An approach to antibiotic-associated diarrhoeal syndromes

Poor use of antibiotics has resulted in the emergence of superinfections, among them antibiotic-associated diarrhoea.

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Among the advances in modern medicine so far, the advent of antibiotics has had one of the most significant impacts on patient survival. Unfortunately with all that is good must come some that is bad! The emergence of superinfections and multidrug-resistant pathogens is a direct consequence of poor antibiotic stewardship and indiscriminant usage of available antibiotics. One of the greatest challenges currently facing the medical fraternity is the increasing emergence of antibiotic-associated diarrhoea.[1]

Diarrhoea is defined as increased stool weight, in excess of 200 g/day, and having more than 3 bowel movements per day. An acceptable clinical definition for diarrhoea is having more than 3 loose or watery bowel movements per day compared with individual baseline. Diarrhoeal stools are defined as those that take the shape of their container.

Faecal leukocytes and lactoferrin help in the distinction between inflammatory and non-inflammatory causes of diarrhoea.

Aetiology of acute diarrhoeal syndromes

The chronicity of symptoms helps to distinguish acute from chronic diarrhoea and helps to guide the diagnostic approach and treatment strategy. Acute diarrhoea usually lasts less than 2 weeks and is often infectious in nature. Diarrhoea is considered to be persistent if it lasts more than 2 weeks and chronic if it lasts more than 4 weeks. The initial work-up for an acute diarrhoeal illness should include microscopy of the stool specimen. This information must be interpreted in relation to the patient's clinical presentation and medical history.

The pathogenesis of acute diarrhoea can be divided into 4 broad categories:

- osmotic
- secretory
- inflammatory
- infective.

Faecal leukocytes and lactoferrin help in the distinction between inflammatory and non-inflammatory causes of diarrhoea. Elevated faecal leucocytes and the isolation of pathogenic microbes strongly suggest an infective aetiology of the diarrhoea. The absence of an identifiable microbe or microbial toxin with the presence of red blood cells may suggest an inflammatory bowel disease or underlying bowel ischaemia as possible aetiologies in the appropriate clinical setting.

The aetiology of non-infectious, non-inflammatory acute diarrhoea includes:

- **Faecal impaction** – this is associated with absent or hypoactive bowel sounds, minimal abdominal distension and no systemic signs of note.
- **Side-effects of drugs** – especially osmotic laxatives, digitalis, β-blockers, ACE inhibitors, antiarrhythmics, diuretics, cholesterol-lowering drugs and anti-Parkinson disease drugs such as levodopa.
- **Secretory diarrhoea** – this is usually associated with toxin production from pathogenic bacteria, but occasionally may be due to an underlying abdominal malignancy.[2]
- **Osmotic diarrhoea** – this is usually due to malabsorption syndromes, bowel bacterial overgrowth, and blind-loop syndromes. One of the most underrecognised causes of osmotic diarrhoea in hospitalised patients is enteral feeding. This can occur in up to 39% of patients in general medical beds and in up to 63% of patients in critical care units. It is believed that the composition of the enteral formula coupled with broad-spectrum antibiotics may have an adverse effect on the colonic microflora. The colonic microflora normally produces short-chain fatty acids (SCFAs); these SCFAs are tropic to the colonic flora and are used as a fuel by the enterocytes. The SCFAs are normally absorbed in the colon, enhancing water and electrolyte absorption. Thus, the excess of medium- and long-chain fatty acids in the supplemented enteral feeds and lack of metabolism to SCFAs by the disrupted enteral microflora exacerbates the osmotic effects of enteral feeds.[3]

Antibiotic-associated diarrhoea

Antibiotic-associated diarrhoea is defined as 'otherwise unexplained diarrhoea that occurs in association with the administration of antibiotics'. The frequency of this complication varies among antibacterial agents. Diarrhoea occurs in approximately 5 - 10% of patients who are treated with ampicillin, 10 - 25% of those who are treated with amoxicillin-clavulanate, 15 - 20% of those who receive cefixime, and 2 - 5% of those who are treated with other cephalosporins, fluoroquinolones, azithromycin, clarithromycin, erythromycin, and tetracycline.

The pathogenesis is thought to be related to the fact that antibiotics may substantially reduce the concentration of faecal anaerobes that are normally present. As a consequence, the metabolism of carbohydrates may decrease, which causes osmotic diarrhoea. Furthermore, the rate of breakdown of primary bile acids may be reduced, and these are potent colonic secretory agents. Antibiotic-associated diarrhoea may also be caused by other enteric pathogens, by the direct effects of antimicrobial agents on the intestinal mucosa (e.g. macrolide antibiotics), and by the metabolic consequences of reduced concentrations of faecal flora.

The clinical findings in antibiotic-associated diarrhoea range from colitis to nuisance diarrhoea. Nuisance diarrhoea is defined as frequent loose and watery stools with no other complications. Antibiotic-associated colitis maybe associated with abdominal cramping, fever, serum leukocytes, faecal leukocytes, hypoalbuminaemia from malabsorption, colonic thickening on computed tomography (CT) and pseudomembrane formation.

The most common pathogen implicated in antibiotic-associated diarrhoea is *Clostridium difficile*. It accounts for between 10% and 20% of the cases of antibiotic-associated diarrhoea. Other enteric pathogens that can cause diarrhoea include *Salmonella* sp., *Clostridium perfringens, Staphylococcus aureus* and possibly *Candida albicans*. The remainder of this article will be dedicated to *C. difficile*-associated diarrhoea (CDAD) because it is emerging as a significant pathogen in the aetiology of nosocomial diarrhoea and carries with it a significant mortality risk.

C. difficile-associated diarrhoea

C. difficile is the leading identified cause of nosocomial diarrhoea associated with antibiotic therapy. About 20% of hospitalised patients who receive antibiotics will develop diarrhoea. *C. difficile* has been implicated as the causative organism in 10 - 25% of those patients who have antibiotic-associated diarrhoea. Mortality figures range from 6% to 30% depending on the severity of the underlying illness (co-morbidities) and the complications associated with the *Clostridium* infection. Furthermore, and most importantly, the length of stay of hospitalised patients with CDAD is prolonged. The average length of stay is increased from 18 days to 30 days. Unfortunately, this added time to discharge is associated with increased hospital costs and further nosocomial complications.[4]

C. difficile is an obligate, anaerobic, spore-producing Gram-positive rod. It is a large microbe and grows well on a culture medium consisting of cycloserine, cefoxitin, and fructose agar in an egg-yolk agar base. It produces 3 toxins: toxin A, toxin B, and the binary toxin. Each toxin has the potential to contribute to the underlying diarrhoeal disease process. Toxin A causes fluid secretion and intestinal inflammation and is a chemo-attractant for neutrophils. Toxins A and B activate the release of cytokines from monocytes. Fomites containing *C. difficile* spores can be isolated from various hospital surfaces including furniture, bedpans, toilets, bathtubs, stethoscopes, clothing and hands.

Risk factors for acquiring CDAD

The main risk factor associated with symptomatic infection by *C. difficile* is antibiotic treatment within the previous 6 - 8 weeks. The most commonly implicated agents are clindamycin and the cephalosporins, but the recent surge of cases suggests that the newer fluoroquinolones with the extended anaerobic cover may now also play a prominent role. The antimicrobials least associated with CDAD are aminoglycosides, co-trimoxazole, benzyl penicillin and ureido or piperacil penicillins.

The next important risk factor for the infection is age.[5] The increased susceptibility of the elderly, especially patients over the age of 65, may be related to the presence of underlying co-morbidities to the higher exposure to antimicrobials in this age group, or to the presence of lower antibody titres against *C. difficile* (senile immune paresis). Oncological diseases, haemodialysis, immunosuppression, ulcerative colitis, malnutrition, solid-organ transplantation and HIV infection are also important risk factors.

Additional predisposing factors include the regular use of proton pump inhibitors and histamine-2 receptor blockers.[6] It has been theorised that the use of gastric acid suppressive medications can decrease the acid concentration of the stomach, thereby permitting *C. difficile* to pass unharmed into the duodenum and from there into the colon.

Another procedure that has been associated with increased risk of *C. difficile* infection is post-pyloric tube feeding.[7] The exact pathogenetic mechanism whereby post-pyloric enteral feeding increases the risk of developing CDAD has not been clearly elucidated. The proposed mechanisms include:

- handling of equipment by contaminated health care workers
- tube feeding, which renders the intestinal environment more conducive to growth of *C. difficile* infection
- bypassing of stomach acid preventing *C. difficile* sterilisation.

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Pathogenesis of CDAD

There are several theories as to why patients develop CDAD, but the most widely accepted view is that there is a disruption of the indigenous microflora of the bowel. The microflora is of paramount importance in maintaining innate host defense mechanisms through an inhibitory effect on incoming, non-indigenous bacterial species. This phenomenon has been called 'colonisation resistance'. How the colonised bacteria exert their inhibitory effects on invading organisms is not fully understood, but probably reflects competition for nutrients and adhesion sites, and suppression of growth by local metabolic products such as hydrogen sulphide and volatile fatty acids.

However, if the normal flora is disrupted, colonisation resistance is lost and organisms such as *C. difficile* then proliferate within the bowel and become pathogenic. The most frequent reason for the loss of the indigenous microflora of the bowel is exposure to antimicrobial agents, especially those antibiotics that exert the greatest effect on colonic bacteria. Moreover, colonic populations of bifidobacteria, which are thought to be protective, are known to decline naturally with advancing age.

After colonisation the *C. difficile* organism has a number of virulence factors that assist it in adherence to the mucosal lining. These include flagellar proteins, surface-layer proteins and surface-exposed adhesion proteins. The organism then produces cytopathic toxins termed toxin A, toxin B and a binary toxin. Toxin A, apart from being cytopathic, is also chemo-attractant for neutrophils and loosens tight junctions between the epithelial cells that facilitate entry of toxin B into the epithelial cells. The subsequent damage to the epithelial layer by the toxins and the associated severe inflammatory response lead to the clinical syndrome of CDAD.

Thus CDAD results when a pathogenic strain of *C. difficile* first colonises and then causes disease in patients rendered susceptible by exposure to antibiotics, old age, or immunosuppression by toxin production.[8,9]

Severity of CDAD

The severity of the disease depends on several factors. The most important of these are:

- host characteristics, which include immune status, nutritional status, underlying co-morbidities and age of the patient
- pathogen characteristics, especially organism virulence, innoculum burden and ability to produce pathogenic toxins, especially the binary toxin.

Mild CDAD is defined as the absence of any systemic symptoms coupled with mild non-bloody diarrhoea. There is no associated systemic inflammatory response and the patient's clinical and laboratory parameters are within normal range.

Moderate CDAD occurs in the setting of profuse diarrhoea that may be accompanied by marked leukocytosis, generalised diffuse abdominal pain and increased temperature. On endoscopy, white-yellowish pseudo-membranes are often present in the wall of the colon.

Severe CDAD exists with the occurrence of a paralytic ileus or toxic megacolon that may lead to decreased stools or even no diarrhoea being produced. It also can occur in the setting of peritonitis, sepsis, dehydration, and hypotension and eventually may lead to death. This represents a poor prognosis with a high mortality.

Diagnosis of CDAD

Before the diagnosis of CDAD is entertained several issues need to be taken into consideration. Firstly, diarrhoea occurring after 48 hours of hospital admission may still be community-acquired. Secondly, secretory and osmotic causes of diarrhoea need to be excluded, e.g.concomitant drugs, faecal impaction and parenteral nutrition. Finally, the temporal relationship between the development of the diarrhoea and the usage of broad-spectrum antibiotics, especially within the last 8 weeks, needs to be determined.

The sample of choice for the diagnosis of CDAD is a fresh sample of diarrhoeal stools. The gold standard for the diagnosis of the disease is the toxin-B cytotoxicity test in cell cultures. The assay is performed by exposing cell monolayers to stool filtrates, and observing the cells for evidence of cytopathic effect. The possible *C. difficile* toxin is then neutralised by cross-reacting it with *C. sordelli* antitoxin. If the cytopathic effects of the toxin can be neutralised with the antitoxin then the toxin present is presumed to be a *C. difficile* toxin. The cell cytotoxicity assay remains the only laboratory method of detecting *C. difficile* toxin by means of its biological properties but, importantly, the result can take up to 3 days to be conclusively reported.

An alternative technique is the use of enzyme-linked immunosorbent assays (ELISA), which have excellent specificity but their sensitivity allows only for the detection of toxin quantities between 100 pg and 1 000 pg. False negatives can therefore occur in up to 20% of cases. This false negativity can be reduced by repeating the study. The advantage of ELISA tests is that they are rapid, producing results within 1 hour. Furthermore, the latest ELISA can detect both toxin A and B, which improves the sensitivity of the tests.[10-12]

In most cases, endoscopy is not required to confirm the diagnosis of CDAD. It is an invasive procedure that poses an unnecessary risk for the critically ill patient. An imaging technique useful for the diagnosis of CDAD is a CT scan of the abdomen. The presence of segmental colonic wall thickness greater than 0.4 mm involving predominantly the rectum and sigmoid colon is the main finding.

Antimicrobial treatment

The most important intervention in the management of CDAD is to withdraw antimicrobials whenever possible.[13-15] This usually results in resolution of symptoms in up to 25% of patients. If this fails or is not possible, then one is forced to administer antibiotics that are effective for CDAD. Oral metronidazole (500 mg 3 times daily or 250 mg 4 times per day) and oral vancomycin (125 mg every 6 hours) have similar efficacy, with response rates near 90 - 97%, respectively. The normal duration of therapy is 10 - 14 days. The preferred method of administration is oral, as the organism is within the colonic lumen. However, metronidazole may be administered intravenously as it is actively excreted within the colonic lumen.[16,17]

Metronidazole is the initial preferred antibiotic of choice not only because of its lower costs but also because it minimises the risk of selecting vancomycin-resistant enterococci. The indications for oral vancomycin as first-choice antibiotic are:

- pregnancy
- breast-feeding
- metronidazole intolerance
- therapeutic failure of metronidazole therapy after 3 - 5 days of treatment
- patients who present with features of severe disease.

In a recently published double-blind, prospective comparison of metronidazole and vancomycin, metronidazole has been shown to be distinctly inferior to oral vancomycin in moderately severe or severe cases.[18]

Alternative antibiotcs that can be used to treat CDAD include:[16,17]

- bacitracin
- teicoplanin
- fusidic acid – but this is associated with increased recurrence rates
- rifaximin and ramoplanin, both non-absorbable rifampicin derivitaves
- nitazoxanide (500 mg twice per day): this drug blocks anaerobic metabolic pathways of micro-organisms and is effective against *C. difficile*
- tiacumicin B, a novel 18-membered macrocyclic antibiotic that is 8 - 10 times as active as vancomycin against *C. difficile*.

Non-antimicrobial treatment of CDAD

Antimotility agents are not indicated, since they impair host responses and increase the risk of toxic megacolon.

Colestipol and cholestyramine, which are exchange resins, have the ability to bind to *C. difficile* toxin, but may also to bind to antimicrobials used to treat CDAD. Therefore their clinical use is not recommended. Tolevamer is a new polyanionic resin that binds to *C. difficile* toxin only and is currently undergoing phase 4 clinical trials.[16]

Intravenous immunoglobulins have been used in patients with severe disease or multiple recurrences, but no prospective and comparative studies have established their role in the treatment of this disease.

Faecal bacteriotherapy has also been attempted in refractory patients. This involves the administration of faecal enemas, containing fresh faeces from a healthy relative to an infected patient.[17]

Surgery is a last resort for the treatment of unmanageable CDAD with toxic megacolon or colon perforations.

One of the main complications of CDAD is recurrence. A meta-analysis from 6 randomised trials showed that probiotics had significant efficacy for the management of recurrent CDAD. Probiotic therapy involves the use of live micro-organisms to repopulate the colon with normal colonic flora in the hope of preventing the colonisation or infection with *C. difficile*. Examples of probiotics include *Lactobacillus* and *Bifidobacterium*. Another such organism is the non-pathogenic yeast *Saccharomyces boulardii*. The proviso with the use of *Saccharomyces* sp. is in elderly patients and immunocompromised patients, who are at risk of developing a fungaemia, although it is very rare. Encouraging patients to add yoghurt to their diet at multiple meals can also can help to achieve the objective of probiotic supplementation.[19]

Preventive strategies

The most effective form of therapy of CDAD is to prevent colonisation and cross-infection. Therefore infection control measures are paramount in the fight against *C. difficile*.[5,7,8,13,14,16,20]

The Society of Health Care Epidemiology recommends the following:

- Antimicrobial use should be restricted after *C. difficile* colitis has been confirmed.
- Hands should be washed with an antimicrobial agent or soap after contact with patients, their body substances, or contaminated environmental surfaces. Of note, *C. difficile* spores are not eradicated with alcohol-based cleaning solutions.
- Hospital rooms occupied by CDAD-infected patients must be cleaned thoroughly with a solution containing bleach to properly disinfect all potentially contaminated environmental surfaces.
- Gloves must be used at all points of contact with patients and contaminated substances.
- Patients must be isolated in private rooms, especially if they are incontinent or have diarrhoea.
- Disposable thermometers must be used when the rate of *C. difficile* infection is high.

References

1. Granowitz E, Brown R. Antibiotic adverse reactions and drug interactions. *Crit Care Clin* 2008; 24: 421-442.
2. Musher MD, Musher B. Contagious acute gastrointestinal infections. *N Engl J Med* 2004; 2: 351-359.
3. Fishman N. Antimicrobial stewardship. *Am J Infect Control* 2006; 34: S55-63.
4. Bishara J, Peled N, Pitlik S, Samra Z. Mortality of patients with antibiotic-associated diarrhoea: the impact of *Clostridium difficile*. *J Hosp Infect* 2008; 68: 308-314.
5. Brandt LJ, Kosche KA, Greenwald DA, *et al.* *Clostridium difficile*-associated diarrhea in the elderly. *Am J Gastroenterol* 1999; 94: 3263-3266.
6. Horwood J. *Clostridium difficile* and PPIs. *Lancet Infect Dis* 2006; 6: 691.
7. Bouza E, Munoz P, Alonso R. Clinical manifestations, treatment and control of infections caused by *Clostridium difficile*. *Clin Microbiol Infect* 2005; 11(Suppl 4): 57-64.
8. Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of *Clostridium difficile*-associated disease. *Gastroenterol Clin N Am* 2006; 35: 315-335.
9. Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. *Ann Intern Med* 2006; 145: 758-764.
10. Delmee M, Van Broeck J, Simon A, *et al.* Laboratory diagnosis of *Clostridium difficile* associated diarrhoea: a plea for culture. *J Med Microbiol* 2005; 54: 187-191.
11. Mohan SS, McDermott BP, Parchuri S, Cunha AB. Lack of value of repeat stool testing for *Clostridium difficile* toxin. *JAMA* 2006; 119: 356.
12. Sloan LM, Duresko BJ, Gustafson D, Rosenblatt J. Comparison of a real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in the diagnosis of *Clostridium difficile* infection. *J Clin Microbiol* 2008; 46:1996-2001.
13. O'Conner KA, Kingston M, O'Donovan M, *et al.* Antibiotic prescribing policy and *Clostridium difficile* diarrhoea. *Ir Med J* 2004; 97: 423-429.
14. Price MF, Dao-Tran T, Garey KW, *et al.* Epidemiology and incidence of *Clostridium difficile*-associated diarrhoea diagnosed upon admission to a university hospital. *J Hosp Infect* 2007; 65: 42-46.
15. Eriksen HM, Koch AM, Elstrøm P, *et al.* Healthcare-associated infection among residents of long-term care facilities: a cohort and nested case control study. *J Hosp Infect* 2007; 65: 334-340.
16. Bouza E, Burillo A, Munoz P. Antimicrobial therapy of *Clostridium difficile*-associated diarrhea. *Med Clin N Am* 2006; 90: 1141-1163.
17. Musher DM, Aslam S. Treatment of *Clostridium difficile* colitis in the critical care setting. *Crit Care Clin* 2008; 26: 279-291.
18. Zar FA, Bakkanagari SR, Moorthi KM, *et al.* A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; 45: 302-307.
19. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis* 2006; 6: 374-382.
20. Laffan AM, Bellantoni MF, Greenough WB III, et al. Burden of *Clostridium difficile* associated diarrhea in a long-term care facility. *J Am Geriatr Soc* 2006; 54: 1068-1073.
21. Torres JF, Lyerly DM, Hill JE, Monath TP. Evaluation of formalin-inactivated *Clostridium difficile* vaccines administered by parenteral and mucosal routes of immunization in hamsters. *Infect Immun* 1995; 63: 4619-4627.
22. Kotloff KL, Wasserman SS, Losonsky GA, *et al.* Safety and immunogenicity of increasing doses of a *Clostridium difficile* toxoid vaccine administered to healthy adults. *Infect Immun* 2001; 69: 988-995.
23. Kink JA, Williams JA. Antibodies to recombinant *Clostridium difficile* toxins A and B are an effective treatment and prevent relapse of *C. difficile* associated disease in a hamster model of infection. *Infect Immun* 1998; 66: 2018-2025.
24. Kyne L, Warny M, Qamar A, *et al.* Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000; 342: 390-397.
25. Shim JK, Johnson S, Samore MH, *et al.* Primary symptomless colonisation by *Clostridium difficile* and decreased risk of subsequent diarrhoea. *Lancet* 1998; 351: 633.

In a nutshell

- The mainstay of management of patients with CDAD is to minimise the unnecessary use of broad-spectrum antibiotics.[13]
- Minimising the use of proton pump inhibitors and post-pyloric tube feeding also reduces the incidence of CDAD.
- Strict infection control is the most important prevention strategy for CDAD.
- ELISA analysis of stools for *C. difficile* toxin is a reasonable test to confirm the presence of *C.difficile* cytotoxin.
- Patients with mild to moderate CDAD should be started empirically on metronidazole.
- Oral vancomycin should only be used for recurrent or severe disease.[18] None of the newer antibiotic agents undergoing final clinical trials are superior to vancomycin or metronidazole.
- There are several vaccines undergoing clinical trials that aim to sensitise the host immune system to produce neutralising antibodies to toxins A and B, thereby preventing symptomatic infection.[21-23]
- Treatment of asymptomatic patients is currently not recommended.[24,25]