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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 Therapeutic Newsletters are on the Web at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. Clarithromycin XL 500 mg, 1000 mg (Biaxin XL®)

- Sustained release macrolide antibiotic to replace regular release clarithromycin
- Effective May 2, 2005, all orders for clarithromycin will be interchanged to clarithromycin XL as per Table 1.

Table 1. Therapeutic Interchange for Clarithromycin XL

Ordered as:	Interchanged to:
Clarithromycin Immediate Release	Clarithromycin XL
250 mg po BID	500 mg po daily
500 mg po BID	1000 mg po daily

2. Celecoxib 100mg, 200mg caps (Celebrex®)

- COX-2 inhibitor to replace rofecoxib (Vioxx®)

3. Amphotericin B liposomal 50mg/vial (AMBISOME®)

- Antifungal antibiotic for treatment of disseminated mycotic infections in patients who are refractory to or intolerant of conventional amphotericin B therapy
- Restricted to consult by Infectious Diseases (ID) and Pharmacy; BMT, SOT, ICU exempt from ID consult. Pre-printed orders must be completed as they specify creatinine clearance thresholds for which amphotericin B liposomal may be prescribed.
- There are two lipid-based formulations in Canada, Abelcet® and Ambisome®. These products are considered therapeutically equivalent. Previously, Abelcet® was the low cost alternative lipid formulation for use in patients requiring amphotericin B who have serum creatinine levels exceeding established thresholds. The manufacturer of Ambisome® has reduced the cost to be equivalent to that of Abelcet®. Thus, it is no longer necessary to carry two amphotericin B lipid formulations. Due to the lower incidence of infusion-related reactions with Ambisome®, it will now replace Abelcet® on formulary with the same restrictions.

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Updated Policies

1. MODIFICATION TO HEPARIN/WARFARIN PROTOCOL

The VGH Laboratory switched to a new reagent for measuring aPTT on January 10, 2005. As such, the therapeutic aPTT range for treatment of deep vein thrombosis and pulmonary embolism has increased to 70-100 seconds from 60-85 seconds. This new range falls within recommended anti-Xa heparin levels of 0.3-0.7U/mL.

The therapeutic aPTT range on the CCU Heparin Protocol has also changed to 60-85 seconds (from 51-75 seconds). Slightly lower heparin dosing relative to treatment of venous thrombosis is recommended for these patients as they frequently receive additional potent anti-thrombotic agents (e.g. glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, fibrinolytics).

All heparin/warfarin standardized protocols have been replaced with the new aPTT ranges. A further change to the protocol is to determine CBC every 2 days (from every 3 days).

2. Y-SITE COMPATIBILITY CHART 2004

An updated Y-site compatibility chart (Version 7.0, Dec 2004) has been updated on all the nursing units. Hydromorphone (Dilaudid®) has been added to this chart and aminophylline has been removed.

3. HOSPITAL FORMULARY 2005

The 2005 VCH formulary (Vancouver General Hospital, UBCH, GF Strong) has been added to all nursing units. Pocket formularies are also available and can be obtained by calling the Pharmacy (L. 54077). The following sections are contained in this formulary:

- **Green pages**: Policy and Procedures
  Related to drug prescribing, dispensing and administration
- **Yellow pages**: Therapeutic Tools
  Comparison charts of several classes of drugs, dosing guidelines, and monitoring for select drugs
- **White Pages**: Drug Formulary
  All drugs in the pharmacy inventory
- **Pink Pages**: Alphabetical Drug Index
  Generic and Brand names included

4. MODIFICATION TO FELODIPINE: AMLODIPINE INTERCHANGE

Based on supporting literature, the therapeutic interchange of felodipine to amlodipine has been changed from a 2:1 conversion to a 1:1 conversion.[1,2] The physician will be contacted for conversion to doses of amlodipine greater than 10mg daily.

References

1. Koening W et al. Felodipine and amlodipine in stable angina pectoris: results of a randomized double-blind crossover trial. J Cardiovasc Pharmacol 1997;29:520-4.\
2. Parra D et al. Retrospective evaluation of the conversion of amlodipine to alternative calcium channel blockers. Pharmacotherapy 2000;20:1072-8.

5. MODIFICATION TO SIMVASTATIN THERAPEUTIC INTERCHANGE

The maximum dose for conversion of other statin drugs to simvastatin is 40mg daily. This recommendation is based on a recent study showing a higher incidence of myopathy (creatine kinase >10 times the upper limit of normal associated with muscle symptoms) with simvastatin doses of 80mg daily.[1]

Reference

1. De Lemos JA et al for the A to Z investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. JAMA 2004;292:1307-16.

6. PHENYTOIN AND PICC LINES

Phenytoin should not be administered intravenously through a PICC line due to the concern of clogging the line. Once a PICC line is blocked, it is very difficult to unblock and often requires catheter removal. The parenteral formulation of phenytoin precipitates into insoluble crystals at pH of 11.5 or less.[1] Phenytoin is incompatible with D5W and can only be diluted with NS or 0.45% saline solutions. Published case reports suggest that the pH of phenytoin as well as the small internal lumen and long catheter length of the PICC catheters may be key factors in causing precipitation and blockage of these lines.[2-4]

References

1. Phenytoin product monograph 2005
2. Tse CS et al. Dissolving phenytoin precipitate in central venous access device. Ann Emerg Med 1998;128:1049.
3. Akinwande KI et al. Dissolution of phenytoin precipitate with sodium bicarbonate in an occluded central venous device. Ann Pharmacother 1995;29:707-9.
4. Ault MJ. Catheter occlusion from intravenous phenytoin. Ann Emerg Med 2004;44:428-9.

7. REPORTING OF METHICILLIN-RESISTANT *Staphylococcus aureus* (MRSA)

Currently, the Microbiology Laboratory reports only vancomycin susceptibilities for methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. In patients for whom vancomycin therapy is contraindicated, or for the treatment of non-invasive infections, additional antimicrobial susceptibilities are available. Please contact the Medical Microbiologist or Microbiology Laboratory at 875-4140, or the Infectious Diseases Physician at 875-4588 if you have any questions.

8. LABORATORY TESTING OF CLINDAMYCIN RESISTANCE IN STAPHYLOCOCCI AND BETA HEMOLYTIC STREPTOCOCCI

The Clinical Laboratory Standards Institute (CLSI, formerly known as NCCLS), which provides guidelines for the standardization of antimicrobial susceptibility testing, has recommended that the "D-test" be performed on selected staphylococci and beta hemolytic streptococci isolates in order to detect the presence of inducible clindamycin resistance. This test involves the placement of an erythromycin and a clindamycin disk at a specific distance from each other. The culture plate is then observed for the presence of zone blunting around the clindamycin disk (a "D" shaped zone), which is considered a positive test for the induction of resistance.

The VGH Microbiology Laboratory will be performing the "D-test" on all staphylococci (both *S. aureus* and coagulase negative staphylococci) and beta-hemolytic streptococci that normally have susceptibility tests performed, and that show an erythromycin resistant "R" and clindamycin susceptible "S" pattern on initial testing. Isolates that initially test either "S" or "R" to both antibiotics will not be tested. When the "D-test" is positive, clindamycin will be reported as "R", and the following comment will be appended to the report:

"*This organism is presumed to be resistant based on the detection of inducible clindamycin resistance. Clindamycin may still be effective in some patients."*

Please phone the microbiologist on call (5-5000) or the Microbiology Laboratory at 875-4140 if you have any questions.

9. RANITIDINE ADDITION TO IV-PO DOSAGE CONVERSION SERVICE

Ranitidine has been added to the list of approved drugs that clinical pharmacists are authorized to step-down from the IV to PO route if patients are taking other PO/NG medications or food. The oral dosage will be adjusted for renal dysfunction.

10. PATIENT TEACHING SHEETS ONLINE

Patient teaching sheets have been recently updated by Pharmaceutical Sciences CSU. These monographs are in PDF format and are available for viewing and printing from the VCH intranet. The following are instructions to access this site:

- From a computer within VCH, use internet explorer to navigate http://www.vcha.ca
- Click on "Programs and Services"
- Scroll down the Vancouver Acute column to the Clinical Support Services section and click "Pharmaceutical Sciences-Vancouver Acute"
- Click the "Patient Counseling Materials" link in the left column
- The resulting page links to all current patient counseling monographs.

11. PDTM CHANGES

- **Physicians in the cath lab may administer enoxaparin IV direct** as a top-up dose prior to PCI if PCI is performed 8-12 hours since the last enoxaparin subcutaneous dose.
- **Y-site compatibility** information has been added to the **pantoprazole** monograph. Check the intranet version of the PDTM for the most current information (click on PDTM link under Regional Web sites on the VCH intranet homepage).
- **Y-site compatibility** information has been updated on the **ketorolac IV** monograph. Check the intranet version of the PDTM for the most current information.

Pharmacy Awards

Dr. Kerry Wilbur is the recipient of the 2004 New Hospital Pharmacy Practitioner/Sabex Award. This honour is awarded to a pharmacist (5 years or less in practice) by the Canadian Society of Hospital Pharmacists for outstanding achievement in hospital pharmacy practice.

IMIPENEM UTILIZATION AT VGH: AN EVALUATION OF USAGE CHARACTERISTICS

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Introduction

Imipenem-cilastatin (imipenem) is the carbapenem antibiotic currently on formulary at Vancouver Acute (VGH, UBCH, GF Strong). This agent has broad spectrum antimicrobial coverage with excellent activity against many of the pathogens encountered in both the community and nosocomial environment.[1] Common indications for its use include severe intra-abdominal infections where polymicrobial coverage is necessary and infections caused by multi-drug resistant bacteria.

Imipenem is designated as a Reserved Antimicrobial Drug (RAD). Patients receiving a RAD are monitored by clinical pharmacists to ensure appropriate usage. Imipenem is a RAD as a result of its broad spectrum of activity, high cost and potential for suboptimal use. Inappropriate use could lead to development of bacterial resistance and patient adverse effects.[2,3] Also, due to the broad spectrum of action, imipenem may have a propensity to predispose patients to superinfections such as *Clostridium difficile*-associated diarrhea and candidiasis. Imipenem expenditures at VGH were $217,000 for fiscal year 2004. Characterization of imipenem use, other than expenditure data, has not been previously documented at VGH. We, therefore, undertook an evaluation to characterize imipenem use over a 5-month period (June 28 to Nov 24, 2004).

Data was collected by an evaluator (first author) who, on a daily basis, contacted those clinical pharmacists monitoring patients receiving imipenem during the study period. The following information was analysed: the number of new imipenem treatment courses started, patient's location at therapy initiation, the initial dosage regimen, duration of imipenem therapy, indications for initiation, appropriateness of therapy (according to pre-determined criteria listed in Appendix 1), and whether or not imipenem was continued for the duration of antimicrobial therapy or if alternative antibiotics were initiated at some point during the antimicrobial treatment course.

Results

There were 220 new imipenem treatment courses initiated during the study period. A convenience sample of 125 (57%) of these treatment courses was characterized. The Intensive Care Unit (ICU) had the most new imipenem starts at 38% (Table 2). The most common initial dosage regimen was 500mg IV q6h and indication for use was nosocomial pneumonia. The mean and median duration of therapy was 7.3 and 4 days, respectively. The majority of treatment courses were classified as 'appropriate'.

Table 2. Imipenem Utilization Results

Parameter	Percent of Treatment Courses (N = 125)
Area of Initiation	
ICU	38%
Emergency - Acute	9%
T15A (BMT)	6%
T10A (Urology/Gynecology)	6%
Other Units (≤ 5 starts/unit)	41%
Initial Dose	
500mg IV q6h	57%
500mg IV q8h	22%
500mg IV q12h	14%
Other regimen	7%
Indication	
Nosocomial pneumonia	28%
Multi-drug resistant bacteria (documented)	20%
Severe intra-abdominal infection	20%
Bacteremia	17%
Skin/soft tissue or genitourinary tract	15%
Appropriateness of Therapy*	
Appropriate	64%
Acceptable but suboptimal	24%
Inappropriate	4%
No data available	8%

*see Appendix 1 for definitions

In 32% of cases, imipenem was the only antibiotic used during the treatment course. In 48% of cases, imipenem therapy was switched to 1 or more antibiotics to complete the course of therapy. In the remaining 20% of cases, it is unknown if imipenem was switched to another antibiotic due to incomplete follow-up for reasons such as patient death or discharge. When imipenem was changed to an alternative antibiotic during a treatment course, the most common single agent used was ticarcillin-clavulanate or ciprofloxacin. If more than one antibiotic was used, the majority of regimens contained a fluoroquinolone.

Discussion

The ICU was the most common location for new imipenem starts which may reflect the severity of illness encountered in the critically ill population and the fundamental principle of initiating early, broad spectrum antibiotics for serious infections and to tailor therapy once patient-specific data becomes available. While the balance of imipenem prescriptions were dispersed throughout VGH, this may be confounded by the fact that the sample characterized was not randomly selected but selected based on availability of the evaluator.

The most common initial dosing regimen (500 mg q6h) prescribed is consistent with published dosing recommendations. Individual patient-specific dosing evaluations were not done as part of this evaluation. The average duration of imipenem therapy was approximately one week, but there were outliers on both ends of the spectrum. The shorter median duration of 4 days may reflect an aggressive approach undertaken in the ICU to step-down imipenem therapy after 72 hours. It is not known whether this project influenced prescribing patterns as a result of daily clinical pharmacist follow-up. It is possible that the duration of therapy was shorter during the study period due to the intensive follow-up required by the clinical pharmacists monitoring the imipenem patients. The most common indications for starting imipenem are consistent with its conventional role for treating serious infections and infections caused by multi-drug resistant bacteria. Imipenem initiation does not require pre-requisite microbiological confirmation of suspected pathogens and the majority of new courses were initiated empirically pending further microbiological, clinical, or radiological information.

Imipenem was initiated appropriately in the majority of cases as per pre-defined criteria (Appendix 1). We chose a practical definition that should be used on a daily basis by clinicians when considering initial therapy for a bacterial infection. The acceptable but suboptimal category may be considered a gray area, however, the common theme with these prescriptions was that there were no convincing patient-specific data or published data that directed a switch to another antibiotic. Despite these limitations, 88% appropriate or acceptable initiation reflects judicious prescribing of this agent at VGH. Also, once initiated, imipenem treatment courses were frequently converted to alternative antibiotics to complete the full treatment course. This study did not document patient-specific clinical outcomes or antibiotic-resistance patterns at VGH.

Conclusion

This concurrent drug use evaluation of imipenem provides evidence of judicious and largely appropriate use of imipenem at VGH. There remains some opportunity for streamlining the use of this agent by targeting a more directed therapy during the antimicrobial treatment course.

References

Available upon request.

Appendix 1. Definitions for Appropriateness of Imipenem Initiation

Category	Definition
Appropriate	• Empiric therapy for a serious community or nosocomial associated infection; awaiting microbiology results • Empiric therapy in a patient suspected to be infected with multi-drug resistant bacteria • Directed therapy in a patient with known multi-drug resistant bacteria • Directed therapy in a patient with a serious polymicrobial infection where single-drug therapy with imipenem is advantageous • Therapy in a patient with a documented intolerance to alternative antibiotics • Any other scenario deemed to be appropriate by primary author
Acceptable but Suboptimal	• Imipenem was started for a susceptible bacterial infection amenable to other antibiotic therapy with excellent activity and delivery to the site of action, however, evidence for using one antibiotic over another is equivocal
Inappropriate	• Imipenem was started for an infection known to be fully susceptible to other antibiotics that have been shown to produce outcomes that are no worse, equal, or superior • Imipenem was started as prophylactic therapy • Imipenem was started in a patient known to not tolerate imipenem

Adverse Drug Reaction Report 2004

There was a total of 15 suspected adverse drug reactions (ADRs) reported at VGH in 2004 (Table 3). Of note, 7 adverse reactions were considered to have been the cause of hospitalization and 1 resulted in prolonged hospitalization. The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in an improved assessment of the magnitude and nature of adverse events. To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to Pharmaceutical Sciences CSU, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists will complete all ADR report forms and forward copies to the B.C. Regional ADR Centre. This Centre does preliminary analysis of the data and then submits all reports to the Canadian ADR program in Ottawa who then forwards them to the World Health Organization.

Table 3. Adverse Drug Reactions Reported in 2004

Drug	Suspected Reaction
Carbamazepine[a]	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Ciprofloxacin	Severe leg pain, trouble standing or walking due to pain
Clarithromycin[a]	Prolonged QTc interval > 600 msec and complete heart block
Fluconazole, Metoclopramide	Sinus bradycardia, QTc prolongation
Infliximab	Severe arm pain, face flushed and clammy skin 5 minutes into infusion
Iron Dextran	Hip pain during test dose
Methadone[a] (high dose 180mg po TID)	Ventricular tachycardia, prolonged QTc interval 505 msec
Methadone + Ciprofloxacin interaction[b]	Decreased respiratory rate to 6-8/minute
Methylprednisolone	Hiccups (1); blurred vision, shaky and painful knees, pre-syncope (1)
Minoxidil[a]	Acute pulmonary edema
Simvastatin 40mg daily	Bilateral leg pain (normal creatine kinase 113 U/L)
Ramipril[a]	Angioedema after receiving 2 doses
Rofecoxib[a] 25mg daily	Duodenal ulcer with *H pylori* after 2 days of therapy
Terazocin[a]	Collapsed ~2.5 hours after initial 5mg dose (therapy was interrupted for 2 weeks, then restarted at previous high dosage)

[a]hospitalized due to ADR ; [b]prolonged hospitalization due to ADR