Provincial Clinical Knowledge Topic
Clostridioides difficile (previously *Clostridium difficile*) Infection, *Adult - Inpatient*
V 1.0

Revision History

Version	Date of Revision	Description of Revision	Revised By
1.0	February 2021	Completion of CKT	

Important Information Before You Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

Guidelines

This Clinical Knowledge Topic is based on the following references:

- Association of Medical Microbiology and Infectious Disease Canada Treatment Practice Guidelines for *Clostridium difficile* infection[1]
- Cochrane Review[2]
- Canadian Agency for Drugs and Technologies in Health (CADTH)[3]
- Role of metronidazole in mild *Clostridium difficile* infections[4]
- Clinical Practice Guidelines for *Clostridium difficile* infection in Adults and Children: 2017 Update by the Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)[5]

Keywords

- Clostridium difficile infection
- Clostridioides difficile infection
- Clostridium difficile colitis
- Clostridioides difficile colitis
- Antibiotic - associated diarrhea
- C-diff
- CDI

Goals

Optimal management of CDI to reduce patient morbidity, mortality and transmission.

Decision Making Algorithms

Clostridioides (Clostridium) difficile **Infection (CDI) Management Algorithm**

Suspected CDI:
- ≥ 3 loose unformed stools (i.e. takes the shape of the container) within 24 hours, or pseudomembranous colitis suggested by imaging or endoscopy

AND
- CDI risk factors, including but not limited to:
  - Antibiotic use within 8 weeks
  - Acid suppressive therapy use within 8 weeks
  - ≥ 65 years of age
  - hospitalized

Start contact precautions. Notify IPC as per site process. Send stool sample for *C. difficile* testing

C. difficile stool test **negative** → Assess for other causes of diarrhea

C. difficile stool test **positive**

1st Episode

SEVERITY ASSESSMENT:
- WBC > 15 x 10^9/L
- Serum Creatinine > 130 umol/L

If one or more of these criteria → STANDARD THERAPY:
Vancomycin 125 mg po QID x 10 days**

If neither of these criteria → RISK ASSESSMENT:
Any of:
- Age > 65 years
- Inflammatory Bowel Disease
- Hematologic malignancy
- Neutropenia
- Serum albumin <30g/L
- Ongoing concomitant antibiotics (excluding tetracycline-containing regimens)

YES → STANDARD THERAPY

NO → MILD DISEASE/LOW RISK:
Metronidazole 500 mg po TID x 10 days**

Metronidazole allergy or intolerance:
Vancomycin 125 mg po QID x 10 days**

Clinically improving at day 3-5 of metronidazole?
- YES → Complete therapy
- NO → STANDARD THERAPY

1st Recurrence

Previous CDI therapy with metronidazole → STANDARD THERAPY:
Vancomycin 125 mg po QID x 10 days**

Oral vancomycin allergic or intolerant:
Fidaxomicin (Restricted – with guidelines)
200 mg po BID x 10 days**

Previous CDI therapy with standard oral vancomycin regimen → VANCOMYCIN TAPER:
125 mg po QID x 14 days, then

125 mg po BID x 1 week, then
(continue at this dose if referred or accepted for FMT)

125mg po daily x 1 week, then

125 mg po q2days x 4 doses, then

125mg po q3days x 4 doses

If FULMINANT CDI (hypotension or shock, ileus, megacolon)*:
- 3 views abdominal X-Ray or CT abdomen
- Add metronidazole 500 mg IV q8h x 10 days**
- If ileus, add vancomycin 500 mg PR by retention enema q6h x 10 days**
- Consider General Surgery, ID, GI and/or ICU consult.

REFER for fecal microbiota transplant (FMT) if:
- ≥ 2 episodes of CDI, both requiring hospitalization
- ≥ 3 episodes of CDI
- Edmonton Zone referrals for FMT can be sent to Dr. Dina Kao by fax 780-492-8305

Subsequent Recurrence(s)

VANCOMYCIN TAPER:
125 mg po QID x 14 days, then

125 mg po BID x 1 week, then
(continue at this dose if referred or accepted for FMT)

125mg po daily x 1 week, then

125 mg po q2days x 4 doses, then

125mg po q3days x 4 doses

If FMT is available → REFER for fecal microbiota transplant (FMT) if:
- ≥ 2 episodes of CDI, both requiring hospitalization
- ≥ 3 episodes of CDI
- Edmonton Zone referrals for FMT can be sent to Dr. Dina Kao by fax 780-492-8305

If FMT not available and inadequate response to vancomycin taper → Consider fidaxomicin (Restricted – with guidelines) 200 mg po BID x 10 days**

* Some experts advise using increased vancomycin dose (500 mg PO QID) in fulminant disease; no clinical trial evidence, however.
** Duration: 10 days is standard; extending to 14 days may be considered when there is a slow clinical response.

Textual Decision Making Information

Current guidelines (Canadian and American) were reviewed from the viewpoint of both feasibility of operationalization, as well as the evidence base behind recommendations. It is noted that there is little new data underpinning the new recommendation for oral vancomycin use in mild CDI, and both Canadian and U.S. guidelines recommend metronidazole as alternate therapy in that setting. The newest data which offers a direct comparison is from 2 multinational RCTs of metronidazole, vancomycin or tolevamer, in which the cure rates overall were 72.7% with metronidazole, and 81.1% with vancomycin (P = 0.02) but in the subgroup with mild CDI, metronidazole was not inferior to vancomycin with cure rates of 78.7% and 82.7% respectively (P=0.54).

Furthermore, patients with mild disease are often treated as outpatients (unless the CDI occurs while hospitalized for other reasons), and the price of oral vancomycin could be prohibitive to the point of not accessing therapy for some patients. In the absence of risk factors that could be associated with poor outcomes (either identified through literature review or considered robustly clinically probable), mild CDI can be effectively treated with oral metronidazole. If there is not a prompt clinical improvement, vancomycin should be used.

In addition, although there is considerable interest in probiotic use in CDI, existing literature and guideline review suggests that there is insufficient evidence to support the use of probiotics in the treatment of CDI and they are therefore not recommended. CDI prevention is outside the scope of this document.

Possible Or Proven *Clostridioides difficile* (*previously Clostridium difficile*) Infection (CDI) Adult – Inpatient Order Set

Order Set Restrictions: For adult patients with diarrhea and possible or proven *Clostridioides difficile* infection (CDI)
Order Set Keywords: Cdiff, C difficile, CDI, diarrhea

Patient Care

For patients with diarrhea:

- ☑ Initiate Contact Precautions for confirmed or suspected *C. difficile*
  Suspected CDI risk factors, including but not limited to:
  - *Antibiotic use within 8 weeks*
  - *Acid suppressive therapy use within 8 weeks*
  - *65 years of age or older*
  - *hospitalized*
- ☑ Clinical communication to nurse: Initiate stool flowsheet with Bristol Stool chart
- ☐ Clinicians:
  - ☐ assess for non-infectious causes of diarrhea, and
  - ☐ infectious causes of diarrhea other than *C. difficile* if patient does not have CDI risk factors but does have food/travel/contact risks and consider appropriate testing such as:
    - bacterial culture if diarrhea onset less than 3 days from hospital admission, or
    - gastroenteritis viral panel.

Laboratory Investigations Routine

Microbiology
C. difficile testing is NOT indicated in patients with solid/formed stool and is NOT indicated after symptom resolution or for test of cure.

- ☐ Send unformed stool for C. *difficile* test, if not already ordered or a known positive.
- ☐ If *C. difficile* stool test is positive, notify physician.
- ☐ If C. difficile stool test is negative, notify physician regarding discontinuation of CDI therapy, assessment for alternate causes of diarrhea, and to consider removal of contact precautions if warranted
- ☑ Do not repeat testing for *C. difficile* unless diarrhea resolves then recurs
  Lab will reject stool specimen if sent within 7 days of a previous stool specimen.

Laboratory Investigations Routine

Hematology

- ☑ Complete Blood Count with differential

Chemistry

- ☑ Electrolytes
- ☑ Serum creatinine

Laboratory Investigations Repeating

Hematology

☐ Complete Blood Count with differential every _____ day(s)

Chemistry

☐ Electrolytes every _____ day(s)

☐ Serum creatinine every _____ day(s)

Medications

Assess whether any medications contributing to CDI or diarrhea can be discontinued: consider antimicrobials, laxatives, stool softeners, pro-motility agents, and acid reducing drugs (proton pump inhibitors and H2 receptor blockers). Review medication list with pharmacist if possible and assess whether other medications that contribute to C. difficile disease or complicate its therapy can be discontinued (see list here). Re-evaluate need for opioids.

☑ Discontinue anti-diarrheal medications: attapulgite (Kaopectate), bismuth preparations (Pepto-Bismol), diphenoxylate-atropine (Lomotil), loperamide (Imodium).

Anti-Infective Agents

For non-severe *C. difficile* infection: WBC less than 15 x 10^9/L and serum creatinine less than 130 umol/L

☐ No therapy. (C. *difficile* test pending)

A) First episode in patients less than 65 years old, no inflammatory bowel disease, no hematologic malignancy, not neutropenic, serum albumin greater than 30 grams/L and not on concomitant antibiotics

☐ metroNIDAZOLE 500 mg PO/NG TID x 10 days. *Ten 10 days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*

OR

If NPO for oral medications

☐ metroNIDAZOLE 500mg IV every 8 hours x 10 days (Switch to PO/NG as soon as possible). *Ten days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*

OR

If metroNIDAZOLE allergy or intolerance

☐ vancomycin 125 mg PO/NG QID x 10 days. *Ten days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*

B) If failure to respond to metroNIDAZOLE in 3 to 5 days:

☐ Discontinue metroNIDAZOLE

☐ vancomycin 125 mg PO/NG QID x 10 days. *Ten days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*

C) First episode in patients 65 years or older, or with inflammatory bowel disease, hematologic malignancy, neutropenic, serum albumin less than 30 grams/L or on concomitant antibiotics

☐ vancomycin 125 mg PO/NG QID x 10 days
OR
If vancomycin allergy or intolerance
☐ fidaxomicin 200 mg PO BID x 10 days

D) Second episode if previous episode treated with metronidazole
☐ vancomycin 125 mg PO/NG QID x 10 days. *Ten days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*
OR
If vancomycin allergy or intolerance
☐ fidaxomicin 200 mg PO BID x 10 days

E) Second episode if previous episode treated with vancomycin
☐ vancomycin 125 mg PO/NG QID x 14 days, then
vancomycin 125 mg PO/NG BID x 1 week, then
vancomycin 125 mg PO/NG daily x 1 week, then
vancomycin 125 mg PO/NG every 2 days x 4 doses, then
vancomycin 125 mg PO/NG every 3 days x 4 doses
OR

IF vancomycin allergy or intolerance
☐ fidaxomicin 200 mg PO BID x 10 days

F) Third or greater episode
☐ vancomycin 125 mg PO/NG QID x 14 days, then
vancomycin 125 mg PO/NG BID x 1 week, then
vancomycin 125mg PO/NG daily x 1 week, then
vancomycin 125 mg PO/NG every 2 days x 4 doses, then
vancomycin 125 mg PO/NG every 3 days x 4 doses
OR
If vancomycin allergy or intolerance
☐ fidaxomicin 200 mg PO BID x 10 days

For severe *C. difficile* infection
One or more of the following:
- *WBC greater than 15 x 10^9/L*
- *Acute kidney injury with rise in serum creatinine to greater than 130 µmol/L*

Diagnostic Imaging
General Radiology
☐ Xray - 1 view of chest and 2 views of abdomen
OR
☐ CT abdomen

Medications
Anti-Infective Agents

☐ vancomycin 125 mg PO/NG QID x 10 days. *Ten days is standard duration; extending to 14 days may be considered when there is a slow clinical response.*

If vancomycin allergy or intolerance
☐ fidaxomicin 200 mg PO BID x 10 days

For fulminant *C. difficile* infection
One or more of the following:
- *Toxic megacolon*
- *Hypotension*
- *Shock*
- *Ileus*

Diagnostic Imaging
General Radiology
☐ Xray - 1 view of chest and 2 views of abdomen
OR
☐ CT abdomen

Medications
Anti-Infective Agents
☐ vancomycin 125 mg PO/NG QID x 10 days. *Some experts advise using increased vancomycin dose (500 mg PO QID) in fulminant disease; no clinical trial evidence however.*
AND
☐ metroNIDAZOLE 500 mg IV every 8 hours. Administer IV metroNIDAZOLE until patient is no longer critically ill (usually 5 to 7 days).

If Ileus, ADD**:**
☐ vancomycin 500 mg in 100 mL normal saline via colonic tube every 6 hours, clamped x 3 hours each, x 10 days

Consults/Referrals
Referrals

Inpatient Specialty Consults
Consider: ID, General Surgery or GI, and/or ICU
☐ Consult:_____

Consider referral for Fecal Microbiota Transplant (FMT) if:
- *2 or more episodes of CDI, both requiring hospitalization*
- *3 or more episodes of CDI*
- *Fulminant CDI – inquire if there is an investigational protocol available for CDI FMT*

☐ Referral for Fecal Microbiota Transplant (FMT)
☑ If referred for FMT, provide prescription for vancomycin 125 mg PO BID

Admission/Transfer/Discharge Planning

Considerations for Discharge/Transfer

- Can patient afford drug on discharge?
- If referred for FMT, provide prescription for vancomycin 125 mg PO BID

Analytics

Analytics – Outcome Measure #1

Name of Measure	Compliance to clinical standards of CKT i.e. Scoring tools, specific items/orders in the Possible Or Proven *Clostridioides difficile* (previously *Clostridium difficile)* Infection (CDI) Adult – Inpatient Order Set
Definition	The elements of the CKT for which it is important to measure compliance against in the order set are: • How many patients met definition of nonsevere, standard risk and of those how many received metroNIDAZOLE? • How many patients met definition of nonsevere, higher risk and of those how many received vancomycin? • How many patients met definition of severe, and of those how many received vancomycin? • How many patients met definition of fulminant, and of those how many received vancomycin PO/NG, PR, and metro IV? • How many patients had IBD, hematologic malignancy, neutropenic, serum albumin less than 30 grams/L or were on concomitant antibiotics? • How many patients received vancomycin PO and metroNIDAZOLE PO? • How many patients eligible for FMT got referred for FMT?
Rationale	Measure compliance to specified clinical standards within the CKT

Analytics – Outcome Measure #2

Name of Measure	Cost impact realized by using the clinical standards within Possible Or Proven *Clostridioides difficile* (previously *Clostridium difficile)* Infection (CDI) Adult – Inpatient Order Set
Definition	How many times vancomycin PO/NG ordered at higher than 125 mg QID?

Rationale	Show cost impact of standards implementation

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