day prior to prayer.

Treatment

Though onychomycosis has a high prevalence and could cause serious medical problems if left untreated, many sufferers do not take it seriously. One survey found that 43% of patients did not seek medical advice and 25% were never treated (Jain & Sehgal, 2000). Because a long course of treatment is required, it has been a challenge for both physicians and patients to achieve clinical efficacy.

Efficacy of treatment is assessed by mycological cure, clinical cure, and complete cure achieved about 48–52 weeks after initiation of treatment. Mycological cure is defined as having achieved negative results for both KOH testing and mycological culture. Clinical cure is defined as complete clearance of a diseased appearance from the nail. Complete cure is achieved when a patient has achieved both mycological cure and clinical cure.

It is very rare to have a spontaneous resolution of onychomycosis. The current treatment options include systemic, topical, or mechanical therapies. Systemic antifungal agents are often considered to be the first line of treatment. Nail removal is considered only when there is a significant morbidity or treatment failure.

Treatment success requires a correct diagnosis because treatment efficacy varies by causative organisms (Roberts et al., 2003). Severity of nail infection affects the choice of treatment as well. When a nail matrix is infected, the choice of treatment is different from cases without matrix involvement. Topical treatment such as nail lacquer has been

recommended to treat cases without an infected matrix, whereas oral or combination treatments (such as oral plus topical) are recommended for cases with an infected matrix (Effendy et al., 2005).

Topical treatment usually requires daily applications for up to 48 weeks. Though it can minimize the systemic exposure of the drug, its efficacy rate is generally lower. The reported complete cure rate for Ciclopirox, the topical medication currently available in the U.S. market, is between 5.5% and 8.5% after daily application for 48 weeks (Aventis Pharmaceutical, 2003). The special challenge for topical treatment arises from the nail anatomy itself: nail keratin is not easily permeated, thus topical drugs are restricted from reaching infectious organisms. Topical drugs might also be easily removed by washing or wiping. Therefore, it is often difficult to maintain effective drug concentrations in the nail (Baran & Kaoukhov, 2005).

Mechanical removal of the nail is not widely used because the procedure does not improve the cure significantly. Combinations of surgical nail avulsion and topical treatment failed to show improved efficacy in a randomized clinical trial of 40 patients in a four-way comparison (Grover, Bansal, Nanda, Reddy, & Kumar, 2007).

Systemic therapy has one of the highest success rates in the treatment of onychomycosis. First-line agents, such as terbinafine and itraconazole, have been reported to have mycological cure rates in toenail onychomycosis as high as 80% and 86%, respectively. However, a complete cure was only achieved in 30–50% of patients treated with terbinafine, and in 25–40% of patients treated with itraconazole (Baran &

Kaoukhov, 2005). The standard treatment duration for oral antifungal agents is daily dosing for up to 12 weeks.

Various combination therapies have been tested. Though the success rates varied from trial to trial, there appeared to be an improvement in treatment outcome (Olafsson, Sigurgeirsson, & Baran, 2003; Jennings, Pollak, Harkless, Kianifard, & Tavakkol, 2006).

Gupta and Tu (2006) also recommend recognizing both nail and patient characteristics when planning a treatment strategy. Though it is considered off-label use, they suggest that booster therapy (1 week for itraconazole and 4 weeks for terbinafine) may be considered at 6 to 9 months after the initiation of a standard course of oral treatment: if the diseased area has < 50% reduction in the initial nail plate area, or the diseased nail is > 2 mm thickness, or culture results continue to be positive, or > 75% of the nail plate is involved. However, this strategy seems to come from empirical evidence instead of well designed study findings. They do not mention how big an improvement would be expected with the booster treatment.

Therefore, the treatment strategy will ultimately be a balance between using an effective agent, easy application, safety considerations, and treatment duration.

Many studies assessed the efficacy of antifungal treatment (Drake et al., 1997, Sigurgeirsson et al., 2006; Tang, Chong, Leung, Ho, & Wong, 2000; Warshaw et al., 2005). Some studies assessed predicting factors related to the treatment outcome (Sigurgeirsson, Paul, Curran, and Evans, 2002). Among these studies, commonly examined factors were age, sex, extent of the disease, infection in the nail matrix area, treatment history, and duration of the infection.

Sigurgeirsson, Paul, et al. (2002) studied factors associated with mycological cure 72 weeks after starting a full course of treatment among 496 patients participating in a randomized clinical trial. They concluded that the results of mycological culture at Week 12 and 24 and KOH test at Week 24 can help with early identification of patients who would fail the conventional systemic oral antifungal treatment. A negative culture at either Week 12 or 24 was significantly associated with continued mycological cure at Week 72 ($p < 0.05$). The percentage change in infected nail area at Week 24 after initiating treatment was positive, but was small in the magnitude associated with mycological cure at Week 72.

Disease severity, especially infection of matrix, may be a factor for failure of achieving a complete cure. When the nail matrix is involved, the onychocytes may be destroyed so that it will become much more difficult for this type of patient to grow a completely new healthy nail. However, matrix involvement is often difficult to assess because nail appearance is not a good indicator for the infection of the matrix. Therefore, its value as a treatment predictor is often limited.

Treatment noncompliance may also be a factor contributing to treatment failure. Noncompliance includes failure to follow a dose regimen, such as skipping doses, underdosing, or early termination of treatment.

Other factors that may indicate a poor treatment outcome include lateral nail disease and certain types of nail morphology such as notable streaks (Scher & Baran, 2003). Treatment outcome may also be affected by concomitant disease or treatment, or drug-resistant strains of disease.

Recurrence-Related Factors

Treatment failure may also be attributed to reinfection or relapse. Recurrence of onychomycosis is fairly common. Tosti, Piraccini, Stinchi, and Colombo (1998) found that 22.2% of patients experienced a relapse after achieving successful treatment with systemic antifungals. The relapse rate increased from 8.3% at month 12 to 19.4% at month 24 and to 22.2% at month 36.

The risk factors for disease recurrence are similar to those for treatment failure. Scher and Baran (2003) summarized that potential factors for recurrence include age greater than 60 years old, family history, occupation, lifestyle, inherent susceptibility to fungal infection such as two-feet-one-hand syndrome (defined as bilateral plantar tinea pedis, fungal infection of the foot, with coexistent unilateral tinea manuum, fungal infection of the hand), concomitant diseases such as peripheral vascular disease or tinea pedis, early termination of treatment or use of an inappropriate dose. Elderly with arthritis or bone abnormalities may likely have recurrence due to physical trauma.

Also, recurrence may be the result of ineffective treatment. As mentioned by Tosti et al. (2005), there is lack of effective treatment for onychomycosis from molds or nails with notable streaks.

Since a history of tinea pedis has been linked to the onychomycosis, concomitantly treating the tinea pedis and other skin dermatomycoses may help prevent the recurrence of the onychomycosis.

Can Treatment Success Be Predicted Early?

In order to achieve a complete cure (mycological cure and clinical cure) , a new nail must be grown--from proximal to distal--to replace the diseased nail and make it devoid of any further fungal infection. The time required for visible clearance of the infection depends on the rate of nail growth and the type of clinical presentation. Such rates should be relatively consistent within a patient during this limited study time period. Thus, there is a possibility of predicting treatment success based on the rate of healthy nail growth during the early treatment phase.

Some factors have been found to affect nail growth. Onychomycosis had been found to slow down the growth rate, but antifungal treatment could speed nail growth (Geyer et al., 2004). Yu, Kwon, Oh, and Kim (2004) compared the growth rate in one diseased great toenail in one foot versus normal great toenail growth on another foot for the same patient. They found that a diseased toenail had a slower growth rate than an unaffected great toenail if affected area was spread over 50% of the nail. After the affected nail became normal following antifungal treatment, such differences disappeared. So disease severity could affect treatment success by affecting nail growth. It should noted that about 5–10% of severe onychomycosis patients will still have an abnormal nail surface even when the mycological cure is maintained (Hay, 2005).

Can the treatment outcome be predicted by disease features or progress during treatment? Sommer et al. (2003) tried to answer this question in a small study. The authors randomized 35 patients to receive either 125 mg or 250 mg oral terbinafine for 12 weeks. They then assessed the mycological cure and clinical cure at Week 48 in relation

to baseline characteristics such as the length of unaffected nail, hyperkeratosis, onycholysis, presence of a dermatophytoma, and the growth rate of unaffected nail over the course of the study. The study failed to produce any significant predictors. It could be that the study was not properly powered to detect any meaningful difference.

As yet, no study has provided convincing evidence to either prove or disprove the link between the nail growth at early stage of treatment and a complete cure as a final treatment outcome. A study with a large sample size may provide a better and more reliable assessment. Therefore, this proposed study will aim to examine the relationship between nail growth during the study period and the final treatment outcome after a standard course of terbinafine treatment. If there is a positive relationship between the nail growth rate and a complete cure, the study will also explore the best indicator and the earliest time to predict the treatment outcome.

CHAPTER 3:

RESEARCH METHOD

This population-based study was designed to explore the relationship between nail growth patterns during the trial period and the treatment outcome up to 48 weeks after the initiation of treatment. Nail growth patterns were compared between patients who achieved complete cure and patients who failed treatment, with and without adjusting for factors such as age, gender, disease severity, and antifungal treatment history. The treatment pattern is referred to as either the actual length or alternatively as the proportion of total healthy nail grown. It has been postulated that a positive response to treatment will be reflected in the growth of healthy nail along with negative mycological results. This chapter describes the study design, study population and sample size, hypotheses, data analysis, data source, and protection of human subjects.

Research Design

Using only patients treated with the standard oral antifungal agent terbinafine from two identically designed Phase III randomized clinical trials that assessed drug efficacy, two groups were created based on the achievement of complete cure during the trial period: cured or failed. Selected factors at each scheduled trial visit were compared between patients who were cured and patients who failed treatment in order to explore the important factors that may predict the achievement of a complete cure.

There were a total of 998 patients treated with terbinafine in two Phase III global clinical trials. Patients were enrolled in the studies from three continents between September 2002 and October 2002. After a 6-week screening period, patients were

treated for 12 weeks and observed for an additional 36 weeks, making the total trial duration for a patient 54 weeks. The patients were seen by the trial investigators at office visits scheduled for Weeks 4, 8, and 12 during the treatment period, and for Weeks 16, 24, 36, and 48 during the follow-up period. Data gathered at each of these visits included photographs of the nail with required markings, clinical assessment of the nail, mycological testing results, and safety parameters. The primary efficacy endpoint was the achievement of complete cure (both mycological cure and clinical cure) on the target great toenail by Week 48; a dichotomous variable with a yes or no answer. Complete cure was defined as the growth of a completely healthy target great toenail with negative KOH microscopy and negative culture for dermatophytes from the target great toenail sample. The trials were completed in November 2003. Among 998 patients treated with terbinafine, 798 of them completed the trials without committing major protocol violations.

Since the data were gathered under well-controlled clinical trial settings, the quality of data was well suited for quantitative analysis. Independent variables for this research included patient demographics (age, race, sex, baseline body weight, country or trial center), baseline disease characteristics (onycholysis, percentage of nail infected, antifungal treatment history), mycological test results at each scheduled visit, healthy nail growth on the target great toenail at each scheduled visit, and number of days dosed with trial medication regardless of dosing pattern.

The primary efficacy endpoint–complete or incomplete cure–was the dependent variable for the study.

Study Population and Sample

Any trial participant who met all of the following eligibility criteria were selected for this study. These criteria included any patients who:

1. Met the original trial inclusion and exclusion criteria.

2. Had been treated with terbinafine and received 80–120% of the prescribed dose regimen regardless the missing pattern.

3. Had been observed for the entire 48 weeks after the initiation of the treatment.

4. Had provided sufficient measurements of the healthy target great toenail growth (i.e., the researcher needed to have at least the measurements obtained at baseline, Week 12, 16, and 24 visits) during the trial period. Prior to trial randomization, an infected great toenail was identified as the target to monitor the treatment response during the trial. This great toenail was referred as the “target great toenail” or simply called “target toenail”.

The original trial protocol limited the trial participants to those who were 18 years of age or older; had a great toenail diagnosed as onychomycosis from dermatophytes; and had a confirmed growth of the infected great toenail of a minimum of 1 mm during the 6-week screening period, a sign showing that the infected great toenail was capable of regrowth. Though patients with spikes, lateral involvement, and white superficial onychomycosis were included in the trial, such data were not recorded in the database.

The trials also implemented a set of exclusion criteria to minimize factors that could interfere with efficacy assessments or jeopardize patient safety. Patients were excluded if they had received systemic or topic antifungal therapy in a specified time

period prior to screening, or if they had active psoriasis. Patients were also excluded if they had any conditions that could affect compliance with administration of the medication or the absorption, metabolism, or excretion of the trial drug.

The trial was powered to show the noninferiority margin of 10% with 80% power at a 5% significance level. The planned sample size for each trial was 1,250 screened patients, 900 enrolled patients, and 740 evaluable patients. For each trial, 370 patients would be treated with the standard terbinafine treatment.

The original trials aimed to compare the efficacy of two different drugs. The results were published by Sigurgeirsson et al. (2006). However, this study focused only on patients treated with terbinafine. It measured the growth of healthy nail over time, which was omitted from the original trial, and associated growth with the achievement of a complete cure among these patients.

The sample size used for this study was not based on statistical considerations. It was based upon data availability and fulfillment of the study entry criteria.

Data Source and Quality

The original trial data were collected using a validated electronic system that met high industrial standards and regulatory requirements. The data were recorded according to the protocol specifications and were managed by skilled personnel. Data discrepancies were checked and verified. All data points were certified to be complete and accurate by the trial investigators.

Mycology samples were processed through two central mycology laboratories and the results were sent electronically to the sponsor. The database was locked after the data

had been declared to be complete and accurate, then the treatment code was revealed for the analysis.

All data points, except the length of healthy nail growth, were obtained directly from the clinical trial database. Length of clear healthy nail at each visit was measured manually by this researcher from the digitalized photos of the target toenails taken for that visit. Each photo contains a ruler and the markings of all borders that indicate diseased versus healthy areas. The length of healthy nail was the shortest distance in millimeters (mm) from the middle of the proximal nail fold to a horizontal line of the lowest part of the healthy-diseased border (see Figure 2). This was the same definition used by Sommer et al (2003). A divider caliper was used to measure the distance and then compared with the embedded ruler to obtain the length in millimeters. For each patient, the length of the entire target toenail was also measured using the same method to indicate the size of the fully grown target great toenail. The measurements were reviewed by a dermatologist associated with the original clinical trials. These lengths were used to create two variables for the analysis:

1. Length of healthy target toenail regrown. It was defined as the change from baseline to postbaseline in the shortest length of healthy target toenail grown.

2. The proportion of total target toenail length regrown as healthy. It was defined as change from the baseline to postbaseline as the ratio of the length of healthy target toenail regrown over total target toenail length

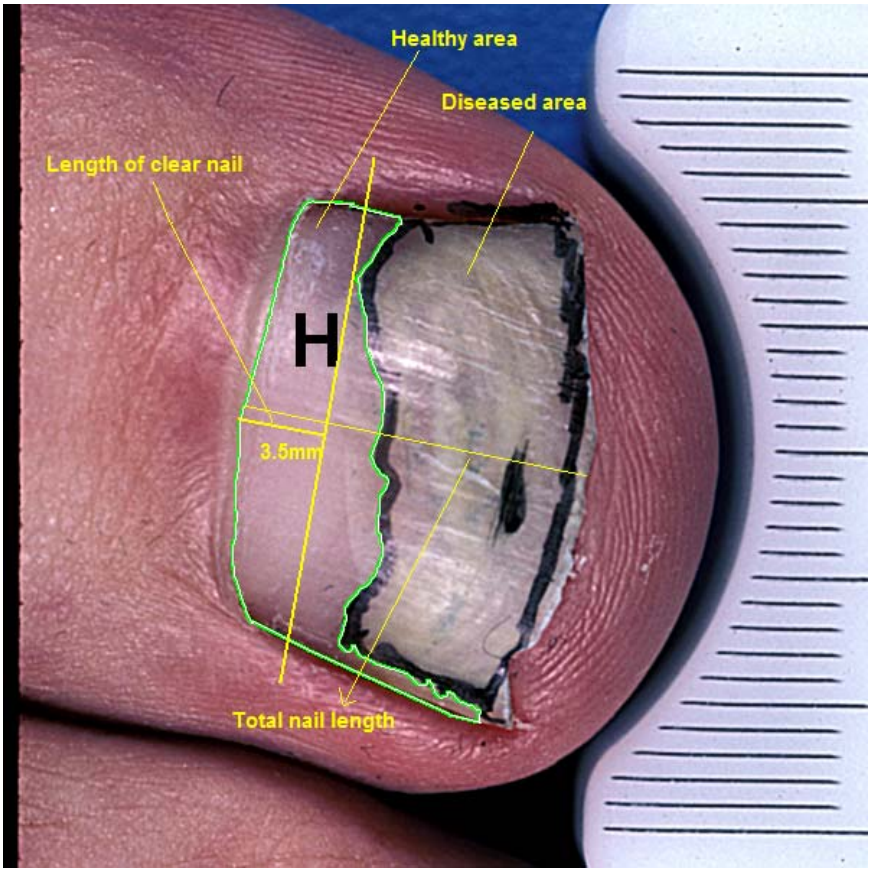

Figure 2. Digitalized photograph with the markings of the diseased and healthy nail areas. It depicts the measurements of the shortest length of healthy nail growth and total full nail length.

A previous study (Sommer et al, 2003) failed to demonstrate the link between the treatment outcome and the healthy nail growth rate. The failure was partially attributed to the small sample size of 35 patients. This research reassessed the relationship using a much larger sample size along with other possible predictors. Specifically, the final treatment outcome–complete cure–was evaluated against (a) length of healthy toenail regrown and (b) proportion of the total toenail regrown as healthy. Each of these variables was tested in its own hypotheses as specified below.

Hypotheses

First Hypothesis

What is the association between final treatment outcome and the length of healthy nail regrown during trial period?

Null Hypothesis: There is no association between the achievement of complete cure and change in the length of healthy nail growth at any point in time during the 48-week period.

Alternative Hypothesis: There is an association between the achievement of complete cure and change in the length of healthy nail growth during the 48-week period.

The assumption was that if the nail grows uniformly and pushes the nail evenly through the nail bed, the change in healthy nail length will reflect the time needed to grow a completely healthy new nail. The shortest distance between the proximal nail fold and healthy-disease border would require the longest time to replace the diseased nail and should be a good predictor of the final treatment outcome.

Second Hypothesis

What is the association between the final treatment outcome and the proportion of total nail regrown as healthy over the trial period?

Null Hypothesis: There is no association between the achievement of complete cure and the change in the percentage of total full nail length grown as healthy at any point in time during the 48-week period.

Alternative Hypothesis: There is an association between the achievement of complete cure and the change in the percentage of total full nail length grown as healthy at any point in time during the 48-week period.

Since healthy nail length alone does not take into account nail size and the variable amount of time needed to grow a different size of new nail, the length of healthy new nail expressed as the proportion of total full nail length may be a better reflection of the time associated with achievement of the complete cure. Also, the study would identify the earliest point in time at which the treatment outcome could be predicted by each of the variables.

Data Analysis

Descriptive statistics were used to describe the study population by final treatment outcome. Statistics for continuous variables were total sample, mean, median, standard deviation, minimum, and maximum. Statistics for categorical variables were subsample and percentage.

The proposed analyses for this study are summarized in Table 1.

Table 1

Summary of All Proposed Analyses

Topic	Analysis	Statistics
Demographic information	Descriptive analysis.	Continuous variable: *N, M, Mdn, SD,* Range Categorical variables: *n* %
Baseline disease characteristics	Descriptive analysis.	Continuous variable: *N, M, Mdn, SD,*Range Categorical variables: *n* %
Mean change in healthy nail growth from the baseline at each scheduled visit	*t* test	*M, SD, p*-value
Effect of prognostic factors on complete cure	Multivariate Logistic Regression	OR, 95%CI,

The means for the variable of healthy nail regrowth during the trial period were presented in a line plot or a summary table by the treatment outcome. These means were compared by the treatment outcome using a two-sided *t* test at each scheduled visit. The results were evaluated at a 5% significance level.

Also, the associations of the treatment outcome and the healthy nail regrowth variables were assessed using multivariate logistic regressions adjusting for other independent variables. Because the disease affects more in the elderly (> 65 years old) than younger ones (< 40 years old), the age was divided into three groups (< 40, 40–65, > 65). Therefore, two dummy variables for age groups were used in the logistic regression. The logistic regression analysis was done for each scheduled visit. The initial model was the following:

Complete cure (yes/no) = healthy nail regrown parameter at a visit (mm) + KOH at the same visit (negative/positive) + culture at the same visit (negative/positive) + age group 1 (< 40 vs. > 65) + age group 2 (40–65 vs. > 65) + sex (male/female) + percentage of nail infected at baseline (%)+ the history of antifungal treatment (no/yes) + sign of nail onycholysis (no/yes) + length of nail grown at baseline period (mm) + % of expected trial drug were taken (%).

Total nail size was also an independent variable when assessing Hypothesis 1: change in the length of healthy nail from the baseline.

No adjustment was made for multiple hypotheses testing because the main purpose of the research was to explore better predictors for the treatment outcome. For the same purpose, only factors at early phase of the trial would be meaningful to predict the treatment outcome. The key point in time for this prediction would be around Week 12, the end of the treatment period.

The best point in time was selected based on OR for the nail growth. Once the best point was selected, the insignificant variables in the initial model were deleted to produce a final model.

The analysis was done using SAS procedures such as frequency, means, *t* test, and logistic regression in SAS version 8.02.

Protection of Human Subjects

These two clinical trials were designed and implemented in accordance with the most current guidelines available for good clinical practice and applicable regulations for trials on medicinal products in the European Community and United States, and with the

ethical principles specified in the Declaration of Helsinki. The trial was approved by the appropriate Institutional Review Board (IRB) at each trial site. All patients provided written informed consent prior to entering the trial.

Each patient in the original trial was uniquely identified by his or her own trial ID number. The clinical trial data did not contain sufficiently information to identify any participant. Therefore, the participants for this study were considered completely anonymous.

Access rights to the database were granted by the original trial sponsor in writing. The written letter was considered sufficient by Walden University IRB. The construction of the database and analysis commenced after the final approval from the IRB committee (IRB Certification # 07-21-08-0324060).

In line with Walden University's commitment to social change, the study results will be disseminated via publications from the dissertation as abstract and peer-reviewed journal article.

The following section presents the results from the statistical analysis related to the hypotheses testing. The implication of the findings will be discussed afterward.

CHAPTER 4:

RESULTS

A total of 750 patients met the inclusion criteria for this study. Among them, 178 patients achieved complete cures during the course of the trial. This included 23 patients who relapsed at a later stage of the trial period: One patient relapsed at Week 24 after having achieved complete cure at Week 16; 11 patients had complete cure at Week 24 but relapsed at Week 36 ($n = 6$) or Week 48 ($n = 5$); and another 11 patients achieved complete cure at Week 36, but failed to maintain a total healthy nail at Week 48. Since the rate of healthy nail growth was used to predict the achievement of complete cure, the nail growth was only measured before the relapse occurred. This approach was taken under the assumption that the relapse was not associated with baseline risk factors. It was only associated with other factors after the cure was achieved. To assess what factors contributed to the relapse, a future research project will be necessary.

Patients for this study came from 15 countries: 417 (55.6%) patients from the United States; 98 (13.1%) from Iceland; 64 (8.5%) from Germany; 23 (3.0 %) from Guatemala; 21 (2.8%) from Peru; 18 (2.4%) each from Canada, Finland, France, and Slovakia; 15 (2%) from Norway; 11 (1.5%) from Brazil; 10 (1.3%) from Poland; 8 (1%) from Mexico; 6 (0.8%) from Italy; and 5 (0.7%) from Columbia.

As shown in Table 2, the mean age of patients who achieved a complete cure was 6 years younger than patients who failed: 45.7 years old versus 51.7 years old, respectively. The difference was statistically significant ($p < 0.001$). Also, cured patients were more likely to be female, have a lower body weight, and have a smaller body

surface area. Body weight had not been linked to the treatment success in other studies. Caucasian patients had a lower cure rate than other races, although they represented the majority of patients. Caucasians comprised 75% or more of both the cured and failed groups.

Table 2

Baseline Characteristics

Characteristics	Cured *N* = 178	Failed *N* = 572	*p*-value
Age			
Mean (SD)	45.7 (14.1)	51.7 (14.4)	
Min-Max	21-82	18-86	<0.001
Age group			
< 40	67 (37.6%)	118 (20.6%)	
40–65	97 (54.5%)	358 (62.6%)	
> 65	14 (7.9%)	96 (16.8%)	<0.0001
Sex			
Male	108 (60.7%)	398 (69.6%)	
Female	70 (39.3%)	174 (30.4%)	0.0268
Ethnicity			
White	133 (74.7%)	482 (84.3%)	
Other	45 (25.3%)	90 (15.7%)	0.0038
Body weight(kg)			
Mean (*SD*)	79.3 (18.8)	84.1 (17.9)	
Min–Max	45.4–152	48.3–159.9	0.0023
Body surface areas (m^2)			
Mean (*SD*)	1.94 (0.27)	2.02 (0.25)	
Min–Max	1.41–2.88	1.45–2.90	0.0005

* *p*-value is obtained from *t* test for continuous variable or χ^2 test for categorical variable.

Patients who failed to achieve a complete cure had more severe disease, with a higher percentage of nail area infected and longer disease duration. The average percentage of diseased area on the targeted toenail was 60.0% in cured patients, and

65.5% in failed patients. The difference was small but statistically significant with a *p*-value of 0.0159 (see Table 3). The failed patients were also more likely to have prior antifungal treatment, presence of hyperkeratosis, and presence of onycholysis on the target big toenail. As shown in Table 3, only 18% of cured patients had been treated before, compared with 27.3% of failed patients ($p = 0.0125$). The sign of hyperkeratosis existed in 88.2% and 93.7% of cured patients and failed patients, respectively.

Overall, the average total length for a big toenail was 14 mm with $SD = 2.41$ mm. The shortest toenail was 4 mm and the longest one was 24 mm. The mean length was 13.4 mm ($SD = 2.44$ mm) for cured patients, and 14.4 mm ($SD = 2.36$ mm) for failed patients. The difference of 1 mm between two groups was statistically significant ($p < 0.0001$).

Before initiating the treatment, the mean length of healthy nail for all patients was 1.87 mm ($SD = 2.11$ mm). There was no difference between cured and failed patients with mean lengths of 1.85 mm and 1.87 mm, respectively. There also was no difference between the two groups if mean length of healthy nail was expressed as the percentage of the total full nail length. The mean value for cured patients was 13.5% and for failed patients was 12.9%.

Table 3

Disease Characteristics

Characteristics	Cured *N* = 178	Failed *N* = 572	*p*-value*
Percent of target toenail infected			
Mean (*SD*)	60.0 (26.5)	65.5 (23.2)	
Min–Max	1.3–100	6.8–100	0.0159
Length of nail grown (mm)			
Mean (*SD*)	2.35 (1.15)	2.25 (1.01)	
Min–Max	1–8	1–7	0.2956
Duration of current onychomycosis (months)			
Mean (*SD*)	90.9 (93.4)	122.8 (122.1)	
Min–Max	1–540	1–648	0.0003
Total percent of prescribed drug taken			
Mean (*SD*)	98.9 (4.1)	99.2 (4.24)	
Min–Max	84–117	81–117	0.3730
Had sign of onycholysis	144 (80.9%)	482 (84.3%)	0.2910
Had sign of discoloration	172 (96.6%)	558 (97.6%)	0.5043
Had sign of hyperkeratosis	157 (88.2%)	536 (93.7%)	0.0155
Had used antifungal treatment before	32 (18.0%)	156 (27.3%)	0.0125
Total full nail length (mm)			
Mean (*SD*)	13.4 (2.4)	14.4 (2.4)	
Min–Max	7.5–20	4–24	<0.0001
Length of healthy nail (mm)			
Mean (*SD*)	1.85 (2.17)	1.87 (2.09)	
Min–Max	0–12.5	0–12	0.9052
Percent of total full nail length as healthy	13.5 (15.18)	12.9 (13.97)	
Mean (*SD*)	0–69.4	0–81.1	0.6065
Min–Max			

* *p*-value was obtained from *t* test for continuous variable or χ^2 for categorical variable.

Hypothesis 1

Hypothesis 1 aimed to evaluate the association between the growth of the healthy nail in length during the trial period and the achievement of complete cure by Week 48, after adjusting for other risk factors. The length of healthy nail was measured by the shortest distance between the proximal nail fold and the healthy-diseased boarder as depicted in Figure 2. The growth of healthy nail in length was measured by the change from baseline in the length of the healthy nail. It was referred to as the length of healthy nail regrown.

Mean growth (changes from baseline in the length of the healthy nail) among cured patients and failed ones at scheduled study visits are presented in Figure 3 and Table 4. Starting at Week 4 and throughout the trial period, the growth of the healthy nail among cured patients appeared to be at a faster pace than that seen among failed patients (see Figure 3). The mean growth among cured patients was almost twice that of failed patients throughout the trial period (see Table 4). At Week 4, the mean growth of the healthy nail in the cured group was 1.23 mm versus 0.64 mm in the failed group, a ratio of 1.9. At Week 12, the difference was still kept at 1.87 times with a mean growth of 3.56 mm in the cured group and 1.90 mm in the failed group. By Week 36, the mean growth of the healthy nail in the cured group was more than twice that of the failed group (9.41 mm and 4.18 mm, respectively).

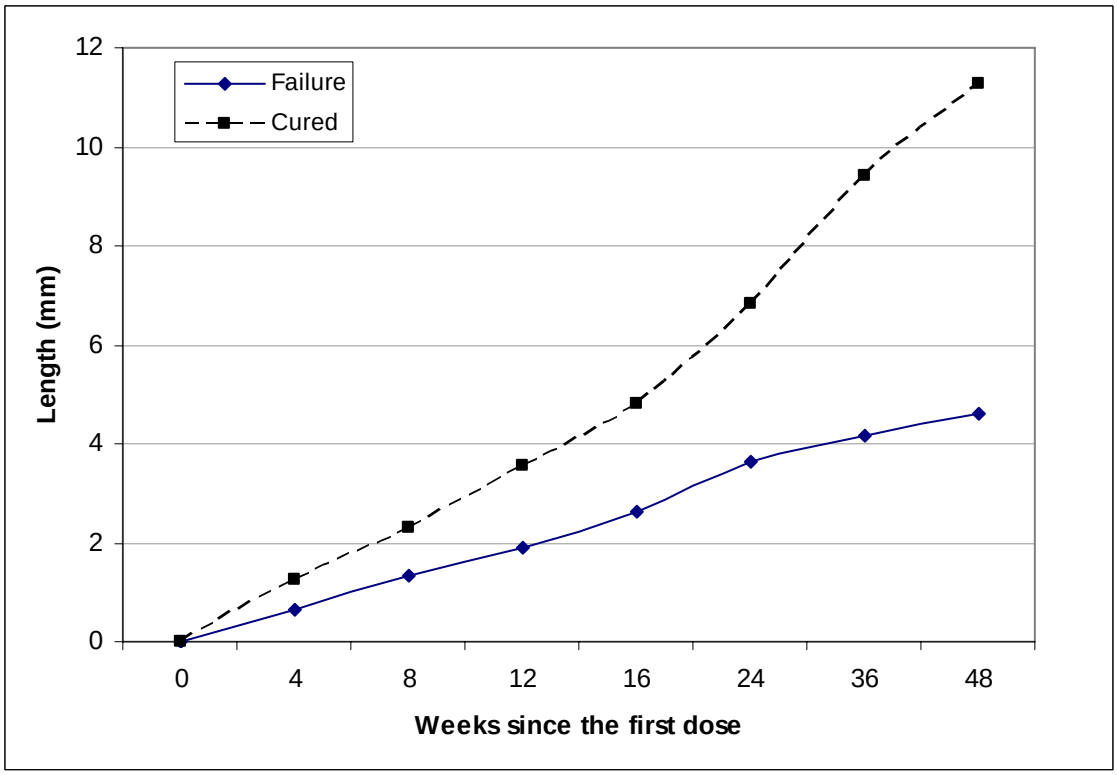

Figure 3. Line graph showing the mean changes in healthy nail growth (mm) during the trial period, by treatment outcome.

Table 4

Comparison of the Mean Change (mm) in Healthy Nail Length During the Trial Period Between Cured Patients and Failed Patients

Week	Cured Mean (*SD*)	Failed Mean (*SD*)	*p*-value
4	1.23 (1.41)	0.64 (1.42)	< 0.001
8	2.32 (1.72)	1.31 (1.66)	< 0.001
12	3.56 (2.08)	1.90 (1.82)	< 0.001
16	4.80 (2.38)	2.64 (2.25)	< 0.001
24	6.82 (3.12)	3.63 (2.82)	< 0.001
36	9.45 (3.06)	4.18 (3.68)	< 0.001
48	11.53 (3.01)	4.62 (4.45)	< 0.001

When measuring the rate of healthy nail growth, the average increases in healthy nail length at 4-week intervals among cured patients were 1.23 mm at Week 4, 1.09 mm at Week 8, 1.24 mm at Week 12 and 16, 1.01 mm at Week 24, 0.88 mm at Week 36, and 0.69 mm at Week 48. The average growth rates among failed patients at the corresponding intervals were 0.64 mm, 0.67 mm, 0.59 mm, 0.74 mm, 0.5 mm, 0.18 mm, and 0.15 mm, respectively. The growth rate of the healthy nail was much faster in cured patients than in failed ones. Healthy nails grew faster during the first 16 weeks than during the last 32 weeks of the trial.

The null hypothesis of no association between the achievement of complete cure and the growth of healthy nail length during the trial period was assessed using a similar multivariate logistic regression at each of the scheduled visits (Weeks 4, 8, 12, 16, 24,

and 36) adjusting for the same set of factors, such as age groups (< 40 vs. > 65; 40–65 vs. > 65), duration of current onychomycosis (months), percentage of prescribed drug taken (%), sign of onycholysis on the target big toenail (no vs. yes), history of antifungal treatment (no vs. yes), sex (female vs. male), percentage of nail infected prior to start the treatment (%), length of nail grown during the baseline period (mm), KOH microscopy result at the corresponding visit (negative vs. positive), mycological culture result at the corresponding visit (negative vs. positive), and total full nail length (mm). Table 5 summarizes the adjusted odds ratio (OR) and 95% confidence interval (CI) of healthy nail growth for all scheduled visits. It shows that change in the length of healthy nail growth was significantly associated with the achievement of complete cure at all visits. Depending on which visit was assessed, the odds of achieving complete cure were increased by 1.4 to 1.6 times for each millimeter of healthy nail growth. So the null hypothesis was rejected. There was a strong association between the change in the healthy nail length and the achievement of complete cure after adjusting for other risk factors.

Comparing crude OR and adjusted OR, the percent change between the two per formula from Sullivan (2005) was less than 5% for each visit. A 10% threshold has been suggested to judge if a factor was an important confounder (Sullivan; Varkevisser, Pathmanathan, & Brownlee, 2003, P. 87). Therefore the relationship between the clear nail length and the treatment status was not strongly confounded by other factors. Also the interaction terms between clear nail length and each of the other risk factors were not statistically significant with *p*-values greater than 0.08 for all.

Table 5

Odds Ratios at Each Trial Visit for Clear Nail Growth Associated With the Complete Cure

Week	Crude OR	Adjusted OR*	95% CI		% change between crude and adj. ORs **
4	1.352	1.349	1.160	1.569	0.22%
8	1.437	1.510	1.328	1.717	4.83%
12	1.602	1.630	1.443	1.841	1.72%
16	1.509	1.527	1.380	1.691	1.18%
24	1.456	1.489	1.369	1.619	2.22%
36	1.510	1.584	1.453	1.728	4.67%

* adjusted for age group, duration of current onychomycosis, percent of prescribed drug taken, sign of onycholysis on the target big toenail, history of antifungal treatment, sex, percent nail infected prior to start the treatment, length of nail grown during the baseline period, KOH microscopy result at corresponding visit, mycological culture result at corresponding visit, and total full nail length.
** %change = (|cOR-aOR|/aOR) x 100.

Since the length at Week 12 produced the biggest OR (1.630) after adjusting for other risk factors, Table 6 presents the results of full logistic regression model at Week 12. This model fitted the data well. The *p*-value from Hosmer and Lemeshow goodness-of-fit test was 0.6412. The analysis showed that less-than-40-year-old patients were more than two and half times likely to be cured than 65-year-old patients. Patients who were 40 to 65 years old were also nearly twice as likely to be cured as 65-year-old patients. Treatment-naive patients (patients who have not received antifungal treatment for onychomycosis) had a higher chance of cure (OR = 1.8, 95%CI: 1.06–3.01). Shorter nail

size and smaller area of infection were also significantly linked to the cure with OR of 0.81 (95% CI: 0.73–0.89) and 0.99 (95% CI: 0.980–0.998), respectively. The odds of cure were also higher for females and for patients with negative mycological culture results at Week 12; however, their 95% CIs included 1.

Table 6

Odds Ratio and 95% Confidence Interval of Risk Factors at Week 12 in Association With Achievement of the Complete Cure From the Full Logistic Model

Factors	OR	95% CI		*p*-value
Age <40 vs. > 65	2.698	1.184	6.150	0.0182
Age 40–65 vs. > 65	1.965	0.919	4.204	0.0816
Duration of current Onychomycosis (months)	0.999	0.997	1.001	0.2698
Percent of prescribed drug taken (%)	1.017	0.968	1.068	0.5072
Sign of onycholysis (no vs. yes)	1.144	0.647	2.025	0.6431
History of antifungal treatment (no vs. yes)	1.784	1.058	3.007	0.0298
Sex (female vs. male)	1.418	0.909	2.212	0.1238
Percent nail infected prior to start the treatment (%)	0.989	0.980	0.998	0.0151
Length of nail grown during baseline (mm)	1.169	0.953	1.434	0.1350
KOH at Week 12 (negative vs. positive)	0.613	0.263	1.427	0.2564
Culture at Week 12 (negative vs. positive)	1.395	0.904	2.155	0.1329
Total full nail length (mm)	0.807	0.733	0.888	<0.0001
Change in healthy nail length at Week 12 from baseline (mm)	1.630	1.443	1.841	<0.0001

Because not all risk factors in the full model were significantly associated with the treatment outcome, those with *p*-values greater than 0.1 were deleted from the final model. The final model fitted the data equally well. The *p*-value from Hosmer and Lemeshow goodness-of-fit test was 0.1571. The risk estimates for all variables in the final model were very similar to ones from the full model (see Table 7). Again, patients who were younger in age, treatment-naive, who have a smaller percentage of nail infected, or who have smaller nail sizes were significantly associated with achieving a complete cure during the 48-week trial period.

Table 7

Odds Ratio and 95% Confidence Interval of Risk Factors at Week 12 in Association With Achievement of the Complete Cure From the Final Logistic Model

Factors	OR	95% CI		*p*-value
Age <40 vs. > 65	3.136	1.432	6.870	0.0043
Age 40–65 vs. >65	2.170	1.033	4.559	0.0408
History of antifungal treatment (No vs. Yes)	1.719	1.032	2.865	0.0375
Percent nail infected prior to start the treatment	0.988	0.980	0.997	0.0093
Total full nail length (mm)	0.807	0.737	0.884	<0.0001
Change in length of clear nail grown at Week 12 from baseline (mm)	1.627	1.443	1.833	<0.0001

The negative mycological culture result at Week 16 was the first time to show a significant association with a complete cure (OR = 1.948, 95% CI: 1.218–3.117). The

association became stronger at Week 24 (OR = 3.420, 95% CI: 1.760–6.649), but it was no longer statistically significant at Week 36 with OR of 2.211 and 95% CI between 0.882 and 5.543.

Negative microscopy results only became significantly associated with a complete cure at Week 36 (OR = 2.846, 95% CI: 1.637–4.950). This is a reasonable finding because fungal hyphae can still be detected under the microscope even long after fungi have been killed and culture result becomes negative.

Hypothesis 2

The purpose of Hypothesis 2 was to evaluate if the percentage of the total nail grown as healthy nail was associated with the achievement of a complete cure after adjusting for other risk factors. The percentage was calculated with the length of healthy nail divided by the total full nail length. Change from baseline in the percentage was used for all analyses related to Hypothesis 2. Comparing the results between Hypothesis 1 and Hypothesis 2 might also provide a clue about which variable would be a better predictor for the achievement of a complete cure.

Similar analytical approaches to Hypothesis 1 were used to test Hypothesis 2. The results are presented in Figure 4 and Table 8–11, which are in the same order as the results for Hypothesis 1.

Figure 4 shows the mean changes in percentage of nail regrown as healthy nail during the course of trial. The percentage of total full nail length regrown as healthy was consistently higher in the cured group than in the failed group.

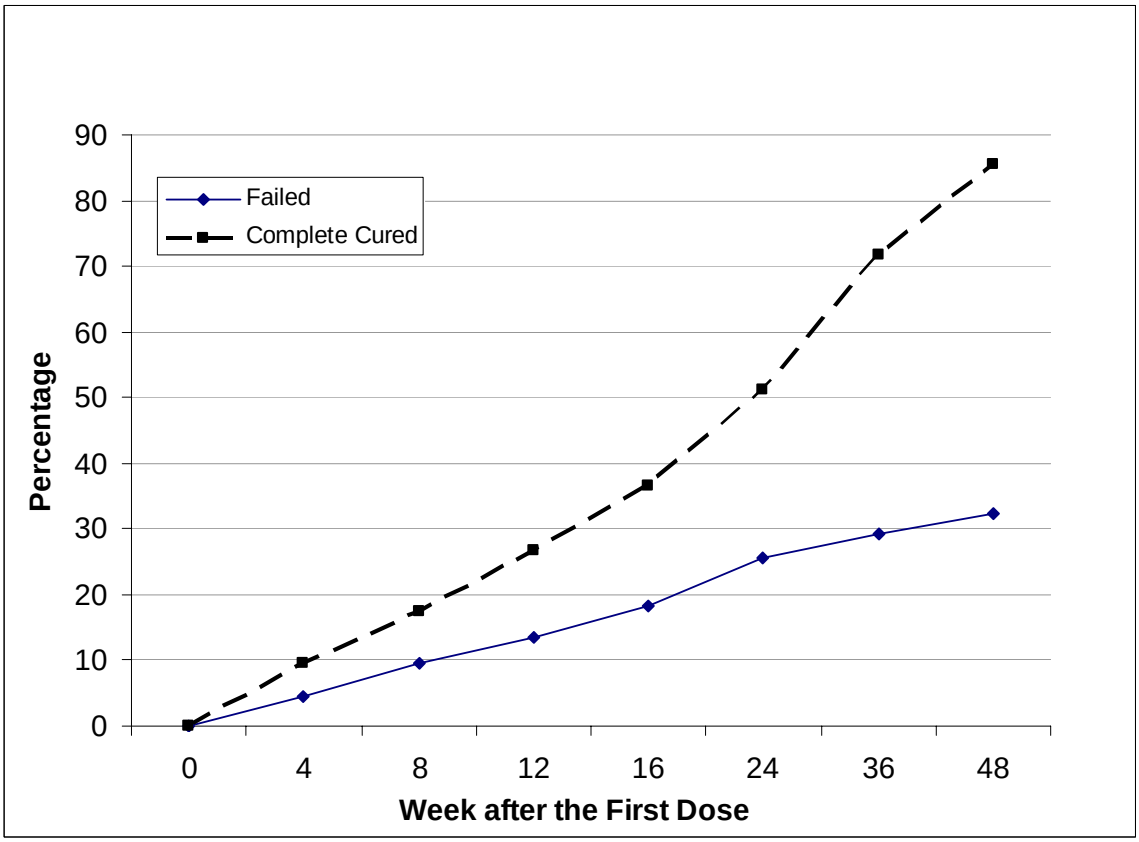

Figure 4. Line graph showing changes in percentage of total nail regrown as healthy nail during the trial period, by treatment outcome.

The average percentage of total nail grown as healthy nail was nearly twice as high in the cured group as in the failed group at each scheduled trial visit (see Table 8). The increase in the percentage during the first 16 weeks was about 8–9.7% for every 4-week interval in the cured group compared to 4.7–5.3% in the failed group. The growth rate slowed down a little during Week 24 to Week 48. The increases in the cured group were 7.3%, 6.7%, and 4.4% for every 4-week interval during this period, respectively. Increases in the failed group were only 3.2%, 1.6%, and 1.2% during the same period.

Table 8

Comparison of Percentage of Total Nail Regrown as Healthy Nail During the Trial Period Between Cured Patients and Failed Ones

Week	Cured mean (*SD*)	Failed mean (*SD*)	*p*-value
4	9.52 (10.70)	4.61 (10.09)	< 0.001
8	17.52 (12.77)	9.43 (11.97)	< 0.001
12	26.85 (15.05)	13.51 (12.91)	< 0.001
16	36.56 (17.82)	18.17 (16.04)	< 0.001
24	51.30 (22.33)	25.65 (19.99)	< 0.001
36	71.66 (21.50)	29.30 (25.42)	< 0.001
48	85.45 (16.95)	32.36 (30.73)	< 0.001

The null hypothesis of no association between the growth in percentage of total full nail length and the achievement of complete cure during the trial period was tested using multivariate logistic regression at each scheduled visit, controlling for factors such as age group (< 40 vs. > 65; 40–65 vs. > 65), duration of current onychomycosis (months), percentage of prescribed drug taken (%), sign of onycholysis on target big toenail (no vs. yes), history of antifungal treatment (no vs. yes), sex (female vs. male), percentage of nail infected prior to start the treatment (%), length of nail grown during the baseline period (mm), KOH result at corresponding visit (negative vs. positive), and mycological culture result at corresponding visit (negative vs. positive).This was a similar model to Hypothesis 1 except total full nail length was removed because the total full nail length was already part of the outcome variable. Table 9 presents the adjusted OR and 95% CI for the percentage of total nail grown as healthy at each scheduled visit.

Adjusted ORs were between 1.045 and 1.074 throughout the trial period. All 95% CIs were above 1 (see Table 9). Starting at Week 4, the odds of cure were increased by 1.045 for every unit change in the percentage of total full nail length grown as healthy nail. So if a patient had a 10% increase, the likelihood of cure is increased by 1.045^{10} or 1.55.

Table 9

Odds Ratios at Each Trial Visit for Percent of Total Nail Grown as Healthy Nail Associated With the Complete Cure

Week	Crude OR	Adj. OR*	95% CI		% Change between Adj. and Crude ORs**
4	1.048	1.045	1.024	1.066	0.29%
8	1.056	1.059	1.041	1.077	0.28%
12	1.076	1.074	1.056	1.092	0.19%
16	1.066	1.063	1.048	1.077	0.28%
24	1.060	1.058	1.046	1.070	0.19%
36	1.071	1.068	1.055	1.081	0.28%

* adjusted for age group, duration of current onychomycosis, percent of prescribed drug taken, sign of onycholysis on the target big toenail, history of antifungal treatment, sex, percent nail infected prior to start the treatment, length of nail grown during the baseline period, KOH microscopy result at corresponding visit, and mycological culture result at corresponding visit.
** % change=(|cOR-aOR|/aOR) × 100.

Since the largest adjusted OR (1.074) was seen at Week 12, results of the full model at Week 12 are presented in Table 10. The results from the final model after dropping variables with a *p*-value >0.1 are presented in Table 11. Both models fitted the data well. The *p*-values from Hosmer and Lemeshow goodness-of-fit test for both models

were 0.8864 and 0.4589, respectively. Two models showed that a complete cure was significantly associated with younger age group, first time treated with an antifungal agent, and a smaller area of infection. Sex was also significantly associated with the cure. Female patients were more likely to be cured than male patients (OR = 1.60, 95% CI 1.033–2.474 from Table 10). There was no significant interaction between each of these factors and percentage of total nail as healthy.

Table 10

Odds Ratio and 95% Confidence Interval of Potential Risk Factors at Week 12 in Association With Achievement of the Complete Cure From the Full Logistic Model

Factors	OR	95% CI		*p*-value
Age < 40 vs. > 65	2.902	1.278	6.591	0.0109
Age 40–65 vs. > 65	2.028	0.950	4.332	0.0678
Duration of current Onychomycosis (months)	0.999	0.997	1.001	0.3166
Percent of prescribed drug taken	1.018	0.968	1.069	0.4923
Sign of onycholysis (no vs. yes)	1.128	0.638	1.995	0.6778
History of antifungal treatment (no vs. yes)	1.841	1.091	3.104	0.0221
Sex (female vs. male)	1.599	1.033	2.474	0.0350
Percent nail infected prior to start the treatment	0.991	0.982	0.999	0.0355
Length of nail grown during the baseline period (mm)	1.127	0.924	1.374	0.2385
KOH at Week 12 (negative vs. positive)	0.586	0.252	1.367	0.2165
Culture at Week 12 (negative vs. positive)	1.439	0.932	2.220	0.1002
Change in % of total nail grown as healthy nail at Week 12 since baseline (%)	1.074	1.056	1.092	<0.0001

Table 11

Odds Ratio and 95% Confidence Interval of Risk Factors at Week 12 in Association With Achievement of the Complete Cure From the Final Logistic Model

Factors	OR	95% CI		*p*-value
Age < 40 vs. > 65	3.237	1.474	7.108	0.0034
Age 40–65 vs. >65	2.160	1.027	4.547	0.0425
Sex (female vs. male)	1.618	1.056	2.477	0.0270
History of antifungal treatment (no vs. yes)	1.808	1.081	3.024	0.0241
Percent nail infected prior to start the treatment	0.990	0.981	0.999	0.0227
Change in % of total full nail length regrown as healthy	1.073	1.056	1.091	<0.0001

Similar to the results seen in testing Hypothesis 1, the negative culture result was significantly associated with a complete cure at Week 16 (OR = 1.969, 95% CI: 1.232–3.147), and at Week 24 (OR = 3.367, 95% CI: 1.738–6.525). Then it was no longer statistically significant at Week 36 (OR = 2.089, 95% CI: 0.834–5.235). A negative microscopy result was only significantly associated with a complete cure at Week 36 with OR = 2.870 (95% CI = 1.647–5.002).

Hypothesis 1 and Hypothesis 2 showed the similar results in assessing the relationship between the healthy nail growth and achievement of complete cure. The logistic regression models produced a similar set of risk factors. The ORs in Hypothesis 2 were smaller than those in Hypothesis 1, but this might be the result of the smaller measuring unit used in Hypothesis 2 (1 %) than in Hypothesis 1 (1mm). Both predictors could be used for the evaluation of complete cure in future studies. However, the length

in millimeters may be more intuitive for users than percentage. The former is also easier to measure.

The next chapter presents the summary of findings, its implications for public health, and recommendation for actions. It also covers the experience with data gathering and suggestions for future studies.

CHAPTER 5:

SUMMARY, CONCLUSION, AND RECOMMENDATIONS

The success of antifungal treatment for onychomycosis is evaluated with a dichotomous variable of complete cure. Complete cure is defined as regrowth of a completely healthy big toenail and negative mycological results for both KOH and culture approximately 36 weeks after a standard 12-week daily oral dose of terbinafine treatment had stopped. The long gap between the final outcome and treatment cessation is the result of slow anatomical growth of the big toenail due to the fact that it normally takes 12 to 18 months to completely replace a big toenail. Current systemic antifungal treatments only achieve a complete cure rate of 20-50% (Baran & Kaoukhov, 2005; de Berker, 2004). Because of the long wait time for treatment outcome, various approaches have been proposed to improve the rate of complete cure and ensure a better outcome (Baran & Kaoukhov; Gupta & Ryder, 2003; Gupta & Tu, 2006). However, these approaches have been based on empirical evidence. The rate of healthy nail growth is considered an important predictor for the successful outcome of antifungal drugs for onychomycosis; however, there is little evidence to support this assertion. This population-based study may be the first to provide a statistically significant positive link between these two variables.

This study shows that healthy nails among patients who have achieved complete cures with a full-course of terbinafine treatment grow faster and at a more constant rate during the 48-week trial period than patients who have failed from the same treatment. This is true when growth is measured by the nail length or when growth is measured as a

percentage of the total full nail length. The difference in the healthy nail growth becomes statistically significant as early as Week 4. At this point in time, the mean change in the healthy nail length among cured patients is nearly double of that seen among failed patients (1.23 mm vs. 0.64 mm). At the completion of 12-weeks treatment with terbinafine oral tablets, the average length of healthy nails among cured patients is 3.6 mm while the average length of healthy nails among patients who failed treatment is only 1.9 mm.

Speed and consistency of healthy nail growth play important roles in the achievement of a complete cure as shown in Figure 3 and Figure 4. Regardless of the final treatment outcome, toenails generally grow faster while on treatment than posttreatment. Patients whose healthy nails grow at a faster and steadier speed are more likely to achieve a complete cure during the 48-week period.

Nail growth is still significantly associated with the achievement of a complete cure at each scheduled visit after controlling for significant factors such as age, gender, disease severity, nail size, and antifungal treatment history. Adjusted odds ratios range from 1.349 to 1.630 throughout the trial period when the healthy nail is measured in millimeters. Adjusted odds ratios are between 1.045 and 1.074 throughout the trial period when healthy nail growth is measured as a percentage of the total full nail length. For both measurements, adjusted OR is the highest at Week 12 and the lowest at Week 4. The same magnitudes of risk are presented from the final model by dropping variables with a *p*-value greater than 0.05.

Mycological microscopy and culture results are integral parts of achieving a complete cure. However, the significance of their associations with a complete cure comes at a later time than the pattern of clear nail growth. Furthermore, the culture results are associated with a cure at a much earlier time than KOH test results. In testing Hypothesis 1, a negative culture result is significantly associated with a complete cure outcome at Week 16, while negative KOH microscopy results only become significantly associated with complete cure at Week 36. The result is logical because fungal hyphae will still be visible under a microscope even though the fungi have been killed and cannot be grown in the culture medium. This pattern of significance of the mycological results with the achievement of complete cure is similar to that found by Sigurgeirsson, Paul, et al (2002), in which authors also identified the earlier significance of culture results than KOH testing.

Healthy nail growth also reflects the mycological results. Without killing fungi, the nail will not grow out healthily. To maintain continuous growth of healthy nail posttreatment and eventually achieve a complete cure, negative mycological results are absolutely required. Since healthy nail growth is linked to treatment outcome much earlier than a mycological culture or KOH test, it would be a more valuable indicator of treatment outcome.

Healthy nails—as measured in actual length or in percentage of total nail—produce a similar relationship with the achievement of complete cure. Logistic regression models produce a similar set of risk factors for both variables. Though ORs for the percentage (in Hypothesis 2) are smaller than those for length (in Hypothesis 1), this

might be the result of the small units used in Hypothesis 2 (1 %) as compared to those used in Hypothesis 1 (1 mm). Both variables can be used to monitor treatment response and predict final treatment outcome. In this manner, the selection of an indicator could be the user's own preference. Use of the nail length indicator may be more intuitive than use of percentages; they are also easier to calculate.

Besides nail growth and mycological results, other factors significantly associated with achievement of complete cure include patients of a younger age, treatment naïve patients (i.e., patients who have not received antifungal treatment for onychomycosis), less severe infection, and smaller nail size. Patients under the age of 40 are three times more likely to be cured than a 65-year-old patient. A patient between the ages of 40 and 65 years old is also twice likely to be cured than a 65-year-old. Treatment naive patients have a double chance of cure than those who had received prior antifungal treatment. Female patients appear to have better response to the treatment than male patients. A smaller area of infection is also significantly linked to the cure rate, though the OR and its 95% CI are very close to 1. When nail growth is not measured by the percentage of the total full nail length, shorter nail size indicates a better chance of cure (OR = 0.81, 95% CI: 0.733–0.888).

It has been demonstrated that terbinafine can speed nail growth (Geyer et al, 2004). This study supports such findings because the toenail grows faster while on treatment than in the posttreatment period. This may relate to terbinafine concentration in the nail: A higher concentration results in faster nail growth. This may be an indication

that additional posttreatment therapy may speed nail growth and increase the rate of complete cure.

Experience With Measuring Nail Length

The length of healthy nail was measured from the proximal nail fold to the lowest point on the healthy-diseased border. The measurement was taken from the middle of the nail. Measurement of nail growth as analyzed from a photograph of the nail had been a challenging task. A good measurement of nail length required a proper camera angle, proper light exposure, clear markings, and well-defined nail shape. At times, the toenail surface grew at a concave angle downward. Therefore, some nails were twisted instead of being straight in the mid-nail area. So the correct measurement of actual nail length was nearly impossible to ascertain. The site of the infection also affected the measurement: Because the length of the lateral edge was normally shorter than the one mid-nail, a large change in clear nail length from one visit to another could be seen when only the lateral edge was diseased.

It was definitely an advantage to have a complete set of nail photographs during the trial period for each patient as it allowed a chronological review of the changes in disease and nail growth over time. The lessons learned from this study could help physicians and researchers assess the nail better. Since marking the healthy-diseased border for this study was performed at each trial visit without comparison to previous photographs, these photographs revealed the tough challenges in disease assessment. There were some inconsistencies in marking the healthy-diseased border over time within a patient. Some markings changed dramatically from one visit to another, even though

the disease itself did not change much. There was also a difference between how individual investigators marked the healthy-diseased border; different investigators might make differing assessments of the appearance of the nail and one might consider the area healthy while another considered it diseased. Additionally, there was a tendency for investigators to be more critical in marking the healthy-diseased border when the nail became clear than when it was not clear. Since nails normally appeared much cleaner after treatment with terbinafine, the healthy area might become smaller than when nails were covered with diseased tissue. This might come as a result of it being easier to see the nail when it was clean than diseased.

Reviewing each set of photographs showed that nails did not always grow out uniformly. The location of the lowest point of the healthy-diseased border changed from visit to visit. Therefore, it was not feasible to use one fixed point to monitor healthy nail growth.

These study results represented nail growth in general. It should be remembered that there were some unique cases, as documented by the photographs. For example, some patients grew new nail at a much faster rate than others. For some cases, it was somewhat difficult to measure the total nail size at the beginning of treatment because nails had been destroyed or were misshapen. Closely clipped nails could affect the measurement as well, as some nails were clipped much shorter while others had nails that extended beyond the free edge of the nail bed.

Implications for Social Change

Because of the relatively high prevalence of onychomycosis in the general population and the lack of optimal treatment, this study bears public health importance. Only when the disease is effectively managed can the spread of the disease be reduced. Improved treatment outcome will also minimize patients' sufferings and avoid more severe consequences.

This study has demonstrated a clear association between the growth of healthy toenails and achievement of a complete cure. This could set a foundation for a future treatment strategy for the disease and affect future research of antifungal agents. These positive results may help physicians to better monitor the progression of healthy nail growth during both the treatment and posttreatment periods. Physicians may track the nail growth over time and predict the treatment outcome in comparison with the results presented here, resulting in better treatment of the disease since it could help them to decide if and when booster treatment is necessary. It will be useful to take nail photographs regularly and compare the current photo with previous ones when assessing a treatment response.

For pharmaceutical researchers, these results may help them to better selection of future antifungal treatment. For example, instead of conducting a full scale and large sampled clinical trial at the early development phase, they could shorten the trial duration to 12 or 16 weeks and use nail growth rate as a surrogate marker for treatment success. This can also be used to develop combination therapy by testing when to add a second agent. By reducing the cost of research and development, the prices of newer antifungal

agents could be reduced. This will be good news for both individual patients and the entire healthcare system.

Of course, the findings would need to be confirmed by future studies because this may well be the first study to reveal such a relationship.

Recommendations for Action

Antifungal treatment is required to eradicate fungi from the nail because there is rarely a spontaneous cure for onychomycosis. The positive findings from this study should be shared with physicians, patients, and pharmaceutical researchers.

First, this could be done through publication and scientific conferences so results would be made public to target audiences. Second, a growth chart is recommended for each patient to monitor nail growth.

Area for Further Studies

Since this is the first time a positive link between the healthy nail growth and achievement of complete cure has been demonstrated in a population-based study, these results should be confirmed by additional studies. Some background noise or risk factors apparent in other studies were not entirely controlled in the current study, so future studies may be designed to include a placebo arm as well as assessment of important clinical features such as matrix infection and nail thickness. Future studies may also have a longer observational period to see if a higher cure rate can be achieved with a longer follow-up period.

Nail growth patterns and relapse rates may need to be examined more closely. It will be important to understand what the risk factors are and how the nail would subsequently show signs of relapse so preventive procedures could be implemented.

Additional studies could be performed to evaluate if booster treatment can improve efficacy. Such studies need to explore the type of boosters to use, time to start, and duration of treatment.

Conclusion

The healthy nail growth measured in length (mm) or in percent of total full nail length is significantly associated with the achievement of a complete cure. The significance could be observed after 4 weeks of terbinafine treatment. With every millimeter increase in healthy nail length, the chance of cure could increase by 1.35 times. Week 12 seems to be the best time to assess the treatment outcome because healthy nail length and percent of total nail grown as healthy at this visit had the largest odds ratios, 1.63 and 1.07, respectively. Also the mean healthy nail length at Week 12 in cured patients is much longer than that seen in failed patients (3.56 mm vs. 1.90 mm). Speed and consistency of healthy nail growth are important to achieve a cure. Significant baseline factors for cure are younger in age, are treatment naïve, and having less severe disease. Healthy nail growth appears to be a better predictor than negative mycological results because significance of negative mycological culture results started at Week 16 and negative KOH microscopy results started at Week 36. Booster treatment may increase the chance of cure because healthy nails grow faster when terbinafine

concentration in the nail is higher. Further studies may be required to assess the effects of matrix infection, nail thickness, and threat of relapse.

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CURRICULUM VITAE

EDUCATION:

Ph.D in Epidemiology: Walden University, Minneapolis, MN (11/08).Thesis title 'Prognostic Factors of Varying Treatment Outcomes for Onychomycosis (Nail Fungal Infection) Patients'

M.S. in Biostatistics, Harvard University School of Public Health, Boston, MA (6/92)

M.P.H. in Epidemiology and Biostatistics, Boston University School of Public Health, Boston, MA (1/88)

M.D., Tongji Medical University, Wuhan, Hubei Province, The People's Republic of China. (8/83)

PROFESSIONAL EXPERIENCE:

2/08–present **Associate Director,** Integrated Medical Safety, Novartis Pharmaceutical Co., East Hanover, NJ

- Co-author Risk Management Plans in support of investigational and marketed products.
- Designs, coordinates, implements and evaluates observational epidemiologic studies
- Provides epidemiological and risk management support and consultation to project and product teams.
- Works closely with medical safety teams to proactively identify, clarify and resolve safety questions.
- Provides evaluations and commentaries on manuscripts and publications of epidemiological studies of importance to company.
- Reviews study proposals from internal and external sources and provides consultation and critique of design, and potential effects of various outcomes on company products.
- Supports company products through participation at team meetings, external symposia and presentations, publication of in house or contracted studies, etc.
- Maintains professional relationships with pharmacoepidemiologists community and maintains knowledge / expertise of existing large databases and data sources which may be suitable to conduct epidemiological studies.
- Coaches other members in Global Epidemiology
- Develops, and support TA or BU wide strategy and project management.

3/03–2/08 **Associate Director,** Clinical Information System
9/01–2/03 **Sr. Principal Statistician**, Novartis Pharmaceutical Co., East Hanover, NJ
Major responsibility:

- Provided input to the strategy and planning of international dermatology and

respiratory projects and its clinical studies and their approvals from various internal development boards.

- Co-authored the target project profile, clinical development plan, study protocols, study reports, analysis plan, manuscripts, registration dossiers, product label, and marketing materials.
- Explored and ensure implementation of innovative methodology for the study design and analysis.
- Overseen the timeline and quality of all deliverables and manage the resource and external cost
- Prepared briefing books for various meeting with Health Authorities
- Attended face-to-face discussion with external experts, health authorities, and trial investigators
- Participated in NDA submission and provide responses to review comments for the approval of LAMISIL Oral Granules.
- Participated in due diligence for potential in licensing products
- Participated in development of process streamline, inter-department collaboration, information exchange, and as business representative for a new electronic data management system.
- Supervised a group of statistician and programmers

4/98–8/01 **Sr. Staff Statistician**, Berlex Laboratories Inc., Montville, NJ

Major responsibility:

- Provided statistical support and clinical input to Phase 2−4 studies of CNS project, phase 1-3 of gene therapy project for cardiovascular disease.
- Provided statistical support for all PK/PD studies related to cardiovascular research.
- Supervised statistical programmers.
- Worked with CRAs to monitor the study progress and data queries
- Prepared and Implemented domain database concept.
- Prepared the documents for project management, report, and regulatory purpose.
- Involved with the database management and electronic data transfer.
- Worked with individual investigator to further explore the certain indication

2/97–3/98: **Senior Biostatistician**, Genetics Institute Inc., Cambridge, MA

7/94–2/97: **Biostatistician**

Major responsibility:

- Project statistician for phase I/II/III studies evaluating the safety and effect of rhIL-11 on platelet restoration in cancer patients.
- Primary statistician for studies of evaluating the safety and effect of rhIL-11 on Inflammatory Bowel Disease in U.S. and in Europe.
- Primary statistician for phase I studies evaluating the safety and effect of rhIL-11 on intestinal mucosa integrity and hematological recovery in breast cancer patients.
- Involved with designing the study, writing protocol, calculating the sample size, preparing analysis plan, performing statistical analysis and writing

study report.
- Participated in preparing IND, BLA, MAA submission and BRMAC meeting.
- Reviewed the CRFs design, Database Design, and Data Listing.
- Interacted with CRO for study analysis plan and study reports.
- Interacted with contractor for drug packing and randomization.
- Reviewed study protocols and concept sheets.
- Oversaw the programmers assigned to the projects.

2/88–6/94: **Research Associate**, Institute for Urban Health Policy and Research, Boston Department of Health and Hospital, Boston, MA
Major responsibility:
- Participated in design and conduct of several longitudinal epidemiological studies on AIDS.
- Developed and implemented analysis plans.
- Wrote study reports.
- Supervised data management personnel.

PROFESSIONAL AFFILIATIONS:

Member of International Society for Pharmacoepidemiology 2008 -
Member of American Public Health Association 1988-1995, 2006 -