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Inpatient diarrhoea and *Clostridium difficile* infection

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Diarrhoea is common in hospital. *Clostridium difficile (C.difficile)* is the most frequently diagnosed and serious cause and the main focus of this article. Other causes are outlined in Table 1.

C.difficile is a Gram-positive anaerobic spore-forming bacillus first described as a human pathogen in 1978.[1] It causes a wide spectrum of illness ranging from mild diarrhoea to a life-threatening colitis. *C.difficile* infection (CDI) rates now form part of the key performance measures for NHS Trusts in England and Wales and every case is reported to the Health Protection Agency (HPA). With CDI rates rising dramatically in the early 2000s, the HPA set up the *C.difficile* Ribotyping Network (CDRN) in 2007. This monitors and publishes CDI rates and investigates outbreaks.[2]

Transmission and pathogenicity

C.difficile is widely present in the environment and found in colonic flora in up to 70% of neonates and 4% of healthy adults.[3] *C.difficile* is spread via the faecal-oral route, with transmission and pathogenicity based on two key factors: its ability to form endospores and to produce cytotoxic toxins.

Endospore formation

Clostridia species form endospores when environmental conditions are not suitable for their survival as vegetative bacteria. A spore contains bacterial DNA surrounded by a protective coating which makes it resistant to environmental stresses and can lie dormant and viable for several years.[4] Excretion of *C.difficile* spores and bacteria in large numbers by patients with CDI can result in a *C.difficile* reservoir in hospitals.

After being ingested, spores germinate in the jejunum, at least in part as a result of contact with bile salts.[5] Once germinated, *C.difficile* enters a period of vegetative growth causing CDI in susceptible individuals.[6]

Toxin production

C.difficile produces two main toxins, A and B. The relevant genes are coded together on the pathogenicity locus (PaLoc).[7] Presence of the PaLoc is essential for *C.difficile* pathogenicity because in non-enterotoxic *C.difficile* strains it is replaced with a non-coding section of DNA.[7]

Both toxins A and B are enterotoxic. They enter colonic epithelial cells and induce release of pro-inflammatory cytokines, with consequent mucosal inflammation and damage.[8] Neutrophils migrate into and through the colonic mucosa causing the classic, although not invariable, endoscopic appearances of pseudomembranous colitis. The histological correlates of these macroscopic findings are fibrin and neutrophil-containing 'volcano' lesions.[8]

C.difficile also produces a third toxin (binary toxin)[7] which is not thought to play a part in the development of CDI.

Ribotype 027 (NAP1) is a particular strain of *C.difficile* that has been associated with several major outbreaks of CDI.[9,10] It has an 18 base-pair deletion in a regulatory region of its DNA, resulting in a 10-fold increase in the amount of toxin produced and a substantial increase in virulence.[7]

Epidemiology

The incidence and mortality associated with CDI is changing (Fig 1). The recent fall in CDI rates is probably due to a combination of greater clinical awareness of CDI, tighter antibiotic prescribing policies and improved infection control practices.

Risk factors in the development of *C.difficile* infection

The most important risk factor for CDI is antibiotic use. Other predisposing factors include increasing age, prolonged length of stay in hospital prior to acquisition, comorbidities such as renal failure, use of proton pump inhibitors (PPIs), chemotherapy, immunosuppression, enteral feeds and inflammatory bowel disease (IBD).[12–14]

Antibiotics

Concurrent or recent antibiotic use is by far the biggest risk factor for developing CDI. Antibiotics alter gut bacterial flora, allowing *C.difficile* to flourish in the colon. The increased risk of CDI persists for up to three months after antibiotic use.[15]

Of the stool samples examined by the CDRN in 2011, 70% were from patients with a history of antibiotic exposure — indeed, 59% of patients had been exposed to more than one antibiotic.[2]

Until recently, cephalosporins were the agents most strongly implicated in CDI but, with their more restricted prescribing, co-amoxiclav and piperacillin-tazobactam are now the antibiotics most commonly associated with CDI.[2]

Pre-existing inflammatory bowel disease

CDI is more common in patients with active IBD, particularly ulcerative colitis, and its outcome in IBD inpatients may be worse than in people without IBD.[16] Identified IBD-specific risk factors include immunosuppressants and antibiotics. Sigmoidoscopy (see below) rarely shows pseudomembranes and is unhelpful for diagnosing CDI in IBD.[16]

Clinical presentation

The hallmark of CDI is new-onset diarrhoea, mild to severe but not usually bloody. Abdominal pain, fever and, in severe cases, hypotension and tachycardia are common. Indeed, patients may present fulminantly with signs of toxic megacolon and need to be actively managed as septic patients.[17] A rise in C-reactive protein or

white cell count (WCC) and fall in serum albumin occur in most patients. In severe cases, these changes are more pronounced and serum urea and creatinine also rise. It is important to assess all patients with CDI daily, recording not only stool frequency, temperature, pulse, blood pressure and the blood tests mentioned above but, when there is concern about possible deterioration, also Glasgow Coma Scale blood gases (including pH) and lactate (Fig 2).[17]

Diagnosis

Microbiology

There are several microbiological techniques with which to diagnose CDI (Table 2). Note that stool should be sent for testing only if it is diarrhoeal, but diarrhoeal samples from patients on laxatives should not be tested.

In most hospitals, commercial toxin ELISA kits are used but these are poorly standardised and of widely varying sensitivity.[20] As a result, the Department of Health has issued new guidance for the diagnosis of CDI which is being implemented imminently.[21] There will now be a two-step process which has a false-negative rate of 0.7%.[22]

- The first diagnostic test will have a high negative predictive value and should either be a glutamate dehydrogenase detection assay or a polymerase chain reaction.
- For samples that test positive by either of those two methods, the second step should be a sensitive ELISA to detect toxin[21] as the presence of toxin is essential for a microbiological diagnosis of CDI.

If a stool sample gives negative results but clinical suspicion remains, a further sample should be sent after three days and a gastroenterological referral is recommended to assist in diagnosis.

Flexible sigmoidoscopy

Before the advent of the above relatively rapid microbiological tests, sigmoidoscopy or colonoscopy was widely used to look for the characteristic appearances of pseudomembranous colitis.[23] Mucosal examination, with or without biopsy, is now largely confined to patients with on-going diarrhoea and negative (whether true or false) microbiological tests, to look for pseudomembranes and other diagnoses including ulcerative colitis and colorectal cancer.

Management

Metronidazole and vancomycin

As shown in Fig 2, oral or intravenous (IV) metronidazole and oral vancomycin are used for the treatment of CDI (IV vancomycin does not reach the bowel lumen and should not be used to treat CDI). In severe attacks, oral vancomycin is superior to metronidazole and should be selected.[12] In mild-to-moderate disease, metronidazole and vancomycin are almost equally efficacious, with cure rates of 90% and 98%, respectively, in one

Table 1. Causes of inpatient diarrhoea.

Diagnosis	Key points in history
Infective: • bacterial, especially *C.difficile* • viral, especially norovirus	Ward outbreak of diarrhoea
Drugs/iatrogenic	Examples: • antibiotics: recent usage as inpatient or prior to admission • laxatives • NSAIDs • metformin • chemotherapy
Enteral feeding	Recent initiation of enteral feeding
Faecal impaction/overflow diarrhoea	Elderly Immobility Opiate analgesia Other constipating medications Preceding history of constipation
Bile salt malabsorption	Recent surgery: • cholecystectomy • terminal ileal resection

C.difficile = *Clostridium difficile*; NSAIDs = non-steroidal anti-inflammatory drugs.

Key points

Clostridium difficile infection (CDI) remains the most commonly diagnosed cause of diarrhoea in hospital inpatients. The incidence of CDI is now falling but its mortality remains high

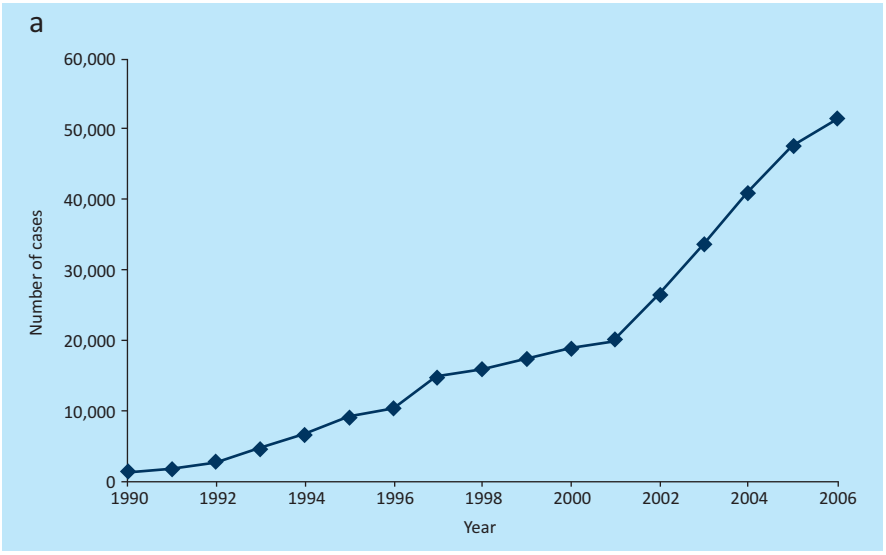
Co-amoxiclav and piperacillin-tazobactam are the antibiotics most frequently associated with causation of CDI

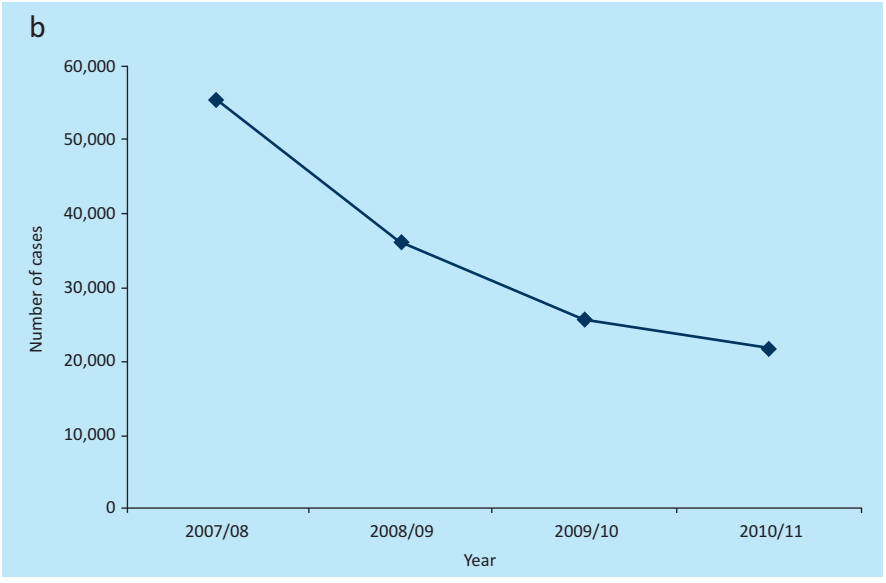
Microbiological diagnosis of CDI is changing to a nationally standardised system involving, first, a sensitive screening tool then, for those testing positive, a specific toxin assay

Treatment of mild-to-moderate and severe CDI is with metronidazole and oral vancomycin, respectively

Prevention of CDI comprises immediate isolation of suspected cases, meticulous handwashing by all hospital staff and visitors, frequent cleaning of the hospital environment and use of targeted antibiotic prescribing policies

KEY WORDS: _Clostridium difficile_, inpatient diarrhoea, metronidazole, vancomycin





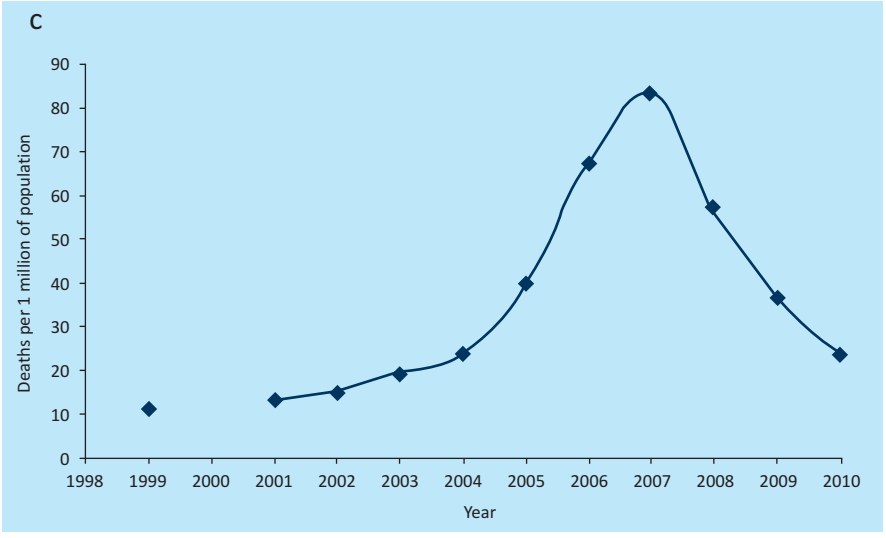


Fig 1. Epidemiology of C.*difficile* infection (CDI). (a) The number of cases of CDI in England from 1990 to 2006 (voluntary reporting). (b) The number of cases of CDI in England from 2007 to 2011 (mandatory reporting). Until 2007, Trusts reported CDI cases to the Health Protection Agency on a voluntary basis. Reporting became mandatory in 2007.[2,11] Although (a) and (b) cannot be directly compared, infection rates rose sharply in the early 2000s and have declined since 2007. (c) shows age-standardised *C.Difficile*-related mortality in England from 1990 to 2010. As with incidence, there was a sharp increase in mortality until 2007 and a decline thereafter (data provided by the Office for National Statistics).

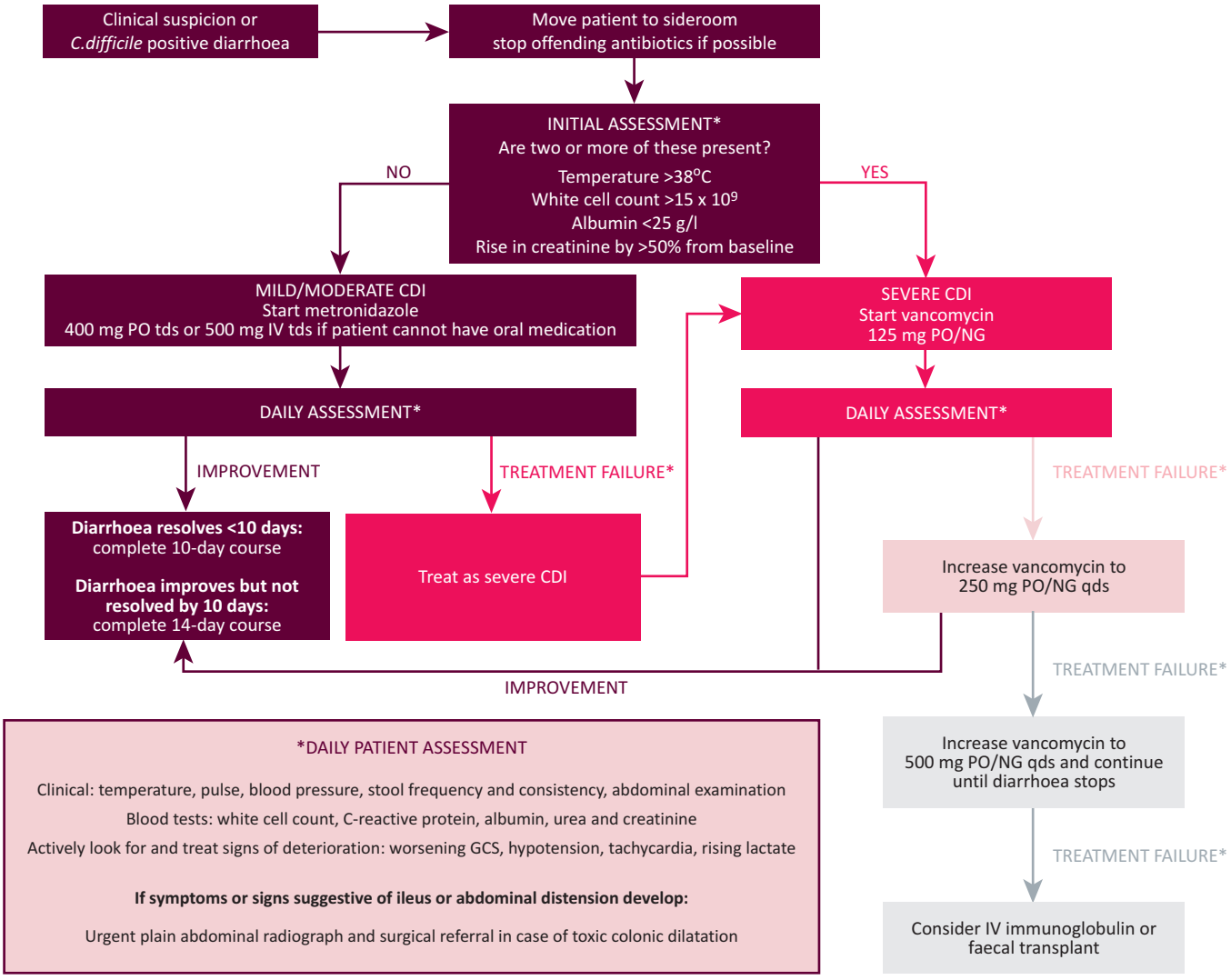


Fig 2. Management of *C.difficile* infection (CDI).[12,17–19] Treatment failure is defined as persistence of diarrhoea for seven days or clinical deterioration. CDI = *C.difficile* infection; GCS = Glasgow Coma Scale; NG = nasogastric; IV = intravenous; PO = by mouth; qds = four times per day; tds = three times per day.

study[12] but metronidazole is the cheaper choice.

There is a paucity of evidence on overall failure rates of metronidazole and vancomycin,[24] but a very recent review of prospective studies quotes overall failure rates of 26% for metronidazole and 6% for vancomycin.[25]

Relapse rates. CDI relapse on antibiotics is defined as recurrence of *C.difficile*-positive diarrhoea within 28 days of recovery from the previous episode. Prospective studies report relapse rates of 22% for metronidazole and 11% for vancomycin.[25] First relapses should be retreated with standard treatment. For a second relapse, oral vancomycin 125 mg qds should be given for 14 days, followed by a tapering dose over the next six weeks.[18]

Resistance. A potential concern is resistance of *C.difficile* to metronidazole and vancomycin but it has not yet been detected by the CDRN.[2] However, reduced susceptibility to metronidazole and vancomycin has been reported in 8% and 2% of *C.difficile* isolates, respectively.[2]

Other approaches

IV immunoglobulin,[26,27] faecal transplants[28] and monoclonal antibodies against *C.difficile* toxins[29] have been used for treatment of persistent CDI but evidence for their efficacy is limited. Fidaxomicin is a new non-absorbable macrocyclic antibiotic which has shown non-inferiority compared to oral vancomycin with a lower recurrence rate.[30] The Scottish Medicines Consortium has recently concluded that, while fidaxomicin should not be used as a first-line therapy in CDI, it can be used on a restricted basis in patients with a recurrence of CDI.[31] Lastly, vaccines against toxin are undergoing trials.[32]

Supportive treatment

Patients with CDI should receive nutritional support including IV fluids, if required. Pressure areas should be checked

frequently as these patients are often immobile and elderly. Unless contraindicated, prophylactic low-molecular heparin should be prescribed.

Surgery

Colectomy is indicated in CDI if colonic dilatation develops (about 1 in 250 hospital-acquired cases).[33] Clinically, there is increasing abdominal tenderness and distention. The diagnosis is confirmed by plain abdominal radiograph. If perforation is suspected, an urgent abdominal computed tomography scan is needed. These patients are extremely unwell and require close monitoring and supportive care in a high dependency setting (see above and Fig 2).

Outcome

Thirteen per cent of affected patients die while still in hospital.[34] Increasing age, renal dysfunction, raised WCC and low albumin at diagnosis appear to confer a poor prognosis,[12] but prospective data with which to predict outcome is limited.[35]

Table 2. Current laboratory techniques available for the diagnosis of *Clostridium difficile infection*.[20]

Detection method	What is detected	Sensitivity (%)	Specificity (%)	Advantages & disadvantages
Initial tests				
ELISA	GDH (enzyme produced by *C.difficile)*	71–100	76–98	✓Easy ✓Cheap ✓Results available in hours ✓High negative predictive value **x** Cannot differentiate toxigenic and non-toxigenic strains
PCR	Genes coding for toxin A and/or B	77–99	93–99	✓Results available in hours ✓High negative predictive value **x** Commercial kits expensive **x** Does not detect toxin
Specific tests				
ELISA	Toxin A and/or B	31–99	84–100	✓Easy ✓Cheap ✓Results available in hours **x** Poorly standardised
Cytotoxic assay	Direct measurement of cytotoxic action of *C.difficile* toxin on cultured cell line	67–100	85–100	✓Gold standard **x** Expensive **x** Results take 3 days
Anaerobic culture	*C.difficile* bacteria	N/A	N/A	✓Highly sensitive **x** Expensive **x** Results take 3 days **x** Poorly standardised **x** Non-toxigenic strains can give false-positives

ELISA = enzyme-linked immunosorbent assay; GDH = glutamate dehydrogenase; N/A = not available; PCR = polymerase chain reaction.

Prevention

Reducing spread from person to person

As soon as CDI is suspected, enteric isolation is fundamental to reducing spread. All who come into physical contact with affected patients should wear disposable gloves and aprons, discarding them in clinical waste bins before leaving the patient's sideroom. Hands must then be washed with soap and water (alcohol-sanitising gel does not kill *C.difficile* spores).[36]

Reducing spread of C.difficile spores from hospital surfaces

Clinical areas must be cleaned daily with a chlorine-containing solution of at least 1,000 ppm.[36] Deep cleaning of ward areas, including beds, should be performed after discharge, transfer or death of a patient with CDI.[36]

Prescribing practice

Moving to targeted rather than broad-spectrum prescribing of antibiotics is the main way to reduce primary infection and Trusts should insist on and monitor implementation of frequently updated antibiotic prescribing guidelines.[36]

Although there have been reports of a preventive effect of probiotics in some inpatients given antibiotics,[37] the data are as yet insufficiently strong to allow recommendation of this approach routinely.[38] Avoiding inessential use of PPIs may also reduce the risk of CDI.

Conclusions

Although CDI rates in the UK have declined in the last five years,[2] its associated morbidity and mortality[34] ensure that it remains a serious concern in modern health care provision. Clinicians need to be alert to the diagnosis of CDI and to maintain close liaison with hospital infection control and

microbiology teams in order to maximise its prevention and optimise its management.

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