Acute diarrhoea and fever

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ABSTRACT Although infectious agents remain the most common causes of acute diarrhoea and fever amongst otherwise healthy adults, their true incidence remains considerably underestimated and the epidemiology is changing. *Campylobacter* species are now the most frequently isolated organisms to cause sporadic infective gastroenteritis in the UK. *Norovirus* infections have increased in importance over the last decade whilst *Salmonella* infections have declined. *Escherischia coli* O157 infection has attracted significant media interest but remains a rare, if serious, cause of illness. A clear history and targeted investigations will help to identify the causative organism. Negative stool cultures are relevant and should lead to consideration of alternative diagnoses. Management involves careful infection control, appropriate fluid replacement, and the avoidance of antibiotic therapy except in specific circumstances. The significant likelihood of alternative, non-infectious causes of acute diarrhoeal illness must be considered, particularly in the elderly.

KEYWORDS Bacterial infection, diarrhoea, fever, viral infection

LIST OF ABBREVIATIONS *Clostridium difficile*-associated diarrhoea (CDAD), haemolytic uraemic syndrome (HUS), ova, cysts, and parasites (OCP), Shiga-toxin producing *E. coli* (STEC)

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INTRODUCTION

Diarrhoeal disease is an important cause of morbidity worldwide and represents a leading cause of childhood death in the developing world. In the developed world, the mortality rate has fallen sharply, due to a decline in illness caused by *Clostridium perfringens* and *Salmonellas*. The elderly remain especially susceptible to the complications of diarrhoea and account for 85% of related deaths.

Diarrhoea may be defined as acute if present for less than two weeks, persistent if present for 2–4 weeks, and chronic if greater than four weeks in duration. Acute diarrhoea and fever may be the presenting symptoms of a number of underlying conditions and although infectious agents account for 90% of cases, inflammatory bowel disease, ischaemic colitis, acute diverticulitis, toxins, medications, and overflow from constipation should also be considered.

INFECTIOUS GASTROENTERITIS

The majority of patients with acute diarrhoea do not seek medical attention, and investigations are frequently omitted in those who do, therefore the prevalence of infectious diarrhoea is grossly underestimated. Most cases are viral with bacterial stool cultures positive in less than 5% of presentations.

Higher rates of stool culture positivity are observed in more severe cases, those with bloody diarrhoea, and those admitted to hospital.

Patients at increased risk of infectious gastroenteritis include travellers who have visited tropical or semitropical regions, the elderly, men who have sex with men, infants, the immunocompromised, or those who have received antibiotic agents.

In the UK, notifications of organisms isolated in infectious gastroenteritis are collated by the Health Protection Agency and Health Protection Scotland. *Campylobacter* species (46%) are the most commonly isolated organisms and account for almost half of confirmed infections. *Rotavirus* (19%), small round structured virus (14%), and *Salmonella* (12%) infections are confirmed with similar frequencies. Shiga toxin-producing *Escherischia coli* (2%) and *Shigella* (1%) infections are infrequent.

CLINICAL FEATURES

A careful history may determine a possible source of infection, or whether the diarrhoea is of small or large bowel origin, thereby indicating the most likely pathogen (see Table 1). Relevant details are the duration of diarrhoea, the frequency and volume of stools, and the presence of blood or fever. Suspect foods within

TABLE 1 Major food-borne organisms by principal presenting gastrointestinal symptom. (From UptoDate, Waltham, Massachussetts, USA. © 2006 UptoDate.)

Major presenting symptom	Organism	Incubation period	Likely food sources
Vomiting	*S. aureus*	1–6 h	Prepared foods (salads, dairy, meat)
	B. cereus	1–6 h	Rice, meat
	Norwalk-like viruses	24–48 h	Shellfish, prepared foods, sandwiches, fruit
Watery diarrhoea	*C. perfringens*	8–16 h	Meat, poultry, gravy
	Enterotoxigenic *E. coli*	1–3 days	Faecally contaminated food or water
	Enteric viruses	10–72 h	Faecally contaminated food or water
	C. parvum	2–28 days	Vegetables, fruit, unpasteurised milk, water
Inflammatory diarrhoea	Campylobacter	2–5 days	Poultry, unpasteurised milk, water
	Non-typhoidal salmonella	1–3 days	Eggs, poultry, meat, unpasteurised milk
	VTEC*	1–8 days	Ground beef, unpasteurised milk, water, raw vegetables
	Shigella	1–3 days	Faecal contamination of food and water
	Vibrio parahaemolyticus	2–48 h	Raw shellfish

*VTEC: verocytotoxin-producing *E. coli*.

relevant incubation periods, recent antibiotic use or travel, hobbies, pets, medications, and affected contacts should also be considered. Indications for hospitalisation and investigation include profuse diarrhoea with signs of hypovolaemia, grossly bloody stools, fever, duration greater than 48 hours without improvement, severe abdominal pain, and diarrhoea in the elderly or immunocompromised.

Incubation period

Symptoms that begin within six hours suggest the ingestion of preformed toxin of *Staphylococcus aureus* or *Bacillus cereus*. Symptoms that occur 8–14 hours after ingestion suggest *C. perfringens*. Symptoms that begin more than 14 hours after ingestion can result from viral or bacterial infection.

Fever

Fever suggests infection with invasive bacteria such as *Campylobacter, Salmonella,* or *Shigella*, enteric viruses, or a cytotoxin-producing organism such as *Clostridium difficile* or STEC.

Diarrhoea

The enteric locus of infection and the dominant pathogenic process will determine the clinical presentation.

Acute dysentery is defined as frequent, small bowel movements accompanied by blood and mucous with tenesmus or pain on defecation. The syndrome implies inflammatory invasion of the colonic mucosa and in this context, invasive bacteria such as *Campylobacter, Shigella,*

and STEC are the most likely causes. Faecal leukocytes are present. The epidemiological patterns of acute dysentery are influenced by the low inoculum required for infection and consequently there is a high risk of person-to-person spread.

Large-volume watery diarrhoea and diffuse abdominal cramps are typical of small intestinal infection. There is only a modest increase in the number of stools because the colonic reservoir is intact. This is a non-inflammatory process confirmed by the absence of faecal leukocytes. The diarrhoea is mediated by bacterial enterotoxins that alter fluid and electrolyte transport (*Vibrio cholerae,* enterotoxigenic *E. coli,* enteropathogenic *E. coli, Salmonella* species, *Cryptosporidium, Clostridium perfringens, Bacillus cereus*) or organisms that characteristically affect the proximal small bowel (*Giardia lamblia, Rotavirus, Norovirus*: previously known as Norwalk agent).

INVESTIGATIONS

Faecal leukocytes

The ability of faecal leukocytes to predict inflammatory diarrhoea has varied greatly, with reported sensitivity and specificity ranging from 20–90%. Consequently, it is not recommended as a routine investigation of diarrhoea.

Stool cultures

Stool culture is important in those with severe illness, the immunocompromised, and for employees such as food handlers, who require negative stools to return to work. A routine culture will identify *Campylobacter,*
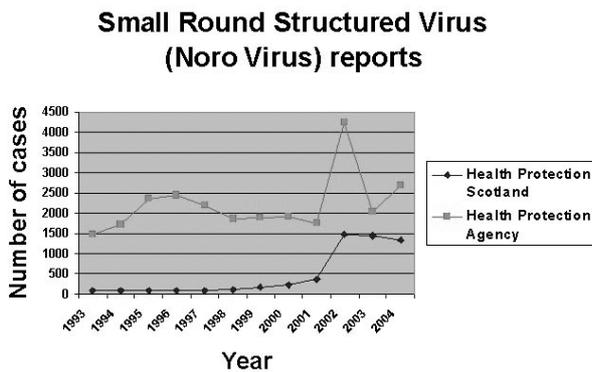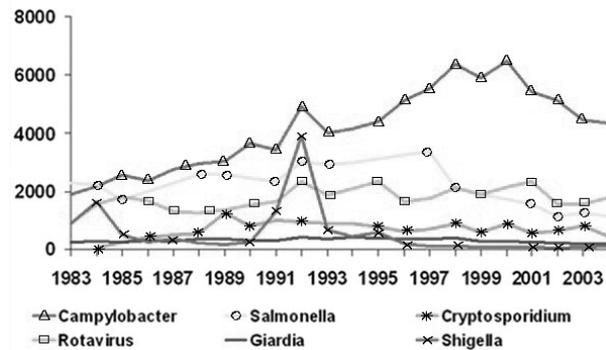
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Small Round Structured Virus (Noro Virus) reports

Salmonella, and *Shigella*. Culture for Shiga toxin-producing organisms such as *E. coli* O157, although requiring a specific McConkey sorbital medium, is now carried out routinely in the UK. Bacterial pathogens are excreted continuously and a negative result is generally accurate. Stool cultures are of little value in those developing diarrhoea following more than 72 hours hospitalisation, in whom stool examination for *C. difficile* toxin is a much more relevant investigation.

Routine stool examination for OCP, such as *Giardia*, *Cryptosporidium, Cyclospora, Entamoeba histolytica*, is not cost effective. Stools should be investigated for OCP in cases of persistent diarrhoea, patients who have travelled to an endemic area such as Eastern Europe, within a community water-borne outbreak, in men who have sex with men, and in cases of bloody diarrhoea where amoebiasis is suspected. Due to the intermittent excretion of OCP, three stool specimens should be sent on consecutive days.

Further investigation

Flexible sigmoidoscopy or colonoscopy are rarely indicated but may be required to identify inflammatory bowel disease or ischaemic colitis, and in immunocompromised patients. Additional investigations are determined by the most likely pathology, and abdominal CT, barium enema, or isotope-labelled white cell scan may be required in specific circumstances.

MANAGEMENT

All suspected infective cases require single-room isolation with 'enteric' precautions.

Fluid and electrolyte replacement constitutes the cornerstone of treatment of diarrhoeal illness. Intravenous rehydration is grossly overused and rehydration should preferably be by the oral route with solutions that contain water, salt, and sugar. Antimotility

agents should be avoided as they may exacerbate or prolong symptoms.

In otherwise healthy patients there is a lack of benefit from antibiotic therapy. The British Infection Society has identified patients with 'high risk criteria' for whom antibiotics should be considered on admission. These are:

- Age >60 years
- Reduced gastric acid
- Immunocompromised
- Significant co-morbidity
- Elevated white cell count
- Fever or bloody diarrhoea

The duration of gastroenteritis and the most likely organism should also be taken into consideration. If criteria for antibiotic therapy are met, oral ciprofloxacin, to which the majority of isolates remain susceptible, is generally recommended.

IMPORTANT ORGANISMS

Viral infections

Thirty to forty per cent of all acute episodes of gastroenteritis are caused by viruses, which may be grouped into four categories: *Rotavirus*, enteric adenovirus, astrovirus, and calicivirus (including *Norovirus*).

Norovirus infections have become the most important cause of institutional, particularly healthcare-associated, outbreaks of gastroenteritis and are difficult to contain. (See Figure 1.) A large human reservoir of infection, a very low infectious dose, and the ability to be transmitted by a variety of routes, including aerosol and faecal–oral, contribute to the impact of the disease. Infection by this virus has now become the most common cause of gastroenteritis in adults in the UK. A new genotype (2.4) has emerged recently and the previous clear winter peak has changed with the

loss of the seasonal characteristic. Generally there is little merit in sending stools for viral cultures or PCR as knowing the identity of the virus does not alter management, which involves careful infection control and supportive fluids as above.

Bacterial pathogens

The annual number of cases of notified gastroenteritis by causative organism is shown in Figure 2.

Campylobacter

Campylobacter is now the most common cause of bacterial infective gastroenteritis in the UK. Infection is transmitted from raw or undercooked meat, especially poultry, and is often linked to fast food outlets, unpasteurised milk, and domestic pets with diarrhoea. Person-to-person transmission is unusual. The organism does not multiply in food and food-borne outbreaks are rare. The incubation period is 2–5 days. Presentation is usually with abdominal pain and bloody diarrhoea, and vomiting is uncommon. *Campylobacter* may be confused with ulcerative colitis or Crohn's disease and findings on rectal biopsy are not specific. Toxic megacolon has been reported and may necessitate colectomy. Transient bacteraemia occurs in 1% of infections and does not require specific treatment in the immunocompetent host. The majority of patients do not require antibiotics and although patients with 'high-risk' features are usually treated with ciprofloxacin, significant resistance is emerging and recommendations may change.

Salmonella

Salmonella infections have reduced considerably in the UK over the last decade largely due to rigorous management of infection in poultry flocks. Transmission is predominantly from red and white meats, raw or undercooked eggs, milk, and dairy products. Person-to-person spread is common during the diarrhoeal phase of illness. Salmonellosis presents with watery diarrhoea, vomiting, and fever. Blood cultures are positive in 1–4% of infections and the elderly and the immunocompromised are at increased risk of both bacteraemia and metastatic infection. Endovascular infection occurs in 10–25% of persons over 50 years of age, usually involves the aorta, and most commonly results from seeding of atherosclerotic plaques or aneurysms. Mortality rates from endovascular infection range from 14–60% and are lower with prompt diagnosis and combined medical and surgical therapy. Ciprofloxacin is the antibiotic of choice for 'high-risk' patients with severe gastrointestinal infection and bacteraemia. Prolonged antibiotic therapy is required for endovascular infection. Following the resolution of gastrointestinal symptoms the mean duration of carriage is 4–5 weeks but may be prolonged by antibiotic therapy.

Shiga-toxin producing E. coli

Shiga-toxin producing *E. coli* infections such as *E. coli* O157, although infrequent, attract significant attention because of potentially serious complications, particularly the HUS. Transmission is from undercooked ground beef, water, and cross-contamination of cooked products. The low infectious dose of STEC strains, estimated to be less than 100 organisms, facilitates transmission. Gastrointestinal symptoms range from mild diarrhoea to haemorrhagic colitis with often dominant and severe abdominal pain.

Haemolytic uraemic syndrome develops in 10% of patients overall, with children under the age of five and the elderly most at risk. Haemolytic uraemic syndrome is characterised by acute renal failure, haemolytic anaemia, and thrombocytopenia. Although the kidneys are the most vulnerable target organs, any tissue may be affected. Mortality rates following HUS have improved recently but remain around 5% in children and more in the elderly due to an increased incidence of neurological complications. Antibiotics should be avoided, as there is some evidence that they may promote the release of Shiga toxin and increase the risk of HUS.

Clostridium difficile-*associated diarrhoea*

Clostridium difficile-associated diarrhoea usually occurs 4–9 days after starting antibiotics, and almost all antibiotics have now been implicated in causation. It predominantly affects frail elderly people in whom the mortality rate may be as high as 25%. Clinical severity varies from mild watery diarrhoea to severe bloody diarrhoea. Complications include hypovolaemic shock, toxic megacolon, perforation, haemorrhage, and sepsis. *Clostridium difficile* is spread indirectly by the faecal–oral route via spores left on surfaces. *Clostridium difficile*-associated diarrhoea is characterised by progression from an uncolonised state through to *C. difficile* colonisation followed by, in response to antibiotic pressure, toxin production. Asymptomatic colonisation occurs in over 20% of hospital patients and UK infection rates are increasing exponentially, particularly in vulnerable hospitalised patients.

To eradicate CDAD, oral metronidazole, 400 mg every eight hours, is the treatment of choice. Oral vancomycin, in an initial dose of 125 mg every six hours, is at least as effective as metronidazole but in view of its greater cost should be reserved for those who have failed to respond to metronidazole or for the severely unwell patient. If patients are unable to take oral medications, a nasogastric tube is necessary because the enteral route is required to treat infection. Current antibiotic therapy should be withdrawn if possible. Evidence is inadequate to support the use of prebiotics or probiotics for treatment of established CDAD.

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KEYPOINTS

- All cases of acute diarrhoea must be considered infective until proven otherwise and managed in appropriate single-room isolation with 'enteric precautions'.
- The incidence of the well-known pathogens in the aetiology of food poisoning/acute gastroenteritis has changed significantly in the last decade.

- In adults, viral gastroenteritis due to *Norovirus* has become a major cause of institutional outbreaks of diarrhoea.
- *Clostridium difficile* is an increasingly important cause of healthcare-associated infection.
- Diarrhoea and fever as a syndrome has a heterogeneous aetiology and antibiotics should not be administered unless there are indications of specific risk or severity.

FURTHER READING

- Farthing M, Feldman R, Finch R *et al.* The management of infective gastroenteritis in adults. A consensus statement by an expert panel convened by the British Society for the Study of Infection. *J Infect* 1996; **33(3):**143–52.
- Riley TV. Nosocomial diarrhoea due to *Clostridium difficile. Curr Opin Infect Dis* 2004; **17(4):**323–7.
- Health Protection Agency. www.hpa.org.uk/
- Tarr PI. *Escherichia coli* O157:H7: clinical, diagnostic, and epidemiological aspects of human infection. *Clin Infect Dis* 1995; **20(1):**1–8; quiz 9–10.

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