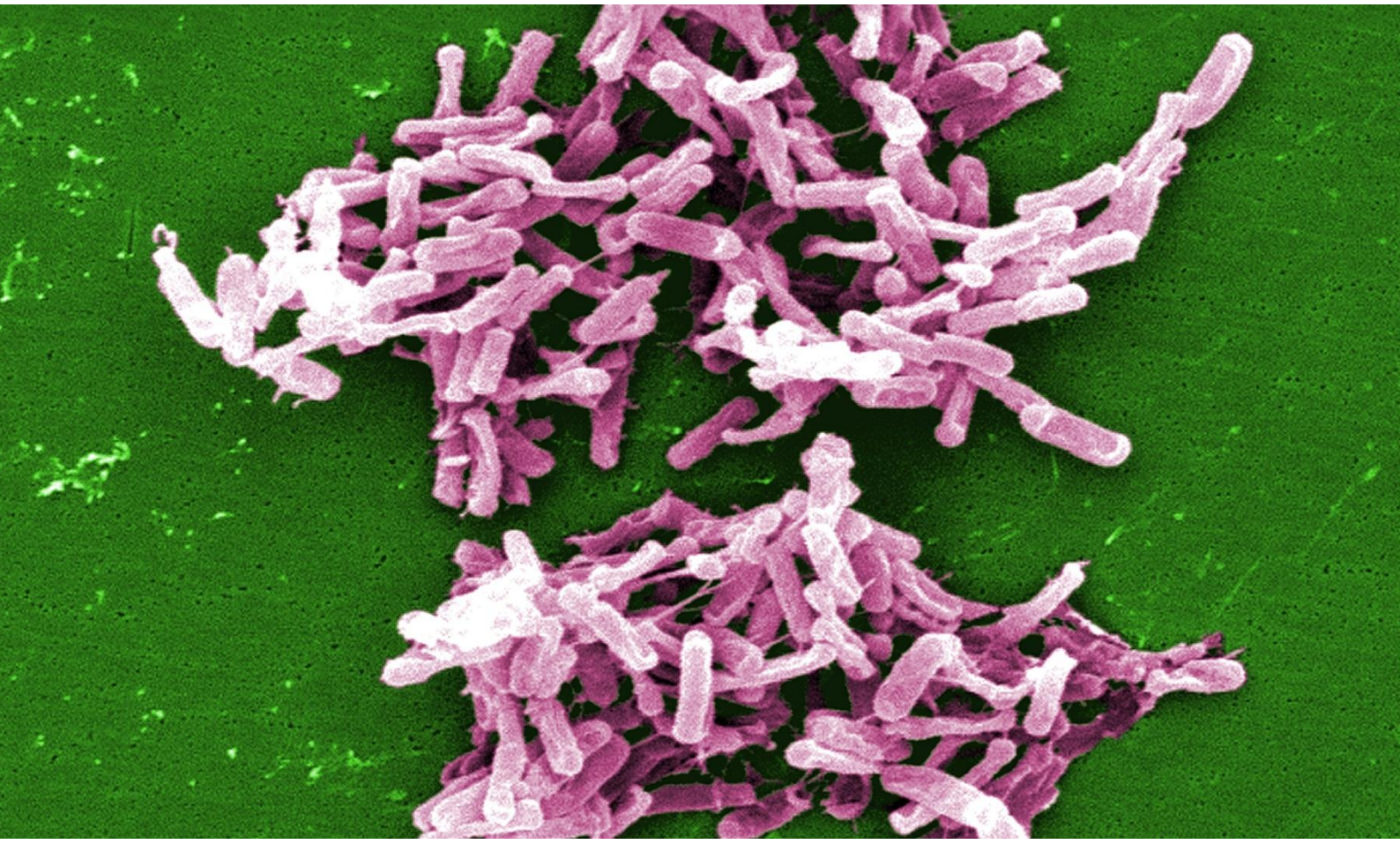
Public Health England

Updated guidance on the management and treatment of *Clostridium difficile* infection



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Contents

Executive summary

Clostridium difficile infection (CDI) is associated with considerable morbidity and risk of mortality. Ensuring the optimal treatment of CDI is important given the multiple options that have been described for potential patient management. There is evidence to support some interventions in preference to others, according to patient and infection types, including the severity of CDI. Crucially, the management of CDI should be reviewed regularly, preferably by a multidisciplinary team, to ensure that patients, who typically have multiple co-morbidities, receive optimised care.

The following chapter from '*Clostridium difficile* infection – How to Deal with the Problem' (published in December 2008) has been revised in line with new evidence. This treatment/management guidance replaces the previous version. The new guidance was agreed by a small sub-group (Appendix 2) and endorsed by Public Health England's Healthcare Associated Infection, Antimicrobial Resistance and Stewardship (HCAI & AMRS) Programme Board.

Management and treatment of CDI

1. Evidence base

1.1 Previous high profile reports have been critical of the general standard of care of CDI patients, including lack of regular review and lack of multidisciplinary assessment of patients prone to electrolyte imbalance, dehydration, malnutrition and pressure sores (Healthcare Commission, 2007b).

1.2 Supportive care should be given, including attention to hydration, electrolytes and nutrition. Antiperistaltic agents should be avoided in acute infection. This is because of the theoretical risk of precipitating toxic megacolon by slowing the clearance of *C. difficile* toxin from the intestine (Novak *et al.,* 1976; Poutanen and Simor, 2004; Aslam *et al.,* 2005; Bouza *et al.,* 2005). The precipitating antibiotic should be stopped wherever possible; agents with less risk of inducing CDI can be substituted if an underlying infection still requires treatment.

1.3 There is increasing evidence that acid-suppressing medications, in particular proton pump inhibitors (PPIs) may be a risk factor for CDI (Dial *et al.,* 2005 & 2006; Howell *et al.,* 2010; Janarthanan *et al.,* 2012). Notably, Howell *et al.,* (2010) reported a correlation between the degree of acid suppression and risk of CDI (i.e. a 'dose response' effect), which ranged from none (Odds Ratio 1), to H_2 receptor antagonists (OR 1.53, 95% CI 1.12-2.10) to once daily PPI (OR 1.74, 1.39-2.18) to more frequent PPI (OR 2.36, 1.79-3.11). It remains possible that these associations are confounded by other CDI risk factors (Cohen *et al.,* 2010). However, given that acid suppression drugs, especially PPIs, may be over-prescribed and frequently not reviewed to determine if long-standing prescriptions are still justifiable, consideration should be given to stopping/reviewing the need for PPIs in patients with or at high risk of CDI.

1.4 Until recently there were only two main alternatives (metronidazole or vancomycin) for the treatment of CDI (Cohen *et al.,* 2010). Oral fidaxomicin was approved for the treatment of CDI in Europe in 2012 (Johnson & Wilcox, 2012; Wilcox, 2012), and has been reviewed by the National Institute for Clinical Excellence (NICE; the information published by NICE is not formal guidance) and the Scottish Medicines Consortium (SMC). Two, phase 3, multi-centred, randomised, double-blind trials had almost identical designs and compared oral fidaxomicin (dose: 200 mg bd for 10–14 days) with oral vancomycin (dose: 125 mg qds for 10–14 days) (Louie *et al.,* 2011; Cornely *et al.,* 2012). The studies had essentially similar results. Fidaxomicin was non-inferior to vancomycin in the initial clinical cure of CDI (relative risk (RR) 0.88 (95% CI 0.64, 1.19), p=0.396), but was superior in reducing

recurrence (RR 0.54 (95% CI 0.42, 0.71), p<0.001) and sustained clinical cure (RR 0.68 (95% CI 0.56, 0.81), p<0.001) (all modified intention to treat analysis of combined study results) (Crook *et al.,* 2012). The side-effect profile of fidaxomicin appears similar to that of oral vancomycin. The acquisition cost of fidaxomicin is considerably higher than vancomycin (which is more expensive than metronidazole).

1.5 A systematic review published in 2011 concluded that no antimicrobial agent is clearly superior for the initial cure of CDI, but that recurrence is less frequent with fidaxomicin than with vancomycin (Drekonja *et al.,* 2011). SMC concluded that fidaxomicin is appropriate for the treatment of adults with a first episode of CDI recurrence, on the advice of local microbiologists or specialists in infectious diseases (SMC, 2012). NICE reviewed the strengths and weaknesses of the relevant evidence regarding fidaxomicin, but **its summary does not represent formal NICE guidance.** NICE concluded that fidaxomicin may have advantages in reducing the rate of recurrence, and that local decision makers should take into account the potential benefits alongside the medical need, the risks of treatment, and the relatively high cost of the antibiotic in comparison with other CDI treatment options.

1.6 Only limited cost effectiveness data on the use of fidaxomicin in CDI have been published. SMC accepted that there was an economic case to justify the use of fidaxomicin in patients with first CDI recurrence. For the population of patients with severe CDI, however, a convincing economic case for fidaxomicin was not demonstrated. Using a number-needed-to-treat for sustained clinical response of 7.1 patients, Sclar *et al.,* (2012) calculated that fidaxomicin represented value for money from the perspective of the US health system. Until further NHS specific data are available, some local decision making will be required to determine cost-effective use of fidaxomicin.

Mild disease

1.7 Patients with mild disease may not require specific *C. difficile* antibiotic treatment. If treatment is required, oral metronidazole is recommended (dose: 400–500 mg tds for 10–14 days) as it has been shown to be as effective as oral vancomycin in mild to moderate CDI (Zar *et al.,* 2007; Louie *et al.,* 2007; Bouza *et al.,* 2008).

Moderate disease

1.8 For patients with moderate disease, a 10- to 14-day course of oral metronidazole is the recommended treatment (dose: 400-500 mg tds). This is because it is

cheaper than oral vancomycin and there is concern that overuse of vancomycin may result in the selection of vancomycin-resistant enterococci (HICPAC, 1995; American Society of Health-System Pharmacists, 1998; Gerding, 2005).

Severe disease

1.9 For patients with severe CDI, oral vancomycin is preferred (dose: 125 mg qds for 10–14 days). This is because of relatively high failure rates of metronidazole in recent reports and a slower clinical response to metronidazole compared with oral vancomycin treatment (Wilcox and Howe, 1995; Musher *et al.,* 2005; Lahue and Davidson, 2007; Zar *et al.,* 2007). Two double-blind randomised studies reported that vancomycin is superior to metronidazole in severe cases of CDI (Louie *et al.,* 2007; Bouza *et al.,* 2008). A pooled analysis of these two phase 3 studies has shown that metronidazole was overall inferior to vancomycin (Johnson *et al.,* 2012). Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics (Hu *et al.,* 2009; Wilcox 2012).

1.10 Vancomycin preparation for injection is now licensed for oral use and is cheaper than the capsules (~£32 versus £90 for a 10- to 14-day course). It is also easier to swallow. The contents of vials for parenteral administration may be used for oral administration. After initial reconstitution of the vial, the selected dose may be diluted in 30 ml of water and given to the patient to drink, or the diluted material may be administered by a nasogastric tube.

1.11 CDI due to ribotype 027 strains is associated with increased severity, requirement for switching from metronidazole to vancomycin, recurrence and mortality (Ellames *et al.,* 2007; Hubert *et al.,* 2007; Goorhuis *et al.,* 2007; Miller *et al.,* 2009; Wilcox *et al.,* 2012). However, a large retrospective cohort study reported no superiority of vancomycin over metronidazole. This suggests that both treatments are suboptimal for at least some strains of this ribotype (Pépin *et al.,* 2007). Recent clinical trials of fidaxomicin in comparison with vancomycin have reinforced the poorer outcome of CDI caused by ribotype 027 strains (Louie *et al.,* 2011; Cornely *et al.,* 2012); hence, for cases of CDI due to ribotype 027 there was no benefit, in terms of clinical cure or reduced risk of recurrence, in comparison with vancomycin.

1.12 There is evidence of the emergence of reduced susceptibility to metronidazole in some *C. difficile* isolates, with evidence for clonal spread (Baines *et al.,* 2008). Notably, MIC methodology is crucial to the detection of reduced susceptibility to metronidazole; E-tests in particular under-estimate the MIC (Baines *et al.,* 2008,

Moura *et al.,* 2012). There is also evidence of inferior microbiological efficacy of metronidazole in comparison with vancomycin (Al-Nassir *et al.,* 2008; Kuijper and Wilcox, 2008). Poor gut concentrations of metronidazole alongside reduced susceptibility to metronidazole logically could affect treatment efficacy. A case-control study found no significant differences in clinical outcome for CDI cases from which strains with reduced susceptibility to metronidazole were recovered versus matched (metronidazole susceptible) controls. Response to metronidazole was generally poor (slow and prone to recurrence) and the frail elderly patients had a 21% 30 day mortality. Much larger study groups are needed to determine the clinical significance of CD isolates with reduced susceptibility to metronidazole (Purdell *et al.,* 2011). It is not practicable to recommend that laboratories routinely (carry out *C. difficile* culture and) measure metronidazole MICs, as this is a technically difficult area. However, reference laboratories should perform periodic surveillance using appropriate methodology to determine if the epidemiology of metronidazole susceptibility in *C. difficile* is changing.

1.13 There are, however, no definitive markers of severity. The three most frequently recognised risk factors for severe CDI are age, peak leukocytosis and blood creatinine (Pépin *et al.,* 2004; Loo *et al.,* 2005; Pépin *et al.,* 2007). However, such observations are retrospective and age is too non-specific to be used as a predictor of severe CDI. No single parameter alone is highly predictive of severe CDI, with the possible exception of very high WCCs. Zar *et al.,* (2007) used a score based on age, WCC, temperature, albumin, endoscopy findings and admission to an intensive therapy unit to define severe cases. Louie *et al.,* (2006) used number of stools, WCC and abdominal pain to define severe CDI. Importantly, a definition of severe CDI based on number of diarrhoeal stools may suffer from difficulties in recording such episodes, especially in elderly patients with faecal incontinence. Furthermore, severe CDI may occasionally be characterised by ileus with no diarrhoea. A severity score is needed that is prospectively validated in more than one setting. Until such time as this is available, clinicians need to be alert to the possibility of severe CDI.

1.14 We recommend using any of the following to indicate severe CDI and so to use oral vancomycin (or fidaxomicin) in preference to metronidazole:

- WCC >15 10^9/L;
- acutely rising blood creatinine (e.g. >50% increase above baseline);
- temperature >38.5°C; or
- evidence of severe colitis (abdominal signs, radiology).

1.15 A conservative WCC threshold of 15 has been chosen, as higher cut-off values may miss severe cases and relative immune paresis is common in the frail elderly who are most at risk of severe CDI. Elevated blood lactate >5 mmol/L is associated with extremely poor prognosis, even with colectomy (Lamontagne *et al.,* 2007).

1.16 In severe CDI cases not responding to oral vancomycin 125 mg qds, oral fidaxomicin (200mg bd) should be considered. Alternatively, high dosage oral vancomycin (up to 500 mg qds, if necessary administered via a nasogastric tube) plus intravenous (iv) metronidazole 500 mg tds is an option. The addition of oral rifampicin (300 mg bd) or iv immunoglobulin (400 mg/kg) may also be considered. Although there are no robust data to support these recommendations, the very poor prognosis may justify aggressive therapy (Abougergi *et al.,* 2011). Severe (or recurrent) CDI is considered an appropriate use of IV immunoglobulin (Department of Health, 2011).

1.17 Life-threatening disease (i.e. hypotension, partial or complete ileus or toxic megacolon, or CT (computerised tomography) evidence of severe disease) can be treated by vancomycin given via a nasogastric tube (which is then clamped for one hour) and/or by rectal installation (Apisarnthanarak *et al.,* 2002).

1.18 Colectomy is required in some patients with megacolon (dilatation >10 cm), perforation or septic shock, and should be done before the blood lactate rises above 5 mmol/L (Lipsett *et al.,* 1994; Longo *et al.,* 2004; Koss *et al.,* 2006). A recent systematic review concluded that total colectomy with end ileostomy is the preferred surgical procedure; other procedures are associated with high rates of re-operation and mortality. Less extensive surgery may have a role in selected patients with earlier-stage disease (Bhangu *et al.,* 2012). An alternative approach, diverting loop ileostomy and colonic lavage, has been reported to be associated with reduced morbidity and mortality (Neal *et al.,* 2011).

1.19 Recurrent disease occurs in about 20% of patients treated initially with either metronidazole or vancomycin (Teasley *et al.,* 1983; Bartlett, 1985; Wenisch *et al.,* 1996). The same antibiotic that had been used initially can be used to treat the first recurrence (Pépin *et al.,* 2006). A variable proportion of recurrences are reinfections (20-50%) as opposed to relapses due to the same strain; relapses tend to occur in the first two weeks after treatment cessation (Wilcox *et al.,* 1998; Figueroa *et al.,* 2012).

1.20 After a first recurrence, the risk of another infection increases to 45–60% (McFarland *et al.,* 1999). In line with the recent evidence reviewed in 3.4, and

SMC/NICE conclusions, fidaxomicin should be preferred for patients with recurrent CDI, whether mild, moderate or severe, because of their increased risk of further recurrences. The efficacy of fidaxomicin in patients with multiple CDI recurrences is unclear. Depending on local cost-effectiveness based decision making, oral vancomycin is an alternative.

1.21 It should be noted that there is no evidence of a benefit of using metronidazole or vancomycin to prevent CDI (in patients receiving antibiotic therapy); indeed this approach may actually increase risk.

1.22 Tapering followed by pulsed doses of vancomycin may be of value. There are various regimens, such as 125 mg qds for one week, 125 mg tds for one week, 125 mg bd for one week, 125 mg od for one week, 125 mg on alternate days for one week, 125 mg every third day for one week (six weeks in total) (Tedesco *et al.,* 1985). Clearly, this may provide a considerable selective pressure for vancomycin resistance, e.g. in enterococci.

2. Agents other than metronidazole, vancomycin or fidaxomicin

Probiotics

2.1 Meta-analyses have usually failed to demonstrate statistically significant efficacy in treating or preventing CDI (Dendukuri *et al.,* 2005; Pillai and Nelson, 2008). A randomised, double-blind, placebo-controlled trial showed a beneficial effect of using a proprietary yoghurt as prophylaxis in patients receiving antibiotics (Hickson *et al.,* 2007), but suffered from major methodological flaws threatening the validity and generalisablity of the study (Wilcox and Sandoe, 2007). Crucially, only 7% of those screened for inclusion were recruited to the study, and controls received a milkshake as placebo, which may have increased the risk of diarrhoea because of lactose intolerance (Wilcox and Sandoe, 2007). A recent review (Johnson *et al.,* 2012) concluded that studies of sufficient size and with rigorous design are needed to determine if the findings of smaller and/or flawed studies on probiotics for the prevention of CDI are robust. Similarly, a systematic review and meta-analysis found that while probiotics may be associated with a reduction in antibiotic associated diarrhoea (AAD), more research is needed to determine which probiotics are most efficacious, for which patients receiving and in relation to which particular antibiotics (Hempel *et al.,* 2012). Thus, we cannot at present recommend the use of probiotics for the prevention of AAD or CDI.
The role of prebiotics in the prevention of CDI has been under-explored and further research is desirable (Novak *et al.,* 2006; Kondepudi *et al.,* 2012).

Saccharomyces boulardii

2.2 This is not available as a licensed product in the UK. It has been studied extensively but with conflicting results. Subset analysis suggested possible benefit in some recurrent cases (McFarland *et al.,* 2002). However, it has caused fungaemia in immunocompetent and immunosuppressed patients, and is not recommended for widespread usage (Enache-Angoulvant and Hennequin, 2005). Notably, variable strain virulence of *S. boulardii* obtained from different sources was seen in an animal model; such issues are important considerations for probiotic preparations in general (McCullough *et al.,* 1998).

Intravenous immunoglobulin

2.3 Several case reports and small series have been published regarding the use of this method to treat refractory disease (Leung *et al.,* 1991; Warny *et al.,* 1995; Salcedo *et al.,* 1997; Beales, 2002; Wilcox, 2004; McPherson *et al.,* 2006; Murphy *et al.,* 2006). A dosage of 400 mg/kg given intravenously as a stat dose has been beneficial in about two-thirds of intractable cases. No randomised, controlled clinical trials have been performed to evaluate the efficacy of immunoglobulin in recurrent or severe CDI (Abougergi *et al.,* 2011). Severe (or recurrent) CDI is considered an appropriate use of IV immunoglobulin (Department of Health, 2011).

Anion exchange resin

2.4 Oral cholestyramine (4 g packet tds) has been used in the treatment of refractory CDI because it is thought to bind *C. difficile* toxins. There is no robust evidence to support the use of cholestyramine as an adjunctive agent, and there is a risk that it may bind antibiotics used to treat CDI. It is not recommended.

Non-toxigenic *C. difficile* (NTCD)

2.5 Two patients who had multiple relapses were given non-toxigenic *C. difficile* immediately following treatment, with successful interruption of relapse, but this is not recommended on such scant evidence (Seal *et al.,* 1987). A NTCD strain has completed phase 2 clinical trials for the treatment of CDI (Villano *et al.,* 2012).

Faecal transplant

2.6 A recent systematic review concluded that, although there are a variety of methods used to infuse intestinal microorganisms (as part of a suspension of healthy donor stool) into the intestine of patients in order to restore the microbiota, of 317 patients treated across 27 case series and reports, this approach was highly effective at achieving resolution of recurrent CDI (92% resolved). Adverse events have rarely been reported (Gough *et al.,* 2011). Typically, fresh manipulated faeces (30–50g) from a healthy donor is administered in normal saline by enema, slurries via nasogastric tube, or colonoscopy. This is generally used as a last resort option, not least because of practical and aesthetic concerns. van Nood *et al.,* (2013) have just reported the first randomised study of faecal transplantation for recurrent CDI, which was stopped after an interim analysis.

Resolution of CDI occurred in 4/13 patients (31%) receiving vancomycin alone, 3/13 patients (23%) receiving vancomycin with bowel lavage, and 13/16 (81%) given faecal transplants via a nasoduodenal tube (P<0.001 for either vancomycin regimen compared with faecal transplantation). A cost-effectiveness evaluation of donor faeces transplantation has not been performed, which is notably considering the complexity of the procedure (donor testing, consenting, sample processing and endoscopy).

Fusidic acid

2.7 The response rates in a prospective randomised, double-blind trial comparing metronidazole 400 mg tds (n=55) with fusidic acid 250mg tds 7 days (n=59) showed no significant difference (Noren *et al.,* 2006). Recurrence rates were similar, but development of fusidic acid resistance was seen in 55% of recipients who remained culture-positive. Fusidic acid should not be used as a first-line treatment in CDI; its role in treating recurrences is unclear but resistance (in *C. difficile* and/or in skin bacteria) is likely to limit this use.

Rifampicin

2.8 No randomised, controlled trials have been reported; there is no robust evidence to support the use of rifampicin as an adjunctive agent.

Rifaximin

2.9 Rifaximin, is an oral, non-absorbed rifamycin (related to rifampicin). A randomized, double-blind, placebo-controlled pilot study found that patients given rifaximin 400 mg tds for 20 days, given immediately after finishing standard anti-CDI antibiotics, had a decreased incidence of recurrent diarrhoea (Garey *et al.,* 2011). While these results are interesting, the intensive antibiotic use in this regimen raises concerns about possible emergence of rifamycin resistance, which has been reported in CDI cases, and prolonged flora disturbance (Johnson *et al.,* 2007; Johnson *et al.,* 2009; Carman *et al.,* 2012).

3. Recommendations

3.1 A simple grading system for the recommendations is given in Table 1. A grade A, B or C appears in brackets after each recommendation.

Grade	Strength of evidence
A	Strongly recommended and supported by systematic review of randomised controlled trials (RCTs) or individual RCTs
B	Strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the Code
C	Recommended and supported by group consensus and/or strong theoretical rationale

3.2 Clinicians (doctors and nurses) should apply the following mnemonic protocol (SIGHT) when managing suspected potentially infectious diarrhoea:

S	Suspect that a case may be infective where there is no clear alternative cause for diarrhoea B
I	Isolate the patient and consult with the infection control team (ICT) while determining the cause of the diarrhoea B
G	Gloves and aprons must be used for all contacts with the patient and their environment B
H	Hand washing with soap and water should be carried out before and after each contact with the patient and the patient's environment A
T	Test the stool for toxin, by sending a specimen immediately B

3.3 Patients should be monitored daily for frequency and severity of diarrhoea using the Bristol Stool Chart (see Appendix 1). B

3.4 All antibiotics that are clearly not required should be stopped, as should other drugs that might cause diarrhoea. Consideration should be given to stopping/reviewing the need for PPIs in patients with or at high risk of CDI. B

3.5 CDI should be managed as a diagnosis in its own right, with each patient reviewed daily regarding fluid resuscitation, electrolyte replacement and nutrition review. Monitor for signs of increasing severity of disease, with early referral to ITU as patients may deteriorate very rapidly. B

3.6 CCGs should ensure that trusts have a multidisciplinary clinical review team consisting of a microbiologist, an infectious diseases or infection prevention and control doctor, a gastroenterologist or surgeon, a pharmacist, a dietician, and an infection prevention and control nurse.

3.7 The team should review all CDI patients at least weekly to ensure that the infection is being treated optimally and that the patient is receiving all necessary supportive care. B

3.8 Assess severity of CDI each day as follows:

- **Mild CDI** is not associated with a raised WCC; it is typically associated with <3 stools of type 5–7 on the Bristol Stool Chart per day. B
- **Moderate CDI** is associated with a raised WCC that is <15 □ 109/L; it is typically associated with 3–5 stools per day. C
- **Severe CDI** is associated with a WCC >15 □ 109/L, or an acute rising serum creatinine (i.e. >50% increase above baseline), or a temperature of >38.5°C, or evidence of severe colitis (abdominal or radiological signs). The number of stools may be a less reliable indicator of severity. C
- **Life-threatening CDI** includes hypotension, partial or complete ileus or toxic megacolon, or CT evidence of severe disease. B

3.9 Treat according to severity (see also the treatment algorithms):

- **Mild and moderate CDI** – oral metronidazole 400–500 mg tds for 10–14 days. A
- **Severe CDI** – oral vancomycin 125 mg qds for 10–14 days. A
  Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics. B
  In severe CDI cases not responding to oral vancomycin 125 mg qds, oral fidaxomicin 200 mg bd is an alternative; or high-dosage oral vancomycin (up

to 500 mg qds, if necessary administered via a nasogastric tube), +/- iv metronidazole 500 mg tds is recommended. The addition of oral rifampicin (300 mg bd) or iv immunoglobulin (400 mg/kg) may also be considered. C

- **Life-threatening CDI** – oral vancomycin up to 500 mg qds for 10–14 days via naso-gastric tube or rectal installation plus iv metronidazole 500 mg tds.

3.10 Such patients should be closely monitored, with specialist surgical input, and should have their blood lactate measured. 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 (Lamontagne *et al.,* 2007). B

3.11 If diarrhoea persists despite 20 days' treatment but the patient is stable and the daily number of type 5–7 motions has decreased, the WCC is normal, and there is no abdominal pain or distension, the persistent diarrhoea may be due to post-infective irritable bowel syndrome. The patient may be treated with an anti-motility agent such as loperamide 2mg prn (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. C

3.12 **For recurrent CDI**, oral fidaxomicin 200 mg bd is recommended; oral vancomycin 125 mg qds is an alternative. B

3.13 **For multiple recurrences**, consider the alternatives listed in the treatment algorithms. C

4. Treatment algorithms

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

▼

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

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

▼

DAILY ASSESSMENT

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
(see protocol appendix 1)

▼

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

▼

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

▼

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

▼

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

▼

Symptoms improving

Diarrhoea should resolve in 1-2 weeks

▼

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 Form Scale

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces, a mushy stool
Type 7		Watery, no solid pieces ENTIRELY LIQUID

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Appendix 2: Members of the sub-group

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