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## *Changes to Formulary*

### **Additions**

Clinicians should review medication information prior to administering any unfamiliar medication. Resources include: VCH PDTM, Lexicomp®, or UpToDate®.

#### **1. Instillagel® (Lidocaine 2% plus Chlorhexidine 0.05%) topical gel**

- Anesthetic, lubricant, and antiseptic for use prior to urologic procedures

#### **2. Valsartan 40 mg, 160 mg tabs (Diovan®)**

- Angiotensin II receptor blocker (ARB)
- See Therapeutic Interchange for all ARBs to candesartan except valsartan and losartan (see page 2).

### **Deletions**

#### **1. Tetanus + Diphtheria + Polio vaccine (Td-IPV®)**

- This combination vaccine is no longer available through BCCDC
- Alternative: order individual vaccines  
⇒ Tetanus + Diphtheria (Td®) and  
⇒ Polio inactivated (Imovax® Polio)

## *Drug & Policy Revisions*

### **1. METHADONE TABLETS**

- Any physician with methadone privileges may now order methadone tablets as an alternative to oral solution for pain management. Tablets offer the advantage of reduced dosing errors when compared to measuring from the liquid formulation.

### **2. SMOFlipid® 20% lipid emulsion (Soyabean oil 6%, medium-chain triglycerides 6%, olive oil 5%, fish oil 3%)**

- Alternate source of calories and omega-3 fatty acids for patients with total parenteral nutrition (TPN)-associated liver disease and in the critically ill when long-term TPN is required
- Requires DEHP-free administration sets
- Restricted to review by TPN pharmacist

### **3. CELECOXIB DOSAGE CEILING**

Health Canada has reported that celecoxib at doses higher than 200 mg/day may be linked with an increased risk of serious cardiovascular (CVS) events. This risk is similar to those associated with high doses of diclofenac (≥ 150 mg/day) or ibuprofen (≥ 2400 mg/day).

All Pre-Printed Orders (PPOs) will be revised to limit the dose of celecoxib to a maximum of 100 mg BID (or 200 mg daily). This will include the POPS Pain Management order set.

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**4. ANGIOTENSIN II RECEPTOR BLOCKER THERAPEUTIC INTERCHANGE REVISION**

All angiotensin II receptor blockers (ARBs) will be therapeutically interchanged to candesartan except valsartan and losartan (see Table 1).

**Table 1. Angiotensin II Receptor Blocker Therapeutic Interchange**

| Drug                    | Dose (mg*)      |     |     |
|-------------------------|-----------------|-----|-----|
|                         | 4               | 8   | 16  |
| Candesartan (Atacand®)  | 4               | 8   | 16  |
| Azilsartan (Edarbi®)    | n/a             | 40  | 80  |
| Eprosartan (Teveten®)   | 400             | 600 | 800 |
| Irbesartan (Avapro®)    | 75              | 150 | 300 |
| Losartan (Cozaar®)      | No Substitution |     |     |
| Olmesartan (Olmotec®)   | 10              | 20  | 40  |
| Telmisartan (Micardis®) | 20              | 40  | 80  |
| Valsartan (Diovan®)     | No Substitution |     |     |

\*The total daily dose of the original ARB order will be used to calculate an equivalent candesartan dose for once daily administration.

**5. HYPERKALEMIA MANAGEMENT PPO**

A new Hyperkalemia Management PPO #960 is now available for use hospital-wide for any patient presenting with hyperkalemia (defined as a serum potassium of 5.5 mmol/L or greater).

**6. EPINEPHRINE LABELING CHANGE**

- The Institute for Safe Medication Practices (ISMP) has directed that epinephrine strengths be relabeled as:
  - ⇒ Epinephrine 1 mg/mL (1:1000)
  - ⇒ Epinephrine 0.1 mg/mL (1:10,000)
- This labeling change was made due to the following factors: 1) lack of understanding of ratio expression by some health practitioners, and 2) potential confusion due to apparent similarities in concentrations when written (i.e. difference of only one zero between “1:1000” and “1:10,000”).

**7. VGH ANTIBIOGRAM 2014-2015**

The updated VGH antibiogram for 2014-15 is a collaborative effort between Medical Microbiology, SPIRES and Pharmacy (Figure 1). For further details, please refer to the SPIRES intranet site.

Figure 1

**VGH ANTIBIOGRAM 2014-2015**

Compiled by Medical Microbiology, Pharmaceutical Sciences, and SPIRES

| ANTIMICROBIAL           | % SUSCEPTIBLE        |                          |                       |                |  |                       |                          |                       |                      |                  |                 |                    |                        |                     |                     |                    |                        |                            |                      |                        |
|-------------------------|----------------------|--------------------------|-----------------------|----------------|--|-----------------------|--------------------------|-----------------------|----------------------|------------------|-----------------|--------------------|------------------------|---------------------|---------------------|--------------------|------------------------|----------------------------|----------------------|------------------------|
|                         | GROUP A STREPTOCOCCI | STREPTOCOCCUS PNEUMONIAE | VIRIDANS STREPTOCOCCI | STAPHYLOCOCCUS | METHICILLIN-RESISTANT S. AUREUS (MRSA) | STAPHYLOCOCCUS AUREUS | ENTEROCOCCUS EPIDERMIDIS | ENTEROCOCCUS FAECALIS | HAEMOPHILUS FAECALIS | ESCHERICHIA COLI | KLEBSIELLA COLI | PROTEUS PNEUMONIAE | ENTEROBACTER MIRABILIS | SERRATIA MARCESCENS | CITROBACTER CLOACAE | ACI NETOBACTER SP. | PSEUDOMONAS AERUGINOSA | STENOTROPHOMAS MALTOPHILIA | BACTEROIDES FRAGILIS | PEPTOSTREPTOCOCCUS SP. |
| AMOXICILLIN/CLAVULANATE | 100                  | 100                      | 85                    | 100            | 0                                      | 0                     | 99                       | 16                    | 100                  | 78               | 91              | 91                 | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 90                   | 100                    |
| AMOXICILLIN             | 100                  | 100                      | 85                    | 19             | 0                                      | 0                     | 99                       | 16                    | 83                   | 52               | 0               | 74                 | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 96                     |
| AMPICILLIN              | 100                  | 100                      | 85                    | 19             | 0                                      | 0                     | 99                       | 16                    | 83                   | 52               | 0               | 74                 | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 96                     |
| CLOXACILLIN             | —                    | 0                        | 0                     | 100            | 0                                      | 31                    | 0                        | 0                     | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 0                      |
| PENICILLIN G SOD        | 100                  | 100                      | 85                    | 19             | 0                                      | 0                     | 99                       | 16                    | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 96                     |
| PENICILLIN V POT        | 100                  | 100                      | 85                    | 19             | 0                                      | 0                     | 99                       | 16                    | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 96                     |
| PIPERACILLIN/TAZOBACTAM | —                    | —                        | —                     | 100            | 0                                      | 0                     | 99                       | 16                    | —                    | 98               | 96              | 99                 | 74                     | 100                 | 82                  | 92                 | 95                     | 0                          | 98                   | 98                     |
| IMIPENEM/CILASTATIN     | —                    | —                        | —                     | —              | 0                                      | 0                     | 99                       | 0                     | —                    | 100              | 99              | 95                 | 99                     | 97                  | 100                 | 99                 | 87                     | 0                          | 98                   | 100                    |
| MEROPENEM               | —                    | —                        | —                     | —              | 0                                      | 0                     | —                        | 0                     | —                    | 100              | 99              | 100                | 99                     | 97                  | 100                 | 99                 | 93                     | 0                          | 96                   | 100                    |
| CEPHALEXIN              | 100                  | 0                        | 0                     | 100            | 0                                      | 31                    | 0                        | 0                     | 0                    | 81               | 87              | 39                 | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | —                      |
| CEFAZOLIN               | 100                  | 0                        | 0                     | 100            | 0                                      | 31                    | 0                        | 0                     | 0                    | 83               | 88              | 39                 | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | —                      |
| CEFUROXIME              | —                    | 100                      | —                     | —              | 0                                      | 0                     | 0                        | 0                     | 97                   | —                | —               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | —                      |
| CEFTAZIDIME             | —                    | 0                        | 0                     | 0              | 0                                      | 0                     | 0                        | 0                     | 100                  | 88               | 94              | 98                 | 72                     | 98                  | 72                  | 85                 | 89                     | 56                         | 0                    | —                      |
| CEFTRIAZONE             | 100                  | 100                      | 97                    | —              | 0                                      | 0                     | 0                        | 0                     | 100                  | 88               | 94              | 96                 | 70                     | 98                  | 72                  | 30                 | 0                      | 0                          | 0                    | —                      |
| CIPROFLOXACIN           | —                    | 0                        | —                     | —              | —                                      | —                     | —                        | 0                     | 100                  | 74               | 94              | 85                 | 98                     | 99                  | 94                  | 95                 | 83                     | 0                          | 0                    | 0                      |
| MOXIFLOXACIN            | —                    | 99                       | —                     | —              | —                                      | —                     | 0                        | 0                     | 100                  | —                | —               | —                  | —                      | —                   | —                   | 0                  | 0                      | 0                          | 65                   | 63                     |
| COTRIMOXAZOLE           | 0                    | —                        | —                     | 95             | 95                                     | 41                    | 0                        | 0                     | 70                   | 73               | 90              | 83                 | 93                     | 100                 | 86                  | 94                 | 0                      | 99                         | 0                    | 0                      |
| GENTAMICIN              | 0                    | 0                        | 0                     | —              | —                                      | —                     | —                        | —                     | —                    | 89               | 97              | 92                 | 99                     | 96                  | 95                  | 93                 | 95                     | 0                          | 0                    | 0                      |
| TOBRAMYCIN              | 0                    | 0                        | 0                     | —              | —                                      | —                     | —                        | —                     | —                    | 87               | 95              | 90                 | 99                     | 81                  | 96                  | 97                 | 98                     | 0                          | 0                    | 0                      |
| AZITHROMYCIN            | —                    | —                        | —                     | —              | —                                      | —                     | —                        | —                     | —                    | —                | —               | —                  | —                      | —                   | —                   | —                  | —                      | —                          | —                    | —                      |
| CLARITHROMYCIN XL       | 80                   | 68                       | —                     | —              | 0                                      | 0                     | 0                        | 0                     | 95                   | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | 0                      |
| ERYTHROMYCIN            | —                    | —                        | —                     | —              | —                                      | —                     | —                        | —                     | —                    | —                | —               | —                  | —                      | —                   | —                   | —                  | —                      | —                          | —                    | —                      |
| DOXYCYCLINE             | —                    | 84                       | —                     | 95             | 89                                     | 89                    | —                        | —                     | 95                   | 69               | 82              | 0                  | 88                     | 0                   | 100                 | 91                 | 0                      | 0                          | 0                    | —                      |
| TETRACYCLINE            | —                    | 59                       | —                     | 95             | 89                                     | 89                    | 22                       | 31                    | 95                   | 69               | 82              | 0                  | 88                     | 0                   | 80                  | 91                 | 0                      | 0                          | 0                    | —                      |
| CLINDAMYCIN             | 80                   | —                        | 67                    | 84             | 40                                     | 44                    | 0                        | 0                     | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 72                   | 63                     |
| METRONIDAZOLE           | 0                    | 0                        | 0                     | 0              | 0                                      | 0                     | 0                        | 0                     | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 96                   | 96                     |
| NITROFURANTOIN          | 0                    | 0                        | 0                     | —              | —                                      | 0                     | 99                       | 0                     | 0                    | 98               | 34              | 0                  | 18                     | 0                   | 95                  | 0                  | 0                      | 0                          | 0                    | 0                      |
| LINEZOLID               | —                    | —                        | —                     | 100            | 100                                    | 100                   | —                        | —                     | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | —                      |
| VANCOMYCIN              | 100                  | 100                      | 100                   | 100            | 100                                    | 100                   | 100                      | >95                   | 0                    | 0                | 0               | 0                  | 0                      | 0                   | 0                   | 0                  | 0                      | 0                          | 0                    | —                      |

**LEGEND**  
 — Not considered first-line therapy, but may be appropriate in specific clinical situations.  
 0 Organism is inherently resistant or not recommended due to poor clinical response.  
 Contact Medical Microbiologist on-call, SPIRES, or Pharmaceutical Sciences for details.

## 8. PDTM 2016 UPDATE

All Parenteral Drug Therapy Manuals (PDTMs) at VA have been updated with the 2016 hard copy version. Note that the on-line PDTM is the most up-to-date and clinicians are encouraged to use the on-line version where possible. If a new binder is required, please contact Karen Shalansky at karen.shalansky@vch.ca or call 604-875-4839.

### *Pharmacy Awards*

Congratulations to **Cesilia Nishi**, Pharm.D. who was honoured with the **Best Preceptor Award** by the UBC Pharm.D. graduating class of 2016.

### *Focus Forum*

#### **CLOSTRIDIUM DIFFICILE INFECTION: Flushing Out the Myths**

Dr. Ted Steiner, Division of Infectious Diseases, VGH

*Clostridium difficile* infection (CDI) remains an important cause of hospital-acquired illness in BC, and is becoming increasingly common in the outpatient setting. While many cases of CDI are mild and may resolve spontaneously when non-CDI-related antibiotics are stopped, other cases require specific treatment. Our VCH-PHC CDI clinical treatment algorithm was developed by a Provincial expert group based on the 2010 IDSA/SHEA Guidelines.<sup>1</sup> The next set of guidelines are due to be published later this year.

While prescribers are generally compliant with the guidelines, there are situations where individual judgment may lead to prescribing practices that are not evidence-based or necessarily in the best interest of the patient. Examples are as follows:

#### **1. Prolonged use of metronidazole**

While metronidazole is generally effective in mild-moderate cases of CDI, a recent Phase III trial indicated that it is statistically inferior to oral vancomycin even in mild disease (78.7% vs 82.7% clinical success;  $p=0.02$ ).<sup>2</sup> However, since the difference in efficacy is relatively small, it is still appropriate to use metronidazole in mild cases, particularly in the outpatient setting where its cost is much lower. However, metronidazole can cause irreversible neurotoxicity with prolonged use, and hence should not be given for extended or tapered courses, or in patients experiencing multiple CDI relapses.

***“Key point: Metronidazole should not be used for extended courses or tapering regimens in multiple relapses, due to irreversible neurotoxicity.”***

#### **2. Overuse of combination therapy**

The IDSA/SHEA guidelines recommend to “**consider**” adding IV metronidazole to oral vancomycin for severe, complicated cases of CDI.<sup>1</sup> The rationale for this is not synergistic nor more rapid killing of *C. difficile*; rather, it is out of concern that patients with a severe ileus or toxic megacolon may have impaired intestinal transit leading to subtherapeutic vancomycin concentrations in the colon. A prospective trial of combination therapy has never been published, and retrospective studies have been troubled by problems related to patient heterogeneity. The only evidence of a mortality benefit was observed in ICU patients who received combination oral vancomycin and IV metronidazole.<sup>3</sup> However, that study presented significant biases since more patients receiving IV metronidazole were also given intrarectal vancomycin. There is also some evidence suggesting that combination therapy may lead to an increased relapse risk.<sup>4</sup> In the absence of a significant ileus or toxic megacolon, there is insufficient evidence to recommend combination therapy for severe CDI. Other combinations (e.g. oral vancomycin plus oral metronidazole) should never be used.

***“Key point: Evidence for the combination oral vancomycin plus IV metronidazole therapy is lacking and should only be considered when subtherapeutic colon concentrations of vancomycin are a concern (e.g. significant ileus or toxic megacolon).”***

#### **3. High dose vancomycin**

High dose vancomycin (250-500 mg PO QID) is recommended as a treatment option to “**consider**” in fulminant cases<sup>1</sup>, although there are no data to support this use. Fecal concentrations at the standard dose of 125 mg PO QID are, on average, 1000 times above the minimum inhibitory concentration (MIC) for *C. difficile*. Higher doses may be an option when patients require nasogastric suction or are otherwise unlikely to be achieving drug delivery to the colon after oral administration. High dose vancomycin should not be used in relapsing disease, as this causes greater disturbance of the intestinal microbiota.

***“Key point: There is no likely benefit in using higher vancomycin doses.”***

#### 4. Inappropriate response to stool testing

The Polymerase Chain Reaction (PCR) test currently used to diagnose CDI cannot distinguish between colonization and active disease due to toxin production. The PCR frequently remains positive for weeks after successful treatment, so a “test of cure” should **never** be ordered. New evidence is emerging suggesting patients whose stool is PCR+ but negative by toxin Enzyme Immunoassay (EIA) assays may not require treatment. For the moment, we continue to recommend treatment for patients whose stool is reported as positive by the laboratory based on PCR, provided their diarrhea is continuing; however, patients whose symptoms have resolved spontaneously (e.g. after other antibiotics are discontinued) should not be treated.

**“Key point: Test of cure should never be ordered, as PCR remains positive for weeks after treatment.”**

#### 5. Use of fidaxomicin

Fidaxomicin, a macrolide antibiotic, is approved by Health Canada for the treatment for CDI; it is currently non-formulary at VA. In Phase III studies, it was equivalent to vancomycin in initial cure, with a significantly reduced relapse rate leading to increased global cure.<sup>5</sup> Due to lack of cost-effectiveness data to justify its significantly higher price, BC Pharmacare has restricted fidaxomicin use to severe CDI cases that fail to respond to oral vancomycin or cannot be treated with vancomycin because of allergy or other intolerance. However, there is a tendency to use the drug in “salvage” situations, such as multiply relapsing patients or severely ill patients in whom colectomy is not a good option; however, there is absence of data supporting its use in these settings. Ongoing clinical trials should further clarify the most appropriate use for this medication. Fidaxomicin remains a reasonable treatment alternative to vancomycin for outpatients whose prescription drug plan provides coverage.

**“Key point: Fidaxomicin should not be used for “salvage” therapy in multiple relapses as data for benefit is lacking.”**

#### 6. Probiotics

Probiotics are not recommended for the prevention or treatment of CDI due to lack of supporting evidence, and the possibility (albeit rare) of bacteremia or fungemia associated with the probiotic strains. Patients who wish to continue taking their probiotic due to perceived symptomatic benefit may do so. However, they should not be prescribed by physicians specifically for CDI prevention or treatment.

**“Key point: Probiotics are not recommended for prevention or treatment of CDI, as data is lacking and there is a potential for associated fungemia.”**

#### 7. Fecal transplant

Fecal transplant is currently limited to clinical trials, but guidelines for its therapeutic use are under review. It will likely be available and recommended only for patients with two or more CDI relapses who have failed a vancomycin pulse or taper regimen. Patients with multiple relapses should currently be referred to an Infectious Diseases specialist with experience managing these challenging cases.

**“Key point: Consult Infectious Diseases for patients with multiple relapses.”**

#### References

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