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Clostridium difficile diarrhoea

A side effect of health care

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Clostridium difficile **is the most common bacterial cause of antibiotic-associated diarrhoea. Treatment with metronidazole is usually successful but recurrence is common. A range of treatment options exist for recurrence, from antibiotics to faecal microbial transplantation.**

REMEMBER

- Depending on the antibiotic, between 5 and 25% of patients prescribed a course of antibiotics will experience diarrhoea. *Clostridium difficile* is the most commonly identified bacterial cause, accounting for 10 to 20% of cases. Severe *C. difficile* infection can lead to toxic megacolon, perforation and death through enterotoxin-mediated inflammation.
- Rates of *C. difficile* colonisation range from 5% in healthy adults up to 50% in healthcare workers, nursing home residents and hospitalised patients.
- *C. difficile*-associated diarrhoea (CDAD) generally requires a disturbance of the faecal microbiota (most commonly caused by antibiotic use) and colonisation through the faecal–oral route. *C. difficile* spores are detectable on the hands, stethoscopes and clothing of healthcare workers and can persist for months on objects such as toilets and other hospital furnishings.
- Soap and water are effective for removing spores from hands, but alcohol-based hand washes are not. Ten per cent hypochlorite solution (bleach) is effective for environmental cleaning.
- The risk of developing CDAD is increased seven to 10 times in the month following a course of antibiotics and persists for up to three months. Antibiotics most associated with CDAD include penicillins, cephalosporins, clindamycin and fluoroquinolones. Concomitant use of probiotics does not reduce the risk of CDAD in patients prescribed a course of antibiotics.
- Although most CDAD is associated with recent hospitalisation, community-acquired CDAD is increasing in incidence and accounts for up to 45% of cases. Proton pump inhibitor use is linked to CDAD even in patients who have not been exposed to antibiotics. Other risk factors include age over 65 years, enteral feeding, gastrointestinal surgery, obesity, chemotherapy and haematopoietic stem cell transplantation. Patients with inflammatory bowel diseases have both an increased incidence and mortality associated with CDAD.

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- Recurrent CDAD is more likely in patients aged over 75 years, those who have renal impairment and those who have a stool frequency of greater than 10 per day at the beginning of the illness.
- Nontoxigenic *C. difficile* does not cause CDAD and does not require treatment. Toxin A (enterotoxin) causes inflammation, mucosal injury and intestinal fluid secretion through neutrophil activation and cytokine upregulation. Toxin B (cytotoxin) is 10 times more potent. A hypervirulent strain of *C. difficile* (NAP1/BI/027) that produces an additional 'binary toxin' is associated with increased mortality.

ASSESSMENT

- Patients with new-onset watery diarrhoea and abdominal cramps should be assessed for CDAD, especially if they have been hospitalised or had a course of antibiotics.
- Signs of severe disease include diffuse abdominal tenderness, distension, temperature over 38.5°C and leucocytosis (more than 15 x 10^9 white cells/L). Patients with severe disease are at risk of developing fulminant colitis requiring emergency colectomy and should be admitted to hospital.
- Stool testing should be carried out. Most pathology laboratories test for *C. difficile* only if specifically requested. The tests usually performed include:
  - enzyme immunoassay (EIA) for glutamate dehydrogenase (an essential enzyme); this test cannot distinguish toxigenic and nontoxigenic *C. difficile* strains but is useful before specific EIA toxin testing
  - EIA for toxins A and B, which has reasonable sensitivity (75%) and good specificity (99%)
  - polymerase chain reaction (PCR) tests for toxins A and B, which are sensitive and specific but are more expensive than EIA
  - faecal culture and toxin studies using cell culture cytotoxicity assays; these are the 'gold standard' but require more than 48 hours for a result.
- Colonoscopy (which may be limited to inspection of the rectum and sigmoid) should be considered if:
  - stool tests are negative despite high suspicion for CDAD
  - an urgent diagnosis is required or
  - the presentation is atypical, such as ileus.
- Pseudomembranes are a common finding in CDAD. These consist of serum proteins, mucus and inflammatory cells (Figures 1 and 2).
- CDAD recurs in 20% of patients even after effective initial treatment. Recurrence is usually due to relapse; spores are not killed by antibiotic treatment and can germinate after cessation of treatment. Retesting is required only if symptoms persist, as asymptomatic carriage of *C. difficile* may occur after treatment and does not itself require treatment.

MANAGEMENT

First-line therapy

- First-line therapy for mild to moderate CDAD is discontinuation of the antibiotic (if possible) and oral metronidazole (400 mg three times daily for 10 days).
- Severe CDAD is treated with oral vancomycin (125 mg four times daily

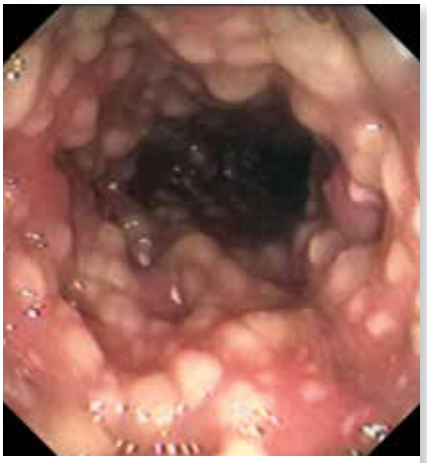

Figure 1. Endoscopy of the colon in a patient with pseudomembranous colitis caused by *Clostridium difficile*. Note the pseudomembranes covering the colonic mucosa.

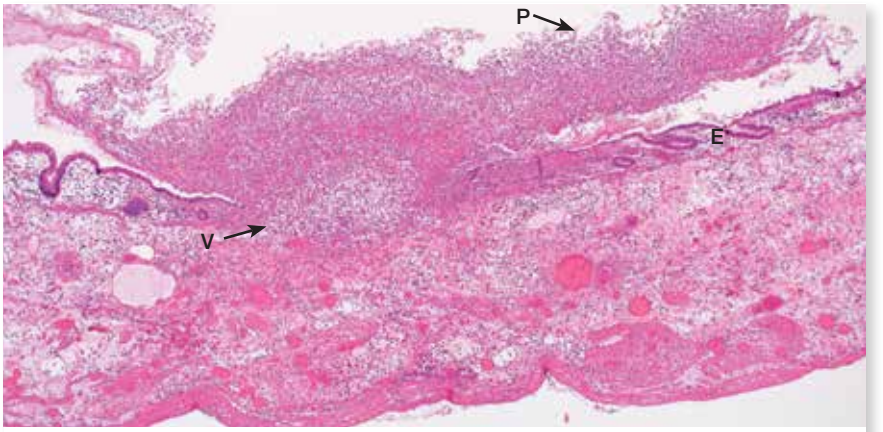

Figure 2. Low magnification photomicrograph of a section of colonic epithelium from a patient who required a colectomy for severe pseudomembranous colitis. Note the characteristic appearance of a 'volcanic eruption' (V) from the epithelial layer (E), comprising karyorrhectic debris and neutrophils within a pseudomembrane (P), which exudes from degenerated crypts.

IMAGE COURTESY OF DR MITALI FADIA, DEPARTMENT OF ANATOMICAL PATHOLOGY, CANBERRA HOSPITAL, ACT.

for 10 days), which has low intestinal absorption and achieves high concentrations in the bowel.
- Complicated CDAD (with toxic megacolon, ileus) is treated using intravenous metronidazole (500 mg three times daily) and oral or rectal vancomycin (500 mg four times daily).
- Other options for severe disease include tigecycline and intravenous immunoglobulins, which may provide passive immunotherapy against toxins A and B.

Treatment of relapse and recurrence

- Twenty per cent of patients will have a relapse, and 60% of these will have further recurrences, usually within two months of the initial infection. An expert opinion is recommended in the case of recurrence.
- Treatment of relapse or recurrence is with metronidazole or vancomycin. Fidaxomicin (200 mg twice a day orally for 10 days), a member of a new family of antibiotics termed macrocycles, is as effective as vancomycin for recurrence.
- A tapered regimen of vancomycin is sometimes used, which targets persisting spores. This would usually be undertaken with the advice of an infectious diseases physician.
- In specialised centres, recurrent CDAD can be treated using faecal microbial transplantation, which can be more effective than further antibiotic therapy. Donor stool is sourced from a household member who has not had recent exposure to antibiotics or from a universal donor. Donors are screened for bloodborne and intestinal infections.

Prevention

- Patients who recover from CDAD and subsequently require antibiotic therapy for another condition should be monitored carefully. Antibiotics that carry a lower risk of CDAD (e.g. aminoglycosides, tetracyclines and metronidazole) should be considered over those with a higher risk.
- Prevention of the spread of spores is vital to reducing the incidence of CDAD. The key aspects are:
  - isolation of affected patients
  - effective hand washing
  - environmental decontamination.
- Healthcare workers in contact with affected patients should wash their hands with soap and water as alcohol-based hand washes are ineffective. Gloves and gowns should be worn. Contaminated furnishings and equipment should be cleaned using 10% bleach. MT

FURTHER READING

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COMPETING INTERESTS: None.