FUNGAL SKIN INFECTIONS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Fungal skin infections Clinical Guidance- Issued May 2020

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Abbreviations

CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
DLSO	Distal Lateral Subungual Onychomycosis
FDA	Food and Drug Administration
F-RVCZ	Fosravuconazole L-Lysine Ethanolate
HPCH	Hydroxypropyl Chitosan
IDF	Insurance Drug Formulary
KOH	Potassium Hydroxide
NDM	Non-Dermatophyte Mold
NTP	Non-Thermal Plasma
OTC	Over the Counter
P-3051	Ciclopirox Hydrolacquer
PDT	Photodynamic Therapy
SFDA	Saudi Food and Drug Authority
TC	Tinea Capitis
TTO	Tea Tree Oil

Executive Summary

Skin infections are widespread across the globe, with dermatophytes being the primary culprits behind fungal infections affecting the skin, hair, and nails. Dermatophytes infections give rise to a range of clinical presentations, including conditions like tinea pedis, tinea corporis, tinea cruris, tinea capitis, dermatophyte onychomycosis (commonly referred to as tinea unguium[1]. Non-dermatophyte fungal skin infections include candida and aspergillus.

Fungal skin infections have been documented on a global scale, impacting approximately 20–25% of the world's population. In areas with a significant prevalence, the occurrence of dermatophytosis can escalate to as much as 40–60%[1]. A Systematic Review and Meta-Analysis were conducted to study the epidemiological Patterns of Skin Disease in Saudi Arabia. Dermatophytosis (6.6%) and onychomycosis (2.8%) were the two most common types of fungal skin infections[2].

Cutaneous dermatophyte infections can often be reasonably suspected through a physical examination. Nevertheless, since the physical symptoms can resemble those of other skin conditions, diagnosis is typically validated through testing[3].

The principal technique for diagnosing dermatophyte infections of the skin's outermost layer (e.g., tinea corporis, tinea pedis, tinea cruris, tinea manuum, tinea faciei) involves conducting a potassium hydroxide (KOH) preparation using skin scrapings obtained from the affected regions[3]. Fungal cultures can also be used for the diagnosis. The KOH smear exhibited a sensitivity of 73.3% while the culture sensitivity was 41.7%. Conversely, culture showed a specificity of 77.7%, and the KOH smear had a specificity of 42.5%[4].

Potential complications associated with dermatophyte infections include the risk of secondary bacterial infections, the development of tinea incognito, the occurrence of Majocchi's granuloma, and id reactions (autoeczematization). The recommended treatment approach involves the use of topical or systemic antifungal medications with activity against dermatophytes[3].

For instance, in the case of tinea pedis, topical medications such as azoles, allylamines, butenafine, ciclopirox, tolnaftate, and amorolfine have proven effective. When patients with confirmed tinea do not respond to topical therapy, oral antifungal drugs like terbinafine, itraconazole, fluconazole, and griseofulvin may be prescribed[3].

Different options are available for the treatment of onychomycosis, which can result from dermatophyte, yeast, or nondermatophyte mold nail infections. First-line approaches for managing mild to moderate onychomycosis encompass the use of

oral terbinafine and various topical agents, including efinaconazole, amorolfine, tavaborole, and ciclopirox[3].

CHI issued new guidelines related to the management of Fungal Skin Infections. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an **addendum** to the prior CHI Fungal Skin Infections clinical guidance and seeks to offer guidance for the effective management of Fungal Skin Infections. It provides an **update** on fungal skin infections Antifungal Prescribing **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

The previous CHI report included 4 guidelines and review articles:

Guidelines Requiring Revision	
Old Version	**Updated Version**
British Association of Dermatologists Guidelines for the Management of Tinea Capitis (2014)	N/A
British Association of Dermatologists Guidelines for the Management of Onychomycosis (2014)	N/A
American Academy of Family Physicians Diagnosis and Management of Tinea Infections (2014)	N/A
Review Article (Indian Dermatology Online Journal): Management of Tinea Corporis, Tinea Cruris, and Tinea Pedis (2016)	N/A

No updated versions of these guidelines have been issued by the respective medical societies.

Main triggers for the update are the inclusion of additional guidelines and review articles:

Additional Guidelines
Journal of the **German Society of Dermatology** S1 Guideline: Onychomycosis (**2023**)
Journal of the **German Society of Dermatology** S1 Guideline: Tinea Capitis (**2020**)
Indian Academy of Pediatrics (IAP) Standard Treatment Guidelines for Tinea Infections (**2022**)
Review Article: Trichophyton indotineae, from epidemiology to therapeutic (Journal of Medical Mycology 2023)

Clinical Practice Guideline for the Management of Candidiasis: **2016** Update by the **Infectious Diseases Society of America**
Practice Guidelines for the Diagnosis and Management of Aspergillosis: **2016** Update by the **Infectious Diseases Society of America**
Review Article by the Royal Australian College of General Practitioners: Superficial Fungal Infections (Australian Journal of General Practice **2019**)
Review Article: Updated Perspectives on the Diagnosis and Management of Onychomycosis (Clinical, Cosmetic and Investigational Dermatology **2022**)

After carefully examining clinical guidelines and reviewing the SFDA drug list, there **have been no changes or updates made to any of the previously listed drugs** in terms of drug information and **prescribing edits since May 2020**. Furthermore, **there are no new drugs that have received SFDA approval since then.** Additionally, it is advisable to remove **Bifonazole, Griseofulvin** (although it is still used for pediatric tinea capitis), **Naftifine** and **Tolnaftate** as they are no longer registered on the SFDA Drug List of September 2023.

All above recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the fungal skin infections therapeutic management.

Tables 1 and 2 summarize the major changes based on the fungal skin infections different guidelines used to issue this report:

Table 1. General Recommendations for the Management of Superficial Fungal Skin Infections

Management of Superficial Fungal Skin Infections		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
While relying solely on topical treatment is insufficient for curing tinea capitis, it is recommended to incorporate topical agents to reduce infectivity, restrict the transmission of spores, expedite the need for systemic antifungal drugs, and address asymptomatic carriers with a minimal load of fungal spores.	Not graded	Journal of the German Society of Dermatology S1 Guidelines: Tinea Capitis (2020)[5]

In the case of tinea capitis, the selection of the appropriate systemic antifungal medication is primarily based on the specific fungal species that has been identified. When dealing with Trichophyton spp., it is advisable to use terbinafine as the treatment of choice, whereas infections caused by Microsporum/Nannizzia spp. are most effectively treated with griseofulvin or itraconazole. Fluconazole has also been used as a substitute for terbinafine in tinea capitis treatment. However, its use has been relatively restricted due to its side effects and the absence of a cost-saving advantage.	Not graded	Journal of the German Society of Dermatology S1 Guidelines: Tinea Capitis (2020)[5]
Most cases of tinea corporis, tinea cruris, and tinea pedis can be efficiently managed using topical treatments. The suggested initial topical treatment for tinea corporis, tinea cruris, and tinea pedis involves the application of terbinafine 1% cream once or twice a day for a period of one to two weeks.	Not graded	The Royal Australian College of General Practitioners (2019)[6]
Oral treatment should be considered in the following situations: fungal nail infection (onychomycosis), scalp fungal infection (tinea capitis), extensive fungal skin infections, unsuccessful topical treatment, and individuals with compromised immune systems.	Not graded	The Royal Australian College of General Practitioners (2019)[6]
In cases of mild to moderate onychomycosis, topical antifungals are often sufficient for treatment, whereas oral antifungal medications are usually prescribed for moderate to severe cases.	Not graded	Clinical, Cosmetic and Investigational Dermatology (2022)
The widely accepted approach for the gentle removal of nails, without causing	Not graded	Journal of the German Society of

harm, involves keratolysis using 40% urea preparations in combination with occlusion.		Dermatology S1 Guideline Onychomycosis (2023)[7]
In cases of topical treatment with nail polish, it is recommended to use either amorolfine (a water-insoluble acrylic polish) or ciclopirox (available in both water-insoluble acrylic polish and water-soluble polish forms).	Not graded	Journal of the German Society of Dermatology S1 Guideline Onychomycosis (2023)[7]
Treatment for tinea manuum is similar to the treatment of tinea pedis.	Not graded	Indian Academy of Pediatrics (2022)[8]
The use of oral antifungal therapy is crucial for the treatment of tinea barbae.	Not graded	Indian Academy of Pediatrics (2022)[8]
Laser treatments may offer temporary improvements in nail appearance, but there is limited evidence to support their ability to sustain long-term clinical improvements or completely eliminate disease-causing fungi.	Not graded	Clinical, Cosmetic and Investigational Dermatology (2022)[9]
The primary systemic drugs approved and widely used for the treatment of onychomycosis are the allylamine terbinafine and the triazole itraconazole. Griseofulvin is also licensed for treating onychomycosis but is much less commonly used now given the higher efficacy and compliance rates and lower relapse rates of the other systemic agents. Fluconazole is not licensed for the treatment of onychomycosis and may represent a useful third-line therapy. Ketoconazole also demonstrates efficacy but the risk of hepatotoxicity with long-term therapy limits its use.	Not graded	British association of dermatologists' guidelines (2014)
It is worth considering the potential for extended antifungal prevention using	Not graded	Journal of the German Society of

nail polish products containing amorolfine or ciclopirox. This is typically applied less frequently after the successful treatment of onychomycosis.		Dermatology S1 Guideline Onychomycosis (2023)[7]

Table 2. General Recommendations for the Management of Potentially Systemic Fungal Skin Infections (Mainly in Immunocompromised Individuals)

Management of Potentially Systemic Fungal Skin Infections (mainly in immunocompromised individuals)		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
In patients at risk of systemic fungal infections, skin lesions can potentially signify the presence of a widespread infection, we strongly advise initiating voriconazole treatment while simultaneously investigating the existence of a primary infection source.	Strong recommendation; low-quality evidence	Infectious Diseases Society of America (2016): Clinical Practice Guideline for the Management of Aspergillosis[10]
In instances of aspergillosis occurring in burn injuries or extensive soft tissue wounds, it is strongly recommended to perform surgical debridement alongside antifungal therapy.	Strong recommendation; moderate-quality evidence	Infectious Diseases Society of America (2016): Clinical Practice Guideline for the Management of Aspergillosis[10]
First-line treatment for candidiasis should involve the administration of fluconazole.	Not graded	Infectious Diseases Society of America (2016): Clinical Practice Guideline for the Management of Candidiasis[11]
Individuals with Candida infections that do not respond to fluconazole should receive the same treatment approach as patients with AIDS who develop infections resistant to azole drugs.	Not graded	Infectious Diseases Society of America (2016): Clinical Practice Guideline for the

		Management of Candidiasis[11]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **fungal skin infections clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI fungal skin infections report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

There are no guidelines that were updated since May 2020.

Table 3. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Version	**Updated Version**
British Association of Dermatologists Guidelines for the Management of Tinea Capitis (2014)	N/A*
British Association of Dermatologists Guidelines for the Management of Onychomycosis (2014)	N/A*
American Academy of Family Physicians Diagnosis and Management of Tinea Infections (2014)	N/A*
Review Article (Indian Dermatology Online Journal): Management of Tinea Corporis, Tinea Cruris, and Tinea Pedis (2016)	N/A*

*: Not available

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI fungal skin infections report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
Journal of the **German Society of Dermatology** S1 Guideline: Onychomycosis (**2023**)
Journal of the **German Society of Dermatology** S1 Guideline: Tinea Capitis (**2020**)
Indian Academy of Pediatrics (IAP) Standard Treatment Guidelines for Tinea Infections (**2022**)
Review Article: Trichophyton indotineae, from epidemiology to therapeutic (Journal of Medical Mycology **2023**)
Clinical Practice Guideline for the Management of Candidiasis: **2016 Update by the Infectious Diseases Society of America**
Practice Guidelines for the Diagnosis and Management of Aspergillosis: **2016 Update by the Infectious Diseases Society of America**
Review Article by the Royal Australian College of General Practitioners: Superficial Fungal Infections (Australian Journal of General Practice **2019**)
Review Article: Updated Perspectives on the Diagnosis and Management of Onychomycosis (Clinical, Cosmetic and Investigational Dermatology **2022**)

1.2.1 Journal of the German Society of Dermatology S1 Guideline: Onychomycosis (2022)

The S1 guideline for the treatment of onychomycosis was published and endorsed by various professional societies including the German Society of Dermatology, the German-Speaking Mycological Society, the German Society of Pediatric and Adolescent Medicine, the Working Group for Pediatric Dermatology, and the Association of German Dermatologists[7]. The main recommendations are detailed below.

Diagnosis

- The diagnosis relies on clinical evaluation, which involves the patient's medical history and visual examination, including histological analysis when necessary. Pathogen detection can be achieved through either culture or, as it is becoming more prevalent, molecular biological techniques.

- The medical history should encompass the following elements: preexisting medical conditions (like diabetes or circulatory issues), progression of the condition, risk factors (such as sports involvement), and any instances of the disease in the patient's surroundings.
- Visual inspection is particularly important, focusing on the nature of the involvement and any other clinical signs of dermatophytosis, including tinea unguium in the fingernails, tinea pedum, and additional cases of tinea corporis.
- For diagnosis, a direct microscopic examination should be conducted. Identifying the causative agent through culture is a critical part of the diagnosis process before initiating (systemic) antifungal treatment. The direct molecular identification of dermatophyte DNA in the nail material significantly enhances diagnostic sensitivity and notably shortens the time required to initiate targeted treatment.
- Histological examination is recommended when a fungal infection is suspected but cannot be confirmed through other methods or when these methods are not accessible.
- To perform direct microscopy, it is advised to treat the sample on a slide with a 10-20% potassium hydroxide (KOH) solution, a 0.025% Congo red solution (in 5% SDS), or a 20% tetraethyl ammonium hydroxide (TEAH) solution. Utilizing fluorescence optical staining enhances the sensitivity of the microscopic examination and is a recommended practice.
- Conducting a fungal culture for pathogen identification is advisable. In cases where definitive species-level identification is challenging due to the absence of well-defined macroscopic and/or microscopic characteristics, employing molecular methods for identification is preferred.
- For patients who have previously received treatment and exhibit negative mycological test results, it is advisable to consider histological examination along with fungal staining (such as PAS or Grocott-Gomori staining). Currently, pathogen differentiation can be achieved through PCR and/or DNA sequencing. Combining a KOH preparation with histology enhances the diagnostic sensitivity.
- Regular resistance testing is presently not advised for onychomycosis. However, when clinical response to oral terbinafine treatment is insufficient in cases of onychomycosis, it's crucial to always take into account the potential decrease in sensitivity to the antifungal agent being used.
- The following goals should be defined in the treatment of onychomycosis:

1. Complete elimination of the pathogen as quickly and safely as possible, defined by negative repeat test (PCR method* if possible).
2. Largely healthy nails clinically (defined usually as < 5 to 10% residual change at the distal nail margin).
3. Prevention of further spread and/or interruption of infection chains.

Start of treatment

- When determining whether topical treatment, systemic treatment, or a combination of both is advisable, factors such as the nail matrix's involvement, the number of affected toenails or fingernails, the extent of surface area affected per nail, the presence of multiple health conditions in the patient, potential drug interactions, and the expected level of patient compliance should all be taken into consideration.

Atraumatic nail removal for onychomycosis of the toenails

- Keratolysis using 40% urea preparations with occlusion has become the established method for gently removing nails without causing trauma. Typically, the 40% urea preparation is applied daily to the affected nails under occlusion, and the treatment spans a duration of 2 to 3 weeks.
- It is advisable to consider a gentle nail removal procedure, known as atraumatic nail removal, before initiating topical and systemic antifungal treatment for onychomycosis. This helps reduce the accumulation of fungus-infected and excessively keratinized nail material and is recommended as an additional step in the treatment process.
- Atraumatic nail removal can be combined with systemic antifungal treatment.
- Traumatic (surgical) nail extraction is not recommended.
- Drilling the affected nails can be recommended.

Topical treatment with antifungal nail polish

- For mild to moderate nail infections, which include conditions like distal subungual onychomycosis, white superficial onychomycosis, and when the infection affects a maximum of 40% of the nail surface and/or a maximum of 3 out of 10 toenails, it is advisable to consider topical antifungal nail polish as a recommended treatment option.
- Filing or roughening to reduce the diseased parts of the nail is recommended.

- For topical treatment using nail polish, amorolfine (water-insoluble acrylic polish) or ciclopirox (water-insoluble acrylic polish or water-soluble polish) is recommended.

Table 5. Antifungal Nail Polish Preparations Currently Approved in Germany with Corresponding Ingredients and Application Frequencies. Adapted from the 2022 S1 Guidelines for Onychomycosis.

Nail polish preparation	Application frequency
Amorolfine HCl 5% acrylic nail polish (up to80% nail surface)	Once per week
Ciclopirox 8% acrylic nail polish	Every 2 days, twice per week from the second month
Ciclopirox 8% nail polish water-soluble + HP-chitosan (hydroxypropyl chitosan biopolymer [HPCH])	Once a day
Terbinafine (78.22 mg terbinafine/ml nail polish) water-soluble nail polish + HP-chitosan (hydroxypropyl chitosan biopolymer [HPCH])	Once a day for 4 weeks, then once per week

Systemic treatment

- In cases of moderate to severe onychomycosis and in the absence of contraindications, it is advisable to opt for oral (systemic) treatment. A combined approach involving both oral and topical antifungal treatment is considered beneficial.
- Continuous systemic treatment with terbinafine is recommended.
- Continuous systemic treatment with itraconazole can be recommended.
- Pulse treatment with itraconazole can be recommended.
- Pulse treatment with fluconazole can be recommended.
- Intermittent long-term treatment with low-dose terbinafine can be recommended in elderly multimorbid patients. [Expert opinion]
- Intermittent long-term treatment with low dose itraconazole can be considered.

Table 6. Systemic Treatment of Onychomycosis in Adults. Adapted from the 2022 S1 Guidelines for Onychomycosis.

Terbinafine	Fluconazole	Itraconazole
250 mg once daily. Toenail infection: 12 weeks Fingernail infection only: 6 weeks	150 mg once a week for 3–6 months for onychomycosis of the fingernails and 6–12 months for toenail infection	*Pulse treatment:* 400 mg daily (2 100-mg capsule twice a day (400 mg) for 1 week, then three-week interval = 1 pulse. Three pulses (1-week itraconazole + 3-week interval) or 3 months for toenail infection. Shorter for fingernail onychomycosis, possibly only 2 pulses. *Continuous dosing:* Conventional itraconazole 200 mg (2 hard capsules) once a day for 3 months, shorter for fingernail infection. SUBA-itraconazole For tinea unguium: 2 50-mg capsules (= 100 mg/d) daily for 12 weeks.
*Intermittent low-dose terbinafine treatment** (*off-label use, not confirmed by studies [expert opinion]) *Loading dose:* 250 mg terbinafine daily for 3 days, then 250 mg once a week until clinical healing (up to 1 year).		*Intermittent low-dose itraconazole treatment** (*off-label use, not confirmed by studies [expert opinion]) *Loading dose:* 100 mg SUBA-itraconazole (2 50-mg capsules) twice a day for 3 days, then maintenance treatment of 100 mg SUBA-

		itraconazole (=2 50-mg capsules SUBA-itraconazole) twice a day once a week until clinical healing (up to 1 year).

Choice of antifungal agent for systemic and topical treatment

- When choosing the antifungal agent for treating onychomycosis, it is crucial to always take into account the specific pathogen causing the infection.

Table 7. Choice of Antimycotic Agents Based on the Organisms Identified. Adapted from the 2022 S1 Guidelines for Onychomycosis.

Organism	Treatment
Dermatophytes: *T. rubrum* (most frequent cause) *T. interdigitale* (second most frequent cause)	**Topical**: amorolfine or ciclopirox nail polish **Systemic**: terbinafine (*T. rubrum* + *T. interdigitale*), fluconazole (*T. rubrum*), itraconazole (*T. rubrum* + *T. interdigitale*)
Yeasts: *Candida albicans* and *Candida parapsilosis* (often in fingernails)	**Topical**: amorolfine or ciclopirox nail polish Also, if applicable: **systemic**: fluconazole p.o. (continuous or interval therapy) or itraconazole, terbinafine also possible for *Candida parapsilosis*.
Molds: *Scopulariopsis brevicaulis* (frequent)	**Topical**: atraumatic nail removal with 40% urea paste. amorolfine or ciclopirox nail polish,possibly amphotericin B* (as suspension,*off-label use). Often no response to systemic antifungal treatment; exception: *Aspergillus* spp., *Onychocola canadensis* (*Arachnomyces nodosetosus*), terbinafine p.o. effective in individual cases.

Prophylaxis after treatment of onychomycosis

- One can contemplate the possibility of extended antifungal prophylaxis using nail polish preparations that contain amorolfine or ciclopirox. This is typically applied at reduced frequencies following successful treatment of onychomycosis.

Prevention of recurrence by disinfection of footwear

- It is advisable to suggest to patients that they disinfect their footwear as a preventive measure to avoid a recurrence and to maintain a clean environment.

Candida Onychomycosis

- For cases of Candida onychomycosis, it is advised to consider topical treatment using either ciclopirox or amorolfine nail polish.
- In addition to topical therapy, the use of fluconazole in continuous or intermittent (pulse) systemic treatment can also be recommended.

1.2.2 Journal of the German Society of Dermatology S1 Guideline: Tinea Capitis (2020)

The aim of the present update of the interdisciplinary German S1 guidelines is to provide dermatologists, pediatricians, and general practitioners with a decision tool for selecting and implementing appropriate diagnostic and therapeutic measures in patients with tinea capitis. The guidelines were developed based on current international guidelines, in particular the 2010 European Society for Pediatric Dermatology guidelines and the 2014 British Association of Dermatologists guidelines, as well as on a review of the literature conducted by the guideline committee. This multidisciplinary committee consists of representatives from the German Society of Dermatology (DDG), the German-Speaking Mycological Society (DMykG), the German Society for Hygiene and Microbiology (DGHM), the German Society of Pediatric and Adolescent Medicine (DGKJ) and the German Society for Pediatric Infectious Diseases (DGPI)[5]. Table 8 details the wording, symbols, and interpretation of the strength of recommendations.

Table 8. Strength of Recommendations and Interpretation

Strength of recommendations	Wording	Symbol	Interpretation
Strong recommendation for a measure	"Is recommended" or "... shall ..."	↑↑	We believe that all or nearly all people appropriately informed would make this decision. Clinicians will require less time with the patient for decision making. In most clinical situations, the recommendation can be adopted as a generally accepted approach.
Weak recommendation for a measure	"May be recommended" or "... should ..."	↑	We believe that most people appropriately informed would make this decision, but there is a substantial percentage of individuals who would not. Clinicians and other health care providers will need to devote more time to ensure that the choice of the intervention along with the consequences potentially associated therewith reflects the values and preferences of the individual patient. Decision-making processes in the health care system require thorough discussions and the involvement of various stakeholders.
No recommendation with respect to a measure	"...may be considered..."	0	For specific reasons, no recommendation in favor or against a specific intervention can be made at present (e.g., lack of evidence available, unclear or unfavorable risk-benefit ratio, and others)
Recommendation against a measure	"Is not recommended" "... shall not ..."	↓	We believe that all or nearly all people appropriately informed would make this decision.

Diagnosis

- The differential diagnosis for tinea capitis (TC) encompasses a broad spectrum of conditions, including any medical issue characterized by patchy hair loss, scalp scaling, and inflammation.
- The diagnosis of TC is based on clinical examination and laboratory tests.
- To ensure the accuracy of test results, it is crucial to conduct proper sampling, preferably with the use of sterile instruments.
- For direct microscopy, the sample is positioned on a glass slide and then covered with a 10-20% potassium hydroxide (KOH) solution.
- Molecular techniques, including traditional PCR followed by species identification through sequencing or specialized methods like ELISA, microarray, blot, as well as real-time PCR, along with MALDI-TOF mass spectrometry, are highly sensitive and precise methods.
- In patients who have undergone previous treatments and have negative mycological test results, performing histological analysis of biopsies combined with fungal stains (PAS, Calcofluor white) and, if needed, PCR, can be beneficial.
- Trichoscopy (scalp dermoscopy) as a diagnostic tool in TC patients may reveal certain characteristics, including black dots (representing dead hairs in hair follicles), scaling around hair follicles, comma-shaped, and corkscrew-shaped hairs. It's important to note that none of these features are unique or specific to TC.

Treatment

- The treatment of TC should be directed by the following treatment objectives:
    1. promptly and safely eliminating the causative organism, leading to clinical and, notably, mycological cure (indicated by negative KOH preparation and negative culture)
    2. alleviating symptoms
    3. preventing permanent hair loss
    4. averting further transmission and the disruption of infection chains.
- To achieve these objectives, a combination of systemic and topical therapies is typically necessary.
- TC patients are commonly treated on an outpatient basis, with hospitalization being an exceedingly rare occurrence.

- It is crucial to strictly avoid surgical interventions resulting from the misdiagnosis of deep dermatophytosis as an abscess, often due to insufficient mycological evaluation.

Topical treatment

- Although using topical treatment by itself is inadequate for treating TC, it is advisable to employ topical agents to decrease infectivity, limit the spread of spores, expedite the need for systemic antifungals, and address asymptomatic carriers with a minimal fungal spore burden.
- Topical agents employed include shampoos containing selenium (di)sulfide 1 %, ketoconazole 2 %, clotrimazole 2 % or ciclopirox 1 %, and – especially in the Anglo-American region – povidone-iodine.
- Shampoos need to be used for a duration of 2–4 weeks, applied for five minutes twice weekly.
- In addition, a daily application of an antifungal solution for one week is recommended.
- It is crucial not to restrict topical treatment to the specific affected area but to treat the entire length of the scalp hair with the antifungal solution.
- In a clinical trial, the efficacy of shampoos containing either selenium sulfide 1 % or ciclopirox 1 % as adjunctive treatments for pediatric was compared. Both shampoo formulations were similarly effective (mycological cure rates after 8 weeks: 91.7 % for griseofulvin plus selenium sulfide vs. 90.4 % for griseofulvin plus ciclopirox).
- Selenium sulfides, sometimes called selenium disulfide when combined, are compounds of heavy-metal salts that lead to the denaturation of enzymes in dermatophytes, ultimately causing sporicidal effects. However, these preparations are associated with disadvantages, such as a strong sulfuric odor and the potential for dehydration. They are commonly utilized in the form of anti-dandruff shampoos.

Systemic treatment

- Generally, systemic antifungal medications exhibit notably higher effectiveness in treating endothrix infections (e.g., Trichophyton spp.) compared to ectothrix infections (e.g., M. canis). Controlled clinical trials have provided evidence that the selection of antifungal therapy should be based on the specific species responsible for the infection.
- The selection of the appropriate systemic antifungal medication is primarily based on the specific fungal species that has been identified. When dealing

with Trichophyton spp, it is advisable to use terbinafine for treatment, while Microsporum/Nannizzia spp. infections are best treated with griseofulvin or itraconazole.

- If treatment needs to start before the exact species identification is confirmed, the choice of the antifungal agent should depend on the local epidemiological data and the likelihood of a particular dermatophyte's involvement.

Table 9. Choice of Antifungal Agents Based on the Organism Identified. Adapted from the 2020 S1 Guidelines for Tinea Capitis.

Organism	Treatment
Trichophyton mentagrophytes, benhamiae, tonsurans, violaceum, soudanense, and other *Trichophyton spp.*	Terbinafine
Microsporum canis, M. audouinii, M. ferrugineum	Itraconazole or griseofulvin (no longer available)*
Nannizzia gypsea	Itraconazole or griseofulvin (no longer available)*
*Although no longer available on the German market, griseofulvin is included in this list as it is still recommended internationally, particularly for *Microsporum*/*Nannizzia* infections. In Germany, the drug is available through international pharmacies.	

Table 10. Oral Treatment of Adult Tinea Capitis. Adapted from the 2020 S1 Guidelines for Tinea Capitis.

Drug	Daily dose	Treatment duration*
Itraconazole	100-200 mg once daily, directly after the main meal	4 weeks
Fluconazole	50 mg once daily; alternatively, 150 mg once a week	4-7 weeks 4-8 weeks
Terbinafine	250 mg	4-6 weeks
*The treatment durations listed above are mere recommendations; individual treatment durations are based on clinical presentation and the results of mycological tests, which should be performed at 14-day intervals starting in the 4th week of treatment. The goal is mycological cure. In adults too, adjuvant topical		

treatment (see below) is indispensable. Adults may expect a more rapid cure than children.

Table 11. International Recommendations for the Treatment of Pediatric Tinea Capitis. Adapted from the 2020 S1 Guidelines for Tinea Capitis.

Drug	Dosage	Treatment duration for Trichophyton spp.[5]	Treatment duration for Microsporum/ Nannizzia spp.[5]
Itraconazole[1,2]	5 mg/kg once daily, taken with the main meal; suspension (fasting; no food intake for 1 h) or for individuals < 20 kg, 50 mg/day; for individuals > 20 kg, 100 mg/day	4 weeks	6 weeks
Fluconazole[1,3]	6 mg/kg daily	3-4 weeks	6-8 weeks
Terbinafine[1]	for individuals < 20 kg: 62.5 mg; for individuals 21–40 kg: 125 mg; for individuals > 40 kg 250 mg, once daily	4 weeks	8-12 weeks; the drug's relevance in the treatment of these organisms remains controversial
Griseofulvin ultramicronized[4]	20 mg/kg (one or two single doses; taken with the main meal)	6-8 weeks	8-12 weeks

[1]Drugs not approved for children; in Germany, they may only be used if declared as "individual treatment attempt".

[2]Maximum daily dose is 100 mg/d, irrespective of body weight.

[3]In Germany, fluconazole is not approved for treatment of pediatric dermatophyte infections. The maximum daily dose is 400 mg/ day, irrespective of body weight.

[4]Griseofulvin is no longer available in Germany.

[5]The treatment durations listed above are mere recommendations; individual treatment durations are based on clinical presentation and the results of mycological tests, which should be performed at 14-day intervals starting in the

4th week of treatment (compare paragraph on “Treatment strategy in patients with tinea capitis and follow-up”).

Intermittent treatment

- Among a group of ten children diagnosed with TC (species: T. tonsurans in 6 instances, T. violaceum in 2 instances, and one case each of T. soudanense and M. gypseum), a treatment regimen involving three rounds of itraconazole therapy (administered at a dosage of 5 mg/kg daily for 1 week with 2-week intervals) led to full recovery in one case, clinical improvement in six cases, and eradication of the fungal infection in three cases.
- Administering fluconazole at a dose of 8 mg/kg once a week resulted in complete recovery in eight out of 20 children with TC due to M. canis, with treatment durations ranging from 5 to 17 weeks. Using the same dosage, the srudy reported significantly higher success rates in their study of 61 children with TC, including 33 cases of T. violaceum, 11 cases of T. tonsurans, and 17 cases of M. canis: 100% cure rate for Trichophyton species infections (treatment duration ranging from 8 to 12 weeks) and a 94% cure rate for M. canis infections (treatment duration spanning 8 to 16 weeks).
- All intermittent treatment methods in these trials were well-tolerated by the patients. Nevertheless, it is important to note that there remains insufficient evidence to provide a recommendation for intermittent treatment in general.

Description of individual agents

Griseofulvin

- Griseofulvin has fungistatic effects by inhibiting nucleic acid synthesis and thus arresting cell division during metaphase, as well as by disrupting cell wall synthesis.
- Dose: 20 mg/kg daily (one or two single doses; taken with the main meal; in Germany, the dosage approved for children < 14 years is 10 mg/kg; internationally, a daily dose of 20 mg/kg is usually given to patients with TC).
- Consuming the medication alongside a meal that contains fats enhances absorption and, consequently, improves bioavailability.
- Treatment duration is 6–8 weeks or more for infections caused by Trichophyton spp. and 8–12 weeks or more for Microsporum spp., or until fungal cultures are negative.
- Advantages: Vast experience, no resistance.

- Disadvantages: Currently taken off the German market and only available through international pharmacies; no liquid formulations; longer treatment durations required.
- Contraindications: Lupus erythematosus, porphyria, severe liver diseases.
- Drug interactions: Warfarin, cyclosporine, oral contraceptives, and others.

Terbinafine

- Terbinafine is a fungicidal allylamine antifungal that inhibits ergosterol synthesis in the cell wall.
- Even though it demonstrates efficacy against all dermatophyte species in laboratory settings, this treatment has proven to be more potent in combating Trichophyton spp. compared to Microsporum/Nannizzia spp.
- While increasing the dosage may enhance its effectiveness against the latter group, it doesn't surpass the efficacy of griseofulvin.
- Prolonging the treatment duration does not result in a higher level of effectiveness.
- In children, the dosage of terbinafine is based on body weight.
- The drug is well tolerated and shows no differences in safety profile in children compared to adults.
- Advantages: Fungicidal activity; shorter treatment duration, possibly associated with better compliance; very cost effective; safety profile.
- Disadvantages: No suspension formulation available; not the treatment of choice for Microsporum/Nannizzia infections.
- Drug interactions: Terbinafine is an inhibitor of CYP2D6; relevant drug interactions are possible in this context. Contraindications and potential interactions with other drugs must be considered.

Itraconazole

- Depending on the tissue concentration achieved, itraconazole has either fungicidal or predominantly fungistatic effects. The drug inhibits ergosterol synthesis in the cell wall.
- Doses of 50–100 mg/day for four weeks and 5 mg/kg/day for 2–4 weeks have been shown to be similarly effective as griseofulvin and terbinafine.
- Itraconazole is effective against both Microsporum/Nannizzia and Trichophyton species.
- It is well tolerated, even when used in the first year of life.

- Advantages: Short treatment duration; liquid formulation available.
- Disadvantages: Not approved for pediatric treatment in Germany. The liquid formulation (suspension) frequently causes diarrhea (cyclodextrin component). It should be stored in the refrigerator, as this also improves the bitter taste frequently disliked by children (personal recommendation by DeDoncker/JANSSEN-CILAG).
- Drug interactions: Itraconazole – and to a lesser extent also fluconazole (high doses) – are inhibitors of CYP3A4 and CYP2C. Especially CYP3A4 is involved in the metabolism of numerous drugs, whose levels are therefore elevated when azoles are taken concomitantly.
- Azoles antifungal agents are known to cause QT-prolongation, except for isavuconazole[12].

Fluconazole

- Fluconazole too has been employed as an alternative to terbinafine in the treatment of TC. However, its use has been relatively limited due to adverse effects and lack of a cost advantage.
- Dose: 6 mg/kg/day for 3–6 weeks. The maximum daily dose is 400 mg.
- In a comparative clinical trial, it was shown that a daily dose of 4 mg/kg/day is associated with a longer treatment duration than 6 mg/kg/day. Once-a-week dosing may also be effective.
- Drug interactions: Same as itraconazole.

Voriconazole

- Although voriconazole displays superior in vitro effectiveness against dermatophytes when compared to griseofulvin and fluconazole, its use in patients with TC is constrained due to concerns about its side effects, high costs, and the fact that it lacks current approval for this specific use.

Safety profile

- Griseofulvin, itraconazole, terbinafine, and fluconazole have consistently shown excellent tolerance, even in children, and have exhibited a favorable safety record in all documented cases so far.

Treatment strategy in patients with tinea capitis and follow-up

1. Following the identification of fungi or a positive KOH preparation, it is recommended to initiate a treatment regimen (both systemic and topical) lasting initially for four weeks. The choice of the specific drug should be based

on the patient's medical history, KOH/PCR test results, and local epidemiological factors.

2. Afterward, conduct a repeat fungal culture, with a maximum incubation period of 4 weeks. Continue topical treatment while awaiting culture results, even if oral treatment is discontinued, as long as there is noticeable clinical improvement, particularly if hair regrowth has commenced (as determined by trichoscopy). If this is not the case, both forms of treatment may be sustained.
3. If the fungal culture still yields positive results, extend the treatment for an additional two weeks.
4. Repeat steps 2 and 3 until fungal cultures return negative results. Achieving a mycological cure is the ultimate goal of any effective treatment, so treatment adjustments should be based on individual patient responses.
5. Regarding laboratory monitoring, traditionally, routine testing of liver enzymes (AST, ALT, GGT) has been performed during systemic antifungal therapy.

Nonetheless, the utility of these tests has been subject to frequent examination, especially since severe liver-related complications manifest within a brief timeframe, making them challenging to identify through standard monitoring conducted over 4 to 6 weeks. The suggested course of action is outlined in table 11.

Table 12. Laboratory Monitoring During Systemic Antifungal Therapy. Adapted from the 2020 S1 Guidelines for Tinea Capitis.

Patients with a history of impaired liver function, those taking other hepatotoxic drugs, or individuals with other comorbidities that may impair liver function	It is recommended to measure AST, ALT, and GGT levels prior to treatment initiation and after 2–4 weeks. Thereafter, further testing should be based on any abnormalities possibly found in the preceding tests.
Patients without risk factors	There is currently no final consensus as to whether laboratory tests are required or not. The decision should be made (and documented) together with the patient on a case-by-case basis, depending on dosage, treatment duration, and other possible factors.
Patients or their legal guardians should be advised on the clinical symptoms of acute liver damage (in particular, jaundice, nausea, vomiting, dark urine). If these	

symptoms occur, treatment should be discontinued, and a physician should be consulted as soon as possible.

Supplementary measures

- **Exclusion from school and childcare centers:** Children receiving the correct systemic treatment along with supplementary topical therapies like antifungal shampoo and solution can resume attending school or childcare centers after one week if their infection is attributed to anthropophilic species (T. tonsurans, T. violaceum, T. soudanense, M. audouinii). In the case of infections caused by other dermatophytes, they can return immediately.
- **Shaving of scalp hair/use of headgear:** Because contemporary treatment incorporates the use of potent fungicidal topical medications, there is no longer a necessity for shaving. Likewise, the recommendation to wear a hat is no longer necessary.
- **Treatment of contaminated objects and personal effects:**
    1. It has been shown that vital spores of anthropophilic species can be isolated from hairbrushes and combs. Consequently, if there is any suspicion of fungal contamination, it is recommended to disinfect or dispose of items of personal hygiene such as combs, hairbrushes, razors, towels, washcloths, bed linen, scarves, hats, stuffed animals, and toys, or to replace them with single-use items.
    2. To prevent fungal contamination, it's important to keep the storage area for hair, skin, and nail care products used by the affected person separate from those used by other family members. These items should be disinfected, and the shelves and potentially contaminated floors also need to be disinfected following the guidelines provided by the VAH list.
    3. Furthermore, in settings such as childcare centers or households with pets that might transmit zoophilic TC infections, home furnishings like curtains and furniture upholstery should be adequately disinfected if there's a likelihood of fungal contamination.
    4. For laundering and other textile items, chemothermal methods (following VAH list recommendations) can be used, similar to hospital laundry practices. If the fabrics can withstand high temperatures, washing at 60°C with a bleach detergent or a hygienic rinse is sufficient.
    5. In cases where zoophilic species are identified, it is advisable to have pets evaluated and treated by a veterinarian. Even if pets do not display

clinical symptoms, they could still carry the respective organisms without showing any signs of illness.

- **Use of corticosteroids:** In cases of inflammatory TC variants, where robust immune reactions and itching result from the use of very potent antifungal medications leading to rapid fungal elimination, the situation can be addressed with topical combination therapy. This therapy includes the use of corticosteroids and antifungal agents, typically administered for an initial duration of around seven days.

Treatment failure

- Reasons for treatment failure may include:
    1. Non-compliance – especially in cases requiring long treatment durations
    2. Underdosing (in particular, insufficiently low doses for insufficiently short periods of time or reduced efficacy due to co-medication)
    3. Relative resistance of the causative organism (insufficient drug levels at the target site)
    4. Reinfection
    5. Comorbidities that result in an impaired immune response
- If there is no observable improvement in the patient's condition, it is crucial to verify that the chosen antifungal treatment is sufficient for eliminating the responsible dermatophyte.

  If it is not, then the following alternatives can be considered:

    1. Increase the dose of the antifungal agent initially chosen or extend the treatment duration.
    2. Switch antifungal agents, for example:
        - Griseofulvin → itraconazole (for M. canis infections)
        - Terbinafine → itraconazole (for T. tonsurans infections)
        - Itraconazole → terbinafine (for T. tonsurans infections)

1.2.3 Indian Academy of Pediatrics (IAP) Standard Treatment Guidelines for Tinea Infections (2022)

The following recommendations are retrieved from the 2022 Indian Academy of Pediatrics standard treatment guidelines for tinea infections[8]:

Epidemiology and Etiology

- Dermatophytosis is the medical term for fungal infections commonly referred to as tinea infections.
- Tinea capitis is the most frequent form of infection in children, particularly observed among urban preschool-aged and school-aged children.
- In adolescents, tinea pedis, tinea manuum, tinea corporis, tinea barbae, and tinea cruris are more common.
- These infections spread primarily through contact with infected individuals or animals, as well as through contaminated objects like combs, brushes, caps, hats, couches, and the floors of swimming pools, among other items.

Table 13. Causative Agents and Types of Tinea Infections. Adapted from the 2022 IAP Guidelines for Tinea Infections.

Causative agents	*Trichophyton*— causes infections on skin, hair, and nails	*Microsporum*— causes infections on skin and hair	*Epidermophyton*— causes infections on skin and nails
Types	• Tinea corporis (skin) • Tinea manuum/pedis (hands/feet) • Tinea capitis (scalp) • Tinea barbae (bearded areas) • Tinea unguium (nail)	Most common is tinea capitis	

- Dermatophytosis is the medical term for fungal infections commonly referred to as tinea infections.
- Tinea capitis is the most frequent form of infection in children, particularly observed among urban preschool-aged and school-aged children.

- In adolescents, tinea pedis, tinea manuum, tinea corporis, tinea barbae, and tinea cruris are more common.
- These infections spread primarily through contact with infected individuals or animals, as well as through contaminated objects like combs, brushes, caps, hats, couches, and the floors of swimming pools, among other items.

Tinea Capitis

- Tinea infection is prevalent among children aged 2 to 9 years who reside in densely populated regions.
- The main symptoms include:
    a. Diffuse itchy scaling of the scalp resembling dandruff
    b. Patches of hair loss
    c. Spreads through combs, pillows, hats, etc.
- Treatment options include:
    a. Topical application of shampoo with 2.5% selenium sulfide/zinc pyrithione/ketoconazole.
    b. Oral griseofulvin (microcrystalline—20–25 mg/kg/day maximum 1,000 mg or ultramicrosize—10–15 mg/kg/day maximum 750 mg) for 6 weeks.
    c. Oral terbinafine at 3–6 mg/kg/day for 4–6 weeks can be used in cases of noninflammatory tinea capitis in 4 years and older.

Tinea Corporis

- This condition affects areas of the body without hair, such as the face and arms.
- It presents as one or several prominent, itchy, red, circular lesions with well-defined borders, and these circular areas may be adorned with small bumps, blisters, pustules, or scabs, often featuring a clear center.
- For the treatment:
    a. Mild-to-moderate: Topical antifungal agents (imidazole, terbinafine, butenafine, and naftifine) twice daily for 2–4 weeks.
    b. Oral itraconazole for 1–2 weeks can be added if more than two sites involved.
    c. Extensive involvement cases: Oral griseofulvin for 2–8 weeks or oral terbinafine for 2–6 weeks along with topical antifungal agents.

Tinea Pedis

- Typically, this condition manifests in teenagers and is uncommon before reaching puberty.
- The responsible fungal agents are Trichophyton rubrum, Trichophyton interdigitale, and Epidermophyton floccosum.
- It presents as different types including:
    a. Interdigital tinea pedis: Pruritic erosions or scales between the toes, especially in the third and fourth digital interspaces. Interdigital fissures may cause pain.
    b. Hyperkeratotic (moccasin) tinea pedis: Diffuse, erythematous, hyperkeratotic eruption involving the soles and medial and lateral surfaces of the feet, resembling a “moccasin” distribution.
    c. Vesiculobullous tinea pedis: Pruritic, sometimes painful, vesicular, or bullous eruption.
- Treatment options include:
    1. Avoid wearing tight or airtight shoes, ensure thorough drying between the toes after bathing, and employ absorbent antifungal powder like zinc undecylenate.
    2. Topical therapy with imidazole, allylamines, and tolnaftate for 2–4 weeks.
    3. Oral griseofulvin (microsized) at 10–20 mg/kg/day for 6–8 weeks
    4. Oral terbinafine at 62.5 mg/day (40 kg) for 2 weeks.
    5. Hyperkeratotic tinea pedis, a condition characterized by thickened skin, may find relief through a combination of antifungal therapy and the use of a topical keratolytic agent like salicylic acid.

Tinea Manuum

- Tinea manuum is a fungal infection of the hand caused by dermatophytes.
- Patients typically exhibit a thickened skin eruption on the palm or develop circular plaques resembling tinea corporis on the back of the hand.
- Tinea manuum is frequently linked to tinea pedis and often affects just one hand, a scenario sometimes termed the "two feet-one hand syndrome."
- Treatment for tinea manuum is similar to the treatment of tinea pedis.

Tinea Cruris

- Tinea cruris, commonly referred to as jock itch, is a fungal infection caused by dermatophytes that affects the groin area, specifically the creases or folds of the upper thigh.
- They are usually caused by T. rubrum, E. floccosum, and T. interdigitale.
- The predisposing factors for this infection include copious sweating, obesity, diabetes, and immunodeficiency.
- Patients usually present with the following clinical manifestations:
    a. Erythematous or hyperpigmented patch on the proximal medial thigh. Spreads centrifugally, with partial central clearing and a slightly elevated, erythematous or hyperpigmented, and sharply demarcated border.
    b. Infection may spread to the perineum and perianal areas, into the gluteal cleft, or onto the buttocks. In males, the scrotum is typically spared.

Tinea Unguium (Onychomycosis)

- It impacts the nail surface.
- Superficial variations appear as irregular, isolated, or multiple white patches on the nail's surface and are not linked to deep paronychial infection.
- Invasive variations present as an infection beneath the nail, typically starting at the outer, lower edges of the nail and often preceded by mild paronychia. The nail takes on a yellowish hue, becomes thicker, more fragile, and detaches from the nail bed. In advanced stages, the nail darkens to brown and may fracture or detach.
- Treatment options include:
    a. Topical antifungal like ciclopirox without matrix involvement.
    b. Oral itraconazole—5 mg/kg/day for 1 week of each month for 3–4 months
    c. Oral terbinafine at 62.5 mg/day (40 kg) for 6 weeks for fingernails and 12 weeks for toenails
    d. Oral griseofulvin (microsized) at 10–20 mg/kg/day for 6 months for fingernails and 6–12 months for toenails

Tinea Barbae

- Tinea barbae is a fungal infection caused by dermatophytes affecting the facial hair, primarily in adolescent and adult males.
- Oral antifungal treatment is essential for managing this condition.

1.2.4 Review Article: Trichophyton indotineae, from Epidemiology to Therapeutic (Journal of Medical Mycology 2023)

The following recommendations are retrieved from a review article published by Jabet et al. in the Journal of Medical Mycology in August 2023. This review summarizes main features of *T. indotineae* taxonomy, epidemiology, clinical manifestations, identification, antifungal profile, treatment, and prevention[13].

Introduction

- A recently identified dermatophyte species, Trichophyton indotineae, has emerged in India.
- This fungal pathogen is associated with persistent or recurring extensive superficial infections.

Epidemiology and Resistance Patterns

- Dermatophyte infection considered prevalent in India and have also been reported in Europe, Canada, the Middle East, and other locations in Asia.
- The dermatophyte species is associated with frequent resistance to antifungal therapy, particularly terbinafine.

Clinical Manifestations

- Infections caused by T. indotineae primarily manifest as widespread cases of tinea cruris and tinea corporis, often occurring together.
- Tinea faciei is also a common occurrence, observed in up to 20% of patients.
- However, reports of tinea manuum, tinea barbae, tinea pedis, and tinea unguium are infrequent and to the best of our knowledge, there have been no documented cases of tinea capitis.
- Infections caused by T. indotineae are distinguished by their extended progression over time.
- T. indotineae infections are categorized as chronic, recurrent, or relapsing.

Species identification and antifungal susceptibility testing

- Fungal culture cannot reliably distinguish T. indotineae from some other Trichophyton species.
- Identifying T. indotineae presents a dual challenge: distinguishing it from T. interdigitale and T. mentagrophytes for species identification and assessing the antifungal susceptibility of the isolates.
- Many macroscopic and microscopic morphological characteristics in culture are common among T. interdigitale, T. mentagrophytes, and T. indotineae.
- However, a notable distinction lies in the fact that the reverse side of T. indotineae colonies is more frequently pale brown to yellow-orange, unlike the darker reverse side of T. interdigitale and T. mentagrophytes colonies.
- The definitive diagnosis is only achieved through the sequence analysis of the ITS (Internal Transcribed Spacer) region.

Treatment

- Terbinafine is frequently recommended as the initial treatment.
- The standard prescription for oral terbinafine is 250 mg daily for 4-8 weeks, and it results in clinical cure for patients with T. indotineae strains that are susceptible to terbinafine.
- If there is no clinical improvement after this terbinafine course, higher doses (250 mg twice a day) have shown some level of success, although the failure rate remains high at 30%.
- In patients with terbinafine-resistant T. indotineae infections, itraconazole can be administered as an alternative treatment at a daily dose of 200 mg in adults for a recommended duration of 4-6 weeks. However, insufficient clinical responses may arise, likely due to the variable pharmacokinetic profile of itraconazole.
- Griseofulvin and fluconazole have been proposed as alternative treatments; however, both antifungals exhibit limited efficacy when compared to terbinafine or itraconazole.
- Given to patients with verified multidrug-resistant infections, voriconazole treatment demonstrated success in a set of familial cases. Subsequently, in a clinical study, voriconazole was assessed, revealing a favorable efficacy and safety profile with a minimal relapse rate in addressing recurrent and resistant dermatophytosis. However, the necessity to safeguard this effective treatment, commonly used in invasive mold infections, from developing

resistance implies that it should only be considered for confirmed isolates exhibiting multidrug resistance.

- In the treatment of widespread dermatophytosis, combining topical therapy with systemic treatment is a viable approach. The choices include azoles (miconazole, bifonazole, clotrimazole, ketoconazole, oxiconazole, sertaconazole, luliconazole, eberconazole, fenticonazole), ciclopirox olamine, terbinafine, butenafine, naftifine, and amorolfine.
- Topical therapy alone can be employed for elderly individuals with substantial comorbidities, infants, and pregnant women, particularly when systemic therapy is not advisable.
- Additionally, keratolytics like Whitfield's ointment (consisting of 3% salicylic acid and 6% benzoic acid) have been suggested, although not for application on flexures, the face, or inflamed lesions.

Prevention

- Practicing good hygiene is likely a crucial factor in preventing the transmission and recurrence of infections.
- To avoid T. indotineae infections, as well as any form of dermatophytosis, it is important to refrain from sharing personal items, close body contact, and prolonged skin maceration.
- For decontaminating textiles, the efficacy of quaternary ammonium has been demonstrated against three terbinafine-resistant T. indotineae isolates.
- Similar to other dermatophyte species, washing at 60 °C is likely effective against T. indotineae, whereas heat drying, freezing at -20 °C for up to one week, and direct heat exposure at 60 °C for up to 90 minutes may not be as effective.

1.2.5 Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

The clinical practice guideline for the management of candidiasis published in 2016 by the Infectious Diseases Society of America[11] covers all types of candida infections, whether local or systemic. For the purpose of this report, **only infections related to the skin will be covered**. Listed below are the main statements (ungraded) on chronic mucocutaneous candidiasis:

- Chronic mucocutaneous candidiasis is an uncommon condition characterized by persistent onychomycosis and/or mucocutaneous lesions caused by Candida species.

- Some individuals with this condition may also have a thymoma or autoimmune polyendocrinopathy syndrome type 1.
- Initial therapy for candidiasis in these patients should involve the use of fluconazole.
- It is important to note that the response to antifungal treatment might be delayed when there is extensive skin or nail involvement.
- Due to their inherent immunodeficiency, most patients require ongoing suppressive antifungal treatment and frequently develop infections that do not respond to azoles.
- In cases of fluconazole-refractory Candida infections, the treatment approach should be similar to that used for patients with AIDS who develop azole-resistant infections.

1.2.6 Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

The practice guidelines for the diagnosis and management of aspergillosis published in 2016 by IDSA covers all types of aspergillus infections[10]. For the purpose of this report, **only infections related to the skin will be covered**. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to rate the quality of evidence and strength of recommendations (figure 1).

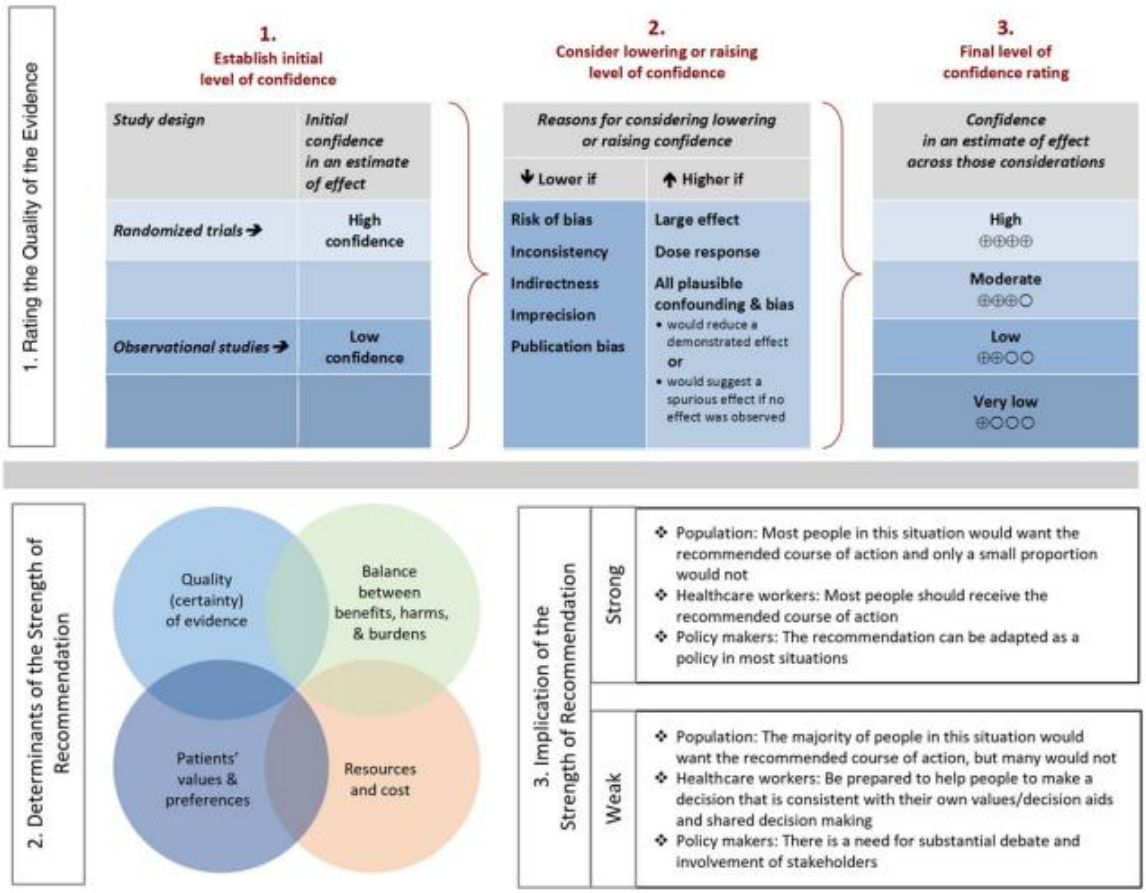

Figure 1. *GRADE Methodology (Retrieved from the IDSA 2016 Guidelines)*

- Cases of primary cutaneous aspergillosis have been documented in individuals with compromised skin barriers, including burn patients and neonates in proximity to vascular areas.
- Since skin lesions could indicate widespread infection, we strongly advise administering **voriconazole** treatment while also assessing the presence of a primary infection source. (Strong recommendation; low-quality evidence).
- Combinations therapy with azoles (posaconazole or isavuconazole) and another class of antifungal like echinocandins or polygenes can be used as alternatives to voriconazole.
- In situations involving aspergillosis occurring in burn injuries or extensive soft tissue wounds, it is strongly recommended to perform surgical debridement in conjunction with antifungal therapy. (Strong recommendation; moderate-quality evidence).

1.2.7 Review Article by the Royal Australian College of General Practitioners: Superficial Fungal Infections (Australian Journal of General Practice 2019)

Recommendations summarized below are retrieved from a review article on superficial fungal infections published in October 2019 in the Australian Journal of General Practice (journal of the Royal Australian College of General Practitioners)[6]:

Practical approach to diagnosis

- Clinical history and examination can raise suspicion of a tinea infection. However, because various conditions can imitate the symptoms of tinea infections, it is advisable to conduct further investigations to validate the diagnosis.

Table 14. Differential Diagnosis of Onychomycosis. Adapted from the RACGP 2019 Review Article.

Differential diagnosis	Clinical features
Nail psoriasis	• Shares many common clinical and histopathological features with onychomycosis • Fingernails are usually more affected by psoriasis than tinea • Nail pitting is the most common sign of nail psoriasis and rare in onychomycosis • Nail bed 'oil drops': pink discoloration in the nailbed due to nailbed inflammation • Other psoriatic skin changes • Family history of psoriasis • Can coexist with onychomycosis in 20% of people with psoriasis
Lichen planus	• Typically affects several or most nails • Other cutaneous features of lichen planus • Pterygium unguis: Scarring between nail matrix and proximal nailfold • Nail plate thinning and longitudinal ridging
Yellow nail syndrome	• Association with bronchiectasis, chronic sinusitis and lymphoedema
Traumatic onychodystrophy	• Usually only single nail affected • Distal onycholysis
Alopecia areata	• Red-spotted lunula

	• Regularly distributed nail pitting
Age-related nail dystrophies	• Onychauxis and onychoclavus can be clinically identical to onychomycosis

Table 15. Differential Diagnosis of Tinea Corporis (Annular Rash). Adapted from the RACGP 2019 Review Article.

Differential diagnosis	Clinical features
Discoid eczema (nummular)	• Less likely to have central clearing (but can occur) • More confluent scales
Annular psoriasis	• Silvery scale • Nail pitting • Family history of psoriasis
Pityriasis rosea	• Herald patch progressing to generalized rash
Subacute cutaneous lupus erythematosus	• More common in females • Photosensitive areas
Erythema annulare centrifugum	• Trailing scale rather than leading scale in tinea

Diagnostic tests

- Diagnosing a tinea infection involves the use of fungal microscopy and culture, enabling both the identification of the specific fungus and an evaluation of its viability. Fungal microscopy is conducted on skin scrapings and nail clippings, typically using potassium hydroxide (KOH), which can provide quick results.

Treatment modalities

- The treatment approach is determined by the extent and site of the tinea infection.

<u>Tips for tinea management</u>

- Examination of the skin and nails should be performed for all patients with tinea infection to identify the extent of involvement and potential reservoirs for dermatophytes.
- Topical treatments are usually ineffective against onychomycosis.

- Most nails still look abnormal after effective therapy because new nails take nine to 12 months to grow.
- Two simple methods to monitor the effect of onychomycosis therapy:
    1. photographic monitoring,
    2. marking the nail using a scalpel at the proximal end of the dystrophy. As the nail grows out, if the nail abnormality remains distal to the mark, then no further therapy is required. Consider referral to an expert if therapy fails.
- Topical antifungal shampoos for tinea capitis can reduce the risk of fungal transmission to others but are ineffective in treating the infection.

1- Topical antifungal therapy

- Most instances of tinea corporis, tinea cruris, and tinea pedis can be effectively treated with topical medications.
- The recommended first-line topical treatment involves applying terbinafine 1% cream once or twice daily for a duration of one to two weeks.
- For cases of onychomycosis where systemic therapy is contraindicated, an alternative approach is to use ciclopirox 8% nail lacquer once daily for nine to 12 months or amorolfine 5% nail lacquer once daily.
- In addition to the topical therapy in onychomycosis, debridement of hyperkeratotic nails can also be performed. However, it is important to note that these treatments have relatively low mycological cure rates, with ciclopirox at 29–36% and amorolfine at 38%.

2- Oral antifungal therapy

- Oral treatment should be contemplated under the following circumstances:
    1. Onychomycosis
    2. Tinea capitis
    3. Extensive tinea on the skin
    4. Failed topical treatment
    5. Immunocompromised patients
- Terbinafine 250 mg once daily for adults is the recommended first-line therapy.
- Terbinafine is generally safe for use in healthy patients without the need for interval blood monitoring. However, it is contraindicated for patients with

severe liver impairment and dose reduction is required for patients with moderate-to-severe chronic kidney disease (CrCl < 50 mL/min).

- The length of oral treatment with terbinafine varies based on the location:
    a. Scalp: four weeks
    b. Fingernails: six weeks
    c. Toenails: 12 weeks (longer duration therapy is required because of diminished blood supply in the area, especially in the elderly)
    d. Other than scalp and nails: two weeks.
- According to a Cochrane review from 2017, terbinafine outperformed both fluconazole and itraconazole in terms of achieving clinical and mycological cure in onychomycosis. Additionally, there were no distinctions in the recurrence rates and the occurrence of adverse events.

Table 16. Head-to-Head Comparison of Oral Terbinafine Versus Azoles in Onychomycosis Treatment. Adapted from the RACGP 2019 Review Article.

	Terbinafine	**Azoles (fluconazole and itraconazole)**
Recommended line of therapy	First line	Second line
Dosage	Adult: 250 mg daily Child < 20 kg: 62.5 mg daily Child 20-40 kg: 125 mg daily Duration: 6 weeks for fingernails, 12 weeks for toenails	Both itraconazole pulse and continuous therapy have similar efficacy Pulsed itraconazole 200 mg twice daily for one week per month for two months (fingernails) and three months (toenails) Continuous itraconazole 200 mg daily for six weeks (fingernails) and 12 weeks (toenails) Fluconazole Fluconazole 150–300 mg once weekly for 12–24 weeks (fingernails) and 24–52 weeks (toenails)

Recurrence rate (follow-up 10-13 months)	33.3%	37.0%
Adverse effects	Gastrointestinal upset, rash, headache, myalgia	Gastrointestinal upset, diarrhea, rash, abdominal pain, hypokalemia More drug interactions than terbinafine due to its inhibition on multiple cytochrome P450 (CYP) enzymes
Recommended monitoring	Routine interval blood monitoring may be unnecessary in healthy adults and children without underlying hepatic or hematological conditions	Continuous itraconazole: Baseline liver function test (LFT) and regular LFT monitoring every four to six weeks Pulsed itraconazole: none recommended Fluconazole: Baseline LFT and full blood examination; no repeat test required for once weekly therapy
Precautions	Psoriasis and lupus may be exacerbated by terbinafine Contraindicated in severe hepatic disease Dose adjustment required if CrCl < 50 mL/min	Dose adjustment may be required in renal impairment Avoid in severe hepatic disease Fluconazole can cause prolonged QT – correct the risk factors and use with caution Itraconazole is relatively contraindicated in congestive failure Itraconazole is also poorly absorbed when used with proton pump inhibitors
Pregnancy categorization	Category B1	Fluconazole: category D Itraconazole: category B3
Breastfeeding compatibility	Avoid, insufficient data	Fluconazole: compatible; may cause diarrhea in infant Itraconazole: avoid, insufficient data

- Griseofulvin is the initial treatment choice for tinea capitis caused by Microsporum infections and should be administered for a duration of six to eight weeks (with pediatric dosing at 10 mg/kg, up to a maximum of 500 mg).
- In contrast, for tinea corporis, griseofulvin is not the preferred option as it is less effective than terbinafine and azoles. In this case, it is recommended as a third-line treatment.
- Griseofulvin is generally not recommended for onychomycosis due to its longer treatment duration, higher rate of adverse events, and its comparable effectiveness to terbinafine and azoles.
- The dosages for griseofulvin vary depending on its intended use: 500 mg once daily is suitable for tinea capitis, tinea corporis, and tinea cruris, while 1 g once daily is the recommended dosage for tinea pedis and onychomycosis.

Laser therapy

- Laser therapy for onychomycosis yields cure rates that are notably lower when compared to topical and oral treatments. Due to its restricted effectiveness and the associated high expenses, laser therapy cannot be endorsed as the primary treatment option for onychomycosis.

Prevention of recurrence

- Following treatment for onychomycosis, there is a potential for a recurrence or reinfection rate of up to 25%.
- Patients should be counseled to address modifiable risk factors to prevent tinea infection. This includes practices like refraining from sharing personal items such as hairbrushes, clothing, or shoes, avoiding walking barefoot in communal showers and pool areas, and regularly changing footwear and socks.
- After a successful cure, prophylactic use of topical antifungal therapy (ciclopirox, amorolfine, bifonazole, terbinafine) on a weekly basis is recommended. This approach has demonstrated a significant reduction in recurrence rates in a retrospective study.
- The optimal duration of prophylaxis remains unclear and may extend indefinitely.

1.2.8 Review Article: Updated Perspectives on the Diagnosis and Management of Onychomycosis (Clinical, Cosmetic and Investigational Dermatology 2022)

The following recommendations are retrieved from the Clinical, Cosmetic and Investigational Dermatology: Updated Perspectives on the Diagnosis and Management of Onychomycosis 2022 article[9].

Physical examination

- Onychomycosis can impact fingernails, toenails, or both, but it more frequently affects toenails.
- Typical physical examination findings encompass discoloration of the nail plate in a yellowish hue, nail thickening, and the buildup of skin or tissue beneath the nail (subungual hyperkeratosis), which can lead to the separation of the nail plate (onycholysis).
- In severe instances, onychomycosis may lead to nail abnormalities characterized by ridges, further thickening, fragmentation, ingrown nails (onychocryptosis), and even complete nail loss.

Dermoscopy

- Dermoscopy can aid in differentiating between other nail diseases, including onychomycosis, psoriasis, pseudomonas colonization, and traumatic onycholysis.

Diagnostic testing

- Relying solely on the patient's history, clinical examination, and dermoscopy is inadequate to establish a conclusive diagnosis of onychomycosis.
- To confirm the presence of the condition, mycologic laboratory tests are essential and offer a cost-effective approach.
- Fungal components can be observed through microscopic analysis (positive direct microscopy) of nail scrapings that have been treated with potassium hydroxide (KOH) solutions ranging from 5% to 40%. Although KOH is the most frequently used reagent, alternative reagents include sodium sulfide, sodium hydroxide, Parker blue black ink, or calcofluor white.
- Fungal culture is the only technique that can identify both the organism and determine its viability.
- Histopathology is conducted on nail plate clippings preserved in 10% buffered formalin. This method provides results within days and offers greater sensitivity compared to both KOH testing and fungal culture.

- PCR is a modern method that employs specialized primers to magnify DNA segments for the purpose of detecting dermatophytes, non-dermatophyte molds (NDMs), and Candida species.
- Artificial intelligence has also been applied for diagnosis of onychomycosis.

Treatment

- The objective of treating onychomycosis should be to eradicate the fungal pathogen and return the nail to its normal condition.
- Various treatment options are available for onychomycosis, encompassing oral and topical antifungal medications, device-based treatments such as lasers, surgical removal of the nail (nail avulsion), nail debridement, and combinations of these therapies.
- Oral antifungals are typically recommended for moderate to severe cases, while mild to moderate onychomycosis can often be treated with topical antifungals.
- Nail debridement can help reduce fungal load and is sometimes used in conjunction with topical treatments. Nail avulsion is limited in its application, primarily reserved for situations involving a painful or non-growing single nail.
- Laser treatments have received approval from the United States Food and Drug Administration (FDA) for temporary cosmetic improvements, but their cure rates are lower compared to oral and topical antifungals, as the FDA's criteria for approval are less stringent, and definitive guidelines for laser therapy use are currently lacking.
- However, it is essential to tailor treatment strategies to each patient, taking into account factors such as the seriousness of the condition, the specific causative agent, the cost of medication, any other medical conditions the patient may have, their medical history, and their likelihood of adhering to the treatment.
- Initial consideration should not be given to combination therapy but rather reserved for individuals with unfavorable prognostic factors (such as advanced age, weakened immune systems, or mixed infections) or for those who have not responded to single-drug treatment for onychomycosis.

1. **Oral therapies**

- Systemic medications are widely used for the treatment of onychomycosis due to their accessibility, high efficacy, and comparatively low cost.
- Currently, terbinafine, itraconazole, and griseofulvin are US FDA approved for onychomycosis treatment.

- Fluconazole is not US FDA approved of onychomycosis treatment but is frequently used off-label.

a. Terbinafine

- Terbinafine is an allylamine that inhibits squalene epoxidase, with broad-spectrum activity against dermatophytes and some activity against NDMs and Candida spp.
- It is dosed at 250 mg daily for 6 and 12 weeks for fingernails and toenail infections, respectively.
- Potential side effects are mild and include headaches, rashes, and gastrointestinal symptoms. Rarely, hepatotoxicity and taste disturbances can occur.
- Terbinafine can be given in intermittent, pulse-based regimens as an alternative treatment for onychomycosis, although it is not officially approved by the US FDA. This approach is considered off-label but may offer cost-effective benefits and enhance patient adherence. It has been investigated in clinical studies to assess its effectiveness.

b. Itraconazole

- Itraconazole is a triazole that inhibits lanosterol 14a-demethylase and is efficacious against dermatophytes, Candida spp. and NDMs.
- Potential side effects include headaches, upper respiratory tract infections, gastrointestinal symptoms, hypertriglyceridemia, elevated transaminases, and rarely, peripheral neuropathy and hepatitis.1,88 Drug–drug interactions are common and a thorough medication history should be performed prior to treatment initiation. Ventricular dysfunction, including congestive heart failure, is a contraindication to use.
- The dosing for toenails is 200 mg daily for 12 weeks and for fingernails is 200 mg twice daily for 1 week separated by 3 weeks of washout for 2 treatment pulses.

<u>Booster therapy</u>

- Supplemental doses of terbinafine or itraconazole can be considered after the initial full course of antifungal treatment in cases of onychomycosis.
- The recommended approach involves four more weeks of terbinafine or itraconazole administered six to nine months following the initial antifungal treatment.

- It is worth noting that there is limited clinical trial evidence regarding booster therapy, but due to the low risk associated with extra oral therapy, it can be justified in challenging cases.

c. Fluconazole

- Fluconazole is a triazole that inhibits lanosterol 14a-demethylase. It is approved for onychomycosis treatment in Europe and China and is used off-label in the US, with efficacy against dermatophytes, Candida spp., and some NDMs.
- Dosing for fingernails and toenails are 150 mg weekly for 6–9 months and 12–18 months, respectively.
- The most common side effects include nausea, rash, headache, abdominal pain, and elevated LFTs. Rarely, liver injury or failure can occur, but is more common in immunosuppressed patients.
- Drug–drug interactions are also common, especially with warfarin and hypoglycemic agents.
- Fluconazole has advantages over itraconazole, including absorption that is non-dependent on gastric pH or food, once-weekly dosing, and ability to use in patients with comorbidities, including cardiac dysfunction.

<u>Novel oral therapies</u>

- Considerable attention has been directed towards innovative oral treatments for onychomycosis.
- Posaconazole, an extended-spectrum triazole, has gained approval in the United States and Europe for the management of oropharyngeal candidiasis and for preventing invasive fungal infections.
- In a phase IIb study that involved multiple centers and randomized 218 adult patients with toenail onychomycosis, various treatment groups were established. Patients received posaconazole (in oral suspension form) at doses of 100 mg, 200 mg, or 400 mg once daily for 24 weeks, or posaconazole 400 mg once daily for 12 weeks. Additionally, oral terbinafine at 250 mg once daily for 12 weeks and a placebo group for 24 weeks were included. It was observed that all the posaconazole groups showed significantly higher proportions of patients achieving a complete cure compared to the placebo group at the 48-week mark (with p-values of 0.012 or less).
- Fosravuconazole L-lysine ethanolate (F-RVCZ) is an azole prodrug of ravuconazole with improved bioavailability and hydrophilicity that is approved in Japan (100 mg/day for 3 months) for onychomycosis treatment.

- In a phase-III, multicenter, randomized, double-blind study,128 153 Japanese patients with toenail onychomycosis received either 100 mg F-RVCZ or placebo once daily for 12 weeks. At 48 weeks, the complete and mycologic cure rates were significantly higher in the F-RVCZ group (59.4%, 82.0%, respectively) vs placebo (5.8%, 20.0%, respectively) ($p < 0.001$, both).
- Otesesconazole is a tetrazole that inhibits the lanosterol demethylase (CYP51) enzyme, which is required to produce the membrane lipid ergosterol necessary for fungal survival. It is not yet US FDA approved for onychomycosis treatment, but has been studied in recent clinical trials. In a phase II, multicenter, randomized, placebo-controlled, double-blind study, 259 patients with toenail onychomycosis received either oteseconazole 300 mg or 600 mg once daily for 14 days, followed by a once-weekly dose for 10 or 22 weeks. At week 60, complete and mycologic cure rates were higher in the oteseconazole groups (41–45%, 65–75%, respectively) vs placebo (0%, 13%, respectively) ($p < 0.001$, all).
- These innovative drugs hold potential as effective treatments for onychomycosis, known for their good tolerability. However, it is crucial that their effectiveness is confirmed through phase III studies before making widespread treatment recommendations.

2. Topical therapies

- The popularity of topical medications for treating onychomycosis is on the rise. This is due to their ability to potentially penetrate biofilms, their reduced risk of drug interactions because they have minimal systemic absorption, and the fact that they don't necessitate laboratory monitoring.
- Currently, ciclopirox 8% nail lacquer is US FDA approved for the treatment of fingernail and toenail onychomycosis and efinaconazole 10% solution and tavaborole 5% solution are approved for toenail onychomycosis. Amorolfine 5% nail lacquer is approved in Europe for onychomycosis treatment but is not available in the US.

a. Ciclopirox

- Ciclopirox 8% nail lacquer is a hydroxypyridone that chelates trivalent cations, resulting in inhibition of metal-dependent enzymes. It is effective against dermatophytes, Candida spp., and some NDMs and gram-positive and gram–negative bacteria.
- Effectiveness is enhanced when patients regularly trim their nails each week and receive in-office debridement on a monthly basis. Patients should be advised to use alcohol to remove the lacquer weekly.

- Localized side effects are typically limited to symptoms such as redness around the nails, a burning sensation, and reactions at the application site.

b. Efinaconazole

- Efinaconazole 10% solution is a triazole that inhibits lanosterol 14a-demethylase, thereby disrupting ergosterol synthesis in the fungal cell membrane. It has activity against dermatophytes, Candida spp., and NDMs1 and is the preferred treatment in cases of dermatophytoma.
- Efinaconazole should be applied to the affected toenails once daily for 48 weeks, including the skin around the nails (nail folds, hyponychium, and ventral surface of the nail plate) to increase medication delivery.

c. Tavaborole

- Tavaborole 5% solution is a benzoxaborole that inhibits fungal aminoacyl transfer RNA synthetase and therefore protein synthesis, with broad-spectrum activity against dermatophytes, yeasts, and NDMs.
- Nail penetration of tavaborole is good due to its small size and hydrophilicity.

d. Amorolfine

- Amorolfine 5% nail lacquer is a morpholine derivative that inhibits fungal enzymes 14-α reductase and 7,8 isomerase, thereby disrupting fungal sterol synthesis.
- It has activity against dermatophytes, molds, and some yeasts.
- Amorolfine should be applied once or twice weekly to a cleaned nail plate and left for 3–5 minutes until dry.
- It is important to refrain from using organic solvents when taking off the lacquer.
- Tavaborole, as it infiltrates the nail bed via the nail plate, maintains its concentrations for a minimum of 14 days post-application.

<u>Novel topical therapies</u>

- Innovative topical formulations for onychomycosis, which serve as substitutes for conventional topical treatments, have recently gained significant attention.
- In a phase III, multicenter, randomized, double-blind study,163 365 patients (ages 12–74) with 20–60% distal and lateral subungual onychomycosis of at least one toenail received a once daily application of topical terbinafine (MOB-015 formulation) or matching vehicle for 48 weeks. At week 52, mycologic and

complete cure were higher in the MOB-015 (69.9%, 4.5%, respectively) vs vehicle (27.7%, 0%, respectively) groups ($p < 0.001$, $p = 0.0195$, respectively).

- Several other topical terbinafine formulations are still under investigation.
- Ciclopirox hydrolacquer (P-3051) is a different new topical treatment that, while not sanctioned for onychomycosis treatment in the United States, has received approval and is available in over 40 nations, with common usage in Europe.
- In a 2020 Cochrane review, it was determined, based on moderate-quality evidence from two studies involving 490 participants, that P-3051 is likely more successful than amorolfine 5% or ciclopirox 8% lacquer in achieving a complete cure (RR: 2.43, 95%, CI: 1.32–4.48), but not in achieving a mycologic cure (RR: 1.08, 95%, CI: 0.85–1.37).

3. Over-the-counter (OTC) treatments

- Tea tree oil (TTO) is a volatile oil utilized in Australia, Europe, and North America to treat tinea pedis. Research has demonstrated its impact on Candida albicans, including its ability to reduce glucose-induced acidification around the fungi and influence respiration and plasma membrane permeability. In a six-month, double-blind trial involving 117 patients with Distal Lateral Subungual Onychomycosis (DLSO) of the toenails, those who applied either 100% TTO or 1% clotrimazole solution twice daily did not exhibit a significant difference in culture cure rates (18% vs. 11%, respectively).
- Home remedies for onychomycosis have included the use of topical cough suppressants. These suppressants contain eucalyptus oil (1.2%), camphor (4.8%), and menthol (2.6%) as active ingredients, along with inactive ingredients like nutmeg oil, cedar leaf oil, thymol, petrolatum, and turpentine oil. In a preliminary study involving 18 adult patients with toenail onychomycosis who applied this topical cough suppressant (Vicks VapoRub from The Proctor & Gamble Company, Cincinnati, OH) once daily, the results showed that 27.8% (5/18) achieved mycologic cure, 22.2% (4/18) achieved complete clinical cure, 55.6% (10/18) experienced partial clinical improvement, and 16.7% (3/18) had no clinical improvement.
- Natural coniferous resin, derived from the Norway spruce tree (Picea abies) and mixed with boiled butter or animal fat, has been used for centuries to treat wounds and infections.166 In a prospective, randomized, controlled, investigator blinded study,175 73 patients with toenail onychomycosis received either natural coniferous resin 30% once daily for 9 months, amorolfine lacquer 5% once weekly for 9 months, or 250 mg oral terbinafine

once daily for 3 months. At 10 months, mycologic cure rates were 13% (95% CI, 0–28%), 8% (95% CI, 0–19%) and 56% (95% CI, 35–77), respectively ($p \leq 0.002$).

- Historically in Mexico, Ageratina pichinchensis (AP) extract has been employed to address fungal infections and has demonstrated effectiveness in the treatment of tinea pedis.
- Ozonized sunflower oil is a substance with a texture similar to petroleum jelly, produced through the reaction of ozone with sunflower plant (Helianthus annuus) oil. In Cuba, it is used for clinical purposes in treating impetigo and tinea pedis.
- While these remedies seem to be well-tolerated and safe, further research is required to establish their effectiveness through larger randomized controlled trials.
- Doctors should inquire about any over-the-counter (OTC) or natural remedies that patients have used or attempted for self-treatment of onychomycosis since these substances could potentially have significant pharmacological interactions with prescribed antifungal treatments.

4. Devices

a. Laser therapies

- Lasers were approved by the US FDA in 2012 for temporary increases in clear nail.
- Short-pulsed and Q-switched 1064 nm Nd:YAG lasers have been approved, although others, including carbon dioxide and the diode 870, 930 nm laser, are in development.
- Laser treatments might offer temporary improvements in the appearance of nails, but there's limited evidence to support their ability to sustain clinical improvements or completely eliminate pathogenic fungi.
- Notably, the criteria for inclusion, endpoints, and definitions of efficacy outcomes vary significantly between clinical trials for lasers and oral/topical therapies for onychomycosis. This disparity makes it challenging and unreliable to compare results across studies.
- The appeal of lasers lies in their minimal potential for causing systemic adverse events since they target the infecting fungi on the nail plate.
- Additionally, they require less patient compliance as they are administered by healthcare professionals. For effective laser treatment, it's important to use a wavelength between 750–1300 nm to penetrate the nail, and the pulse

duration period should be shorter than the thermal relaxation time of the pathogen.

b. Photodynamic therapy

- Photodynamic therapy (PDT) is an approved non-invasive device-based treatment by the US FDA for actinic keratoses. It is also used off-label for onychomycosis.
- This method combines light-based techniques with photosensitizers like 5-aminolevulinic acid, methyl aminolevulinate, or methylene blue.
- Photodynamic therapy (PDT) is not particularly practical for onychomycosis due to its need for multiple treatment sessions, preliminary steps involving urea or nail avulsion, and the associated discomfort.
- To consider PDT as a standard off-label treatment for onychomycosis, further comprehensive randomized controlled trials involving larger patient groups are essential.

c. Plasma therapy

- Non-thermal plasma (NTP), also known as low-temperature plasma, is an emerging technique under investigation for onychomycosis treatment.
- NTP is generated through the application of brief pulses, lasting about 10 nanoseconds of high-intensity electric fields, reaching around 20 kilovolts per millimeter at its peak. This process leads to the production of active chemical species, such as ions, electrons, nitric oxide, ozone, and hydroxyl radicals.
- NPT is a non-invasive therapeutic method that holds promise for enhancing the treatment of onychomycosis, although its effectiveness needs to be confirmed through larger randomized controlled trials.

d. Microdrilling

- Nail drilling regimens have been investigated to improve penetration of medications through the nail plate.
- Antifungal treatments in combination with nail drilling may improve treatment efficacy.

5. Combination Treatments

- The concept of combining multiple therapies to treat onychomycosis is appealing because it can potentially enhance the effectiveness of the drugs and reduce the risk of antifungal resistance.

- However, it has not been extensively researched, and there are no established standardized treatment protocols for combination therapy.
- Considering the expense of combination treatment, the risk of interactions between drugs, and the absence of well-designed, long-term randomized controlled trials, combination therapy should be considered a second-line treatment option for patients with unfavorable prognostic factors or cases of onychomycosis that do not respond to initial treatments.

Treatment in Children

- There are no US FDA approved systemic therapies to treat onychomycosis in children, although terbinafine, itraconazole, and fluconazole are used-off label.
- Topical tavaborole 5% and efinaconazole 10% solution are US FDA approved for treating onychomycosis in children ages ≥6 years old.
- Topical ciclopirox 8% nail lacquer is US FDA approved for children ≥12 years old.198 There is no data on the efficacy of medical devices for treating pediatric onychomycosis.

1. **Oral terbinafine**

- In a study involving 17 children who received continuous oral terbinafine for 12 weeks (with dosage adjusted according to their body weight), 88.2% (15 out of 17) achieved mycologic cure within one to five months after the treatment was stopped.
- In another study with 14 children treated with terbinafine for a duration ranging from two to five months, 77% of patients achieved mycologic cure, and 62% achieved complete cure.
- Importantly, no serious or adverse side effects were reported in either of these studies.

2. **Oral itraconazole**

- In a study involving 18 children, itraconazole was administered at a dosage of 200 mg once daily for 12 weeks, and this treatment resulted in mycologic cure in 94.7% of the patients (18 out of 19).
- In another study with 27 children, itraconazole was used (with 16 receiving continuous treatment and 11 receiving pulsed treatment) for a period of 2 to 4 months. In this study, mycologic cure was achieved in 84% of patients, while 76% achieved complete cure.

It is important to mention that the capsule formulation of itraconazole may be challenging for children to swallow, but it can be opened, and the granules can be mixed with food, such as applesauce or mashed potatoes.

- The oral suspension (10 mg/mL) should be administered under fasting conditions to enhance its bioavailability.

3. Oral fluconazole

- In the case of oral fluconazole, two children with toenail onychomycosis were treated with fluconazole at doses of 200 mg or 300 mg once weekly for 20 weeks, and both achieved clinical cure.

4. Topical ciclopirox

- In a study that followed a prospective, randomized, double-blind design and utilized a vehicle control, 37 children with toenail onychomycosis were administered either ciclopirox lacquer or a control lacquer on a daily basis for 32 weeks, while also having their lacquer removed and toenails trimmed weekly. In cases where children in the control group showed poor responses (as indicated by an Investigator Global Assessment score exceeding 3 or a positive fungal culture at week 8), they were switched to the ciclopirox group at week 12.
- The study found that at 12 and 32 weeks, the ciclopirox group exhibited higher rates of mycologic cure (70% and 77.1%, respectively) compared to the vehicle group (20% and 22.0%, respectively), with a statistically significant p-value of 0.03.

5. Topical efinaconazole

- In a Phase 4 clinical trial conducted at multiple centers and without blinding, involving 62 children who had mild to severe toenail distal lateral subungual onychomycosis (DLSO), they were treated with efinaconazole once daily for a duration of 48 weeks. The results showed that mycologic cure and complete cure rates were 65% and 40%, respectively. Additionally, clinical efficacy, which was defined as having less than 10% of the target area of the big toenail affected, was achieved by 50% of the participants.

6. Topical tavaborole

- In an open-label, single-arm study involving 55 children suffering from toenail distal lateral subungual onychomycosis (DLSO), the participants applied tavaborole once a day, using two drops on the big toenail and one drop on the other toenails, for a duration of 48 weeks. The results at 52 weeks indicated

that mycologic cure was accomplished by 36.2% of the patients, and complete cure was observed in 8.5% of them.

Elderly Adults

- Elderly individuals face particular risk factors that make them more likely to experience suboptimal outcomes with antifungal treatment, such as a gradual rate of nail growth, recurrent nail issues, and a higher incidence of conditions like diabetes mellitus and peripheral vascular disease.
- Additionally, a significant portion of the elderly population takes multiple medications to manage various concurrent health problems.
- Consequently, topical therapy is the preferred treatment approach for this specific group.
- In cases where systemic treatment is necessary, oral terbinafine is the initial choice because it carries a lower risk of interactions with other medications when compared to azoles.

Pregnant and Lactating Women

- Oral itraconazole is pregnancy class C and oral fluconazole is pregnancy class D when >1 dose is consumed. Neither should be used during pregnancy.
- Oral itraconazole should be avoided for 2 months before planning pregnancy and oral fluconazole is secreted into breast milk and therefore should not be started until breastfeeding is complete.
- Oral terbinafine is pregnancy class B and is excreted into breast milk. Due to the scarcity of data and the non-urgent nature of onychomycosis treatment, it is advisable to refrain from starting oral terbinafine treatment while pregnant or breastfeeding.
- Topical ciclopirox is classified as pregnancy category B, but its excretion into breast milk remains uncertain. As a precaution, it is advisable to avoid its use in individuals who are pregnant or breastfeeding.
- Topical efinaconazole falls into pregnancy category C due to observed embryotoxic effects in rats. Consequently, it should not be used during pregnancy. Although it was detected in the milk of nursing rats that received repeated subcutaneous doses, there is a lack of human milk data, so efinaconazole should also be avoided during breastfeeding.
- Topical tavaborole is categorized as pregnancy category C, with no available data on its use in pregnant women or during lactation. Therefore, it is recommended to steer clear of this treatment in such patients.

Prevention of Recurrence

- Following the initial treatment of onychomycosis, there is an observed recurrence rate of 20-25%, which includes both relapse (reappearance of the same infection after an incomplete cure) and reinfection (return of the same infection after a complete cure).
- Individuals with genetic predispositions, a family history of onychomycosis, and those who are immunosuppressed are at a higher risk of experiencing recurrences.
- Preventing recurrence is of utmost importance and can be achieved through a combination of patient education and the use of appropriate medications.
- Once the antifungal agent has reached stable levels in the nail plate, a twice-weekly application of a topical antifungal can be employed for preventive measures. However, the optimal duration for this prophylactic approach is uncertain and might be necessary for a lifetime.
- Patients should also receive guidance on lifestyle adjustments to prevent recurrence, such as keeping their feet cool and dry, refraining from tight-fitting footwear, either discarding or treating infected footwear with topical antifungals, ultraviolet light, or ozone, dealing with infected socks by washing them in hot water, maintaining short nail length to prevent injury, using flip-flops in wet and public areas, and promptly addressing any affected family members.

Section 2.0 Drug Therapy in Fungal Skin Infections

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs not included in the previous report, that are approved by the FDA and/or EMA but are not currently SFDA registered.

2.1 Additions

After May 2020, there have been no drugs for fungal skin infections that have received SFDA approval.

2.2 Modifications

No modifications have been made since May 2020.

2.3 Delisting

The medications below are no longer SFDA registered[14], therefore, it is advisable to delist the following drugs from CHI formulary.

- Bifonazole
- Griseofulvin
- Naftifine
- Tolnaftate

2.4 Other Drugs

Tavaborole 5% solution is a type of benzoxaborole that operates by blocking fungal aminoacyl transfer RNA synthetase, consequently inhibiting protein synthesis. It is US FDA approved for treating onychomycosis in children ages ≥6 years old and mentioned in different guidelines. Furthermore, it has shown its efficacy in the management of onychomycosis in an open-label, single-arm study involving 55 children suffering from toenail distal lateral subungual onychomycosis (DLSO)[9].

Fosravuconazole L-lysine ethanolate (F-RVCZ) is a prodrug of ravuconazole, which belongs to the azole class of antifungal drugs. F-RVCZ has enhanced bioavailability and water solubility. It is approved for the treatment of onychomycosis in Japan, with a recommended dosage of 100 mg per day for a duration of 3 months[9]. The effectiveness and safety of F-RVCZ were evaluated in a double-blind, randomized study involving Japanese onychomycosis patients with at least 25% clinical

involvement of the target toenail. The results showed that administering F-RVCZ (equivalent to 100 mg of ravuconazole) once daily for 12 weeks was more effective than a placebo. The treatment was also well-tolerated by onychomycosis patients, indicating its potential as a promising drug for onychomycosis treatment[15].

Section 3.0 Key Recommendations Synthesis

- The diagnosis of a tinea infection includes employing fungal microscopy and culture, which serves two purposes: identifying the particular fungus responsible and assessing its vitality. Fungal microscopy is carried out on skin scrapings and nail clippings, typically employing potassium hydroxide (KOH), which can yield rapid results[6].
- While relying solely on topical treatment is insufficient for curing tinea capitis, it is recommended to incorporate topical agents to reduce infectivity, restrict the transmission of spores, hasten the requirement for systemic antifungal drugs, and address asymptomatic carriers with a minimal load of fungal spores[5].
- For tinea capitis, the choice of the right systemic antifungal drug is predominantly determined by the fungal species that has been identified. When dealing with Trichophyton spp., terbinafine is recommended as the treatment of choice, whereas infections caused by Microsporum/Nannizzia spp. are most effectively addressed with griseofulvin or itraconazole[5].
- Fluconazole has also been used as an alternative for terbinafine in tinea capitis treatment. However, its use has been relatively restricted due to its side effects and the absence of a cost-saving advantage[5].
- In tinea capitis cases, modern treatment involves the use of potent fungicidal topical medications, eliminating the need for hair shaving. Similarly, the previous recommendation to wear a hat is no longer relevant[5].
- Most cases of tinea corporis, tinea cruris, and tinea pedis can be efficiently managed using topical treatments[6].
- The suggested initial topical treatment for tinea corporis, tinea cruris, and tinea pedis entails the application of terbinafine 1% cream once or twice a day for a period of one to two weeks[6].
- Oral treatment should be considered in the following situations: onychomycosis, tinea capitis), extensive tinea on the skin, failed topical treatment and immunocompromised patients[6].
- The goal of treating onychomycosis is to eliminate the fungal infection and restore the nail to its healthy, natural state[9].
- In cases of mild to moderate onychomycosis, topical antifungals are often sufficient for treatment, whereas oral antifungal medications are usually prescribed for moderate to severe cases[9].

- Keratolysis using 40% urea preparations in combination with occlusion is recommended for the gentle removal of nails, without causing harm[7].
- Filing or roughening are advised to diminish the affected sections of the nail[7].
- In cases of topical treatment with nail polish, it is recommended to use either amorolfine (a water-insoluble acrylic polish) or ciclopirox (available in both water-insoluble acrylic polish and water-soluble polish forms)[7].
- Laser treatments may provide temporary enhancements in nail appearance, but there is limited evidence to substantiate their capacity to maintain long-term clinical improvements or entirely eradicate disease-causing fungi[9].
- The primary systemic drugs approved and extensively employed in onychomycosis treatment are terbinafine and itraconazole[16].
- Although griseofulvin is sanctioned for treating onychomycosis, it is far less frequently utilized today due to the superior effectiveness, patient compliance, and lower recurrence rates of the other systemic agents[16].
- While fluconazole lacks official approval for onychomycosis treatment, it could potentially serve as a valuable third-line treatment[16].
- It is worth considering the potential for prolonged antifungal prevention through the use of nail polish products containing amorolfine or ciclopirox. This is typically applied less frequently after the successful treatment of onychomycosis[7].
- Treatment for tinea manuum is similar to the treatment of tinea pedis[8].
- Oral antifungal treatment is recommended for the treatment of tinea barbae[8].
- Patients should be encouraged to sanitize their shoes as a preventive measure to prevent a recurrence and to uphold a hygienic environment[7].
- Laundry items that have direct contact with the fungal infection, like socks and towels, should be washed at a temperature of 60°C[7].
- The primary treatment for candidiasis in these patients should entail the administration of fluconazole[11].
- Because of their intrinsic immune system weakness, the majority of patients need continuous maintenance antifungal therapy and often experience infections that do not react to azole medications[11].
- When dealing with Candida infections resistant to fluconazole, the treatment strategy should resemble the one employed for AIDS patients facing azole-resistant infections[11].

- Given that skin lesions may suggest a systemic infection, we strongly recommend the use of voriconazole treatment while simultaneously investigating the existence of a primary infection source. (Strong recommendation; low-quality evidence)[10].
- When dealing with cases of aspergillosis in burn injuries or extensive soft tissue wounds, it is strongly advised to conduct surgical debridement alongside antifungal therapy. (Strong recommendation; moderate-quality evidence)[10].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Fungal Skin Infections report** and aims to provide recommendations to aid in the management of fungal skin infections. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with fungal skin infections. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Fungal Skin Infections Scope

2020	Changes	2023	Rationale
Section 1.0 Fungal Skin Infections Clinical Guidelines			
British Association of Dermatologists' guidelines for the management of tinea capitis 2014	N/A		
British Association of Dermatologists' guidelines for the management of onychomycosis 2014	N/A		
Management of tinea corporis, tinea cruris, and tinea pedis: A comprehensive review	N/A		
	Missing	S1 Guideline onychomycosis: Journal der Deutschen Dermatologischen Gesellschaft. 2023[7]	**Diagnosis** • The diagnosis relies on clinical evaluation, which involves the patient's medical history and visual examination, including histological analysis when necessary. Pathogen detection can be achieved through either culture or, as it is becoming more prevalent, molecular biological techniques. **Treatment** **Start of treatment**

			• When determining whether topical treatment, systemic treatment, or a combination of both is advisable, factors such as the nail matrix's involvement, the number of affected toenails or fingernails, the extent of surface area affected per nail, the presence of multiple health conditions in the patient, potential drug interactions, and the expected level of patient compliance should all be taken into consideration. **Atraumatic nail removal for onychomycosis of the toenails** • Atraumatic nail removal can be combined with systemic antifungal treatment. • Traumatic (surgical) nail extraction is not recommended. • Drilling the affected nails can be recommended. **Topical treatment with antifungal nail polish** • For mild to moderate nail infections, which include conditions like distal subungual onychomycosis, white superficial onychomycosis, and when the infection affects a maximum of 40% of the nail surface and/or a maximum of 3 out of 10 toenails, it is advisable to consider topical antifungal nail polish as a recommended treatment option. • Filing or roughening to reduce the diseased parts of the nail is recommended. • For topical treatment using nail polish, amorolfine (water-insoluble acrylic polish) or ciclopirox (water-insoluble acrylic polish or water-soluble polish) is recommended. **Systemic treatment** • In cases of moderate to severe onychomycosis and in the absence of contraindications, it is advisable to opt for oral (systemic) treatment. A combined approach involving both oral and topical antifungal treatment is considered beneficial.

			• Continuous systemic treatment with terbinafine is recommended. • Continuous systemic treatment with itraconazole can be recommended. • Pulse treatment with itraconazole can be recommended. • Pulse treatment with fluconazole can be recommended. • Intermittent long-term treatment with low-dose terbinafine can be recommended in elderly multimorbid patients. [Expert opinion] • Intermittent long-term treatment with low-dose itraconazole can be considered. **Choice of antifungal agent for systemic and topical treatment** • When choosing the antifungal agent for treating onychomycosis, it is crucial to always take into account the specific pathogen causing the infection. **Prophylaxis after treatment of onychomycosis** • One can contemplate the possibility of extended antifungal prophylaxis using nail polish preparations that contain amorolfine or ciclopirox. This is typically applied at reduced frequencies following successful treatment of onychomycosis. **Prevention of recurrence by disinfection of footwear** • It is advisable to suggest to patients that they disinfect their footwear as a preventive measure to avoid a recurrence and to maintain a clean environment. **Candida Onychomycosis** • For cases of Candida onychomycosis, consider topical treatment using either ciclopirox or amorolfine nail polish.

			• In addition to topical therapy, the use of fluconazole in continuous or intermittent (pulse) systemic treatment can also be recommended.
	Missing	Journal of the German Society of Dermatology S1 guidelines: Tinea capitis (2020)[5]	**Diagnosis** **Treatment** • A combination of systemic and topical therapies is typically necessary. • TC patients are commonly treated on an outpatient basis, with hospitalization being an exceedingly rare occurrence. **Topical treatment** • Although using topical treatment by itself is inadequate for treating TC, it is advisable to employ topical agents to decrease infectivity, limit the spread of spores, expedite the need for systemic antifungals, and address asymptomatic carriers with a minimal fungal spore burden. • Topical agents employed include shampoos containing selenium (di)sulfide 1 %, ketoconazole 2 %, clotrimazole 2 % or ciclopirox 1 %, and – especially in the Anglo-American region – povidone-iodine. **Systemic treatment** • As a general rule, systemic antifungal medications exhibit notably higher effectiveness in treating endothrix infections (e.g., Trichophyton spp.) compared to ectothrix infections (e.g., M. canis). Controlled clinical trials have provided evidence that the selection of antifungal therapy should be based on the specific species responsible for the infection. • The selection of the appropriate systemic antifungal medication is primarily based on the specific fungal species that has been identified. When dealing with Trichophyton spp, it is advisable to use terbinafine for treatment, while

			Microsporum/Nannizzia spp. infections are best treated with griseofulvin or itraconazole. • If treatment needs to start before the exact species identification is confirmed, the choice of the antifungal agent should depend on the local epidemiological data and the likelihood of a particular dermatophyte's involvement. **Intermittent treatment** • All intermittent treatment methods in these trials were well-tolerated by the patients. Nevertheless, it is important to note that there remains insufficient evidence to provide a recommendation for intermittent treatment in general. **Description of individual agents** **Safety profile** **Treatment strategy in patients with tinea capitis and follow-up** • Following the identification of fungi or a positive KOH preparation, it is recommended to initiate a treatment regimen (both systemic and topical) lasting initially for four weeks. The choice of the specific drug should be based on the patient's medical history, KOH/PCR test results, and local epidemiological factors. • Afterward, conduct a repeat fungal culture, with a maximum incubation period of 4 weeks. Continue topical treatment while awaiting culture results, even if oral treatment is discontinued, as long as there is noticeable clinical improvement, particularly if hair regrowth has commenced (as determined by trichoscopy). If this is not the case, both forms of treatment may be sustained. • If the fungal culture still yields positive results, extend the treatment for an additional two weeks.

			• Repeat steps 2 and 3 until fungal cultures return negative results. Achieving a mycological cure is the ultimate goal of any effective treatment, so treatment adjustments should be based on individual patient responses. • Regarding laboratory monitoring, traditionally, routine testing of liver enzymes (AST, ALT, GGT) has been performed during systemic antifungal therapy. **Supplementary measures** • Exclusion from school and childcare centers • Shaving of scalp hair/use of headgear • Treatment of contaminated objects and personal effects • Use of corticosteroids: In cases of inflammatory TC variants, where robust immune reactions and itching result from the use of very potent antifungal medications leading to rapid fungal elimination, the situation can be addressed with topical combination therapy. This therapy includes the use of corticosteroids and antifungal agents, typically administered for an initial duration of around seven days. **Reasons for treatment failure** • If there is no observable improvement in the patient's condition, it is crucial to verify that the chosen antifungal treatment is sufficient for eliminating the responsible dermatophyte. If it is not, then the following alternatives can be considered: 3. Increase the dose of the antifungal agent initially chosen or extend the treatment duration. 4. Switch antifungal agents, for example: Griseofulvin → itraconazole (for M. canis infections) Terbinafine → itraconazole (for T. tonsurans infections) Itraconazole → terbinafine (for T. tonsurans infections)

	Missing	Indian Academy of Pediatrics: Standard treatment guidelines for tinea infections (2022)[8]	**Epidemiology and Etiology** • Tinea capitis is the most frequent form of infection in children, particularly observed among urban preschool-aged and school-aged children. • In adolescents, tinea pedis, tinea manuum, tinea corporis, tinea barbae, and tinea cruris are more common. **Tinea Capitis** • Treatment options include: a) Topical application of shampoo with 2.5% selenium sulfide/zinc pyrithione/ ketoconazole . b) Oral griseofulvin (microcrystalline—20–25 mg/kg/day maximum 1,000 mg or ultramicrosize—10–15 mg/kg/day maximum 750 mg) for 6 weeks. c) Oral terbinafine at 3–6 mg/kg/day for 4–6 weeks can be used in cases of noninflammatory tinea capitis in 4 years and older. **Tinea Corporis** • For the treatment: a) Mild-to-moderate: Topical antifungal agents (imidazole, terbinafine, butenafine, and naftifine) twice daily for 2–4 weeks. b) Oral itraconazole for 1–2 weeks can be added if more than two sites involved. c) Extensive involvement cases: Oral griseofulvin for 2–8 weeks or oral terbinafine for 2–6 weeks along with topical antifungal agents. **Tinea Pedis** • Treatment options include: 6. Avoid wearing tight or airtight shoes, ensure thorough drying between the toes after bathing, and employ absorbent antifungal powder like zinc undecylenate.

			7. Topical therapy with imidazole, allylamines, and tolnaftate for 2–4 weeks. 8. Oral griseofulvin (microsized) at 10–20 mg/kg/day for 6–8 weeks 9. Oral terbinafine at 62.5 mg/day (40 kg) for 2 weeks. 10. Hyperkeratotic tinea pedis, a condition characterized by thickened skin, may find relief through a combination of antifungal therapy and the use of a topical keratolytic agent like salicylic acid. **Tinea Manuum** • Treatment for tinea manuum is similar to the treatment of tinea pedis. **Tinea Cruris** • Patients usually present with the following clinical manifestations: a. Erythematous or hyperpigmented patch on the proximal medial thigh. Spreads centrifugally, with partial central clearing and a slightly elevated, erythematous or hyperpigmented, and sharply demarcated border. b. Infection may spread to the perineum and perianal areas, into the gluteal cleft, or onto the buttocks. In males, the scrotum is typically spared. **Tinea Unguium (Onychomycosis)** • Treatment options include: a) Topical antifungal like ciclopirox without matrix involvement. b) Oral itraconazole—5 mg/kg/day for 1 week of each month for 3–4 months

			c) Oral terbinafine at 62.5 mg/day (40 kg) for 6 weeks for fingernails and 12 weeks for toenails d) Oral griseofulvin (microsized) at 10–20 mg/kg/day for 6 months for fingernails and 6–12 months for toenails **Tinea Barbae** • Oral antifungal treatment is essential for managing this condition.
	Missing	Trichophyton indotineae, from epidemiology to therapeutic review article (2023) published in Journal of Medical Mycology[13]	**Introduction** **Epidemiology and Resistance Patterns** • Dermatophyte infection considered prevalent in India and have also been reported in Europe, Canada, the Middle East, and other locations in Asia. • The dermatophyte species is associated with frequent resistance to antifungal therapy, particularly terbinafine. **Clinical manifestations** **Species identification and antifungal susceptibility testing** • Fungal culture cannot reliably distinguish T. indotineae from some other Trichophyton species. **Treatment** • Terbinafine is frequently recommended as the initial treatment. • In patients with terbinafine-resistant T. indotineae infections, itraconazole can be administered as an alternative treatment along with other options. **Prevention** • Practicing good hygiene is likely a crucial factor in preventing the transmission and recurrence of infections.

	Missing	Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America[11]	• Due to their inherent immunodeficiency, most patients require ongoing suppressive antifungal treatment and frequently develop infections that do not respond to azoles. • In cases of fluconazole-refractory Candida infections, the treatment approach should be similar to that used for patients with AIDS who develop azole-resistant infections.
	Missing	Clinical Practice Guideline for the Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America	• Since skin lesions could indicate widespread infection, we strongly advise administering voriconazole treatment while also assessing the presence of a primary infection source. (Strong recommendation; low-quality evidence). • In situations involving aspergillosis occurring in burn injuries or extensive soft tissue wounds, it is strongly recommended to perform surgical debridement in conjunction with antifungal therapy. (Strong recommendation; moderate-quality evidence).
	Missing	The Royal Australian College of General Practitioners: Superficial fungal infections 2019 article[6]	- **Practical approach to diagnosis and Diagnostic tests** **Treatment options**: **1- Topical therapy:** - Recommended first-line for tinia pedis and tinea cruris: terbinafine 1% cream once or twice daily for one to two weeks. - In cases of onychomycosis with contraindication to systemic therapy, nine to 12 months of ciclopirox 8% nail lacquer once daily or amorolfine 5% nail lacquer once daily with debridement of hyperkeratotic nails can be offered but has

			low mycological cure rates of 29–36%21 and 38%,22 respectively. **2- Oral therapy** - Terbinafine is considered first-line therapy. the length of oral treatment varies based on the location. - Second-line therapy includes azoles (itraconazole, fluconazole). - Griseofulvin is the initial treatment choice for tinea capitis caused by Microsporum infections and should be administered for a duration of six to eight weeks (with pediatric dosing at 10 mg/kg, up to a maximum of 500 mg). In contrast, for tinea corporis, griseofulvin is not the preferred option as it is less effective than terbinafine and azoles. In this case, it is recommended as a third-line treatment. 3- **Laser therapy:** laser therapy cannot be recommended as first-line treatment for onychomycosis. **Prevention of recurrence** - Patients should receive guidance on mitigating factors that can be altered to prevent tinea infections. These include refraining from activities such as sharing hairbrushes, clothing, or shoes, avoiding walking without footwear in communal shower and pool areas, and adopting practices like regularly switching footwear and changing socks. - After a successful treatment resulting in a cure, patients can use weekly prophylactic topical antifungal therapy (ciclopirox, amorolfine, bifonazole, terbinafine) to maintain prevention.
	Missing	Clinical, Cosmetic and Investigational Dermatology: Updated	**Physical Examination** **Diagnostic tests** **Treatment**

		Perspectives on the Diagnosis and Management of Onychomycosis 2022 article[9]	- The objective of treating onychomycosis should be to eradicate the fungal pathogen and return the nail to its normal condition. - Various treatment options are available for onychomycosis, encompassing oral and topical antifungal medications, device-based treatments such as lasers, surgical removal of the nail (nail avulsion), nail debridement, and combinations of these therapies. - Oral antifungals are typically recommended for moderate to severe cases, while mild to moderate onychomycosis can often be treated with topical antifungals. - Nail debridement can help reduce fungal load and is sometimes used in conjunction with topical treatments. Nail avulsion is limited in its application, primarily reserved for situations involving a painful or non-growing single nail. - Laser treatments have received approval from the United States Food and Drug Administration (FDA) for temporary cosmetic improvements, but their cure rates are lower compared to oral and topical antifungals, as the FDA's criteria for approval are less stringent, and definitive guidelines for laser therapy use are currently lacking. - Oral therapies - Novel Oral Therapies - Topical therapies - Novel Topical therapies - OTC options - Laser therapy - Photodynamic therapy: Not recommended. - Plasma Therapy: Not recommended. - Microdrilling - Combination Treatments - Treatment in Children

			- Elderly Adults - Pregnant and Lactating Women

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Arthrodermataceae

The term fungal skin infections was not found as a mesh term.

The following is the result of the PubMed search conducted for the search:

Query	Filters	Search Details	Results
((((((((((((((Arthrodermataceae[MeSH Terms]) OR (Dermatomyces[Title/Abstract])) OR (Dermatomyce[Title/Abstract])) OR (Cutaneous Fungus[Title/Abstract])) OR (Dermatophytes[Title/Abstract])) OR (Dermatophyte[Title/Abstract])) OR (Cutaneous Fungi[Title/Abstract])) OR (Fungi, Cutaneous[Title/Abstract])) OR (Fungus, Cutaneous[Title/Abstract])) OR (Ctenomyces[Title/Abstract])) OR (Ctenomyce[Title/Abstract])) OR (Keratinomyces[Title/Abstract])) OR (Keratinomyce[Title/Abstract])) OR (Arthroderma[Title/Abstract])) OR (Arthrodermas[Title/Abstract])) OR (Nannizzia[Title/Abstract])) OR (Nannizzias[Title/Abstract])	Guideline, in the last 5 years	("arthrodermataceae"[MeSH Terms] OR "Dermatomyces"[Title/Abstract] OR "cutaneous fungus"[Title/Abstract] OR "Dermatophytes"[Title/Abstract] OR "Dermatophyte"[Title/Abstract] OR "cutaneous fungi"[Title/Abstract] OR "fungi cutaneous"[Title/Abstract] OR "fungus cutaneous"[Title/Abstract] OR "Ctenomyces"[Title/Abstract] OR "Keratinomyces"[Title/Abstract] OR "Arthroderma"[Title/Abstract] OR "Nannizzia"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	1

Appendix D. Treatment Algorithm

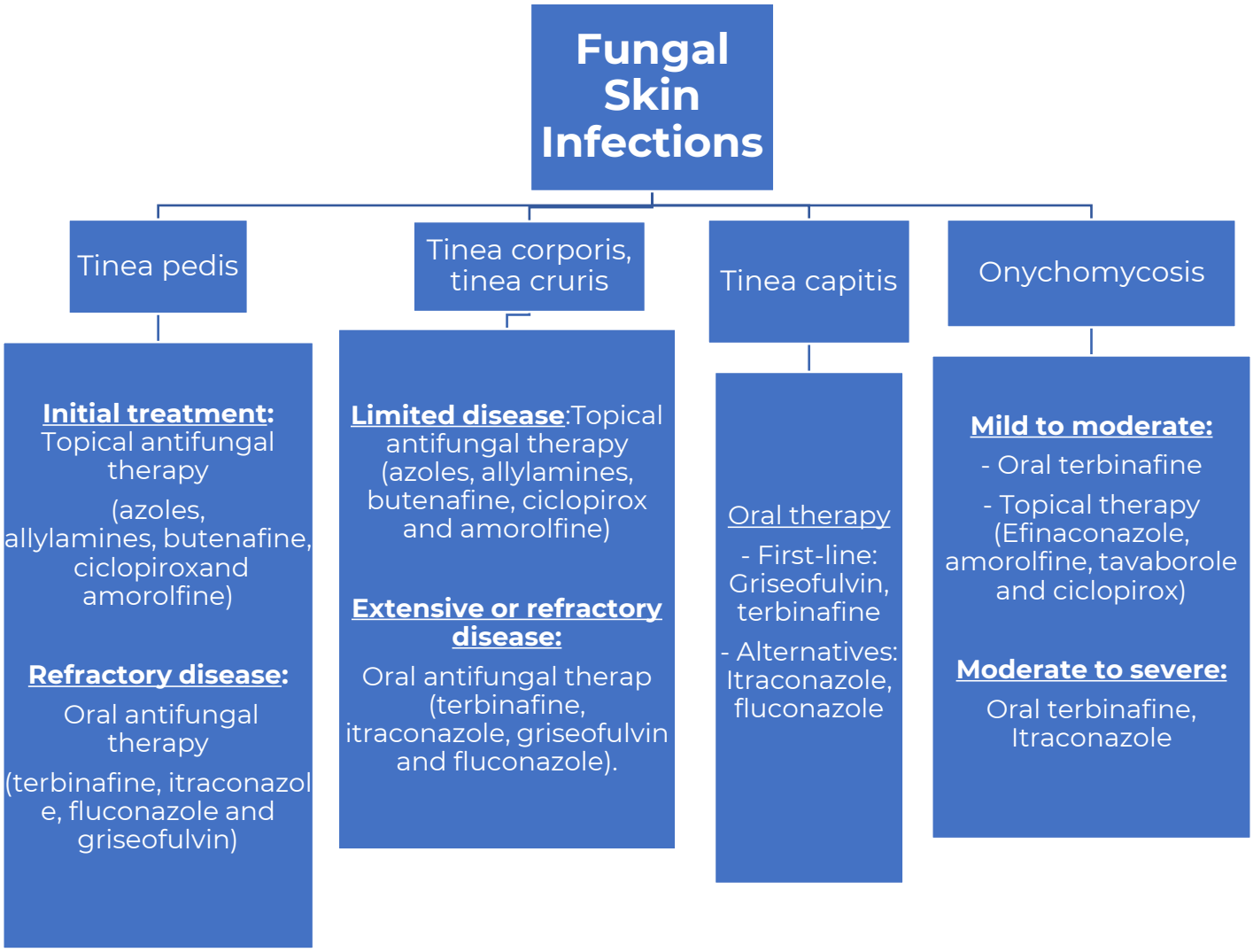

Figure 2. *Treatment Algorithm for the Management of Fungal Skin Infections*[5–7,9,17]