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Acute Gastroenteritis in Children

What Role for Antibacterials?

Nopaorn Phavichitr and *Anthony G. Catto-Smith*

Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Parkville, Victoria, Australia

Abstract

The aim of this article is to define the currently accepted role of antibacterials in the treatment of acute gastroenteritis in children. Most cases of acute gastroenteritis in children are viral, self-limited, and need only supportive treatment. Appropriate fluid and electrolyte therapy, with close attention to nutrition, remain central to therapy.

Antibacterial therapy serves as an adjunct, to shorten the clinical course, eradicate causative organisms, reduce transmission, and prevent invasive complications. Selection of antibacterials to use in acute bacterial gastroenteritis is based on clinical diagnosis of the likely pathogen prior to definitive laboratory results. Antibacterial therapy should be restricted to specific bacterial pathogens and disease presentations. In general, infections with *Shigella* spp. and *Vibrio cholera* should usually be treated with antibacterials, while antibacterials are only used in severe unresponsive infections with *Salmonella, Yersinia, Aeromonas, Campylobacter, Plesiomonas* spp., and *Clostridium difficile*. Antibacterials should be avoided in enterohemorrhagic Escherichia coli infection. However, empiric therapy may be appropriate in the presence of a severe illness with bloody diarrhea and stool leucocytes, particularly in infancy and the immunocompromised.

The benefits and risks of adverse drug reactions should be weighed before prescribing antibacterials. Moreover, a major concern is the emergence of antibacterial-resistant strains due to the widespread use of antibacterial agents.

Acute gastroenteritis is one of the most common illnesses amongst children, accounting for 16% of childhood emergency department presentations.[1] The worldwide admission rate for acute gastroenteritis has increased significantly during the past decade, and each year diarrheal disease accounts for the lives of nearly 2 million children under the age of 5 years.[2] Clinical outcome and therapies are best understood by classifying acute gastroenteritis on the basis of specific causative pathogens. Although this approach is useful, it is important to recognize that no pathogen is isolated in 20–30% of patients.[3,4]

Rotavirus is still the most common cause of acute gastroenteritis, both in developed and developing countries (table I).[3-6] There are no specific antimicrobial agents for viral gastroenteritis.[7] The most commonly recognized bacterial enteric pathogens in developing countries are *Escherichia coli*, *Salmonella* and *Shigella* spp., whereas *Campylobacter* and *Salmonella* spp. are the most common causes of bacterial enteritis in developed countries.[5,6] Bacterial enteritides are usually self-limited diseases in healthy children. However, in a minority of children, the clinical course may be complicated and become life-threatening. Antibacterials are not required or appropriate as routine therapy for all cases of bacterial gastroenteritis. When used, their role is to shorten and lessen the severity of the clinical course, decreasing the excretion of causative organisms in order to reduce the spread of infection and to prevent serious extraintestinal complications.[7-9] Viral infections tend to target the small bowel, resulting in mid-abdominal cramping pain, with large volumes of watery stool. On stool examination, blood and leucocytes are found to be rare. By comparison, bacteria enteritides tend to target the large bowel, causing lower abdominal pain with smaller volumes of bloody mucoid

Table I. Enteric pathogens isolated from children, Royal Children's Hospital (RCH), Melbourne, July 1998–June 1999[a], compared with pediatric data derived from Gastanaduy and Begue[5]

Enteric pathogen	RCH (%) [n = 896 <16y]	Developed countries (%)	Developing countries (%)
Bacteria			
Clostridium difficile	14	ND	ND
Clostridium difficile toxin positive	6.5	ND	ND
Campylobacter jejuni	8.4	1–7	2–32
Campylobacter (other species)	1.0	ND	ND
Salmonella species	4.8	2–4	1–24
Shigella species	0.7	1–3	1–27
Vibrio species	0	<1	0–31
Enterohemorrhagic *Escherichia coli* toxin positive	0.7	1-4	1–37
Aeromonas species	0.6	Rare	1–42
Viruses			
Rotavirus	42	8–50	2–49
Adenovirus	6.3	5–20	0–6
Norwalk	0	5–15	2–5
Protozoa			
Blastocystis hominis	4.7	ND	ND
Giardia lamblia	3.7	0–8	1–24
Entamoeba coli	2.4	ND	ND
Endolimax nana	1.7	ND	ND
Entamoeba histolytica	0.8	Rare	0-9
Hymenolepsis nana	0.8	ND	ND
Cryptosporidium spp.	0.4	2–12	2–12
Ascaris lumbricoides	0.3	ND	ND
Strongyloides stercoralis	0.2	ND	ND

a Data courtesy of Dr Mike Starr, RCH, Melbourne, with permission.

ND = no data.

diarrhea. Leucocytes are usually noted on stool microscopy. Fluid and electrolyte replacement, with close attention to nutritional rehabilitation, remains the central therapy of acute gastroenteritis.[10] Breast-feeding should be continued where possible. The importance of micronutrients, and in particular zinc supplementation, has recently been recognized.[11] The efficacy of biologic agents, such as probiotics, is still being evaluated.

The widespread use of antibacterials has lead to a significant increase in the resistance of enteric pathogens over the past decade, which varies between specific geographic locations.[9,12] This has become a major issue in defining the role of antibacterials in the management of bacterial gastroenteritis. There is a sparsity of published evidence supporting the role and efficacy of antibacterials in childhood infectious diarrheal disease. We need to consider many factors and weigh their benefits and disadvantages before prescribing specific antibacterial agents. In many cases, this has lead to the recognition that certain clinical patterns of disease are more likely to benefit than others.

1. Specific Pathogens

1.1 *Shigella* spp.

Shigella spp. are Gram-negative, nonlactose fermenting, nonmotile bacilli, and the most common cause of bacillary dysentery. There are four species: *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*. *S. sonnei* accounts for most infections in developed countries, whereas *S. flexneri* and *S. dysenteriae* are responsible for

most infections in developing countries.[8] The mode of transmission is predominantly feco-oral, and humans are the only natural hosts. As few as 10 organisms can produce infection, hence the disease is highly contagious. Symptoms in mild infection are restricted to watery or loose diarrhea. Systemic symptoms, including fever, headache, malaise, and occasional vomiting, occur in severe infection. Abdominal cramps, rectal tenesmus, and mucoid stools, with or without blood, are the characteristics of bacillary dysentery. Life-threatening, rare complications include bacteremia, hemolytic-uremic syndrome, colonic perforation, and toxic encephalopathy, especially in children.[8,13]

Appropriate antibacterial treatment in shigella dysentery shortens the duration of diarrhea and fever, reducing intestinal protein loss and pathogen excretion within 1–2 days.[8,9,13,14] In severely ill patients, antibacterial therapy can be administered intravenously. Current choices include either a third-generation cephalosporin, ciprofloxacin (for multiply-resistant strains), or cotrimoxazole (trimethoprim/sulfamethoxazole). The clinical response to treatment of *S. sonnei* or mild infection is controversial.[8] Here, however, antibacterials can be justified on the basis of reducing transmission. Ampicillin or cotrimoxazole have, in the past, been recommended for the treatment of suspected shigellosis,[9,15] but since the mid 1980s, an increased rate of resistance of *Shigella* spp. to one or both drugs has been identified all over the world, particularly in Asia, Africa, and North America.[15-19] More than 50% of shigella isolates have been reported to be resistant to ampicillin and cotrimoxazole, with an increasing rate of resistance to chloramphenicol, cephalosporins, and amoxicillin/clavulanic acid.[17,19]

Most shigellae are, however, completely sensitive to ciprofloxacin, third-generation cephalosporins, and aminoglycosides.[16,17,19] The routine use of quinolones in children is discouraged because of the theoretical potential for damaging epiphyseal cartilage. Nevertheless, several studies have established their tolerability and efficacy in children during short-term treatments. A double-blind study in Bangladesh confirmed the efficacy of oral ciprofloxacin in children with shigellosis, using a dosage of 10 mg/kg every 12 hours for 5 days.[20] Arthropathy did not develop. Nalidixic acid (55 mg/kg/day in four divided doses for 5 days) is also an effective treatment with childhood shigellosis.[21] Quinolones currently play an important role in the treatment of multiply-resistant strains, but as antibacterial resistance develops to them,[22] recent interest has focused on azithromycin[22,23] as an alternative.

1.2 *Salmonella* spp.

Salmonella spp. are Gram-negative, motile and nonlactose fermenting bacilli. *S. enteritidis* is the most common cause of nontyphoidal salmonella infection in the US, and transmission is usually food-borne. The major reservoirs for nontyphoidal salmonella are animals, including poultry, cattle, rodents, reptiles, and pets. On the other hand, *S. typhi* and *S. paratyphi* infect only humans and are transmitted by the feco-oral route. Typhoid infection (enteric fever) is usually acquired during close contact with patients or asymptomatic carriers, as well as by consumption of contaminated food or water.

Nontyphoidal salmonella infection is typically an acute self-limited gastroenteritis; however, severe extra-intestinal infection can occasionally occur in young infants, in the immunocompromised, and in patients with underlying chronic medical illnesses.[8,24] Diarrhea can be either watery or mucoid with blood, and may be associated with fever, abdominal pain, and vomiting. Bacteremia is the most common manifestation of extra-intestinal infection,[24] and is most likely to occur during the first year of life, especially in infants younger than 3 months of age.[24-26] Common focal infections include meningitis, osteomyelitis, and lung infection.[8,24]

Enteric fever is the severe systemic illness caused by *S. typhi* and *S. paratyphi*, and remains a health problem in developing countries with a high mortality rate.[27] The common clinical symptoms of enteric fever are fever, abdominal pain, enterocolitis with diarrhea, and rose spots on the trunk in approximately 30% of patients.[8,28] Neurologic, gastrointestinal, and cardiovascular complications have been found in 3–17% of patients with enteric fever.[29] Sustained or intermittent bacteremia can occur.[13]

Antimicrobial therapy is usually not indicated in uncomplicated nontyphoidal salmonella gastroenteritis[8,9,13] as there is no evidence that therapy shortens the duration of disease, but may indeed prolong salmonella excretion.[30-32] Although the benefits are unproven, antibacterials are recommended for salmonella gastroenteritis in patients with high risk of invasive disease. These include infants younger than 3 months of age, patients with malignancy, immunodeficiency, hemoglobinopathies, HIV infection, and chronic or severe colitis.[1,8,9,12]

Recommended antibacterials in patients with enteric fever and salmonella gastroenteritis in whom therapy is indicated, include ampicillin, amoxicillin, cotrimoxazole, cefotaxime, or ceftriaxone.[8,13] Fluoroquinolones and ceftriaxone or cefotaxime are rec-

ommended for multidrug-resistant strains, particularly in developing countries.[13,28] Increasing resistance to antimicrobial agents, including third-generation cephalosporins, is now a worldwide problem, and is thought to result from unnecessary antibacterial therapy and the routine use of antibacterials in livestock.[33]

Restrictions on the use of fluoroquinolones in children (see section 1.1) mean that resistance to third-generation cephalosporins has become a public health problem in this age group.[13,33] Ciprofloxacin has been used in children <6 years of age who have been diagnosed with typhoid fever, and no adverse effects on growth or joints were identified.[34] The recommended duration of therapy for susceptible *S. typhi* is usually 14 days of ampicillin, chloramphenicol, or cotrimoxazole.[13] Multidrug-resistant typhoid fever should be treated with either 7–10 days of ceftriaxone, or 5–7 days of fluoroquinolones.[13] A prolonged course (21–28 days) of norfloxacin has been recommended for treatment of the chronic carrier state,[35] but resistance is well recognized and there is little published evidence of alternative therapies. A 4–6 week course of antibacterial therapy is recommended for focal infections such as osteomyelitis.

An alternative antibacterial for children infected with *S. typhi*, a facultative intracellular organism, is azithromycin, a macrolide with intracellular activity. Randomized trials to study the efficacy of azithromycin in the treatment of uncomplicated typhoid fever have been carried out during recent years.[36-39] A 7-day course of oral azithromycin for the treatment of uncomplicated enteric fever due to either sensitive or multi drug-resistant strains is at least as effective as ceftriaxone,[36] fluoroquinolones,[37,39] and chloramphenicol.[38] Further studies are needed to confirm these data and establish whether azithromycin could be a safer alternative in children with typhoid fever.[36]

1.3 *Campylobacter* spp.

Campylobacter spp. are flagellated spiral-shaped Gram-negative bacteria which have rapid darting motility. *C. jejuni* is one of the most common causes of acute bacterial gastroenteritis worldwide, particularly in developed countries. Poultry are the major reservoir of *C. jejuni*. Outbreaks occur by ingestion of contaminated food, water, or unpasteurized milk. Person-to-person transmission occasionally occurs by direct contact with fecal material. Reinfection is particularly common during outbreaks in daycare centers, and eradication is difficult.[40] In developed countries, there are two peak ages of infection – infancy and in young adulthood.[41] A definitive diagnosis of campylobacter enteritis is established by isolation of the micro-organism from stools. However, the bacteria grows slowly in culture, and isolation from stool samples may be delayed for up to 72–96 hours.[41]

The typical clinical manifestation of *C. jejuni* is an acute, self-limited gastroenteritis with diarrhea, fever, and abdominal cramps. Diarrhea can be either watery or bloody, and lasts 4–5 days; however, relapses can occasionally occur. Abdominal pain can be severe and mimic acute surgical conditions. Extra-intestinal complications rarely occur, but include meningitis, endocarditis, septic arthritis, osteomyelitis, and neonatal sepsis.[41] Guillain-Barre syndrome occurs after *C. jejuni* infection in slightly less than 1/1000 patients.[41-44]

Campylobacter enteritis is usually a self-limited illness, and antibacterial therapy is not normally required. Antibacterials should be reserved for those patients with severe illness or in certain high risk clinical circumstances. These include high fever, dysentery, and prolonged illness, as well as pregnancy, HIV infection, systemic infection, or immunosuppression.[8,41] There is evidence that antibacterial therapy given early enough may shorten the duration of illness, eradicate the organism from stools, and prevent relapse.[13,45] The recommended antibacterial for campylobacter enteritis in children is erythromycin at a dosage of 40 mg/kg/day in two divided doses for 5 days.[8,13,41] Fluoroquinolones have historically also been effective, but fluoroquinolone-resistant *C. jejuni* has recently emerged worldwide,[41,46-48] while erythromycin-resistant strains are unusual.[41,46] The reason for the development of fluoroquinolone-resistant strains has been their widespread use in food animal production and veterinary medicine.[48-50] This issue is an important public health concern and requires the urgent implementation of more appropriate strategies for the use of antibacterials in food animals. Other new macrolides (azithromycin, clarithromycin) are as effective as erythromycin against *C. jejuni*, but are more expensive.[41] There is evidence of a high rate of resistance of *Campylobacter* species to tetracycline, cephalosporin, amoxicillin, aztreonam, and metronidazole.[17,41] Prevention and control measures remain crucially important.

1.4 *Escherichia Coli*

E. coli is a Gram-negative, lactose-fermenting motile bacillus. It can produce septicemia and meningitis in neonates, or diarrheal diseases with high morbidity and mortality in pediatric age groups,

particularly in developing countries. At least five classes of diarrheogenic *E. coli* have been identified by their specific virulence characteristics, epidemiology, and clinical manifestations.[51]

1.4.1 Enteropathogenic E. Coli

In the 19th century, enteropathogenic *E. coli* (EPEC) was associated with diarrheal outbreaks in nurseries and infant diarrhea in summertime in industrialized countries.[8,51] EPEC remain a health problem in developing countries where they cause both sporadic cases and outbreaks of diarrhea.[13,51] Illness occurs almost exclusively in neonates and children younger than 2 years of age.[13,51,52] Acute secretory diarrhea may be associated with fever, abdominal cramps, and vomiting. Persistent or chronic diarrhea can result in growth retardation in children in developing countries.[13,51-53] Infection by EPEC requires a high inoculum ($\approx 10^9$ colony forming units) and has a short incubation period (6–48 hours). The specific characteristic of EPEC is their ability to induce attaching and effacing lesions in small intestinal enterocytes, resulting in destruction of microvilli with pedestal formation at the area of attachment.[51,52,54] In contrast to enterohemorrhagic *E. coli* (EHEC), EPEC does not produce shiga toxins.[51] Diagnosis is difficult as identification tests for EPEC are generally limited to research facilities.

There is little data to guide the use of antibacterial therapy in EPEC diarrhea, but appropriate antibacterials appear to reduce morbidity. For mild diarrhea in infants, nonabsorbable antibacterials, such as colistin, neomycin, or gentamicin, can be given orally for 3–5 days.[8,13] Cotrimoxazole should be considered in susceptible EPEC that cause moderate, severe, or intractable diarrhea.[13] Nutritional support should be given early after the rapid rehydration period. Continuation of breast-feeding is advisable, and some authors recommend the use of lactose-free protein hydrolysate-based formulas.[52]

1.4.2 Enterotoxigenic E. Coli

Enterotoxigenic *E. coli* (ETEC) is an important cause of diarrhea in weaning infants in developing countries, and also causes traveler's diarrhea at all ages. The fucosylated oligosaccharide of human milk has the ability to protect against heat-stable enterotoxin of *E. coli* in animal models.[55] ETEC causes acute secretory diarrhea by producing either heat-labile or heat-stable enterotoxin without intestinal mucosal invasion. It also has colonization-factor antigens to help adherence to the mucosa. A high inoculum is required and symptoms develop with a short incubation period of <24 hours to 2 days. Illness is typically self-limited, lasting less than one week. Cholera-like diarrhea can occur in severe cases. Repeated ETEC infection adversely affects nutrition in infants and children. Diagnosis is based on demonstration of the enterotoxin through polymerase chain reaction (PCR), DNA probes, or immunologic methods.[51] Fluid and electrolytes are the mainstay of therapy. Antibacterials are not necessary in most cases and should be reserved for the most severe cases. Cotrimoxazole, fluoroquinolones, and furazolidone have been shown to shorten the duration of illness in some clinical trials.[56]

ETEC is the leading bacterial cause of traveler's diarrhea, followed by *Salmonella*, *Shigella*, and *Campylobacter*.[57] The emergence of resistance of ETEC to cotrimoxazole, ampicillin, and tetracycline has been reported worldwide.[57-59] However, fluoroquinolones, are well tolerated and are still effective in the early treatment of traveler's diarrhea.[57] Bismuth salicylate is a prophylactic drug which has a 65% efficacy in preventing traveler's diarrhea.[57,60] Recommendations for antibacterials to be used in children developing traveler's diarrhea include furazolidone, or cotrimoxazole with erythromycin if *Campylobacter* is suspected.[56] The avoidance of contaminated food and water is still the single most important preventive measure.

1.4.3 Enterohemorrhagic E. Coli or Verotoxigenic E. Coli

EHEC produce cytotoxins known as shiga-like toxins, or verotoxins and enterohemolysin. This group of *E. coli* causes epidemic and sporadic cases of diarrhea and hemorrhagic colitis which may progress to severe hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). *E. coli* O157:H7 is the prototype of EHEC, and also the most commonly associated with HUS. *E. coli* O157:H7 infection can occur worldwide, but is more common in Northern Europe, Canada, USA, Argentina, and Japan, with an annual incidence rate of 8 cases per 100 000 (general population),[61] and results in HUS in 5–10% of infected children.[13,62] The predominant mode of transmission is by ingestion of contaminated food, especially undercooked ground beef, but person-to-person transmission can occur and has been documented after swimming in contaminated water.[63] The inoculum dose is low, and as few as 100 organisms can cause illness. EHEC adhere tightly to the brush border[64] and produce an attaching effacing lesion.[13,51] In contrast to EPEC, shiga-like toxins are elaborated, which cause a hemorrhagic colitis and also induce the endothelial cell damage, white blood cell activation, and platelet-endothelial cell interaction which are responsible for HUS.[62] Illness often begins with watery diarrhea and cramping abdominal

pain, followed by bloody diarrhea for 2–3 days which can mimic surgical conditions. Fever is usually absent or low grade. These symptoms precede the HUS by 1–15 days.[65] Risk factors for the development of HUS or TTP include youth or old age, bloody diarrhea, fever, high initial white blood cell count, and the use of antimotility agents.[66-69]

Antibacterial therapy does not seem to prevent HUS, and in some studies resulted in a worse outcome.[69,70] One prospective cohort study has shown that antibacterial treatment of *E. coli* O157:H7 infection increased the risk of HUS in children.[69] Current recommendations are to avoid the use of antibacterial therapy in EHEC infection. Careful follow-up and aggressive supportive therapy are the key to reducing morbidity and mortality. Definitive diagnosis of *E. coli* O157:H7 is based on its inability to ferment sorbitol on Sorbitol-MacConkey agar in contrast to 90% of human intestinal *E. coli* strains. The sorbitol-negative colonies can then be serotyped for confirmation. Other EHEC strains can be diagnosed by demonstration of shiga- like toxins in stools. Bloody stools should be cultured and tested for *E. coli* O157:H7.[51]

1.4.4 Enteroinvasive E. Coli

Enteroinvasive *E. coli* (EIEC) invade the intestinal mucosa and cause dysentery similar to *Shigella* species. Diarrhea is usually watery, and symptoms are milder than in shigella infection, but fever, crampy abdominal pain, and bloody stools with mucus can occur. The epidemiology is similar to shigella in developing countries.[8] However, EIEC infection requires a higher inoculum than shigella. Outbreaks have been attributed to contaminated food, but person-to-person transmission has also been reported.[51] Diagnosis of EIEC is classically based on the demonstration of invasiveness in an animal model.[51] DNA probes and enzyme-linked immunosorbent assay are available in research laboratories. Antibacterial therapy is usually given in EIEC dysentery, as shigella infection is difficult to exclude. Recommended antibacterials are the same as for shigellosis, but should be based on susceptibility testing of the isolates.

1.4.5 Enteroaggregative E. coli

Enteroaggregative *E. coli* (EAEC) has recently emerged as an important enteric pathogen which is particularly responsible for persistent diarrhea (>14 days) in young children in the developing world.[71,72] It can cause both acute and persistent diarrhea, with an incubation period reported in a massive outbreak in Japan to average 40–50 hours.[73] Patients typically have watery diarrhea with low grade fever. However, bloody stools have occasionally been reported. The most important characteristic of EAEC is the ability to adhere to Hep-2 cells and the intestinal mucosa with a 'stacked-brick' adherence pattern.[51,71] There are other identified virulence factors, including enterotoxin, which is similar to the heat-stable toxin of ETEC, hemolysins, fimbriae, and outer membrane proteins that may promote the adhesion process, but their roles in the disease have been unclear.[71] Diagnosis depends on either the demonstration of the aggregative pattern in the Hep-2 cell assay or DNA probes, or PCR for detection of the genes encoding cell adhesion.[51,71] Acute diarrhea is usually a self-limited illness and antibacterials are unnecessary; however, persistent diarrhea may benefit from antibacterial and nutritional therapy. There is a high rate of antibacterial resistance, and susceptibility testing is recommended.[74]

1.5 Cholera

Vibrio cholerae is a curved, motile Gram-negative rod that causes profuse watery diarrhea without abdominal cramps or fever, leading to severe dehydration and electrolyte imbalance. Hypovolemic shock can occur in 4–12 hours[13] unless rehydration therapy is given.

There have been seven pandemics of cholera. The three most recent have been caused by two biotypes of *V. cholerae* group O1 – classical and El Tor.[75] Until 1993, only the O1 serotype was believed to cause epidemics, but in late 1992 a non-O1 strain (O139 Bengal) was reported to be the causative agent of epidemics in India and Bangladesh. If the outbreaks of *V. cholerae* O139 Bengal still persist it may represent the beginning of the eighth pandemic.[76] Cholera is a highly contagious disease which is transmitted by consumption of fecally-contaminated water and foods. *V. cholerae* O1 and O139 can grow well in foods that have high moisture and organic content, neutral or an alkaline pH, low temperature, and where there are no other competing bacteria.[77] Epidemics in many countries have resulted from ingestion of raw or undercooked shellfish, crabs, oysters, and clams. Stools are typically colorless with mucus, and described as rice-water.

Because of the potential development of life-threatening severe dehydration, oral and parenteral rehydration are crucially important to correct fluid and electrolyte abnormalities. Antibacterial therapy has been demonstrated to eradicate vibrios and reduce the duration of diarrhea and amount of fluid loss.[8,13] Recommended antibacterials are tetracycline (50 mg/kg/day, maximum 2 g/day in

Table II. Recommended antibacterials in acute gastroenteritis. The role of antibacterial therapy is unclear for gastroenteritis due to enterohemorrhagic *Escherichia coli*, enteroaggregative *E. coli*, *Yersinia enterocolitica*, *Aeromonas* spp. and *Plesiomonas shigelloides*

Pathogen/disease presentation	Antibacterial agents (dosage)
Shigellosis	Fluoroquinolones, e.g. ciprofloxacin (20 mg/kg/day PO q12h for 5 days)
	Nalidixic acid (55 mg/kg/day PO q6h for 5 days)
	Third-generation cephalosporins, e.g. ceftriaxone (50 mg/kg/day IV od for 3–5 days)
	Cotrimoxazole or ampicillin for susceptible strains (Trimethoprim 8 mg/kg/day PO q12h for 5 days)
Salmonella gastroenteritis where there is high risk of invasive disease	Ceftriaxone (50 mg/kg/day IV/IM od for 7–10 days)
Enteric fever	Cefotaxime (150 mg/kg/day IV q8h for 7–10 days); fluoroquinolones [ciprofloxacin] (20 mg/kg/day PO/IV q12h for 5–7 days
	Ampicillin, amoxicillin, and cotrimoxazole only for susceptible strains
	Azithromycin still in research studies
Campylobacter gastroenteritis – only in certain circumstances (high fever, dysentery, prolonged illness, other host risk factors)	Erythromycin (40 mg/kg/day PO q6h for 5 days); azithromycin, clarithromycin, fluoroquinolones
Enteropathogenic *E. coli* gastroenteritis in infants and older children with moderate to severe diarrhea	Nonabsorbable antibacterials, e.g. neomycin (100 mg/kg/day PO q6–8h for 5 days); also colistin, gentamicin
Enterotoxigenic *E. coli* with severe diarrhea and traveler's diarrhea	Cotrimoxazole (trimethoprim 8 mg/kg/day PO q12h for 5 days); fluoroquinolones, furazolidone
Enteroinvasive *E. coli* dysentery	Same as shigellosis
Cholera	Tetracycline (50 mg/kg/day max 2 g/day PO q6h for 3 days); doxycycline (6 mg/kg PO single dose); fluoroquinolones, erythromycin, furazolidone
Clostridium difficile-associated diarrhea	Oral metronidazole (20–40 mg/kg/day PO q6h for 7 days) or vancomycin (40 mg/kg/day PO q6h for 7 days)
	Probiotics (further clinical trials are needed to confirm efficacy)

IM = intramuscular; **IV** = intravenous; **od** = once daily; **PO** = orally; **q*x*h** = every *x* hours.

four divided doses) for 3 days, or doxycycline (6 mg/kg, maximum 300mg single dose).[13] The use of tetracyclines is generally not recommended for children younger than 8 years of age, but in the case of severe cholera, the benefits may offset the risk of staining developing teeth.[13] Alternative drugs for resistant strains are cotrimoxazole, erythromycin, furazolidone, ciprofloxacin, or ofloxacin. In a recent study in Bangladesh, 100% of *V. cholerae* O139 strains were susceptible to tetracycline, erythromycin and ciprofloxacin, 92% to furazolidone, and only 5% to cotrimoxazole.[78]

1.6 *Clostridium difficile*

C. difficile is a spore-forming Gram-positive anerobic bacteria which is the leading cause of nosocomial infectious diarrhea. Infections vary in severity from asymptomatic carriage and acute self-limited diarrhea to pseudomembranous colitis, toxic megacolon, and recurrent infections.[79,80] Neonates have high frequencies of asymptomatic colonization, whereas older children have the same prevalence as in adults.[79] Disease in both children and adults usually results from a complication of broad spectrum antibacterial therapy, especially with third-generation cephalosporins and clindamycin.[81] Normal intestinal microflora which inhibit the overgrowth of pathogenic organisms are disrupted by antibacterial therapy,[79] allowing colonization and overgrowth of pathogens. Toxins A and B, produced by *C. difficile*, cause intestinal inflammation and fluid secretion, resulting in diarrhea and colitis. Up to 20% of antibacterial-associated diarrhea has been attributed to *C. difficile*.[82] Other host factors, such as age, diet, and immune response, are also significant determinants of disease.[79] A retrospective review of hospitalized patients with hematologic malignancies identified *C. difficile*-associated diarrhea in 7.0% of all cycles of chemotherapy-induced neutropenia.[83] Annual reports from the UK show a significant increase of *C. difficile* infection during the last decade.[84] Diagnosis is made by stool testing for toxins, or by cell cytotoxin assay.

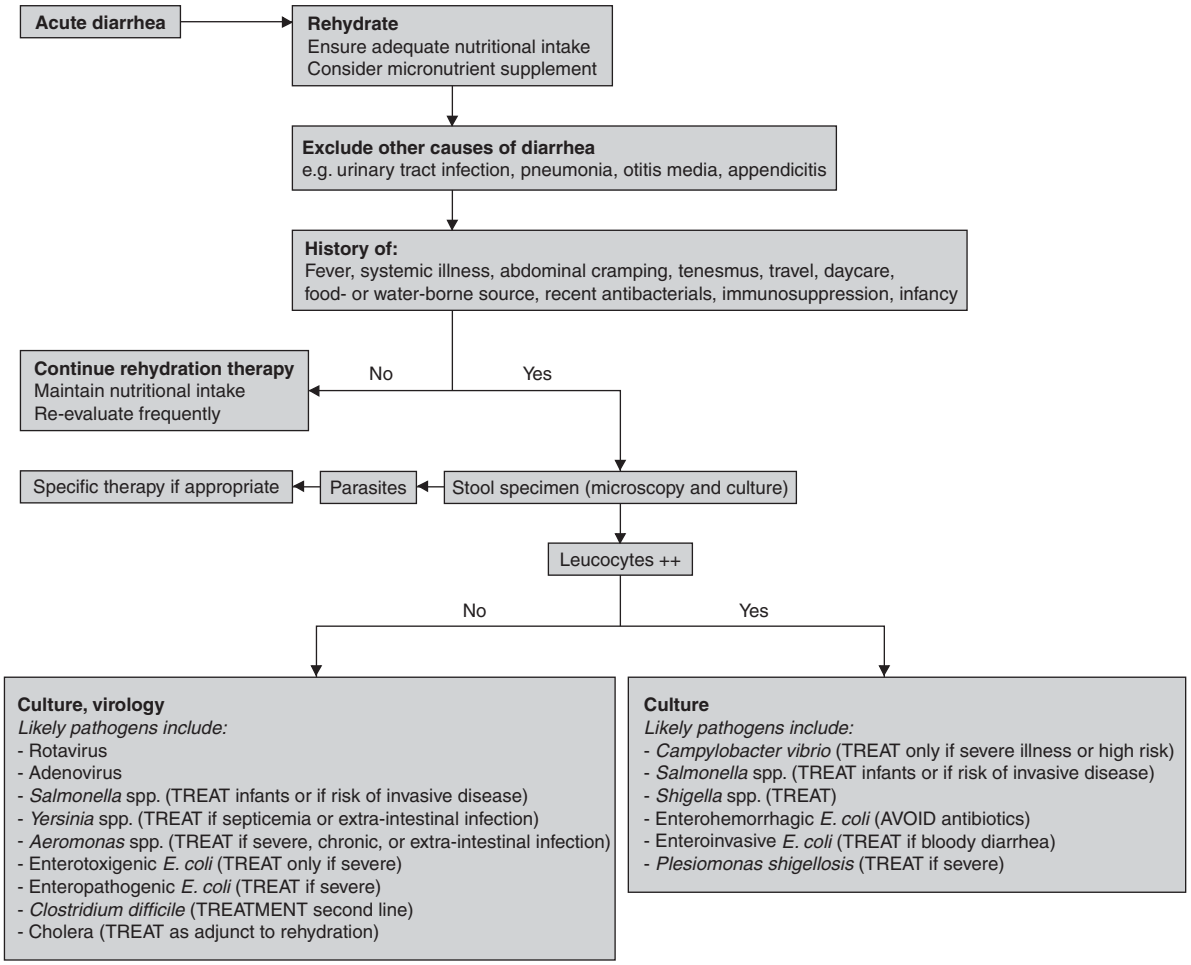

Fig. 1. Management flow chart for acute diarrheal disease in children. Refer to text for specific antibacterials to be used in treatment.

First of all, offending antibacterials should be discontinued as soon as possible. Both metronidazole and oral vancomycin are effective against *C. difficile*. If symptoms persist after discontinuing the offending antibacterial, oral metronidazole should be offered as first-line therapy for economic reasons and to reduce the risk of development of vancomycin resistance.[79,82,83] Metronidazole can also be used intravenously; intravenous vancomycin will be ineffective because of poor intestinal secretion. In children, metronidazole has been prescribed at a dosage of 20–40 mg/kg/day, while vancomycin (40 mg/kg/day) is used in severe pseudomembranous colitis, recurrent colitis, immunocompromised patients, and after failure of metronidazole.[79] The recommended duration of treatment is usually 7–10 days.[13]

Several clinical reviews have advocated the use of probiotics in the management of both adults and children with viral gastroenteritis, antibacterial-associated diarrhea, *C. difficile* diarrhea, and traveler's diarrhea.[85-87] Biller et al.[88] demonstrated the efficacy of *Lactobacillus* GG in the successful treatment of four young children with multiple relapses of *C. difficile* colitis. A nonblind trial with *S. boulardii*, in infants with *C. difficile*-associated enteropathies, showed clinical improvement.[89] Two randomized trials have also demonstrated the efficacy of *Lactobacillus* GG in the prevention of antibacterial-associated diarrhea in children.[90,91] However, further clinical trials of probiotics are clearly needed.

1.7 *Yersinia enterocolitica*

Yersinia enterocolitica is a Gram-negative bacillus which causes a wide range of age-specific clinical manifestations. Enterocolitis with fever and diarrhea is the most common presentation in young children, while pseudoappendicitis syndrome occurs primarily in older children and young adults.[92] Focal extraintestinal infection and bacteremia are less common; however, infants younger than 3 months of age are at the highest risk of bacteremia.[93] Patients with iron-overload or other predisposing

diseases, such as malnutrition, cirrhosis, and the immunosuppressed, have an increased risk of bacteremia.[92] Symptoms of *Y. enterocolitis* in children may mimic Crohn's disease,[94] and infection can result in granulomatous appendicitis.[95] Consumption of chitterlings (raw pork intestine), untreated water, and unreticulated sewerage are important risk factors of infection.[93,96,97]

In vitro studies show the susceptibility of *Y. enterocolitica* to cotrimoxazole, aminoglycosides, third-generation cephalosporins, and quinolones.[92,93] However, in a placebo-controlled, double-blind evaluation of cotrimoxazole treatment of *Y. enterocolitica* gastroenteritis in children, therapy failed to shorten or improve the clinical course.[98] A recent retrospective review in children has shown the efficacy of cefotaxime in treating bacteremia in young infants.[93] There was no difference in clinical improvement in patients with enteritis treated with oral cotrimoxazole compared with those who were not treated.[93] The benefits of antibacterials in uncomplicated enterocolitis have not been proven, but patients with septicemia or extra-intestinal infection should receive antibacterial therapy.[13]

1.8 *Aeromonas* spp.

Aeromonas species (*A. hydrophila, A. caviae, A. sobria*) are Gram-negative, facultative anaerobic bacilli that are regarded as water- and food-borne enteropathogens. Most aeromonas infections occur during the hot, humid season and affect young children, particularly those younger than 3 years of age.[99,100] The most prevalent species is *A. caviae*.[99,100] Despite many known virulence factors, the mechanism of gastroenteritis in aeromonas infection is still unclear.[99-101] Enterotoxin and cytotoxin can be identified from *A. hydrophila* and *A. sorbria*, but not *A. caviae*.[99] Aeromonas infection can result in a wide spectrum of diseases, including asymptomatic carriage, watery diarrhea, dysentery, chronic diarrhea,[8] and bacteremia which usually occurs in patients with either liver cirrhosis or malignancy.[102] Diarrhea is typically a self-limited illness lasting no longer than 7 days and rehydration therapy is the most important management.

Antibacterials should be considered in chronic disease[8] or extra-intestinal infection.[103] Most strains are susceptible to ciprofloxacin, gentamicin, and nalidixic acid,[103] but resistant to ampicillin.[104,105] *A. sobria*, which has caused outbreaks of acute gastroenteritis, has been found to be sensitive to chloramphenicol, cotrimoxazole, tetracycline, and gentamicin.[104] A broad spectrum cephalosporin is indicated for the treatment of bacteremia.[102]

1.9 *Plesiomonas shigelloides*

Plesiomonas shigelloides is a Gram-negative, facultative, anaerobic bacillus which causes acute gastroenteritis in all age groups.[106,107] The risk of infection increases with a history of tropical travel,[106-108] consumption of seafood or uncooked food[106,107] and untreated water.[106] Clinical manifestations vary, but include acute watery, bloody, and chronic diarrhea.[107,108] Most patients have an acute illness with abdominal pain and colitis.[106] The majority of patients have a self-limited diarrhea[107,108] but antibacterial therapy has been demonstrated to reduce the duration of illness.[106] A retrospective study in Hong Kong has shown the superiority of quinolones and ceftriaxone in treating severe cases of *P. shigelloides* infection compared with ampicillin, tetracycline, cotrimoxazole, and chloramphenicol.[107]

2. Conclusions

Most cases of acute gastroenteritis in children are self-limited and need only supportive treatment. The primary therapies should be appropriate fluid and electrolyte replacement, and close attention to nutrition. Antibacterial therapy should be restricted to specific bacterial pathogens and disease patterns, as summarized in table II. The aims of antibacterial therapy are to shorten the clinical course, eradicate the causative organisms, reduce transmission, and prevent invasive complications. Figure 1 outlines a suggested management algorithm for acute diarrheal disease. Selection of antibacterials to use in acute bacterial gastroenteritis is based on clinical diagnosis of the likely pathogen prior to definitive laboratory results, but there is a real need for more studies to be carried out to define the role and efficacy of antibacterials in childhood infectious diarrheal disease. The benefits and risks of adverse drug reactions should be weighed before prescribing antibacterials. This particularly applies to drugs such as tetracyclines in cholera, where benefit may outweigh the adverse effect of tooth staining, and quinolones where there is risk of damage to the epiphysial cartilage. Moreover, a major concern is the emergence of antibacterial-resistant strains due to the widespread use of antibacterial agents. In part, this may have resulted from the inappropriate overuse of antibacterials.

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References

1. Armon K, Stephenson T, MacFaul R, et al. An evidence and consensus based guideline for acute diarrhoea management. Arch Dis Child 2001; 85: 132-42
2. Harlem G. WHO report on infectious disease: removing the obstacle to healthy development. Brunotland: World Health Organization, 1999
3. Khuffash FA, Sethi SK, Shaltout AA. Acute gastroenteritis: clinical features according to etiologic agents. Clin Pediatr 1988; 27 (8): 365-8
4. Fruhwirth M, Heininger U, Ehlken B, et al. International variation in disease burden of rotavirus gastroenteritis in children with community- and nosocomically-acquired infection. Pediatr Infect Dis J 2001; 20 (8): 784-91
5. Gastanaduy AS, Begue RE. Acute gastroenteritis. Clin Pediatr 1999; 38: 1-12
6. Crowley DS, Ryan MJ, Wall PG. Gastroenteritis in children under 5 years of age in England and Wales. Communicable Dis Rep CDR Rev 1997; 7: R82-6
7. Pickering LK. Antimicrobial therapy of gastrointestinal infections. Pediatr Clin North Am 1983; 30 (2): 373-85
8. Fasano A. Intestinal infections. In: Walker WA, Durie PR, Hamilton JR, et al., editors. Pediatric gastrointestinal disease: pathophysiology, diagnosis, management. 3rd ed. Hamilton (ON): BC Decker Inc., 2000: 463-84
9. Ashkenazi S, Cleary TG. Antibiotic treatment of bacterial gastroenteritis. Pediatr Infect Dis J 1991; 10: 140-8
10. Guerrant RL, Gilder TV, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001; 32: 331-50
11. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation in young children with acute diarrhoea in India. N Engl J Med 1995; 333: 839-44
12. Goossens H, Sprenger MJ. Community acquired infections and bacterial resistance. BMJ 1998; 317: 654-7
13. Red book 2000: report of the committee on infectious diseases. 25th ed. Elk Grove Village (IL): American Academy of Pediatrics, 2000
14. Murphy MS. Guidelines for managing acute gastroenteritis based on a systematic review of published research. Arch Dis Child 1998; 79: 279-84
15. Tauze RV, Puhr ND, Wells JG, et al. Antimicrobial resistance of Shigella isolates in the USA: the importance of international travelers. J Infect Dis 1990; 162: 1107-11
16. Ahmed AA, Osman H, Mansour AM, et al. Antimicrobial agent resistance in bacterial isolates from patients with diarrhea and urinary tract infection in the Sudan. Am J Trop Med Hyg 2000; 63 (5-6): 259-63
17. Wasfy MO, Oyofo BA, David JC, et al. Isolation and antibiotic susceptibility of Salmonella, Shigella, and Campylobacter from acute enteric infections in Egypt. J Health Pop Nutr 2000; 18 (1): 33-8
18. Sirivichayakul C, Thisyakorn U. Severe shigellosis in childhood. Southeast Asian J Trop Med Public Health 1998; 29 (3): 555-9
19. Jamal WY, Rotimi VO, Chugh TD, et al. Prevalence and susceptibility of Shigella species to 11 antibiotics in Kuwait teaching hospital. J Chemother 1998; 10 (4): 285-90
20. Salam MA, Dhar U, Khan WA, et al. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998; 352 (9127): 522-7
21. Rawashdeh MO, Ababneh AM, Shurman AA. Shigellosis in Jordanian children: a clinico-epidemiologic prospective study and susceptibility to antibiotics. J Trop Pediatr 1994; 40: 355-9
22. Hoge CW, Gambel JM, Srijan A, et al. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. Clin Infect Dis 1998; 26: 341-5
23. Khan WA, Seas C, Dhar U, et al. Treatment of shigellosis (V): comparison of azithromycin and ciprofloxacin: a double-blind, randomised, controlled trial. Ann Intern Med 1997; 126: 697-703
24. Lee WS, Puthucheary SD, Parasakthi N. Extra-intestinal non-typhoidal Salmonella infections in children. Ann Trop Paediatr 2000; 20: 125-9
25. Kupperman N. Occult bacteremia in young febrile children. Pediatr Clin North Am 1999; 46: 1073-109
26. Wittler RR, Bass JW. Non-typhoidal Salmonella enteric infections and bacteremia. Pediatr Infect Dis J 1989; 8: 364-7
27. Edelman R, Levine MM. Summary of an international workshop on typhoid fever. Rev Infect Dis 1986; 8: 329-49
28. Kabra SK, Madhulika, Talati A, et al. Multidrug-resistance typhoid fever. Trop Doctor 2000; 30 (4): 195-7
29. Okome-Nkoumou M, Ayo Nkana E, Bekale J, et al. Typhoid and paratyphoid fever in adults in the internal medicine department at Libreville (Gabon) [in French]. Sante 2000; 10 (3): 205-9
30. Barbara G, Stanghellini V, Berti-Ceroni C, et al. Role of antibiotic therapy on long-term germ excretion in faeces and digestive symptoms after Salmonella infection. Aliment Pharmacol Ther 2000; 14 (9): 1127-31
31. Murase T, Yamada M, Muto T, et al. Fecal excretion of Salmonella enterica serovar typhimurium following a food-borne outbreak. J Clin Microbiol 2000; 38 (9): 3495-7
32. Sirinavin S, Garner P. Antibiotics for treating salmonella gut infections (Cochrane Review). Available in the Cochrane Library (database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Oxford Update Software, 2000
33. Fey PD, Safranek TJ, Rupp ME, et al. Ceftriaxone-resistant salmonella infection acquired by a child from cattle. N Engl J Med 2000; 342 (17): 1242-9
34. Doherty CP, Saha SK, Cutting WA. Typhoid fever, ciprofloxacin and growth in young children. Ann Trop Paediatr 2000; 20 (4): 297-303
35. Cherubin CE, Kowalsky J. Non-typhoidal Salmonella carrier state treated with norfloxacin. Am J Gastroenterol 1990; 85: 100-1
36. Frenck Jr RW, Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis 2000; 31 (5): 1134-8
37. Chinh NT, Parry CM, Ly NT, et al. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. Antimicrob Agents Chemother 2000; 44 (7): 1855-9
38. Butler T, Sridhar CB, Daga MK, et al. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999; 44 (2): 243-50
39. Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrob Agents Chemother 1999; 43 (6): 1441-4
40. Ashkenazi S, Danziger Y, Varsano Y, et al. Treatment of campylobacter gastroenteritis. Arch Dis Child 1987; 62: 84-5
41. Allos BM. Campylobacter jejuni infections: update on emerging issues and trends. Clin Infect Dis 2001; 32: 1201-6
42. Wassenaar TM, Blaser MJ. Pathophysiology of Campylobacter jejuni infections of humans. Microb Infect 1999; 1 (12): 1023-33
43. Altekruse SF, Stern NJ, Fields PI, et al. Campylobacter jejuni: an emerging foodborne pathogen. Emerg Infect Dis 1999; 5 (1): 28-35
44. Allos BM. Association between Campylobacter infection and Guillain-Barre syndrome. J Infect Dis 1997; 176 Suppl. 2: S125-8
45. Salazar-Lindo E, Sack RB, Chea-Woo E, et al. Early treatment with erythromycin of Campylobacter jejuni-associated dysentery in children. J Pediatr 1986; 109: 355-60
46. Afset JE, Maeland JA. Erythromycin and ciprofloxacin resistant Campylobacter jejuni [in Norwegian]. Tidsskrift for Den Norske Laegeforening 2001; 121 (18): 2152-4
47. Smith KE, Besser JM, Hedberg CW, et al. Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998. Investigation Team. N Engl J Med 1999; 340 (20): 1525-32

48. Fields PI, Swerdlow DL. Campylobacter jejuni. Clin Lab Med 1999; 19 (3): 489-504
49. Aarestrup FM, Wegener HC. The effects of antibiotic usage in food animals on the development of antimicrobial resistance of importance for humans in Campylobacter and Escherichia coli. Microb Infect 1999; 1 (8): 639-44
50. Teuber M. Spread of antibiotic resistance with food-borne pathogens. Cellular Mol Life Sci 1999; 56 (9-10): 755-63
51. Noguera-Obenza M, Cleary TG. Diarrheogenic Escherichia coli. Curr Probl Pediatr 1999; 29: 208-16
52. Fagundes-Neto U, Scaletsky IC. The gut at war: the consequences of enteropathogenic Escherichia coli infection as a factor of diarrhea and malnutrition. Sao Paulo Med J 2000; 118 (1): 21-9
53. Clausen CR, Christie DL. Chronic diarrhea in infants caused by adherent enteropathogenic Escherichia coli. J Pediatr 1982; 100 (3): 358-61
54. DeVinney R, Gauthier A, Abe A, et al. Enteropathogenic Escherichia coli: a pathogen that inserts its own receptor into host cells. Cell Mol Life Sci 1999; 55 (6-7): 961-76
55. Newburg DS. Do the binding properties of oligosaccharides in milk protect human infants from gastrointestinal bacteria. J Nutr 1997; 127 (5 Suppl.): 980-4S
56. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. N Engl J Med 1993; 328 (25): 1821-6
57. Wolfe MS. Protection of travelers. Clin Infect Dis 1997; 25: 177-86
58. Gomi H, Jiang ZD, Adachi JA, et al. In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions. Antimicrob Agents Chemother 2001; 45 (1): 212-6
59. Vila J, Vargas M, Ruiz J, et al. Quinolone resistance in enterotoxigenic Escherichia coli causing diarrhea in travelers to India in comparison with other geographical areas. Antimicrob Agents Chemother 2000; 44 (6): 1731-3
60. Ansdell VE, Ericsson CD. Prevention and empiric treatment of traveler's diarrhea. Med Clin North Am 1999; 83 (4): 945-73
61. Rocchi G, Capozzi M. Enterohemorrhagic Escherichia coli O157:H7 infection [in Italian]. Recenti Prog Med 1999; 90 (11): 613-8
62. Robson WL. Haemolytic uraemic syndrome. Pediatr Drugs 2001; 2 (4): 243-52
63. Keene WE, McAnulty JM, Hoesly FC, et al. A swimming-associated outbreak of hemorrhagic colitis caused by Escherichia coli O157:H7 and Shigella sonnei. N Engl J Med 1994; 331: 579-84
64. Mariani-Kurkdjian P, Bingen E. Hemolytic-uremic syndrome: microbiological aspects. Arch Pediatr 2001; 8 Suppl. 4: 785-91S
65. Loirat C. Post-diarrhea hemolytic-uremic syndrome: clinical aspects. Arch de Pediatr 2001; 8 Suppl. 4: 776-84S
66. Pavia AT, Nichols CR, Green DP, et al. Hemolytic-uremic syndrome during an outbreak of Escherichia coli O157:H7 infections in institutions for mentally retarded persons: clinical and epidemiologic observations. J Pediatr 1990; 116: 544-51
67. Griffin PM, Tauxe RV. The epidemiology of infections caused by Escherichia coli O157:H7, other enterohemorrhagic E. coli and the associated hemolytic uremic syndrome. Epidemiol Rev 1991; 13: 60-98
68. Siegler RL, Pavia AT, Christofferson RD, et al. A 20-year population-based study of postdiarrheal hemolytic uremic syndrome in Utah. Pediatrics 1994; 94: 35-40
69. Wong CS, Jelacic S, Habeeb RL, et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections. N Engl J Med 2000; 342: 1930-6
70. Igarashi T, Inatomi J, Wake A, et al. Failure of pre-diarrheal antibiotics to prevent hemolytic uremic syndrome in serologically proven Escherichia coli O157:H7 gastrointestinal infection. J Pediatr 1999; 135: 768-9
71. Law D, Chart H. Enteroaggregative Escherichia coli. J Applied Microbiol 1998; 84 (5): 685-97
72. Chan KN, Phillips AD, Knutton S, et al. Enteroaggregative Escherichia coli: another cause of acute and chronic diarrhoea in England. J Pediatr Gastroenterol Nutr 1994; 18: 87-91
73. Itoh Y, Nagano I, Kunishima M. Laboratory investigation of enteroaggregative Escherichia coli O untypeable:H10 associated with a massive outbreak of gastrointestinal illness. J Clin Microbiol 1997; 35: 2546-50
74. Yamamoto T, Echeverria P, Yokota T. Drug resistance and adherence to human intestines of enteroaggregative Escherichia coli. J Infect Dis 1992; 165: 744-9
75. Faruque SM, Albert MJ, Mekalanos JJ. Epidemiology, genetics, and ecology of toxigenic Vibrio cholerae. Microbiol Mol Biol Rev 1998; 62 (4): 1301-14
76. Swerdlow DL, Ries AA. Vibrio cholerae non-O1: the eighth pandemic. Lancet 1993; 342: 382-3
77. Rabbani GH, Greenough III WB. Food as a vehicle of transmission of cholera. J Diarrhoeal Dis Res 1999; 17 (1): 1-9
78. Hossain MS, Salam MA, Rabbani GH, et al. Vibrio cholerae O139 Bengal: a descriptive study. J Health Pop Nutr 2000; 18 (1): 27-32
79. McFarland LV, Brandmarker SA, Guandalini S. Pediatric Clostridium difficile: a phantom menace or clinical reality. J Pediatr Gastroenterol Nutr 2000; 31: 220-31
80. Yassin SF, Young-Fadok TM, Zein NN, et al. Clostridium difficile-associated diarrhea and colitis. Mayo Clin Proc 2001; 76 (7): 725-30
81. Freeman J, Wilcox MH. Antibiotics and Clostridium difficile. Microbes Infect 1999; 1 (5): 377-84
82. Gorenek L, Dizer U, Besirbellioglu B, et al. The diagnosis and treatment of Clostridium difficile in antibiotic-associated diarrhea. Hepatogastroenterology 1999; 46 (25): 343-8
83. Gorschluter M, Glasmacher A, Hahn C, et al. Clostridium difficile infection in patients with neutropenia. Clin Infect Dis 2001; 33 (6): 786-91
84. Wilcox MH, Smyth ET. Incidence and impact of Clostridium difficile infection in the UK, 1993-1996. J Hospital Infect 1998; 39 (3): 181-7
85. Alvarez-Olmos MI, Oberhelman RA. Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. Clin Infect Dis 2001; 32: 1567-76
86. Vanderhoof JA. Probiotics: future directions. Am J Clin Nutr 2001; 73: 1152-5S
87. Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. J Pediatr Gastroenterol Nutr 1998; 27: 323-32
88. Biller JA, Katz AJ, Flores AF, et al. Treatment of recurrent Clostridium difficile colitis with Lactobacillus GG. J Pediatr Gastroenterol Nutr 1995; 21: 224-6
89. Buts JP, Corthier G, Delmee M. Saccharomyces boulardii for Clostridium difficile-associated enteropathies in infants. J Pediatr Gastroenterol Nutr 1993; 16: 419-25
90. Vanderhoof JA, Whitney DB, Antonson DL, et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J Pediatr 1999; 135: 564-8
91. Arvola T, Laiho K, Torkkeli S, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. Pediatrics 1999; 104: 1121-2
92. Cover TL, Aber RC. Yersinia enterocolitica. N Engl J Med 1989; 321 (1): 16-24
93. Abdel-Haq NM, Asmar BI, Abuhammour WM, et al. Yersinia enterocolitica infection in children. Pediatr Infect Dis J 2000; 19: 954-8
94. Tuohy AM, O'Gorman M, Byington C, et al. Yersinia enterocolitis mimicking Crohn's disease in toddler. Pediatrics 1999; 104 (3): E36
95. Lamps LW, Madhusudham KT, Greenson JK, et al. The role of Yersinia enterocolitica and Yersinia pseudotuberculosis in granulomatous appendicitis: a histologic and molecular study. Am J Surg Pathol 2001; 25 (4): 508-15
96. Bien JP. Anticipatory guidance and chitterlings. J Pediatr 1998; 133 (5): 712-3
97. Satterthwaite P, Pritchard K, Floyd D, et al. A case-control study of Yersinia enterocolitica infections in Auckland. Aust NZ Public Health 1999; 23 (5): 482-5
98. Pai CH, Gillis F, Tuomanen E, et al. Clinical and laboratory observations: placebo-controlled double-blind evaluation of trimethoprim-sulfamethoxazole treatment of Yersinia enterocolitica gastroenteritis. J Pediatr 1984; 104 (2): 308-11
99. San Joaquin VH, Pickett DA. Aeromonas-associated gastroenteritis in children. Pediatr Infect Dis J 1988; 7 (1): 53-7

100. Teka T, Faruque AS, Hossain MI, et al. Aeromonas-associated diarhoea in Bangladeshi children: clinical and epidemiological characteristics. Ann Trop Paediatr 1999; 19: 15-20
101. Albert MJ, Ansaruzzaman M, Talukder KA, et al. Prevalence of enterotoxin genes in Aeromonas spp isolated from children with diarrhea, healthy controls and the environment. J Clin Microbiol 2000; 38 (10): 3785-90
102. Ko WC, Lee HC, Chuang YC, et al. Clinical features and therapeutic implications of 104 episodes of monomicrobial Aeromonas bacteraemia. J Infect 2000; 40 (3): 267-73
103. Ghenghesh KS, Bara F, Bukris B, et al. Characterization of virulence factors of Aeromonas isolated from children with and without diarrhoea in Tripoli, Libya. J Diarrhoeal Dis Res 1999; 17 (2): 75-80
104. Taher AA, Rao BN, Alganay KG, et al. An outbreak of acute gastroenteritis due to Aeromonas sobria in Benghazi, Libyan Arab Jamahiriya. East Mediterr Health J 2000; 6 (2-3): 497-9
105. Juan HJ, Tang RB, Wu TC, et al. Isolation of Aeromonas hydrophila in children with diarrhea. J Microbiol Immunol Infect 2000; 33 (2): 115-7
106. Kain KC, Kelly MT. Clinical features, epidemiology, and treatment of Plesiomonas shigelloides diarrhea. J Clin Microbiol 1989; 27: 998-1001
107. Wong TY, Tsui HY, So MK, et al. Plesiomonas shigelloides infection in Hong Kong: retrospective study of 167 laboratory-confirmed cases. Hong Kong Med J 2000; 6 (4): 375-80
108. Shigematsu M, Kaufmann ME, Charlett A, et al. An epidemiological study of Plesiomonas shigelloides diarrhoea among Japanese travelers. Epidemiol Infect 2000; 125 (3): 523-30

Correspondence and offprints: Associate Professor *Anthony G. Catto-Smith*, Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Flemington Rd, Parkville, VIC 3052, Australia.
E-mail: tony.cattosmith@rch.org.au