INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Non-Invasive Fungal Infections***
-August 2024-

Background:

In August 2024, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed treatment of non-invasive fungal infections (dermatophytosis, onychomycosis, and oral candidiasis). This marks the first NPTC review of medications specific to these conditions. Medications listed on the IHS National Core Formulary (NCF) relevant to this condition include clotrimazole (topical) and fluconazole (oral). Following clinical review and analysis, the NPTC voted to **add oral terbinafine** to the NCF.

Discussion:

Dermatophytosis (tinea, ringworm) is a superficial fungal infection of the skin which typically presents as an itchy, red rash (circular or ovoid lesions with central clearing or peeling/maceration/fissuring in intertriginous areas). Causative dermatophytes include *Trichophyton, Epidermophyton, and Microsporum* species with *Trichophyton rubrum* accounting for the majority of cases. Predisposing factors include diabetes mellitus, immunocompromised status, excessive sweating, occlusive clothing, prolonged exposure to water, athletic participation in contact sports, and family members with tinea.[1-3]

A 2014 Cochrane Review evaluating topical treatments for tinea cruris and tinea corporis showed that terbinafine was more effective than placebo for clinical cure (RR 4.51, 95% CI: 3.10 to 6.56, NNT 3, 5 studies), naftifine was more effective than placebo for clinical (RR 2.42, 95% CI: 1.41 to 4.16, NNT 3, 1 study) and mycological cure (RR 2.38, 95% CI: 1.80 to 3.14, NNT 3, 3 studies), and clotrimazole was more effective than placebo for mycological cure (RR 2.87, 95% CI: 2.28 to 3.62, NNT 2, 2 studies).[4] A 2022 systematic review on the treatment of tinea pedis revealed that topical allylamines and azoles were both more effective than placebo for mycological cure (terbinafine vs. placebo RR 3.9, 95% CI: 2.0 to 7.8, 5 studies, 488 participants). With regard to systemic therapy, terbinafine was more effective than itraconazole for mycological cure (RR 1.3, 95% CI: 1.1 to 1.5, 2 studies, 554 participants).[5]

Onychomycosis is a fungal infection of the nail unit caused by dermatophytes, yeasts, and non-dermatophyte molds. Clinical subtypes include:

- Distal lateral subungual onychomycosis (DLSO): Discoloration, hyperkeratosis, and onycholysis of the distal lateral aspects of the nail
- White superficial onychomycosis (WSO): White, chalky deposits on the surface of the nail
- Proximal subungual onychomycosis (PSO): Discoloration overlying the nail matrix, seen in immunocompromised patients.

Trichophyton rubrum is the most frequently identified causative agent. Predisposing factors include aging, diabetes, mellitus, immunocompromised status, tinea pedis, frequent exposure to water and family members with onychomycosis.[6]

An American Academy of Dermatology contribution to the American Board of Internal Medicine Foundation's Choosing Wisely campaign specifically recommends against prescribing oral antifungal therapy for suspected nail fungus without confirmation of fungal infection. Diagnostic testing includes potassium hydroxide preparation, fungal culture, biopsy plus periodic acid-Schiff stain, and polymerase chain reaction.[7] The 2014 British Association of Dermatologists' Guidelines for the Management of Onychomycosis recommends terbinafine and itraconazole as first-line systemic therapy for onychomycosis. Itraconazole can be prescribed continuously or as pulse therapy with suggestions to monitor hepatic function in patients with known hepatic impairment, in those receiving continuous therapy for more than one month, and with concomitant use of hepatotoxic drugs. Terbinafine is prescribed continuously with recommendations for baseline liver function tests and blood count in adult patients with history of hepatotoxicity or hematological abnormalities. Topical therapy (ciclopriox lacquer) is limited to WSO, DLSO if <80% of the nail plate is involved, or when systemic therapy is contraindicated.[8]

A 2017 Cochrane Review evaluating systemic treatments for toenail onychomycosis revealed that both terbinafine and azoles are more effective than placebo for clinical and mycological cure, but terbinafine was probably more effective than azoles for clinical (RR 0.82, 95% CI: 0.72 to 0.95, 15 studies, 2168 participants) and mycological cure (RR 0.77, 95% CI: 0.68 to 0.88, 17 studies, 2544 participants). Azoles and griseofulvin had similar efficacy in achieving clinical (RR 0.94, 95% CI: 0.45 to 1.96, 5 studies, 222 participants) and mycological cure (RR 0.87, 95% CI: 0.50 to 1.51, 5 studies, 222 participants), but the risk of adverse effects was probably higher for griseofulvin (RR 2.41, 95% CI: 1.56 to 3.73, 2 studies, 143 participants). Terbinafine may be more effective than griseofulvin for clinical (RR 0.32, 95% CI: 0.14 to 0.72, 4 studies, 270 participants) and mycological cure (RR 0.64, 95% CI 0.46 to 0.90, 5 studies, 465 participants) with

griseofulvin associated with a higher risk of adverse effects (RR 2.09, 95% CI: 1.15 to 3.82, 2 studies, 100 participants).[9] A 2020 Cochrane Review on topical and device-based treatments for fungal infections of the toenails concluded that there was evidence supporting the effectiveness of efinaconazole 10% solution (RR 3.54, 95% CI: 2.24 to 5.60; 3 studies, 1716 participants), ciclopirox 8% lacquer (RR 9.29, 95% CI: 1.72 to 50.14, 2 studies, 460 participants, low-quality evidence), and tavaborole 5% solution (RR 7.40, 95% CI: 2.71 to 20.24, 1198 participants) compared to vehicle for complete cure.

Oral candidiasis is an infection of the oral cavity caused by *Candida* species. Clinical subtypes include pseudomembranous (thrush), atrophic (denture stomatitis), chronic hyperplastic, midline glossitis, and angular cheilitis candidiasis. *Candida albicans* is the most common causative species (>80%), but non-albicans species including *C. glabrata, C. krusei, C. dubliniensis,* and *C tropicalis* have been isolated as well. Predisposing factors include age extremes, immunocompromising conditions, metabolic disease, steroid use, antibiotic use, etc. [11, 12]

The Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America recommends the use of clotrimazole troches or miconazole mucoadhesive buccal tablets as first-line treatments for mild disease with nystatin as an alternative option. For moderate to severe disease, the guideline recommends fluconazole with itraconazole and posaconazole as alternatives.[13]

A 2021 meta-analysis regarding efficacy of antifungal treatment concluded that itraconazole, miconazole, clotrimazole, fluconazole, nystatin, and amphotericin B all increased the odds of mycological cure, with fluconazole having higher odds of mycological cure than any other treatment studied (OR: 2.40, 95% CI: 1.10 to 3.80).[14]

Findings:

Dermatophytosis, onychomycosis, and oral candidiasis are common non-invasive fungal infections. These infections can cause significant morbidity for patients, but there are effective treatments. For most tinea infections, topical azoles and allylamines (naftifine, terbinafine) are effective with minimal side effects. Systemic treatments are most effective for onychomycosis with terbinafine preferred over itraconazole, fluconazole, or griseofulvin due to its effectiveness and side effect profile. Topical therapies are an option for white superficial onychomycosis, distal lateral subungual onychomycosis when the majority of the nail plate isn't involved, or when systemic therapy is contraindicated (hepatic failure, congestive heart failure, etc); ciclopirox 8% lacquer and efinaconazole solution are effective treatments though duration of treatments is long. Topical formulations specifically designed to treat onychomycosis such as lacquers and solutions are preferred to creams, lotions, ointment, and gels due to improved penetration of the nail bed. For mild oral candidiasis, clotrimazole, miconazole, and nystatin are all effective treatments. For moderate to severe oral candidiasis, fluconazole is the preferred treatment.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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