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 http://bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Onychomycosis.pdf [1]

Review Articles:
- NEJM: Fungal nail disease 2009 http://content.nejm.org/cgi/reprint/360/20/2108.pdf [2]
- Cochrane:Topical fungal treatments of the skin & foot 2007 http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001434/pdf_fs.html [3]

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

Patient Resources:
- BMJ Clinical Evidence http://clinicalevidence.bmj.com/ceweb/conditions/skd/1715/fungal-toenail-infections-standard-ce_patient_leaflet.pdf

Highlights:
1) Not all abnormal nails are fungal, treat only if culture positive for dermatophyte
2) To minimize potential for false negative, culture nail clipping and deep scrapings
3) Treat with terbinafine for 12-16 weeks (drug of choice for toenail onychomycosis)
4) Mark nail at end of treatment to monitor treatment success

RxFiles Related:
Antifungal chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-antifungal.pdf

Topical Steroid Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-SteroidClassPotencyCOLOR.pdf

OTC Chart: Fungal Infections http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-OTCs.pdf

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see www.RxFiles.ca

General Overview – Onychomycosis[4,5,6,7,8]
- Onychomycosis is a fungal infection of the nails most commonly caused by dermatophytes. Less often *Candida* and molds may affect the nail.
- Onychomycosis is recognized by thickening of the distal end of the nail associated with some loosening of the nail plate from the nail bed. The nail plate shows *butter yellow* coloured, vertical bands starting at the distal end of the nail.
- Both toenails and finger nails may be affected, but dermatophyte infections of fingers seldom occur in the absence of toenail infections.
- Fungal infections of the foot are not life-threatening but can cause discomfort and become unsightly. For some, they predispose to recurrent cellulitis of the legs.

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 discoloration mainly under the distal end of a thickened toenail.

Risk factors for onychomycosis[9]
- Risk factors include: age (increased risk with older age), gender – males 2.4x at risk than females[10], 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[11].
- 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.

Oral treatment
- **Terbinafine *LAMISIL* 250mg PO once daily** is the drug of choice (cure rate >50-80%, however relapse is common). Terbinafine is more effective than itraconazole[12] and able to maintain cure for a longer duration (2 year follow-up).[13] Terbinafine also has less risk for potential drug interactions.
- Alternate treatments
  - Itraconazole *SPORANOX* pulse therapy is an alternative if terbinafine contraindicated.
  - Fluconazole *DIFLUCAN* is less effective but is useful in patients unable to take the above.

Duration & approach to treatment [14,15]
- Duration of treatment for terbinafine and itraconazole: ⇨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). Cure rates are similar with pulsed vs. continuous treatments. {Continuous daily dosing is more effective than pulse therapy for terbinafine.}[16]
  - Fluconazole 150mg po once weekly (x 6-12 months for toenail; x ≥3 months for fingernail).[17,18]
- 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.

Cautions including contraindications and side effects
- A meta-analysis[19] 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).

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 & triamcinolone; Lotriderm:clotrimazole + betamethasone).

Oral candidiasis
- The nystatin dose for oral candidiasis (adult) is usually **5ml** QID to ensure enough liquid to cover area in mouth

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 [20]

- 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-rhabdomyolysis; 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? [21]

- Penetration into the nail is limited and use is of minimal value. It is slightly more effective when compared to placebo[22]; no additive benefit when combined with oral terbinafine[23]
- 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.[24]

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Best Educational Booth
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Case Discussion (continued):

- Nail clipping and scraping was cultured and came back positive after 4 weeks. Due to patient's diabetes, potential risk for cellulitis and history of tinea pedis, it was decided to recommend pharmacological treatment.
- The option of treating, including the benefits, risks and costs were discussed. Since he had diabetes, he was deemed to derive substantial benefit.
- Terbinafine 250mg once daily x 12 weeks was initiated
- Mr T. returned 3 months later after completing a course of treatment and noticed an improvement in his toe appearance. However, it still did not look "normal". He was reassured that he did not require additional treatment at this time. The nail was marked at the margin proximal to the infection and patient counseled to return if the infection moved past the mark or failed to grow out in the coming 12-18 months. He was instructed to trim & file the nail as it grew.

Prevention topics to discuss with patient…

- *Treatment of tinea pedis*
- *Proper footwear e.g. wear sandals/slippers in communal areas such as swimming pools, locker rooms, gyms, mosque, etc.*
- *Avoid going barefoot where possible*
- *Proper nail hygiene – trim nails short & straight across*
- *Avoid using same nail clippers or files on both diseased and normal nails; have separate tools for infected nails or disinfect between use*
- *Disinfection of socks & shoes*
- *Clean bathroom surfaces with bleach*

Coming soon …

♦ **Summer 2010: RxFiles Drug Comparison Charts book – 8th Ed.**
- ➔ ~140 pages; 14 new charts (e.g. anti-infectives for common infections, CKD, osteoporosis, sexual dysfx, SMBG, substance abuse, transplantation drug tx considerations, vaccines (adult), etc
- ➔ Pre-release ordering now available. See our online store or form: http://www.rxfiles.ca/rxfiles/uploads/documents/1A-CHT-Book-ORDERFORM.pdf

♦ **Information Mastery Course – Saskatoon, May 7-8, 2010**
- ➔ a practical approach to evidence based medicine for clinicians
- ➔ guest faculty from Tufts School of Medicine/Health Care Institute
- ➔ limited registration space for this very special event
- ➔ co-hosted with Continuing Professional Learning, U of S. http://www.rxfiles.ca/rxfiles/uploads/documents/Information-Mastery-Course.pdf

Acknowledgements: Dr. Hull (SHR-Dermatology); Dr. Lichtenwald, (Dermatology), Dr. Yvonne Shevchuk (College of Pharmacy, U of S); Dr. Sanche (SHR-Infectious Disease), Dr. T. Laubscher CCFP (FM, U of S), M. Jin (Pharm D, Hamilton), A. Bhalla (Pharm D, Ontario)& the RxFiles Advisory Committee *Shannon Stone* BSP, *Loren Regier* BSP, BA , *Brent Jensen* BSP

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Pages 1 & 2 of the Antifungal Drug Comparison Chart are included with this newsletter. These pages include the antifungals most used in primary care. Go online to www.RxFiles.ca where the complete antifungal drug chart can be found which has a 3rd page covering several other antifungals (e.g. ketoconazole NIZORAL, voriconazole Vfend, posaconazole POSANOL, caspofungin CANCIDAS, micafungin MYCAMINE, anidulafungin ERAXIS, & amphotericin-B FUNGIZONE, ABELCET, AMBISONE).

Produced by RxFiles – a provincial academic detailing service funded by Saskatchewan Health.
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Antifungal Treatment Chart [1,2,3,4,5,6,7]

Shannon Stone BSP www.RxFiles.ca May 10

Onychomycosis [8,9]

Key signs: nail thickening, discoloration, & separation from nail bed.[10,11,12,13] **C&S to confirm** prior to tx. (Clip, scrape & deep nail sample to avoid false negatives.) **Cause**: toenail→commonly dermatophytes; fingernail→may be yeast[14] [yeast e.g. candida; dermatophyte=filamentous fungi (eg. tinea)]

Pearls: uncommon to have finger without toenail involvement; file & mark margin of fungus on nail at completion of tx to monitor success!

Risk factors: ↑ prevalence with ↑ age (15-20% in pts ≥ 40 yrs); swimming, barefoot, tinea pedis, diabetes, immunodeficiency, living with an infected family member [15,16]

Tx: ◆**Oral terbinafine** or itraconazole: x12-16wks toe; success:50-80%; relapse: ~25-30%[17]; topical terbinafine weekly to prevent relapse? {Effectiveness: terbinafine > itraconazole >> fluconazole if unable to tolerate other tx; consider cost, success rate, SE risk}[18]

- Itraconazole pulse tx less $$ & SE, but requires scheduling; however terbinafine pulse treatment lower cure rate than daily dose[19]
- Topical: Nail lacquer in mild, distal dx, minimal penetration; combo with po no added benefit

Prevention: tx tinea pedis; wear sandals/slippers in communal areas bathing places, locker rooms, gyms, mosque

◆ Home remedies eg. Vicks VapoRub, vinegar no proven tx benefit. Tea tree oil: little evidence for benefit[20]; allergy.

Common Fungal Skin Infections [36,37,38]

Causes: Candida, epidermophyton, trichophyton, microsporum **Risk factors:** animal exposure (ie. vets, vet techs), skin trauma (ie. wrestlers), diabetes, immunodeficiency, ↓ circulation, poor hygiene, warm/humid climate.

General tx info: Apply antifungal to **affected & surrounding area** (**1-2 inches beyond rash**).

- Continue x **1wk after** sx's gone & skin looks healed to ensure eradication (often ~10-14 days).
- Keep area clean & dry (use non-scented talc or powder baby powder, Goldbond, tolnaftate as prophylaxis).
- Nystatin not useful for dermatophyte infections; effective for candidal infections.
- Oral tx: nail, scalp Kerion: inflammed purulent mass, from livestock,? add prednisone, beard, severe/widespread 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 & hot dryer or line dry & expose to UV rays; disinfect shoes.

i) Seborrheic dermatitis:[30] Commensal overgrowth of yeast. Topical/shampoo azoles & ciclopirox olamine useful. Intermittent shampoo use once weekly or every other week after tx may ↑remission. {limited comparison data}

ii) Tinea capitis (Scalp): **Common in kids** cats, cows; oral terbinafine$_{DOC}$ x 4-8wks +/- selenium sulfide shampoo 2-3x per wk (x5mins) to ↓ spread. Other options: oral fluconazole, itraconazole, (griseofulvin).

iii) Tinea corporis (Body): Tx options: topical azoles (clotrimazole, miconazole) & terbinafine. Consider topical azoles first, terbinafine slightly more effective/rapid but ↑ cost. Tx: x2-4 wks.

iv) Tinea Cruris (Groin): Common in adolescent & young adult ♂; if wear tight jean/pantyhose. Overdiagnosed? **Tx**: Topical azole clotrimazole, miconazole x 2-4wk or terbinafine cream/ spray daily x 2-4wk. Assess for tinea pedis.

v) Tinea pedis (Foot): **Tx** Effective: terbinafine > azole (clotrimazole, miconazole) > tolnaftate; consider cost & dosing schedule[31]. **Treat topically x 4wks**. {Common: elderly⇨dry cracked skin; adolescent⇨between toes.}

vi) Tinea Pityriasis versicolor:[32,33] Commensal overgrowth of Malassezia yeast. Use topical antifungals 1st mild dx. Apply azole to whole affected area (ie. chest) every day x 1wk, then q. weekly for prophylaxis). If severe/recurrent consider **short-term** 1-5 days po (keto-, flu-, itra-conazole (↑ SE). Oral terbinafine ineffective[34]. Suggest selenium sulfide 2.5% or ketoconazole 2% shampoo ↓ recurrence weekly or 1-2x /month x 40+ yrs (ie. long-term)

Candidal Intertrigo[35]: 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

Oral Candidiasis [21,22]

Key Signs: Pseudomembranous form: white plaques on oral mucosa; atrophic form: erythema without plaque (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 2+days after improved.)

- ***Dentures***: disinfect chlorhexidine rinse ~20-30min & tx with topical antifungal to mucosa & denture base [23].
- ***Refractory, recurrent or esophageal*** infections need systemic azoles fluconazole; topical tx ineffective. May indicate compromised immune system; consider referral to ID (? HIV).

Prevention: If on inhaled steroid, use aerochamber, rinse mouth & spit after each use. Dentures: daily cleaning recommended (chlorhexidine useful, rinse well)[24]; +/- nystatin but not at same time [25,26]

Infant: ◆ Nystatin safe, ↓cost but ↓effective → poor oral adherence & QID. comparison data limited

- Fluconazole more effective, once daily dosing but ↑ cost; not officially approved in newborns.
- Gentian violet 0.5-1% aqueous soln BID effective, but longer tx period, messy, & associated with ulceration.[27,28]
- Breastfeeding infant: consider topical tx of nipple[29] (eg. clotrimazole, miconazole, nystatin) lack safety data

Vulvovaginal Candidiasis [39]

Key signs: pruritus, soreness, dyspareunia, external dysuria; possibly thick & curdy discharge

Causes: *Candida albicans*, occasionally non-albicans; associated with antibiotic use; rule out UTI/STI

Tx: Topical azoles (see table) or oral fluconazole. Oral route often preferred by pts; consider cost.[40] {Cochrane: no difference in effectiveness of fluconazole oral vs intra-vaginal OTC routes}

- 1-3days topical as effective as 6-7days with better compliance. Allow ~3 days for sx resolution.
- **Recurrent** cases (≥4/yr) may benefit by addressing risk factors uncontrolled diabetes, high dose estrogen OC (?HIV); try 1) longer initial course of topical (7-14days) then clotrimazole 200mg pv 2x weekly or 500mg Supp pv weekly; or 2) fluconazole 150mg q72h x 3 doses[41] then fluconazole 150mg po weekly. Treat male partner?: controversial, but may benefit if *Candida balanitis* present.; tx-topical azole BID x 1 week[42,43,44]
- **Complicated** vaginitis~10% : ≥7days topical tx or fluconazole 150mg q72hr for 3 doses-IDSA guidelines
- **Pregnancy**: requires longer tx interval (eg. 7 days azoles; 14 days nystatin; 1 day fluconazole po) topical azole (clotrimazole, miconazole) more effective & convenient than nystatin; tx topical 1st line systemic absorption low; ↓ risk of birth defects [45]; oral fluconazole 2nd line Avoid 1st trimester & ≥ 400mg daily as teratogenic.[46]
- Topical boric acid 600mg cap PV hs x2wks an option if *C. glabrata* (rare); compounded not commercially available
- Dietary yogurt (with live culture) or oral Lactobacilli caps: do NOT prevent post-antibiotic vulvovaginitis, but may help restore normal flora[47] {Vaginal yogurt controversial.}
- topical vaginal tx containing mineral or vegetable oil {e.g. miconazole vaginal ovules problem} may ↓ effectiveness of **condoms**, or other vaginal contraceptive devices (eg. **diaphragms**) during treatment & up to 3 days post-tx [48] {Okay: clotrimazole products & miconazole cream.}

Diaper Rash [49]

- Apply antifungal underneath barrier cream until rash is resolved. ⇨Topical nystatin, clotrimazole, miconazole, or ketoconazole if rash candidal or >3 days.
- Combo topical corticosteroid/antifungal products not routinely recommended as may result in dilution,↑ SE & mask Sx of infection. eg. Viaderm-KC, Kenacomb If necessary: use only **low**-potency, short-term corticosteroid!!! Best to apply creams separately allowing a few minutes between applications. {Alternately, add hydrocortisone powder 1% to azole cream. See also OTC dermatology section.}

Antifungals: Topicals & Vaginal: (therapeutic use ⇨⇨⇨⇨⇨)	Tinea pedis/cruris/corporis	Comments:
Ciclopirox olamine **LOPROX**$_{Pr}$ 1% top crm ⊗(45gm); 1% top lotion ⊗(60ml) **PENLAC**$_{Pr}$ 8% Nail lacquer ^{x} ⊗; **STIEPROX**$_{Pr}$ 1.5% Shampoo^{x} ⊗(100ml)	Apply bid x 2-4 weeks	◆ **Cost Considerations:** - terbinafine more expensive but more rapid effect ∴azoles generally used first; consider amount of product required, dosing schedule & length of tx - Cost/30gm tube: clotrimazole $12-15; miconazole $12-15; terbinafine $20-25
Clotrimazole **CANESTEN**$_{OTC}$ 1% top crm ▼(15,30 & 500gm); 200,500mg vag tab; 1, 2 & 10% vag crm Generic$_{OTC}$ 1% top crm ▼(20,30,50 & 500gm); 1, 2% vag cream [higher % for shorter term tx]	Apply bid x 2-4 weeks	
Ketoconazole Generic$_{(Pr)}$ 2% top crm ▼(30gm) **NIZORAL**$_{OTC}$ 2% Shampoo^{x} ▼(60,120ml)	Apply once daily x 2-4 wk (x 6wks tinea pedis)	
Miconazole **MONISTAT-DERM**$_{OTC}$ 2% top crm▼(15,30gm) **MONISTAT**, Generic$_{OTC}$ 100, 400,1200mg vag ovules; 2, 4% vag cream;	Apply bid x 2-4 weeks	
Nystatin **MYCOSTATIN**, Generic 100,000 U/G top crm & oint ▼ {bulk powder available for compounding topical powder} $_{OTC}$ (15,30 & 450gm); 25,000 & 100,000 U/G vag cream$_{Pr}$ ▼	Nystatin NOT effective for dermatophytes!	◆ Consider **oral tx** if widespread, recurrent or failure with topical tx
Terbinafine **LAMISIL**$_{Pr}$ 1% crm▼(15,30gm); 1% top spray soln ⊗(30ml)	Apply daily x 2-4wk (x 1-2wk mild tinea pedis)	◆ **Creams or spray soln preferred** over powders, except in skin folds.
Tolnaftate **TINACTIN**$^{x,▼}$ $_{OTC}$ 1% top crm; powder; soln; top spray Others(Undecylenic acid-Desenex / Fungicure, Tolnaftate-Dr. Scholl's OTC products): less data, less effective	Apply bid x 2-4wks	

Vaginal candidiasis All OTC	Cost
CANESTEN 1 Combi Pak 500mg pv / 1%crm▼ or Cream 10% ⊗ x 1 day, CANESTEN 3 Combi Pak 200mg pv / 1%crm▼ or Cream 2% ▼ x 3 days, CANESTEN 6 Cream 1% ▼ x 6 days.	$14-18
MONISTAT 1 Vag Ovule 1200mg ⊗ x1 day or Combi Pak 1200mg/2%crm ⊗ x1day, MONISTAT 3 Dual Pak 400mg pv / 2%crm ▼ or Vag Ovule 400mg ▼ or Vag Cream 4% x, ⊗ x3 day, MONISTAT 7 Dual Pak 100mg pv / 2%crm ▼ or Vag crm 2% ▼ x 7day.	$16-20
TERAZOL 3 Supp 80mg x, ▼ or Dual Pak 80mg pv / 0.8% crm▼ or Vag crm 0.8% x3day TERAZOL 7 0.4% crm ▼ x 7 day.	$20-30
CanesOral fluconazole 150mg po; & CombiPAK	$25-33

AZOLE antifungals: Topical: clotrimazole, ketoconazole, miconazole, terconazole. Oral: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole. IV: fluconazole, voriconazole.

Fungal infection: *ask yourself why* - ? risk factors, ? immune suppression, ? HIV.

Generic/TRADE (Strength & forms) g=generic	P 50	Side effects / Contraindications CI Cautions	√ = therapeutic use / Comments / Drug Interactions DI (not exhaustive)[51] / Monitor M	INITIAL; MAX /USUAL DOSE {Drug of Choice highlighted in brown.}	$ /course
Terbinafine HCL ▼g **Lamisil** 250mg tab ς	B	**Common**: PO: headache, GI diarrhea, dyspepsia, abdominal pain, taste disturbance may persist after tx stopped, rash mild **Serious**: (≥0.01% to 0.1%) ↑AST & ALT or hepatotoxicity, (≤0.01%) SJS, toxic epidermal necrosis, erythema multiforme, pancytopenia, neutropenia **Precaution: liver**/kidney disease, lupus erythematosus	√ Onychomycosis & skin infections due to dermatophytes Tx severe tinea corporis, cruris, pedis unresponsive to topicals DI: **CYP2D6** inhibitor: ↑effect of: TCA ↑TCA level, Possible: Beta blockers & Antipsychotics ↓level of terbinafine: rifampin. M: LFT's at baseline & at 4-6 wks of tx [52]	**Onychomycosis**: 250mg po daily (**Fingernail**: x 6wks; **Toenail**: x12-16 wks) **Tinea capitis**: 250mg po once daily x 4-**8**wk Pediatric dosing ≥ 4 yrs: (e.g. Tinea capitis x4wk) <20kg: 62.5mg/day po, 20-40kg: 125mg/day po, >40kg: 250mg/day po [53]	108/6wks 225/12wk 41-75/ 2-4wks
Fluconazole g **Diflucan** (50, 100mg tab) ▼ ☎ ; 150mg cap▼, regular benefit SK formulary [CanesOral: new OTC formulation of fluconazole 150mg tab +/- clotrimazole 1% vag cream] 10mg/ml powder for oral suspension (P.O.S.) **Diflucan** IV soln 200mg/100ml vial, 400mg/200ml vial	C	**Common**: well tolerated; headaches, GI upset, rash **Serious**: Stevens-Johnson syndrome(SJS), hepatotoxicity, QT prolongation CI: cisapride: ↑↑ drug level cause ↑QT & torsades des pointes; ergot alkaloids : ↑↑ ergot levels **Cautions**: -High dose≥ 400mg/d in pregnancy & 1st trimester. -Pts on rifampin, phenytoin, valproic acid, isoniazid & po sulfonylureas may be at ↑ hepatic risk. Thrush in Newborns: NOT officially indicated but is an off-label, more effective alternative to nystatin. - Full-term (37-44 wk GA) & 0-14 days: 3mg/kg q48h - Full-term (37-44wk GA) & >14 days: 3mg/kg q24h[54] Dose varies on site &/or severity of infection	√ Active against most *Candida* species except *C.krusei* & some *C. glabrata*, *Coccidioides*, *Histoplasma*, *Cryptococcus* sp. in high doses Consider for oropharyngeal, esophageal or vaginal candidiasis DI: ↓ fluconazole level: rifampin. [Less DI's than azoles in general.] Moderate CYP3A4 inhibitor: ↑level of alfentanil, carbamazepine, cyclosporine, midazolam, quinidine, rifabutin, statins, tacrolimus,& triazolam. Strong CYP 2C9,2C19 inhibitor: ↑level of ergot alkaloid, glimepiride, nevirapine, phenytoin, warfarin, zidovudine. Prolong QT interval: amiodarone, cisapride, clarithromycin, TCA's Renal dx: **no** adjustment needed for single-dose vaginal candidiasis M: liver enzymes, renal function; baseline & periodically if risk factors/long-term tx Comments: • Bioavailability of PO similar to IV; use PO if possible • ↓ DI due to ↑ renal excretion~80% & ↓ hepatic metabolism effect • Compatible with breastfeeding • May require dose ↑ if obese with severe/systemic infection	Dose range:100-800mg /day. Pediatric: 3mg/kg/day-12mg/kg/day. {≤ adult dose.} **Onychomycosis**: 150mg po once weekly (**Fingernail**: x 3mos; **Toenail**: x 6-12mos) [55] (3rd line adults; useful if ++DI's, peds pts) **Oropharyngea1** candidiasis: Load: 200mg po x1 →100mg po daily x 7 day (Peds: Load 6mg/kg→ 3mg/kg/day x 14day) **Esophageal** candidiasis: 200-400mg od x 2-3wk **Tinea versicolor**: 400mg po x 1 dose **Vulvovaginitis** candidal:150mg po once OTC **Candidemia** neutropenic & non-neutropenic: Load day 1:800mg→400mg daily until 14day post-signs/sx & after last +ve blood culture ; obese patients: consider 6-12mg/kg IDSA (56)	141/3mos 282/6mos 64 /wk 178-349 /2 wks 32 17 178/wk
Itraconazole ▼ ☎ **Sporanox** 100mg cap [Give cap with food acidic PH ↑ absorption; In past, was often given with cola.] 10mg/ml solution -soln more bioavailable than cap[57]; solution prefered for oral/esophageal candidiasis. [Take on empty stomach] **Dosage forms NOT interchangeable**	C	**Common**: dose-related nausea, diarrhea, abdominal discomfort, rash, edema, hypokalemia , ↑ transaminases, & dizziness **Serious**: SJS, hepatotoxicity failure, HF dose related negative inotropic effect at 400mg/d CI: pts with ventricular dysfunction or HF; pts on negative inotropics or erythromycin; pts using drugs metabolized by CYP 3A4 (ie. cisapride, dofetilide, eletriptan, ergot alkaloids, lovastatin, midazolam, nisoldipine, pimozide, quinidine, simvastatin, triazolam); : pregnant women **Caution:** hepatic dysfunction, pts at risk for arrhythmias [See note at bottom for "Hepatic Risk" comment.]	√ Broader spectrum of activity than fluconazole: including *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp., *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, & dermatophytes. Consider for fluconazole resistant mucosal candidiasis DI: Strong **CYP3A4** inhibitor: ↑ level of: amio-/drone-darone, astemizole, atorvastatin some, buspirone, CCB nifedipine, nisoldipine, felodipine, cisapride, cyclosporine, digoxin, dofetilide, eletriptan, ergot alkaloids, fentanyl, indinavir, lovastatin, midazolam, pimozide, quinidine, ritonavir, saquinavir, simvastatin, sirolimus, steroids ↑ level: budesonide, dexamethasone, fluticasone, methylprednisolone , tacrolimus, triazolam & vincristine. ↑ itraconazole level: indinavir, ritonavir ↓ itraconazole level: antacids, H2 receptor blockers, PPI due to ↓ acidity; carbamazepine, efavirenz, grapefruit juice, nevirapine, phenytoin, rifampin, rifabutin ↓ levels of oral contraceptives. ↑ level of: warfarin M: liver enzymes (every month if on long-term tx ie >1month) Comments: • most DI's, ↑ toxicity compared to other azoles	Dose range:100-400mg/day **Onychomycosis** (if terbinafine contraindicated) Toenail: 200mg po daily x12wks or "pulse" tx: 200mg po BID x 1wk (3wks off & rpt 1wk x 2 cycles) Fingernail: 200mg po daily x 6wks or "pulse" tx: 200mg BID x 1 wk (3wks off & rpt x 1wk) **Oropharyngeal** candidiasis: if fluconazole resistant 200mg po once daily of soln x 14 days **Esophageal** candidiasis: if fluconazole-resistant 200mg po daily of soln x 14-21 days **Tinea versicolor**: 200mg po daily x 5-7 days (pityriasis versicolor) or 400mg x 1 dose [58,59] ***Caps less expensive** (~half the cost) but less bioavailable; solution used for pricing of oral/esophageal candidiasis only.*	822 /12wks 408/6wks (daily dose) 423/3mos 282/2mos (pulse tx) 283/ 14days 55/5days- 74/7days 26/single dose
Nystatin ▼g 500,000 unit tab 100,000 units/ml susp	A C	**Common**: well-tolerated; nausea, vomiting, diarrhea at high doses **Caution**: contains sucrose; may ↑ risk for dental caries	√ Fungi-static & cidal; may be used for candidal skin infections, Oropharyngeal & vulvovaginal candidiasis; for topical skin & vaginal candidal infections during **pregnancy** • slightly less effective for most conditions but safe, inexpensive	Children & adults: {liquid; swish & swallow!} **Thrush** (mild): 500,000units (5ml) qid **x 7days or 2days after** improvement. Pediatric: [may use 0.5ml & swab for infants] Infants⇨thrush: 100,000-200,000 units qid	15 / 7days

=↓ dose for renal dysfunction ς=scored tab ✗=Non-formulary SK ☎=Exception Drug Status SK ⊗=not covered by NIHB ▼=covered by NIHB ✆=prior NIHB approval CCB=calcium channel blocker CI=contraindication crm=cream DI=drug interaction DOC=drug of choice Dx=disease fx=function g=generic avail. GA=gestational age GI=gastrointestinal HF=heart failure LFT=liver function tests n/v=nausea/vomiting OC=oral contraceptive OTC=over the counter pc=after meals po=oral PPI=proton pump inhibitor Pr=prescription Pt=patient pv=per vagina SAP=special access program SE=side effect SJS=Stevens-Johnson syndrome STI=sexually transmitted infection Sx=symptoms TCA=tricyclic antidepressant Tx=treatment UTI=urinary tract infection vag=vaginal wt=weight

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

Comments: When not to use fluconazole: positive fungal urine cultures without symptoms of upper genitourinary disease, systemic candidiasis, or an impending genitourinary tract procedure; positive sputum cultures.

Special Considerations: **Hepatic Risk**: Overall incidence <2% for all; for oral tx of onychomycosis treatment: ketoconazole>itraconazole>terbinafine. Pulse treatment may reduce risk, but less effective for terbinafine.

Useful links: www.dermnet.com www.RxFiles.ca

See page 53 (book or online) for: voriconazole VFEND, posaconazole SPRIAFIL, POSANOL, ketoconazole , echinocandins CANCIDAS, MYCAMINE, ERAXIS, amphotericin B. FUNGIZONE, ABELCET, AMBISOME

Other drugs: flucytosine SAP – add-on po tx of Candida endocarditis/meningitis with Amphotericin B. •griseofulvin FULVICIN: not available in Canada but bulk supply available for compounding; is available in some areas of the world; especially useful in T. capitis; newer options available for tinea infection. •butoconazole – 2% vag crm available, more expensive, no advantages over other indicated treatment for vaginal candidiasis; contains mineral oil: caution with condoms, diaphragms.

Investigational Drugs: Ravuconazole, Isavuconazole invasive aspergillosis & candidiasis, Pramiconazole & Albaconazole onychomycosis.

Acknowledgements: Contributors & Reviewers: Dr. P. Hull (MD, Dermatology, Saskatoon) Dr. D. Lichtenwald (MD, Dermatology, Saskatoon); Y. Shevchuk (PharmD, C of Pharmacy, U of S, Saskatoon); S. Sanche (MD, Infectious Diseases - Internal Med, Saskatoon), S. Skinner (MD, Infectious Diseases - Internal Med, Saskatoon), B.Tan (MD, SHR-Ped ID), M Jin (Pharm D, Hamilton), A Bhalla (Pharm D, Ontario) & the RxFiles Advisory Committee. Prepared by: *Shannon Stone* BSP; *Brent Jensen* BSP, *Loren Regier* BSP, BA

Ketoconazole ▼ ☎ **Nizoral** 200mg tab (see topicals section above for topical, shampoo)	C	**Common**: poorly tolerated; anorexia, nausea, vomiting high doses, pruritus, rash dizziness, ↓testosterone level: gynecomastia, ↓libido & loss of potency in ♂, menstrual irregularities in ♀ **Serious**: ↓steroidogenesis adrenal & ↓cortisol; hepatotoxic **CI**: astemizole, cisapride, triazolam	√ Rarely used orally **DI**: similar to itraconazole (see above) Strong **CYP3A4** inhibitor: ↑ level of amio-/drone-darone, cyclosporine, digoxin potential, ergot alkaloid, lovastatin, pimozide, quinidine, rifabutin, simvastatin, tacrolimus, (similar to itraconazole) **M**: liver transaminases Comment: ◆With food & at bedtime to ↓SE ◆ breastfeeding compatible	200; 400mg 200-400mg once daily at bedtime Pediatrics ≥ 2 yrs: 3.3-6.6mg/kg/day po once daily **Tinea versicolor** (pityriasis versicolor) 60,61: 400mg x 1 dose or 200mg daily x 5-7 days	10 /400mg dose 15-17/ 5days
Voriconazole ✆ ☎ **Vfend** 50, 200mg tab; (Good oral absorption)62 (Take on empty stomach) IV 200mg/vial Relatively new drug; often requiring Infectious Disease Service consult!	D	**Common**: rash~7%, photosensitivity, confusion, hallucinations, ↑ transaminases, transient visual disturbances~20-23% including blurred vision, photophobia, & altered perception of color/image may resolve early **Serious**: SJS rare, hepatotoxicity **CI**: astemizole, barbiturates, carbamazepine, cisapride, efavirenz, ergot alkaloids, pimozide, quinidine, rifabutin, rifampin, high dose ritonavir >400mg BID, sirolimus, St. John's wort & terfenadine. : pregnant women **Caution:** hepatic dysfunction, pts at risk for arrythmias	√ Similar spectrum to itraconazole; More active: *Aspergillus* spp & *Candida glabrata & krusei*, *Fusarium* **DI**: ↓ levels of voriconazole: barbiturates, carbamazepine, efavirenz, phenobarbital, phenytoin, rifampin, rifabutin, ritonavir, & St John's wort. Moderate CYP3A4 inhibitor ↑ levels of: alfentanil, amio-/drone-darone , cisapride, cyclosporine, efavirenz, methadone, midazolam po (& higher iv dose), omeprazole, sirolimus, tacrolimus, triazolam & vincistine Strong CYP 2C9, weak 2C19 inhibitor ↑ levels of: methadone, warfarin Liver dx: Initial loading dose, but half maintenance dose if liver cirrhotic Renal dx: if CrCl<50ml/min-use only po formulation solubilizing agent can accumulate **M**: liver enzymes; serum level monitoring for serious infections only Comments: ◆ DOC-invasive aspergillosis 63 ◆ serum levels may vary 64 ◆ poor CYP2C19 metabolizers (ie Asian ~20-30%) 65 -↑drug level	Dose range: 200-600mg/day **Aspergillosis**: 6mg/kg q12h x 1day → then 4mg/kg or: if >40kg ⇨ 200-300mg po q12h If <40kg ⇨ 100-150mg po q12h Adjust dose based on levels if not responding. {Above dosing higher then previously recommended (200mg po q12h >40kg)} **Oropharyngeal**: if fluconazole resisitant 200mg po bid x 14-21day **Esophageal** candidiasis: if fluconazole-resistant 200mg po bid x 14-21day	 148 /200mg vial 1,509-2,259 /14-21 days
Posaconazole 66 χ ⊗ **Posanol** Spirafil 40mg/ml suspension (cherry flavored) (Take with **high-fat** meal or meal replacement to ↑ absorption) Relatively new drug; often requiring Infectious Disease Service consult!	C	**Common**: fairly well-tolerated; diarrhea, nausea~6%, vomiting, headache~6%, hypokalemia ↑transaminases similar to fluconazole **Serious**: hepatic necrosis, QT prolongation & arrhythmias **CI**: ↑level of astemizole, cisapride, ergot alkaloid, pimozide, quinidine, sirolimus, terfenadine : pregnant women **Caution:** hepatic dysfunction, pts at risk for arrythmias	√ Similar spectrum to itraconazole with activity against Zygomycetes (alternative to amphotericin B), *Cryptococcus*, *Aspergillus*; refractory oropharyngeal/esophageal candidiasis; prophylaxis of Aspergillus & Candida infection in neutropenics & stem cell transplant recipients; option for prophylaxis & tx of invasive fungal dx (broad spectrum; potentially less resistance) **DI**: Moderate-strong CYP3A4 inhibitor 67: ↑level of amio-/drone-darone theoretical, atazanavir, cyclosporine, digoxin potential, midazolam68, rifabutin, sirolimus, tacrolimus, terfenadine, triazolam & vincristine ↓ levels of posaconazole: cimetidine, efavirenz, phenytoin, rifabutin. **M**: liver enzymes; electrolytes (K^+, Mg^{++}, Ca^{++}) Comments: ◆ Less DI's; metabolized by glucuronidation	**Consult with Infectious Disease Specialist/Service for Posaconazole use!** Dose range:100-800mg/day {Pts > 13yrs} **Oropharyngeal** candidiasis: Load: Day 1: 100mg bid→100mg od x 13day Fluconazole-refractory oropharyngeal dx: 400mg po BID x3d → 400mg daily x 4wk IDSA 69 **Esophageal,** fluconazole refractory: 400mg po BID x 14-21 day; **Prophylaxis** of invasive infection:200mg tid - duration based on neutropenia/ immunosuppression recovery **Tx invasive** aspergillosis: 200mg po qid then 400mg bid if stable {If no food 200mg qid}	410 /14 d 3,659 /4wks 3,015-4,519/ 400mg BIDx14-21days
Echinocandins - **IV**: **Caspofungin acetate** C **Cancidas** 50, 70mg vial **Micafungin sodium** M **Mycamine** 50mg vial **Anidulafungin** A **Eraxis** 100mg vial Broad spectrum; often requiring Infectious Disease Service consult!	C	**Common**: well tolerated; **C:** fever, phlebitis infusion site, ↑ALT & AST, histamine-like effects: rash , pruritus, facial swelling **M**: nausea, vomiting, ↑ALT, AST & ALP **A**: diarrhea & hypokalemia, ↑ALT **Serious:** **C:** hepatotoxicity **M**: anaphylaxis rare, febrile neutropenia, hepatic abnormalities, renal insufficiency, hemolytic anemia **A**: anaphylaxis, hepatic abnormalities, DVT, low BP & flushing (minimize with infusion rate<1.1mg/min)	√ Active: most *Candida* spp(incl. azole-resistant), *Aspergillus* spp; **C**: invasive & esophageal candidiasis; invasive Aspergillosis refractory/intolerant **M**: esophageal candidiasis & prevent stem cell transplant invasive candidiasis; **A**: esophageal candidiasis & candidemia **DI**: ↓ levels of caspofungin: enzyme inducers ie. carbamazepine & rifampin; dexamethasone, efavirenz, nevirapine, phenytoin → consider ↑dose 70mg OD ↑caspofungin levels: cyclosporine ↑ hepatic enzymes **M**: ↑ level of: itraconazole, nifedipine, sirolimus Do not adjust in renal failure; **C** requires adjustment in liver failure. **M**: **A**: LFT's; **C**: K^+, LFT's; **M**: Lytes (K^+, Mg^{++}), Scr, BUN, LFT's, CBC Comment: Preferred for *C. Glabrata* candidemia IDSA guidelines	**C**: Candidemia neutropenic & non-neutropenic: Load: 70mg iv x 1 →50mg iv once daily Esophageal candidiasis: 50mg iv once daily Liver impairment (Child-Pugh score 7-9): 70mg load → 35mg iv once daily **M**: Candidemia neutropenic & non-neutropenic: 100mg iv daily; Esophageal candidiasis: 150mg iv daily; Prophylaxis stem cell transplant : 50mg iv daily **A**: Candidemia neutropenic & non-neutropenic: Load:200mg iv x1→100mg iv od x 14day minimum; Esophageal candidiasis: Load 100mg iv x 1→50mg iv od x 14day minimum	446 /70mg vial 271 /50mg vial 98 /50mg vial 214 /100mg vial
Amphotericin B - IV **Amphotericin** B deocycholate (AmBd): **Fungizone** 50mg vial **Lipid formulations**: i)Amphotericin B lipid complex (ABLC): **Abelcet** 100mg vial ii)Liposomal Amphotericin B (L-Am B):**Ambisome** 50mg vial iii)Amphotericin B colloidal dispersion (ABCD) in US Infectious Disease consult!	B	**Common**: infusion reactions: fever, chills, shakes, headache, nausea, vomiting, hypotension & tachypnea (worse with early infusions; may pretreat with acetaminophen/NSAID, diphenhydramine & meperidine) 70,71, malaise, weight loss, mild leukopenia, thrombocytopenia **Serious**: nephrotoxicity (may reduce with Na+ loading /lipid formulations), cardiac toxicity, K^+ & Mg^{++} wasting (may tx with po spironolactone), myopathy ◆liver toxicity lipid formulations **Precautions**: nephrotoxic drugs; liposomal amphoB (L-Am-B) has 900mg sucrose/vial –caution diabetes	√Active against most fungi & protozoa including Zygomycetes; reserved for serious infections; low therapeutic index, ↑↑toxicity; traditional ampho B_{AmBd} preferred tx for severe fungal infections during **pregnancy.** **DI**: ↑ nephrotoxicity: aminoglycosides, cyclosporine, tacrolimus, & other nephrotoxins including chemotherapy ↑ toxicity: digitalis low K+ **M**: CBC, electrolytes K+, Mg++, liver transaminases if lipid, renal fx BUN, Scr Comments: good CNS penetration; lipid formulations: better tolerated, less nephrotoxicity & less infusion reaction problems, but expensive	Dose varies based upon formulation used & indication/organism treated; duration dependent on response; poorly dialyzed. {usual dose range: AmBd: 0.25-1mg/kg/day; Other formulations: 3-5mg/kg/day} ◆no longer need for traditional test dose or gradual titration Broad spectrum; often requiring Infectious Disease Service consult!	Fungizone 68 /50mg vial Abelcet 198 /100mg vial Ambisome 121 /50mg vial

Extras: Tinea alba: sometimes confused with tinea versicolor; non-fungal in origin and does not require treatment beyond usual care for eczema; **Tinea barbae** : fungal infections of the beard area; oral antifungal required.

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