

Health PEI: Antimicrobial Stewardship Subcommittee  
*Clostridioides (Clostridium) difficile* Infection Treatment Guidelines for Adults

<p><b><i>Clostridioides difficile</i></b>  <b>“C. diff”</b></p> <p><b>Antibiotic Associated Colitis/Diarrhea</b></p>	<p style="text-align: center;">Non-SIRS / Pre-SIRS</p> <p><i>Note:</i> Definition of “Recurrence” (Relapse):  <b>Symptoms returning less than 8 weeks after stopping therapy.</b></p>	<p>SIRS / Sepsis (2 of 4)          &gt;38.3&lt;36.0; HR&gt;90;          RR&gt;20 or PaCO<sub>2</sub>&lt;32;          WBC &lt;4 &gt;12 or Bands</p>	<p>Severe Sepsis(1 of 7+)          Mottled, anuria,          Lactate&gt;2, Plt&lt;100, DIC,          ARDS, fastΔLOC...</p>	<p>Septic Shock (Pressors)          Refractory Septic Sh.          (More Pressors)</p>
<p>Vanco=vancomycin (IV is NOT effective)          Metro=metronidazole</p> <p style="text-align: center;"><u>Prevention</u></p> <ul style="list-style-type: none"> <li>Hand hygiene (soap if visibly soiled). Also applies to those caring for patients with diarrhea.</li> <li>Cleaning of shared equipment, including stethoscopes.</li> <li>Adherence to contact precautions</li> <li>Use antibiotics wisely!</li> </ul> <p style="text-align: center;"><u>Treatment Measures</u></p> <ul style="list-style-type: none"> <li><b>STOP:</b> unnecessary antibiotics, or...</li> <li><b>CHANGE:</b> to lower risk antibiotics</li> </ul> <p><u>Ordered by risk:</u>          clindamycin &gt; moxifloxacin &gt; ciprofloxacin &gt; levofloxacin &gt; carbapenems &gt; 2nd and 3rd generation cephalosporins &gt; amox-clav &gt; amox</p> <ul style="list-style-type: none"> <li><b>STOP:</b> Unnecessary proton-pump inhibitors, anti-diarrheal agents.</li> <li>Add fiber, reduce dairy</li> </ul> <p style="text-align: center;"><u>Secondary prophylaxis</u></p> <ul style="list-style-type: none"> <li>Patient with a history of <i>C. diff</i> requiring abx therapy for another indication(s) - giving prophylactic metro or vanco is <u>not routinely recommended</u>.</li> </ul>	<p style="text-align: center;"><u>Initial episode</u>          Vanco 125 mg PO QID x 10 days</p> <p style="text-align: center;"><u>1<sup>st</sup> Recurrence</u>  <u>Vanco Pulse:</u> 125 mg PO QID x 5 days,          125 mg PO BID x 3 days,          125 mg PO daily x 3 days          125 mg PO q2days x 3 doses  <b>OR</b>          Fidaxomicin 200 mg PO BID x 10 days Ⓢ</p> <p style="text-align: center;"><u>2<sup>nd</sup> Recurrence</u>  <u>Vanco Taper:</u> 125 mg PO QID x 10 days,          125 mg PO BID x 7 days,          125 mg PO daily x 7 days,          125 mg PO q2days x 2 weeks  <b>OR</b>          Fidaxomicin 200 mg PO BID x 10 days</p> <p style="text-align: center;"><u>3<sup>rd</sup> Recurrence</u>          Consult expert on use of repeat Vanco taper/pulse, Fidaxomicin standard dose or taper Ⓢ or fecal transplant.</p>	<p style="text-align: center;"><b>AND (specifically for C diff):          WBC ≥ 15 or Albumin &lt;30</b></p> <p>Vanco 125 mg PO q6h x 14 days</p> <p>(once stabilized, can switch to QID dosing)</p>	<ul style="list-style-type: none"> <li>Vancomycin 500 mg PO/NG q6h x 3 days, <b>then</b> Vancomycin 125 mg PO/NG q6h x 11 days (can continue to 2<sup>nd</sup> recurrence strategy if indicated)</li> <li><b>AND</b></li> <li>Metro 500 mg IV q8h (administer until no longer critically ill)</li> <li><b>AND</b></li> <li>Consider surgical consult</li> </ul>	<p>Investigate alternative diagnosis and:</p> <ul style="list-style-type: none"> <li>For toxic megacolon: consult surgery for possible subtotal colectomy or loop ileostomy.</li> <li>Vanco 500 mg (PO/NG) q6h</li> <li><b>AND</b></li> <li>Metro 500 mg IV Q8h</li> <li><b>AND</b></li> <li>Consult infectious disease and surgery ASAP</li> </ul> <div style="border: 1px solid black; padding: 5px; text-align: center;">             Abd flat plate to rule out toxic megacolon, repeat in 3 days if no clinical improvement         </div> <div style="border: 1px solid black; padding: 5px; text-align: center;">             If <u>presence of ileus:</u> add <b>Vanco 500 mg PR q6h</b> (500 mg in 500 mL N/S by retention enema via Foley catheter held for 3 hours)         </div>

Ⓢ = Not covered under the Provincial Formulary for this indication      Ⓢ Fidaxomicin 10 day course cost is ~ \$2000.00

# Health PEI: Antimicrobial Stewardship Subcommittee

## *Clostridioides (Clostridium) difficile* Infection Treatment Guidelines for Adults

### WHEN TO SEND A STOOL SAMPLE:

#### **Diarrhea:**

- taking the shape of the receptacle, or corresponding to Bristol stool chart types 6–7 (\*\*NOTE: formed stool typically NOT processed, unless concern for ileus.)
- greater than or equal to 3 unformed stools in 24 or fewer consecutive hours
- cannot be explained for any other reason

#### **Ensure patient is NOT receiving:**

- laxatives for the past 24-48 hours

\*\*If you have questions about whether or not to send a stool sample, please contact the Medical Microbiologist for clarification.

### TESTING:

- Do NOT test stool from asymptomatic patients.
  - C. Diff toxin positive **without current symptoms** is NOT considered C. Diff disease
  - ~10% of pts will test positive within one week of hospitalization, some studies suggest up to 50% of patients will be colonized after >4 weeks in hospital.
  - Colonization rates are ~10% in LTC.
- **Repeat testing for cure is NOT indicated.**

\*\*Stat testing is available. PCR testing in the setting of a negative screen with high clinical suspicion is also available.

### PROBIOTICS:

#### **Who are they strongly recommended for?**

- Patients taking antibiotics!
  - Especially those at risk of antibiotic associated diarrhea and *C. difficile* due to their current antibiotic regimen or their past history.
  - May be more effective with higher baseline incidence of *C. diff* (>5%) and higher risk (ie. multiple *C. diff* recurrences or taking 2 or more antibiotics).
  - Low quality or weak evidence for using probiotics as an adjunctive therapy for treating *C. diff*.

#### **Which probiotic is best?**

- No consensus in the literature on strain, strength, or dose.
- Commonly used species with individual evidence include:
  - *Lactobacillus rhamnosus GG* (most evidence)
  - *Lactobacillus casei*
  - *Lactobacillus acidophilus*
  - Kefir (\*Expert opinion, 1 cup BID-TID, avoid in diabetics)
  - *Saccharomyces boulardii*
  - Mixed strain formulations (often proprietary blends)

\*\*Pooled results of different strains still show benefit, indicating that positive effect may be seen regardless of strain.

#### **What patients should be cautioned about their use?**

- Neutropenic patients
- Patients under the age of 18 (for the purposes of these guidelines)
- Patients admitted to the ICU.

#### **How should probiotics be taken?**

- Timing:
  - Studies indicate that initiating probiotics **as close to the first dose of antibiotic therapy** as possible is most effective.
  - Separating the dose from abx dosing is **not** generally required.
- Duration of therapy – no strong consensus.
  - Options include:
    - fixed 14 day course
    - duration of antibiotic exposure
    - duration of antibiotic exposure and up to 7 days following completion
- Dose:
  - **Single strain:** some trials indicate at least 5 billion CFU (colony-forming units) per day. Others say at least 15 billion CFU.
  - **Multi-strain:** some suggestion that 50 billion CFU daily is best, depending on blend.

# Health PEI: Antimicrobial Stewardship Subcommittee

## *Clostridioides (Clostridium) difficile* Infection Treatment Guidelines for Adults

### References:

1. Perras C et al. 2011 Vancomycin or Metronidazole for Treatment of *Clostridium difficile* Infection: Clinical and Economic Analyses [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; (Technology report; no. 136).
2. Janarthanan S et al. 2012 *Clostridium difficile* -Associated Diarrhea and Proton Pump Inhibitor Therapy: A Meta-Analysis. Am J Gastroenterol **107**:1001.
3. Kwok CS et al. 2012 Risk of *Clostridium difficile* Infection with Acid Suppressing Drugs and Antibiotics: Meta-Analysis. Am J Gastroenterol **107**:1011.
4. McFarland LV et al. 2002 Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent *Clostridium difficile* Disease. Am J of Gastroenterol **97**(7):1769.
5. Johnston BC et al. 2012 Probiotics for the prevention of *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med **157**:878.
6. Zar FA et al. 2007 A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clinical Infectious Diseases **45**:302.
7. Surawicz CM et al. 2013 Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. Am J Gastroenterol **108**:478.
8. Clabots CR et al. 1992 Acquisition of *Clostridium difficile* by hospitalized patients: evidence for colonized new admissions as a source of infection. J Infect Dis **166**(3):561.
9. Loo, V., Davis, I., Embil, J., Evans, G., Hota, S., Lee, C., Lee, T., Longtin, Y., Louie, T., Moayyedi, P., Poutanen, S., Simor, A., Steiner, T., Thampi, N. and Valiquette, L. (2018). Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for *Clostridium difficile* infection. *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada*, 3(2), pp.71-92.
10. Brown, C., Manis, M., Bohm, N. and Curry, S. (2018). Oral Vancomycin for Secondary Prophylaxis of *Clostridium difficile* Infection. *Annals of Pharmacotherapy*, 53(4), pp.396-401.
11. Crook, D., Walker, A., Kean, Y., Weiss, K., Cornely, O., Miller, M., Esposito, R., Louie, T., Stoesser, N., Young, B., Angus, B., Gorbach, S. and Peto, T. (2012). Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection: Meta-analysis of Pivotal Randomized Controlled Trials. *Clinical Infectious Diseases*, 55(suppl\_2), pp.S93-S103.
12. Debast, S., Bauer, M. and Kuijper, E. (2014). European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for *Clostridium difficile* Infection. *Clinical Microbiology and Infection*, 20, pp.1-26.
13. Carignan, A., Poulin, S., Martin, P., Labbé, A., Valiquette, L., Al-Bachari, H., Montpetit, L. and Pépin, J. (2016). Efficacy of Secondary Prophylaxis With Vancomycin for Preventing Recurrent *Clostridium difficile* Infections. *American Journal of Gastroenterology*, 111(12), pp.1834-1840.
14. Crowther, G., Chilton, C., Longshaw, C., Todhunter, S., Ewin, D., Vernon, J., Karas, A. and Wilcox, M. (2016). Efficacy of vancomycin extended-dosing regimens for treatment of simulated *Clostridium difficile* infection within an in vitro human gut model. *Journal of Antimicrobial Chemotherapy*, 71(4), pp.986-991.
15. Hota, S., Sales, V., Tomlinson, G., Salpeter, M., McGeer, A., Coburn, B., Guttman, D., Low, D. and Poutanen, S. (2016). Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial. *Clinical Infectious Diseases*, 64(3), pp.265-271.
16. R Kaki, A Brooks, C Main, P Jayaratne, D Mertz. Does Extending *Clostridium Difficile* Treatment In Patients Who Are Receiving Concomitant Antibiotics Reduce The Rate Of Relapse?. The Internet Journal of Infectious Diseases. 2016 Volume 15 Number 1.
17. Murphy, M., Patatanian, E. and Gales, M. (2018). Extended duration vancomycin in recurrent *Clostridium difficile* infection: a systematic review. *Therapeutic Advances in Infectious Disease*, 5(6), pp.111-119.
18. Van Hise, N., Bryant, A., Hennessey, E., Crannage, A., Khoury, J. and Manian, F. (2016). Efficacy of Oral Vancomycin in Preventing Recurrent *Clostridium difficile* Infection in Patients Treated With Systemic Antimicrobial Agents. *Clinical Infectious Diseases*, 63(5), pp.651-653.
19. Gerding, D. (2018). Is pulsed dosing the answer to treatment of *Clostridium difficile* infection?. *The Lancet Infectious Diseases*, 18(3), pp.231-233.
20. Guery, B., Menichetti, F., Anttila, V., Adomakoh, N., Aguado, J., Bisnauthsing, K., Georgopali, A., Goldenberg, S., Karas, A., Kazeem, G., Longshaw, C., Palacios-Fabrega, J., Cornely, O. and Vehreschild, M. (2018). Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *The Lancet Infectious Diseases*, 18(3), pp.296-307.
21. Soriano, M., Danziger, L., Gerding, D. and Johnson, S. (2014). Novel Fidaxomicin Treatment Regimens for Patients With Multiple *Clostridium difficile* Infection Recurrences That Are Refractory to Standard Therapies. *Open Forum Infectious Diseases*, 1(2), pp.ofu069-ofu069.
22. Johnson, S., Louie, T., Gerding, D., Cornely, O., Chasan-Taber, S., Fitts, D., Gelone, S., Broom, C. and Davidson, D. (2014). Vancomycin, Metronidazole, or Tolevamer for *Clostridium difficile* Infection: Results From Two Multinational, Randomized, Controlled Trials. *Clinical Infectious Diseases*, 59(3), pp.345-354.
23. Stevens, V., Nelson, R., Schwab-Daugherty, E., Khader, K., Jones, M., Brown, K., Greene, T., Croft, L., Neuhauser, M., Glassman, P., Goetz, M., Samore, M. and Rubin, M. (2017). Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With *Clostridium difficile* Infection. *JAMA Internal Medicine*, 177(4), p.546.
24. Vardakas, K., Polyzos, K., Patouni, K., Rafailidis, P., Samonis, G. and Falagas, M. (2012). Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *International Journal of Antimicrobial Agents*, 40(1), pp.1-8.
25. Blaabjerg, S., Artzi, D. and Aabenhus, R. (2017). Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients—A Systematic Review and Meta-Analysis. *Antibiotics*, 6(4), p.21.
26. Cai, J., Zhao, C., Du, Y., Zhang, Y., Zhao, M. and Zhao, Q. (2017). Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. *United European Gastroenterology Journal*, 6(2), pp.169-180.
27. Johnston, B., Lytvyn, L., Lo, C., Allen, S., Wang, D., Szajewska, H., Miller, M., Ehrhardt, S., Sampalis, J., Duman, D., Pozzoni, P., Colli, A., Lönnermark, E., Selinger, C., Wong, S., Plummer, S., Hickson, M., Pancheva, R., Hirsch, S., Klarin, B., Goldenberg, J., Wang, L., Mbuagbaw, L., Foster, G., Maw, A., Sadeghirad, B., Thabane, L. and Mertz, D. (2018). Microbial Preparations (Probiotics) for the Prevention of *Clostridium difficile* Infection in Adults and Children: An Individual Patient Data Meta-analysis of 6,851 Participants. *Infection Control & Hospital Epidemiology*, 39(07), pp.771-781.
28. Shen, N., Maw, A., Tmanova, L., Pino, A., Ancy, K., Crawford, C., Simon, M. and Evans, A. (2017). Timely Use of Probiotics in Hospitalized Adults Prevents *Clostridium difficile* Infection: A Systematic Review With Meta-Regression Analysis. *Gastroenterology*, 152(8), pp.1889-1900.e9.
29. Newberry, S. (2012). Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea. *JAMA*, 307(18), p.1959.

# Health PEI: Antimicrobial Stewardship Subcommittee

## *Clostridioides (Clostridium) difficile* Infection Treatment Guidelines for Adults

30. McFarland, L. (2015). Probiotics for the Primary and Secondary Prevention of *C. difficile* Infections: A Meta-analysis and Systematic Review. *Antibiotics*, 4(2), pp.160-178.
31. CADTH (2018). *Probiotics for antibiotic-associated diarrhea and Clostridium difficile infection: a review of clinical effectiveness.* [online] CADTH. Available at: <https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC1022-Probiotics%20for%20AAD%20and%20C.pdf> [Accessed 31 May 2019].
32. Allen, S., Wareham, K., Wang, D., Bradley, C., Sewell, B., Hutchings, H., Harris, W., Dhar, A., Brown, H., Foden, A., Gravenor, M., Mack, D. and Phillips, C. (2013). A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and *Clostridium difficile* diarrhoea in older people admitted to hospital: a multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). *Health Technology Assessment*, 17(57).
33. Goldenberg, J., Yap, C., Lytvyn, L., Lo, C., Beardsley, J., Mertz, D. and Johnston, B. (2017). Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews*.
34. Bakken, J. (2014). Staggered and Tapered Antibiotic Withdrawal With Administration of Kefir for Recurrent *Clostridium difficile* Infection. *Clinical Infectious Diseases*, 59(6), pp.858-861.
35. Merenstein, D., Foster, J. and D'Amico, F. (2009). A Randomized Clinical Trial Measuring the Influence of Kefir on Antibiotic-Associated Diarrhea. *Archives of Pediatrics & Adolescent Medicine*, 163(8).
36. Lau, C. and Chamberlain, R. (2015). Sa1792 Probiotics Are Effective At Preventing *Clostridium difficile*-Associated Diarrhea in Both Adult and Pediatric Populations: A Meta-Analysis. *Gastroenterology*, 148(4), pp.S-333-S-334.

Health PEI Physician Reviewers: Dr. Greg German, Dr. Jeremy Beck, Dr. Bill Walker, Dr. Patrick McCrea, Dr. Michael Irvine, Dr. Matt Kutcher, Dr. Steve Scales.