

In This Issue...

<i>Changes to Formulary</i>	1
<i>Automated Unit Dose System</i>	1
<i>Newly Designated Controlled Drugs</i>	2
<i>Potassium Chloride 20 mEq/50 mL</i>	2
<i>PDTM Update</i>	2
<i>No Changes to Orders after Faxing</i>	2
<i>New Anti-Infective Comparison Card</i>	2
<i>Multi-Drug Resistant Acinetobacter baumannii</i>	3
<i>Treatment of Invasive Aspergillosis</i>	3

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. Black Widow Spider Antivenin

- Antidote for Black widow spider bite (*Latrodectus mactans*).
- Part of the Special Access Drug program

Deletions

1. Dolasetron tablets and injection

- Alternative: Ondansetron tabs and injection

Updated Policies

1. VA AUTOMATED UNIT DOSE (AUD) MEDICATION SYSTEM

The AUD medication distribution system will be implemented at VGH, UBCH, and GF Strong (GFS) for all inpatient units and the ED between Sept 15 and Dec 15, 2008. The goal of this new distribution system is to improve medication safety by reducing medication dispensing and administration errors.

Medications supplied through the AUD system include all regularly scheduled oral tablets and capsules for in-patients. The medication is delivered to nursing units three times per day at VGH and once daily at UBC and GFS, no later than one hour before the doses are required. The medications are placed in individual strip packages attached to a label with the administration time and patient's identification. The order of medications in the AUD strip packages matches the MAR for ease of verification prior to administration.

Distribution of medications excluded from the AUD system will remain unchanged. **Excluded AUD medication are:**

- One time doses
- PRN doses
- Medications that may require daily dosage adjustments (e.g. warfarin)
- Medications for outpatients
- Liquids, topical medications, patches, and injectables
- Narcotics & Controlled medications
- Non-formulary medications
- Patient's own medications
- Study and Special Access Program medications

Procedural Changes as a result of AUD

- Pharmacists will call the prescriber to clarify the dose or frequency if regularly scheduled oral solid medication are written with a dosing or frequency range. For example:

EDITORIAL STAFF:

Karen Shalansky, Pharm.D., FCSHP

Tim Lau, Pharm.D., FCSHP

Jane Day, B.Sc.(Pharm)

Nilu Partovi, Pharm.D., FCSHP

Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email karen.shalansky@vch.ca Find us on the Web at www.vhpharmsci.com

"Docusate 100-200mg PO QAM" will be clarified to either "Docusate 100mg PO QAM" or "Docusate 200mg PO QAM". Narcotics and controlled drugs are exempt from this policy.

- All delayed release dosage forms now include "long acting" as part of their generic name. The manufacturer's designation (e.g. CD, SR, XL, etc.) is incorporated into the brand name. For example: "Diltiazem CD 240 mg cap" will now appear as "diltiazem long acting 240 mg CAP (CARDIZEM CD EQUIV).

For more information on the AUD system , go to:

http://www.vcha.ca/programs_services/regional_pharmacy/projects/hospital_unit_dose_dispensing/page_41161.htm

2. ORAL BENZODIAZPINES and CODEINE COMBINATIONS - CONTROLLED DRUGS

As of Sept 9, 2008, **all oral** benzodiazepines and codeine combination products are considered controlled drugs. This means they must be managed as per other narcotic and controlled drugs. These include: alprazolam, clonazepam, diazepam, lorazepam, oxazepam, temazepam, clobazam, Tylenol # 1, 2, and 3, 222 and 292.

- For Omnicell units: follow current narcotic and controlled drugs procedure in Omnicell
- For non-Omicell Units: document in Narcotic Pink Book.

For additional information, please contact Tonya Ng at local -66292.

3. POTASSIUM CHLORIDE 20 mEq/50 mL

Due to the standardization of available drug concentrations, potassium chloride 20 mEq/100 mL minibags have been deleted from the hospital formulary. Potassium Chloride 20 mEq/50 mL minibags will remain as the standard concentration for central line administration only. For general nursing units, the maximum rate of administration remains at 20 mEq over 1 hour.

4. PARENTERL DRUG THERAPY MANUAL (PDTM) UPDATE

The new regional PDTM has been distributed to all nursing units. The size of the printed PDTM is now in a larger 8x12 full page format. The content is based on the original Vancouver Acute (VA)

PDTM. The main formatting changes are 1) routes of administration and VA policy sections have been merged into "VA Administration"; and 2) prescribing restrictions by physician group are now found in the first heading "Indications/Ordering Restrictions". The on-line version is located on the VHnet home page (choose Parenteral Drug Therapy Manual, then PDTM Vancouver Acute). Note that the on-line version is the most up-to-date. Pages can be printed from the on-line source and inserted into the manuals, as necessary.

Recent on-line PDTM Updates

- A **linezolid monograph** has been added
- **Bronchoscopy nurses** may administer **alfentanil via direct IV** with appropriate monitoring as listed in the monograph
- Nurses in **PAR** may **administer and titrate propofol and remifentanil infusions**, as well as administer **dantrolene IV direct**.

For any questions regarding this manual, please contact Lisa James at local - 61857 or email PDTM@vch.ca.

5. NO CHANGES TO ORDERS AFTER BEING FAXED TO PHARMACY

Once an order has been processed and/or faxed to Pharmacy, no orders written on the physician's order form may be changed with add-ins, write-overs or by crossing an order out. A discontinued order must be written, along with the new order.

6. ANTI-INFECTIVE COMPARISON CARD 2008

Pharmacy has updated the yellow anti-infective comparison card. All staff physicians at Vancouver Acute, medical residents and medical students will receive copies of this card, which now includes:

- Updated antibiotic susceptibility chart
- Oral and Parenteral Anti-infective Dosage Adjustments according to renal function
- VA Antibiotic Therapeutic Interchanges
- Restricted Antimicrobial Drugs (whereby only a 72 hour supply of medication is dispensed)

A pdf version of this card is also available on the pharmacy website at www.vhpharmsci.com

MULTIDRUG RESISTANT *Acinetobacter baumannii* - UPDATE

Dr. Elizabeth Bryce, MD, FRCP(C), Regional Medical Director, Infection Control Vancouver Coastal Acute

Acinetobacter baumannii (ACBA) is a Gram negative bacillus that is normally widely distributed in water and soil and can inhabit the skin and mucous membranes. Similar to methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* (VRE), it can survive on both dry and moist surfaces for prolonged periods of time. ACBA has little impact on the normal host, however, in those with compromised immune systems, infections with significant morbidity and mortality can develop. Of note, ventilator associated pneumonias and wound infections can be particularly problematic. What makes ACBA even more troublesome is the frequency of antimicrobial resistance, its potential to cause outbreaks and its ability to survive under a wide variety of conditions and environments.¹

Multidrug resistant ACBA has most recently been noted in soldiers returning from Afghanistan.^{2,3} Canadian cases have been linked with stays in US army hospitals and ventilator associated pneumonias. More recently within our region, multidrug resistant ACBA has been noted in returning travelers from Pacific Rim and African countries (and one recent case from Las Vegas!). A minor outbreak with resistant ACBA in one of our facilities was contained only after diligent efforts of the involved wards directed both at environmental cleanliness and hand hygiene.

Previous single isolates throughout our region have had varying resistance to carbapenems but remained susceptible to tigecycline and colistin. During the outbreak, the same pattern was observed, however, some of the isolates had demonstrated increasing resistance to tigecycline. Colistin is an older agent that acts as a cationic detergent to lyse cell walls. Its use is limited because of its nephrotoxicity. Tigecycline is a parenteral broad-spectrum antibiotic that is bacteriostatic (not bacteriocidal) and is generally well tolerated. Clearly the emergence of this bacterium is a worrisome situation that we wish to avoid in the future.

To that end, all newly admitted patients/soldiers from outside of Canada will be placed on **Contact Precautions upon admission**, pending results from screening swabs. This is in addition to routine appropriate admission screens for MRSA and VRE. Screening specimens consist of sputum, wounds and perirectal swab samples. The requisition should be

labeled "multiple antibiotic resistant Gram negative bacilli search". Ventilated patients are placed on Airborne and Contact precautions pending the results of the admission screen. Ventilated patients who are positive for resistant ACBA will continue to be maintained on these precautions while all other patients will be maintained on Contact Precautions for the duration of their stay.

For further questions or information, please contact the Medical Microbiologist on-call through Central Locating at 604-875-5000.

References

1. Montefour K et al. *Acinetobacter baumannii*: an emerging multidrug resistant pathogen in critical care. *Critical Care Nurse* 2008;28:15-25
2. Anon. *Acinetobacter baumannii* infections among patients at military medical facilities treating injured US Service members, 2002-2004 *MMWR* 2004;53:1063-1066.
3. Tien HC et al. Multi-drug resistant *Acinetobacter* infections in critically injured Canadian forces soldiers. *BMC Infect Disease* 2007;7:95-100

TREATMENT OF INVASIVE ASPERGILLOSIS

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

Introduction

Invasive aspergillosis (IA) is a major infection seen in patients with prolonged neutropenia, advanced HIV infection, and those who have undergone allogeneic hematopoietic stem cell transplantation or lung transplantation.¹ *Aspergillus fumigatus* is by far the most common species (50-60%) followed by *A. flavus*, *A. niger* and *A. terreus* (10-15% each) whereas *A. nidulans*, *A. ustus* and other rare *Aspergillus* spp. represent less than 2% of isolates.¹

Treatment Options

Amphotericin B deoxycholate, with its broad-spectrum fungicidal activity, has long been the standard of therapy for IA.² However, patient tolerability is often limited by its infusion-related reactions and nephrotoxicity. Liposomal amphotericin B has a decreased incidence of these adverse reactions, but it is associated with significantly higher costs.

Newly updated 2008 Infectious Diseases Society of America guidelines now recommend voriconazole, a new generation azole, as primary therapy for the treatment of IA.² These recommendations were based on a randomized trial comparing voriconazole (n=144) and amphotericin B deoxycholate (n=133) in the treatment of definite or probable invasive

aspergillosis.³ At week 12, there were greater complete and partial responses in the voriconazole group compared to amphotericin B (52.8% vs 31.6%, absolute difference 21.2%; 95% CI 10.4-32.9) Twelve-week survival was 70.8% in the voriconazole group and 57.9% in the amphotericin B group (hazard ratio 0.59; 95% CI 0.40-0.88). Patients treated with voriconazole had significantly fewer severe drug-related adverse events, but 44.8% of voriconazole-treated patients had transient visual disturbances. Limitations of this study include its open-label design and the allowance of patients with intolerance or no response to initial therapy to switch to another antifungal agent (36% in voriconazole and 80% in amphotericin B groups). Median duration of voriconazole treatment was 77 days compared to a median of only 10 days for amphotericin B treatment. Because of these limitations, although voriconazole is better tolerated than amphotericin B, its superiority with regards to efficacy is not conclusive.

Second line agents for the treatment of IA include the echinocandins (e.g. caspofungin) as well as other azole antifungals such as itraconazole. These agents have mainly been studied in smaller trials in patients refractory to standard treatment and have shown favourable response rates.^{5,6} Fluconazole is not active against aspergillus species and should not be used.

Clinical Recommendations

In patients with proven or probable aspergillosis, voriconazole and amphotericin B deoxycholate are both reasonable first line therapies. If oral absorption is not an issue, patients can be initiated on oral voriconazole. (Table 1). For IV therapy, amphotericin B deoxycholate should be initiated in patients with normal renal function (CrCl > 50 mL/minute) who have a low risk for developing renal dysfunction. Otherwise, in patients at high risk to develop renal dysfunction, IV voriconazole should be used. If patients already have renal dysfunction, liposomal amphotericin B is the treatment of choice as the vehicle in the IV formulation of voriconazole can accumulate in renal dysfunction. Of note, voriconazole is a potent inhibitor of the cytochrome P450 system and interacts with several medication (Table 1). Certain medications should not be given concurrently with voriconazole or may need to have their dosage adjusted.

Second-line agents such as caspofungin, which is fungistatic against *Aspergillus*, should be reserved for salvage therapy in patients who are intolerant or refractory to primary antifungal therapy. Itraconazole is no longer recommended due to its variable

absorption and gastrointestinal side effects and the availability of oral voriconazole. Combination therapy using two antifungal compounds is promising, but properly designed clinical trials are lacking at this time and dual antifungal therapy should only be considered in consultation with Infectious Diseases.⁷

Table 1. Comparison of Amphotericin B and Voriconazole for Treatment of IA

Drug	Amphotericin B	Voriconazole
Activity vs <i>Aspergillus</i>	Fungicidal	Fungicidal
Indication: First-line (Note: Initiate or step-down to oral voriconazole if possible)	Deoxycholate: CrCl > 50 mL/min and <u>low risk</u> for renal failure Liposomal: CrCl < 50 mL/min and requires IV therapy	PO: Initiate at any level of renal dysfunction IV: CrCl > 50 mL/min and <u>high risk</u> for renal failure (e.g. ICU, SCT, SOT patients)
Renal Impairment (CrCl < 50 mL/min)	Avoid Amphotericin B deoxycholate	Avoid IV as vehicle (cyclodextran) may accumulate
Side Effects	Infusion-related reactions (fever, chills, headache, hypotension), N/V, ↓ K, ↓ Mg, nephrotoxicity	Visual disturbances (30%), N/V/D, headache, photosensitivity, ↑ LFTs (13.4%), QT prolongation
Drug Interactions	Caution with other nephrotoxic drugs or drugs that may be affected by ↓ K	Inhibits CYP2C9, 3A4 May ↑ levels of: cyclosporine, methadone, statins, tacrolimus, vincristine, warfarin
Dose (Cost*/day for maintenance dose)	Deoxycholate : 1 mg/kg IV daily (\$78) Liposomal (Ambisome®): 3-5 mg/kg IV daily (\$440-735)	PO: 400mg BID x 24 hrs, then 200-300mg BID (\$95-140) IV: 6mg/kg Q12H x 24 hrs, then 4 mg/kg Q12H (\$420)

*based on VGH acquisition costs for 70kg patient

References

- Maschmeyer G et al. Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. *Drugs* 2007;67:1567-1601.
- Walsh TJ et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Disease Society of America. *Clin Infect Dis* 2008;46:327-60.
- Herbrecht R et al. Voriconazole versus Amphotericin B for primary therapy of invasive aspergillosis. *NEJM* 2002;347:408-15.
- Corney OA et al. Liposomal Amphotericin B as initial therapy for invasive filamentous fungal infections: A randomized trial comparing high loading dose regimen with standard dosing. *Clin Infect Dis* 2007;44:1289-97.
- Maertens J et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis* 2004;39:1563-71.
- Caillot D. Intravenous itraconazole followed by oral itraconazole for the treatment of Amphotericin B refractory invasive pulmonary aspergillosis. *Acta Haematol* 2003;109:111-18.
- Leather H et al. Is combination antifungal therapy for invasive aspergillosis a necessity in hematopoietic stem-cell transplant recipients? *Curr Opin Infect Dis* 2006;19:371-9.