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DRUG AND THERAPEUTICS NEWSLETTER

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Vancouver General Hospital, UBC Hospital, GF Strong

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In This Issue...

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

This and other Drug and Therapeutics Newsletters are on the Web at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. Micafungin 50 mg injection (Mycamine®)
- Echinocandin antifungal agent for treatment of candidemia and invasive candidiasis
- To replace caspofungin on Dec 15, 2008
- Indicated for patients in whom fluconazole is not an option and who are at high risk for developing renal insufficiency from amphotericin B
- See page 3 for review of invasive candidiasis and role of echinocandins

2. Formoterol 6 mcg, 12 mcg turbuhaler (Oxeze®)
- Long-acting beta-2 agonist inhaler for use in the control of asthma and COPD
- Faster onset (1-3 minutes) and less costly compared to salmeterol
- Formoterol 12 mcg is equivalent to salmeterol 50 mcg

3. Quetiapine Long-Acting tablets 50 mg, 200 mg, 300 mg, 400 mg (Seroquel XR®)
- Long-acting quetiapine that is administered once daily for the management of the symptoms of schizophrenia

Deletions

1. Ticarcillin-Clavulanate injection (Timentin®)
- To be deleted on Dec 8, 2008
- Alternative: Piperacillin-tazobactam
- See Therapeutic Interchange, page 2

2. Caspofungin injection (Cancidas®)
- To be replaced by micafungin on Dec 15, 08

3. Salmeterol 50 mcg Diskus (Serevent®)
- Alternative: Formoterol turbuhaler
- Effective Dec 8, 2008

4. Psyllium powder (Metamucil®)
- Psyllium powder is a bulk forming laxative for the treatment of constipation. Due to the potential of allergic reactions from inhalation of the powder, psyllium will be deleted from formulary on Dec 8, 2008
- Alternative: Fiber 469 mg tablet (Fibyrax®, Novo Fibre-Tab®)
- Each 2.5 mL psyllium powder will be automatically interchanged to 1 fiber 469 mg tablet to a maximum of 12 tablets per day.

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Updated Policies

1. THERAPEUTIC INTERCHANGE: TICARCILLIN-CLAVULANATE TO PIPERACILLIN-TAZOBACTM

Piperacillin-tazobactam and ticarcillin-clavulanate provide similar antibacterial coverage against Gram-positive, Gram-negative and anaerobic bacteria. Piperacillin-tazobactam has better *in vitro* activity against *Enterococcus* and selected Gram-negatives. It has also been studied in more severe infections than ticarcillin-clavulanate. Piperacillin-tazobactam is now available as a generic product and estimated cost savings of up to 40% is anticipated if used exclusively over ticarcillin-clavulanate. On Dec 8, 2008 ticarcillin-clavulanate will become a non-formulary drug and all orders for this drug will be automatically interchanged to piperacillin-tazobactam as listed on Table 1.

Table 1. Therapeutic Interchange of Ticarcillin-Clavulanate to Piperacillin-Tazobactam

Estimated GFR (mL/min)	Ordered as ticarcillin-clavulanate	Interchanged to piperacillin-tazobactam
greater than 50	3.1 g IV Q4H	4.5 g IV Q6H
	3.1 g IV Q6H	3.375 g IV Q6H
30 to 50	3.1 g IV Q6H	3.375 g IV Q6H
less than 30	3.1 g IV Q8H	2.25 g IV Q6H
Hemodialysis/ CAPD	3.1 g IV Q12H	2.2.5 g IV Q8H

2. PDTM UPDATES (on-line version

- Erythropoietin is currently restricted to Jehovah's Witness patients and surgery patients to reduce allogeneic blood exposure. **Hematology consult is only required for perioperative use** in non-Jehovah's Witness patients.
- **Nurses in ICU may administer propofol via direct IV or infusion** for the treatment of procedural sedation or refractory agitation in intubated, mechanically ventilated patients.

3. DEXTRAN 40 INTERPRETATION

Dextran 40 is now supplied by Pharmacy, and is available in two diluents: NS and D5W. Orders for dextran 40 with no solution specified will be filled as dextran 40 in NS.

4. ONE YEAR AUTOMATIC STOP DATE

All Acute Care Medication orders (inpatient, outpatient, pre-admission) are valid for ONE YEAR except when listed with a 3-day or 7-day automatic stop (primarily anti-infectives). Standing outpatient orders must be re-ordered annually.

Table 2. Automatic Stop Policy: 3 day or 7 day

Medication Category	Auto-Stop
Restricted Antimicrobial Drugs	3 days*
Narcotic and Controlled Drugs (except phenobarb)	7 days
Anti-infectives (topical & systemic; antiretrovirals, TB drugs and ketoconazole shampoo exempt)	7 days
Anticoagulants - oral	7 days
Inhalation solution by nebulizer	7 days
Total Parenteral Nutrition (TPN)	7 days
Ophthalmic preps except for glaucoma or lubrication	7 days

*7 day auto-stop for Stem Cell Transplant & Medical Day Care Unit

5. DILTIAZEM LONG-ACTING INTERCHANGE

If long-acting dilitiazem is ordered and the medication needs to be administered via naso-gastric tube, the following interchange will occur:

Table 3. Therapeutic Interchange: Diltiazem Long-Acting to Regular Release

Ordered as: dilitiazem CD or SR for nasogastric use	Interchanged to: equivalent dose of regular release tablets
120 mg NG DAILY	30 mg NG QID
180 mg NG DAILY	60 mg NG TID
240 mg NG DAILY	60 mg NG QID
300 mg NG DAILY	75 mg NG QID (use 2½ x 30 mg tablets)
360 mg NG DAILY	90 mg NG QID

ADDENDUM: Anti-Infective Comparison Card

The newly revised 2008 anti-infective comparison card was a collaborative effort between Pharmacy, the Division of Medical Microbiology and Infection Control, and the Division of Infectious Diseases. Please call Pharmacy to obtain a copy of this card.

New Drug/Drug Products

Treatment of Invasive Candidiasis

Mildred Tang, B.Sc.(Pharm.), Dawn Warkentin, Pharm.D.

Introduction

Invasive fungal infections are a major cause of morbidity and mortality in immunocompromised patients. Individuals at high risk for serious fungal infections include critical care and general surgery patients, and those who are immunocompromised, e.g. high dose steroid therapy, hematological malignancies such as leukemia and lymphoma, and solid organ (SOT) and hematopoeitic stem cell transplant (SCT) recipients.

In a recent Canadian epidemiology surveillance of candidemia, *Candida albicans* was the most common species comprising 62% of isolates, followed by *C. glabrata* (17%), *C. parapsilosis* (9%) and *C. tropicalis* (5%).[1] A similar incidence of *C. albicans* infections has also been observed at Vancouver Acute (VA). The rate of infection due to non-*albicans* species is increasing, which is a concern as they are generally less susceptible to traditional antifungal agents.

Treatment Options

Previously, the primary agents of choice for invasive candidiasis included fluconazole and amphotericin B deoxycholate.[2] Fluconazole is generally well tolerated with few adverse effects. Renal toxicity and infusion related reactions are a major concern with amphotericin B deoxycholate.

The echinocandins class of antifungals (caspofungin, micafungin, and anidulafungin) are used in the treatment of invasive candidal infections.[3] These agents have been associated with a more favourable adverse event profile compared to amphotericin B.[2] There have been 3 randomized controlled non-inferiority trials comparing echinocandins to traditional therapy for the treatment of invasive candidiasis (Table 1).[3-5] The trials found the echinocandins to be non-inferior to either amphotericin B products (with fewer adverse events) or fluconazole.

Micafungin will replace caspofungin on formulary at VA on Dec 15, 2008 due to its equivalent efficacy and cost-effectiveness (Table 2). Micafungin has been shown in a randomized double-blind trial to be non-inferior to caspofungin for the treatment of candidemia and other forms of invasive candidiasis.[6] There were no significant differences in outcomes between micafungin doses of 100 mg and 150 mg daily versus caspofungin 50 mg daily.

Table 1. Comparison of Echinocandins to Traditional Antifungal Agents for Treatment of Invasive Candidiasis

Comparison (N)	Primary Outcome	Results	Conclusion
Caspofungin (n=109) vs Amphotericin B (n=115)[3]	Resolution of signs & symptoms; negative cultures	73.4% vs 61.7% (p=0.09)	Caspofungin non-inferior to Amphotericin B
Micafungin (n=202) vs Liposomal Amphotericin B (n=190)[4]	Clinical and mycological response at end of therapy	89.6% vs 89.5% (Diff = 0.1%; 95%CI: 5.9-6.2)	Micafungin non-inferior to Amphotericin B
Anidulafungin (n=127) vs Fluconazole (n=118)[5]	Clinical and microbiologic success	75.6% vs 60.2% (p<0.02)	Anidulafungin non-inferior to Fluconazole

Clinical Recommendations

Newly updated Infectious Diseases Society of America (IDSA) guidelines on invasive candidiasis will be released in Spring 2009. Preliminary guidelines indicate that fluconazole and echinocandins are the preferred choices with a de-emphasis on the use of amphotericin B (both deoxycholate and lipid formulations).[7]

Fluconazole is still recommended as first-line therapy for uncomplicated patients who are non-neutropenic, are hemodynamically stable, have not had recent azole exposure, and are not colonized with *Candida glabrata* or *krusei*.

Echinocandins or amphotericin B are recommended for complicated patients who are neutropenic, have unknown *Candida* isolates, are hemodynamically unstable, or have had recent azole exposure.[7] Echinocandins are recommended over amphotericin B for amphotericin B resistant strains (e.g. *C. lusitaniae*), or in patients who are intolerant to amphotericin B or are at high risk of developing nephrotoxicity.

Echinocandins are fungicidal against most candidal species, however, it remains unclear if

this class is the best choice for *C. parapsilosis*.[7] Echinocandins are not recommended for CNS candidiasis due to poor penetration. There is limited data with micafungin for the treatment of endophthalmitis.[7]

Step down therapy to oral options such as fluconazole is also strongly encouraged for susceptible isolates. Voriconazole is a new generation azole antifungal that is more costly and offers no advantage over fluconazole as primary therapy of invasive candidiasis except in the transition to oral therapy in selected fluconazole resistant cases (e.g. *C krusei*).[8] Duration of therapy for candidemia is at least 2 weeks after the last positive blood culture and resolution of symptoms. Treatment duration for invasive candidiasis is unclear and varies from 3-6 months.

Micafungin is restricted to Infectious Diseases approval, except for ICU, SCT or SOT patients.

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Table 2. Comparison of Selected Antifungal Agents

Antifungal Drug	Micafungin	Caspofungin (non-formulary)	Fluconazole	Amphotericin B
Class	Echinocandin	Echinocandin	Azole	Polyene
Dose (invasive candidiasis)	100 mg IV daily	70 mg IV load, then 50 mg IV daily	400 mg IV/PO daily	Deoxycholate: 0.5-1 mg/kg IV daily* Liposomal formulation: 3-5 mg/kg IV daily*
Renal/Hepatic Impairment	No dose adjustments (not studied in severe liver dysfunction)	35 mg IV daily for moderate hepatic impairment (Child-Pugh Score 7-9)	Dose adjust for GFR < 30 mL/minute	Avoid Amphotericin B deoxycholate in renal impairment
Side Effects	≥ 2%: rash, ↑ LFTs (AST, ALT) ↑ alkaline phosphatase, nausea, constipation, hypokalemia	≥ 2%: rash, ↑ LFTs (AST, ALT) ↑ alkaline phosphatase, nausea, constipation, hypokalemia	Headache (13%), nausea (7%), abdominal pain (6%), increased LFTs	Infusion-related reactions (fever, chills, headache, hypotension), nausea, vomiting, hypokalemia, hypomagnesemia, nephrotoxicity
Drug Interactions	Micafungin may increase sirolimus, cyclosporine and nifedipine levels	- Caspofungin ↓ tacrolimus levels - Cyclosporine may ↑ caspofungin levels - Enzyme inducers (e.g. rifampin, CBZ, phenytoin) may ↓ caspofungin levels	Fluconazole may ↑ toxicity of phenytoin, warfarin, NSAIDS, oral hypoglycemics by inhibiting CYP 2C9 enzymes	Use with caution with other nephrotoxic drugs or drugs that may be affected by hypokalemia (e.g. digoxin)
Activity vs *Candida* sp.	Fungicidal	Fungicidal	Fungistatic	Fungicidal

* high doses recommended for *C. glabrata and krusei*