

Diarrhea caused by primarily non-gastrointestinal infections

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SUMMARY

Infectious diseases that do not primarily affect the gastrointestinal tract can cause severe diarrhea. The pathogenesis of this kind of diarrhea includes cytokine action, intestinal inflammation, sequestration of red blood cells, apoptosis and increased permeability of endothelial cells in the gut microvasculature, and direct invasion of gut epithelial cells by various infectious agents. Of the travel-associated systemic infections presenting with fever, diarrhea occurs in patients with malaria, dengue fever and SARS. Diarrhea also occurs in patients with community-acquired pneumonia, when it is suggestive of legionellosis. Diarrhea can also occur in patients with systemic bacterial infections. In addition, although diarrhea is rare in patients with early Lyme borreliosis, the incidence is higher in those with other tick-borne infections, such as ehrlichiosis, tick-borne relapsing fever and Rocky Mountain spotted fever. Unfortunately, it is often not established whether diarrhea is an initial symptom or develops during the course of the disease. The real incidence of diarrhea in some infectious diseases must also be questioned because it could represent an adverse reaction to antibiotics.

KEYWORDS antibiotic-associated diarrhea, malaria, pneumonia, primarily non-gastrointestinal infection, SARS

REVIEW CRITERIA

PubMed was used for a literature search from 1966 to present. English and non-English journals were included in the search. Combinations of the following search terms were used: "diarrhea", "gastroenteritis", "antibiotic-associated diarrhea", "malaria", "community-acquired pneumonia", "primarily non-gastrointestinal infection", "SARS", "Ebola", "HIV", "dengue", "avian", "influenza", "hanta", "candida", "legionella", "plague", "bacteremia", "leptospirosis", "ehrlichiosis", "tularemia", "Rocky Mountain spotted fever", "pneumococci", "Lyme", "borrelia", "ticks", "brucella", "meningococci". Selected papers were also searched for relevant references.

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INTRODUCTION

Diagnostic algorithms classify diarrhea as either infectious or non-infectious. Infectious diarrhea is caused by direct infection of the gastrointestinal tract by such organisms as rotavirus or salmonella. Very little consideration is usually given to diarrhea in patients with infectious diseases that do not primarily affect the gastrointestinal tract but are systemic or affect other organ systems.

In one report, of 594 patients diagnosed with gastroenteritis, 71% had gastrointestinal infections, 15% had non-infectious gastrointestinal diseases, 8% had systemic infections, including urinary tract infections (19 patients), respiratory tract infections (8 patients), septicemia (6 patients), pelvic inflammatory disease (5 patients), malaria (2 patients) and others,¹ and 6% had systemic non-infectious diseases. Although the urinary tract infections detected in this study might be a consequence of diarrhea,² other systemic infections are directly or indirectly responsible for diarrhea.

Unfortunately, in many cases the definition of diarrhea remains unclear and it is not established whether the diarrhea is an initial symptom or has developed during the course of the disease, or whether it occurred before or after the initiation of antibiotic treatment. The reported incidence of diarrhea in extraintestinal infections can be questioned, because many cases of diarrhea are adverse events associated with antibiotics and most reports lack controls.

This review focuses on the wide spectrum of clinically relevant infectious diseases that do not primarily affect the gastrointestinal tract, but in which diarrhea is common (table 1).

PATHOGENESIS OF DIARRHEA IN SYSTEMIC INFECTIONS

The pathogenesis of diarrhea in systemic infections is not well understood because basic data on the mechanisms that lead to diarrhea are lacking.

Several cytokines have been shown to have a role in the pathogenesis of diarrhea. For

example, interferon-gamma (IFN- γ), interleukin (IL)-6 and IL-10 concentrations were elevated in the sera of children with diarrhea caused by rotaviruses.³ The level of IL-6 was higher in those patients with fever, and increased tumor necrosis factor alpha (TNF- α) levels also correlated with the presence of fever and the number of diarrheal episodes.³ TNF- α is a central mediator of intestinal inflammation and also known to be involved in chloride secretion by intestinal epithelial cells.⁴

Polyclonal T-cell activation with an anti-CD3 antibody in mice leads to a release of cytokines such as TNF- α , IFN- γ , IL-2, IL-3, IL-4 and IL-6 into the circulation, which results in a severe but self-limiting syndrome consisting of diarrhea, hypothermia and hypomotility.⁵ The expression of the proinflammatory cytokine IL-8 can be stimulated by the flagella proteins of various bacteria,⁶ and has been shown to predict the severity of enterocolitis in pediatric oncology patients.⁷ IL-8 is strongly chemoattractant for CD8⁺ intraepithelial lymphocytes and a strong inducer of CD4⁺ T cells; it probably has a role in the generation of the mucosal immune response to rotavirus infection.⁸ The anti-inflammatory cytokine IL-10 was recently shown to protect IL-10 knockout mice from severe diarrhea and the loss of intestinal villi induced by T-cell activation through administration of anti-CD3 monoclonal antibodies.⁹ These cytokines might be of particular interest as an explanation of gastrointestinal symptoms in systemic infections.

In addition to the cytokine and humoral alterations, diarrhea-causing factors in systemic infections might include direct invasion of gut epithelial cells by various pathogens, inflammation of the lamina propria and other layers of the intestinal wall (including elements of the enteric nervous system), and rosetting and sequestration of red blood cells, which causes ischemia, endothelial apoptosis, increased permeability of the gut microvasculature and edema (Figure 1). In the following sections we describe the mechanisms that lead to diarrhea whenever data are available.

COMMUNITY-ACQUIRED PNEUMONIA

In a study of 1,812 patients with community-acquired pneumonia (CAP), diarrhea was noted at presentation in 24%.¹⁰ Diarrhea occurred in 29% of younger patients, between 18 and 44 years of age, compared with 18–22% of patients older than 44 years of age. Cough

Table 1 Diarrhea associated with selected pathogens that do not primarily affect the gastrointestinal tract.

Cause of diarrhea	Percentage of patients with diarrhea (%)	References
Viral		
HIV	15–60	28
Dengue virus	37	39
Influenza A virus (children)	8–18	13
Avian influenza virus	7	15
Hantavirus	25–40	17
SARS coronavirus	38–74	35
Ebola virus	86–96	42
Bacterial		
Community-acquired pneumonia (non- <i>Legionella</i>)	6	11
<i>Legionella</i> spp.	25	11
Pneumococci	6–8	23
Meningococci	Rare	29
Bacteremia	20–40	20, 21
<i>Leptospira</i> spp.	58	25
<i>Yersinia pestis</i>	23–51	45
<i>Brucella</i> spp.	6–16	43
<i>Borrelia burgdorferi</i>	2	46
<i>Borrelia hermsii</i>	19	46
<i>Ehrlichia</i> spp.	10	46
<i>Francisella tularensis</i>	40	48
<i>Rickettsia rickettsii</i>	19–45	46
Protozoan		
<i>Plasmodium falciparum</i>	5–38	31
Fungal		
<i>Candida</i> spp.	Rare	50
Others		
Antibiotic-associated diarrhea	5–25	49

was the first symptom of disease, occurring 7 days before presentation; fever started 3 days before presentation, and diarrhea, vomiting and abdominal pain occurred 2 days before presentation. This indicates that the diarrhea followed the spread of the infection throughout the body or the administration of antibiotics.

Bacterial etiology

In a prospective study of 392 patients with CAP, *Legionella pneumophila* was found in 48 patients

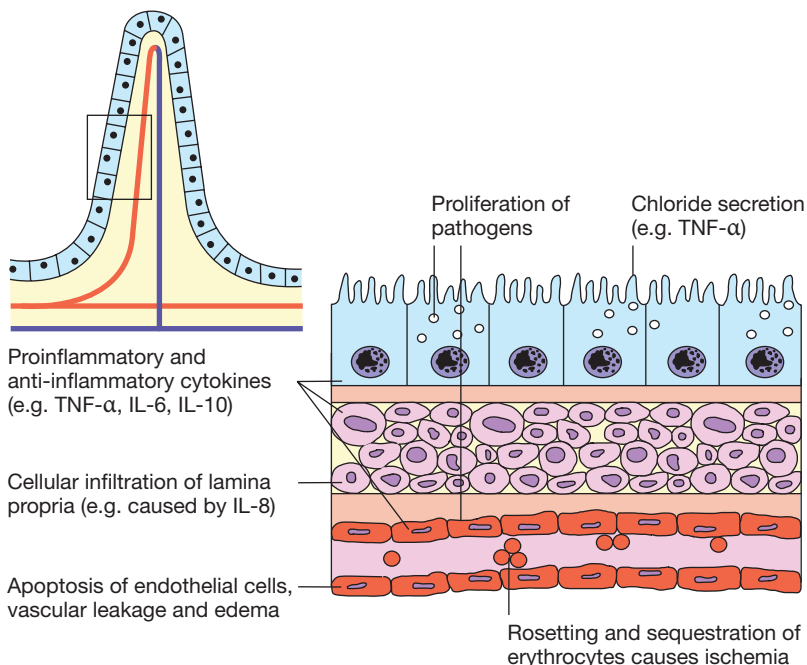


Figure 1 Intestinal villus with epithelial layer and schematic capillary loop. Mechanisms leading to diarrhea are shown in the magnified area on the right (enclosed by the box on the left) with epithelial layer and mucosal capillary. Direct invasion of intestinal epithelial cells and intracellular proliferation of pathogens causes inflammation or villous blunting, fluid imbalances and electrolyte shifts. Proinflammatory and anti-inflammatory cytokines, produced locally or originating from other organs, induce inflammation and cellular infiltration of the lamina propria and other layers of the intestinal wall. Rosetting and sequestration of red blood cells cause ischemia, endothelial apoptosis, increased vascular permeability, and edema. IL, interleukin; TNF, tumor necrosis factor.

and another bacterial etiology was established in 125 patients (pneumococci in 68, *Chlamydia pneumoniae* in 41, and others). Significantly more patients with legionellosis (25%) had diarrhea than those with pneumonia caused by other bacteria (6%).¹¹ In another study, diarrhea occurred more frequently in patients with CAP who were infected with *Legionella* spp. (21%) and *C. pneumoniae* (20%), than pneumococci (4%), *Haemophilus influenzae* (5%), and gram-negative bacteria (5%), although the number of positively identified pathogens was low in this study.¹² Diarrhea in patients with CAP should therefore bring to mind possible infection with *Legionella*.

Viral etiology

Influenza and avian influenza

Influenza is characterized by the acute onset of fever and respiratory symptoms complicated by pneumonia, meningoencephalitis and

myopericarditis. Of 84 children with influenza A, diarrhea occurred in 11 of 60 children (18%) who were younger than 5 years of age and in 2 of 24 of the older children (8%).¹³ Diarrhea is less common in adults with influenza than in children under 16 years of age.¹⁴

In a recent outbreak of avian influenza A (H5N1) in Vietnam, all 10 adult patients presented with fever, respiratory symptoms and significant lymphopenia. Seven patients also had diarrhea.¹⁵ Atypical avian influenza can also present with fever and diarrhea but without respiratory symptoms.¹⁶

Hantaviruses

In North, Central and South America, the New World hantaviruses (e.g. Sin Nombre virus) cause a pulmonary syndrome, and half of the patients infected with these viruses also suffer from diarrhea.¹⁷ In Europe, the predominant hantavirus serotype is Puumala (other serotypes include Hantaan, Dobrava, Seoul), which causes epidemic nephropathy, a mild form of hemorrhagic fever with nausea, vomiting, headache, stomachache, back pain, tenderness in the kidney area, red throat, neurologic symptoms and diarrhea or constipation. In one outbreak, of 401 patients with Puumala or Dobrava virus infection, 25% had diarrhea.¹⁸ In Hanta hemorrhagic fever with renal syndrome, TNF- α , IL-1, IL-2 and nitric oxide are potent mediators of vascular permeability associated with increased intestinal protein loss and diarrhea.¹⁹

SYSTEMIC INFECTIONS AND MENINGITIS

Septicemia

Diarrhea has been reported in up to 20% of patients with systemic infections caused by gram-negative bacteria.²⁰ In one study in Brazil, 205 children presented to a hospital with septicemia caused by *Staphylococcus aureus* (25%), *Klebsiella pneumoniae* (23%), *Pseudomonas aeruginosa* (15%), *Enterobacter* sp. (11%), *Escherichia coli* (7%) and others (19%).²¹ Gastrointestinal problems appeared in two-thirds of these patients, with diarrhea present in 40% of all cases. Unfortunately no data were provided about possible stool pathogens. In another study, pneumococcal septicemia was associated with severe watery diarrhea in 8% of patients.²² Other authors considered this kind of diarrhea to be a consequence of the direct invasion of the intestinal wall by pneumococci, as pneumococci have been cultured from the stool of a boy with bloody diarrhea.²³

Group A streptococcal infections

In 397 patients with severe invasive group A streptococcal infections, 40 patients had primary gastrointestinal symptoms, but not necessarily diarrhea.²⁴ In the same study, 3 cases, for which diarrhea, nausea and vomiting were reported as the initial symptoms of disease, were fatal.²⁴

Leptospirosis

Symptoms of leptospirosis include fever, chills, myalgia, headache, vomiting, jaundice, conjunctival bleeding, rash, abdominal pain, and diarrhea. In an outbreak of leptospirosis in athletes, 58% of patients had diarrhea.²⁵ Leptospiral endotoxin inhibits Na⁺ K⁺ ATPase and in this way induces cellular dysfunction that is associated with diarrhea.²⁶

HIV

In one study, gastrointestinal symptoms including nausea, vomiting and diarrhea were present in 60% of patients with primary HIV infections,²⁷ and 15–40% of HIV patients suffer from diarrhea without any causal factor being identified.²⁸ The real incidence of diarrhea induced by HIV per se (HIV enteropathy) is difficult to establish, however, because anti-retroviral therapy or opportunistic gastrointestinal pathogens overlap the picture. HIV enteropathy is characterized by a jejunal villous atrophy with hyper-regeneration in early-stage disease and hyporegeneration and dysmaturation of intestinal epithelial cells in late-stage disease, which indicates that there might be two distinct types of immunologically mediated mucosal transformation. Increases in paracellular permeability were shown to be mediated by viral envelope glycoprotein (gp120) and TNF- α .²⁸

Meningococcal septicemia and meningitis

In rare cases, fever, diarrhea and abdominal pain have been reported as the presenting symptoms of meningococcal septicemia and meningitis 12–24 h before the appearance of the rash that is typical of this disease. This might lead to misdiagnosis and a lethal outcome.²⁹ Of 81 children studied in Ghana who survived meningitis caused by pneumococci, meningococci and *H. influenzae*, 15 children (33%) had mild to moderate diarrhea. All children were, however, treated for meningitis with ceftriaxone, suggesting the possibility of antibiotic-associated diarrhea.³⁰

TRAVEL-ASSOCIATED INFECTIOUS DISEASES

Malaria

The major clinical features of malaria caused by *Plasmodium falciparum* are fever, headache and arthralgia. In addition to other abdominal symptoms, such as anorexia, nausea, vomiting and abdominal pain, diarrhea occurs in 5–38% of cases. Patients can pass stools containing blood, pus, mucus or epithelial cell debris, and this condition can be indistinguishable from acute bacillary dysentery.³¹ Malaria that presents with such severe diarrhea meets the WHO criteria for complicated malaria and has an increased mortality.

Complex mechanisms interact in the pathogenesis of diarrhea in patients with *P. falciparum* malaria. Rosetting and sequestration of red blood cells lead to capillary occlusion and ischemia. Adherence of parasitized erythrocytes to endothelial cells results in cytokine activation, apoptosis of the endothelium and an intestinal inflammatory response, with subsequent capillary leakage and increased gastroduodenal permeability. This is followed by edema of the submucosa and infiltration of the lamina propria by lymphocytes, plasma cells, eosinophils and malaria pigment-laden macrophages, with shortening and widening of the villi.^{31–33} Malabsorption of sugars, amino acids and fats has been documented.³⁴ Occasionally, rupture of the villi or other mucosal elements produces gastrointestinal bleeding; this occurs more often in the stomach and small intestine than in the colon.

Severe Acute Respiratory Syndrome

The clinical features of SARS (Severe Acute Respiratory Syndrome) are similar to influenza. There is a sudden onset of fever, headache, myalgia, and pulmonary symptoms such as cough or shortness of breath and pneumonia occurring on day 5. Diarrhea has been reported in 1–24% of SARS patients at the time of hospital admission, and in 38–74% of cases overall.^{35–37} In one study, diarrhea occurred in 20% of younger SARS patients and in 4% of older SARS patients, though it is unclear why older patients have diarrhea less often.³⁸ Diarrhea was most common, occurring in 74% of all SARS cases, during an outbreak in Hong Kong, where the transmission was also suspected to be mediated by sewage.³⁶ At day 14 after hospital admission, the SARS coronavirus was detected in the stool of 97% of patients,³⁶ supporting the theory of

feco-oral transmission. The presence of the SARS coronavirus in gastrointestinal epithelial cells can be visualized by electron microscopy; however, there is no evidence of inflammation in the gut mucosa or submucosa and no, or only slight, villous blunting in patients with SARS-associated diarrhea.³⁵ It is worth noting that the viral load of SARS coronavirus in nasopharyngeal aspirates was significantly higher in patients with diarrhea and in patients who died than in the other SARS patients; nonetheless, diarrhea did not predict death.³⁷

Dengue fever

Although most cases of dengue fever have a mild or subclinical course, the typical symptoms of the full-blown disease consist of fever, retrobulbar headache, rash, severe arthralgia (hence 'break-bone fever'), diarrhea, nausea, vomiting, and abdominal pain. In one study, diarrhea was reported to occur in 35% of children living in endemic areas.³⁹ In another study, 37% of adult travelers with serologically confirmed dengue fever had diarrhea, compared with 30% of patients with dengue-like illness and 17% of patients with malaria.⁴⁰ IL-8 has a major role in the pathogenesis of dengue fever,⁴¹ and IL-8 might also be involved in the pathogenesis of dengue-associated diarrhea.^{6,8}

Other hemorrhagic fevers

During the 1995 Ebola outbreak in Kikwit (Congo), symptoms of fever, asthenia, abdominal pain, anorexia, diarrhea, nausea, headache, arthralgia, redness of the oral mucosa and conjunctivitis improved after the first week for a period of 1–2 days, but were then followed by hemorrhagic manifestations, neuropsychiatric symptoms and oligoanuria.⁴² Diarrhea occurred in 86–96% of the patients during the first phase. During the second phase, melena was seen in 10–43% of all patients, grossly bloody stools in 7% and hematemesis and gum bleeding in 13–30%. Most of these patients died.^{42,43}

In addition to dengue fever, Ebola and hantavirus infection, diarrhea has also been reported to occur frequently in other hemorrhagic fevers.

Other travel-associated infections

In three large series including 757 patients with brucellosis, 30–68% of the patients had gastrointestinal symptoms and 6–16% had diarrhea due to mesenteric lymphadenitis or inflammation

and ulceration of Peyer's patches.⁴⁴ In one report, 18% of patients had gastrointestinal bleeding or melena, and diarrhea was also reported as the first manifestation of brucellosis.⁴⁴

A review of 71 cases of human plague showed that in septicemic patients, gastrointestinal symptoms and diarrhea occurred in 72% and 51%, respectively, and in 39% and 23% of patients with bubonic plague, respectively.⁴⁵

TICK-BORNE INFECTIONS

Zaidi and Singer recently reviewed the gastrointestinal and hepatic manifestations of tick-borne diseases.⁴⁶ In 5–23% of patients with early Lyme borreliosis, there are gastrointestinal symptoms such as anorexia, nausea, vomiting, abdominal pain, hepatitis, hepatomegaly and splenomegaly. Diarrhea is rare, occurring in only 2% of cases.

In tick-borne relapsing fever (caused by *Borrelia hermsii* and other species), fever, headache, arthralgia, nausea, vomiting, abdominal pain and hepatitis are frequent symptoms, along with jaundice, hepatomegaly and splenomegaly. Diarrhea occurs in 19% of cases. Hematemesis and bloody diarrhea, as a consequence of thrombocytopenia, are common but rarely severe.⁴⁶

Ehrlichiosis is characterized by fever, leukopenia, thrombocytopenia and elevated concentrations of liver transaminases. Such gastrointestinal symptoms as nausea, vomiting, abdominal pain and jaundice might be seen early in the course of the disease. Diarrhea occurs in up to 10% of patients and can be the primary manifestation. Gastrointestinal hemorrhage due to thrombocytopenia has also been reported.⁴⁶

Rocky Mountain spotted fever classically presents with fever, eschar and exanthema, particularly in spring and summer. In the early course of the disease, gastrointestinal symptoms including abdominal tenderness and vomiting, and elevated concentrations of liver transaminases can be misinterpreted as peritonitis, cholangitis or appendicitis. Diarrhea occurs in 19–45% of patients and can be the main presenting symptom. Gastrointestinal hemorrhage has also been reported. A mononuclear-predominant vasculitis in the stomach, small and large intestines and pancreas is the main pathological finding.⁴⁷

Tularemia presents as an ulceroglandular or typhoidal form. The latter form includes hepatic

involvement, anorexia, nausea, vomiting, abdominal pain and diarrhea in up to 40% of patients.⁴⁸ Jaundice, cholangitis, ascites, granulomatous hepatitis and liver abscess have been reported. Diarrhea can be watery and severe but is rarely bloody.

ANTIBIOTIC-ASSOCIATED DIARRHEA

In patients with primarily non-gastrointestinal infections, diarrhea occurs in 5–25% of those receiving antibiotic treatment.⁴⁹ The major mechanisms of antibiotic-associated diarrhea (AAD) involve disturbances of the gut microflora and the direct effects of antibiotics on the mucous membranes. The anaerobic gut microflora metabolizes high-molecular-weight carbohydrates to absorbable short-chain fatty acids. When the gut microflora is altered by antibiotics, high-molecular-weight carbohydrates accumulate in the colon and cause osmotic diarrhea. Bile acids, which escape absorption in the small bowel, are usually deconjugated and dehydroxylated by bacteria. When the bacterial flora is disturbed, unmetabolized dihydroxy bile acids, which are potent secretory agents, lead to development of secretory diarrhea in the colon.⁴⁹

Disturbances of the gut microflora also promote the overgrowth of distinct pathogenic bacteria. About 16–20% of AAD cases are caused by *Clostridium difficile* and 2–8% by *Clostridium perfringens*.⁴⁹ Rare cases of diarrhea due to *Klebsiella oxytoca* (also known as penicillin-associated colitis) and *Salmonella* spp. have been reported after antibiotic treatment. *Candida* overgrowth has long been postulated to cause AAD, but recent studies clearly indicate that elevated *Candida* counts in the stool are a result of antibiotic treatment or diarrhea per se rather than a cause of AAD.⁵⁰

CONCLUSIONS

Although direct infections of the gastrointestinal tract are the major cause of gastroenteritis and diarrhea, systemic infections or infections that affect other organ systems, as outlined in this review, represent a wide spectrum of causes of diarrhea and must be included in the differential diagnosis and diagnostic approach to diarrhea. When there is a history of travel, such infections as malaria caused by *P. falciparum*, dengue fever and legionellosis should be considered in addition to the pathogens known to cause travelers' diarrhea.

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Competing interests

The authors declared they have no competing interests.

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