Onychomycosis Treatment & the Antifungal Drug Chart
(Chart Pages 1 & 2 printed; 3rd page available online)
April 2010

Recent Guidelines:
- Canadian:
  Bugs and drugs 2006
  http://www.bugsanddrugs.ca/
- American:
  IDSA Candida guidelines 2009
  http://www.journals.uchicago.edu/doi/pdf/10.1086/596757
- UK Guideline 2003

Review Articles:
- NEJM: Fungal nail disease 2009
- Cochrane: Topical fungal treatments of the skin & foot
- Cochrane: Clinical%20Guidelines/Onychomycosis.pdf

Other Resources:
- Images of skin diseases, includes other dermatologic links: www.dermnet.com

Case discussion
- Mr. T., a 69 yr old man reports that his big toenail has some yellow "streaks" and looks different. He has a history of recurring tinea pedis.
- He has diabetes and is on metformin BID and a small dose of Humulin N at bedtime. He started swimming a year ago to improve his health after he had a "mild" heart attack.
- Upon examination, you notice a yellowish discolouration mainly under the distal end of a thickened toenail.

Risk factors for onychomycosis:
- Risk factors include: age (increased risk with older age), gender – males 2.4x at risk than females, history of tinea pedis or known infected family members.
- Medical conditions that increase risk of infection include diabetes, immunodeficiency, psoriasis or genetic factors.
- Other contributory factors include: poor peripheral circulation, nail trauma, occlusive shoes, smoking, sports activities or other activities involving bare feet.

When to consider treatment:
- Patients with diabetes and/or additional risk factors for cellulitis (i.e. prior cellulitis, venous insufficiency, edema). Onychomycosis may be a predictor of foot ulcer in a diabetic patient.
- Patient experiencing nail pain or discomfort.
- Cosmetic improvement desired.

Diagnosis:
- Nail clippings, scrapings under the nail and deep nail samples are essential to confirm diagnosis of dermatophyte infection. This is recommended before starting treatment!
- If negative for dermatophytes, assess for possible psoriasis, lichen planus, nail trauma, onycholysis (e.g. distance runners), changes due to aging or gel nails, & yellow-nail syndrome.

Cautions including contraindications
- A meta-analysis found the risk of severe liver injury or asymptomatic elevations of serum transaminases with all treatments to be ~2%. Liver enzymes should be done at baseline and after 4-6 weeks with terbinafine and monthly for itraconazole.
- Itraconazole is contraindicated in patients with heart failure or ventricular dysfunction and in patients using drugs metabolized by CYP 3A4 (see Antifungal Chart).

Oral candidiasis
- The nystatin dose for oral candidiasis (adult) is usually 5ml QID to ensure enough liquid to cover area in mouth
- Fluconazole is less effective but is useful in patients unable to take the above.

Duration & approach to treatment
- Duration of treatment for terbinafine and itraconazole: to toenail 12-16 weeks; fingernail 6 weeks.
- Weekly topical terbinafine cream application after completion of oral treatment may be tried to prevent reinfection (expert opinion). The cream is applied between toes and around nail margin.
- Alternate treatments
  - Itraconazole pulse therapy (ie. 200mg po BID for 1 week per month) may decrease costs, side effects when compared to fixed dose (ie. 200mg po daily).
  - Fluconazole 150mg po once weekly (x 6-12 months for toenail; x ≥3 months for fingernail).
  - To monitor for treatment success, mark the nail at completion of oral treatment. This can be done by filing a line in the nail at the proximal part of known infection and marking with a permanent marker. Ask the patient to return if mark and affected toenail do not grow out or if infection moves proximal past the marked line.

Other Fungal Infections: Clinical Pearls from the Antifungal Chart (chart, next page &/or online)

Common skin infections:
- Nystatin only effective for Candida infections (e.g. diaper rash, intertrigo, vulvovaginal infection).
- Combination products that contain steroids and/or nystatin should not be used for dermatophyte infections (e.g. Viaderm®; nystatin, neomycin, gramicidin & trimcinolon; Lotriderm: clotrimazole + betamethasone).

Oral candidiasis
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Vulvovaginal candidiasis (uncomplicated)
- 1-3 days with a topical azole as effective as 6-7 days for treatment but allow ~3 days for symptom resolution.
- 7 day topical azole treatment recommended in pregnancy
Select drug interactions with antifungals

- Terbinafine has minimal significant drug interactions and is a good antifungal option for patients on multiple drug regimens. As an inhibitor of CYP 2D6, it does still have some potential for drug interactions including increasing the levels and effect of TCAs, beta-blockers and antipsychotics. (See also Antifungal Treatment Chart.)

- Itraconazole is a strong CYP 3A4 inhibitor resulting in many frequent and significant drug interactions. The majority of drug interactions result in increased levels of drugs that may: prolong QT interval (i.e. amiodarone, quinidine, erythromycin), increase side effects (digoxin-nausea, vomiting; nifedipine-hypotension, dizziness; simvastatin/lovastatin-hydrabdomyolysis; repaglinide, pioglitazone- hypoglycemia) or increase toxicity (i.e. cyclosporine, tacrolimus)

- Strong CYP 3A4 inducers (i.e. phenytoin, grapefruit juice) and antacids may decrease itraconazole levels.

- Fluconazole has less potential for major drug interactions than itraconazole because of its renal elimination and lesser effects as an enzyme inhibitor. (Agent is 3rd line in onychomycosis due to limited efficacy.)

Is ciclopirox nail lacquer: penlac an option?1

- Penetration into the nail is limited and use is of minimal value. It is slightly more effective when compared to placebo2; no additive benefit when combined with oral terbinafine23

- Recurrence is common on discontinuation.

- Consider cost of solution: $140 / 12gm bottle

- The application process may be difficult for elderly & those with vision impairment. (Daily application 5mm beyond nail margin, on the bottom of the nail and skin under nail recommended. Remove weekly with isopropyl alcohol, trim or remove any damaged nail.) Treat x 48 weeks.

Home remedies – Do they work?

- Home remedies like vinegar, Listerine, Vicks Vaporub, vitamin E or thyme oil have no proven benefit.

- There is minimal evidence to support use of tea tree oil. It is a potent sensitizer and can cause local irritation and inflammation, producing skin reactions similar to those seen with poison ivy.

References – RxFiles Newsletter: Antifungal newsletter (April 2010)


Key signs: nail thickening, discoloration, & separation from nail bed. C&S to confirm to tx. (Clip, scrape & deep nail sample to avoid false negatives.) Cause: toenail—commonly dermatophyte; fingernail—may be yeast (eg. candida). pearls: uncommon to have finger without toenail involvement; file & mark margin of fungus on nail at completion of tx to monitor success.

Risk factors:
- ↑ age (15-20% in pts ≥ 40 yrs); swimming, barefoot, tinea pedis, diabetes, immunodeficiency, living with an infected family member.
- 

Tx: topical terbinafine or itraconazole; x2-10wk s; success, 50-80%; relapse, 25-30% (topical terbinafine weekly to prevent relapse).
- Itraconazole pulse tx less $$$ & SE, but requires scheduling; however, terbinafine pulse treatment cure rate rarely more than daily dose.
- Topical: Nail lacquer in mild, distal, dx minim, perf. combo with va no added benefit.

Prevention: tx tinea pedis; wear sandals/flipper in communal areas bathings, locker rooms, gym, mosque.
- Home remedies: lactic acid, Bifidobacteria, vinegar, no proven tx benefit. Tea tree oil: little evidence benefit; allergy.


General tx info: Antifungal to affected & surrounding area (1-2ches beyond rash).
- Continue x1wk after sx’s gone & skin looks healed to eradicate infection (90%–10-14 days).
- Keep area clean & dry (use non-scented talc or powder baby powder. Goldbaird, tolnaftate [Cochrane: no difference in effectiveness of fluconazole oral vs intra-vaginal OTC routes].
- Nystatin safe, poor oral adherence & QID.
- Oral: nail, scalp. Easier if infected proximal max, then gradually, add, beard, severe/spread/wide or if recurrent.
- Combination with steroids not usually recommended due to ↑ SE, cost & cure rates.

Prevention: Avoid sharing personal items & towels. Avoid wearing tight or occlusive clothing.

Wash linens & clothing in hot water & dryer or dry & expose to UV rays. Disinfect shoes.

i) Scherbor dermatitis.
- Commensal overgrowth of yeast. Topical: shampoo azoles & ciclopirox olamine useful. Intermittent shampoo use once weekly or every other week after tx may remain (limited comparison data).

ii) Tinea capitis (Scalp).
- Common in kids cats, cows; oral terbinafine, top x 4-8wk s. (no azole sulfone shampoo 2–3wx per wk (x5mins) to ↓ spread. Other options: oral fluconazole, itraconazole, griseofulvin.
- Consider topical azoles first, terbinafine slightly more effective/rapid but ↑ cost. Tx: x2-4wks.

iii) Tinea corporis (Body).
- Tx options: topical azoles (clotrimazole, miconazole) & terbinafine.
- Common in adolescent & young adult; if repeat short pant/long sleeves. Overdiagnosed?
- Tx: Topical azole (clotrimazole, miconazole, terbinafine) daily x 2wk or terbinafine cream daily x 4wk. Assess for tx. (pills) or oral.

iv) Tinea pedis (Foot).
- Tx: Effective terbinafine > azole (clotrimazole, miconazole) > tolnaftate; consider cost & dosage scheduling.
- Treat topically x 4wks. (Common: elderly, dry cracked skin; adolescent>between toes.)

v) Tinea cruris (Groin).
- Common in adolescent & young adult; if repeat short pant/long sleeves. Overdiagnosed?
- Tx: Topical azole (clotrimazole, miconazole, terbinafine) daily x 2wk or terbinafine cream daily x 4wk. Assess for tx. (pills) or oral.

vi) Tinea versicolor.
- Commensal overgrowth of Malassezia yeast. Use-Topical antifungals 1% mild dx.
- Apply to whole affected area (max. extent) every day x1wk, then weekly for prophylaxis. If severe/recurrent consider short-term 1-2wks PO keto, flu, itraconazole TSE). Oral terbinafine ineffective.
- Suggest selenium sulfide 2.5% or ketoconazole 2% shampoo weekly x 2-3month x 4-6wks (xlongen).

Candida intertrigo.
- Common in moist skin folds (especially in obese, ostomy, etc.); results in tender, burning, pruritic areas with satellite lesions; Tx: consider nystatin powder, topical antifungals.

Vaginal fungal infections

Key Signs: Pseudomembranous form: white plaques on oral mucosa; atrophic form: erythema without plaques (common in elderly with dentures denture stomatitis). Angular cheilitis may be present. Causes: commonly Candida albicans. Risk factors: smoking, poor dental hygiene, inhaled or systemic steroid use, antibiotics, diabetes, immunodeficiency, ↓ saliva.

Tx: Mild dx: Topical nystatin or oral fluconazole effective x 7days minimum (or 2days after improved).
- Dentures: disinfect antifungals mouthwash 20-25m; with tx and topical antifungal to mucosa & denture base 25.
- Refractory, recurrent or esophageal infections need systemic azoles fluconazole, topical tx ineffective. May indicate immune system impairment; consider referral to ID (??)

Prevention: If on inhaled steroid, use aerosochamber, rinse mouth & spit after each use.

Dentures: daily cleaning recommended (chlorhexidine useful, rinse well)); ↑ nystatin but not at same time 26.

Infant: Nystatin safe, itraconazole effective. ↓ poor oral adherence & QID.
- Fluconazole more effective, once daily dosing but ↑ cost; not effective in newborns.
- Gentian violet 5-7.5% effective, but longer tx period, messiness, & associated with ulceration.27,28
- Breastfeeding infant: consider topical tx of nipple (eg. clotrimazole, miconazole, nystatin).

Causes: candidiasis, non-albicans; associated with antibiotic use; treat with topical fluconazole. 49-51.

Comments:
- Cost Considerations: topical fluconazole more expensive but more rapid effect; azoles generally used first; consider amount of product required, dosage schedule & length of tx.
- Cost/30mg tube:
  - clotrimazole: $12-15;
  - miconazole: $12-15;
- Consider oral tx if widespread, recurrent or failure with topical tx.
- Creams or spray spin preferred over powders, except in skin folds.

Azoal antifungals:
### Generic/TRADE

**Terbinafine HCL**

**Lamisil**

250mg tab

### Side effects / Contraindications

**Cautions**

- **Common**: PO: headache, GI dizziness, epigastric pain; taste disturbance may persist after discontinuation; Rash; milti, eczema, rash; Throat & mouth ulcers; transient photophobia,

- **Serious**: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, erythema multiforme, pancytopenia, neutropenia; 

- **Precaution**: liver/kidney disease, lupus erythematosus

### Drug Interactions

**Serious**

- **CYP3A4** inhibitor: level of terbinafine ↑; ↑dose of amiodarone, carbamazepine, cyclosporin, midazolam, quinidine, rifabutin, statins, tacrolimus, triazolam. 

**Strong CYP 2C9,2C19** inhibitor: level of ergot alkaloid, glimepiride, nevirapine, phenytoin, zidovudine. 

**Monitor QT & torsades des pointes; ↑risk of digitalis toxicity (e.g. Tinea capitis x4wk) (<20kg: 8mg/day, 20-40kg: 16mg/day, >40mg: 24mg/day).**

### Onychomycosis

- **Fingernail**: 250mg po daily 

- **Thrush in Newborns**: Diflucan 150mg cap /

### Tinea capitis

- **Infants**
  - Full-term (37-44 wk GA) & 0-14 days: 3mg/kg q48h & 14 days: 3mg/kg q24h

- **≥4 yrs**:
  - ±100mg po daily 7 days (Peds: Load 6mg/kg → 3mg/kg/day x 14day)

### Cautions

- New formulation of Diflucan

### Drug of Choice highlighted in brown.

**Fluconazole g (50, 150mg tab) √; 150mg cap; regular benefit SK formulary**

**Cranial**: oral suspension (OTC)

10mg/ml powder for oral suspension (P.O.S.)

**Diflucan**

IV soln 400mg/200ml vial

### Cautions

- High dose: 40mg/ml in pregnancy & 1st trimester

- For rufinamide, phenytoin, valproic acid, isoniazid & po sulfoxides may be ↑ at hepatic risk.

### Thrush in Newborns:

- NOT officially indicated but is an off-label, more effective alternative to nystatin.

### Common

- Full-term (37-44wk GA) & >14 days: 3mg/kg q48h - Full-term (37-44wk GA) & >14 days: 3mg/kg q24h

### Dose varies on site &/or severity of infection

**Itraconazole ▼ ▼ Sporanox**

100mg cap

**[Give cap with food to help with absorption]**

In past, was often given with cola.

10mg/ml solution

- Soln more bioavailable than cap

**Exception Drug Status SK**

**Hepatic Risk**

10/6wks

225/12wk

41.75-

2.4wks

413mos

282/6mos

178-249

178/wk

52

When choosing drug in keep in mind: frequency of dosing, dosing with regards to food, & organism coverage.

### Comments

- When to not use fluconazole: 
  - Fungal perianal, vulvar, groin, or intertriginous infections caused by non-candidal organisms
  - C. albicans ball, chronic vulvovaginal candidiasis

### Nystatin ▼ ▼

500,000 unit tab

100,000 units/ml susp

### Common

- Well-tolerated; nausea, vomiting, diarrhea at high doses

### Caution:

- Contains sucrose; may ↑ risk for dental caries

### Nystatin ▼ ▼

500,000 unit tab

100,000 units/ml susp

### Common

- Dose-related nausea, diarrhea, abdominal discomfort, rash, edema, hypokalemia, transaminases, & dizziness

### Serious

- SJS, hepatotoxicity; SJS/FDF - HD dose related neutropenic effect at 400mg/ml

### Caution:

- Hepatic dysfunction; pts at risk for arrhythmias

**[See note at bottom for “Hepatic Risk” comment.]**

### Common

- Well-tolerated; nausea, vomiting, diarrhea at high doses

### Caution:

- Contains sucrose; may ↑ risk for dental caries

### Flucytosine ▼

500mg cap

500mg/100ml vial

500mg/200ml vial

**[Cranial]: oral suspension (OTC)**

10mg/ml powder for oral suspension (P.O.S.)

**Diflucan**

IV soln 400mg/200ml vial

May 10
### Antifungal Treatment Chart

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Common</th>
<th>Serious</th>
<th>DI:</th>
<th>SE:</th>
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<tbody>
<tr>
<td><strong>Ketoconazole</strong></td>
<td>poorly tolerated; anorexia, nausea, vomiting (high dose), pruritus, rash dizziness, ↓ testosterone level: gynecomastia, ↓ libido &amp; loss of potency in♂, menstrual irregularities in♀</td>
<td>steriodogenisis altered &amp; ↓ cortisol; hepatoxicity</td>
<td>astemizole, cisapride, triazolam</td>
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<tr>
<td><strong>Voriconazole</strong></td>
<td>rash, ↑ photosensitivity, confusion, hallucinations, ↑ transaminases, transient visual disturbances, including blurred vision, photophobia, altered perception of color/imagetowards early oropharyngitis</td>
<td>Δ: similar to itraconazole (see above)</td>
<td>↑ levels of: allantoin, amido-drone-darone, cisapride, cyclosporine, efavirenz, methadone, midazolam, rifabutin, rifampin, St John’s wort &amp; terfenadine</td>
<td>↓ testosterone level: gynecomastia, ↑↓ testosteron, △♂, ↑ liver transaminases, ↑ patient levels; hepatic dysfunction, pts at risk for arrhythmias</td>
</tr>
<tr>
<td><strong>Posaconazole</strong></td>
<td>fairly well-tolerated; diarrhea, nausea, vomiting, headache, ↓ hypokalemia</td>
<td>Δ: similar to fluconazole</td>
<td>△: liver enzymes; serum level monitoring for serious infections only</td>
<td></td>
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<tr>
<td><strong>Echinocandins</strong></td>
<td>well tolerated; C: fever, phlebitis, △ALT &amp; AST, histamine-like effects: rash, pruritus, facial swelling</td>
<td>M: nausea, vomiting, △ALT, AST &amp; ALP</td>
<td>A: diarrhea &amp; hypokalemia, △ALT</td>
<td></td>
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