Who should read this document?

This policy applies to all clinical staff involved the prescribing of antimicrobials.

Key Practice Points

This policy refers to the diagnosis and management of patients with Clostridium difficile.

Background

Antimicrobial agents are among the most commonly prescribed drugs and account for 20% of the hospital pharmacy budget. Unfortunately, the benefits of antibiotics to individual patients are compromised by the development of bacterial drug resistance. Resistance is a natural and inevitable result of exposing bacteria to antimicrobials.

Good antimicrobial prescribing will help to reduce the rate at which antibiotic resistance emerges and spreads. It will also minimise the many side effects associated with antibiotic prescribing, such as Clostridium difficile infection. It should be borne in mind that antibiotics are not needed for simple coughs and colds. In some clinical situations, where infection is one of several possibilities and the patient is not showing signs of systemic sepsis, a wait and see approach to antibiotic prescribing is often justified while relevant cultures are performed.

This document provides treatment guidelines for the most common situations in which antibiotic treatment is required. The products and regimens listed here have been selected by the Trust's Medicines Management Group on the basis of published evidence. Doses assume a weight of 60-80kg with normal renal and hepatic function. Adjustments may be needed for the treatment of some patients.

This document provides treatment guidelines for the appropriate use of antibiotics. The recommendations that follow are for empirical therapy and do not cover all clinical circumstances. Alternative antimicrobial therapy may be needed in up to 20% of cases. Alternative recommendations will be made by the microbiologist in consultation with the clinical team.

This document refers to the treatment of adult patients (unless otherwise stated).

Refer to BNF/SPC for information on interactions, side effects, cautions and contraindications for individual drugs.
What is new in this version?

The need to review indications for proton pump inhibitor (PPI) therapy has been added for patients who have a new or recent diagnosis of *Clostridium difficile* infection (CDI) and are taking PPIs.

Clarification that patients should receive IV metronidazole in place of oral vancomycin if they are nil by mouth or not keeping down oral vancomycin due to vomiting.

Dose of IV immunoglobulin added

Removal of Rifaximin for a 2nd relapse of *Clostridium difficile* as PHE guidelines don’t advise this.

Details of the local centre for Faecal transplantation (Bolton) added.

Guideline

**General Principles**

*Clostridium difficile* Infection

*Clostridium difficile* infection (CDI) is a common cause of diarrhoea in hospitals and usually follows antibiotic therapy. Symptoms range from mild self-limiting diarrhoea to life-threatening pseudomembranous colitis. Clinical staff should apply the following mnemonic protocol (SIGHT) when managing potentially infectious diarrhoea:

- **S**uspect that a case may be infective when there is no clear alternative cause for the diarrhoea
- **I**solate the patient and consult with the infection control team while determining the cause of the diarrhoea
- **G**loves and aprons must be used for all contacts with the patient and their environment
- **H**and washing with soap and water should be carried out before and after each contact with the patient and the patient’s environment
- **T**est the stool for toxin, by sending a specimen immediately

Treatment should be started empirically, without waiting for the results of testing. Rarely, cases of severe *C. difficile* infection (e.g. Pseudomembranous colitis) can present without diarrhoea. However, they will usually have other abdominal symptoms such as pain, distension or tenderness.

A clinical diagnosis of *C. difficile* infection (CDI) is based on the clinical signs and symptoms, such as diarrhoea or signs of colitis. It may be confirmed by detection of the *C. difficile* toxin and/or the (*tcdB*) toxigenic gene in a faeces sample. A positive PCR result indicates that the toxigenic gene is present and therefore demonstrates the potential for CDI, but does not directly detect *C.*
difficile toxin. All PCR positive faeces samples will be processed further to test for C. difficile toxin by enzyme immunoassay (EIA).

Refer to the Diarrhoea Assessment Tool for guidance on when to send samples.

**Specialist Registrar or Consultant must review the patient clinically and authorise processing of the sample. However, obtaining the sample should not be delayed whilst this approval is sought.**

Faeces will be tested for C. difficile in samples which assume the shape of their container (Bristol Stool types 5-7). **Samples should be transported to the laboratory immediately after collection.**

If clinically indicated, treatment may need to be continued even if tests are negative:

- A small proportion (<4%) of patients with C. difficile infection may have a negative C. difficile toxin B gene result. It is reasonable to send a repeat faeces sample if C. difficile infection is strongly suspected on clinical grounds.

- Antacid treatments, calcium carbonate and magnesium or aluminium chloride have been shown to potentially interfere with the PCR assay.

- Rarely, cases of severe C. difficile infection (e.g. Pseudomembranous colitis) can present without diarrhoea. However, they will usually have other abdominal symptoms such as pain, distension or tenderness.

**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.

**Record the following daily as a clinical note** (to facilitate follow-up and review):

- Summary of previous day’s Bristol stool chart (e.g. diarrhoea x5, type 6-7)
- Presence or absence of abdominal distension and tenderness

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**General Management**

- A Bristol Stool Chart must be used to monitor the frequency and severity of diarrhoea
- Discontinue all current antibiotic therapy that is not clearly required. If this is not possible, change to antibiotics less likely to cause CDI. Discuss with Microbiologist.
- Discontinue any other drugs that might cause diarrhoea
• Replace fluid and electrolytes. Antimotility drugs are **contraindicated** (e.g. loperamide or codeine phosphate) unless post-infective irritable bowel syndrome occurs, in which case seek specialist advice from a gastroenterologist

• If a patient with new or recently (within 3 years) diagnosed CDI is taking a PPI (which may increase the risk of future CDI relapse/recurrence), review the PPI indication and stop the PPI if risks outweigh likely benefits. Antacids or alternative acid suppressant therapies should be offered if needed. A list of indications for which PPI therapy should normally be continued is given in the **Appendix**. Where PPIs are discontinued, this should be discussed with the individual patient. In the situation where this is not possible the reason must be recorded.

### Antimicrobial Treatment of CDI

#### Assessment of Disease Severity

Patients should be assessed for indicators of severe disease in order to guide appropriate management. Typical features of the disease are listed in the table below.

<table>
<thead>
<tr>
<th>Mild-moderate disease</th>
<th>Severe disease</th>
<th>Life-threatening disease</th>
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| WBC <15 x 10^9 /L and <6 stools per day **but note that diarrhoea may be absent in the presence of severe disease with colitis** | **any one of the following:**  
  • Leukocyte count >15 x 10^9 /L  
  • Acutely rising serum creatinine (increased by >50% above baseline).  
  • Temperature >38.5 °C  
  • Evidence of severe colitis (abdominal or radiological signs) | Characterised by hypotension and/or ileus/toxic megacolon and/or CT evidence of severe disease |

#### Treatment

**Non-severe disease:** Vancomycin 125 mg PO qds for 10-14 days (or Metronidazole IV 500mg TDS if patient is nil by mouth or vomiting)

**NB:** *Vancomycin IV should not be used for the treatment of CDI*

Patients should be assessed daily for signs of severe disease. If symptoms are worsening, with indicators of severe disease (see above), consider requesting an abdominal CT scan and refer for a surgical and /or gastroenterology review.

Evaluate the response to therapy after one week
• If symptoms are not resolving, increase dose to 250 mg PO qds for a further 10-14 days
• If symptoms have not resolved after 3 weeks, refer for a specialist gastrointestinal and microbiology opinion

**Severe disease:** Vancomycin PO 125mg qds for 10-14 days, (if necessary by nasogastric tube) +/- IV metronidazole 500mg tds.

Please ensure the patient is reviewed by a gastroenterologist and refer to a microbiologist.

**NB:** Vancomycin IV should not be used for the treatment of CDI

Consider:
• extending the oral vancomycin course for a third week if the patient is improving, but symptoms are slow to settle
• increasing vancomycin dose to 250 mg qds if not responding
• rectal instillation of vancomycin (see below)
• IV immunoglobulin if not responding to the above – seek specialist advice

**Life-threatening disease:** Vancomycin PO 500mg qds for 10-14 days (via a nasogastric tube or rectal installation) plus IV metronidazole 500mg tds.

**NB:** Vancomycin IV should not be used for the treatment of CDI

Arrange an urgent review by a gastroenterologist and a lower GI surgeon. These patients should be monitored closely with specialist surgical input and have their blood lactate measured. Colectomy should be considered, especially if caecal dilatation is >10 cm. (Colectomy is best performed before the blood lactate rises above 5 mmol/L).

Consider:
• IV immunoglobulin 400mg/kg as a stat dose if not responding to the above – seek specialist advice from microbiology.

**Haematology patients**
Fidaxomicin 200mg BD for 10 days should be substituted for vancomycin in the treatment recommendations above for non-severe laboratory confirmed CDI. Patients should commence vancomycin pending confirmation of CDI.

**Liquid vancomycin**
Liquid vancomycin is made by the pharmacy extemporaneous department and is available from the pharmacy department during normal pharmacy working hours. Out of hours, vancomycin injection may be used orally or via enteral feeding tubes. Use of the vancomycin injection, via the oral route is unlicensed.

**Preparation of liquid vancomycin**
At the time of use, add 10ml of sterile Water for Injections BP to a 500mg vial of Vancomycin Hydrochloride 500mg Powder for Concentrate for Infusion. Shake each vial to dissolve the powder. This will provide you with a 50mg/ml solution.
After initial reconstitution of the vial, the selected dose 250 mg (5ml) or 125 mg (2.5ml) may be diluted in 30 ml of water and given to the patient to drink or the diluted solution may be administered by a nasogastric tube.

### Treatment of disease recurrence or relapse

Recurrence occurs in approximately 20% of cases after a first episode and 40-60% after a second or subsequent episode.

**First relapse:** Fidaxomicin 200mg BD for 10 days is indicated in a laboratory confirmed relapse within 6 months of the previous episode, and if the patient has not been previously treated with fidaxomicin. Otherwise vancomycin 125mg QDS should be prescribed.

**Management of multiple recurrent episodes**

Treat as above until asymptomatic for 7 days.

Review all medications. Consider stopping PPIs and other GI active agents

Discuss the options with a consultant microbiologist or gastroenterologist:

- Supervised trial of loperamide (if post-infectious inflammatory bowel syndrome is suspected)
- **Rectal installation** of vancomycin (see below)
- **Oral vancomycin tapering therapy** (see below)
- IV immunoglobulin 400mg/kg as a single dose
- **Faecal microbiota transplant** (NICE IPG485)

Seek a specialist gastrointestinal or microbiology opinion if not responding to treatment

**Criteria for repeat *Clostridium difficile* toxin testing**

Do not retest samples from a patient with a positive *C. difficile* toxin test within 28 days, unless symptoms resolve and then recur - this should be discussed and agreed with the duty microbiologist. Any patient with a clinical recurrence of CDI, should normally be treated as above.

**Rectal instillation of vancomycin**

Vancomycin (500 mg in 100–500 ml Sodium chloride 0.9% 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, if the oral route is compromised e.g.by colitis. A bowel management system should be used to administer the vancomycin and this should be retained in the rectum for 1 hour. Consider monitoring serum vancomycin levels if colitis is present.

**Vancomycin tapering therapy regimen**

Oral / NG vancomycin 125 mg qds for 1st week
Oral / NG vancomycin 125 mg tds for 2nd week
Oral / NG vancomycin 125 mg bd for 3rd week
Oral / NG vancomycin 125 mg od for 4th week
Oral / NG vancomycin 125 mg on alternate days for 5th week
Oral / NG vancomycin 125 mg every third day for 6th week

**Faecal microbiota transplant**
For patients where fidaxomicin has been unsuccessful, faecal repopulation should be considered and discussed with the Infection Control team, Microbiologist and patients consultant in an MDT. If agreed, a referral should be made to the Royal Bolton Hospital: sara.hardman@boltonft.nhs.uk or Tel - 01204 390 408.

**Death Certification**
There is a legal duty to mention CDI on a death certificate if it was part of the sequence of events directly leading to death or contributed in some way. If a patient with CDI dies, this should be recorded, as appropriate, in either Part 1 or Part 2 of the death certificate.

### Standards

- Document the Indication/rationale for antimicrobial therapy, including clinical criteria relevant to this.
- Review and document the patient’s allergy status
- Ensure the choice of antibiotic complies with the antibiotic guidelines and you have documented any clinical criteria relevant to the choice of agent.
- Document a management plan including a stop or review date.
- Where relevant, consider drainage of pus or surgical debridement/removal of foreign material.

### Explanation of terms

Not applicable.

### References and Supporting Documents

1. Pepin, J Vancomycin for the treatment of Clostridium difficile infection: for whom is this expensive bullet really magic? Clinical Infectious Diseases 2008; 46:1493-1498


12. Summary of Product Characteristics for Vancomycin Hydrochloride 500mg and 1g Powder for Concentrate for Infusion. Hospira UK Ltd. 30th Jan 2013


Roles and responsibilities

All clinical staff involved in the prescribing of antimicrobials to adhere to this policy including full documentation on EPMAR as detailed.
Appendix - Patients in whom PPIs should continue

- Those patients who have had an upper GI bleed in the last 2 months.
- Those with a history of upper GI bleed who have on-going dyspeptic symptoms.
- Patients with oesophageal strictures secondary to acid reflux.
- Patients with Barrett’s oesophagus already receiving life-long PPIs.
- Patients with Zollinger-Ellison syndrome.
- Bariatric patients for 2 years after gastric bypass surgery.
- Patients with significant renal disease or impairment defined as CKD stage 4-5, eGFr<30mls/min/m² or AKI stage 3
- Those on dual anti-platelet therapy (aspirin and clopidogrel /ticagrelor / prasugrel)(DAPT) and receiving steroids
- Those on dual anti-platelet therapy in patients aged ≥75 years
- Those taking an anticoagulant vitamin K antagonist (VKA, e.g. warfarin) and taking single anti-platelet therapy (SAPT) or DAPT
- Those taking a direct/novel oral anticoagulant (DOAC/NOAC) and taking SAPT or DAPT
- Those taking a NSAID and SAPT, DAPT or an anticoagulant. (Consider whether the patient should continue with the NSAID. Is there an alternative?)
- Those with a PMH of peptic ulcer disease or upper GI bleeding taking SAPT, DAPT or an anticoagulant.
- Those on HDU, ITU or receiving potent chemotherapy in whom the risk of GI bleeding outweighs the risk of C. difficile acquisition.
- Those with intractable dyspeptic symptoms in whom alternative therapies are ineffective or contraindicated.
- Those with a perceived high risk of GI bleeding (following discussion with the GI team)
- Patients > 45 years taking a regular non-steroidal anti-inflammatory drug (NSAID)
- Acid related symptoms unresponsive to antacids or H2 antagonists (or contraindicated)
- Any other patients who, in the clinical opinion of the named Consultant in charge of the episode of care consider the risks of stopping PPI outweigh the benefits where this is documented explicitly in the patient notes.

The above list is not exhaustive and clinicians are invited to discuss individual cases with the gastroenterologists, microbiologists and pharmacy teams for query resolution.