RUH Information for Clinicians

Microbiology Department

Guideline for the Treatment of Patients with *Clostridium Difficile* Infection (CDI)

Clinicians may find the following pneumonic (SIGHT) helpful when managing potentially infectious diarrhoea

S	**Suspect** that a case may be infective where there is no clear alternative for the diarrhoea
I	**Isolate** the patient & consult with the Infection Control team whilst determining the cause of the diarrhoea
G	**Gloves and aprons** must be used for all contacts with the patient and their environment
H	**Hand washing** with soap and water should be carried out before and after each contact with the patient and their environment
T	**Test** the stool for toxin by sending a specimen immediately

Presentation and clinical findings

Symptoms of CDI include: diarrhoea (types 5-6 on Bristol Stool Chart) +/- blood
fever
abdominal pain and distension

The patient may have a neutrophil leukocytosis and a raised CRP

Recurrences occurs in ~ 20% of patients after the 1st episode and in 50-60% of patients after a second episode and beyond

Investigations

If you suspect that a patient has CDI

- **Send a stool sample** (fill sample pot half full) for *C.difficile* toxin testing ASAP
    - If 1st test negative but there is strong clinical suspicion of CDI, discuss with Infection Control Team
    - Microscopy, culture and sensitivity (MC&S) for other bacterial pathogens **may** also be indicated & can be requested on the same sample. Samples from patients who have been in hospital for ≥72 hrs will not be processed with MC&S unless certain criteria are fulfilled e.g. outbreak scenario, immunocompromise, or onset prior to 72hrs of admission

- Stools will NOT be tested for *C.difficile* toxin within 28 days of the last positive result or if the stool is formed

Other diagnostic procedures may be required in patients with suspected "silent" CDI e.g. abdominal imaging, colonoscopy +/- biopsy.

Interpretation and guidance for C difficile results using multi-stage testing

GDH EIA	*C.difficile* toxin EIA	Report	Interpretation	Actions required
Negative	Not Done	*C.difficile* GDH Assay - Negative *Do not send repeat samples but If symptoms/ clinical condition change and CDI remains likely then repeat sample after 3 days*	CDI excluded.	No further samples required. Patient can be moved from isolation if norovirus PCR negative and other causes of infectious diarrhoea is ruled out. Consider alternative causes for symptoms. If symptoms/ clinical condition change and CDI remains likely then repeat sample after 3 days.
Positive	Positive	*C.difficile* GDH Assay - Positive *C.difficile* Toxin Assay - POSITIVE *Toxigenic C.difficile POSITIVE - no further testing required*	CDI confirmed	Maintain patient isolation and infection control measures. Assess severity of CDI, and initiate treatment in accordance with the Trust guidelines. No further testing required
Positive	Negative	*C.difficile* GDH Assay - Positive *C.difficile* Toxin Assay - Negative *C.difficile positive but toxin NOT detected* *This may represent colonisation, rather than CDI but infection control measures should be maintained whilst patient symptomatic*	A strain of *C.difficile* has been detected but there is no detectable toxin. This may represent colonisation, rather than CDI. This organism may carry the toxin gene and start toxin production.	A risk assessment for the possibility of CDI is required. Patients should remain isolated whilst symptomatic, and infection control measures maintained. If unexplained symptoms persist for more than 48 hours then repeat sample. If antibiotics are required for an inter-current infection then discuss with microbiology

Management: Infection Control

- **Isolate** in a side room with en suite facilities or dedicated commode ASAP. Please refer to RUH Infection Control Guidance on *C.difficile* & Isolation Policy. Once stool is formed for 48 hours patients may return to the general ward providing their hand hygiene is good, and with awareness of the risk of relapse

- **Minimise transfer and movement of patients** without compromising their care. Patients should be "last on the list" for investigations whenever possible. The receiving area must be pre-notified of the patient's status and arrangements put in place to minimise the risk to other patients and ensure appropriate cleaning as per infection control guidelines

- **Gloves and aprons** must be used for *all* contact with the patient *&* their environment

- **Wash hands** with **soap & water BEFORE & AFTER every contact** with the patient *&* their environment and after removal of gloves. Alcohol gel is INEFFECTIVE against *C.difficile*

Management: Antibiotics and other Medication

- **Stop antibiotic therapy** for other infections wherever possible; symptoms resolve within 48-72hrs of stopping the offending antibiotic in approximately 25% of cases

- If antibiotics are required, **review** need on a daily basis and consider rationalisation to narrower spectrum, iv to oral therapy or substitution with less *"C. diffogenic"* agents. 2nd and 3rd generation cephalosporins, quinolones and clindamycin have been especially implicated in inducing CDI

- **Avoid** antimotility drugs which may precipitate toxic megacolon. These may be considered in exceptional circumstances of persistent diarrhoea

- **Stop / Review** the need for proton pump inhibitors (PPIs) & H_2 receptor antagonists which may increase the risk of CDI

Management: General Aspects

- **Supportive Therapy** e.g. IV fluids, correct electrolyte imbalance. Review fluid balance & stool chart regularly.

- **Optimise other medical conditions & nutrition** including care of pressure areas

- **Consider other causes for diarrhoea** eg drugs, lactose intolerance, overflow diarrhoea, underlying malignancy etc.

- **Observe closely** for evidence of worsening condition e.g. falling albumin, increasing inflammatory markers, worsening renal function, rising lactate, toxic megacolon

- **Consider surgical or other expert opinion** e.g. in caecal dilatation. Outcome of surgery is much better if performed **before** the serum lactate rises to ≥5 mmol/l

- **Assess severity** using the chart below **at least once/day** and use this to determine management (NB not all the features need to be fulfilled for each classification)

Disease Severity	Stools/ day	Bristol Stool Type (p10)	Inflammatory/ Biochemical Markers	Vital signs	Other Features
Mild	<3/day	5-7	Normal		
Moderate	3-5/day	5-7	WCC↑ but <15x10^9/l CRP≤150		
Severe	Unreliable indicator		WCC ≥15x10^9/l CRP>150 ↑ in creatinine to >50% above baseline, lactate 2.2-4.9mol/l, falling albumin	Temp >38.5°C	Severe colitis (clinical or radiological signs)
Complicated or Life-Threatening	Unreliable indicator		Neutropenia Lactate >5mmol/l	↓BP/ other signs of sepsis	Partial or complete ileus, ulceration, perforation, toxic megacolon (>10cm dilation)

Management: specific CDI therapy

- Follow the treatment algorithms attached to this document (Algorithm 1: 1st episode CDI, Algorithm 2: Recurrent CDI)

- Specific therapy is warranted even in the absence of a positive stool result where there is a high suspicion of *C. difficile* in cases classified as having severe, complicated or life-threatening disease, or in mild to moderate cases where diarrhoea persists after stopping antibiotics or antibiotics cannot be stopped

- Do not treat asymptomatic patients

- Vancomycin levels are not indicated for a patient treated with oral vancomycin as oral vancomycin is not absorbed systemically

- Administration

    - Oral vancomycin should be reconstituted as per iv therapy and then diluted in 30mls of water and administered po or NG. Flavouring or fruit squash may be used to improve the taste
    - If NG route used, clamp NG tube for 1 hour
    - Retention enema - administer 500 mg of Vancomycin in 100-500ml saline 4-12hrly via an 18 gauge Foley catheter with a 30mL balloon inserted per rectum. Instil vancomycin, clamp catheter for 60 minutes then deflate & remove. *(*Apisamthanarak et al *Clin Infect Dis 2002; 35:690-6)*

- If symptoms are not improving after 7 days, go to next line of therapy appropriate for the severity. If symptoms are worsening, adjust treatment according to the severity level. Diarrhoea should resolve within 1-2 weeks of commencing each stage of therapy

1st Line therapy

Mild CDI

- Stopping antibiotic therapy alone may be adequate "treatment"

Mild to Moderate CDI

- Metronidazole 400mg PO/NG tds (or 500mg IV tds if PO and NG routes contraindicated) for 10-14 days

- If Metronidazole contraindicated e.g. pregnancy:
  Vancomycin 125 mg PO/ NG qds for 10 -14 days

Severe CDI

- Vancomycin 125 mg PO/ NG qds for 10 -14 days +/- Metronidazole 500 mg IV tds for10-14 days and consider Vancomycin retention enema for 10-14 days

- If high risk of recurrence e.g. elderly with multiple comorbidities receiving concomitant antibiotics, consider Fidaxomicin 200mg bd PO for 10 days (**discuss with Microbiologist**)

Complicated or Life-threatening CDI

- Refer to appropriate specialist e.g. surgeon, gastroenterologist, ITU, Microbiologist.
- Monitor closely and check lactate. If megacolon, perforation or septic shock are present, colectomy may be required and should ideally be performed before the lactate > 5mmol/l
- Provided degree of ileus allows give:
  Vancomycin 500 mg PO/NG qds **plus** Metronidazole 500 mg IV tds for10-14 days
  and consider Vancomycin retention enema for 10-14 days

2nd Line therapy

Mild to Moderate CDI

If 1st line treatment was metronidazole change to:

- Vancomycin 125mg PO/ NG qds for 10-14 days

If 1st line treatment was vancomycin and metronidazole is not contraindicated:

- Metronidazole 400mg PO/NG tds plus Vancomycin 125mg PO/NG qds for10-14 days

Alternatively:

- Consider Fidaxomicin 200mg PO bd for 10 days - **discuss with Microbiologist**

Severe CDI

Refer to appropriate specialist e.g. surgeon, gastroenterologist, ITU, Microbiologist and:

- Vancomycin 125mg PO/ NG qds for 10-14 days

If previous Vancomycin with no response:

- Vancomycin 500 mg PO/NG qds plus Metronidazole 500mg IV tds for 10-14 days and consider Vancomycin retention enema for 10-14 days

Alternatively:

- Consider Fidaxomicin 200mg PO bd for 10 days – **discuss with Microbiologist**

Persistent Diarrhoea despite 20 days treatment

If diarrhoea persists despite 20 days of treatment but:

- the patient is stable
- the daily number of loose stools has decreased
- the WCC is normal
- there is no abdominal pain or distension

The diarrhoea may be due to non-specific post-infectious causes and an anti-motility agent such as loperamide 2 mg prn MAY be tried. If so, the patient MUST be closely observed for evidence of a therapeutic response and to ensure that there is no evidence of colonic dilatation. Sigmoidoscopy/ gastroenterology referral may be appropriate to exclude alternative diagnoses.

Recurrent CDI

Recurrent CDI occurs in about 20% of patients treated with Metronidazole or Vancomycin

Especially if evidence of malnutrition or wasting**:**

- Review all antibiotic & other drug therapy. Consider stopping PPIs unless required acutely
- Consider Vancomycin 125mg PO/NG qds plus Metronidazole 500mg IV tds for 10-14 days if not already used
- Consider Immunoglobulin 400mg/kg iv stat especially if worsening albumin status (J. Antimicrobial Chemotherapy 2004: 53: 882-4)
- Consider Fidaxamicin 200mg PO bd for 10-14 days if not already received – **discuss with Microbiologist**

- Consider a 6 week tapering dose of Vancomycin (McFarland et al. *Am. J. Gastro* 2002; 97: 1769-75):

  Vancomycin 125mg PO qds for days 1-7
  Vancomycin 125mg PO tds for days 8-14
  Vancomycin 125mg PO bd for days 15-21
  Vancomycin 125mg PO od for days 22-28
  Vancomycin 125mg PO on alternate days for days 29-35
  Vancomycin 125mg PO once every 3 days for days 36-42

There is insufficient evidence for the routine use of:

- Probiotics
- Anion exchange resins eg cholestyramine
- Treatment of non-toxigenic *Clostridium difficile*
- Fucidic acid
- Rifaximin

Related documents

- *Clostridium Difficile* Policy (Infection Control)
- Vomiting and/ or Diarrhoea, Management of Outbreaks of Viral D & V

Reference sources

Clostridium difficile infection: How to deal with the problem. Department of Health January 2009

Updated Guidance on the management and treatment of *Clostridium difficile* infection. Public Health England. May 2013

Clostridium difficile infection: Fidaxomicin. NICE Evidence summary: new medicine. July 2012.

Algorithm 1. 1st episode of *Clostridium difficile* infection (CDI)

Diarrhoea AND one of the following:
Positive *C. difficile* toxin test OR Results of *C. difficile* toxin test pending AND clinical suspicion of CDI

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If clinically appropriate discontinue non-*C. difficile* antibiotics to allow normal intestinal flora to be re-established
Suspected cases must be isolated

▼

Symptoms/signs: not severe CDI
(None of: WCC >15, acute rising creatinine and/or colitis)

Oral metronidazole
400mg 8-hourly 10-14 days

▼

DAILY ASSESSMENT

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Symptoms improving
Diarrhoea should resolve in 1-2 weeks
Recurrence occurs in ~20% after 1st episode; 50-60% after 2nd episode

Symptoms not improving or worsening
Should not normally be deemed a treatment failure until until day 7 of treatment.
However, if evidence of severe CDI:
WCC >15, acute rising creatinine and/or signs/symptoms of colitis

▼

Switch to oral vancomycin 125 mg 6-hourly 10-14 days

Antimotility agents should not be prescribed in acute CDI

Symptoms/signs: severe CDI
WCC >15, acute rising creatinine and/or colitis
Oral vancomycin 125 mg 6-hourly 10-14 days.
Consider oral fidaxomicin 200 mg 12-hourly 10-14 days in patients with multiple co-morbidities who are receiving concomitant antibiotics

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DAILY ASSESSMENT

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Symptoms not improving or worsening
Should not normally be deemed a treatment failure until day 7 of treatment.
However, if evidence of severe CDI continues or worsens

Surgery/GI/Micro/ID consultation

AND, depending on degree of ileus/prior treatment
EITHER Vancomycin 125-500 mg PO/NG 6-hourly +/- Metronidazole 500 mg IV 8-hourly x 10 days
OR Fidaxomicin 200 mg PO 12-hourly
PLUS CONSIDER Intracolonic vancomycin (500 mg in 100–500 ml saline 4–12-hourly) given as retention enema: 18 gauge Foley catheter with 30 ml balloon inserted per rectum; vancomycin instilled; catheter clamped for 60 minutes; deflate and remove (Apisarnthanarak *et al.*, 2002)

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Further Surgery/GI/Micro/ID consultation
Depending on choice of therapy (see above) consider:
1. High dose oral/NG vancomycin (500mg PO 6-hourly)
2. IV Immunoglobulin 400mg/kg 1 dose, consider repeat

Algorithm 2 Recurrent *Clostridium difficile* infection (CDI)

Recurrent CDI occurs in ~15-30% of patients treated with metronidazole or vancomycin

Recurrence of diarrhoea (at least 3 consecutive type 5-7 stools) within ~30 days of a previous CDI episode AND positive *C. difficile* toxin test

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Must discontinue non- *C. difficile* antibiotics if at all possible to allow normal intestinal flora to be re-established
Review all drugs with gastrointestinal activity or side effects (stop PPIs unless required acutely)
Suspected cases must be isolated

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Symptoms/signs: not life-threatening CDI
Oral fidaxomicin 200 mg 12-hourly for 10-14 days
(efficacy of fidaxomicin in patients with multiple recurrences is unclear)
Depending on local cost-effectiveness decision making, Oral vancomycin 125 mg 6-hourly 10-14 days is an alternative

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Daily Assessment
(include review of severity markers, fluid/electrolytes)

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Symptoms improving

Diarrhoea should resolve in 1-2 weeks

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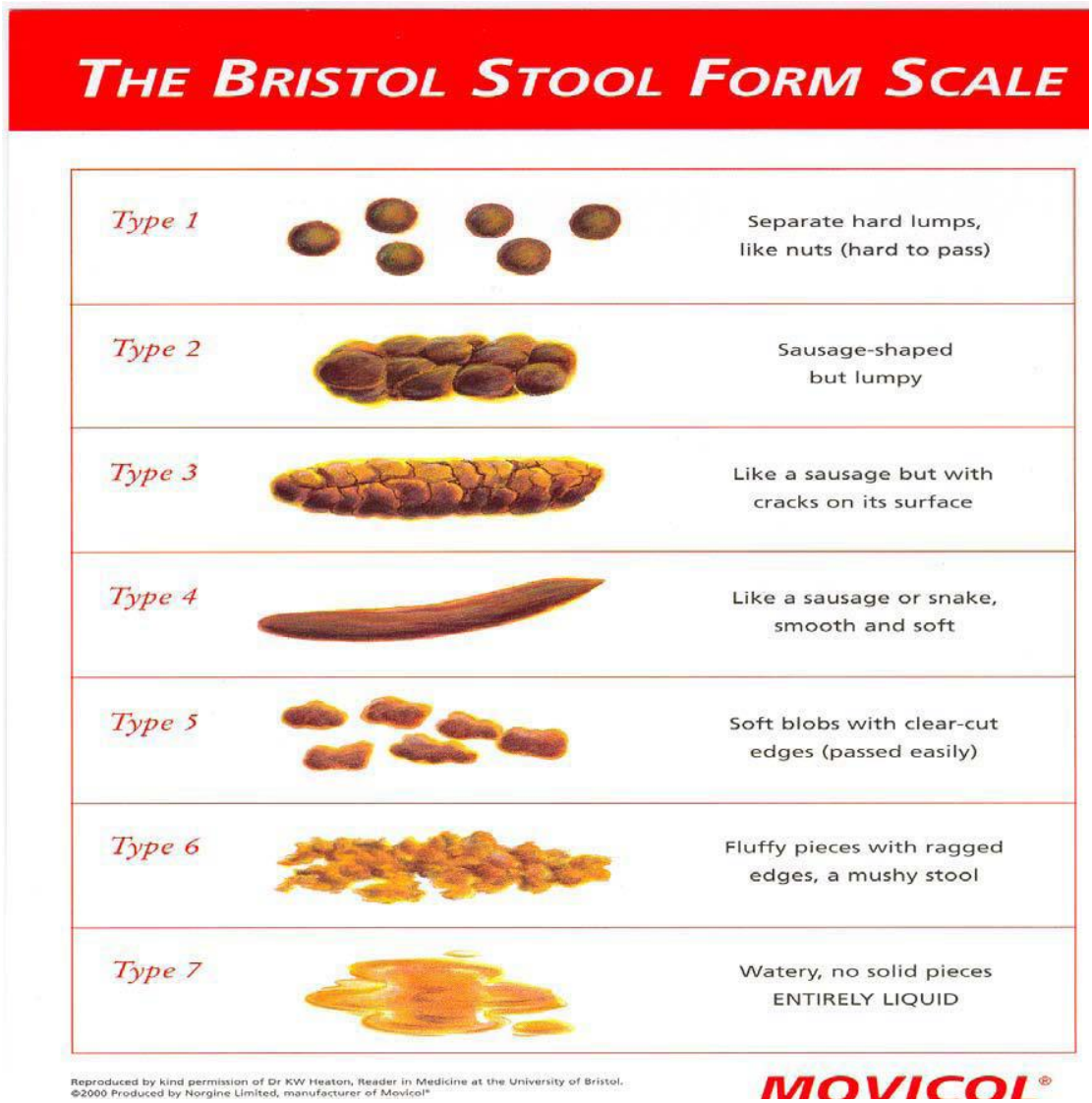
IF MULTIPLE RECURRENCES ESPECIALLY IF EVIDENCE OF MALNUTRITION, WASTING, etc.

1. **Review ALL antibiotic and other drug therapy (consider stopping PPIs and/or other GI active drugs)**
2. **Consider supervised trial of anti-motility agents alone (no abdominal symptoms or signs of severe CDI)**

Also consider on discussion with microbiology:

3. **Fidaxomicin (if not received previously) 200 mg 12-hourly for 10-14 days**
4. **Vancomycin tapering/pulse therapy (4-6 week regimen)** (*Am J Gastroenterol 2002;97:1769-75*)
5. **IV immunoglobulin, especially if worsening albumin status** (*J Antimicrob Chemother 2004:53:882-4*)
6. **Donor stool transplant** (*Clin Infect Dis 2011;53:994-1002.Van Nood et al., NEJM 2013*)

Appendix 1: The Bristol Stool Chart



Document Control Information

Consultation Schedule

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Name and Title of Individual	Date Consulted
Dr Rachel Mayer. Consultant Microbiologist	July 2013
Dr Mohammed Abrishami. Consultant Microbiologist	July 2013
Yvonne Pritchard. Senior Infection Control Nurse	July 2013
Dr Mark Mallett. Consultant Physician in Acute Medicine	July 2013
Dr Jonathan Quinlan. Consultant Gastroenterologist	July 2013

The following people have submitted responses to the consultation process:

Name and Title of Individual	Date Responded

Name of Committee/s (if applicable)	Date of Committee

Ratification Assurance Statement

Dear _____

Please review the following information to support the ratification of the below named document.

Name of Guideline: _____

Name of author: _____

Job Title: _____

I, the above named author, confirm that:

- The Guideline presented for ratification describes best practise known to me at the time of the development of the guideline.
- I will bring to the attention of my clinical director or line manger any information which may affect the validity of this Guideline as soon as this becomes known to me;
- I have undertaken appropriate consultation on this Guideline and have considered all responses.
- I acknowledge that the policy will be kept under review, and that I may be asked to refine the guideline. If no interim changes are required it will then be formally reviewed on its documented review date.

Signature of Author: _____ **Date:** _____

Name of Person Ratifying this Guideline: _____

Job Title: _____

Signature: _____ **Date:** _____

To the person approving this Guideline:

Please ensure this page has been completed correctly, then print, sign and **post this page only** to: The Policy Coordinator, John Apley Building.

The **whole guideline** must be sent electronically to: ruh-tr.policies@nhs.net