Onychomycosis Treatment in the United States

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Practice Points

- Onychomycosis is a common progressive infection of the nails that may result in remarkable morbidity. Effective treatment may reduce the rate of transmission and related morbidities.
- Onychomycosis is most commonly found in patients older than 35 years.
- Terbinafine has been the most commonly prescribed antifungal agent for onychomycosis in the United States between 1993 and 2010, followed by systemic fluconazole, systemic itraconazole, and topical ciclopirox.

Onychomycosis is a common progressive infection of the nails that may result in remarkable morbidity. Although there are a variety of treatments available for fungal nail infections with different efficacy and safety profiles, there are limited reports on the ways in which physicians use these treatments or the frequency with which they prescribe them. In this retrospective study, major trends in the prescription and use of antifungal agents for treatment of onychomycosis in the United States were evaluated using data from the National Ambulatory Medical Care Survey. Results showed that current treatment and trends in use of drugs for onychomycosis in the United States are in accordance with recommendations in current guidelines.

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Onychomycosis is a common progressive infection of the nails caused by dermatophytes, nondermatophyte molds, and yeasts, with *Trichophyton rubrum* being the most common causative organism.[1-3] Onychomycosis affects approximately 2% to 26% of different populations worldwide. It represents 20% to 50% of onychopathies and approximately 30% of fungal cutaneous infections.[4-9] Less than 30% of infected persons seek medical advice or treatment even in developed areas of the world.[10] Onychomycosis may be a source of more widespread fungal skin infections or give rise to complications such as cellulitis. Chronic, long-lasting infection may result in nail dystrophy and can lead to pain, absence from work, and decreased quality of life.[1,11] Because the dermatophyte can contaminate communal bathing facilities and spread to others,[12] it is important to effectively target and treat patients with onychomycosis, thus reducing the rate of related morbidities.[1,9]

The primary aim of onychomycosis treatment is to cure the infection and prevent relapse. Both topical and oral agents are available for the treatment of fungal nail infections. Generally, systemic therapy for onychomycosis is more successful than topical treatment, likely due to poor penetration of topical medications into the nail plate.[1,2,9] However, newer topical drugs have shown promising results in treating some types of onychomycosis.[13] In its guidelines for treatment of onychomycosis, the British

Association of Dermatologists recommends use of topical treatment under the following conditions: (1) when there is not extensive involvement of the nail plate (eg, candidal paronychia, superficial white onychomycosis, early stages of distal and lateral subungual onychomycosis), (2) when systemic therapy is contraindicated, or (3) in combination with systemic therapy.[1] Although there are multiple treatments for fungal nail infections, there are limited reports on the ways in which physicians actually use these treatments or the frequency with which they prescribe them.

This study provides a representative portrayal of onychomycosis visits in the US outpatient setting using a large nationally sampled survey. In particular, we aimed to assess the number of visits related to onychomycosis, the demographics of patients, and the treatments being prescribed for onychomycosis.

Methods

Study Design—Data from January 1, 1993, to December 31, 2010, were collected from the National Ambulatory Medical Care Survey (NAMCS), an ongoing survey of nonfederal employed US office-based physicians who are primarily engaged in direct patient care. The NAMCS has been conducted by the National Center for Health Statistics every year since 1989 to estimate the utilization of ambulatory care services in the United States. Since 1989 including 1993 to 2010, the NAMCS sampled approximately 30,000 visits per year. For each visit sampled, a 1-page patient log including demographic data, physicians' diagnoses, services provided, and medications was completed. In the NAMCS survey, visits were divided into 2 groups: (1) visits from established patients that have been seen in that office before for any reason, and (2) visits for new (ie, first-time) patients. The current study included all visits in which fungal nail infection (code 110.1 according to the *International Classification of Diseases, Ninth Revision* [*ICD-9*]) was listed as 1 of 3 possible diagnoses.

Statistical Analysis—Sampling weights were applied to data to produce estimates for the total US outpatient setting.[14] Data were analyzed using SAS version 9.2, and SAS survey analysis procedures were used to account for the clustered sampling of the survey. The total numbers of visits for which onychomycosis was 1 of 3 possible diagnoses and for which it was the sole diagnosis were reported. Visit rates per population by demographic characteristics (ie, patient sex, age, race, and ethnicity) were calculated. Population estimates were based on the 2001 NAMCS Public Micro-Data File Documentation records of the US census estimates for noninstitutionalized civilian persons.[15] Trends in proportion of visits linked with an onychomycosis diagnosis over time were evaluated using the SAS SURVEYREG procedure. Types of physicians who attended to these visits as well as leading comorbidities that had been diagnosed and documented in the medical record were characterized. Onychomycosis-related medications prescribed at these visits were reported and prescribing trends over time were evaluated. Differences in the treatment prescribed according to the type of visit (ie, first-time or return visit); physician specialty; and patients' gender, race, and health conditions (eg, obesity, diabetes mellitus) were examined. To exclude the possibility that fluconazole and other broad-spectrum antifungals were being used for secondary diagnoses, we determined the number of visits that had an additional diagnosis of either candidiasis (*ICD-9* codes 112.0–112.9) or "other specified erythematous conditions" (*ICD-9* code 695.89).

Results

During the 18-year study period, 636 visits with a diagnosis of onychomycosis were recorded in the NAMCS database. This unweighted number of visits corresponded with approximately 19,350,000 visits (an average of 1,075,000 visits per year) to physicians' offices with a diagnosis of onychomycosis in the United States during this period. Among these visits, there were an estimated 4,250,000 visits with fungal nail infection as the only diagnosis (no other comorbidities recorded). The recorded visits included more female (57.6%) than male (42.4%) patients, and 85% of patients were white (Table). Patients aged 35 to 44 years accounted for the largest number of visits; however, the estimated rate of onychomycosis visits per 100,000 US citizens was highest among those aged 65 to 74 years (Figure 1).

The number of US outpatient visits with a recorded diagnosis of onychomycosis increased from 1993 to 2010 (Figure 2); however, there was no change in the ratio of onychomycosis visits to the total number of recorded visits in NAMCS database during the study period ($P=.9$). A combined total of 91% of onychomycosis visits were to general and family practitioners, dermatologists, or internal medicine practitioners (Figure 3). Although cardiovascular diseases and diabetes mellitus accounted for a large proportion of comorbidities, conditions affecting the feet (eg, tinea pedis, ingrown nails) also were among the most common comorbidities (Figure 4).

In both topical and systemic form, terbinafine was the most commonly prescribed antifungal agent, followed by systemic fluconazole, systemic itraconazole, and topical ciclopirox (Figure 5). Over

Estimation of Demographics of Visits With a Diagnosis of Onychomycosis in the United States (1993-2010)[a]

Characteristic	Percentage of Patients	No. of Visits Per 100,000 Persons Per Year[b]	*P* Value
Gender			*P*=.005
Female	57.6	400	
Male	42.4	306	
Race			*P*<.001
White	84.6	376	
Black	7.6	211	
Asian	1.9	144	
Native American/ Alaskan	0.3	93	
Unknown	5.6		
Ethnicity			*P*=.08
Hispanic or Latino	13.7	400	
Other	71.4	310	
Unknown	14.9	Not calculable	

[a]N=636 for the number of unweighted visits recorded in the study. N=19,350,000 as an estimation of the number of visits in the United States.

[b]Estimated number of visits related to each demographic variable was divided by the US population corresponding to the same demographic variable.

the 18-year study period, there was an increasing trend in the frequency of terbinafine prescription (regression coefficient [*r*]=0.01319; *P*=.004); a decreasing trend for fluconazole (*r*=−0.0053851; *P*=.04), itraconazole (*r*=−0.0113988; *P*<.001), griseofulvin (*r*=−0.0073942; *P*<.001), and econazole prescription (*r*=−0.0032405; *P*=.01); and no significant trend for ketoconazole (*r*=−0.0034553; *P*=.1), naftifine (*r*=−0.0029067; *P*=.06), sulconazole (*r*=−0.0001619; *P*=.8), ciclopirox (*r*=0.0032684; *P*=.1), and miconazole prescription (*r*=0.0002074; *P*=.5).

Eighty-six percent of visits were for established patients who had been seen in the related office with any diagnosis before the recorded visit and 14% of visits were for new (first-time) patients. Fluconazole was the most frequently used antifungal drug for new patients, while terbinafine was the most frequently used in other visits. Terbinafine was the most frequently prescribed antifungal drug by general and family practitioners, dermatologists, internal medicine practitioners, and all other specialties not listed.

Terbinafine was the most frequently prescribed antifungal drug in both genders and in white and black patients. Itraconazole was the most frequently prescribed antifungal drug for Hispanic patients and those of other ethnicities not listed. Terbinafine was the most frequently prescribed antifungal drug for patients with diabetes and obesity (ie, body mass index ≥30). In 19,330,000 of 19,350,000 total estimated visits included in this study, onychomycosis was the only diagnosis with a potential indication for an antifungal drug therapy, ruling out the possibility that fluconazole or other drugs were used for patients who also had candidiasis or "other specified erythematous conditions."

Discussion

Onychomycosis is a common progressive infection of the nails that is more prevalent in older age groups, with equal prevalence in both genders and a higher prevalence in males. The NAMCS data showed higher rates of onychomycosis visits among older age groups, which is in agreement with

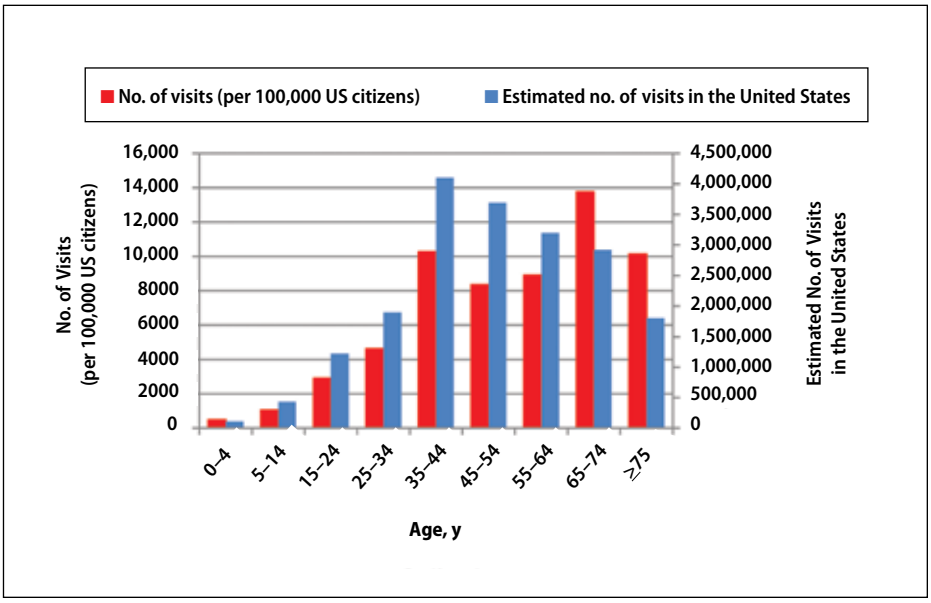

Figure 1. Health care utilization for onychomycosis from 1993 to 2010 stratified by patient age, as defined as: (1) the total estimated number of US outpatient visits that included a diagnosis of onychomycosis (right-hand y axis and blue bars), and (2) the estimated number of visits per 100,000 US citizens (left-hand y axis and red bars). To calculate the average number of visits per US citizen in a defined age group, the total number of visits for a given age group was divided by the estimated population size for that age group.

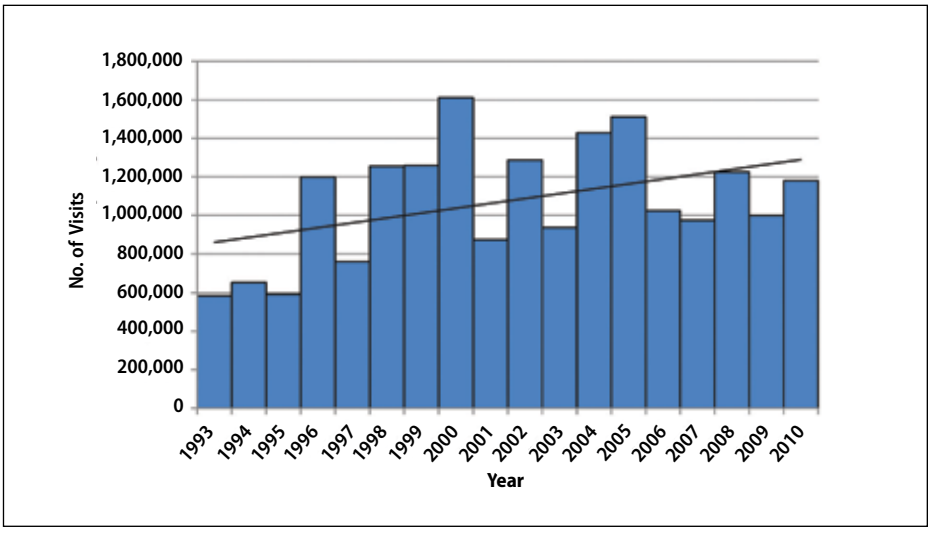

Figure 2. Estimated number of US outpatient visits with a recorded diagnosis of onychomycosis per year (1993-2010). Solid line represents the linear regression best fit line.

results from prior studies.[16,17] In the current study, we observed a higher prevalence of onychomycosis visits among females as well as white and Hispanic patients. These results may be due to a higher prevalence of onychomycosis in these populations or simply a result of difference in socioeconomic level or importance of aesthetics. Although there are limited data regarding the prevalence of onychomycosis among different races and ethnicities in the United States, a high incidence of onychomycosis has been reported in Mexico.[18]

Repeated trauma to the great toenail from ill-fitting shoes is a predisposing factor for onychomycosis.[16] In the current study, ingrown nails were among the most common comorbidities found in onychomycosis patients. Although nail dystrophy caused by onychomycosis may lead to ingrown nails, it also is possible that both conditions may be caused by trauma.

Patients with immunodeficiencies (eg, diabetes) may be predisposed to onychomycosis as well as its associated complications and morbidities (eg, cellulitis).[16,19] Diabetes affects 4% to 22% of

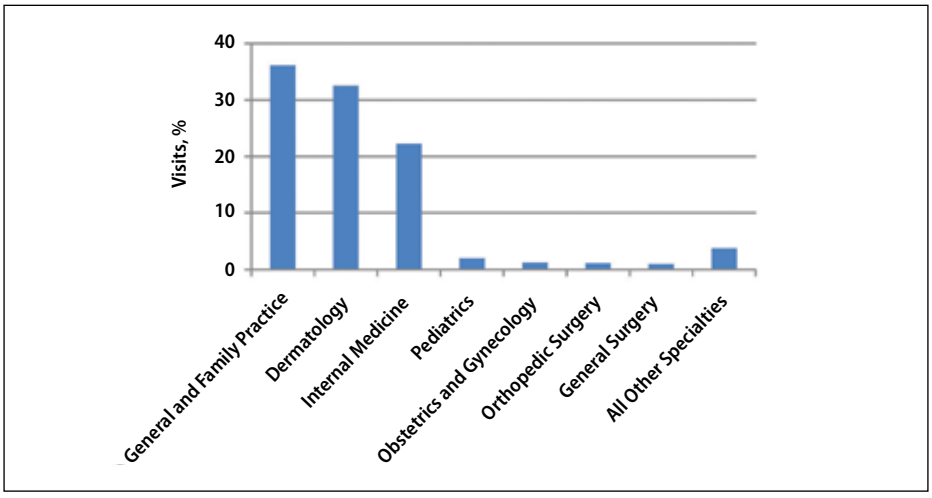

Figure 3. Estimated number of US outpatient visits with a recorded diagnosis of onychomycosis by specialty (1993-2010).

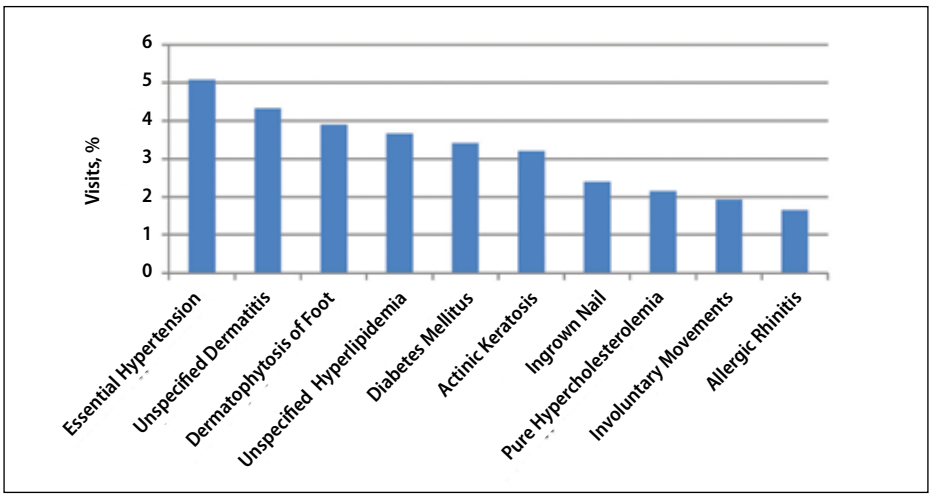

Figure 4. Top 10 comorbidities observed at US outpatient visits with a recorded diagnosis of onychomycosis (1993-2010).

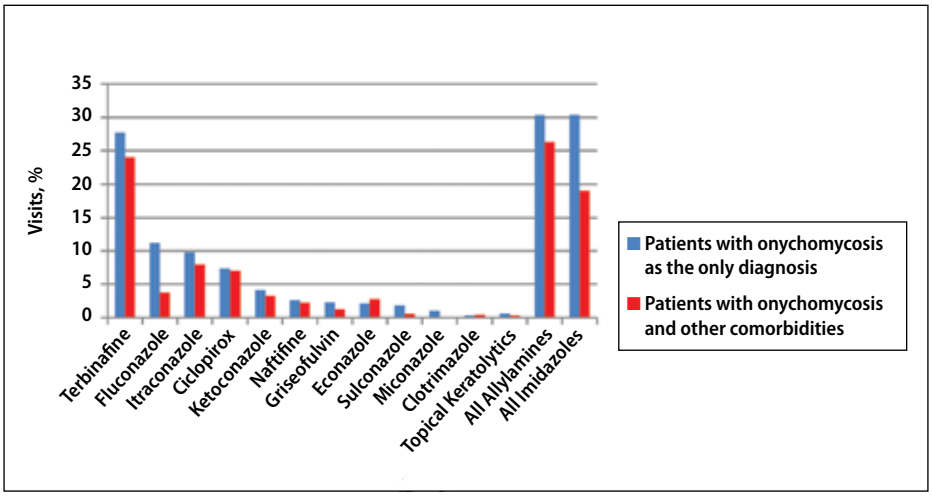

Figure 5. Leading antifungal agents prescribed at US outpatient visits with a recorded diagnosis of onychomycosis (1993-2010).

patients with onychomycosis in different populations, including Denmark, Mexico, and India.[18,20,21] In our study, diabetes was among the most common recorded comorbidities reported during onychomycosis visits, with a prevalence of 3.4%. It is likely that many more visits involved patients with diabetes that had not been diagnosed or reported. With the increased risk for complications with diabetes, it is important for physicians to treat these patients when they have a nail infection.

The available systemic therapies for treatment of onychomycosis include griseofulvin, allylamines, and imidazoles. Comparison of griseofulvin with newer systemic antifungal agents such as terbinafine and itraconazole suggests that griseofulvin has lower efficacy and therefore is not a first-line treatment of onychomycosis.[1] Terbinafine is the most active of the currently available antidermatophyte drugs both in vitro and in vivo, with synergistic effects with imidazoles and ciclopirox.[1,22-27] A combination of topical and systemic therapies may improve cure rates of onychomycosis or possibly shorten the duration of therapy with the systemic agent.[1,2] Treatment strategies can vary according to the specialty of the treating physician, with general practitioners often preferring monotherapies and dermatologists preferring combination therapies.[28] In Europe, the most commonly prescribed medication for onychomycosis was topical amorolfine followed by systemic terbinafine and itraconazole.[28] In the current study, we could not separate data for topical versus systemic terbinafine because the NAMCS uses similar names for reporting the drug; however, the rates of prescription for allylamines and imidazoles were nearly equal (Figure 5), with terbinafine showing an increased use over time as opposed to a decreased use of imidazoles. Although fluconazole is not approved by the US Food and Drug Administration for treatment of onychomycosis, oral fluconazole was the second most common treatment prescribed in our study. Griseofulvin, which is not considered as a drug of choice in onychomycosis,[1] was prescribed in a small fraction of the visits, with a decreasing trend of usage over time.

Conclusion

Our analysis of the NAMCS data revealed that the treatment of onychomycosis in the United States is in accordance with recommendations in current guidelines. An encouraging finding was the notable downward trend in use of griseofulvin, suggesting that health care providers are changing practice to meet standard of care. Increased efforts must be made to uniformly modify practices in compliance with evidence-based recommendations and to minimize unnecessary risk and cost associated with use of drugs with lower efficacy.

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