Appendix 1: CDI Clinical Management Algorithm

SUSPECTED OR CONFIRMED CDI
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 (GI 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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MILD OR MODERATE
(Does not meet criteria for SEVERE or FULMINANT)

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FIRST 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
- **Metronidazole 500 mg PO/NG TID x 10-14 d ^**
- If not clinically improving by day 4-6, or patient intolerant to oral metronidazole **change to Vancomycin 125 mg PO/NG QID x 10-14 d ++ Δ**
- If symptoms worsen, re-evaluate for CDI severity and follow appropriate algorithm pathway

SEVERE (any of the following):
- WBC >15,000/mm3 **# OR**
- Acute kidney injury with rising serum creatinine (SCr) (e.g. SCr >1.5 times premorbid level or SCr >175 µmol/L) **OR**
- Pseudomembranous colitis **OR**
- Clinical judgment (age >60 y, fever, etc.)

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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 Δ**
- Consider ID, GI, and/or General Surgery consult
- Consider CT scan of the abdomen, if clinically indicated

FULMINANT (any of the following):
- Toxic megacolon
- Perforation
- Signs of peritonitis
- Ileus
- Severe sepsis/septic shock
- Severe acute renal failure (e.g. oliguria or dialysis requirement)

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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 * with OR without Metronidazole 500 mg IV Q8H for 10-14 d**
- **If complete ileus OR if unable to take PO/NG vancomycin, consider adding Vancomycin 500 mg via cecal tube or rectal administration ♣**
- Obtain specialist (ID, GI, and/or General Surgery) and ICU consult immediately as directed by level of care

FIRST RECURRENCE (MILD OR MODERATE)

- Confirm that episode is the 1st recurrence (not 2nd or more recurrences)
- 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
- **Metronidazole 500 mg PO/NG TID x 10-14 d ^**
- If diarrhea not resolving by Day 4-6, **change to Vancomycin 125 mg PO/NG QID x 10-14 d ***
- If symptoms worsen,
  - o Re-evaluate for CDI severity
  - o Obtain ID or GI opinion

SECOND OR FURTHER RECURRENCES

- **Vancomycin 125 mg PO/NG QID x 14 d ***, then may consider vancomycin tapering over 4 weeks (e.g. vancomycin 125 mg BID x 7 days, then 125 mg once daily x 7 days, then 125 mg every 2 or 3 days for 2 weeks)**†**
- Obtain ID or GI opinion

Footnotes for algorithm

∆	Consider testing patients for CDI if high ileostomy outputs >2 L in 24 hours.
$	For Contact (GI Plus) Precautions, please refer to: http://vchconnect.vch.ca/programs_services/infection_control/gastroenteritis_toolkit/binary_104508.pdf
^	May change to Vancomycin if patient intolerant to Metronidazole
++	Vancomycin IV is **not** effective for the treatment of CDI
#	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 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. episodes occurring after 8 weeks are considered a new first episode).

Antibiotics used by C. *difficile* Infection

Metronidazole

Oral metronidazole is effective for the treatment of mild to moderate CDI disease. In the past, metronidazole was widely used in the treatment of CDI; however, recent observational reports and some clinical studies have suggested that metronidazole may not be as effective and may not act as rapidly as vancomycin for the treatment of severe CDI. Metronidazole IV is considered a second-line agent compared to metronidazole PO and vancomycin PO treatment. Metronidazole oral suspension is poorly received in the pediatric population due to its offensive taste.

Vancomycin

Oral vancomycin is a highly effective CDI treatment for patients who cannot tolerate oral metronidazole or for those with severe disease. Vancomycin is considerably more expensive than metronidazole. Orally administered vancomycin is not well 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.

Other Antibiotics

Fidaxomicin is an "excluded agent"* that may be made available on a case-per-case basis. If fidaxomicin is being considered, an Infectious Diseases consultation is recommended. 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.

* "Excluded agent" = a drug that has been evaluated by the BCHA Pharmacy & Therapeutics Committee and has been intentionally excluded from the formulary.

Alternative Therapies

Probiotics

The available evidence does not support the routine use of probiotics for 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, except a risk to the severely immunosuppressed. They should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with a central line in place nor 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 Transplants

Fecal transplant treatments have been used for cases of recurrent CDI with success in several uncontrolled case series and individual case management reviews. This treatment is still in the investigational stage. If fecal transplant is being considered, the donor should be screened for transmissible agents. Logistic issues also need to be considered including the timing, safe collection and processing of the stool donation, preparation of the recipient, and the route of administration (e.g. enema or nasogastric tube).

An ID consult is required, and all patients must provide informed consent prior 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.