

July 2005

Volume 12, Number 3

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

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Changes to Formulary

Additions

- Caspofungin 50mg, 70mg vials (Cancidas[®])**
 - Antifungal agent indicated at VGH for invasive candidiasis in patients who are refractory to or intolerant of other antifungal therapies. Also indicated for febrile neutropenia in leukemia/stem cell transplant (SCT) patients who are intolerant of amphotericin B.
 - Infectious Diseases consult required; ICU, SCT and Solid Organ Transplant (SOT) patients exempt from ID consult
 - See page 3 for review
- Voriconazole 200mg vial, 50mg and 200mg tablets (Vfend[®])**
 - Antifungal agent indicated at VGH for invasive aspergillosis in patients who are refractory to or intolerant of amphotericin B
 - Infectious Diseases consult required; ICU,

- SCT & SOT patients exempt from ID consult
- See page 3 for review

- Candesartan 8mg, 16mg tablets (Atacand[®])**
 - Angiotensin II receptor blocking agent similar in mechanism of action to losartan (Cozaar[®])
 - Cost: \$1.19 per 8mg and 16mg tablet; (comparison losartan: \$1.10 per 25mg and 50mg tablets)
 - See Candesartan Therapeutic Interchange page 2

Deletions

- Nitroglycerin 0.3mg, 0.6mg sublingual tablets**
 - Due to minimal usage of the sublingual tablets and continuous expiration of stock
 - Alternative: Nitroglycerin 0.4mg spray
 - Once supplies are used up, all orders for nitroglycerin sublingual tablets will be interchanged to nitroglycerin 0.4mg sublingual spray
- Nystatin vaginal tablets**
 - Discontinued by manufacturer
 - Alternative: Nystatin vaginal cream
- Penicillin G Potassium injection**
 - Discontinued by manufacturer
 - Alternative: Penicillin G Sodium injection

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4. Sodium Sulfacetamide 10%, 30% eye drops

- Discontinued by manufacturer
- Alternatives: sodium sulfacetamide 10% ophthalmic ointment, other antibiotic eye drops (e.g. Neosporin[®], Polysporin[®] eye drops)

Updated Policies

1. Candesartan Therapeutic Interchange

Until May 2005, losartan was the sole angiotensin II receptor blocker (ARB) on formulary at Vancouver Acute and all ARB orders were therapeutically interchanged to losartan. Candesartan has been recently added to formulary due to more favourable outcome data supporting its use in patients with heart failure including those with a history of myocardial infarction (MI). As a result, all orders for ARBs other than losartan will now be therapeutically interchanged to candesartan as per Table 1.

Drug	Dose Equivalence	Maximum Daily Dose
Candesartan (Atacand [®])	8mg	32mg
Eprosartan* (Teveten [®])		800mg
Irbesartan (Avapro [®])	150mg	300mg
Losartan (Cozaar [®])	50mg	100mg
Telmisartan (Micardis [®])	40mg	80mg
Valsartan (Diovan [®])	80mg	160mg**

*Physicians will be called for eprosartan orders as there are no head-to-head trials verifying an appropriate dose equivalence of this drug to either candesartan or losartan
 **Valsartan 160mg BID used in heart failure studies

2. Enoxaparin Prophylaxis For Major Orthopedic Trauma and Spinal Cord Injury

Enoxaparin has replaced dalteparin as the low molecular weight heparin (LMWH) for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in major orthopedic trauma and acute spinal cord injury patients. Enoxaparin is also the preferred LMWH for management of unstable angina and non-ST elevation MI. Dalteparin will be retained for prevention of thromboembolism following elective orthopedic surgery (e.g. total hip and knee arthroplasty),

general surgery and in medicine patients. Dalteparin is also the formulary LMWH for treatment of DVT and PE.

3. Fentanyl Patches Restriction Removed

Fentanyl patches are no longer restricted and can be ordered by any physician. Fentanyl patches should be prescribed for chronic pain management, not acute pain.

4. Intracarotid Administration of Propofol

Intracarotid propofol replaces sodium amytal (not available in Canada anymore) for ipsilateral hemisphere anesthesia to test for speech and memory (Wada test). Intracarotid use is restricted to neurology in conjunction with radiology.

5. Acetylcysteine Pre-printed Orders Revision

Acetylcysteine use with radiographic contrast dye has been revised to include a threshold glomerular filtration rate (GFR) for prescribing this drug (GFR < 60 mL/minute). As well, the hydration orders have been revised (italics) and include the following options:

- IV normal saline at rate of 2mL/kg/hr x 12 hrs prior to and 12 hrs after administration of contrast dye
- *IV normal saline at rate of 1mL/kg/hr x 12 hrs prior to and 12 hrs after administration of contrast dye*
- *If volume restricted:*
IV normal saline at rate of 0.5mL/kg/hr x 12 hrs prior to and 12 hrs after administration of contrast dye

Please order PPO # 37 if your unit requires replacement with these new orders.

6. Parenteral Drug Therapy Manual (PDTM)

We are in the process of creating an on-line regional PDTM for the entire Vancouver Coastal Health (Richmond, Vancouver Acute, Providence Healthcare and North Shore/Coast Garibaldi Hospitals). As a result, there will not be a 2005 PDTM hardcopy update this year for Vancouver Acute (VA). The VA on-line version is the most up-to-date and accurate. Hard copy updates are placed in manuals on various nursing units that are affected by specific changes. The on-line version can be accessed through the VCH intranet homepage (<http://www.vcha.ca>). Click on the PDTM link under Regional Web sites.

New Drugs/Drug Products

New Antifungal Agents: Caspofungin, Voriconazole

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Caspofungin

Caspofungin is an echinocandin antifungal agent that inhibits the synthesis of β (1,3)-D-glucan, an essential component of the cell wall of filamentous fungi and yeast.¹ *In vitro*, caspofungin exhibits fungicidal activity against *Candida* species, including those that are resistant to azoles and amphotericin B, and fungistatic activity against *Aspergillus* species (Table 2).²

Comparison to Formulary Antifungals

Amphotericin B is generally indicated for invasive candidiasis and aspergillosis infections, and for empiric fungal coverage in febrile neutropenia, but its use is associated with potential infusion-related and nephrotoxic adverse effects. Fluconazole is an effective agent for the treatment of invasive candidiasis. The main indication for itraconazole is as an oral step-down agent for aspergillosis.

Randomized, double-blind trials have demonstrated that caspofungin is at least as effective as amphotericin B for the treatment of invasive candidiasis and candidemia³, febrile neutropenia⁴, and esophageal candidiasis^{5,6}. Fewer drug-related events including nephrotoxicity and infusion-related reactions were observed with caspofungin than with amphotericin B.^{3,4} While caspofungin is effective for esophageal candidiasis, less costly alternatives should be prescribed (e.g. fluconazole).

There are no clinical trials to support the use of caspofungin as a first-line agent for the treatment of aspergillosis infections. There is one study of 83 patients with invasive aspergillosis refractory or intolerant to amphotericin B (regular and lipid formulations) and triazoles who were administered caspofungin.⁷ Overall, a favourable response was seen in 45% of patients. Limited clinical data suggests a potential additive or synergistic effect when caspofungin is used in combination with amphotericin B, fluconazole or voriconazole.⁸

Adverse Reactions and Drug Interactions

The most common adverse effects reported with caspofungin include fever, phlebitis, nausea, vomiting, and flushing.¹ Elevated liver function tests (ALT, AST, alkaline phosphatase) may occur.

Caspofungin is not an inhibitor or inducer of cytochrome P450 or P-glycoprotein transport. When administered with tacrolimus, caspofungin reduces tacrolimus levels by ~20%. Tacrolimus serum levels should be monitored closely as the dose may need to be increased.² The combination of cyclosporine and caspofungin increases caspofungin levels by ~35% due to an increased uptake of caspofungin in tissues. This may result in elevated liver function tests and, as such, caspofungin use in patients receiving cyclosporine should be limited to those in whom the benefit outweighs the potential risk.¹ Co-administration with inducers and/or mixed inducers/inhibitors, such as carbamazepine, dexamethasone, phenytoin, and rifampin reduces caspofungin concentrations; this may necessitate an increase in the daily caspofungin dose to 70 mg if patients are not responding to the usual 50mg daily dose.⁹

Table 2. Susceptibility of Antifungal Agents to *Candida* sp. and *Aspergillus* sp.

Organism	Amphotericin B	Fluconazole	Itraconazole	Caspofungin	Voriconazole
<i>Candida</i>					
<i>C. albicans</i>	+	+	+	+	+
<i>C. glabrata</i>	+	±**	-	+	+
<i>C. guilliermondi</i>	-	+	+	+	+
<i>C. krusei</i>	+	-	-	+	+
<i>C. lusitaniae</i>	-	+	+	+	+
<i>C. parapsilosis</i>	+	+	±**	±*	+
<i>C. tropicalis</i>	+	+	+	+	+
<i>Aspergillus</i>					
<i>A. flavus</i>	+	-	+	+	+
<i>A. fumigatus</i>	+	-	+	+	+
<i>A. niger</i>	+	-	+	+	+

*Less activity *in vitro*, but clinically effective; only rare failures reported. *In vitro* testing for caspofungin not standardized

**Susceptible with dose escalation

Table 3. Dose and Acquisition Costs of Formulary Antifungal Agents

Drug	Treatment Dose	Cost/day
Amphotericin B	0.5-1mg/kg/day	\$26-52*
Amphotericin B Liposomal	3-5mg/kg/day	\$440-735*
Fluconazole	200-400mg IV/PO daily	\$11-21 (PO) \$43-86 (IV)
Itraconazole	200mg PO bid	\$17 (capsule)
Caspofungin	70mg IV x 1, then 50mg IV daily	\$567 (70mg) \$440 (50mg)
Voriconazole	400mg PO q12h x 2, then 200mg PO q12h 6mg/kg IV q12h x 2, then 4mg/kg IV q12h	\$380, then \$95 \$1400*, then \$420*

*based on 70kg patient

Role of Caspofungin at Vancouver Acute

Caspofungin is an effective alternative against azole-resistant *Candida* species. Currently, fluconazole is commonly used for the treatment of candidiasis due to its efficacy and relatively safe adverse effect profile. In cases of azole resistance, amphotericin B is generally selected as the alternative, but its use may be limited by its nephrotoxic effects which renders the use of more costly lipid-based products. Caspofungin may be considered an alternative in this situation due to its similar cost to amphotericin B lipid formulations and demonstrated efficacy (Table 3). Caspofungin is restricted to Infectious Disease consult (ICU, SCT, SOT patients exempt) for:

- Invasive candidiasis in patients refractory to other antifungal therapies (fluconazole, amphotericin B) or intolerant to amphotericin B despite optimization of pre-medications
- Invasive candidiasis refractory to fluconazole in ICU patients with severe sepsis/septic shock and urine output < 0.5mL/kg/hr x 2 hrs despite volume replacement and/or vasopressors
- Febrile neutropenia in leukemia/SCT patients who are intolerant to amphotericin B despite optimization of pre-medications

Voriconazole

Voriconazole is a second-generation triazole antifungal agent synthetically derived from fluconazole. It has the broadest spectrum of activity when compared to fluconazole or itraconazole. *In vitro* data suggest fungicidal activity against *Aspergillus* species and fungistatic activity against all *Candida* species, including *C. krusei* and *C. glabrata*.

Comparison to Formulary Antifungals

Voriconazole was compared to amphotericin B in a randomized, open-label, non-inferiority trial of 277 immunocompromized patients with invasive aspergillosis. Although the study had limitations, voriconazole was deemed superior with 52.8% versus 31.6% of amphotericin patients achieving the primary outcome (complete or partial response in terms of both clinical and radiological parameters) (ARR 21.2%; 95% CI 10.4-32.9).¹⁰ For the treatment of febrile neutropenia, voriconazole failed to achieve non-inferiority compared with liposomal amphotericin B in 837 patients in an open-label, randomized trial.¹¹ Due to minimal published data, voriconazole has not been approved for use in invasive candidiasis.

Adverse Reactions and Drug Interactions

The most common adverse events include transient visual impairment, skin reactions, dose-related hepatotoxicity, and gastrointestinal distress (nausea, vomiting, abdominal pain). Other less common adverse events include tachycardia, flushing, fever, sweating, chest tightness, dyspnea, faintness, nausea, pruritis, rash, and rare reports of QTc prolongation.

Voriconazole is both metabolized by and an inhibitor of CYP450 enzymes 3A4, 2C9 and 2C19; therefore, drug interactions are numerous, and will pose a therapeutic challenge for the clinician. Of note, tacrolimus should be reduced to 1/3 of the original dose and cyclosporine doses should be decreased by 50% as voriconazole increases serum levels of both these drugs.

Role of Voriconazole at Vancouver Acute

Voriconazole has been added to formulary for the treatment of invasive aspergillus in:

- Patients who are refractory, intolerant or have infusion-related reactions to amphotericin B despite optimization of pre-medications
- ICU patients with severe sepsis/septic shock and urine output < 0.5mL/kg/hr x 2 hrs despite volume replacement and/or vasopressors
- Allogeneic SCT patients within 2 weeks of chemotherapy and at risk for renal dysfunction that may prevent administration of GVHD prophylaxis
- SOT patients on other nephrotoxic agents and at risk of renal dysfunction

As with caspofungin, an Infectious Disease consult is required (ICU, SCT, SOT exempt).

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