Appendix 1: CDI Clinical Management Algorithm (in Adults)

SUSPECTED OR CONFIRMED CDI

Unexplained & new-onset diarrhea (unformed or watery stools ≥3 in 24 h) [Δ]

AND

1. Pending *C. difficile* test with high clinical suspicion **OR**
2. Positive *C. difficile* test **OR**
3. Endoscopic or histologic evidence of pseudomembranous colitis

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INSTITUTE CONTACT PLUS PRECAUTIONS [$]

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EVALUATE CDI SEVERITY

Assess and document patient's clinical status (e.g. vital signs, clinical symptoms, abdominal exam, etc.)
Obtain baseline CBC and differential, electrolytes, and serum creatinine

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NON-SEVERE (MILD TO MODERATE)

- WBC <15,000/mm^3 **AND**
- Serum creatinine (SCr) ≤1.5 times baseline

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INITIAL EPISODE

- Review all antibiotics and discontinue unless clearly indicated, or document reason for continuation
- Discontinue all proton pump inhibitors (PPIs) unless clearly indicated, or document reason for continuation
- Stop all anti-peristaltic & pro-motility agents
- **First-line: Vancomycin 125 mg PO/NG QID x 10-14 d** [++] **OR**
  Second-line: Metronidazole 500 mg PO/NG TID x 10-14 d, if costs of Vancomycin prohibit use or on a case-by-case basis
- If not clinically improving by day 4-6 while on oral Metronidazole, change to Vancomycin
- If symptoms worsen, re-evaluate for CDI severity and follow appropriate algorithm pathway

SEVERE (any of the following):

- ↑ WBC >15,000/mm^3 **# OR**
- ↑ SCr >1.5 times baseline, or SCr >135 µmol/L (if baseline unavailable) **OR**
- Pseudomembranous colitis

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INITIAL EPISODE

- Review all antibiotics & discontinue unless clearly indicated, or document reason for continuation
- Discontinue all PPIs unless clearly indicated, or document reason for continuation
- Stop all anti-peristaltic & pro-motility agents
- **Vancomycin 125 mg PO/NG QID x 10-14 d** [++]
- Consider ID, GI, and/or General Surgery consult
- Consider CT scan of the abdomen, if clinically indicated

FULMINANT (any of the following):

- Hypotension
- Ileus
- Megacolon
- Shock

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ANY EPISODE

- Review all antibiotics & discontinue unless clearly indicated, or document reason for continuation
- Discontinue all PPIs unless clearly indicated, or document reason for continuation
- Stop all anti-peristaltic & pro-motility agents
- **Vancomycin 125 mg PO/NG QID x 10-14 d** [++] *****
- **If complete ileus OR critically ill, add Metronidazole 500 mg IV Q8H**
- **If unable to take PO/NG Vancomycin, consider adding Vancomycin 500 mg rectally Q6H ♣**
- Obtain specialist (ID, GI, and/or General Surgery) and ICU consult immediately as directed by level of care

FIRST RECURRENCE

MILD TO MODERATE – Recurrent CDI within 8 weeks of diagnostic test of primary episode

- Review all antibiotics & discontinue unless clearly indicated, or document reason for continuation
- Discontinue all PPIs unless clearly indicated, or document reason for continuation
- Stop all anti-peristaltic and pro-motility agents
- **First-line: Vancomycin 125 mg PO/NG QID x 10-14 d ++ OR**
  Second-line: Metronidazole 500 mg PO/NG TID x 10-14 d, if costs of Vancomycin prohibit use or on a case-by-case basis where vancomycin cannot be used

SEVERE

- **Vancomycin 125 mg PO/NG QID x 10-14 d ++**
  - If symptoms worsen, re-evaluate for CDI severity and/or obtain ID or GI opinion

SECOND OR FURTHER RECURRENCES

- **Vancomycin 125 mg PO/NG QID x 10-14 d ++, then should consider vancomycin tapering for ≥6 weeks (e.g. vancomycin 125 mg BID x 7 days, then 125 mg once daily x 7 days, and then 125 mg every 2 or 3 days for 2-8 weeks)†**
- Obtain ID or GI opinion
- Consider fecal microbiota transplantation (FMT) in multiple relapses, especially after failed vancomycin taper. At the time of development of these guidelines, provincial infrastructure for FMT is being developed.

Footnotes for algorithm

Δ Consider testing patients for CDI if high ileostomy outputs >2 L in 24 hours.

$ For Contact Plus Precautions, please refer to: http://ipac.vch.ca/Documents/Additional%20Precautions/Online/Contact%20Plus%20Summary%20Sheet%203Mar2017.pdf

In patients unable to mount a WBC response >15,000/mm^3, an increasing WBC with pronounced left shift may also be considered in these criteria; threshold of >15,000/mm^3 is based on expert opinion.

++ Vancomycin IV is **NOT** effective for the treatment of CDI

***** Vancomycin doses of 125-500 mg may be considered; appropriate dose has not been established in clinical trials. However, there is no evidence that doses higher than 125 mg are more effective. Prolonging full-dose therapy beyond 14 days should be avoided, as there is no evidence of effectiveness and it is likely to delay reconstitution of normal intestinal bacteria.

♣ Physician assessment for perforation risk is required prior to rectal tube placement.

† Tapering therapy regimens (a stepwise decrease in dose over a period of time) may vary considerably, as clinical data are limited. Specialist referral should be obtained in patients with more than 2 recurrences.

Notes:

- Metronidazole tapering is **NOT** recommended
- Prophylactic treatment for patients on antibiotics who have previously had *C. difficile* is NOT recommended. Consider obtaining Infectious Diseases opinion.
- Consider obtaining Special Authority approval for vancomycin PO coverage by Pharmacare for outpatient treatment.
- Recurrent CDI is defined as a CDI episode occurring within 2 – 8 weeks of a previous episode from the date of diagnosis providing symptoms had resolved (i.e. CDI episodes after 8 weeks are considered a new first

For CDI Clinical Management in Pediatrics, please refer to the BC Children's Hospital CDI Order Set and Algorithm for guidance at the Provincial Health Services Authority ePOPS website (http://policyandorders.cw.bc.ca/):

ePOPS, *Clostridium difficile* (Pediatric), Order Set
http://policyandorders.cw.bc.ca/resource-gallery/Documents/Order%20Sets/PED%20Clostridium%20Difficile%20PDC%20May%2017,%202016.pdf

Antibiotics used by C. *difficile* Infection

Metronidazole

Oral metronidazole is effective for the treatment of non-severe (mild) CDI disease. In the past, metronidazole was widely used in the treatment of CDI; however, recent observational reports and randomized clinical studies have suggested that metronidazole is not as effective and may result in more relapses than vancomycin for the treatment of CDI. Metronidazole IV is considered a second-line agent compared to vancomycin PO treatment. It may be used in fulminant disease if it is thought that vancomycin is not being delivered to the colon, but data in support of this approach are of low quality and are limited to critically ill patients. Metronidazole oral suspension is poorly received in the pediatric population due to its offensive taste.

Vancomycin

Oral vancomycin is a highly effective CDI treatment. Vancomycin is considerably more expensive than metronidazole. For patients who are unable to afford vancomycin in the outpatient setting, metronidazole should remain an option for mild disease only. Orally administered vancomycin is minimally absorbed from the gastrointestinal tract, allowing luminal drug levels to be very high. There is no evidence that doses higher than 125 mg QID are superior to the standard dosing.

Fidaxomicin

Fidaxomicin is non-inferior to vancomycin for the initial treatment of CDI and is associated with fewer relapses, but as a more costly “excluded*” drug, its role in routine practice remains to be determined. If fidaxomicin is being considered, an Infectious Diseases consultation is recommended.

* “excluded” = a drug that has been evaluated by the BCHA Pharmacy & Therapeutics Committee and has been intentionally not added to formulary. Drug can be used on a case-by-case basis.

Other Antibiotics

There are several other antibiotics with demonstrated activity against *C. difficile*, but they have only been studied in small clinical trials or case series. These agents, which include rifaximin, nitazoxanide, fusidic acid, linezolid, bacitracin and tigecycline, should only be considered in rare situations and only in consultation with a specialist expert.

Alternative Therapies

Probiotics
The available evidence does not support the routine use of probiotics for primary prevention or treatment of CDI; however, they may be considered as an adjunct to antimicrobial therapy in patients with recurrent disease. There has been no documented harm from probiotics in the general patient population; however they should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with a central line in place or to patients with bloody diarrhea or severe abdominal pain, as there have been reports of bacteremia and fungemia associated with probiotics in such settings.

Fecal Microbiota Transplantation
Fecal microbiota transplant treatments have been used for cases of recurrent CDI with success in several randomized controlled trials. This treatment still has limited availability, and eligible patients should be referred to a provider with experience in the procedure until provincial infrastructure has been established.

An expert consult is required, and all patients must provide informed consent prior to treatment.

Cholestyramine
The ability of cholestyramine to bind to the toxins produced by *C. difficile* has been found to be negligible. In addition there is potential for adverse effects because it does bind with a variety of oral medications, including vancomycin. Therefore, the use of cholestyramine and colestipol is not recommended for treatment of CDI.

Intravenous Immunoglobulin
There are no data to support the use of intravenous Immunoglobulin in the treatment of CDI.