Paediatric Clostridium Difficile Infection – Treatment Guidelines

**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 CHQ staff caring for children who have Clostridium Difficile Carriage and CDI.

**Related documents**

**Procedures, Guidelines, Protocols**
- CHQ Protocol: Clostridium Difficile - Patient Care
- CHQ-GDL-04700 Faecal microbiota transplant

**Guideline**

**Background**

*C. difficile*, a gram positive spore-forming anaerobic bacillus, is part of the normal bowel flora (3% in healthy adults, 16-35% in hospitalised patients). Asymptomatic carriage is common in young children (50-70% 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. Symptoms range from mild to severe diarrhoea, pseudomembranous colitis to toxic megacolon and fatal colonic perforation.

Clinical illness is rarely reported before 12 to 24 months 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 3 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.

**Severity assessment:**

<table>
<thead>
<tr>
<th>Criteria for severity of <em>C. difficile</em> infection in children</th>
<th>Point</th>
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<tbody>
<tr>
<td>Diarrhoea &gt; 5 times a day</td>
<td>1</td>
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<tr>
<td>Abdominal pain and discomfort</td>
<td>1</td>
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<tr>
<td>Rising WBC count</td>
<td>1</td>
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<tr>
<td>Raised C reactive protein</td>
<td>1</td>
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<tr>
<td>Pyrexia &gt; 380°C</td>
<td>1</td>
</tr>
<tr>
<td>Evidence of pseudomembranous colitis</td>
<td>2</td>
</tr>
<tr>
<td>Intensive care unit requirements</td>
<td>2</td>
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</tbody>
</table>

**Score:**

1 - 2 = mild disease

3 - 4 = moderate disease

> 5 = severe disease
Severe CDI:
Unusual in children, however any of the following features are suggestive:

Clinical
- Fever (>38.5°C), rigors
- Haemodynamic instability
- Peritonitis or evidence of bowel perforation
- Ileus or toxic megacolon

Laboratory
- WBC count >15x10⁹/L and < 20% neutrophils
- Elevated lactate level
- Rise in creatinine level (> 50% above baseline)
- Albumin level <25g/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 CT evidence of severe disease such as perforation.

Treatment of CDI

General measures
1. Assess hydration and manage appropriately (refer to CHQ Paediatric intravenous fluid guideline)
2. Avoid and/or stop therapy with antibiotics, antiperistaltic agents, opiates and H2 antagonists and proton pump inhibitors where possible/clinically indicated.
3. Promote the use of narrow spectrum antimicrobial agents
4. Stop therapy with other antibiotics if possible; if not, a prolonged course of treatment for CDI may be required
5. Perform serial clinical assessments and assess severity
Treatment: Mild CDI (score 1-2)
- No need to treat if symptoms settle within 24 hours and diarrhoea frequency or consistency decreases.
- **Metronidazole oral** (30 mg/kg/day in 3 divided doses; maximum 2 g/day) for 10-14 days.

Treatment: Mild and moderate CDI (score 3-4)
- **Metronidazole oral** (30 mg/kg/day in 3 divided doses; maximum 2 g/day) for 10-14 days.
- For patients who fail to respond to initial therapy after 3 days, switching to oral vancomycin should be considered. **Vancomycin oral** (20 mg/kg/day in 4 divided doses; Max 125mg/dose) for 10-14 days.

Treatment: Severe CDI (score >= 5)
- **Vancomycin oral** (40 mg/kg/day in 4 divided doses; Max 500mg/dose) for 10-14 days. (Vancomycin serum trough levels should be monitored if max dose of 40mg/kg/day orally is given.)
- In severe or complicated CDI cases **not** responding to oral vancomycin, **add intravenous metronidazole** (30 mg/kg/day in 3 divided doses; maximum 2 g/day).
- Such patients should be closely monitored, with specialist surgical input:
  - Measure blood lactate
  - Colectomy should be considered, especially if caecal dilatation is >10 cm
  - Colectomy is best performed before blood lactate rises >5 mmol/L, when survival is extremely poor.

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 four to five 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 0.2mg/kg/dose up to 3 to 4 times a day. Max 2mg/dose, max 8mg/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.
**First recurrence CDI: (relapse or re-infection)**

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

OR

New signs of severe CDI after apparent improvement

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**ALERT**

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

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**Treatment first recurrence**

Conservative treatment 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 vancomycin should be used.

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**For subsequent recurrences: (discuss with Paediatric Infectious Diseases)**

**Vancomycin in a pulsed/tapering course**:9,12:

**Vancomycin** 5mg/kg/dose (Max 125mg/dose) orally, four times daily for 14 days, then

5mg/kg/dose (Max 125mg/dose) orally twice daily for 7 days, then

5mg/kg/dose (Max 125mg/dose) orally once daily for 7 days, then

5mg/kg/dose (Max 125mg/dose) orally every second day 7 days, then

5mg/kg/dose (Max 125mg/dose) orally every 3 days 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.
Recurrences after a tapered/pulsed oral vancomycin course: (discuss with Paediatric Infectious Diseases)

Vancomycin oral for 2 weeks followed by Nitazoxanide for 2 weeks

(Nitazoxanide dose: 1-3 years of age: 100mg bd for 3 days, 4 - 11 years of age: 200mg bd for 3 days, >12 years of age: 500mg bd).

Other antimicrobial agents with activity against C. difficile include rifaximin, and fidaxomicin (FDA approved for treatment of CDI in adults in 2011); criteria for optimal use of these drugs in children are unknown and there are concerns around rifaximin and the rapid induction of antimicrobial resistance.

**Note:** Nitazoxanide and Rifaximin are not commercially available in Australia (only available via Special Access Scheme and on approval of ID).

Fidaxomicin (discuss with Paediatric Infectious Diseases)

Fidaxomicin is a macrocyclic antibiotic that is approved for the treatment of C. difficile infection in persons ≥18 years of age and now available in Australia. In randomized trials in adults, the efficacy of fidaxomicin was similar to vancomycin, but the risk of relapse was reduced. A preliminary study in children suggests that it is safe with little gastrointestinal absorption. A randomized trial comparing fidaxomicin and oral vancomycin in children with C. difficile infection is underway.

Adult dose: 200 mg orally twice daily for 10 days.

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.

Faecal Transplant

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.

**ALERT**

Oral vancomycin, nitazoxanide and fidaxomicin are restricted antibiotics and require ID approval
Consultation

Key stakeholders who reviewed this version are:

- Director, Infectious diseases, Immunology and Rheumatology (LCCH)
- Paediatric infection management specialist (LCCH)
- Gastroenterology Consultant team (LCCH)
- Infection Control CNC (LCCH)
- Antimicrobial Stewardship Pharmacist (LCCH)

References and suggested reading

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3. HPA and Dept Health UK. Clostridium difficile infection: How to deal with the problem. Dec 2008 [online], Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1232006607827
4. Cohen S et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) infection control and hospital epidemiology may 2010, vol. 31, no. 5
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6. AAP COMMITTEE ON INFECTIOUS DISEASES. Clostridium difficile Infection in Infants and Children. Pediatrics 2013;131:196-200
9. Up to date®: C. difficile in children: treatment and prevention
10. Up to date®: C. difficile in adults: treatment
## Guideline revision and approval history

<table>
<thead>
<tr>
<th>Version No.</th>
<th>Modified by</th>
<th>Amendments authorised by</th>
<th>Approved by</th>
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</tbody>
</table>

### Keywords
- clostridium difficile, CDI, antibiotic treatment, paediatrics, vancomycin, metronidazole, nitazoxanide, faecal transplant, FMT, 01058

### Accreditation references
- EQuIP National Standards: 3, 4, 1