Onychomycosis in primary care practice: major challenges from a minor ailment

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General Introduction

GENERAL INTRODUCTION

Background

Onychomycosis, the fungal infection of nail tissue, is frequently presented in general practice due to its high prevalence amongst the general population.[1,2] From a broader perspective, the nails are part of the skin appendages, and onychomycosis is therefore considered a dermatologic condition.[3,4] In Dutch general practice, skin conditions, including onychomycosis, are the second most frequently presented health concerns after musculoskeletal problems, contributing to an estimated 14% of all consultations.[5,6] Although the different skin conditions presented in general practice are numerous and specific incidence rates regarding onychomycosis are lacking, mycotic skin infections are the most common, having an incidence rate of 41.6 per 1000 patients in Dutch general practice. Of all mycotic skin infections, onychomycosis and tinea pedis are the most common.[7] As such, onychomycosis can be considered a typical example of a common condition frequently presented to the Dutch general practitioner.[8,9]

Onychomycosis is primarily caused by dermatophytes, mostly Trichophyton rubrum and related species. However, onychomycosis can also be caused by yeasts, mainly Candida species, and non-dermatophyte molds, such as Aspergillus spp.[10] Toenails are substantially more often affected than fingernails, and the proportion of causative pathogens differs for finger- and toenails. Toenail onychomycosis is most frequently caused by dermatophytes, whereas onychomycosis of the fingernails is predominantly caused by Candida species.[11-13]

The mean prevalence of onychomycosis in population-based studies varies between 4.3% and 5.5%.[1,14] This makes onychomycosis the most common cause of all nail-related diseases.[1,14] The prevalence reported for patients visiting hospital clinics is higher (8.9%).[1] This is also the case for patients with predisposing comorbidities or advancing age: between 8.8% to one-third of diabetic patients are affected, and the prevalence reported for patients >60 years increases to >20%.[15-19] In contrast, onychomycosis in children is much less common than in adults, with a pooled prevalence of <1%, and fingernails are more frequently affected than toenails.[19,20]

Despite that onychomycosis was already described as early as 1853 by Georg Meissner, who discovered its fungal nature, this 'minor ailment' persists today, posing different challenges to patients and their general practitioners regarding diagnosis, treatment, and prognosis.[10,21-25] These challenges, which form the basis of this dissertation, are outlined in the next paragraphs.

Clinical presentation and burden

Although most patients will initially only notice the visual changes caused by the fungal spread and often do not have more pressing symptoms such as pain or discomfort,

discarding onychomycosis as merely a cosmetic concern would be shortsighted. Numerous studies have shown that in a substantial part of patients, onychomycosis has a significant negative effect on the quality of life due to associated shame, discomfort, and anxiety.[26-29] In contrast, some studies suggest that others may not even be aware of having mild, early-stage onychomycosis due to non-apparent nail changes or absence of symptoms.[30-32] It would be interesting to know how many patients could be considered 'subclinically' affected, but sufficient data on this topic is lacking.[30-32] Patients with more evident symptoms may initially try over-the-counter medications or other home remedies before considering medical consultation.[2,22] Those with persisting or more pressing symptoms will eventually consult their general practitioner, most likely to confirm their suspected diagnosis and to be informed about possible treatment options.[33]

Diagnostic challenges

Onychomycosis is often considered to be easily diagnosed on physical examination.[2,33] This notion is also supported by the current guideline on mycotic skin infections of the Dutch College of General Practitioners (NHG-standaard), which states that confirmatory testing for onychomycosis is usually not required.[11,33,34] However, the differential diagnosis is broad, and previous diagnostic studies have shown a potential but considerable risk (10-25%) of making an incorrect diagnosis.[10,34-36] This is important because patients might be unnecessarily exposed to particularly oral treatment, given the required treatment duration and potential side effects. However, most diagnostic studies were performed in hospital settings by specialists other than general practitioners, not necessarily representative of Dutch general practice.[23]

Another challenge concerning the diagnostic process is to determine the extent of affliction i.e. the severity of onychomycosis. This is an important clinical aspect to consider as studies have shown that the more severe the affliction gets, the less likely the affected nails will respond to treatment, including oral treatment.[22,37] Having a clinical tool to assess severity could help the general practitioner to choose the most suitable treatment, as well as to predict and evaluate response to treatment. Such an instrument was developed by Carney et al., the Onychomycosis Severity Index (OSI), which is now frequently used to assess severity in clinical trials.[22,37,38] However, the OSI has been primarily validated for use by dermatologists and not for use by general practitioners.[38,39]

Antimycotic treatment

In recent decades, multiple therapeutic studies have shown that the most effective way to treat onychomycosis is by systemic antimycotic treatment i.e. oral antifungals.[37] However, even oral treatment does not guarantee success.[37] To evaluate the efficacy of any type of treatment, it is important to consider the different definitions or types of cure regarding the treatment of onychomycosis. Clinical cure of onychomycosis is defined as

a normal-looking nail after treatment. Mycological cure implies negative confirmatory testing such as direct microscopy (potassium-hydroxide, KOH), polymerase chain reaction (PCR), fungal culture, or, preferably, a combination of tests. Note here that mycological cure can be possible even if the nail is visually still affected. Achieving both clinical and mycological cure is considered complete cure, the most important primary outcome measure in clinical trials.[22,37] Regarding the efficacy of oral antifungal treatment for toenail onychomycosis, the clinical cure rates vary from 36.8-57.5% for terbinafine and 14.4-51.9% for azoles such as itraconazole. Mycological cure rates are generally higher, ranging from 47.4-75.5% and 18.6-66.8% for terbinafine and azoles, respectively.[37]

Besides these variations in treatment success, other potential downsides to systemic treatment exist. Due to physiologically slow nail growth, especially in toenails, an extensive oral treatment period of three months and often longer is required.[34] Furthermore, even after successful treatment, there is a substantial risk of recurrence within the first years after treatment, ranging from 3-33% for terbinafine and 37-55% for azoles.[22,37] Also, the use of oral treatment may be limited due to important drug-drug interactions. Regarding terbinafine, these primarily consist of medications metabolized by the CYP2D6 enzyme, most importantly antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), beta-blockers such as metoprolol, and other antiarrhythmic drugs. Regarding itraconazole, some CYP3A4 metabolized medications are contraindicated, including simvastatin, midazolam, domperidone, dabigatran, quetiapine, and medications that prolong the QT interval.[33] Last but not least, oral antimycotics may have potentially serious side effects, ranging from severe skin reactions to fulminant hepatic failure.[40-44]

Therefore, effective topical treatment could be an important alternative to oral treatment, avoiding potential interactions and side effects described above. The Cochrane review by Foley et al. in 2020 provides a comprehensive overview of topical antifungals and device-based interventions.[22] Sufficient evidence showed that efinaconazole, ciclopirox, and tavaborole were significantly more effective than placebo. Adverse reactions are usually mild, transient, and limited to localized erythema, discomfort, e.g. burning sensation, or changes in shape or colour of the nail exposed.[22] However, the required treatment period is longer, mostly 6-12 months, and clinical cure rates reported so far are lower than for oral treatment (4.1-16.2%), with a wider range in mycological cure rates (30.3-94.5%).[22] When considering Dutch general practice, the most effective topical antifungals included in the Cochrane review are either unavailable (efinaconazole, tavaborole) or not registered for use in onychomycosis (ciclopirox). Topical miconazole (Daktarin®), readily available in the Netherlands, and the more practical once-weekly amorolfine (Loceryl®) available in surrounding countries, were not included in the Cochrane review due to the lack of randomized studies.[22,45] This left the current Dutch guideline without the required evidence to provide solid recommendations on topical

treatments for use in Dutch general practice.[33] The uncertainty about the efficacy of the available topical antifungals was therefore considered a knowledge gap and put on the national research agenda of the Dutch College of General Practitioners in 2018.[46]

Prognostic implications of onychomycosis

Although onychomycosis may be limited to minor visual nail changes in many patients, for others, onychomycosis can be the cause of substantial symptoms and burden, decreasing the affected patient's quality of life.[26,29] Furthermore, onychomycosis may contribute to long-term negative health outcomes in susceptible patients, especially in patients with diabetes.[25,47] This is important since the prevalence of onychomycosis is increased in patients with diabetes and other immunocompromised states, with up to one-third of diabetic patients affected compared to 4.3-5.5% of the general population.[26] Subsequently, the risk of developing complications from onychomycosis, such as bacterial skin infections and lower leg ulcers, is also significantly increased in patients with diabetes.[24,47-50] The development of a diabetic ulcer is the cause of substantial healthcare costs and morbidity due to e.g. secondary bacterial infections, hospital admissions, and surgeries, ultimately leading to lower-extremity amputations and increased overall mortality.[51,52] Therefore, early identification of patients at risk of developing ulcerative complications could reduce the impact of onychomycosis and potentially prevent part of these negative health outcomes.[24,50,52] However, the relationship between onychomycosis and ulcerative complications in patients with diabetes has not been well studied in primary care.[49,53]

THESIS OUTLINE

This thesis consists of three parts, addressing the three clinical stages and their specific challenges in the care path for toenail onychomycosis presented in general practice: diagnosis, treatment, and prognosis.

In Part I, the research focuses on diagnostic challenges. In Chapter 2, the accuracy of the clinical diagnosis of onychomycosis is addressed, as onychomycosis is often assumed to be easily recognizable and effectively diagnosed based on history and physical examination. Secondly, the reliability of the existing Onychomycosis Severity Index (OSI) to assess onychomycosis severity in primary care settings is addressed in Chapter 3.

In Part II, onychomycosis therapy is addressed. A clinical case report describes a severe skin reaction from oral terbinafine (Chapter 4), illustrating potential harms from systemic treatment and serving as an introduction to finding an effective topical treatment. Subsequently, topical treatments for onychomycosis in Dutch general practice are studied through a randomized double-blind, placebo-controlled trial that evaluates

the efficacy of two frequently used but not well-studied topical antifungals, miconazole and amorolfine (Chapter 5).

In Part III, the prognostic implications of onychomycosis in patients with Diabetes are addressed through a large longitudinal cohort study based on routine care data, investigating the association between onychomycosis and ulcerative complications (Chapter 6).

Finally, a general discussion and summary (Chapter 7) provides the overall findings, a comparison with previous literature, methodological considerations, and aims to reflect on implications for daily practice. A Dutch summary is provided at the end.

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