Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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Antibiotic-Associated Diarrhoea

Incidence

Antibiotic-associated diarrhoea (AAD) is a common side effect. The incidence varies between antibiotics, and has been estimated to occur in 15% of patients taking beta-lactams (although up to 25% of those taking amoxicillin/clavulanate), 2 to 5% of those taking cephalosporins, fluoroquinolones or macrolides. Rates with intravenous administration (particularly if a drug undergoes enterohepatic circulation) are similar to those with oral administration.

Mechanism

There are several mechanisms by which AAD may be caused or exacerbated:

- alteration in gut flora
- increase in gastrointestinal motility
- increase in carbohydrate content in the colon
- decrease in breakdown of bile acids

Alteration in gut flora

Antibiotics may dramatically alter the normal composition of the gut microflora, allowing other organisms (e.g. *C. difficile*) to proliferate. *C. difficile* is thought to be present in the gastrointestinal tract of 5% of healthy adults.

C. difficile infection

C. difficile infection is responsible for 10 to 20% of AAD cases and may produce severe, and sometimes fatal, complications. It is most frequently associated with the use of broad-spectrum penicillins, cephalosporins, quinolones and clindamycin.

Antibiotic-associated colitis

C. difficile toxins may cause colitis (including pseudomembranous colitis) and can result in serious underlying disease. Clinical features include fever, abdominal cramping, hypoalbuminaemia, leukocytosis, faecal leucocytes and colonic thickening. *C. difficile* is present in the majority of cases and requires prompt eradication (see table below). Other microbes have also been implicated in colitis and these include *Staphylococcus aureus, Clostridium perfringens* type A and *Klebsiella*.

Increase in gastrointestinal motility

Some antibiotics (e.g. erythromycin) increase gut motility by stimulating motilin receptors and shortening gastric emptying time. Erythromycin can be used for this prokinetic action. Other macrolides (e.g. roxithromycin) do not have this effect.

Increase in carbohydrate content in colon

Some antibiotics (e.g. metronidazole) reduce the number of faecal anaerobes, thereby reducing carbohydrate digestion and absorption. This can result in osmotic diarrhoea.

Decrease in breakdown of bile acids

Some antibiotics (e.g. metronidazole) reduce the number of faecal anaerobes, thereby reducing bile acid metabolism. Primary bile acids are potent colonic secretory agents, and an increase of these may result in diarrhoea.

Treatment

Treatment of AAD depends on whether *C. difficile* is present or not.

- Treatment of cases due to *C. difficile:*
  Stop offending antibiotic immediately and treat with either oral metronidazole (first-line) or oral vancomycin (injectable form given orally). If intravenous therapy is required, metronidazole is used.
- Treatment of cases **not** due to *C. difficile*:
  May require withdrawal of antibiotic +/- fluid and electrolyte replacement, depending on severity.

Rate of relapse after treatment of *C. difficile* with antibiotics is ~20% as spores may persist in the gut. This does not represent resistance, therefore, re-treatment with the same antibiotic is appropriate.

Summary

Diarrhoea is a common adverse effect of antibiotic therapy and may require treatment. It is necessary for *C. difficile* infection and colitis to be ruled out (*see Table 1 for differences between C.difficile-associated and non-C. difficile-associated AAD*). If infection with *C. difficile* is confirmed, prompt treatment is required.

Table 1. Differences between antibiotic-associated diarrhoea due to *C. difficile* and other causes

Characteristic	Diarrhoea due to *C. difficile*	Diarrhoea due to other causes
Commonly implicated antibiotics	Clindamycin, cephalosporins, penicillins, quinolones	Clindamycin, cephalosporins, amoxicillin/clavulanate
History	Usually no relevant history of antibiotic intolerance	History of diarrhoea with antibiotic
Clinical features		
- Diarrhoea	May be florid; often evidence of colitis (cramps, fever, faecal leucocytes)	Usually moderate; no colitis
- CT findings	Evidence of colitis (not enteritis) common	Usually normal
- Complications	Hypoalbuminaemia, toxic megacolon, anasarca	Possibly dehydration
Stool analysis	*C. difficile* toxin positive	*C. difficile* toxin negative
Treatment	Prompt; metronidazole po 400mg TDS or 500mg IV Q8H, or vancomycin 125-500mg po QDS (10 days)	Usually self-resolving