Guideline

Paediatric Clostridium (Clostridioides) Difficile Infection – Treatment Guidelines

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Purpose

This guideline provides recommendations regarding best practice for clinicians diagnosing and treating Clostridium Difficile Infection (CDI) in children.

Scope

This guideline provides information for all Children's Health Queensland (CHQ) staff caring for children who have Clostridium Difficile Carriage and CDI.

Related documents

Procedures, Guidelines, Protocols

- CHQ-PROC-63310 Clostridium Difficile – Assessment and Infection Control
- CHQ-PROC-01036 Antimicrobial: Prescribing and Management
- CHQ Antimicrobial restrictions

Online templates

- CHQ C.GOV Individual Patient approval (IPA)– online IPA request

Guideline

Background

C. difficile, a gram-positive spore-forming anaerobic bacillus, is part of the normal bowel flora (3% in healthy adults, 16 to 35% in hospitalised patients). Asymptomatic carriage is common in young children (50 to 70% in infants) and thus detection of *C. difficile* in formed stools simply reflects carriage.

The development of *C. difficile* gastrointestinal infection results from the production of toxins (Toxins A and B) by overgrown *C. difficile* in a susceptible host. The causes are multifactorial, including altered bowel flora due to antibiotic use, gastric acid suppression, gastrostomy / jejunostomy feeding tubes, immunodeficiency, malignancy, transplantation, and possibly inflammatory bowel disease. In previous meta-analyses clindamycin, fluroquinolones and cephalosporins had the highest *C. difficile* infection (CDI) risk. However, there is a CDI association with all classes of antibiotics. Symptoms range from mild to severe diarrhoea, pseudomembranous colitis to toxic megacolon and fatal colonic perforation.

Clinical illness is rarely reported before two years of age. It is possible that neonates / infants may lack the cellular machinery to bind and process the toxins of Clostridium species.

In the setting of a high prevalence of asymptomatic carriage, detection of *C. difficile* toxin cannot be assumed to be the causative agent for diarrhoea in children before adolescence, particularly children under 2 years of age. This creates challenges in defining infection and deciding whether treatment is required in children.

Definition

C. difficile infection (CDI):

Three or more diarrhoeal stools in 24 hours; defined as stools loose enough to take the shape of a container used to sample it, not attributable to any other cause, including medicines

AND

microbiological evidence of toxin-producing *C. difficile* (positive toxin A / B assay)

OR

endoscopic evidence of pseudomembranous colitis (PMC).

In suspected cases of 'silent' CDI, such as ileus, toxic megacolon or pseudomembranous colitis without diarrhoea, other diagnostic procedures, such as colonoscopy, white blood cell (WBC) count, serum creatinine and abdominal CT scanning, may be required.

More than one test per patient may be required if the first test is negative and there is a strong clinical suspicion of CDI. Retest a second sample 24 hours later. Further tests might be necessary in light of additional clinical evidence.

ALERT

Because of the high prevalence of asymptomatic carriage of toxigenic *C. difficile* in infants, testing for CDI should never be routinely recommended for neonates or infants less or equal to 12 months of age with diarrhoea.

Antimicrobial therapy is not indicated in children with asymptomatic colonization with *C. difficile*.

Severity assessment:

Criteria for severity of *C.difficile* infection in children	Point
Diarrhoea more than 5 times a day	1
Abdominal pain and discomfort	1
White blood cell count (WBC) >15 x10^9/L	1
Raised C reactive protein (CRP)	1
Pyrexia more than 38 degrees Celsius	1
Evidence of pseudomembranous colitis on imaging or scope	2
Intensive care unit requirements	2

Score	Disease severity
1 to 2	Mild
3 to 4	Moderate
5 or more	Severe

Severe CDI:

Unusual in children, however any of the following features are suggestive:

- **Clinical**
  - Fever (more than 38.5 °C), rigors.
  - Haemodynamic instability.
  - Peritonitis or evidence of bowel perforation.
  - Ileus or toxic megacolon.
- **Laboratory**
  - WBC count more than 15 x 10^9 / L and less than 20 % neutrophils.
  - Elevated lactate level.
  - Rise in creatinine level (more than 50 % above baseline).
  - Albumin level less than 25 g/L.
- **Other investigations**

- Radiographic features of large bowel distension, bowel wall thickening, fat stranding, and/or unexplained ascites.
- Pseudomembranous colitis (colonoscopy).

Life-threatening CDI includes hypotension, partial or complete ileus or toxic megacolon, or Computed tomography (CT) evidence of severe disease such as perforation.

Treatment of CDI (see appendix 1)

Treatment: General measures

- Avoid and/or stop all anti-motility agents, opiates and proton pump inhibitors where possible / clinically indicated.
- Avoid and/or stop all non-essential antibiotic therapy where possible / clinically indicated.
- Promote the use of narrow spectrum antimicrobial agents.
- Assess hydration and manage appropriately (refer to CHQ-GDL-01025 Intravenous Fluid Guidelines – Paediatric and Neonatal).
- Perform serial clinical assessments and assess severity.

Treatment: Mild CDI (score 1 to 2)

- No antimicrobial treatment necessary.
- If symptoms don't settle within 24 hours and diarrhoea frequency or consistency increases, then suggest **Metronidazole oral** (10 mg/kg/dose three times a day; maximum 400 mg/dose) for 10 days.

Treatment: Moderate CDI (score 3 to 4)

- For non-oncology patients: **Vancomycin oral** (10 mg/kg/dose four times a day; maximum 125 mg/dose) for 10 days.
- For oncology patients: **Fidaxomicin oral** (16mg/kg/dose twice daily; maximum 200mg/dose) or **Vancomycin oral** (10 mg/kg/dose four times a day; maximum 125 mg/dose) for 10 days.

Treatment: Severe CDI (score 5 or more)

- **Fidaxomicin oral** (16mg/kg/dose twice daily; maximum 200mg/dose) or **Vancomycin oral** (10 mg/kg/dose every 6 hourly; **maximum 500 mg/dose**) for 10 days.[4]
- In severe or complicated CDI cases **not** responding to oral vancomycin or fidaxomicin, **add intravenous metronidazole** (10 mg/kg/dose every 8 hourly; maximum 500 mg/dose). Medication administration information can be found in the Paediatric Injectable Guidelines, or SHPA Australian Injectable Drugs Handbook available online via the Clinicians Knowledge Network.
- Such patients should be closely monitored, with specialist surgical input:
  - Measure blood lactate.
  - Colectomy should be considered, especially if caecal dilatation is more than 10 cm.

– Colectomy is best performed before blood lactate rises above 5 mmol/L, when survival is extremely poor.

Prevention of recurrence

Patients managed for *C. difficile* remain vulnerable to recurrence for many weeks following treatment. During this period, the following may reduce the risk of recurrence:

- Avoidance of antimicrobial treatment; if antimicrobial treatment is necessary in a high-risk patient, we suggest tailoring therapy to achieve the narrowest spectrum and shortest duration possible
- Avoidance of gastric acid suppression where possible – cease proton pump inhibitors to reduce risk of recurrence.

Response to treatment

The response to treatment of *C. difficile* disease is monitored clinically. In patients with mild to moderate disease, fever, systemic manifestations, and frequency of diarrhoea generally improve within 24 to 48 hours of initiating antibiotic therapy, but diarrhoea may not fully resolve for 4 to 5 days.

If diarrhoea persists despite 20 days treatment but the child is stable and the daily number of diarrhoeal stools has decreased, the WBC is normal, and there is no abdominal pain or distension, the persistent diarrhoea may be due to post-infective irritable bowel syndrome.

The child may be treated with an anti-motility agent such as loperamide (Dose: 0.1 to 0.2 mg/kg/dose up to three to four times a day. Maximum 2 mg/dose, maximum 8 mg/day) (instead of metronidazole or vancomycin).

The patient should be closely observed for evidence of a therapeutic response and to ensure there is no evidence of colonic dilatation.

Follow-up faecal toxin assays are not recommended because patients often remain colonized with toxin-producing strains after recovery.

Patients remain vulnerable to relapse or reinfection for up to 10 weeks following treatment for *C. difficile* infection.

ALERT

Re-testing of patients for *C. difficile* toxins is generally not helpful as colonisation may persist for some weeks.

First recurrence CDI (relapse or re-infection) (see appendix 1):

Increasing stool frequency over 2 consecutive days for which no alternative cause is identified.

OR

New signs of severe CDI after apparent improvement

Treatment first recurrence (see appendix 1):

Conservative treatment (no antibiotics) may be appropriate in mild disease.

If antibiotics are needed, repeat the same antibiotic used to treat the initial episode.

Unless the first episode was treated with metronidazole and the recurrence is severe CDI, in which case fidaxomicin or vancomycin should be used.

For subsequent recurrences (discuss with Paediatric Infectious Diseases, see appendix 1)

First line:

Fidaxomicin

- 1 month to 6 years of age: 16 mg/kg/dose (maximum 200 mg/dose) orally twice daily for 10 days
- 6 years of age and older: 200 mg/dose orally twice daily for 10 days

2nd Line: Vancomycin in a pulsed / tapering course: [8, 14]

Vancomycin

10 mg/kg/dose (maximum 125 mg/dose) orally, four times daily for 14 days,

then

10 mg/kg/dose (maximum 125 mg/dose) orally twice daily for 7 days,

then

10 mg/kg/dose (maximum 125 mg/dose) orally once daily for 7 days,

then

10 mg/kg/dose (maximum 125 mg/dose) orally every 48 hours for 7 days,

then

10 mg/kg/dose (maximum 125 mg/dose) orally every 72 hours for 14 days.

The use of intermittent antibiotic therapy is based upon a theory that relapse may be due to the presence of persistent spores that survive antibiotic therapy. Intermittent therapy may allow the spores to germinate on the days when no antibiotics are administered. Once the spores have converted to the fully functional vegetative, toxin-producing forms, they are susceptible to killing when the antibiotics are readministered.

Refractory disease after fidaxomicin or a tapered / pulsed oral vancomycin course: (discuss with Paediatric Infectious Diseases)

The optimal therapy for the third or greater CDI recurrence is unknown. There are a variety of approaches including extended dosing of fidaxomicin (16 mg/kg/dose BD (maximum 200 mg/dose) for day 1 to 5, then every other day for days 7 to 25) or taper-pulse of fidaxomicin (16 mg/kg/dose BD (maximum 200 mg/dose) for 10 days, then once per day for 7 days, then once every other day for 26 days)[14-15]. Other antimicrobial agents with activity against *C. difficile* include rifaximin**, and nitazoxanide criteria for optimal use of these drugs in children are unknown and there are concerns around rifaximin and the rapid induction of antimicrobial resistance.

ALERT

Oral vancomycin suspension, nitazoxanide, rifaximin suspension and fidaxomicin are non-LAM listed antimicrobials and require Infectious Diseases (ID) team approval on Individual Patient Approval form (CGOV IPA).

Cost considerations

10 day course of oral metronidazole costs AUD 5 to 15 (tablets vs suspension)

10 day course of oral vancomycin costs AUD 200 to 500 (capsules vs suspension)

10 day course of oral fidaxomicin costs AUD 2000 (tablets)

Alternative treatments: (discuss with Paediatric Infectious Diseases)

Probiotics

Probiotics, specifically *Saccharomyces boulardii,* may be a useful adjunct to antibiotics in non-severe *C.difficile* infection, however cases of invasive disease associated with the use of probiotics have been described. No published expert policy statements recommend the use of probiotics for either the prevention or the treatment of CDI, as the evidence is inconclusive especially in children.

Probiotics should not be used routinely or in the immunocompromised.

Passive immunotherapy

Anecdotal reports suggest possible improvement with Intravenous Immunoglobulin (IVIG) 400 mg/kg every three weeks. Use of IVIG is not recommended, though may be supported in life threatening disease.

Bezlotoxumab

Bezlotoxumab is a monoclonal antibody against toxin B. We do not recommend routine use of bezlotoxumab in recurrent paediatric CDI however, use can be considered on a case-by-case basis in consultation with Infectious Diseases [8].

Faecal Transplant (FMT)

Faecal transplantation (enteric administration of donor stool flora) is highly effective for severe, intractable infection in adults. Faecal microbiota transplants can be considered in children in consultation with Gastroenterology and Infectious Diseases.

Appendix 1: CDI definition and management

>3 unformed bowel movements in a 24-hour period; defined as stools loose enough to take the shape of the container used to sample it, not attributable to any other cause, including medicines

- *C. difficile* testing is not recommended for children ≤12 months
- For children 1-2 years of age, testing should only be done after excluding other causes of diarrhoea **AND** high clinical suspicion of CDI

- Review medication list
- Remove offending agents (laxatives, non-essential antibiotics, protein pump inhibitors)
- Assess symptoms for CDI:
  - Abdominal pain or discomfort
  - Pyrexia ≥ 38 degrees
  - Evidence of pseudomembranous colitis
  - ICU requirement for CDI
  - Other (less relevant in the oncology cohort) raised CRP, rising white cell count.

Obtain stool *C. difficile* testing

If no improvement in diarrhoea (worsening or unchanged) despite removing offending agents (as above) and suspicion of CDI is high
AND
Microbiological evidence of toxin producing *C. difficile* (positive toxin A/B)

Assess severity of CDI (see page 3):
Score 1-2 → Mild Disease; Score 3-4 → Moderate Disease; Score 5 or more → Severe Disease

For non-oncology patients:

Mild disease: No antimicrobial treatment is necessary.

- If persisting diarrhoea ≥24 hours, Metronidazole oral (10mg/kg/dose three times a day; maximum 400mg/dose) for 10 days.

Moderate disease: Vancomycin oral (10mg/kg/dose four times a day; maximum 500mg/dose) for 10 days

Severe disease: Fidaxomicin oral (16mg/kg orally twice daily, maximum 200mg/dose) **or** Vancomycin oral (10 mg/kg/dose four times a day; maximum 125 mg/dose) for 10 days.

- In severe or complicated CDI cases **not** responding to oral vancomycin, **add intravenous metronidazole** (10 mg/kg/dose every 8 hourly: maximum 500 mg/dose).

For oncology patients:

Mild disease: No antimicrobial treatment is necessary.

- If persisting diarrhoea ≥24 hours, Metronidazole oral (10mg/kg/dose three times a day; maximum 400mg/dose) for 10 days.

Moderate disease: Fidaxomicin oral (16mg/kg orally twice daily, maximum 200mg/dose twice daily) **or** Vancomycin oral (10 mg/kg/dose four times a day; maximum 125 mg/dose) for 10 days.

Severe disease: Fidaxomicin oral (16mg/kg orally twice daily, maximum 200mg/dose twice daily) **or** Vancomycin oral (10 mg/kg/dose four times a day; maximum 125 mg/dose) for 10 days.

- In severe or complicated CDI cases **not** responding to oral vancomycin, **add intravenous metronidazole** (10 mg/kg/dose every 8 hourly: maximum 500 mg/dose).

Assess response at 48-72 hours

- Clinically improving, CDI likely. Continue CDI therapy. No further stool testing recommended.
- If no improvement, consider alternative causes of diarrhoea (ie. other infectious aetiologies or GVHD).

Management of CDI recurrence

- First recurrence: if antibiotics are needed, repeat the same antibiotic used to treat the initial episode (see page 6)
- For subsequent recurrences: fidaxomicin oral **or** vancomycin pulsed/tapering course is recommended (discuss with ID, see page 6)
- Refractory disease after fidaxomicin or a tapered / pulsed oral vancomycin course (discuss with ID, see page 6-7)

Approval requirements
Oral vancomycin suspension and fidaxomicin are non-LAM listed antimicrobials and require Infectious Diseases (ID) team approval on Individual Patient Approval form (CGOV IPA).

Acronyms

AMS	Antimicrobial stewardship
CDI	Clostridium (Clostridioides) Difficile Infection
CHQ	Children's Health Queensland
CRP	C-reactive protein
CT	Computed tomography
FDA	Federal Drug Administration (USA)
FMT	Faecal microbiota transplant
ID	Infectious diseases
IMPS	Infection Management and Prevention service
IV	Intravenous
IVIG	Intravenous immunoglobulin
PMC	Pseudomembranous colitis
QCH	Queensland Children's Hospital
WBC	White blood cell count

Consultation

Key stakeholders who reviewed this version are:

- Director, Infection Management and Prevention Service, Immunology and Rheumatology (QCH)
- Paediatric Infection Management Specialists (QCH)
- Pharmacist Advanced - Antimicrobial Stewardship Pharmacist (QCH)
- CHQ Medicines Advisory Committee (endorsed 30/11/2023)

References and suggested reading

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Guideline revision and approval history

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1.0 (23/07/2013)	Infectious Diseases Consultant-Antimicrobial Stewardship (Infection Management and Prevention Service)	Medicines Advisory Committee (RCH)	General Manager Operations
2.0 (13/04/2017)	Director, Infectious diseases, Immunology and Rheumatology (LCCH)	Medicines Advisory Committee (LCCH)	Executive Director Medical Services
3.0 (11/04/2019)	Director, Infection Management and Prevention Service, Immunology and Rheumatology (QCH) Pharmacist Advanced – Antimicrobial Stewardship (QCH)	Medicines Advisory Committee (QCH)	Executive Director Clinical Services
4.0 (18/11/2021)	Director, Infection Management and Prevention Service, Immunology and Rheumatology Pharmacist Advanced – Antimicrobial Stewardship (QCH)	CHQ Medicines Advisory Committee (QCH)	Executive Director Clinical Services
5.0 07/12/2023	Paediatric Infection Specialist Pharmacist Advanced – Antimicrobial Stewardship (QCH)	CHQ Medicines Advisory Committee (QCH)	Executive Director Clinical Services

Keywords	clostridium difficile, CDI, clostridioides difficile, antibiotic treatment, paediatrics, vancomycin, metronidazole, nitazoxanide, fidaxomicin, faecal microbiota transplant, FMT, 01058, antimicrobial stewardship, AMS
Accreditation references	**National Safety and Quality Health Service Standards (1-8)** – • **Standard 3.** Preventing and Controlling Healthcare-Associated Infection • **Standard 4.** Medication Safety