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A Paradigm Shift in the Treatment and Management of Onychomycosis

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Onychomycosis · Treatment · Management · Superficial mycoses · Paradigm · Antifungal resistance

Abstract
There is an increase in the incidence of onychomycosis, especially in at-risk populations. Onychomycosis is difficult to treat, as the efficacy of most antifungal agents is relatively low. Nondermatophyte molds (NDMs) and mixed infection (dermatophyte plus NDM) onychomycosis are contributing to growing antifungal resistance, as they are often underestimated and ignored due to incorrect diagnosis. There is a need for a paradigm shift in the management of onychomycosis to a patient-centered, holistic approach with an emphasis on laboratory diagnosis prior to initiating treatment, which enables the rational choice of the antifungal agent. Additionally, in the case of resistant infections, antifungal susceptibility testing is recommended. Strategies for effective management of onychomycosis include disinfection of fungal reservoirs in shoes and socks and prophylaxis post-treatment using topical antifungal agents. These measures may reduce the recurrence of onychomycosis and improve long-term clinical success.

Introduction

Superficial mycoses are becoming a major public health concern as they are one of the most common global infections [1, 2]. In some instances, superficial fungal infections may lead to invasive infections, whose incidence is increasing partly due to a rise in at-risk populations [3–5]. Systemic antifungal agents are the most effective treatment for onychomycosis; however, they are associated with serious but uncommon side effects such as hepatotoxicity and drug interactions. Therefore, effective topical therapies may be preferred in certain circumstances [6–9]. Treatment is aimed at the eradication of the fungal pathogen(s) (mycological cure), and, where possible, a return to normal, healthy appearing nails (clinical cure) [6, 7, 10–12].

Successful treatment options for onychomycosis are limited; treatment failures and disease recurrence are frequently encountered [6, 10, 11, 13]. Onychomycosis patients (10–53%) may experience relapse or reinfection after the initial infection has been eradicated [14–19]. This may be due to either failure to fully eradicate the fungal pathogen or reinfection with a new causative strain following subsequent exposure [20]. Several factors contribute to the high relapse and/or reinfection rate, including genetic predisposition to onychomycosis; incorrect diagnosis at baseline; infection with nondermatophyte molds (NDMs);

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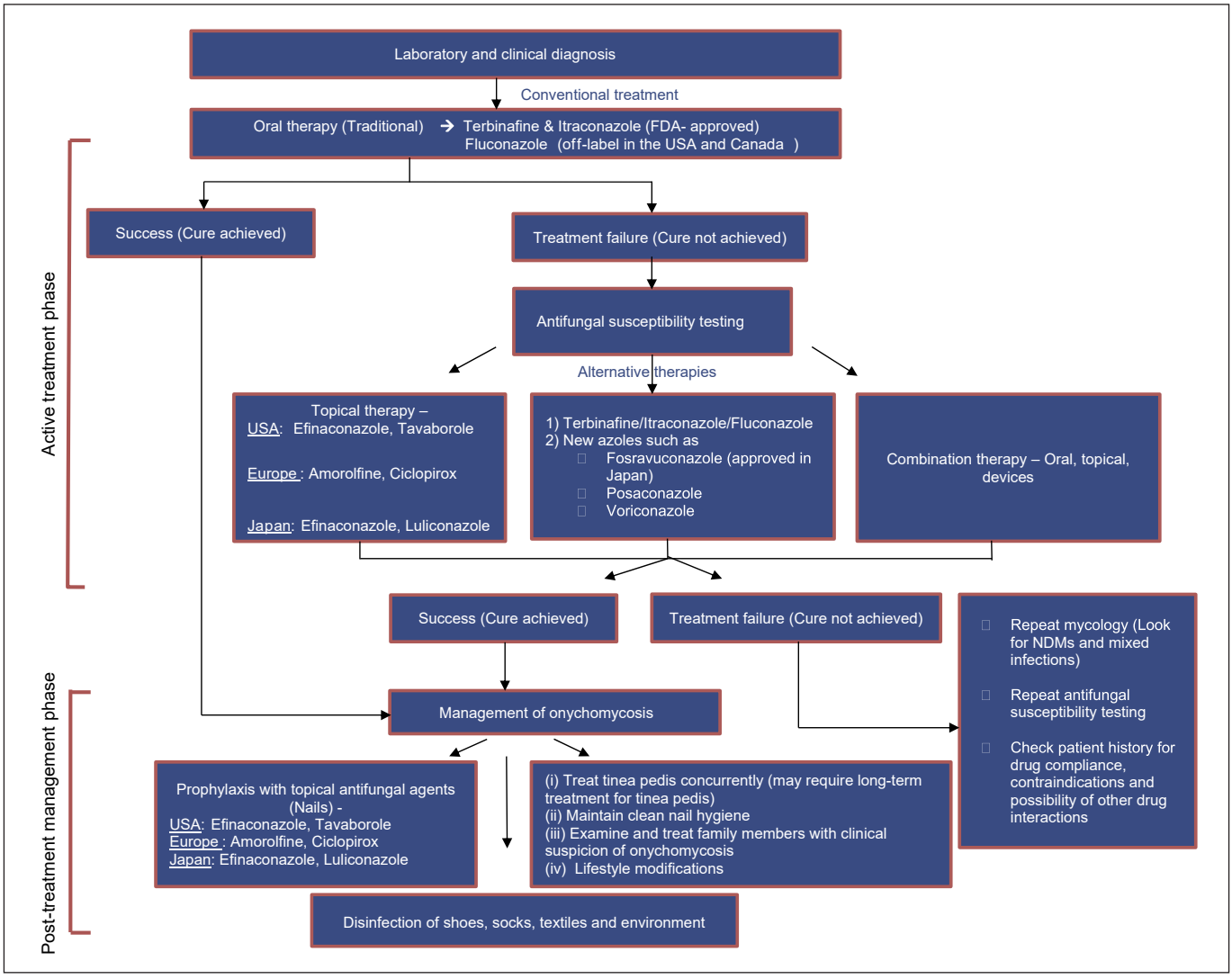

Fig. 1. Management of onychomycosis: an overview. NDMs, nondermatophyte molds.

mixed infections (dermatophyte and NDM); antifungal pharmacokinetics and pharmacodynamics; comorbidities such as diabetes, HIV, and presence of concurrent tinea pedis; the presence of biofilms; antifungal resistance; and dormant fungal reservoirs (arthroconidia) present in the nail bed that are resistant to antifungals [5, 14, 20–24].

Numerous strategies have been recommended for the management of onychomycosis, most of which focus on antifungal therapy, that is, the choice of antifungal and drug regimen. However, due to the multifactorial nature of onychomycosis, focusing solely on antifungal therapy may not result in the successful eradication of the infection. We propose a paradigm shift in the approach to onychomycosis to a holistic practice (Fig. 1), which includes accurate diagnosis to assist in the optimal choice of antifungal agent, disinfection of fungal reservoirs (shoes, socks, and shower stalls), encouraging lifestyle changes, and prophylaxis posttreatment.

Laboratory Diagnosis and the Need for Antifungal Susceptibility Testing

Laboratory diagnosis should be considered wherever possible prior to initiating antifungal therapy. Identification of the fungal pathogen to the species level and its viability can be achieved through appropriate laboratory diagnosis (direct microscopy using KOH, fungal culture,

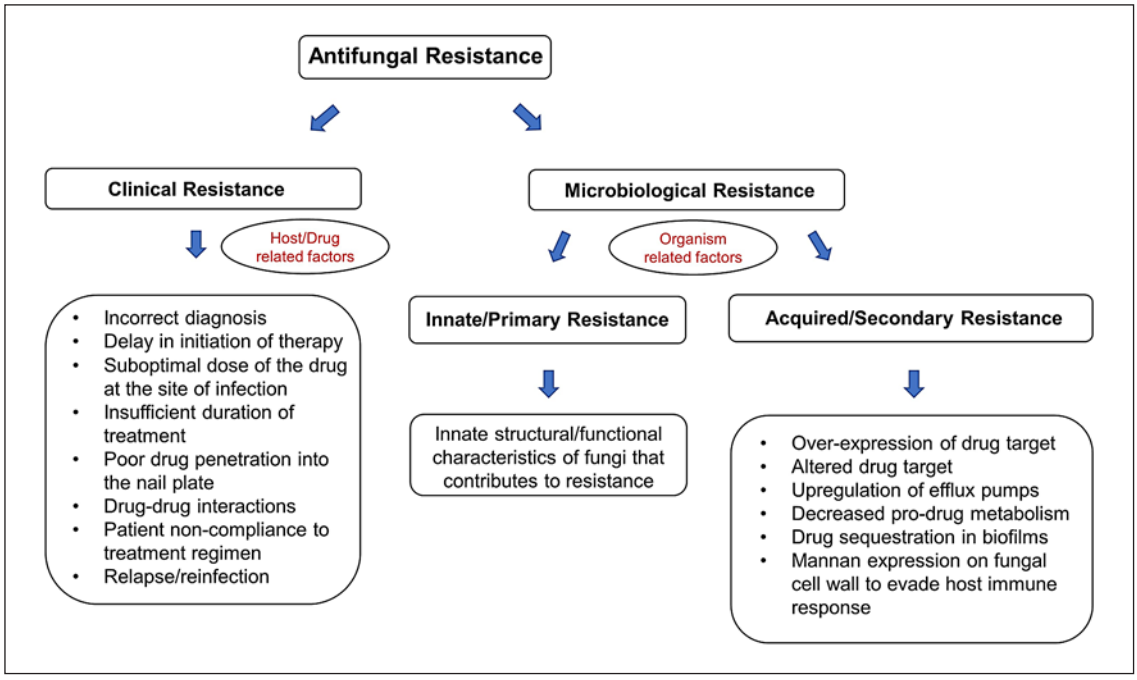

Fig. 2. Dermatomycoses: mechanisms of antifungal resistance.

histopathology, or molecular biology techniques such as polymerase chain reaction). To identify and confirm onychomycosis caused by NDMs, clinical diagnosis with serial mycological confirmation (minimum 2 different time points) from patients taken at approximately 4 weeks apart is recommended [25–27]. Where possible, antifungal susceptibility testing, especially in those patients not responding to primary treatment, should be strongly considered. Minimum inhibitory concentration (MIC) values of the causative organism(s) to the antifungal agent(s) allow for the selection of the most appropriate antifungal agent(s) to manage recalcitrant infections [28].

Treatment Strategies

Antifungal Resistance

Antifungal resistance is being increasingly reported around the globe [21, 29–31]. Antifungal resistance can be clinical or microbiological (Fig. 2) [20, 21, 32]. Clinical resistance is attributed to host-, treatment-, or drug-related factors (e.g., incorrect diagnosis, suboptimal dose of the drug, and patient noncompliance) while microbiological resistance is attributed to organism-related factors (e.g., genetic mutations) [32]. These factors may contribute to resistance individually or in combination [5, 21, 32]. A substantial number of the recalcitrant infections (especially *Trichophyton* isolates) are due to terbinafine resistance [21, 33–36]. However, not all treatment-failure cases are resistant to initial antifungal therapy. For example, Ghannoum et al. [20] reported that the *in vitro* susceptibility testing of all isolates from onychomycosis patients who failed treatment with oral terbinafine did not indicate resistance to terbinafine, itraconazole, fluconazole, and/or griseofulvin (based on the MIC values). Instead, the treatment failures were suggested to be due to host or family factors, that is, clinical resistance. Therefore, when antifungal resistance is suspected, the cause behind it (increased MIC, patient noncompliance, or other factors) must be determined to ensure appropriate action is taken (e.g., change of antifungal drug, encouraging patient compliance, and focusing on patient- or family-related factors).

Overexposure to the conventional antifungal drugs used to treat systemic and cutaneous fungal infections may have contributed to the terbinafine and azole resistance [5, 33, 34, 37–39]. Onychomycosis case studies reporting failure to terbinafine therapy are being increasingly documented in the literature [21, 40–43]. According to a multicenter study, the prevalence of terbinafine-resistant strains (*Trichophyton rubrum* and *Trichophyton mentagrophytes*) in India ranges from 16 to 77% [21, 31]. Terbinafine resistance is spreading across countries with isolates

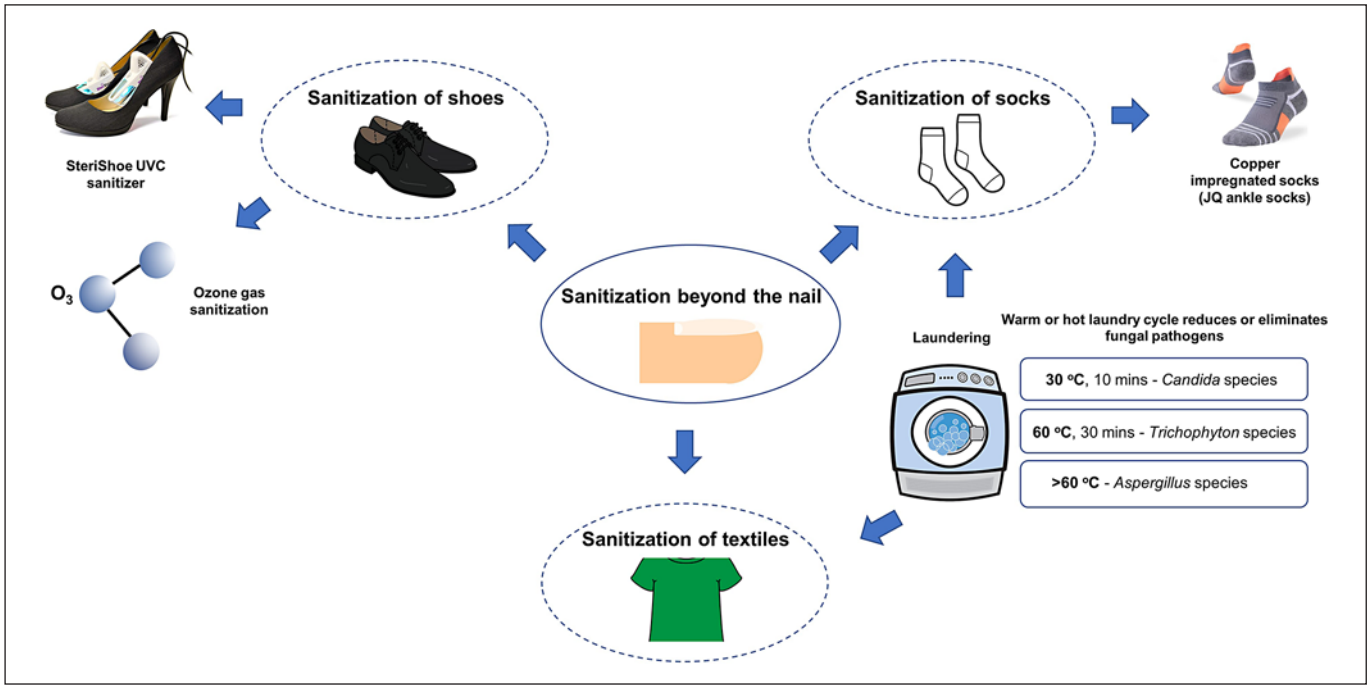

Fig. 3. Onychomycosis: recommendations for sanitization of shoes, socks, and textiles.

reported in Canada, the USA, Iran, Poland, Germany, Switzerland, and Denmark, which may be due to an increase in immigration, travel, and a shift in epidemiology towards more NDMs and mixed infection onychomycosis [21, 36, 44, 45]. Along with clinical terbinafine resistance, mutations in the squalene epoxidase gene are attributed to conferring microbiological terbinafine resistance in *T. rubrum* and *T. mentagrophytes* isolates [21, 33, 34, 36, 46].

A potential for developing azole resistance is generally observed in *Candida* and *Aspergillus* species and primarily occurs due to mutations in the genes encoding drug target (*ERG11*) and upregulation of efflux pumps (*MDR1, CDR1,* and *CDR2*) [5, 39, 47–49]. Since azoles are the only class of antifungals used both in agriculture and in the clinic, environmental fungi and opportunistic pathogens such as *Aspergillus* species may acquire resistance to azoles through exposure to fungicides in agricultural situations, thus are resistant to azole therapeutics even before colonizing the nail unit [5, 50]. Recent studies suggest that azoles also have the potential for developing resistance in dermatophytes through mutations in enzymes in the ergosterol pathways [51]. The global incidence of azole resistance in dermatophytes is roughly 19% [51]. Azole (itraconazole and voriconazole) resistance possibly mediated through multidrug efflux pumps has also been reported in a clinical isolate of *T. rubrum* [52].

One of the major factors contributing to antifungal resistance is the occurrence of mixed infections, which is often underestimated [53, 54]. Mixed infections account for about 6% of all superficial mycoses [55]. The notion of NDMs as sole etiological agents of onychomycosis, or in combination with a dermatophyte in a mixed infection, is often met with skepticism and dismissed since NDMs are often regarded as common laboratory contaminants or commensals of the nail, skin, and hair [27]. We propose that NDM and mixed infections be investigated as possible etiological agents of onychomycosis especially when there is treatment failure. Broad-spectrum antifungal agents such as itraconazole, efinaconazole, and tavaborole may be considerations in the treatment and management of mixed infection onychomycosis [56, 57]. Terbinafine may now be a less attractive choice if there is a concern for terbinafine-resistant dermatophytes.

Alternative Therapies for Recalcitrant Onychomycosis

Treatment of recalcitrant onychomycosis with azoles such as posaconazole, voriconazole, fosravuconazole, or a combination of these with other oral or topical antifungal agents has been documented [40, 58, 59]. Terbinafine- and itraconazole-resistant onychomycoses due to dermatophytes such as *T. rubrum* (fingernails), NDMs such as *Fusarium* species (toenails), or yeasts such as *Candida*

species (fingernails) have been cleared using oral voriconazole (200 mg twice daily for 3 months), oral posaconazole (pulse regimen: 800 mg oral solution/day for 1 week per month for 4 months), or fosravuconazole (100 mg/day for 3 months), respectively [40, 58–60]. Amphotericin B (once daily application for 12 months), a topical broad-spectrum antifungal agent belonging to the polyene class, has been shown to be effective and safe in treating NDM onychomycosis caused by *Fusarium*, *Acremonium,* and *Aspergillus* species [37, 61].

Sequential or combined oral antifungal therapy with terbinafine and itraconazole used off-label is a consideration for those patients who fail therapy or show poor response to initial monotherapy [62]. Alternatively, oral terbinafine and itraconazole may be combined off-label with topical amorolfine, ciclopirox, efinaconazole, or tavaborole. The different routes of administration allow for complementary drug penetration to the infection site in effective concentrations [62]. Additionally, combination antifungal therapy may be effective in treating difficult NDM/*Candida* onychomycosis and mixed infections due to the synergistic action of the drugs involved, broad-spectrum activity, and increased efficacy [63–65].

It is important to examine the patient for the presence of tinea pedis, as onychomycosis often coexists with tinea pedis [11, 66, 67]. The surrounding skin may act as a fungal reservoir and predispose the nail to a cycle of reinfection and recurrence [14, 66, 68]. Concurrent tinea pedis can be effectively treated with topical therapy [69, 70].

Management of Onychomycosis: Beyond the Nail

Relapse and reinfection rates of onychomycosis (10–53%) [14–16, 19] are high, with recurrence likely to occur within 30 months of cure following treatment with systemic antifungal agents [14]. Several nontreatment factors may contribute to recurrence, including family history, underlying physiology, lifestyle, occupation, physical trauma, and environmental conditions [14, 71]. Strategies to reduce recurrence should be encouraged.

Sanitization Techniques

Continued or re-exposure to fungal reservoirs, such as infected shoes, socks, or textiles, can contribute to reinfection (Fig. 3) [72–77]. Dermatophytes are known to colonize and survive for a long duration in footwear worn by patients with onychomycosis and tinea pedis [78]. Fungi may use sweat and skin cells trapped in footwear as a source of nutrients to create and maintain fungal reservoirs [72, 79, 80]. Textiles such as towels, sheets, and blankets are also potential fungal reservoirs [72, 79]. Contaminated socks and shoes can act as a source of reinfection when worn by patients after achieving cure with antifungal therapy [81]. Footwear and textiles can possibly contaminate the sterile laundry of patients when stored in the same laundry basket or when washed in the same washing machine [72, 82]. The basic sanitization recommendations for patients include replacing heavily contaminated footwear with a new pair, changing socks to an absorbent material with once or twice daily replacement, and storing contaminated clothing separately from sterile wear to minimize transmission and contamination [72].

Textiles represent an important link in the chain of dermatophyte infections [82, 83]. The use of functionalized, antimicrobial fabrics is recommended as a measure to reduce the spreading of dermatophyte infections [82]. For example, copper-impregnated socks may be effective against dermatophytes as copper has fungicidal and antibacterial properties [73, 84, 85].

Laundering contaminated clothing plays a role in reducing the fungal burden. Washing at high temperatures reduces or eliminates dermatophytes and *Candida* species [13, 75, 76, 86, 87]. Hammer and colleagues [75] observed that washing at 30°C for 10 min eliminated *C. albicans,* while washing at higher temperatures (60°C) for 30 min was required to completely eradicate *T. rubrum*. However, *Aspergillus* species still persisted in some of the socks washed at 60°C, which may require higher temperature laundering and drying [76]. It is suggested that if laundry machines are not properly sanitized, they may act as a fungal reservoir, contaminating other sterile textiles. This is believed to be the cause of concurrent tinea cruris (jock itch) in a certain percentage of tinea pedis patients [72, 75, 87, 88].

Multiple devices have been developed to sterilize infected footwear. Ozone gas disinfection is another novel technique recommended for sanitization of contaminated footwear, exhibiting fungicidal activity against *T. rubrum* and *T. mentagrophytes* colonies [72, 74, 89, 90]. Ultraviolet shoe sanitizers have been developed to irradiate the inner soles of shoes and reduce fungal burden, as fungi absorb UV light at a wavelength of 200–300 nm with germicidal effects [72, 77, 91–95].

Microwave irradiation has been investigated for its inhibitory effect on dermatophytes such as *T. rubrum*, *T. interdigitale,* and *Microsporum canis* [96]. Complete inhibition of fungal growth occurred on dermatophyte-infected cork and polyethylene sponge insoles after a 30-s exposure to microwaves at 560 W and a maximum temperature of 60°C, without damaging the insoles [96]. The

mechanism of microwave irradiation to disinfect contaminated footwear is not yet fully understood [96].

Environmental and Lifestyle Changes

Wearing shoes or sandals in high-risk areas such as swimming pools and baths, wearing properly fitting footwear, drying feet following a bath or shower, and maintaining personal and nail hygiene by cutting nails short and keeping them clean may help reduce the spread of fungal organisms. Examining and treating infected family members and housemates for onychomycosis and tinea pedis is also important, as they may act as a source of fungal reservoirs [13, 97].

Prophylaxis

Topical antifungal agents such as amorolfine, efinaconazole, and tavaborole should be considered as prophylaxis posttreatment to delay or avoid recurrence [14, 98]. With high concentrations of efinaconazole (well above the MIC of the causative dermatophytes) in the nail for up to 2 weeks posttreatment, twice a week application of efinaconazole as a prophylactic agent may prevent reinfection [14, 99]. Prophylaxis with efinaconazole for the affected nail(s) and a topical antifungal for tinea pedis should be maintained for 2–3 years, or even longer, especially in those patients with diabetes and poor peripheral circulation.

A Holistic Approach with a Laboratory-Directed Focus towards Treatment and Management of Onychomycosis: A Proposed Paradigm Shift

Treating onychomycosis should not be confined to the nail. The proposed paradigm shift in the treatment of onychomycosis from the conventional drug-centered approach to a patient-centered approach is a holistic practice with a laboratory-directed focus. It is important to have mycological confirmation and clinical diagnosis of onychomycosis. In cases of treatment failures and suspected antifungal resistance, antifungal susceptibility testing and investigation into environmental and patient-related factors will assist in determining the most appropriate antifungal agent(s) for targeted therapy. Disinfection of shoes and socks and prophylactic antifungal therapy for the affected nail(s) and surrounding skin may reduce the spread of fungal organisms, which will help to achieve successful long-term management of onychomycosis.

Conflict of Interest Statement

A.K.G. reports grants from Bausch Health and Ortho-Dermatologics outside the submitted work. M.V. and H.J.R. report personal fees from Mediprobe Research Inc. during the conduct of the study. R.C.S. has nothing to disclose. N.H.S. reports personal fees from Alpha Laboratories outside the submitted work. V.P. reports personal fees from Pfizer, Abbvie, Janssen, UCB, Novartis, Almirall, and Celgene and grants from AbbVie, Bausch Health, Celgene, Janssen, LEO Pharma, Lilly, NAOS, Novartis, Pfizer, Pierre-Fabre, Sanofi, and Kyowa Kirin Co., Ltd. outside the submitted work.

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Author Contributions

Aditya K. Gupta contributed to the conceptualization and writing of the manuscript. Maanasa Venkataraman and Helen Renaud contributed to the writing of the manuscript. Richard Summerbell, Neil Shear, and Vincent Piguet provided their critical review of the manuscript.

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