**Pharmacological therapy**

- Choice of therapy depends on causative organism, severity of infection, cost & patient compliance

**Oral Antifungals**

Any one of the following agents:
- Itraconazole
- Terbinafine

**Alternative oral agents:**
- Fluconazole
- Griseofulvin
- Ketoconazole* (Serious hepatotoxicity may occur with the use of oral Ketoconazole. Please see Dosage Guidelines for more information.)

**Topical Antifungal**

Any one of the following agents:
- Amorolfine
- Ciclopirox
- Efinaconazole
- Tavaborole
- Tioconazole

**Combination Therapy**

- Amorolfine + Itraconazole or Terbinafine

**Non-pharmacological therapy**

- Patient education
- Other treatment options
  - Surgical avulsion & debridement
  - Laser therapy
  - Photodynamic therapy (PDT)
  - Alternative therapies

*Serious hepatotoxicity may occur with the use of oral Ketoconazole. Please see Dosage Guidelines for more information.

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TINEA UNGUIUM

• Specific onychomycosis (fungal infection of the nailbed, nail plate, or both) caused by dermatophytes
• Also called dermatophytic onychomycosis; more commonly affects the toenails than the fingernails

Patient Risk Factors

• Aging, male, peripheral vascular diseases, diabetes mellitus (DM), occlusive footwear, human immunodeficiency virus (HIV), presence of Tinea pedis, immunosuppression, atopy, hyperhidrosis, exposure to individuals w/ Tinea pedis or onychomycosis

Clinical Presentation

• Usually asymptomatic & patients first consult for cosmetic reasons
  - Onychomycosis is suspected if there are changes in the 3rd or 5th toenail, involvement of the 1st & 5th toenails on the same foot, & unilateral nail changes
  - Patients may complain of numbness, pain, discomfort affecting manual activities & may cause loss of self-esteem & diminished social interaction
  - May manifest as erythematous swelling of the nail fold (paronychia), separation of the nail plate from its bed

Clinical Subtypes

• Onychomycosis is classified based on route of infection & clinical presentation

Distal & Lateral Subungual Onychomycosis (DLSO)

• Most common type, 90% of infections
• Invasion occurs at distal subungual space & at the distal lateral groove
  - More commonly involves the toenails
• Nail plate looks opacified & hyperkeratotic, its distal portion may break away
• Splinter hemorrhages are seen secondary to mild inflammation compressing small blood vessels
• Most common cause: Trichophyton rubrum
  - May also be caused by: Trichophyton tonsurans, Trichophyton mentagrophytes & Epidermophyton floccosum

Superficial White Onychomycosis (SWO)

• Second most prevalent type, 10% of infections
• Dorsal surface of the nail plate is invaded
• Minimal inflammation; nail becomes soft & crumbly w/ a white-colored rough surface
  - Nail plate is not thickened & remains attached to the nail bed
• Typically caused by T mentagrophytes but may also be caused by non-dermatophyte molds

Proximal Subungual Onychomycosis

• Least common form in healthy individuals & may be an early indicator of HIV infection
• Toenails are more commonly infected than fingernails
• Infection enters at the cuticle & the proximal nail bed is always involved
  - Spreads distally so if left untreated, the entire nail plate will be affected
  - Subungual hyperkeratosis & proximal onychomycosis are usually present
• Usually caused by T rubrum but can be caused by Trichophyton megnini, T tonsurans & T mentagrophytes

Candidal Onychomycosis

• Commonly found in patients diagnosed w/ chronic mucocutaneous candidiasis
• More commonly affects the fingernails
• Candida invades the nail bed or plate directly or may indirectly involve the nail through infecting the nail bed, folds or hyponychium
• Entire nail thickens & turns yellow-brown; progression may lead to total dystrophy of the nails
• Usually caused by Candida albicans or other Candida sp
  - May have some resistance to oral antifungal agents

Total Dystrophic Onychomycosis

• Most advanced form
• Nail plate is almost completely destroyed
• May be the end result of the above four forms

DIAGNOSIS

Onychomycosis typically requires prolonged high-cost therapy; thus, the diagnosis should be confirmed before treatment is started

Microscopy

• Specimen is mounted in 10-15% Potassium hydroxide (KOH) soln w/ calcofluor & heated gently, viewed under light microscope, & examined for hyphae & arthrospores
  - Scrapings of nail bed for distal subungual onychomycosis & scrapings from the nail plate white spots for superficial white onychomycosis
  - Calcofluor may decrease risk of false negative results
• Presence of fungal infection can be detected but the causative organism is not specified
PHARMACOLOGICAL THERAPY

- Treatment for onychomycosis is indicated:
  - In patients experiencing pain or discomfort related to the infected nails
  - In patients with diabetes & other risk factors for cellulitis
  - In patients with history of ipsilateral lower extremity cellulitis
  - To prevent the spread of fungal infection to other parts of the body (e.g., feet, hands, groin) & to close contacts
  - For cosmetic reasons
- Patients with confirmed onychomycosis but are refractory to treatment may benefit from switching to an alternative oral agent

Oral Antifungals

Fluconazole
- Active against common dermatophytes, Candida sp & some non-dermatophytic molds
  - Offers an alternative to Itraconazole & Terbinafine
  - Not approved in most countries for onychomycosis treatment
- Effects: Fungistatic, high-dose pulse therapy for fingernail treatment has been shown to have up to 90% clinical cure rate w/ near-total mycologic elimination
  - Outcome data on toenail treatment shows clinical improvement in 72-89% of patients treated

Itraconazole
- First-line agent for treatment of mild to moderate dermatophyte onychomycosis; 2nd-line therapy for patients with severe dermatophyte onychomycosis who cannot tolerate oral Terbinafine
  - Has broad antifungal coverage that includes dermatophytes, Candida sp & a number of non-dermatophyte molds
- Effects: Fungistatic, mycologic cure rates range from 45-70% & clinical cure rates from 35-80%
  - Studies have shown that both continuous & pulse therapies are effective

Terbinafine
- First-line agent for treatment of mild, moderate to severe dermatophyte onychomycosis
- Active against dermatophytes which are the cause of the majority of onychomycosis infections
  - Not as active against Candida sp or non-dermatophyte molds
- Effects: Fungicidal, mycotic cure rate for toenails is 71-82% & clinical cure rate 60-70%
  - Some comparative trials have shown Terbinafine to be more effective than other agents for onychomycosis treatment

Topical Antifungals
- Limited to mild cases involving very distal nail plate & in those unable to tolerate systemic treatment
  - Low response rate because of poor nail plate penetration
- Used as an adjunct to oral therapy for resistant infections
- May combine w/ surgical nail avulsion

DIAGNOSIS (CONT’D)

Culture
- Adequate sample is inoculated onto Saboraud’s glucose agar w/ or without addition of antibiotics
- Identifies organism & the specific etiologic agent so that treatment can be individualized
- Considered the mainstay of onychomycosis diagnosis

Histology
- Periodic acid-Schiff (PAS) staining w/ histologic exam of the clipped, distal, free edge of the nail & attached subungual debris
  - Most sensitive diagnostic method
- PAS staining of nail plate biopsy or removed nail w/ culture is required to diagnose proximal subungual onychomycosis

ALTERNATIVE DIAGNOSIS

- Dermatologic disorders: Lichen planus, psoriasis, nail dystrophy, eczematous conditions
- Other nail infections: chronic paronychia, viral warts
- Senile ischemia
- Trauma
- Malignancy: Fibroma, melanoma, Bowen disease

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### PHARMACOLOGICAL THERAPY (CONT’D)

#### Topical Antifungals (Cont’d)

**Amorolfine**
- Active against dermatophytes, dimorphic fungi, yeasts, other filamentous & dematiaceous fungi
- **Effects:** May be effective in patients w/ mild infection without nail matrix (lunula) involvement
- Has been used in combination w/ oral Terbinafine or Itraconazole
  - Combination therapy may be useful for patients w/ severe onychomycosis

**Ciclopirox**
- Indicated in mild-to-moderate distal superficial onychomycosis
- Treatment may take 6 months-1 year & cure rates range from 29-47%

**Eflornizazole**
- A triazole antifungal, developed for the treatment of mild-to-moderate DLSO
- Inhibits fungal lanosterol 14α-demethylase, involved in the biosynthesis of ergosterol
- Indicated for onychomycosis of the toenails due to *T rubrum* or *T mentagrophytes*

**Luliconazole**
- An imidazole molecule w/ fungicidal & fungistatic activity
- May be used as treatment for moderate-to-severe DLSO caused by *T rubrum* or *E flaccosum*

**Tavaborole**
- A light-weight, water-soluble oxaborole topical nail lacquer (boron-containing-compound)
- Indicated for onychomycosis of the toenails due to *T rubrum* or *T mentagrophytes*

**Tioconazole**
- Treatment option for superficial & distal onychomycosis

#### Longer courses of antifungals may be needed in:
- Patients whose nails grow slowly
- Patients who have decreased blood supply to the nail as a result of conditions (eg peripheral vascular occlusion, DM)
- Patients who have near-total or total nail plate involvement

### NON-PHARMACOLOGICAL THERAPY

#### Patient Education
- Educate patient about proper foot hygiene
  - Patients should wear breathable footwear & 100% cotton socks
  - Change socks often, if possible
  - Keep feet dry throughout the day, may use antifungal foot powder
  - Recognize & treat *Tinea pedis* to prevent spread to toenails
- Patient should be encouraged to maintain & improve health conditions
  - Eg regularly trim nails short, control DM, quit smoking, exercise, etc
- Assure patient that improvement continues even after cessation of oral treatment since the fungus is continually exposed to the medication secondary to the drug’s binding to keratin in the nail, though recurrence is common
  - May take 9-12 months to assess cure

#### Other Treatment Options
- Further studies are needed to prove the safety & efficacy of the following management options for tinea unguium

**Surgical Avulsion & Debridement**
- Surgical avulsion may be considered for patients w/ single-nail onychomycosis unresponsive to pharmacological agents alone, followed by topical antifungal therapy
- Debridement may be considered as an adjunct to topical or oral pharmacologic interventions

**Laser Therapy**
- Neodymium-doped:yttrium-aluminum-garnet (Nd:YAG) & dual-wavelength (870 & 930 nm) near-infrared diode lasers are newer treatment options that showed significant improvements in nail appearance in several studies when used together w/ topical antifungal agents

**Photodynamic Therapy (PDT)**
- Involves the use of photosensitizing agents & a light source to treat fungal infection

**Alternative Therapies**
- Eg Ageratina pichinchensis (snakeroot) extract, Melaleuca alternifolia (tea tree) oil, menthol
- May help w/ symptom relief but further studies are needed to establish the therapeutic benefit of these agents

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## Dosage Guidelines

### ANTIFUNGALS (ORAL)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>150 mg PO once wkly Continue until infected nail is replaced</td>
<td>• GI effects (abdominal pain, diarrhea, flatulence, N/V, taste disturbance, elevated liver enzyme levels)</td>
<td><strong>Special Instructions</strong>&lt;br&gt;• Use w/ caution in patients w/ renal &amp; hepatic impairment&lt;br&gt;• Periodically monitor liver function tests (LFTs) &amp; for risk of drug interactions&lt;br&gt;• Treat until nail is normal or acceptably improved</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>500-1000 mg PO 24 hrly or in divided doses (At least 4 mth for fingernails or 6 mth for toenails)</td>
<td>• Only effective if dermatophytes are the etiologic agents</td>
<td><strong>Special Instructions</strong>&lt;br&gt;• Should be taken immediately after meals&lt;br&gt;• Long-term use is not advised due to possibility of adverse effects; monitor hepatic, renal &amp; hematopoietic function if used long term</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Fingernails only: 200 mg PO 12 hrly x 2 wk&lt;br&gt;Toenails w/ or w/o fingernail involvement: 200 mg PO 24 hrly x 3 wk&lt;br&gt;Continuous treatment: 200 mg PO 24 hrly x 3 mth</td>
<td>• GI effects (dyspepsia, abdominal pain, nausea, constipation, diarrhea, pyrosis); CNS effects (headache, dizziness); Dermatological effect (pruritus)</td>
<td><strong>Special Instructions</strong>&lt;br&gt;• Two pulse treatment are recommended for fingernail infections &amp; 3 pulse treatments for toenail infections&lt;br&gt;• Pulse treatments are always separated by a 3-week drug-free interval&lt;br&gt;• Clinical response will become evident as the nail regrows, following discontinuation of treatment&lt;br&gt;• Use w/ caution in patients at risk for heart failure, hepatic impairment &amp; renal insufficiency&lt;br&gt;• Monitor LFTs at baseline &amp; regularly throughout therapy&lt;br&gt;• Monitor for symptoms of drug interactions (eg Rifampicin, macrolides, oral anticoagulants, etc)&lt;br&gt;• In patients w/ hypochlorhydia, absorption may be improved by administering the drug w/ an acidic drink (eg cola)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>200-400 mg PO 24 hrly x 6-12 mth</td>
<td>• GI effects (N/V, abdominal pain, serious hepatotoxicity); Dermatological effects (urticaria, angioedema, pruritus, rash, alopecia); CNS effects (headache, dizziness, somnolence); Other effects [inhibition of testosterone &amp; adrenal steroid synthesis (high dose), rarely gynecomastia]</td>
<td><strong>Special Instructions</strong>&lt;br&gt;• Use only to treat serious fungal infection when other therapies are not tolerated or unavailable&lt;br&gt;• Carefully consider the benefits against the potential risk of therapy&lt;br&gt;• Contraindicated in patients w/ acute or chronic liver disease&lt;br&gt;• Monitor LFTs at baseline &amp; wkly during treatment course&lt;br&gt;• Use w/ caution in patients w/ adrenal insufficiency</td>
</tr>
</tbody>
</table>

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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Specific prescribing information may be found in the latest MIMS.
# Tinea Unguium (6 of 7)

## Dosage Guidelines

### ANTIFUNGALS (ORAL) (CONT’D)

<table>
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<tr>
<th>Drug</th>
<th>Dosage</th>
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</tr>
</thead>
</table>
| Terbinafine | **Fingernail treatment:** 250 mg PO 24 hrly x 6 wk  
**Toenail treatment:** 250 mg PO 24 hrly x 12 wk | • GI effects (anorexia, N/V, diarrhea, abdominal pain, loss or disturbance of taste, liver dysfunction); CNS effect (headache); Dermatological effects (rash, urticaria) | **Special Instructions**  
• Do not use in patients w/ hepatic & renal impairment  
• Monitor complete blood count (CBC) & LFTs at baseline & regularly throughout therapy  
• Use w/ caution in patients w/ psoriasis  
• Reduce doses in patients w/ renal impairment |

### ANTIFUNGALS (TOPICAL)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Strength</th>
<th>Dosage</th>
<th>Adverse Reactions</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Clotrimazole¹ | 1% lotion, cream  
| Miconazole | 2% cream, tinct    | Rub on affected areas 8-12 hrly x 2-4 wk                                           | • Dermatological effects (erythema, stinging or burning sensation, blister, skin peeling, edema, itching, urticaria, skin irritation)  
**Special Instructions**  
• Use w/ caution in pregnant & nursing women  
• May be used w/ or w/o occlusive dressing over large areas  
• Contraindicated in patients w/ skin TB, measles, chickenpox, herpes simplex, & syphilitic skin infection | **Special Instructions**  
• Discontinue use if sensitization & irritation develops  
• Avoid contact w/ eyes  
• Contraindicated in patients w/ cracked skin on hand or foot |
| Tioconazole | 1% cream          | Apply thinly 12-24 hrly x 2-4 wk                                                   | • Dermatological effects (mild local irritation, dermatitis, paresthesia, allergic reaction)  
**Special Instructions**  
• Contraindicated in patients allergic to imidazoles, in pregnant & nursing women | **Special Instructions**  
• Product combination w/ a corticosteroid is available. Please see the latest MIMS for specific formulations. |

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## Dosage Guidelines

### ANTIFUNGALS (TOPICAL) (CONT’D)

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<th>Available Strength</th>
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<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amorolfine</td>
<td>5% nail lacquer</td>
<td>Apply once-twice wkly until nail is regenerated &amp; areas are cured</td>
<td>Adverse Reactions • Dermatological effects (occasional local irritation, slight, transient peri-ungual burning sensation)</td>
</tr>
<tr>
<td>Ciclopirox (Ciclopiroxolamine, Ciclopirox olamine)</td>
<td>8% nail lacquer</td>
<td>Apply every other day x 1 mth, then twice wkly x 1 mth, then once wkly for 3rd mth onwards until nail is regenerated &amp; areas are cured Remove coating w/ alcohol once wkly</td>
<td>Adverse Reactions • Dermatological effects (pruritus, redness, scaling, burning sensation, pain)</td>
</tr>
<tr>
<td>Naftifine</td>
<td>1% cream</td>
<td>Apply once daily to affected nail</td>
<td>Adverse Reactions • Dermatological effects (redness, burning sensation, dryness)</td>
</tr>
</tbody>
</table>

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