TABLE 99.2 Enteroinvasive *Escherichia coli* Serotypes

SEROTYPE	DIFCO SEROGROUP TEST[a]
O28	C
O29	—
O112	C
O124	B
O136	C (Trabulsi 193-T-64)
O143	—
O144	—
O152	(Trabulsi 185-T-64)

[a]Difco Laboratories, Detroit.
Modified from references 26, 28, 29, and 184.

with human leukocyte antigen (HLA)-B27.[25] Culture-positive conjunctivitis during acute shigellosis has also been described and may represent autoinoculation of the conjunctiva analogous to that induced in guinea pigs in the Sereny test.[26] Arthritis syndromes have also been described after inflammatory colitis with *Y. enterocolitica, Salmonella enteritidis*, or *C. difficile*, again in association with HLA-B27.[27]

Certain *E. coli* strains may produce a syndrome identical to that seen with acute shigellosis. The incubation period is usually 2 to 3 days after ingestion. Although invasive *E. coli* organisms appear to be limited to certain serotypes (Table 99.2),[26,28,29] to confirm the presence of such organisms, their invasive potential should be demonstrated in research studies with the guinea pig conjunctivitis (Sereny) test[30] or in HeLa cells,[31] or the 120- to 140-megadalton plasmid associated with invasiveness in *Shigella* and invasive *E. coli* should be identified.[32] Invasive *E. coli* organisms were responsible for a single widespread outbreak of dysentery associated with imported French Camembert cheese.[29,33] Although they have been identified as occasional causes of diarrhea in Brazil,[26] invasive *E. coli* organisms do not appear to be frequent causes of sporadic diarrhea in the United States. Because they are often slow to ferment lactose in the laboratory, invasive *E. coli* organisms may be initially mistaken for shigellae,[26,29,31] to which they are closely related. Invasive *E. coli* organisms are also usually lysine negative, often nonmotile,[34] and antigenically related to *Shigella*.[35]

Shiga Toxin–Producing *Escherichia coli*

A significant cause of bloody diarrhea and potentially fatal HUS is now recognized to be due to EHEC organisms (see Chapter 98) that produce Shiga-like toxin, although the frequency with which they cause inflammatory diarrhea is not clear.[2,36] These organisms have attracted particular attention because of widespread outbreaks in popular hamburger chain restaurants[37] and with uncooked produce, such as spinach,[38,39] and a widespread outbreak of bloody diarrhea and severe HUS, starting in Germany and extending across Europe, associated with eating imported Egyptian fenugreek sprouts in the early summer of 2011. The latter, unlike prior EHEC strains that had exhibited EPEC traits of attachment and effacement, was a Shiga toxin–producing EAEC strain.[40,41] Although it accounts for only 0.8% to 3.0% of all cases of diarrhea in the United States and Canada, EHEC (serotype O157) is estimated to account for 15% to 36% of cases of bloody diarrhea.[2] Most recognized EHEC strains are of serotype O157; others include O26:K60:H11, O103:H2, O91:H2, O145:H$^-$, O111:K58:H$^-$, O38:H21, O6:H$^-$, O5:H$^-$, O128, O139, O113:K75, O121, and O172.[2,28,42] EHEC organisms were the most commonly recognized cause of diarrhea (3%) among 5415 patients studied in Calgary in Alberta, Canada, where such cases showed a summer seasonal peak.[43] In addition to causing 15% to 36% of all cases of bloody diarrhea, including outbreaks of hemorrhagic colitis, EHEC is associated with 75% to 90% of cases of HUS in North America, a complication that develops in 8% of EHEC infections.[2]

The incubation period is usually 3 to 4 days after the ingestion of contaminated food or water. Cattle are the major reservoir of the organism. The consumption of inadequately cooked beef, raw milk, or other products contaminated by the intestinal contents of cattle, and occasionally of contaminated water, has been recognized as an important source of O157:H7 infection.[44] A waterborne outbreak of *E. coli* O157:H7 has been documented in upstate New York at a county fair.[45] The infection causes abdominal cramps and watery diarrhea, followed by bloody diarrhea.[46] In contrast to more inflammatory and invasive enteropathies (such as shigellosis or campylobacteriosis), fever is typically absent or minimal on presentation. The HUS and thrombocytopenia may occur 2 to 4 days after the onset of diarrhea, especially in children younger than 5 years and in older adults. EHEC O157:H7 forms characteristic actin pedestals on infected mammalian cells.[47] Previously, typical EHEC organisms shared EPEC traits of secreting their own translocated intimin receptor (Tir) molecule (via a type II secretion system) into the plasma membranes of host cells.[48] The attachment of the organism via its Tir receptor is required to trigger the assembly of actin into focused pedestals beneath bound bacteria. EHEC produces Stx1 or Stx2; the latter is more associated with HUS.[49] Another EHEC virulence factor, H7 flagellin, is also associated with activation of proinflammatory signals in human colonic epithelial cells in response to this noninvasive pathogen.[48] The German outbreak EHEC strain was an EAEC O104:H4 strain that produced Stx2a and was positive for several EAEC genes, including *aggR, aggA* (encoding for the biofilm-producing aggregative adherence fimbriae I [AAF/I]), *sigA, sepA, pic, aatA, aaiC,* and *aap,* but it was negative for the *eae* (*E. coli* attaching and effacing) gene and produced an extended-spectrum β-lactamase.[50,51]

Enteropathogenic and Enteroaggregative *Escherichia coli*

EPEC organisms that cause acute diarrhea in infants may rarely be associated with an insidious persistent or relapsing illness.[52] *E. coli* organisms in O groups 1, 2, 4, 7, and 75 that produce hemolysin and necrotoxin have been isolated from patients with ulcerative colitis. These toxic organisms are not present in healthy people or in patients with acute diarrheal syndromes.[53] In addition, EAEC organisms are recognized as a cause of persistent diarrhea in India, Brazil, and Mexico.[54–56] EAEC infections are an emerging problem (at least in terms of their recognition), and EPEC infections remain important in many parts of the world.[57–59] EAEC organisms have been associated with intestinal inflammation and malnutrition, even in the absence of diarrhea.[60,61] The effects of antibiotic treatment constitute a topic of current interest, and such therapy may be feasible.[62]

Campylobacter Enteritis

Campylobacter spp. have a small genome (1.6–2.0 megabytes) and may live in the GI tract of their natural zoonotic hosts for a long time and can cause intestinal and systemic infection in humans. The genome sequence from multiple *C. jejuni* and several other *Campylobacter* spp. have been published.[63–65] There currently are 16 *Campylobacter* spp. and 6 subspecies. *C. jejuni* and *Campylobacter coli* are the most prevalent species associated with enteric infections. *C. jejuni* is the most prevalent bacteria isolated from enteric infections in industrialized countries. *C. jejuni* and *C. coli* are highly prevalent in developing countries, especially in children younger than 2 years with enteric infection or in asymptomatic carriers. *C. jejuni* systemic infections (see Chapter 216) have been recognized for many years. Although the majority of *Campylobacter* bloodstream infections in humans are with *Campylobacter fetus* (old subspecies, *C. fetus* subsp. *intestinalis*),[66] *C. jejuni* commonly causes an enteric infection in all age groups. This organism was recognized many years ago as a cause of calf and swine dysentery. Commercially available techniques of fecal culture have enabled the culture of *C. jejuni* on highly selective media at 42°C from fecal specimens of patients with diarrhea.[67] *Campylobacter* enteritis results from oral transmission, and a variable but relatively small dose ($5–8 \times 10^2$ cells/mL) is sufficient to cause infection.[68] This organism causes a syndrome of severe abdominal pain, fever, and acute inflammatory enteritis that may range from watery diarrhea to severe dysentery with blood and pus in the stools.[69] Infection has also been associated with sequelae of reactive arthritis and the Guillain-Barré syndrome.[70] Cross-reacting antibodies recognizing both *C. jejuni* lipopolysaccharide and antigenic determinants of nerve gangliosides are speculated to contribute to the development of the

axonal nerve damage after *C. jejuni* infection. Reports from Belgium, England, and central Africa have revealed that in 5% to 14% of unselected cases of diarrhea, *C. jejuni* is present,[69,71] and outbreaks of *Campylobacter* enteritis have been associated with ingestion of contaminated water, raw milk, and uncooked meat and poultry. A review of common source outbreaks of *Campylobacter* infection in the United States between 1997 and 2008 showed that unlike sporadic illnesses, which are primarily attributable to poultry, dairy products were the vehicle most often associated with these outbreaks.[72] There are several genes involved in the adhesion, colonization, invasion, and toxin production by *Campylobacter* spp., and the specific balance between these genes and host susceptibility to *Campylobacter* enteritis remains uncertain.[63]

Clostridioides difficile Colitis

CDI is the most common cause of antibiotic-associated diarrhea. In the past decade the incidence and mortality rates of CDI increased because of the emergence of strains characterized as BI/NAP1/O27/III, which have heightened toxinogenesis.[73] Advanced age is a critical risk factor for severe disease, recurrence, and mortality,[74] although CDI is also now appearing in younger, lower-risk populations.[75] Disruption of normal intestinal microbiota from prior antibiotic use allows *C. difficile* colonization, germination of spores, and production of toxins. The primary virulence factors that are known to cause clinical disease in CDI are two large toxins: *C. difficile* toxin A (TcdA), or toxin A (308 kDa) and TcdB, or toxin B (270 kDa).[76] Both toxins are glucosyltransferases that inactivate Rho, Rac, and Cdc42 proteins and result in actin condensation and subsequent cytoskeletal changes, apoptosis, and cell death of target cells. Tcds also induce an intense inflammatory response characterized by infiltration of inflammatory cells, especially neutrophils; activation of submucosal neurons; secretion of cytokines; chemokines and arachidonic acid metabolites; and production of substance P and reactive oxygen intermediates. Some *C. difficile* strains, including the epidemic RTO27, produce binary toxin that remains poorly characterized but may have a role in host attachment and colonization. Clinical presentation ranges from asymptomatic colonization to severe disease with pseudomembranous colitis (Fig. 99.1) and septic shock. Increased fecal lactoferrin, IL-1β, and IL-8 were observed in patients with CDI.[77] Leukocytosis suggests severe infection, and leukemoid reactions have been described in colitis caused by *C. difficile.*[78]

Vibriosis

In addition to classic and El Tor *Vibrio cholerae* O1 and O139, non-O1 *V. cholerae* and several halophilic *Vibrio* spp. (see Chapters 214 and 215) are now recognized to cause diarrhea and occasional wound or bloodstream infection.[79] The most common and best characterized is *V. parahaemolyticus*, which has been recognized since 1950 in Japan and was identified as a *Vibrio* spp. in 1963. *V. parahaemolyticus* is a cause of seafood poisoning, with onset of signs and symptoms 9 to 25 hours after the ingestion of inadequately cooked fish or shellfish. This has been reported throughout the coastal areas of the United States, especially in warmer waters and on cruise ships and is the most common form of food poisoning in Japan, where raw seafood is commonly eaten as sushi.[80] Diarrhea may be explosive and watery or may be characterized by full-blown dysentery with blood and pus and superficial ulceration on proctoscopic examination.[81] The latter syndrome may be associated with cramps, nausea, vomiting, headache, and fever. The illness is usually self-limited, resolving within 3 to 4 days.

Other halophilic vibrios include *Vibrio alginolyticus, Vibrio fluvialis, Vibrio hollisae, Vibrio damsela*, and *Vibrio vulnificus*, which have been associated with enteric, wound, or systemic infections in humans.[79] *V. vulnificus* has been associated with life-threatening septicemia, often in persons with preexisting liver disease, occurring within 24 hours of ingesting raw oysters.[79,82]

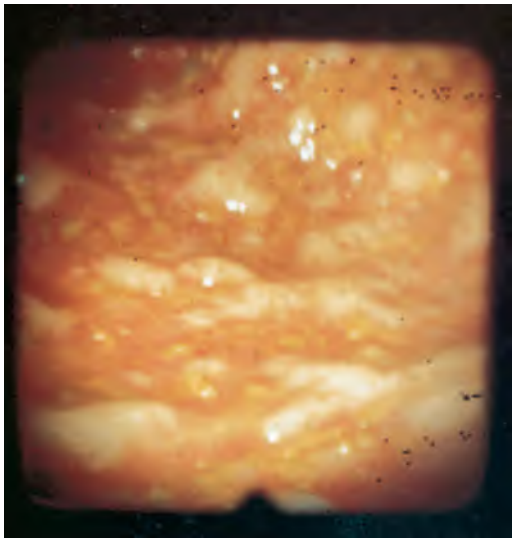

FIG. 99.1 Proctoscopic view of pseudomembranous colitis in a patient who received clindamycin. Note the 4- to 8-mm raised white plaques overlying an erythematous mucosa. *(From Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis.* Ann Intern Med. *1974;81: 429–433.)*

Salmonellosis and Enteric Fever

Salmonella enterocolitis is characterized by fever, cramping, abdominal pain, and diarrhea that begin 8 to 48 hours after ingestion of an infective dose, usually with food, and usually lasts 3 to 5 days (see Chapter 223). The diarrheal stools of patients with salmonellosis often contain a moderate number of polymorphonuclear leukocytes, usually fewer than is typical of shigellosis.

Although *Salmonella* enteritis predominantly involves the lamina propria in the small bowel, several reports have noted *Salmonella enterica* serovar Typhimurium as a cause of colitis, with crypt abscesses and erosion and ulcerations of the colonic mucosa, which result in blood and pus in the stool.[83] Certain other strains of *Salmonella*—including *Salmonella enterica* serovar Choleraesuis and *Salmonella enterica* serovar Paratyphi, and especially *Salmonella enterica* serovar Typhi—tend to elicit a mononuclear response and cause the bacteremia that is characteristic of enteric fever. Animal models for *S.* Typhimurium continue to advance our understanding of the pathogenesis of intestinal and systemic *Salmonella* infections.[84] *Salmonella* flagellin is regulated by the *fliC* gene, which is the major ligand for Toll-like receptor 5 (TLR5), nucleotide oligomerization domain–like receptors, and interleukin-1b–converting enzyme (ICE) protease-activating factor (IPAF) protein. TLR5 is located in the plasma and phagosomal membranes, and the other two are located in the cytoplasm of the host's Peyer patch cells. Flagellin activates TLR5 and leads to the production of IL-12, whereas the activation of IPAF leads to the production of IL-1β and IL-18. Both pathways act synergistically to activate interferon-γ–producing Th1 cells. These proinflammatory cytokines play important roles in the induction of inflammation with *Salmonella* infections.

Typhoid fever may lead to an erosion of the blood vessels in Peyer patches that, without appropriate treatment, could result in gross blood in the feces in 10% to 20% of patients. Severe intestinal hemorrhage may complicate approximately 2% of cases late in the course of untreated typhoid fever. Such intestinal bleeding may precede perforation, another complication of typhoid fever.[85] However, typhoid fever is primarily a systemic illness, not a diarrheal disease (see Chapter 100).

Yersiniosis

Y. enterocolitica (see Chapter 229A) is another increasingly recognized enteric pathogen that may be responsible for an enteric fever–like illness, mesenteric adenitis (which may mimic acute appendicitis), or an inflammatory ileitis or ulcerative colitis syndrome with fecal neutrophils and mononuclear cells.[86] *Y. enterocolitica* and *Yersinia pseudotuberculosis* may cause similar symptoms and signs. The virulence of *Yersinia* is associated with the direct injection of proteins, such as *Yersinia* protein kinase A (YpkA) and *Yersinia* outer protein E (YopE), into eukaryotic cells.[87,88] *Yersinia* infection may also be associated with migratory polyarthritis, reactive arthritis, or erythema nodosum. A syndrome of acute diarrhea and vomiting is especially common in young children. The organism may cause disseminated abscesses in the liver and spleen[89]

or an inflammatory colitis.[90] The causative agent, a gram-negative member of the family Enterobacteriaceae, is in the same genus as the plague bacillus *Yersinia pestis* and is sometimes mistaken for *Proteus* on initial culture plates.

Amebiasis

Entamoeba histolyticum is one of the classic causes of dysenteric syndromes. Although the course and severity of the infection is variable, amebiasis is one infection that can cause sustained febrile diarrhea with stools becoming grossly bloody. For patients living in endemic areas or travelers who have been to such endemic areas and who have dysenteric symptoms, amebiasis should be considered in the differential diagnosis. For further details about amebiasis, please see Chapter 272.

DIAGNOSIS

Diarrhea with fever, blood in the stool, severe abdominal pain, or signs of sepsis necessitates evaluation for enteric pathogens to guide disease management.[91] Clinical and epidemiologic information direct the specific tests to be requested. Examination for fecal leukocytes often reveals sheets of polymorphonuclear leukocytes in clumps of mucus, even in the absence of gross blood in the stool specimen (Fig. 99.2).[92,93] Fewer pyknotic leukocytes are reported in amebic dysentery[94–96]; this may be attributable to the deeper undermining ulcers characteristic of intestinal amebiasis or to a contact-dependent cytolytic effect of the ameba on leukocytes. The diagnosis of shigellosis is made using bacterial cultures or polymerase chain reaction (PCR) assay for the invasiveness plasmid in organisms isolated from stool, rectal swab, or endoscopic biopsy specimens.[97] The use of fresh specimens promptly plated onto appropriate enteric culture media is very important to ensure the isolation of shigellae.[98]

Specialized techniques are required to isolate *Vibrio* (thiosulfate citrate bile salts [TCBS] agar),[99] *Yersinia* (cold enrichment),[100] or *C. jejuni*.[67] The identification of toxigenic *C. difficile* is done by immunoassay for either *C. difficile* toxin A or B, or cell culture cytotoxicity or PCR assay for *C. difficile* toxin B.[101–104]

The diagnosis of infection with EHEC depends on culturing stool on MacConkey culture medium, on which the original O157:H7 EHEC strain yields sorbitol-negative colonies.[105] The isolated *E. coli* is serotyped for somatic (O) and flagellar (H) antigens. Rapid methods for detection of Shiga toxins in the stool samples are now in use.[106,107] The pathogenic Kanagawa-positive strains from patients produce β-hemolysis on special (Wagatsuma) medium—in contrast to environmental isolates—and are best isolated as blue-green colonies (alkaline) on TCBS agar.[99] A PCR method provides a species-specific probe for *V. parahaemolyticus, V. alginolyticus, Vibrio anguillarum*, and a cluster of related species.[108] Cultivation may require cold enrichment techniques.[100] PCR methods for detection of pathogenic *Y. enterocolitica* are more sensitive than culture methods.[109]

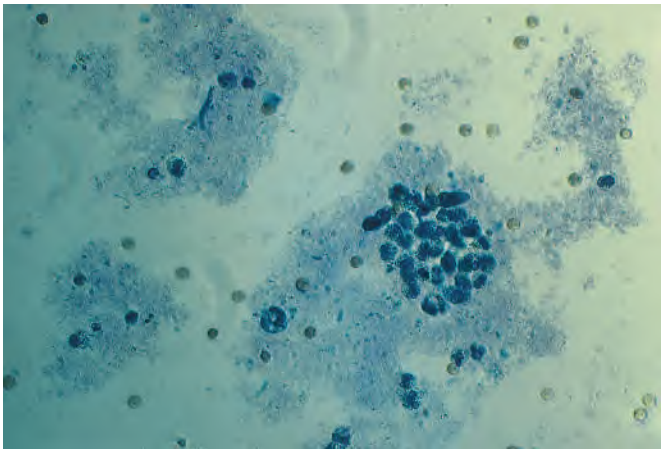

FIG. 99.2 Methylene blue stain of fecal leukocytes from patient with colitis. This exudative response may be seen in any active colitis syndrome, including those caused by the inflammatory or invasive pathogens discussed in this chapter.

Recent approaches using multiple pathogen nucleic acid amplification tests, such as a laboratory-developed TaqMan Array Card (Life Technologies, Grand Island, NY) for simultaneous detection of several enteropathogens, hold promise, with high accuracy, sensitivity and specificity, as well as being potentially suited for surveillance or clinical purposes.[110] However, interpretation of results may be challenging in the presence of multiple pathogens and in determining which specific organisms are clinically relevant. Quantification of burden of infection may assist in the interpretation of results from these molecular assays.[111]

Amebic dysentery is traditionally diagnosed by direct examination of wet mounts of fresh fecal or proctoscopic specimens, which reveal *E. histolytica* trophozoites or cysts characterized by four or fewer delicate nuclei with central karyosomes. Additional patients may be diagnosed by biopsy, which may reveal periodic acid–Schiff stain (PAS)-positive trophozoites or cysts in the undermining ulcer in the lamina propria, or by a fecal or serum *E. histolytica*–specific antigen test, which distinguishes virulent *E. histolytica* from avirulent *Entamoeba dispar* infections.[112]

Sigmoidoscopic examination, especially with biopsy, may be useful in the diagnosis of a pseudomembranous enterocolitis or in the identification of parasites such as *E. histolytica* (with a special PAS stain) or *B. coli*. Amebic colitis is associated with discrete small ulcerations with undermined edges amid relatively normal mucosa. Acute shigellosis causes more widespread, shallow, 3- to 7-mm ulcers with a more intense inflammatory exudate. Barium studies are unnecessary and are relatively contraindicated for toxic patients with acute colitis.

Other considerations in the differential diagnosis of inflammatory colitis are pseudomembranous enterocolitis, which may be associated with antibiotic use, and the potentially rapidly progressive necrotizing enterocolitis syndromes (see Chapters 79 and 243). These diagnoses are suggested by the setting, clinical course, history, and findings on radiologic and proctoscopic examinations. Noninfectious syndromes that may be manifested as acute inflammatory enterocolitis include idiopathic ulcerative colitis and Crohn disease.

Finally, the presence of biomarkers of acute or prolonged intestinal inflammation, such as fecal myeloperoxidase and neopterin, may be associated with growth shortfalls in young children in developing areas.[113]

THERAPY

Therapy consists of careful supportive fluid management with specific antimicrobial therapy directed at a specific pathogen if suspected on the basis of the epidemiologic setting or microbiologic test results. Fluid resuscitation is the primary treatment of all acute diarrheal disease syndromes. Oral rehydration salt solution (World Health Organization formula) is recommended for oral rehydration therapy.[114] Presumptive therapy for the inflammatory colitides varies greatly with the different organisms and is influenced by the increasing resistance of enteric pathogens to antimicrobial therapy.[115] For example, an acute febrile dysenteric illness in a young child with daycare exposure or in an area in which shigellosis is common should be treated with an antimicrobial agent, such as one of the fluoroquinolones. Early administration of empirical antibiotic treatment is justified in children hospitalized for clinical dysentery.[116] Short-course (3 days) oral ciprofloxacin for *S. dysenteriae* type 1 dysentery in children has been effective.[117] If the *Shigella* organism is sensitive, prompt therapy can successfully stop the diarrhea, alleviate systemic symptoms, and reduce shedding of the organisms in the feces.[118–120] Because shigellae are increasingly resistant to multiple antibiotics,[121,122] the practitioner must be familiar with the local resistance pattern of shigellae to treat acute shigellosis appropriately when it is first suspected. Although the fluoroquinolones presently are not approved for use in children in the United States, available data suggest that a short course of therapy is safe.[123] Although ciprofloxacin may shorten the clinical course of *Salmonella* infections, it does not eradicate the organism.[124] Studies have shown increasing resistance of *Campylobacter* and even *Salmonella* to quinolones.[125,126] Azithromycin may reduce the duration of symptoms of *Campylobacter* or *Shigella* enteritis. Zinc 20 mg daily (10 mg of elemental zinc in 5 mL) given in two equally divided doses for 2 weeks showed a significant reduction in the duration of acute shigellosis, promoted better weight gain, and reduced diarrheal morbidity in malnourished children at 6 months

after infection.[127] Vitamin A has also been used to reduce severity and mortality from shigellosis.[128]

Antibiotic therapy has not been shown to be effective for disease caused by EHEC or EIEC. Some EHEC strains may increase their phage-mediated production of Shiga-like toxins when exposed to antibiotics to which they are sensitive, such as ampicillin, tetracycline, sulfamethoxazole-trimethoprim, or quinolones.[129–132]

Most patients with mild-to-moderate *C. jejuni* enterocolitis do not benefit from antibiotic treatment. Severely ill patients, especially those who are debilitated or immunocompromised, appear to benefit from antibiotic therapy, and erythromycin (or other macrolides) or ciprofloxacin are the drugs of choice. Increased fluoroquinolone resistance in *Campylobacter* spp. from humans and animals, the result of mutations in topoisomerase genes, has been well-documented.[133] Two studies now associate symptomatic and asymptomatic *Campylobacter* infections with reduced growth in Brazilian and Peruvian children.[134,135]

Vancomycin and fidaxomicin are the drugs of choice for nonsevere and severe disease caused by CDI (see Chapter 243 for further details).[136,137] Recurrent disease occurs in 20% to 65% of the patients, depending on the number of previous episodes of the disease.[138] Fidaxomicin, the only other US Food and Drug Administration–approved drug for CDI, is reported to be equivalent to vancomycin in treating acute CDI but superior in preventing relapses.[139] However, its advantage over vancomycin is lost in infections caused by the prevalent epidemic strain BI/NAP1/027. Alternative approaches to prevent recurrent disease include probiotics,[140] although their efficacy is marginal; fecal microbiota transplantation (FMT)[141]; or use of monoclonal antibodies.[142] FMT is increasingly being used to prevent recurrent disease or treat refractory CDI. More recently, the monoclonal antibody against TcdB has been shown to confer modest protection against recurrent CDI.[91] Probiotics, when administered in patients receiving antibiotics, may be beneficial for patients at high risk of acquiring CDI.[143]

Antibiotic treatment with tetracycline or doxycycline can diminish the duration and severity of GI symptoms caused by *V. parahaemolyticus*. To prevent *V. parahaemolyticus* infections, consumption of raw or undercooked shellfish and exposure of wounds to seawater should be avoided.[144]

Antibiotic therapy is not required for *Salmonella* enteritis, but patients who are severely ill or those with risk factors for developing extraintestinal spread of infection should be treated with fluoroquinolones or third-generation cephalosporins.

Yersinia infection is usually self-limiting; however, patients with severe illness or systemic infection are usually treated with tetracycline, chloramphenicol, or ciprofloxacin.

PREVENTION

Enteric pathogens are predominantly spread through contaminated food or water and sometimes via direct fecal-oral spread. Spread of infection occurs during ingestion of contaminated food or water or contact with a contaminated environment. Infection control measures include hand hygiene, proper food handling, and access to clean water. In some instances isolation and treatment of infected individuals are necessary to prevent spread of infection, for example, in cases of CDI.

Immunization of susceptible individuals is an important component of prevention. However, for bacterial enteric pathogens, vaccine is only available for typhoid fever and cholera. Typhoid vaccination is recommended for people traveling to endemic areas. Ty21a is a live-attenuated oral vaccine containing *S.* Typhi in capsule formulation. Another typhoid vaccine is the parenteral Vi-polysaccharide. For individuals traveling to areas with recent or ongoing cholera outbreaks, CVD 103-HgR, a live-attenuated oral vaccine, is available. There is a need to develop effective vaccines for most infectious agents causing diarrhea worldwide.

OTHER ACUTE INFECTIOUS/INFLAMMATORY PROCESSES INVOLVING THE INTESTINAL TRACT

Gonococcal Proctitis

Neisseria gonorrhoeae (see Chapter 212) may be the cause of ulcerative proctitis, usually acquired by anal intercourse.[9] The resultant purulent proctitis is accompanied by an erythematous, friable mucous membrane in the rectal vault and occasional abscess or fistula formation. Although copious purulent discharge, tenesmus, and burning rectal pain may be noted, two-thirds of culture-positive patients with anorectal gonococcal infection are asymptomatic.[145] Additional diagnostic possibilities in cases of venereally acquired proctitis are syphilitic, herpetic, and chlamydial proctitis.[146]

Unusual Causes of Dysentery

Spirillar or spirochetal dysentery has been reported to occur in southern France and has been attributed to *Spirillum* spp. Although severe mucoid diarrhea or dysentery has been associated with intestinal spirochetes, their frequency and role in causing enteric disease are unclear. A DNA probe for the 16S ribosomal RNA of the agent of swine dysentery, *Treponema hyodysenteriae*, has been developed and may open new approaches to the recognition of similar infections in humans.[147]

Other unusual causes of colitis include brucellosis[148] and adenovirus infections.[149,150]

Necrotizing Enterocolitis in the Newborn

The syndrome of diffuse, fulminating, necrotizing colitis has been recognized in infants since the 1960s. This syndrome probably represents the same entity described as spontaneous intestinal perforation and peritonitis as early as 1838.[151] Although milder forms of the syndrome doubtless exist, the syndrome of necrotizing enterocolitis (NEC) is defined by the presence of air in the wall of the intestine, portal venous system, or peritoneal cavity, or by necrosis of the bowel wall with mucosal sloughing. This fulminant syndrome often leads to intestinal perforation, peritonitis, and bacteremia. It is a major cause of mortality in low-birth-weight infants (<1500 g) after the first week of life.[152] The diffuse necrotic changes that characterize this syndrome most often occur in the terminal ileum but may be seen in the colon or in the proximal portion of the GI tract.

The pathogenesis of NEC appears to involve mucosal injury that is most often of ischemic origin from hypoxemic or hypotensive episodes; these may occur in premature infants or in the presence of complicating factors, such as an umbilical vein exchange transfusion. Ischemia may also result from the effects of endotoxemia, followed by the effects of epinephrine, to which the vessels supplying the terminal ileum may be especially sensitive. Other factors predisposing to mucosal ischemia include asphyxia in association with hyaline membrane disease in premature infants or cyanotic heart disease. Increased intraluminal pressures may contribute to ischemia and pneumatosis, a process that may also play a role in previously normal infants who develop NEC after protracted periods of diarrhea. Some investigators have suggested a localized Shwartzman reaction to endotoxemia or gram-negative bacteria.[153] The absence of lysozyme (normally present in human breast milk) may allow overgrowth of gram-negative bacilli. EPEC serotype O111:B4 has also been associated with NEC.[154] Because of the association with the use of umbilical vein polyvinylchloride catheters and feeding tubes, the toxic effect of plasticizers leached from the polyvinylchloride materials has also been suggested.[155] Reports of outbreaks of NEC in newborn intensive care units (ICUs)[156,157] have led to a careful search for infectious agents, including viral, fungal, and bacterial pathogens.[158] Among bacteria, *Pseudomonas, Klebsiella*,[159] certain *E. coli* strains,[154,160] *Salmonella*,[161] and *Clostridium butyricum*[157] have been implicated. The roles of ischemia and bacteria have been suggested by Barlow and colleagues[162] with studies in an experimental rat model of NEC, in which breast milk was shown to be protective. On the basis of an acidic intraluminal pH (<5.0) and organic acids in human neonates with NEC,[163] increased numbers of lactose-fermenting *Klebsiella* organisms have been postulated to play a role in the pathogenesis.[164] Other investigators have suggested a role for platelet-activating factor and protection by superoxide dismutase or endogenous nitric oxide.[165,166] The role of the intestinal microbiota in the pathogenesis of NEC is being actively investigated.

Clinical features of this serious condition in newborn infants include apneic spells, vomiting, abdominal distention, and occasionally bloody diarrhea. Most infants are younger than 1 week, and there is an association with prematurity, maternal infections during delivery (e.g., amnionitis with prolonged postruptured membranes status), and exchange transfusion via the umbilical vein. There is no gender or seasonal predilection. The

disease often progresses rapidly to intestinal perforation, shock, septicemia, and pneumatosis intestinalis. Air may also be evident in the portal venous system or biliary tract on plain radiographs. This syndrome is associated with a mortality rate that is often in excess of 70%.

The diagnosis of NEC should be considered in any premature infant with altered GI function, abdominal distention, or apneic spells. Further investigation should include examination of the stool for occult blood and for the presence of reducing substances. Plain abdominal radiographs may reveal air in the bowel wall, peritoneal cavity, or portal venous system, and there may be bloody diarrhea late in the course of the disease. Management must be initiated early and aggressively for any infant suspected of having NEC. Umbilical catheters should be removed, oral feeding should be stopped, and nasogastric aspiration should be initiated. Intravenous fluid therapy is of paramount importance. Laparotomy and excision of the necrotic bowel are often necessary and should be done aggressively if there is any evidence of peritonitis or obstruction.[167]

Prevention of NEC includes avoidance of risk factors and careful infection control measures in newborn ICUs. Hypertonic elemental formulas have been implicated and should be avoided in high-risk patients. NEC rarely occurs in breastfed infants. Explanations for the advantage of human breast milk include the presence of lysozyme, antibodies, and cellular elements that may play a protective role against potential infectious agents. Although oral prophylactic nonabsorbable antibiotics have been suggested, serious questions remain about the use of prophylactic antibiotics, even in high-risk newborn infants weighing less than 1500 g. A few reports have shown that epidermal growth factor, which is found in high concentrations in breast milk, may have a cytoprotective effect, and probiotics may decrease or prevent neonatal necrotizing enterocolitis.[166,168]

Darmbrand, Pig-Bel, Necrotizing Enteritis in Adults (Enteritis Necroticans)

First described as *Darmbrand* (meaning fire bowels) in epidemics of enteritis necroticans in northern Germany in the immediate postwar period in the mid-1940s, a severe necrotizing jejunitis has also been recognized in epidemic and sporadic forms after pork feasting in the highlands of Papua New Guinea.[169] Pig-bel was the name given to the syndrome of abdominal discomfort that followed a large pork meal, commonly eaten after a large pig kill, which takes place every 3 to 10 years among the highland Melanesians of Papua New Guinea. Sporadic cases have been reported from other parts of the world, including the United States.[170]

The pathologic findings are those of acute, patchy, necrotizing disease of the small bowel in previously healthy people, which may proceed rapidly to segmental gangrene, with small amounts of gas in the mucosa, mesentery, or nodes.

Several theories of pathogenesis have been suggested, most of which involve the toxic products of *Clostridium perfringens* type C, including α- and β-toxins. Sporadic cases of NE have been noted in association with nutritional disorders, alcoholism, and malabsorption, and after pancreatic or gastric resection.[171] After gastric surgery, increased numbers of *C. perfringens* organisms and increased levels of α-toxin have been noted in the upper small bowel and stomach. Whether α- or β-toxins are capable of causing NE alone, or whether they initiate the invasion of the mucosa by other organisms, such as gram-negative rods, is currently unclear. An attractive hypothesis was suggested by Lawrence and Walker,[171] which could explain the association of NE with poor nutrition and episodic dietetic overindulgence. The low-protein diet of Papua New Guinea highlanders is associated with low levels of digestive proteases in the intestinal lumen, which can be shown to inactivate the β-toxin. The proteases can be further blocked by the oral intake of trypsin inhibitors, which are found in this population in such dietary staples as sweet potatoes. Proteases return with improved diet, as occurred in postwar Germany. This hypothesis has been confirmed in an animal model that required protease inhibitors for symptomatic infection.[172]

The clinical syndromes of NE range from anorexia, vomiting, severe abdominal pain, and bloody diarrhea to fulminant toxemia and shock. Acute complications that necessitate emergency surgery include paralytic ileus, bowel strangulation, and bowel perforation with peritonitis. These complications are common in the first 2 weeks of illness. Later complications that may also necessitate surgery include scarring, leading to stenosis; obstruction; malabsorption; and fistulas. NE occurs with greater frequency and greater severity in children younger than 10 years. In contrast to European control subjects who rarely have antibodies, 70% of the healthy adults in Papua New Guinea have demonstrable antibody to clostridial β-toxin.[169,171]

The syndrome is defined by the pathologic findings but should be suspected in patients who develop severe abdominal pain, bloody diarrhea, ileus, and toxemia. The course is often too fulminant for radiographic detection of air in the bowel wall to be of any diagnostic value.

Agents held responsible for causing NE include *C. perfringens* type C, once designated as type F in the older classification of *Clostridium welchii.* Most surgically resected bowel specimens from patients with NE contain *C. perfringens*, more than half of which are type C. Furthermore, 12 of 21 cases described had a significant change in serum β-antitoxin titer after illness with pig-bel in Papua New Guinea.[169] Although polyvalent gas gangrene antiserum was ineffective, administration of type C antiserum resulted in a 30% decrease in the need for surgery, and mortality was reduced from 43% to 19%.[169] Furthermore, active immunization against the β-toxin has also proved effective in preventing pig-bel.[173]

Some have suggested that type A *C. perfringens*, staphylococci, or even hepatitis virus may be responsible for NE. The syndrome of enteritis gravis has been described in association with infectious hepatitis, although no viral cause has been documented.

Considerations in the differential diagnosis of NE include acute shigellosis, acute food poisoning syndromes, antibiotic-associated pseudomembranous colitis, and acute ulcerative colitis. The absence of colonic involvement; the epidemiologic setting, especially in poorly nourished patients; and the rapid progression to toxemia and shock are strongly suggestive of NE.

Therapy for NE includes careful supportive care and bowel decompression. Fluid requirements may be substantially greater than what is indicated by fecal output. Resection of the involved bowel must be considered if there is a persistence of paralytic ileus, a rapid increase in signs of toxemia, localized or diffuse signs of peritonitis, persistent pain, or a palpable mass lesion. If subacute obstruction or malabsorption is suspected on the basis of weight loss, elective surgery may be required up to 6 months after the acute illness. Raw peanut or soybean diets should be avoided because they contain trypsin inhibitors. *C. perfringens* type C antiserum containing β-antitoxin or the active β-toxin vaccine should be available for use in areas where NE can be expected to occur.

CHRONIC INFECTIOUS/ INFLAMMATORY PROCESSES INVOLVING THE INTESTINAL TRACT

Chronic inflammatory enteritides are often indolent, slowly progressive infections. Often, there is a history of weeks or months of fever, abdominal pain, weight loss, or other systemic manifestations. Recurring or relapsing symptoms may be seen with *C. jejuni* or *Salmonella* gastroenteritis. In addition, 16% of cases of shigellosis may become prolonged, lasting for 3 weeks or longer.[174] Any diarrheal illness that extends beyond 2 weeks is considered severe and is associated with a high risk of nutritional morbidity in children who live in tropical developing areas.[175–177]

Syphilis

Syphilis (see Chapter 237) can also involve the GI tract, usually in the upper part of the small bowel or stomach. An acute erosive and infiltrative gastritis with motile spirochetes and a positive specific response on treponemal immunofluorescence testing has been reported in late secondary syphilis.[178] The initial complaints are upper abdominal pain, vomiting, and weight loss. More classic are the late GI manifestations of lues: pyloric obstruction, hourglass constriction, and linitis plastica of the stomach. Less commonly, gumma may be seen in the small bowel or colon.

Gastrointestinal Tuberculosis

Intestinal tuberculosis (TB), once considered common, had become a relatively rare disease but is now reemerging in association with

acquired immunodeficiency syndrome and with multidrug-resistant *Mycobacterium tuberculosis* (see Chapter 249).[179] Intestinal involvement with TB may be either primary, from ingestion of the organisms, or secondary, usually from a pulmonary source.

Primary intestinal TB without pulmonary disease often results in hypertrophic mucosal changes. Patients with acute miliary TB may also have GI involvement.[180] Patients with primary intestinal TB may present with abdominal pain, fever, and a tender, fixed, palpable mass in the ileocecal area. Primary hypertrophic intestinal TB continues to occur in the Middle East[181] and in India.[182] Intestinal involvement secondary to pulmonary TB may result from swallowing infected sputum or from biliary excretion of the organism from an infected liver. The frequency of secondary intestinal TB increases with far-advanced pulmonary disease. Hippocrates stated that "diarrhea attacking a person with phthisis is a mortal symptom."

TB may involve any part of the GI tract, but most ulcerative and hypertrophic types occur in the ileocecal region, where there is a predominance of submucosal lymphatic tissue. The most common features are fever and abdominal pain that is often relieved by defecation or vomiting. Weight loss is more common in secondary intestinal TB. Only one-third of the patients with GI TB have diarrhea. Diarrhea may be related to exacerbations of abdominal pain and occasionally occurs with extensive involvement of the small intestine, which may cause steatorrhea and a malabsorption syndrome. Although ulceration and mucous diarrhea are relatively common with secondary intestinal TB, hemorrhage and the presence of gross blood in the stool are distinctly uncommon, perhaps because of the associated obliterative endarteritis.

The diagnosis of GI TB may be very difficult radiologically and even histologically. It must be distinguished from regional enteritis, sarcoidosis, actinomycosis, ameboma, carcinoma, and periappendiceal abscess. In contrast to Crohn disease, GI TB rarely causes anal lesions, fistulas, or perforation. It is often associated with miliary nodules on the serosa, it rarely causes strictures longer than 3 cm, and it may cause circumferential transverse ulcers. TB may also cause fibrosis of the muscularis mucosa, pyloric metaplasia, and epithelial regeneration.[183] There may be minimal or no radiologic changes in the bowel mucosa. Small mucosal ulcerations may result in tiny calcified nodules in the mucosa in association with calcified mesenteric lymph nodes analogous to those seen in the pulmonary Ghon complex. The ileocecal region often reveals radiologic evidence of irritability and hypermotility, with hypersegmentation of the mucosal folds or poor filling of the ileocecal region detected by barium enema. On occasion, frank ulcerations can be noted on contrast studies, and late in the course there is scarring. The diagnosis requires a careful examination of involved tissue for acid-fast bacilli by using special stain and culture. Caseous necrosis is more frequently found in the mesenteric nodes than in intestinal tissue itself. Complications of intestinal TB include perforation, peritonitis, and obstruction from hypertrophy, scarring, or tuberculoma.

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The complete reference list is available online at Expert Consult.

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100 Typhoid Fever, Paratyphoid Fever, and Typhoidal Fevers

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SHORT VIEW SUMMARY

Definition

- Enteric fever, or "typhoid fever," is a nonspecific febrile illness caused by typhoidal *Salmonella* (*Salmonella enterica* serotypes Typhi and Paratyphi); the diagnosis should be considered in any patient with otherwise unexplained prolonged fever who has resided in or recently traveled in a typhoid-endemic setting.
- The term *typhoidal fever* is sometimes used more broadly to refer to a syndrome of persistent high-grade fevers, often with no localizing features. This chapter also covers the broader differential diagnosis and approach to patients with typhoidal fever, relapsing or prolonged fever, and fever accompanied by abdominal pain.

Epidemiology

- An estimated 12 to 24 million cases of enteric fever occur each year, largely in impoverished areas of Asia and Africa.
- Enteric fever is transmitted via the fecal-oral route, with contaminated municipal water supplies being commonly involved in transmission.
- Multidrug-resistant strains of the major causative agents of enteric fever (*S. enterica* serotypes Typhi and Paratyphi A) are now common worldwide.

Clinical Manifestations

- Common life-threatening complications of enteric fever include intestinal hemorrhage, perforation, encephalopathy, and shock.
- Untreated, patients with enteric fever may be febrile for 3 to 4 weeks or longer, with mortality rates exceeding 10%, and prolonged asthenia and fatigue are common among survivors.
- Chronic biliary carriage of typhoidal *Salmonella* may occur after resolution of the acute illness.

Diagnosis

- Current diagnostic tests for enteric fever are imperfect. Blood cultures are 30% to 70% sensitive; bone marrow cultures are more sensitive but are impractical; serologic assays lack both sensitivity and specificity, especially in enteric fever endemic areas; and nucleic acid amplification assays with sufficient sensitivity are not available.

Therapy

- Given the morbidity of typhoid fever, the risk of complications, and the lack of optimal diagnostic tests, the initiation of antibiotics for treating individuals with suspected enteric fever may be based on a presumptive diagnosis, particularly in resource-limited settings.
- The most commonly used agents for treating individuals with enteric fever are fluoroquinolones, azithromycin, and cefixime or ceftriaxone. Chloramphenicol, trimethoprim-sulfamethoxazole, and amoxicillin may be used to treat patients with susceptible strains.

Prevention

- An oral-attenuated typhoid vaccine and injectable polysaccharide vaccine are internationally commercially available and provide 50% to 75% protection for 5 and 2 years, respectively. A Vi-tetanus toxoid conjugate vaccine is now prequalified and recommended by the World Health Organization. No vaccine effective against paratyphoid A is currently commercially available.

ENTERIC FEVER (TYPHOID AND PARATYPHOID FEVER)

History

Historically termed *putrid fever* or *dothienteritis,* the name *typhoid* was coined in 1829 by Pierre Charles Alexander Louis. The name *typhoid* means "typhus-like" and reflects the difficulty in differentiating the illness from epidemic typhus, another common cause of prolonged fever in Europe during the 19th century. Louis used the term *typhoid* in a landmark report comparing the intestinal pathology in 50 patients who died of typhoid fever with 83 patients who died of noninfectious causes, and he described the characteristic inflammation of Peyer patches, intestinal ulceration, and mesenteric adenitis associated with typhoid fever.[1]

William Budd is credited with the recognition of the fecal-oral transmission of typhoid fever in 1839, based on his meticulous observations during a large epidemic in the Taw Valley of England, although these findings were not widely recognized until many years later.[2]

The etiologic agent of typhoid fever was identified in pathologic specimens by Karl Eberth, who referred to it as *Bacillus typhosus*; the organism was subsequently first cultured in 1884 by Georg Gaffky at the Berlin Institute for Infectious Diseases. The term *paratyphoid fever* was first used in 1896 by Raoul Bensaude and Emile Achard, who isolated what would subsequently be recognized as *Salmonella* Paratyphi B. The role of asymptomatic carriers in the transmission of infectious disease was first recognized by Robert Koch, a theory that he derived from his longitudinal observations of patients recovered from typhoid but with continued shedding of *B. typhosus*.[3] An understanding of the role of asymptomatic carriers in disease transmission was soon extended to other organisms and was an established mode of disease transmission at the time of George Soper's association of Mary Mallon (also known as Typhoid Mary) with repeated outbreaks of typhoid fever in households in New York, ultimately leading to her lifelong quarantine on North Brother Island.[4]

Widal developed the first serologic test for typhoid fever in 1896, an agglutination assay that detects the presence of antibodies against the O and H antigens of *Salmonella* Typhi.[5] Despite inherent and significant limitations (see "Diagnosis"), the Widal test remains widely used in many resource-limited settings. The first vaccines for typhoid fever were killed whole-cell vaccines developed in 1896, credit for which is shared by Almroth Wright and Richard Pfeiffer.[6–9] Despite advances in the development of a vaccine, typhoid fever remained a leading cause of morbidity and mortality in the early 19th century. A prominent example was a typhoid fever epidemic in the Spanish-American War, in which 20,000 American Army recruits contracted the disease and 1600 died. This defining event was linked to the first compulsory US military–wide vaccination program, in which a killed whole-cell, injectable typhoid vaccine developed by Frederick Russell was used.[10]

In the early 20th century, "typhomalaria" or "typhomalarial fever" remained an extremely common diagnosis, indicating that differentiating typhoid from malaria (and other causes of persistent fever) on clinical grounds was difficult. The difficulty distinguishing typhoid fever from typhus and other causes of fever proved clinically fortuitous. In 1948, Theodore Woodward and coworkers[11,12] reported the effect of chloramphenicol in two patients who were referred for a study of the efficacy of the drug in scrub typhus. Both were subsequently found to have *Salmonella* Typhi bacteremia, and both patients improved rapidly after antibiotic therapy.[11] Typhoid fever mortality has been reduced from 10% to 1% or lower with the use of antibiotics. However, successive pandemics of antibiotic-resistant organisms have occurred, including, most recently, the emergence of fluoroquinolone- and ceftriaxone-resistant strains of *Salmonella* Typhi. In 2001, the complete sequence of a *Salmonella* Typhi strain (CT18, isolated from a patient in Vietnam in 1993) was published by Parkhill and coworkers[13] at the Wellcome Trust Sanger Institute, ushering in a genomic era in our understanding of typhoid fever. Genomic analysis has opened up new insights into the history and epidemiology of typhoidal *Salmonella,* from zoonotic spillover[1] to previously unrecognized historical outbreaks[2] and recent global dissemination.[3]

Etiologic Agents of Enteric Fever

Nomenclature and Classification of Typhoidal *Salmonella enterica*

Salmonella Typhi and *Salmonella* Paratyphi A, B, and C are gram-negative bacilli that belong to the species *S. enterica* subspecies *enterica.* All *S. enterica* are categorized serologically by the Centers for Disease Control and Prevention (CDC) according to a modified Kauffman and White classification scheme, assigned based both on the O (the O polysaccharide) and H (flagellar) antigens.[14,15] Although assigning a serogroup based on O antigen agglutination tests is a common procedure in many clinical microbiology laboratories, the approach has limited clinical utility. Complete serotyping based on both the O and H antigen is most commonly performed in reference laboratories. In addition to serogrouping and serotyping, standard microbiologic growth and biochemical parameters are also routinely used in the clinical laboratory for the presumptive identification of *S. enterica.* Serologic and selected biochemical characteristics that are used in the identification of *Salmonella* Typhi and *Salmonella* Paratyphi A, B, and C in microbiology laboratories are summarized in Table 100.1.

Clinical Distinction Between Typhoidal and Nontyphoidal *Salmonella enterica*

Salmonella Typhi and *Salmonella* Paratyphi A and B are human-restricted pathogens. *Salmonella* Paratyphi C is pathogenic for animals and humans, and *Salmonella* Typhi and *Salmonella* Paratyphi are classified clinically as typhoidal *Salmonella* strains. This distinction separates these strains from all other pathogenic *S. enterica* serotypes, which are referred to collectively as nontyphoidal *Salmonella* (often abbreviated as NTS; see Chapter 223). Typhoidal strains cause enteric fever in all human hosts, whereas NTS strains are classically associated with inflammatory diarrhea in human hosts or preferentially cause invasive disease in young children and immunocompromised individuals, with particular associations with malnutrition, HIV, and malaria. However, the clinical distinction between typhoidal and NTS is not absolute. NTS may cause invasive infection that includes prolonged bacteremia (with or without pyogenic foci) that may mimic the systemic illness caused by typhoidal strains.[16] Although host factors influence susceptibility to invasive NTS infection, the likelihood of invasive infection is also dependent on characteristics of the bacterial strain. For example, the emergence of a dominant genotype associated with invasive NTS, *Salmonella* Typhimurium ST313, in sub-Saharan Africa, illustrates the clinical overlap between typhoidal and nontyphoidal *S. enterica.*[17]

Genomic Features

Escherichia coli and *S. enterica* diverged over 100 million years ago, and *S. enterica* is now a genetically heterogeneous species.[18] *Salmonella* Typhi is genetically homogeneous, meaning there is very limited genetic diversity across *Salmonella* Typhi isolates throughout the world. Based on standard rates of genetic drift, it is estimated that *Salmonella* Typhi emerged from a single-point origin within the last 50,000 years, coinciding with the time of human migrations out of Africa and into Asia.[19,20] The genetic material of *Salmonella* Typhi consists of a single chromosome that contains approximately 5×10^6 base pairs encoding approximately 4000 genes. *Salmonella* Typhi often harbors additional plasmids that may be cryptic (confer an unknown function) or involved in pathogenesis. The latter include IncHI1 plasmids that comprise the majority of resistance plasmids found in *Salmonella* Typhi and that remain stable in the bacteria without ongoing pressure from antibiotic selection.[21,22]

The genetic core of *S. enterica* consists of genes that are conserved across Enterobacteriaceae and is approximately 90% similar to *E. coli*. In contrast, the genetic core varies approximately 1% between *S. enterica*

TABLE 100.1 Classification and Selected Microbiologic Characteristics of Typhoidal *Salmonella*

SEROTYPE NAME		*SALMONELLA* TYPHI	*SALMONELLA* PARATYPHI A	*SALMONELLA* PARATYPHI B (SCHOTTMUELLERI)	*SALMONELLA* PARATYPHI C (HIRSCHFELDII)	COMMENTS
Serologic classification[a]	Serogroup	D	A	B	C	
	O antigen	**9**, 12	1, **2**, 12	1, **4**, (5), 12	6, 7	
	H antigen Phase 1 : 2	d: –	a: (1, 5)	b: (1, 2)	c: (1, 5)	Uncommon *Salmonella* Typhi H antigen variants include Hj:z66 found in Indonesia
	K antigen	Vi	–	–	Vi	
Selected biochemical characteristics[b]	Lactose fermentation	–	–	–	+	The majority of *Salmonella* Paratyphi C ferment lactose
	Sulfide (H_2S) production	+ (weak)	–	+	+	3% of *Salmonella* Typhi do not produce hydrogen sulfide
	Gas produced during glucose fermentation	–	+	+	+	
	Lysine decarboxylase	+	–	+	+	
	Ornithine decarboxylase	–	+	+	+	

[a]Strong antigenic determinants are listed in bold; weaker or sometimes absent ones are in parentheses.
[b]Isolates can be identified as *Salmonella* using traditional methods. A presumptive diagnosis of *Salmonella* Typhi can often be made for *Salmonella* isolates based on selected biochemical characteristics, in addition to agglutination with D and Vi antisera.
From World Health Organization (WHO), Department of Vaccines and Biologicals. Background Document: The Diagnosis, Treatment and Prevention of Typhoid Fever. *Geneva: WHO; 2003; and WHO, Department of Communicable Disease Surveillance and Response.* Salmonella *serotype Typhi. In:* WHO Manual for the Laboratory Identification and Antimicrobial Susceptibility Testing of Bacterial Pathogens of Public Health Importance in the Developing World. *Geneva: WHO; 2003:103–118.*

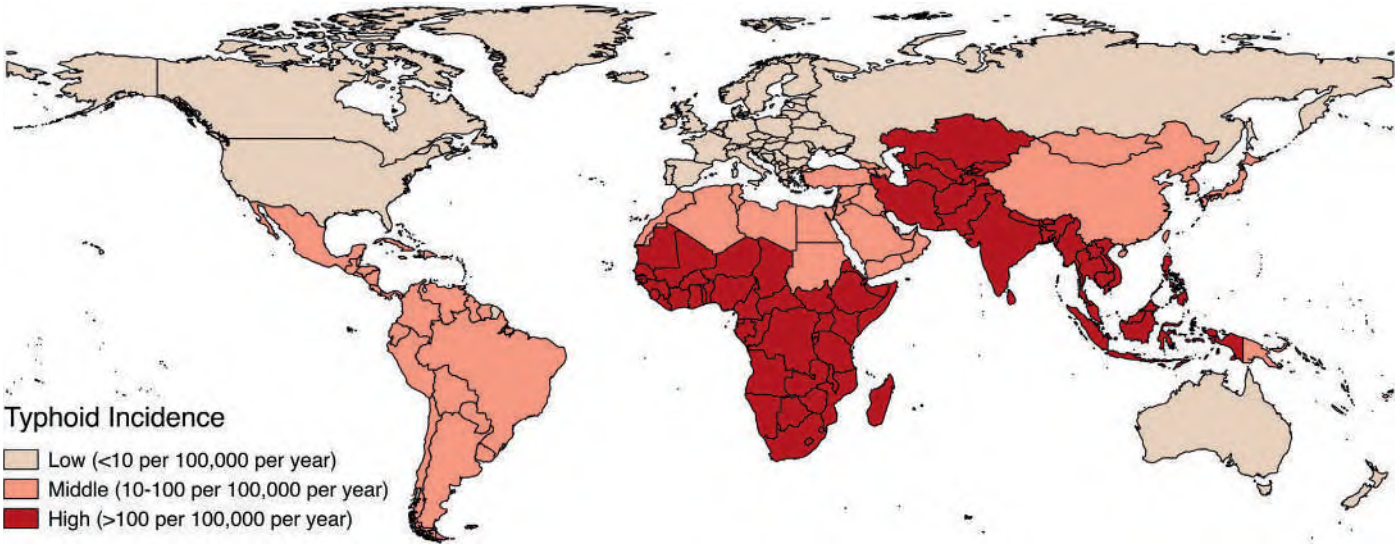

FIG. 100.1 Global distribution of typhoid fever. *(Modified from Mogasale V, Maskery B, Ochiai RL, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment.* Lancet Glob Health. *2014;2:e570–e580; and Kim JH, Mogasale V, Im J, Ramani E, Marks F. Updated estimates of typhoid fever burden in sub-Saharan Africa.* Lancet Glob Health. *2017;5:e969.)*

serovars. In addition to the genetic core, *Salmonella* Typhi contains pathogenicity islands—horizontally acquired genetic elements that are often associated with unique properties of each strain and are essential for specific phenotypes associated with pathogenesis of each serotype.[18] In *S. enterica,* these are specifically identified as *Salmonella* pathogenicity islands, or SPIs, and are designated with a number. *Salmonella* Typhi possesses more than 20 SPIs, many of which are found in other *S. enterica* serotypes. For example, SPI-7 is a 134-kb genetic island that possesses elements encoding the viaB locus, which is involved in production of the Vi capsule and evasion of the host immune response.[23] SPI-7 is widely conserved across *Salmonella* Typhi and is also found in *Salmonella* Paratyphi C.

One of the most remarkable genetic features of *Salmonella* Typhi is the accumulation of more than 200 (apparently) functionally inactive genes known as pseudogenes.[13] This adaptation may play a major role in the host restriction of *Salmonella* Typhi. The accumulation of a large number of pseudogenes is a common feature shared with *Salmonella* Paratyphi A, B, and C, which emerged independently of *Salmonella* Typhi (although subsequent recombination events between *Salmonella* Typhi and *Salmonella* Paratyphi A appear to have occurred),[24] yet are also adapted specifically to cause disseminated infection in humans. The same phenomenon has been observed in *Salmonella* Typhimurium ST313 in sub-Saharan Africa; ST313 has accumulated extensive gene deletions and (apparent) pseudogene formation (more than half of which are common to *Salmonella* Typhi and *Salmonella* Paratyphi A) compared with less invasive *Salmonella* Typhimurium strains.[25]

Epidemiology

Burden and Distribution

Measures of the burden of enteric fever are limited by the absence of surveillance in many regions and also by the limited sensitivity of current diagnostic tests. Recognizing these limitations, estimates of the number of cases of typhoid fever range from 12 to 27 million annually.[4] The incidence of typhoid fever and the mortality of the disease vary dramatically by region (Fig. 100.1). In South Asia and parts of sub-Saharan Africa, the incidence approaches 1000 cases per 100,000 person-years.[5,26] In parts of northern Africa, South America, and Southeast Asia, the incidence is much lower and ranges between 10 and 100 cases per 100,000 person-years. Disease is highly heterogeneous even within endemic countries, and the incidence tends to be considerably higher in urban than in rural areas. In the United States and many other high-resource settings, the disease occurs sporadically, with less than 1 case per 100,000 person-years, and occurs most often in travelers returning from endemic zones (see "Acquisition of Disease in Areas Where Enteric Fever Occurs Sporadically").

Salmonella Paratyphi A is by far the most common cause of paratyphoid fever and is responsible for an estimated 5 million cases of enteric fever annually.[6,27] The proportional burden of enteric fever caused by *Salmonella* Paratyphi A has increased substantially over the past 2 decades, and in some areas of South Asia, *Salmonella* Paratyphi A is responsible for more than 20% to 50% of cases of enteric fever.[6,28] In contrast, *Salmonella* Paratyphi B and C remain less common causes of enteric fever globally, with the proportional incidence of infections caused by these pathogens varying by location.

Severity

In the preantibiotic era, 10% to 15% of clinically recognized cases of typhoid fever were fatal, whereas other cases resolved over a 3- to 4-week course of an often severe and debilitating illness.[7] Prospective surveillance in the postantibiotic era has revealed that the majority of cases of enteric fever are uncomplicated and do not warrant hospitalization. Although the current mortality of typhoid fever is estimated at 0.5% to 1%, this estimate is based on few data.[8] Reported mortality rates in hospitalized patients with enteric fever in resource-limited settings vary widely by location, ranging from 0% to 15%, with a median of 2%.[29] In the United States, the fatality rate of reported cases is 0.2%.[30] In addition to fatal cases, in sub-Saharan Africa and other regions where enteric fever is highly endemic, intestinal perforation caused by enteric fever is a leading cause of peritonitis and acute abdominal conditions requiring surgery in children.[31]

Source of Infection

Salmonella Typhi and *Salmonella* Paratyphi A and B are human restricted. There are no known animal reservoirs of these pathogens that cause enteric fever, and the source of infection is organisms shed in the stool of infected humans. *Salmonella* Paratyphi C can be shed by humans and animals. In the preantibiotic era, patients recovering from enteric fever shed organisms in the stool during acute illness and typically for weeks during convalescence. In addition, a small portion of individuals convalescing from typhoid fever develop chronic asymptomatic carriage (defined as shedding of the bacteria in stool or urine for more than a year), which may persist for life.[32] In the preantibiotic era, up to 5% of typhoid fever survivors developed chronic asymptomatic bacterial shedding in the stool,[33,34] with gallbladder disease being the major risk factor for carriage.[35,36] Risk of carriage appears to be far greater in adults (3%–10%) than in young children (<1%).[9] Studies from Nepal, where

enteric fever is highly endemic, found that 3.5% of individuals undergoing elective cholecystectomy grew *Salmonella* Typhi or *Salmonella* Paratyphi A from biliary cultures.[37] Even higher rates were observed in Santiago, Chile in the early 1980s.[10] Urinary carriage may also occur, frequently in conjunction with urinary schistosomiasis.[38] Although chronic carriers are a source of transmission where enteric fever occurs sporadically,[30,39] their importance in the transmission of enteric fever in highly endemic areas is uncertain.[11]

Mode of Transmission

Infections with typhoidal *S. enterica* are most often acquired via ingestion of fecally contaminated water or food. *Salmonella* Typhi may persist for weeks after passage in water and may persist in a variety of contaminated food items—for example, dehydrated formula and iced beverages.[39–41] Volunteer studies may not optimally mimic natural exposure; however, the inoculum required to produce disease in 50% of adult volunteers (ID_{50}) is $10^{5\text{-}7}$ organisms, although fewer than 10^3 organisms may produce disease.[42,43]

Molecular epidemiologic studies based on high-resolution genotyping implicate waterborne transmission as the most likely route of transmission in the majority of cases of enteric fever.[44] A study in the Kathmandu valley of Nepal revealed that >80% of water collected from public taps contained typhoidal *Salmonella* DNA.[12] Both waterborne and foodborne transmission may contribute to large epidemics, and in some cases, massive epidemics have been associated with water contamination from a single source.[13,45] In contrast, direct person-to-person transmission of the etiologic agents of enteric fever appears less common, and more than 80% of cases of enteric fever occur in individuals with no known contact with an individual with symptomatic infection.[46] Even more remarkably, in households where multiple cases of enteric fever occur, only 20% of those infections shared a common bacterial genotype, suggesting that multiple infections within a household occur through a community-based exposure to multiple circulating genotypes, rather than through direct person-to-person transmission.[44] In highly endemic areas, consistent personal risk factors for infection with typhoidal *S. enterica* include drinking nonboiled water and eating food prepared outside the home, including street-vended foods and beverages.[14,47,48] In South Asia, peak transmission occurs during and immediately after the monsoon season (peaks in June through October),[15] although disease is present year-round.[49]

Acquisition of Disease in Areas Where Enteric Fever Occurs Sporadically

In areas where enteric fever occurs sporadically, most cases are imported through travel. In the United States, >85% of cases occur in travelers to endemic areas.[16,30,50] The rate of typhoid fever is estimated at 10 per 1 million travelers arriving from Asia but increases to 89 per 1 million travelers arriving from India. More than 80% of all travel-associated cases in the United States relate to travel to South Asia.[16] The risk of travel-related enteric fever is higher among travelers visiting friends and relatives.[51] Many of the remaining non–travel-associated cases in the United States are traceable to small, local foodborne outbreaks and/or a chronic carrier.[30] From approximately 1991 to 2010, more than half of foodborne outbreaks in the United States were linked to an asymptomatic carrier.[50,52] In 2010, an outbreak of *Salmonella* Typhi occurred that involved at least 12 cases across three western US states and was attributed to imported fruit pulp from Guatemala.[53] Also, in areas where enteric fever occurs sporadically, small clusters of cases of sexual transmission of *Salmonella* Typhi have been documented in men who have sex with men.[54] Infections and clinical cases have occurred among microbiology laboratory staff, and in at least once instance, secondary cases occurred among family members of laboratory personnel.[17]

Antibiotic Resistance and Emergence of Pandemic *Salmonella* Typhi

Chloramphenicol-resistant *Salmonella* Typhi was first reported in 1950, 2 years after the antibiotic was first used to treat patients with typhoid fever.[55] However, widespread dissemination of antibiotic-resistant strains did not occur until the 1970s. Multidrug-resistant (MDR) *Salmonella* Typhi carrying IncHI1 plasmid-mediated resistance to chloramphenicol, ampicillin, trimethoprim, and sulfonamides became common in the 1980s. Nalidixic acid–resistant strains of *Salmonella* Typhi and *Salmonella* Paratyphi A, with decreased susceptibility to fluoroquinolone antibiotics, emerged in the 1990s,[56] and now the vast majority of typhoidal *Salmonella* isolates from South Asia have reduced susceptibility or high-level resistance to fluoroquinolones.[18,19] At present, reduced susceptibility to ciprofloxacin is less common and more sporadic in sub-Saharan Africa.[20]

Although the lack of genetic diversity of *Salmonella* Typhi previously hindered efforts to characterize the global epidemiology of disease, the increasing use of high-density genotyping methods, including whole-genome sequencing, has circumvented these challenges and resulted in a better understanding of the forces driving the evolution and transmission of *Salmonella* Typhi. Although a general lack of diversity among *Salmonella* Typhi suggests a lack of strong selection pressure over millennia, the recent expansion of a single fluoroquinolone-resistant haplotype known as H58 into a pandemic strain found throughout Asia and Africa, and the emergence of several other lineages with diverse *gyrA* mutations, suggest that fluoroquinolones may be exerting a uniquely strong selection pressure that is shaping the global evolution of *Salmonella* Typhi.[20,57] More recently, *Salmonella* strains with resistance to third-generation cephalosporins (e.g., ceftriaxone) have been reported.[21–24]

Host Factors and Susceptibility to Infection

Historically, enteric fever was considered a disease that predominantly affected school-aged children and young adults. However, prospective community-based surveys in highly endemic areas have demonstrated that the incidence of *Salmonella* Typhi bacteremia is often highest in young children (<5 years old) and that this organism may be responsible for more than 75% of cases of occult bacteremia in these settings.[58] The higher incidence of enteric fever in older children among inpatients may reflect a predisposition to more severe disease in this older age group. In highly endemic areas, *Salmonella* Typhi bactericidal antibodies and anticapsular (Vi) antibodies increase significantly over the first decade of life.[59] In less endemic areas, the median age of patients with typhoid fever increases, suggesting that the age distribution of patients may be influenced by acquired immunity. However, protection from a single episode of infection is limited, as demonstrated by frequent relapse and recurrent infections among patients who have recovered from typhoid fever.[60]

Although invasive NTS infections classically occur in persons who are compromised by extremes of age, malnutrition, immunodeficiency, or genetic risk factors, there is not an overt association between host risk factors and susceptibility to enteric fever. Various candidate gene analyses have drawn associations between single-nucleotide variations in Toll-like receptor 4 (TLR4), cystic fibrosis transmembrane conductance regulator (CFTR), and specific human leukocyte antigen (HLA) types with susceptibility to typhoid fever in Vietnam[61,62]; however, no detailed genome-wide study of typhoid fever associations has yet been reported.

Pathogenesis

Typhoidal *Salmonella* infection is acquired through ingestion of bacilli, typically in contaminated water, drinks, or food. The ID_{50} is often cited to be $10^{5\text{-}7}$ organisms, but low inocula ($<10^3$ organisms) may also produce infections.[25] After passing through the intestinal epithelium, typhoidal *Salmonella* are phagocytosed by macrophages and proliferate in the submucosa before dissemination via the lymphatic system and bloodstream. This period coincides with the onset of systemic symptoms and, in some cases, end organ manifestations. It is during this phase that bacilli enter the hepatobiliary system and may establish carriage in the gallbladder. Disseminated infection is terminated by immune clearance or administration of antibiotics, but bacterial persistence in the bone marrow is often longer.

It is important to note that enteric fever and NTS infections differ in fundamental aspects. With NTS, infections are typically self-limited in immunocompetent hosts and manifest largely as an inflammatory gastroenteritis. In comparison, typhoidal serotypes are able to evade the normal host inflammatory response and cause prolonged bacteremia even in immunocompetent individuals, typically without overwhelming sepsis or pyogenic foci of infection. Specific bacterial adaptations used

by *Salmonella* Typhi to produce persistent bacteremia in the absence of an immediately overwhelming inflammatory response include strategies to breach the intestinal epithelium in the absence of inflammatory diarrhea, to evade detection by host pattern-recognition receptors,[63] to produce an AB5 bacterial toxin that acts through cell-to-cell paracrine signaling pathways,[64] and to persist and disseminate throughout the human host within phagocytic cells.[65] Much of our understanding of host-pathogen interactions in enteric fever is extrapolated from mouse models of enteric fever, which use Nramp1-deficient mice that develop disseminated infection from *Salmonella* Typhimurium. Additional models are under development.

Invasion

In contrast to NTS and other enteroinvasive pathogens, it is thought that soon after ingestion, typhoidal *Salmonella* pass though the intestinal epithelium through specialized microfold cells (M cells) that transport the bacteria across the basolateral membrane, where they are then phagocytosed by macrophages in the intestinal lymphoid tissue.[66] Such a stealth entry mechanism may explain why the invasion phase of *Salmonella* Typhi infection is usually asymptomatic and is accompanied by transient or mild diarrhea in only 10% to 20% of patients.

Latency and Dissemination

Typhoidal *Salmonella* deploy an array of virulence factors that enable them to persist and replicate in an intracellular compartment.[67,68] Important cloaking mechanisms of *Salmonella* Typhi include suppression of flagellar protein synthesis, thus masking a potent inducer of TLR5 responses,[69] and synthesis of the Vi capsule that presumably masks the detection of lipopolysaccharide (LPS) and other outer membrane components.[70] The genes that repress flagellin biosynthesis and are responsible for Vi biosynthesis are encoded on the viaB locus located on SPI7, which is absent in most NTS strains.[23] Induction of other bacterial defenses that are required for survival in the intracellular compartment are regulated by a two-component bacterial sensory-regulatory system, PhoP/PhoQ.[71,72] The sensor PhoQ detects signals present inside the host phagosome and activates the transcriptional regulator PhoP, which in turn controls the expression of a large number of downstream genes involved in modification of lipid A, resistance to antimicrobial peptides, and acidification of the phagosome.[73,74] Consistent with a role in pathogenesis, *phoPQ* mutants are nonvirulent in humans and have been evaluated as candidate live-attenuated vaccines.[75,76]

Quantitative blood cultures demonstrate that more than 60% of culturable circulating *Salmonella* Typhi organisms reside in the intracellular compartment.[77] Presumably, this allows for dissemination throughout reticuloendothelial tissues via the blood and lymphatic systems. The heaviest burden of infection is established in the reticuloendothelial system (intestinal lymphoid tissue, liver, spleen, and bone marrow) and gallbladder. Patients with typhoid fever most often have very low grade bacteremia, a feature that presents a formidable diagnostic challenge. The kinetics of quantitative bacterial cultures has been studied in Vietnam.[77] The median number of culturable bacteria is less than 1 colony-forming unit (CFU) per milliliter of whole blood in adults, and slightly higher (1.5 CFUs/mL) in children.[77] Slightly more culturable organisms are present in the bone marrow, with a median of 10 per milliliter of bone marrow.[78] However, over the course of illness, the number of culturable *Salmonella* Typhi organisms in the blood decreases (median of 2 CFUs/mL in the first week to 0.1 CFUs/mL in the second and subsequent weeks), and the number of culturable bacilli increases in the bone marrow (4.8 CFUs/mL in the first week to 158 CFUs/mL in the third and subsequent weeks). As a result, the proportion of bacteria in the bone marrow increases from 5:1 (marrow to blood) in the first week of illness to more than 150:1 in the third week of illness, reflecting relative clearance of bacteria from peripheral blood but persistence in the marrow compartment.[78] Pathologic examination of bone marrow may demonstrate monocytic infiltrates typical of typhoid fever (see "Intestinal and Other Local Pathology").

The initial period of replication and dissemination represents the incubation period of typhoidal *Salmonella* infection. This period typically lasts 1 to 2 weeks but can range widely (3–60 days), depending on the number of organisms ingested.[79] Ultimately, infection results in the sufficient secretion of inflammatory cytokines, including pyrogenic cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which result in fever. However, unlike what occurs during prototypical gram-negative bacteremia, septicemia with hypotension, neutrophilia, and disseminated intravascular coagulopathy (DIC) are extremely uncommon in patients with typhoid or enteric fever.

Intestinal and Other Local Pathology

Intestinal lymphoid tissue is a predominant site of localized inflammation and persistent bacterial replication in cases of severe enteric fever (Fig. 100.2).[80–83] Early in the course of illness, Peyer patches in the terminal ileum and draining mesenteric nodes are enlarged and contain infiltrates

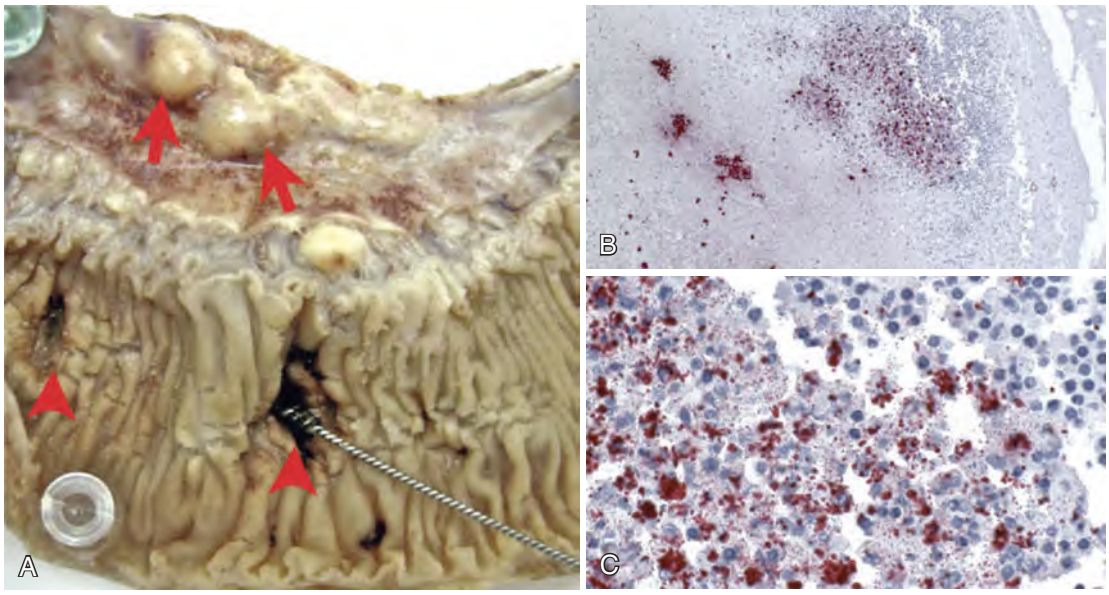

FIG. 100.2 Intestinal pathologic appearance of enteric fever. (A) The visualized mucosal surface of a surgically resected area demonstrates two perforations *(arrowheads)*; the visualized serosal surface demonstrates significant enlargement of lymph nodes *(arrows)*. (B and C) Lower- and higher-magnification views demonstrate immunohistochemical staining for the *Salmonella* O:9 antigen in a necrotic lymph node. *(From Neil KP, Sodha SV, Lukwago L, et al. A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008–2009.* Clin Infect Dis. *2012;54:1096.)*

consisting of mononuclear cells, including macrophages and lymphocytes.[80] As disease progresses, necrosis of intestinal lymphoid tissue occurs, with mixed inflammatory infiltrates, including neutrophils and ulceration and sloughing of overlying intestinal mucosa.[80] Immunohistochemical staining for the *Salmonella* Typhi O antigen reveals abundant organisms in necrotic areas.[81] The clinical manifestations of these changes include hemorrhage and/or intestinal perforation, two of the major life-threatening complications of enteric fever (Fig. 100.3). Other affected organs include the liver, with monocytic infiltrates and foci of parenchymal necrosis, and the spleen, with nodular monocytic infiltrates in the red pulp.[84] Similar monocytic infiltrates may occur in the gallbladder, and gallbladder perforation, which may mimic intestinal perforation, is a rare complication of typhoid fever.[85]

Relapse and Chronic Carriage

Untreated, typhoid fever may persist for up to 4 weeks, and relapse occurs in up to 10% of untreated cases, usually within 2 weeks after initial resolution of fever.[86] Relapse is usually due to the same strain as that associated with the original infection.[87] The gallbladder is the primary site of chronic carriage, although some asymptomatic carriers continue to shed the organism in stool even after cholecystectomy. The in vitro and clinical observations that *Salmonella* Typhi forms biofilms on cholesterol gallstones may explain the strong epidemiologic association between gallstones and carriage.[88,89] An association has been reproducibly observed between chronic carriage of *Salmonella* Typhi and risk of gallbladder carcinoma, but it is unknown whether carriage causes cancer or reflects underlying biliary epithelial surface abnormalities.[90,91]

Clinical Manifestations

The clinical manifestations of enteric fever are nonspecific. Fever is reported in the vast majority of clinically apparent cases, and many other symptoms are variably reported, including headache, cough, nausea, vomiting, constipation, and diarrhea.[8] Although paratyphoid fever was considered less severe than typhoid fever, more recent comparisons suggest that typhoid fever and paratyphoid fever caused by *Salmonella* Paratyphi A are generally indistinguishable on clinical grounds.[92] Most patients with enteric fever are diagnosed in the ambulatory setting, and up to 90% are treated as outpatients.[86] In contrast, classic descriptions of the features of enteric fever are derived from series of hospitalized patients with more severe disease.[93] Complications of enteric fever were generally thought to occur late in the course of disease, usually after 2 weeks of fever. However, experience has demonstrated that major complications of enteric fever, including intestinal perforation and encephalopathy, may occur within days of onset of fever.[81,82,94]

Uncomplicated Typhoid Fever

Clinical features of enteric fever diagnosed in the ambulatory setting are listed in Table 100.2. Fever without localizing signs or symptoms may be the sole manifestation of enteric fever. The onset of fever may be insidious, and fevers typically increase over the first week of illness.[95] A variety of other nonspecific flulike symptoms are common early in the course of enteric fever, and headache, anorexia, myalgias, and malaise may precede the onset of fever.[92,96] Mild confusion may be seen even in ambulatory patients, and a nonproductive cough is also a common feature of uncomplicated enteric fever. Abdominal complaints may include diarrhea, constipation, and abdominal pain. Invasive diarrhea, such as seen in NTS gastroenteritis, does not typically occur in enteric fever.

The physical findings of uncomplicated enteric fever are also nonspecific. Although relative bradycardia, or pulse-temperature dissociation, is a classic sign of enteric fever, it may not be a clinically useful predictor of enteric fever for individual patients, and is absent in the majority of patients.[8,97] Rose spots, the classic cutaneous manifestation of enteric fever, are 1- to 4-mm blanching pink macules, and are most often seen on the chest, back, and abdomen during the second week of fever. However, rose spots are uncommon in uncomplicated typhoid fever. Mild, nonlocalizing, abdominal tenderness may be present. Hepatomegaly and splenomegaly, if present, are usually modest. A white or yellowish-brown coating of the tongue that spares the tongue's edges is a common physical finding.[92]

Laboratory Findings in Uncomplicated Infection

Although abnormal white blood cell counts in peripheral blood are common in patients with bacteremia, the majority of patients with uncomplicated enteric fever do not have leukocytosis, neutrophilia, or increased immature neutrophils.[92] However, either leukocytosis or leukopenia may be present. Both the hematocrit and platelet counts are typically normal or slightly low. Elevated serum aspartate transaminase and alanine transaminase are very common in enteric fever; values two to three times above the upper limit of the normal range are typical.[98] On occasion, more severe hepatitis is observed, but very high levels of blood transaminases (>500 IU/L) should prompt concern for other causes, including viral hepatitis or drug toxicity.[98]

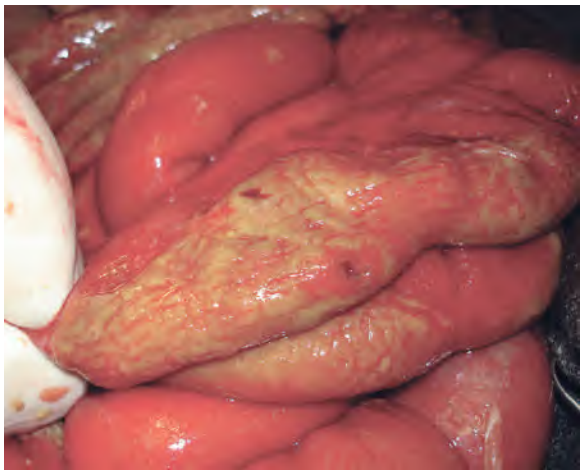

FIG. 100.3 Intraoperative photograph of intestinal perforation caused by *Salmonella* Typhi. Intestinal perforation is visible on the antimesenteric border of the small bowel, which is inflamed with patchy exudates on the serosal surface. *(Courtesy Dr. Pukar Maskey, Patan Hospital, Katmandu, Nepal. From Harris JB, Brooks WA. Typhoid and paratyphoid (enteric) fever. In: Magill AJ, Ryan ET, Hill DR, Solomon T, eds.* Hunter's Tropical Medicine and Emerging Infectious Diseases. *9th ed. Philadelphia: Saunders; 2013:568–576.)*

TABLE 100.2 Clinical Features of Typhoid and Paratyphoid Fever

	CLINICAL FEATURE	APPROXIMATE FREQUENCY[a]
Flulike symptoms	Fever	>95%
	Headache	80%
	Chills	40%
	Cough	30%
	Myalgia	20%
	Arthralgia	<5%
Abdominal symptoms	Anorexia	50%
	Abdominal pain	30%
	Diarrhea	20%
	Constipation	20%
Physical findings	Coated tongue	50%
	Hepatomegaly	10%
	Splenomegaly	10%
	Abdominal tenderness	5%
	Rash	<5%
	Generalized adenopathy	<5%

[a]The proportion of patients demonstrating these clinical features of enteric fever varies, depending on the time, the region, and the type of clinical population (hospitalized or ambulatory) assessed. Estimates are drawn from recent case series in an endemic area, with patients presenting for ambulatory or inpatient care.[92,96] *Modified from Magill AJ, Ryan ET, Hill DR, Solomon T, eds.* Hunter's Tropical Medicine and Emerging Infectious Diseases. *9th ed. Philadelphia: Saunders; 2013:568–576.*

Severe Illness

Classic descriptions of the features of enteric fever are drawn from observations of series of hospitalized patients in the preantibiotic era, in which mortality rates were consistently in the 10% to 15% range. The natural history of untreated disease included progressively increasing fevers over the first week of illness, followed by increasing abdominal complaints and rash over the second week of illness, followed by complications, including intestinal hemorrhage and perforation, or gradual resolution in the third and fourth weeks of illness.[93]

In the present antibiotic era, it remains true that because enteric fever progresses gradually, patients who are severely ill with enteric fever may have been febrile for longer than a week when they first come to clinical attention. Patients with severe enteric fever may appear toxic, and characteristically would have moderate abdominal pain or tenderness, and constipation or diarrhea. Physical findings in severe enteric fever include hepatomegaly and splenomegaly. Patients with severe enteric fever are more likely to have major complications listed in Table 100.3. Complications associated with increased mortality in severe typhoid fever include intestinal hemorrhage and perforation, severe encephalopathy, seizures, and pneumonia.[99]

Gastrointestinal Complications

Intestinal hemorrhage occurs in up to 10% of hospitalized patients with severe enteric fever and is usually self-limited.[86] Intestinal perforation, a major life-threatening complication of enteric fever, occurs in up to 3% of hospitalized patients.[100,101] These complications arise directly from invasion of *Salmonella* into Peyer patches in the small intestines. A series of patients from Vietnam with intestinal perforation resulting from enteric fever demonstrated that the median length of illness preceding perforation was 9 days from the onset of fever, although some cases occurred within the first week.[82] Perforation is suggested by clinical signs of peritonitis, including tachycardia, leukocytosis, neutrophilia, and abdominal pain with guarding and rebound tenderness. The clinical diagnosis of perforation requires a high index of suspicion because patients with severe enteric fever may have a toxic appearance and significant abdominal tenderness even before perforation. Radiographic evidence of pneumoperitoneum may be present in only 50% of cases.

TABLE 100.3 Complications of Typhoid and Paratyphoid Fever

SYSTEM	COMPLICATION	NOTES
Gastrointestinal	Hemorrhage	10%–15% in hospitalized patients
	Perforation	3% in hospitalized patients
Hepatobiliary	Jaundice	1%–3% in hospitalized patients
	Hepatitis	Usually subclinical (↑ ALT/AST)
	Acute cholecystitis	Rare; gallbladder may perforate
Neurologic	Mild encephalopathy	Confusion or apathy common
	Severe encephalopathy	Delirium, stupor, or coma
	Seizures	Common in children ≤5 yr
	Meningitis	Rare, primarily infants
	Guillain-Barré syndrome	Reported
Respiratory	Bronchitis	Dry cough is common
	Pneumonia	May be other concomitant bacterial infection (e.g., *Streptococcus pneumoniae*)
	Empyema	Rare reports
Cardiovascular	Myocarditis	Usually subclinical (ECG changes)
	Endocarditis	Rare reports
Hematologic	Anemia	Usually subclinical
	Disseminated intravascular coagulation	Usually subclinical (↑ PT/PTT)
Other	Musculoskeletal pyogenic infections	Osteomyelitis (particularly vertebral), psoas abscess and others reported
	Hemolytic-uremic syndrome	Reported
	Miscarriage	Reported

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *ECG,* electrocardiogram; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
Modified from Magill AJ, Ryan ET, Hill DR, Solomon T, eds. Hunter's Tropical Medicine and Emerging Infectious Diseases. *9th ed. Philadelphia: Saunders; 2013:568–576.*

Neurologic Complications

Various case series have documented a widely varying prevalence of diverse neuropsychiatric manifestations during enteric fever, ranging from encephalopathy, encephalomyelitis, transverse myelitis, meningitis, ataxia, and Guillain-Barré syndrome.[94,102] Although most of these manifestations are uncommon, patients with severe enteric fever often present with some component of encephalopathy, and a history of confusion or an apathetic affect are common.[86] Of note, typhoid was named for its clinical similarity to typhus, and the name *typhus* was from the Greek term for "smoky" or "cloudy," reflecting the neurologic features that often accompanied this febrile illness. More severe encephalopathy, manifesting with delirium, stupor, and coma, occurs in a smaller number of hospitalized patients and is associated with a high risk of mortality.[99,103,104] Osler described this as a "pseudo-wakeful state" of "muttering" delirium, known as "coma vigil," and noted that it portends poor outcomes. Even in cases of severe encephalopathy, microbiologic evaluation of cerebral spinal fluid is usually unrevealing, and pleocytosis, if present, usually reveals fewer than 35 cells/μL.[103,104] Encephalopathy during enteric fever may be most common among older children and young adults.[105] Seizures during enteric fever are most common in young children and are associated with increased mortality.[99] Meningitis caused by *Salmonella* Typhi is seen primarily in infants.[106]

Metastatic Pyogenic Complication

Enteric fever is a disseminated bacterial infection, but pyogenic abscess formation during enteric fever is notably infrequent, although *Salmonella* Paratyphi C is more likely to cause abscesses and focal infections than the other typhoidal strains. This contrasts with what occurs during invasive nontyphoidal salmonellosis, in which osteomyelitis, joint infection, abscess formation, and endovascular infection more frequently occur. Although uncommon, pyogenic complications during typhoid have been described and include empyema, osteomyelitis, muscle abscess (particularly involving the psoas), and endovascular infections and endocarditis.[107]

DIAGNOSIS

The laboratory diagnosis of enteric fever is often challenging because current culture-based, serologic, and molecular diagnostic tests for enteric fever fail to achieve an optimal combination of sensitivity and specificity.[108,109] For this reason, it is often appropriate to treat patients with suspected enteric fever with empirical antibiotic therapy. The diagnosis of enteric fever should be considered in any person with fever, especially in those with fever lasting longer than 3 days and who have had an exposure in the last 1 to 6 weeks to an area where enteric fever is endemic. In endemic areas, other clinical factors that are associated with a higher likelihood of enteric fever include a temperature greater than 39°C, ill appearance, young age (<5 years), and any abdominal complaints, including abdominal pain, diarrhea, or constipation.[58] As the duration of fever increases, the likelihood of enteric fever increases.[86] Despite this, it is important to recognize that the majority of individuals suspected of having enteric fever, even in endemic settings, do not have enteric fever but rather an alternative infection[18]; therefore, clinical suspicion of and empirical treatment for enteric fever should not halt the search for alternative causes of fever.

Culture-Based Diagnostics

Although a presumptive diagnosis of enteric fever may be sufficient grounds for initiating and continuing antimicrobial therapy, a definitive diagnosis of enteric fever is made only through the isolation of a typhoidal serotype of *S. enterica* (*Salmonella* Typhi or *Salmonella* Paratyphi A,

B, and C) from the blood, bone marrow, stool, urine, or other clinical specimen of a febrile patient. Isolation of the causative organism also allows antimicrobial resistance testing, which facilitates optimal management.

Blood culture is the most common method of diagnosis, where adequate microbiologic facilities exist. The sensitivity of blood culture varies from approximately 40% to 80%,[86,110,111] and a recent meta-analysis estimated an average sensitivity of 61%.[27] The low-grade bacteremia in enteric fever is an inherent limiting factor to the sensitivity of blood cultures, as is prior receipt of antibiotics.[77] To maximize the sensitivity of blood cultures, the World Health Organization (WHO) recommends that cultures be performed using 10 to 15 mL of blood from school-children and adults, and 2 to 4 mL of blood from toddlers and preschool-aged children.[79] The use of a nonselective broth media, as is standard for most blood cultures, is encouraged because it maximizes detection of a wide range of pathogens. The sole use of *Salmonella* selective or enriching media, such as ox bile medium, is discouraged.[79]

Although less sensitive than blood cultures, stool cultures are positive in more than 50% of children and 30% of adults with enteric fever, and they increase the diagnostic yield over blood cultures alone by approximately 5%.[112] To maximize detection, WHO recommends the use of greater than 1 g of stool and selenite enrichment broth.[79] Culturing of bone marrow has the highest sensitivity (80%–95%) of all the culture-based approaches, with culturing of a 1-mL aspirate of bone marrow having the sensitivity of a 15-mL peripheral blood culture in an adult.[77,78] Culturing of bone marrow is, however, not clinically practical for most patients with suspected enteric fever, although microbiologic and hematologic analysis of a bone marrow aspirate may be part of an evaluation of a patient with a prolonged fever of unknown origin when less invasive testing is unrevealing. Other specimens that may yield growth of *Salmonella* Typhi or *Salmonella* Paratyphi A, B, and C include urine, duodenal aspirates, and specimens from skin biopsy of rose spots. However, these approaches are not routinely recommended. Cultures made from intestinal biopsy specimens and peritoneal fluid of patients with perforation are rarely positive.[81,82]

Serologic Tests

The Widal test detects agglutinating antibodies against the O and H antigens of *Salmonella* Typhi. The Widal test was developed over a century ago and remains one of the world's most widely used diagnostic tests but suffers from significant limitations in its sensitivity, specificity, and reliability.[108] As with most serologic tests, a false-negative Widal test result may occur early in the course of illness, and a false-positive Widal test result may be caused by past infection or previous exposure to cross-reactive antigens or vaccination. There are no universal standards that define the cutoff dilution of agglutinating antibodies to indicate a positive Widal test result. The very low specificity of the assay (50%–70%) and the inability to discern active from previous infection or vaccination means that the assay should rarely, if ever, be used.

Other rapid serologic tests for enteric fever have been developed. Major commercial tests include the IDL Tubex and Typhidot assays. The IDL Tubex test (IDL Biotech AB, Bromma, Sweden) is a rapid immunochromatographic test that detects immunoglobulin M (IgM) antibodies to the O:9 antigen (the major antigenic determinant of *Salmonella* Typhi LPS). An advantage of this approach is that T-cell–independent IgM responses that target *S. enterica* O polysaccharide develop early in the clinical course of illness. Studies have suggested that the sensitivity of the IDL Tubex is approximately 70% to 80%, with a specificity of 80% to 90% when evaluated against standards involving patients with blood culture–proven typhoid fever versus other known causes of bacteremia.[26,113–116] The Typhidot assay (Malaysian Biodiagnostic Research, Bangi, Malaysia) that detects both IgM and IgG to a 50-kDa outer membrane protein antigen of *Salmonella* Typhi has similar performance characteristics.[113–115,117]

Several newer serologic approaches have been developed and evaluated in clinical studies. These include detection of anti-*Salmonella* IgA in secretions of peripheral blood lymphocytes[28,29,118] and new antigen targets for enzyme-linked immunosorbent assays (ELISAs).[30,31] These diagnostics have demonstrated greater accuracy in distinguishing typhoid from other febrile illnesses than currently available serologic tests, but these newer assays have not yet been commercialized.

Molecular Approaches

Molecular diagnostic approaches based on nucleic acid detection have met with only mixed and limited success, presumably reflecting the low-level bacteremia that has hindered culture-based methods, and the action of inhibitors in human blood; such assays are not currently commercially available.[32,108] Although some promising results with new approaches have been seen in small studies,[33] further clinical validation is needed to characterize their accuracy. The lack of adequate diagnostic testing for enteric fever means that this remains an active area of investigation.[108]

Screening for Chronic Carriage

Identifying chronic carriers of typhoidal *Salmonella* may be important for prevention of transmission, particularly in the context of enteric fever outbreaks in nonendemic settings in which the source of infection is unknown. The conventional approach to identify carriers involves collection of at least three stool specimens (separated by days to weeks) for microbiologic culture to isolate *Salmonella*. Although specificity is excellent, the sensitivity of this approach is estimated at 70% to 80%.[34] Screening by duodenal string capsules is an alternative which may improve this yield, although the string test is not currently commercially available.[35] There is an extensive body of literature on the use of Vi antibody testing to identify carriers, but the results have been mixed,[36,37] and using Vi as a carrier detection target will be further compromised as Vi-based typhoid conjugate vaccines become key components of global typhoid-control strategies.

Management

Appropriate antibiotic management (Table 100.4) reduces the mortality rate of enteric fever from 10% to 15% to less than 1%, and shortens the duration of fever from 3 to 4 weeks to 3 to 5 days after initiation of therapy.[11] Uncomplicated enteric fever is treated with a single antibacterial drug.[86] However, the widespread emergence of antibiotic resistance in *Salmonella* Typhi and *Salmonella* Paratyphi A limits the arsenal of effective antibiotics in many areas. The selection of an appropriate antibiotic is dependent not only on antibiotic resistance patterns but on the severity of illness, the age of the patient, and the availability and cost of antibiotics in resource-limited settings. In addition to antibiotic therapy, supportive care, monitoring for complications, and adjunctive therapy with pulse-dose steroids for severe disease (see later) are important aspects of management of patients with enteric fever.

Chloramphenicol, Ampicillin, and Trimethoprim-Sulfamethoxazole

Chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were the original first-line antibiotics for treating patients with enteric fever. Widespread resistance emerged in the 1980s, through dissemination of IncH1 plasmids conferring simultaneous resistance to all three agents (Fig. 100.4). Such strains remain widely disseminated and are termed MDR *Salmonella* Typhi. However, over the past several years, there has been a decline in MDR *Salmonella* Typhi concomitant with the rise in fluoroquinolone resistance.[19,38]

Because of the risk of irreversible bone marrow aplasia in up to 1 in 10,000 recipients,[119] chloramphenicol is no longer routinely used in many areas, and oral chloramphenicol is not available in the United States. However, in many resource-limited areas, oral chloramphenicol is still available, has excellent bioavailability and central nervous system penetration, and has broad-spectrum activity against many common causes of serious childhood bacterial infections, including enteric fever. Chloramphenicol reduces the mortality rate of enteric fever substantially and decreases the time to defervescence to 3 to 5 days, and was shown to be equivalent to gatifloxacin in a randomized trial,[39] but its use is associated with a high relapse rate and risk of chronic carriage.[120,121] Oral trimethoprim-sulfamethoxazole may also be used to treat individuals with susceptible strains, although delayed clearance and relapses are common. Both chloramphenicol and trimethoprim-sulfamethoxazole are bacteriostatic agents.[122] Oral amoxicillin may also be used to treat individuals with susceptible strains and may result in a roughly comparable likelihood of relapse.[123]

TABLE 100.4 Antibiotics Commonly Used in Treating Patients With Enteric Fever

	ANTIBIOTIC	ROUTE	TYPICAL PEDIATRIC DOSAGE[b]	ADULT DOSAGE	TYPICAL DURATION	COMMENTS
Original first-line agents	Chloramphenicol	PO/IV	12.5–25 mg/kg qid	2–3 g/day (divided qid)	14–21 days	These agents are effective for susceptible strains; however, multidrug resistance to all of these agents is common in many areas.
	Amoxicillin	PO	25–35 mg/kg tid	1 g tid	14 days	
	Ampicillin	IV	25–50 mg/kg q6h	2 g q6h	14 days	
	TMP/SMX	PO/IV	8–12 mg/kg/day (TMP) 40–60 mg/kg/day (SMX) (divided qid)	160 mg/800 mg qid	14 days	
Fluoroquinolones	Ofloxacin	PO/IV	15 mg/kg bid	400 mg PO bid	5–14 days	Ofloxacin and ciprofloxacin are effective for nalidixic acid–susceptible strains. Short courses of 5–7 days are acceptable in uncomplicated cases. Ten- to 14-day courses are recommended in patients requiring hospitalization or parenteral therapy. Gatifloxacin appears effective for uncomplicated cases caused by NaR strains.
	Ciprofloxacin	PO/IV	15 mg/kg bid	500 mg PO bid	5–14 days	
	Gatifloxacin	PO	10 mg/kg qd	10 mg/kg/day qd	7 days	
Third-generation cephalosporins	Ceftriaxone	IV	50–100 mg/kg qd	1–2 g IV qd	7–14 days[c]	These are an alternative to fluoroquinolones for strains with decreased fluoroquinolone susceptibility, and for empirical therapy in areas where decreased fluoroquinolone susceptibility is common.
	Cefixime	PO	10 mg/kg bid	200 mg PO bid	7–14 days	
	Aztreonam	IV	50 mg/kg q8h	2g q8h		Alternative to ceftriaxone for cephalosporin-allergic patients.
Macrolides	Azithromycin	PO	20 mg/kg qd	500–1000 mg PO qd	7 days	These are an alternative to fluoroquinolones for strains with decreased fluoroquinolone susceptibility, and for empirical therapy in areas where decreased fluoroquinolone susceptibility is common.
Eradication of carriage	Ciprofloxacin	PO	—	500–750 mg bid	28 days	If eradication is indicated for public health reasons, a trial of medical therapy is justified, even in patients with evidence of cholelithiasis. Cholecystectomy may be considered.
	Amoxicillin	PO	75–100 mg/kg/day in 3 divided doses	2 g tid	4–6 weeks	Lower efficacy than fluoroquinolones but may be considered for treatment of carriage in individuals harboring strains with fluoroquinolone resistance.

[a]See text for references.
[b]Weight-based pediatric dosage should not exceed adult maximum.
[c]Recommended that treatment continue for at least 7 days after defervescence to minimize relapse.
NaR, Nalidixic acid resistant (see text); *TMP-SMX,* trimethoprim-sulfamethoxazole.
Modified from Magill AJ, Ryan ET, Hill DR, Solomon T, eds. Hunter's Tropical Medicine and Emerging Infectious Diseases. *9th ed. Philadelphia: Saunders; 2013:568–576.*

Fluoroquinolones

In many areas of the world, fluoroquinolone antibiotics are the preferred therapy for patients with suspected enteric fever, although increasing antimicrobial resistance is occurring globally.[30,124,125] For susceptible isolates, fluoroquinolone antibiotics, such as ciprofloxacin, and the less costly, more widely available ofloxacin, result in defervescence within 3 to 4 days, which is similar to the response associated with chloramphenicol and more rapid than that for third-generation cephalosporins.[126,127] Administration of a fluoroquinolone also results in lower rates of relapse and carriage compared with those associated with use of chloramphenicol or third-generation cephalosporins.[126,127]

Because of the availability and widespread use of fluoroquinolone antibiotics in many areas of the world, fluoroquinolone resistance has become increasingly common in *Salmonella* Typhi and *Salmonella* Paratyphi A in areas where enteric fever is highly endemic.[125] In South and Southeast Asia, strains with reduced susceptibility to fluoroquinolones now predominate.[19] Fever clearance times and treatment response have worsened with this rise in fluoroquinolone nonsusceptibility.[40]

Before 2012, breakpoints for fluoroquinolone susceptibility were standard across all Enterobacteriaceae, although resistance to nalidixic acid (a nonfluorinated quinolone antibiotic) was associated with decreased clinical responsiveness to fluoroquinolone antibiotics, such as ofloxacin and ciprofloxacin.[128–131] Nalidixic acid resistance (NaR) thus became a surrogate marker for predicting clinical failure of fluoroquinolones, even for *Salmonella* Typhi and *Salmonella* Paratyphi strains that met Clinical Laboratory and Standards Institute (CLSI) criteria for fluoroquinolone susceptibility.[56] The CLSI amended its breakpoints for *Salmonella* Typhi and *Salmonella* Paratyphi A, B, and C for ciprofloxacin in 2012 and for levofloxacin and ofloxacin in 2013. For ofloxacin, strains with a minimal inhibitory concentration (MIC) of less than or equal to 0.12 μg/mL are considered susceptible. Patients with strains with an MIC of 0.12 μg/mL defervesce within an average of less than 5 days after initiation of ofloxacin therapy, and patients with strains with an MIC of 0.064 μg/mL or less defervesce in less than 4 days.[131] For ciprofloxacin, the amended breakpoint for defining susceptibility is now less than or equal to 0.06 μg/mL. A complicating factor is that many laboratories are not currently able to implement testing of these lower breakpoints for typhoidal *S. enterica* isolates. For such strains, NaR remains an appropriate marker of reduced susceptibility to fluoroquinolone antibiotics.

Although fluoroquinolones are generally well tolerated, concerns about fluoroquinolone-induced articular toxicity in immature animals have limited their use in children in some areas; however, several studies support the safety of their use in children.[132] Gatifloxacin is a dual

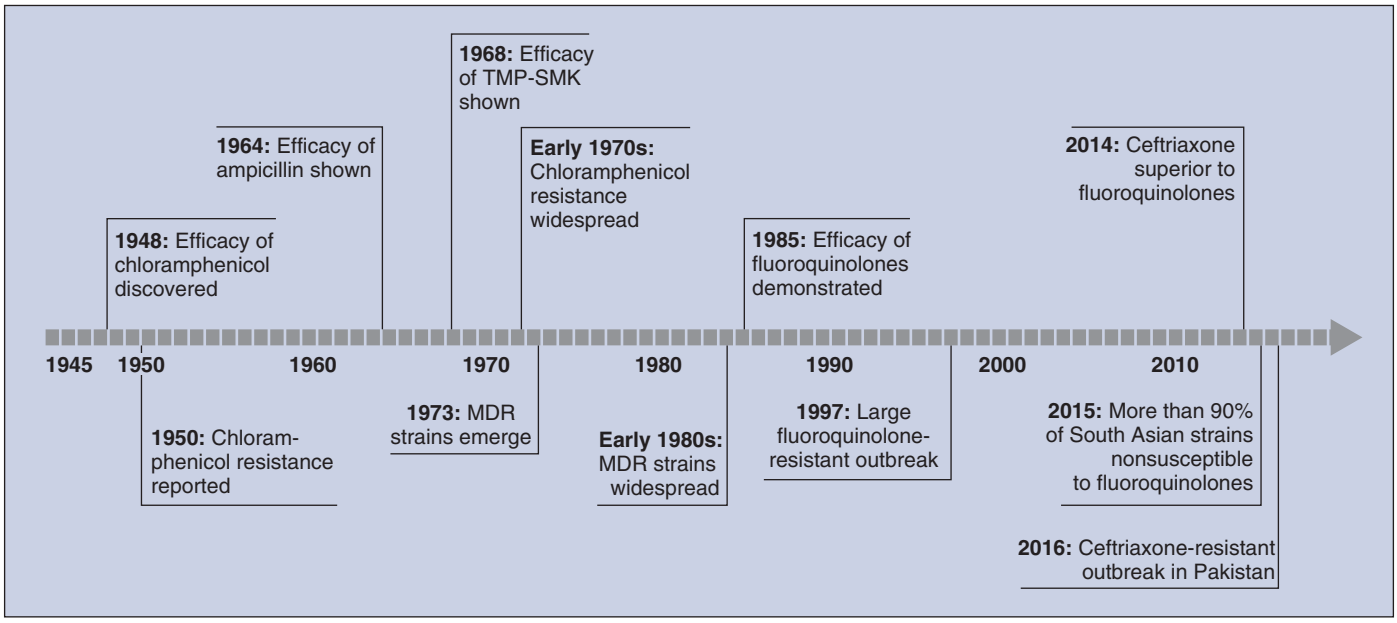

FIG. 100.4 History of antibiotic efficacy studies and the emergence of antimicrobial resistance in *salmonella* typhi. *MDR,* Multidrug resistant; *TMP-SMX,* trimethoprim-sulfamethoxazole. *(From Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time?* N Engl J Med. *2018:379;1493–1495.)*

mechanism-of-action fluoroquinolone that inhibits both DNA gyrase and topoisomerase IV. Gatifloxacin has been associated with increased frequency of hypoglycemia and hyperglycemia, compared with other fluoroquinolones, and for this reason it was withdrawn from the US market. However, gatifloxacin remains available in many countries where enteric fever is endemic and is reported to be clinically effective against some NaR *Salmonella* Typhi.[133] However, in Nepal, a trial comparing gatifloxacin with ceftriaxone was stopped early owing to higher treatment failure in the gatifloxacin arm as a result of fluoroquinolone resistance.[41] In documented cases of fluoroquinolone nonsusceptibility or for empirical treatment in cases acquired in regions where such strains are common, alternative agents should be used.

Cephalosporins

The emergence of *Salmonella* Typhi and *Salmonella* Paratyphi A strains with decreased susceptibility to fluoroquinolones has shifted the choice for empirical treatment of individuals with suspected severe enteric fever toward third-generation cephalosporins. However, although third-generation cephalosporins, such as ceftriaxone and cefixime, may be used, they appear inferior to fluoroquinolones for fully fluoroquinolone-susceptible strains.[127] Of note, both cefixime and short courses of parenteral ceftriaxone (≤7 days) are associated with high relapse rates during enteric fever.[134] In addition, time to defervescence is longer in patients treated with cefixime and ceftriaxone, compared with responses after administration of fluoroquinolones.[127,135] Resistance of typhoidal *S. enterica* to extended-spectrum β-lactam antibiotics has been rare and sporadically reported[42,136,137]; however, in 2017 a large outbreak of extended-spectrum β-lactam *Salmonella* Typhi was reported in Pakistan,[24] raising the concern that strains with resistance to third-generation cephalosporins may become increasingly common. Notably, the strains in this outbreak were MDR and fluoroquinolone resistant, leaving few available treatment options.

Azithromycin

Azithromycin is a highly effective drug for treating patients with enteric fever; favorable attributes include its efficacy, its established safety in children, and its excellent bioavailability and pharmacokinetics, with once-daily dosing. Azithromycin reaches high intracellular concentrations that may contribute to its high rates of cure. A 7-day course of azithromycin treatment for patients with enteric fever results in lower rates of clinical failure and substantially less relapse than third-generation cephalosporins.[138] Defervescence occurs within an average of 4 days.[129,133,138] There are only sparse reports of resistance of *S. enterica* to azithromycin to date.[43,138a] For these reasons, azithromycin is an excellent option for treating patients with enteric fever caused by MDR and fluoroquinolone-nonsusceptible *Salmonella* Typhi and *Salmonella* Paratyphi A.[138]

Other Antibiotics

Four small clinical trials have demonstrated the efficacy of aztreonam for treatment of enteric fever with comparable rates of efficacy and relapse to first-line antibiotics.[44,45] In the setting of cephalosporin-resistant *Salmonella* Typhi, carbapenems have also been successfully used to treat patients with typhoid fever, although no detailed data on efficacy and relapse rates are available.[36]

Adjunctive Therapy

Adjunctive therapy with high-dose dexamethasone has been shown to decrease mortality in cases of severe typhoid fever.[104] A double-blind trial involving 38 adult and pediatric patients with severe typhoid fever in Indonesia, conducted in 1981 and 1982, demonstrated that treatment with chloramphenicol, along with 3 mg/kg of dexamethasone administered over 30 minutes, followed by eight doses at 1 mg/kg every 6 hours, significantly reduced mortality (2 of 20 patients died in the dexamethasone arm) compared with chloramphenicol and placebo (10 of 18 patients died in the placebo arm, $P = .003$).[104] In this study, severe typhoid fever was defined as typhoid fever with shock and/or profound encephalopathy manifesting with delirium or obtundation.[104] More recent studies continue to support the concurrent use of dexamethasone and antibiotics in both children and adults with severe typhoid fever.[103,139] For this reason, administering high-dose steroids to patients who present with shock or, more often, significant mental status changes, and in whom there is strong suspicion of enteric fever, is recommended.

Supportive Care and Management of Complications

Supportive care of patients with severe enteric fever includes rehydration, nutritional management, and mobilization. Contrary to a prevailing historical opinion, it appears that fevers and malaise can be managed safely and more comfortably with a standard regimen of antipyretics.[140] One small double-blind trial showed that ibuprofen was superior to paracetamol in reducing the morbidity of fevers in enteric fever.[140]

Patients with intestinal hemorrhage should be monitored, ideally in an intensive care setting, but can generally be managed through

TABLE 100.5 Typhoid Fever Vaccines Currently Commercially Available Internationally

VACCINE	TYPE	ROUTE	DOSE AND INTERVAL	MINIMUM AGE	PROTECTION AGAINST *SALMONELLA* TYPHI	BOOSTING INTERVAL IN TRAVELERS
Ty21a	Live attenuated	Oral	Four doses (in United States) Administer one dose every other day until complete	5 yr[a]	50%–80%[b]	Every 5 yr
Vi capsule antigen	Polysaccharide	Intramuscular	1	2 yr	50%–80%	Every 2 yr
Vi tetanus toxoid conjugate vaccine[c]	Polysaccharide conjugate	Intramuscular	1	6 mo	80%[d]	Not yet defined

[a]Five years and older per World Health Organization[79]; 6 years and older per US Advisory Committee on Immunization Practices.[51]
[b]Has some efficacy against *Salmonella* Paratyphi B (see text). Additional vaccines are under development, including conjugate vaccines.
[c]Typhoid vaccines: WHO position paper, March 2018—Recommendations.[145]
[d]Preliminary data.
Modified from Magill AJ, Ryan ET, Hill DR, Solomon T, eds. Hunter's Tropical Medicine and Emerging Infectious Diseases. *9th ed. Philadelphia: Saunders; 2013:568–576.*

supportive care. Blood products, including packed red cells and plasma, may be needed in severe cases. Intestinal perforation in enteric fever is associated with a high mortality rate, but prompt surgical intervention is associated with improved survival.[82,100,141] Although the majority of perforations are single, careful inspection is required to determine if multiple perforations are present. Although simple closure may be performed in some cases, a wedge excision or segmental resection is more often necessary because the surrounding bowel is often necrotic.[142,143] Drainage of collections and peritoneal lavage should be performed before wound closure. Antibiotic regimens after perforation should be expanded to cover other intestinal microbiota, including anaerobes.

Treatment of Relapse and Chronic Carriage

Relapse usually occurs within 2 weeks of discontinuation of antibiotics, and relapsing patients typically present with milder symptoms than during the primary episode. Isolates obtained after relapse typically have the same antibiotic susceptibility as during the initial episode. The approach to treating patients with relapsed enteric fever is usually the same as for the primary episode.

Chronic carriage is defined as asymptomatic shedding of typhoidal *S. enterica* for 1 year or more. Asymptomatic shedding does not indicate a recurrence of illness or a high risk of recurrent illness. Although chronic carriage is associated with an increased risk of gallbladder carcinoma,[90] it is unknown whether the eradication of carriage reduces this risk of carcinoma, so the decision to attempt to eradicate carriage is usually based on public health considerations and is essential for individuals whose occupation involves food handling. Several antibiotics used to treat individuals with acute enteric fever reach high concentrations in bile, including fluoroquinolones. A 28-day course of ciprofloxacin has demonstrated 80% to 90% efficacy in eradication of carriage.[144] However, cholecystectomy may be necessary to eradicate carriage in individuals with cholelithiasis who continue to shed typhoidal *S. enterica* after prolonged antimicrobial therapy.[79] In an era of widespread nonsusceptibility to fluoroquinolones, there is a limited evidence base for successful treatment of carriage with antibiotics other than fluoroquinolones. Amoxicillin, administered at high doses (75–100 mg/day for 4-6 weeks), can be used, but tolerability is poor and overall eradication rates in many studies are modest.[46–48] There are even fewer data for treatment of carriers with trimethoprim-sulfamethoxazole with or without rifampin.[49,51]

Prevention

Because enteric fever is transmitted primarily through fecally contaminated water and food, the major preventive strategy to prevent enteric fever is the provision of safe water and adequate sanitation. At a municipal public infrastructure level, this requires appropriate facilities for waste disposal and sewage treatment in addition to provision of a safe water supply. In the United States, the introduction of chlorination and filtration of municipal water supplies in the early 1900s led to rapid and dramatic declines in the burden of typhoid.[52] At a household level, interventions to prevent enteric fever include hand washing with soap before preparing or eating food, avoidance of raw or uncooked foods, and local disinfection of unsafe drinking water, followed by storage in narrow-mouthed containers. Unfortunately, WHO currently estimates that 2 billion people use a drinking water source that is contaminated with feces.[53]

Historically, a heat-phenol–inactivated, whole-cell, killed typhoid vaccine was available for parenteral administration. The vaccine required multiple administrations, induced only short-term protection, and was associated with a high adverse event profile.[145] That vaccine is no longer commercially available in the United States.[146] Currently, two more effective and better-tolerated typhoid fever vaccines (Table 100.5) are commercially available in many areas: a capsular polysaccharide vaccine, licensed in the United States as Typhim Vi (Sanofi Pasteur, Swiftwater, PA), and an oral live-attenuated vaccine containing the *Salmonella* Typhi strain Ty21a, licensed in the United States as Vivotif (Valneva, Lyon, France). The polysaccharide vaccine is composed of the Vi capsular polysaccharide antigen from *Salmonella* Typhi strain Ty2, and the Vi vaccine confers 50% to 80% protection against *Salmonella* Typhi in children 2 years of age and older when administered as a single parenteral dose.[145,147–149] The Vi vaccine is not boosted by additional doses, and protection wanes rapidly after 2 years, at which point revaccination is recommended if risk is ongoing.[51] Ty21a is administered orally and also affords 50% to 80% protection against *Salmonella* Typhi.[145,150–156] Although Ty21a enteric-coated capsules are often used for travelers, a liquid formulation prepared from two sachets, one containing vaccine and a second containing a buffer, have been used for oral administration to children in resource-limited settings. The duration of immunity to the Ty21a vaccine is dependent on the number of doses received. In the United States, a four-dose every-other-day series of Ty21a is recommended and confers significant immunity for up to 7 years, although revaccination is recommended every 5 years if risk is ongoing.[51] Antibacterial drugs should not be given any time from 3 days before until 3 days after administration of a series of Ty21a. For most patients with significant primary immunodeficiencies, Ty21a should not be given; however, the Strategic Advisory Group of Experts for the WHO advises that Ty21a can be safely given to asymptomatic individuals living with human immunodeficiency virus (HIV) infection and a $CD4^+$ T-cell count greater than 200/mm^3.[145]

In 2018, WHO recommended that typhoid vaccination programs be undertaken in settings with high typhoid incidence or high burden of antimicrobial-resistant *Salmonella* Typhi.[54] However, typhoid vaccines are not currently widely used in most endemic regions and are more often used by travelers to endemic areas. For travelers receiving either the Vi or Ty21a vaccine, it is optimal that typhoid vaccination be completed at least 7 days before travel, if possible. Limitations of currently licensed vaccines include limited immunity in young children (<2 years of age) and lack of cross-protection against other causes of enteric fever, primarily *Salmonella* Paratyphi A, although Ty21a appears to provide protection against *Salmonella* Paratyphi B.[157] To improve both immunogenicity in children younger than 2 years and to induce longer-lasting protection, a number of conjugate Vi vaccines are in various stages of development. One version that conjugated Vi to *Pseudomonas aeruginosa*

recombinant exoprotein A (Vi-rEPA) achieved 90% protective efficacy against typhoid fever in a large randomized, double-blind clinical trial involving 11,000 children aged 2 to 5 years in Vietnam,[158] and has been demonstrated to be safe and immunogenic in phase II trials in infants.[159] However, this vaccine has not been licensed internationally. A Vi-tetanus toxoid conjugate vaccine (Typbar-TCV; Bharat Biotech, Hyderabad, India) was licensed in India in 2015 on the basis of immunogenicity data,[55] and was recently shown to have comparable efficacy to Typhim Vi in a human challenge model.[49] Although phase III efficacy data on this vaccine are not yet available, WHO has prequalified this vaccine and recommended its use in high-burden countries.[54] A paratyphoid A conjugate vaccine containing the O-specific polysaccharide of *Salmonella* Paratyphi A has also been reported.[160]

In non–highly endemic areas, other efforts to prevent enteric fever are aimed at limiting the role of carriers in transmission, particularly for carriers who present a significant public health risk, including food handlers and those working in child care or health care settings. In the United States, local and state health departments provide screening and work exclusion policies for individuals with enteric fever. The precise policies vary by location but may require screening of the patient and selected contacts to document clearance of bacterial shedding before discharge from public health follow-up and clearance for the performance of certain occupations.

DIFFERENTIAL DIAGNOSIS OF ENTERIC AND TYPHOIDAL FEVERS

Given the nonspecific clinical features of enteric fever and the current limitations of diagnostic testing, it is important that clinicians give consideration to the broader differential diagnosis when approaching patients with possible enteric fever. Such patients usually present with prolonged or relapsing fever, an acute febrile episode in a resource-limited area, or fever and abdominal symptoms and signs. Considerations in the differential diagnosis of enteric fever include epidemiologic risk factors, such as the relative local prevalence of invasive nontyphoidal salmonellosis, malaria, and other febrile diseases, and the type and timing of possible exposures, the duration and magnitude of fevers, the types of abdominal symptoms and signs, and laboratory features at the time of clinical presentation.

Bacteremia Associated With Nontyphoidal *Salmonella*

Although febrile gastroenteritis is the most common clinical manifestation of human nontyphoidal salmonellosis, nontyphoidal serotypes can also cause prolonged fever and bacteremia, particularly in immunocompromised patients with cell-mediated immunodeficiencies or with concomitant malaria. NTS bacteremia is a leading cause of death of young children and adults with acquired immunodeficiency syndrome (AIDS) in sub-Saharan Africa.[161] NTS can also cause abscess formation (spleen, kidneys, liver), and *Salmonella* and staphylococci are the leading causes of aortic atheroma seeding, mycotic aneurysm formation, and prolonged bacteremia.[162] Individuals with sickle cell disease and individuals with concomitant schistosomiasis are also at risk of prolonged and invasive nontyphoidal salmonellosis (see Chapter 223).[163,164]

TYPHOIDAL FEVER

A number of non-*Salmonella* infections have features that may mimic typhoid or enteric fever (Table 100.6). These illnesses have sometimes been referred to as *typhoidal fevers,* and are usually characterized as nonspecific systemic illnesses associated with fever that lasts longer than a week. Indeed, typhoid itself was named for its clinical similarity to typhus, caused by *Rickettsia* species. Typhus and typhoid are both characterized as febrile illnesses that may be prolonged and associated with encephalopathy or confusion, and if untreated, both diseases are associated with high mortality rates. In South and Southeast Asia, scrub typhus (*Orientia tsutsugamushi*) and murine typhus (*Rickettsia typhi*) are highly endemic, and are often mistaken for typhoid.[56,57] In sub-Saharan Africa, various *Rickettsia* species, including *Rickettsia africae* (the causative agent of African tick-bite fever), are common causes of nonspecific febrile illness. Leptospirosis is also a common cause of nonspecific febrile illness in many typhoid-endemic areas, and is often underdiagnosed owing to lack or underuse of diagnostics.[57] A clinical diagnosis of "typhomalarial fever," a term that appeared in the mid-19th century, highlights the overlap of the clinical syndromes of typhoid with malaria.[58] Individuals with malaria can also present with a wide range of symptoms, including prolonged or recurrent fever, headache, abdominal pain, and cough. Similarly, individuals with brucellosis may present with nonspecific fever, malaise, and abdominal pain. Fever may be prolonged, and infection during brucellosis is often characterized by its chronicity. Manifestations include osteoarticular and genitourinary involvement, granulomatous hepatitis, uveitis, and, rarely, endocarditis. Tularemia is a zoonotic infection caused by *Francisella tularensis*. Most human infections are due to exposure to small rodents or lagomorphs (rabbits), and humans usually become infected through direct contact with infected animals or animal parts, or through the bite of an arthropod as a transmission vehicle. Similar to *Salmonella, F. tularensis* is an intracellular pathogen that is able to survive and multiply within phagocytic cells, including macrophages, and infection spreads throughout the reticuloendothelial system. Without appropriate treatment, typhoidal tularemia is often fatal.

Persistent fever with nonspecific symptoms may also be seen with melioidosis, an infection caused by *Burkholderia pseudomallei*. Melioidosis is usually reported in South and East Asia and northern Australia. Melioidosis may manifest in a number of ways, ranging from a chronic febrile illness to an acute septicemia,[165] and it may include abscess formation (often in the spleen, liver, lungs, or muscles) or pneumonia. Melioidosis is associated with water and soil exposure and can affect anyone, although individuals with diabetes, immunosuppression, chronic renal disease, alcoholism, and cirrhosis are at particular risk. Clinical manifestations may occur years after initial exposure.

A typhoidal-like illness can also be seen with Q fever, caused by the intracellular bacterium *Coxiella burnetii*. Q fever is a zoonotic infection usually associated with exposure to sheep or cattle, and humans become infected through exposure to pseudospores from animal products, especially placental tissues. Individuals with Q fever may present with prolonged fever and a wide range of symptoms, including headache, pneumonia, hepatitis, and endocarditis. Rat-bite fever, caused by *Streptobacillus moniliformis,* may also cause a nonspecific febrile illness that may mimic enteric fever, especially when the route of infection is foodborne (Haverhill fever); arthritis and rash can occur.[166]

TABLE 100.6 Differential Diagnoses of Infectious Diseases to Consider in Patients With Possible Typhoid or Enteric Fever

Common Infectious Causes of Nonspecific Acute Febrile Illness in Resource-Limited Areas

Salmonella bacteremia (typhoidal and nontyphoidal serotypes)
Malaria
Dengue and other arboviral fevers
Leptospirosis
Influenza
Rickettsioses
Bartonelloses

Infectious Causes of Typhoidal Illnesses, Including Prolonged Nonlocalizing Febrile Illnesses

Persistent nontyphoidal bacteremia or abscess formation
Typhus (rickettsiosis)
Brucellosis
Typhoidal tularemia
Q fever
Bartonellosis (including trench fever)
Melioidosis
Rat-bite fever, Haverhill fever *(Streptobacillus moniliformis)*
Relapsing fever (borreliosis)
Infective endocarditis
Malaria
Babesiosis
Visceral leishmaniasis
West African trypanosomiasis
Tuberculosis
Endemic mycoses (histoplasmosis)

A number of *Bartonella* species can cause infections characterized by recurrent or prolonged fever. *Bartonella bacilliformis* is the cause of Carrión disease and is transmitted by sand flies in focal areas of Peru, Colombia, and Ecuador. During the acute illness (Oroya fever), patients present with fever and hemolytic anemia. In survivors, disease can progress to verruga peruana, a chronic illness characterized by vascular, proliferative, nodular skin lesions. In addition, *Bartonella quintana* is the cause of trench fever, a relapsing febrile illness transmitted by body lice. Trench fever usually affects individuals who are displaced or severely impoverished; onset is usually acute with high fever, headache, and retro-orbital pain, bone pain of the shins, and myalgia. Each episode of fever may last for 2 to 4 days, with relapses after 4 to 6 days. Prolonged bacteremia can be detected in 20% to 30% of patients.[167] Relapsing fever can also be caused by a number of *Borrelia* species and can be either louse-borne or tick-borne. Louse-borne relapsing fever is a human-restricted infection caused by *Borrelia recurrentis* and is associated with human body lice. Most cases of louse-borne relapsing fever are reported in Africa. Tick-borne relapsing fever has been reported in Asia, Africa, and the Americas. Relapsing fevers are characterized by relapsing and recurrent episodes of fever associated with spirochetemia. Diagnosis usually rests on detection of *Borrelia* on a thick blood smear with microscopy, although polymerase chain reaction (PCR)–based diagnosis is available. Untreated, louse-borne relapsing fever is associated with a high mortality rate. Fever may be prolonged, with many recurrences over several months.[168]

An enteric fever–like syndrome with abdominal pain may also be caused by a number of enteric pathogens, including *Yersinia enterocolitica, Yersinia pseudotuberculosis,* and *Campylobacter fetus* and *Campylobacter jejuni.* Individuals with these infections may present with a prolonged febrile illness, headache, and abdominal pain. Individuals with *Y. enterocolitica* or *Y. pseudotuberculosis* may have acute diarrhea as a major manifestation.[169,170] Most important, the prolonged enteric fever–like syndromes caused by these agents tend to occur in individuals with significant underlying disease, especially cirrhosis and iron-overloaded states.[169] Diagnosis is usually based on microbiologic culturing of blood.

Additional Causes of Prolonged or Persistent Fever

Most acute febrile illnesses resolve within 3 to 7 days. Individuals with typhoid or enteric fever may have fever that lasts for 1 to 4 weeks before resolution if left untreated. Clinicians assessing individuals with fever that lasts longer than 7 to 10 days need to consider a wide differential, both for infectious and noninfectious processes (see Chapter 56). Noninfectious causes that also need to be considered include lymphoma, malignancy, drug fever, Addison disease, and inflammatory conditions and connective tissue disorders. As described earlier, prolonged fever may also be associated with malaria, brucellosis, yersiniosis, tularemia, Q fever, melioidosis, endocarditis, tuberculosis, and endemic mycoses such as histoplasmosis. Recurrent or relapsing fever may be associated with trench fever and relapsing fever. Clinicians caring for individuals with prolonged fever in resource-limited or tropical areas or caring for individuals who have traveled to such regions need to consider these and other diagnoses. For instance, individuals with babesiosis, caused by an intraerythrocyte protozoal parasite transmitted by ticks, may also present with a nonspecific and prolonged febrile syndrome. Microscopy can confirm the diagnosis. Chronic and relapsing fever are also part of visceral leishmaniasis, a protozoal parasitic infection of the reticuloendothelial system. Individuals with visceral leishmaniasis often present with prolonged and ongoing fever, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia, and absence of eosinophilia. Serologic tests and direct parasitic detection are usually used to confirm the diagnosis. Individuals with human African trypanosomiasis (sleeping sickness) can present with chronic and recurrent fever, weight loss, and lymphadenopathy before neurologic manifestations occur. Serologic tests and direct parasitic detection are usually used to confirm the diagnosis. Prolonged fever can also be associated with a number of viral syndromes, including Epstein-Barr virus (mononucleosis), characterized by prolonged fever, headache, weakness, and fatigue and may include pharyngitis, hepatosplenomegaly, and lymphadenopathy. Serologic assays are available.

Assessing an Individual With an Acute Febrile Illness in a Resource-Limited Area or After International Travel

Most individuals with typhoid or paratyphoid present with an acute febrile illness, and typhoid and paratyphoid fever are common causes of bacteremia in many resource-limited areas of the world. Most cases of typhoid fever reported in North America and Europe are related to international travel, predominantly to South Asia,[16] and affected patients usually develop fever within 1 to 3 weeks of exposure or returning from travel. Because vaccines are 50% to 80% protective and do not protect against *Salmonella* Paratyphi A, previous immunization does not preclude the possibility of enteric fever, and previous immunization can lead to cross-reactive serologic assays. Diagnosis can be confirmed by identifying *Salmonella* Typhi or *Salmonella* Paratyphi in blood cultures, but this assay is only 30% to 70% sensitive.[27] Accordingly, the clinical approach to an individual with possible typhoid fever after travel is usually based on excluding other possible entities and initiation of empirical treatment. Leading other causes of acute febrile illness in individuals at risk of typhoid include urinary, reproductive tract, and respiratory or intestinal tract infections that can be evaluated with standard approaches. Of importance, the differential diagnosis also needs to include influenza, dengue, chikungunya, Zika, leptospirosis, rickettsiosis, bartonellosis, and malaria, among others. An incubation period of less than a week before onset of fever would be most consistent with a viral cause, such as influenza or dengue. International travelers are at particular risk of influenza, and the transmission season in the Southern Hemisphere is March through September, with year-round transmission as one approaches the equator. Most individuals with influenza will have respiratory symptoms. Most individuals with dengue will present within 3 to 7 days of returning from travel to Asia or the Caribbean. Thrombocytopenia and evidence of capillary fragility, such as a positive tourniquet test, would be supportive of consideration of dengue fever (see Chapter 153). The diagnosis can be confirmed through serology or PCR. Leptospirosis is caused by exposure to animal urine, and exposure usually occurs from contaminated freshwater sources. The febrile illness can be biphasic, with conjunctival suffusion, hematuria, proteinuria, renal dysfunction, and hepatitis suggestive of the diagnosis (see Chapter 239). Rapid microscopic examination of peripheral blood should assist with establishing whether a patient may have malaria or borreliosis (see Chapter 240). A careful examination of skin for evidence of eschars or spotted rashes can assist in establishing whether the patient may have a rickettsiosis (see Chapter 186). Microbiologic culturing of blood will assist in confirming infection with a number of bacterial pathogens, including *Salmonella.*

Fever and Mesenteric Adenitis or Ileocecitis

Individuals with mesenteric adenitis or ileocecitis often present with a history of fever and abdominal pain, often localizing to the right lower quadrant. The illness needs to be differentiated from appendicitis, intraabdominal abscess formation, and diverticulitis (Table 100.7).[171] Mesenteric adenitis can be seen with *Y. enterocolitica* and *Y. pseudotuberculosis*; *Y. enterocolitica* can also cause enterocolitis and terminal ileitis. These infections are more commonly reported from Europe than the United States.[172] Fever, abdominal pain, vomiting, and diarrhea are frequent.[173] Fever can be prolonged. Ingestion of undercooked or uncooked pork and pork-related products, such as the small intestine of pigs (chitterlings), are particular risk factors.[174] Septicemia can complicate intestinal yersiniosis, especially in individuals with iron-overloaded states, immune deficiencies, cirrhosis, and alcoholism. Mesenteric adenitis can also be caused by tuberculosis, and *Mycobacterium avium* complex infection in individuals with AIDS, especially in individuals who are becoming immune reconstituted.[175] Children with HIV in Southeast Asia may present with mesenteric adenitis caused by *Talaromyces (Penicillium) marneffei.*[176] Epstein-Barr virus, parvovirus B19, and adenovirus infection may also be associated with mesenteric adenitis.[177,178]

Individuals with ileocecitis may present with fever and abdominal pain, often localizing to the right lower quadrant, potentially with signs of bowel obstruction. Noninfectious causes include Crohn disease and

ulcerative colitis. Infectious causes of ileocecitis include appendicitis, diverticular abscess formation, intestinal yersiniosis, tuberculosis, histoplasmosis, and amebiasis complicated by an inflammatory mass (an ameboma), intestinal schistosomiasis complicated by an inflammatory mass (a bilharzioma), an intestinal actinomycetoma that may include drainage fistula tracks, and intestinal angiostrongyliasis (see "Fever, Abdominal Pain, and Peripheral Eosinophilia").

Fever, Abdominal Pain, and Peripheral Eosinophilia

Individuals will sometimes present with fever, abdominal pain, and peripheral eosinophilia (>400 total eosinophils/mm^3 peripheral blood), a clinical syndrome that may be indistinguishable from enteric fever until the white blood cell count differential is available. The differential diagnosis for these individuals includes a number of entities (see Table 100.7). Fascioliasis caused by the liver fluke *Fasciola hepatica* may manifest as severe, right upper quadrant pain and high-level peripheral eosinophilia and fever. Individuals are often diagnosed incorrectly as having a pyogenic hepatic abscess and drug reaction. *F. hepatica* is transmitted to humans through ingestion of aquatic plants such as fresh watercress. During the initial phase of infection, the flukes can migrate through hepatic parenchyma, causing severe right upper quadrant pain. Imaging studies often disclose migratory hepatic lesions. After a few weeks, the worms localize to the biliary system, and the abdominal symptoms resolve. Peripheral eosinophilia can be very high during the initial stages of infection (>1000–3000 eosinophils/mm^3 of blood), when the parasites are migrating through tissue. Diagnosis is usually based on clinical recognition. Serologic assays are available.

Visceral larva migrans (VLM) may also manifest with abdominal pain, fever, eosinophilia, and hepatosplenomegaly. VLM can be caused by a number of migratory worms, most commonly the dog or cat ascarids *Toxocara canis* and *Toxocara cati,* respectively. VLM is usually an illness of very young children, 2 to 4 years of age. Diagnosis is usually based on clinical recognition. Serologic assays are available. Individuals with trichinosis can also present with fever, eosinophilia, abdominal pain, edema, and myositis. Diagnosis is usually based on clinical recognition. Serologic assays are available. Individuals with intestinal angiostrongyliasis, caused by *Angiostrongylus costaricensis,* can also present with abdominal pain and eosinophilia. Affected individuals are usually children with right lower quadrant pain, ileocecitis, or presumed appendicitis. The disease is present in areas of Latin America. A wide range of other helminthic infections can be associated with abdominal issues, intestinal irregularities, and peripheral eosinophilia, including intestinal strongyloidiasis, hookworm, trichinellosis, and schistosomiasis. Sarcocystosis and isosporiasis can also cause abdominal irregularities and peripheral eosinophilia. Individuals with gastrointestinal involvement during Churg-Strauss eosinophilic angiitis can also present with abdominal pain and eosinophilia.

TABLE 100.7 Other Causes of Fever and Intestinal Syndromes

Causes of Mesenteric Adenitis and Ileocecitis/Ileal Inflammatory Mass

Infectious

Appendicular abscess
Diverticular abscess
Yersiniosis
Salmonellosis
Mycobacterial infection
Mycoses (histoplasmosis, penicilliosis)
Amebiasis (ameboma): ileocecitis
Schistosomiasis (bilharzioma): ileocecitis
Actinomycetoma

Noninfectious

Crohn disease
Ulcerative colitis

Causes of Fever, Abdominal Pain or Intestinal Irregularities, and Peripheral Eosinophilia

Infectious

Fascioliasis *(Fasciola hepatica)*
Visceral larva migrans *(Toxocara canis, Toxocara cati)*
Angiostrongyliasis *(Angiostrongylus costaricensis)*
Schistosomiasis
Strongyloidiasis
Hookworm infection
Trichinellosis
Sarcocystosis
Isosporiasis

Noninfectious

Churg-Strauss eosinophilic angiitis
Eosinophilic enteropathy
Food allergy (e.g., gluten-sensitive enteropathy)

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The complete reference list is available online at Expert Consult.

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101 Foodborne Disease

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SHORT VIEW SUMMARY

Definition
- Foodborne diseases are illnesses that are acquired through ingestion of food contaminated with pathogenic microorganisms, bacterial and nonbacterial toxins, or other substances.

Epidemiology
- An estimated 48 million foodborne illnesses caused by pathogens or their toxins are acquired annually in the United States.
- Many agents that cause foodborne infection can also be acquired in other ways including ingestion of contaminated drinking or recreational water, through contact with animals or their environment, and from one person to another directly or through fomites.
- Some foodborne diseases can lead to long-term sequelae such as impaired kidney function after Shiga toxin–producing *Escherichia coli* infection, Guillain-Barré syndrome after *Campylobacter* infection, and reactive arthritis and irritable bowel syndrome after a variety of infections.
- Groups at higher risk of acquiring or experiencing more severe foodborne disease include infants, young children, pregnant women, older adults, and immunocompromised patients.
- A foodborne disease outbreak should be considered when an acute illness, especially with gastrointestinal or neurologic manifestations, affects two or more people who shared a meal or ate at the same location. However, most foodborne illnesses do not occur in the context of an outbreak.

Microbiology
- Many pathogens including bacteria, viruses, and parasites can cause foodborne disease.
- Some illnesses are caused by ingestion of chemicals (e.g., heavy metals, mushroom toxins) or preformed microbial toxins (e.g., staphylococcal toxin, botulinum toxin).

Diagnosis
- Detection of pathogens has traditionally relied on isolating bacterial pathogens in culture, visualizing parasites by microscopy, and enzyme-linked immunosorbent assays.
- Newer molecular tests present opportunities and challenges to both clinical practice and public health surveillance.
- Many intoxications must be diagnosed based on clinical suspicion alone.

Therapy
- Therapy for most foodborne diseases is supportive; replacing fluid and electrolyte losses is the most important factor in all diarrheal illnesses.
- Antimicrobial agents are used to treat parasitic infections and selected bacterial infections.
- Resistance to antimicrobial agents complicates treatment and can increase the likelihood of clinically apparent infection.

Prevention
- Individuals can reduce their risk of illness by adhering to safe food-handling practices.
- Outbreak investigation is important to identify safety gaps that may be present anywhere in the food production chain, from the farm to the table.
- Clinicians and public health practitioners can reduce risk of secondary transmission by counseling patients on prevention strategies and excluding certain patients from work, school, or daycare until transmission risk is reduced.

Foodborne diseases result from ingestion of a wide variety of foods contaminated with pathogenic microorganisms, microbial toxins, and chemicals. Many diseases transmitted commonly through food can be acquired via other routes of transmission as well. For sporadic cases (i.e., cases that are not part of recognized outbreaks), the route of transmission is generally unknown. Although most foodborne illnesses are sporadic, investigation of outbreaks is an important way to identify the types of foods and contaminants associated with foodborne illness. The major source of information for this chapter comes from foodborne disease surveillance and outbreak investigations in the United States, and the major focus is on US illnesses. During the years 2009–15, 5760 outbreaks of foodborne disease resulting in 100,939 illnesses, 5699 hospitalizations, and 145 deaths were reported to the US Centers for Disease Control and Prevention (CDC) (Table 101.1).[1] However, these figures, restricted to outbreak cases, greatly underestimate the magnitude of the problem. The actual number of foodborne illnesses in the United States is unknown but has been estimated to be approximately 48 million cases, with 128,000 hospitalizations and 3000 deaths each year (Table 101.2).[2,3] The annual cost incurred from these illnesses has been estimated to be between $51.0 billion and $77.7 billion.[4] Thus foodborne diseases are common, can be severe, and lead to considerable economic burden.

Since 1996, in several sites that now comprise approximately 15% of the US population, the CDC Foodborne Diseases Active Surveillance Network has conducted active surveillance for nine enteric pathogens transmitted commonly through food. Compared with 2013–2015, the 2016 incidence of infection with laboratory-confirmed Shiga toxin–producing *Escherichia coli* (STEC), *Yersinia*, and *Cryptosporidium* increased.[5] Interpretation of changes in incidence is complicated by changes in diagnostic tests, particularly the increased availability, use, and sensitivity of culture-independent diagnostic tests (CIDTs) and the challenges of synthesizing surveillance data from different types of laboratory tests.

The spectrum of foodborne diseases has expanded in recent decades in many ways. Noroviruses are now recognized as the most frequent cause of foodborne illness in the United States.[2] Known agents continue to be newly recognized as causes of foodborne disease such as enteroaggregative *E. coli* (EAEC)[6,7] including novel strains that produce Shiga toxin[8]; *Cronobacter* (formerly *Enterobacter*) *sakazakii*[9]; and, in South America, *Trypanosoma cruzi*, causing Chagas disease.[10] Previously uncommonly recognized food vehicles such as fresh produce and flour have become important sources.[11,12] Some pathogens have become increasingly resistant to antimicrobial drugs.[13,14]

Centralization of the food supply in the United States has increased the risk for nationwide outbreaks.[15,16] The global food trade, which is growing faster than increases in food production, forms a complex network that facilitates spread of contaminated foods throughout the world and can delay identification of the source of contamination causing outbreaks.[17]

CLINICAL MANIFESTATIONS AND PATHOGENESIS

Foodborne disease can appear as an isolated sporadic case or, less frequently, as an outbreak of illness affecting a group of people after a

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

TABLE 101.1 Mean Annual Foodborne Disease Outbreaks and Outbreak-Associated Illnesses and Hospitalizations by Etiology (Confirmed and Suspected) —Foodborne Disease Outbreak Surveillance System, United States, 2009–2015

	OUTBREAKS		OUTBREAK-ASSOCIATED ILLNESSES	
ETIOLOGY	**Total**	**%**	**Total**	**%**
Bacterial				
Salmonella	136	23	3453	30
STEC	29	5	352	3
Campylobacter	29	5	330	3
Clostridium perfringens	28	5	1119	10
Staphylococcus aureus enterotoxin	11	2	240	2
Bacillus cereus	9	2	120	1
Vibrio parahaemolyticus	7	1	40	0
Shigella	6	1	175	1
Listeria monocytogenes	5	1	55	0
Clostridium botulinum	3	1	13	0
ETEC	1	0	65	1
Staphylococcus spp.	1	0	8	0
Yersinia enterocolitica	1	0	3	0
Vibrio cholerae	0	0	2	0
Streptococcus group A	0	0	16	0
EAEC	0	0	7	0
Other *Vibrio* spp.	0	0	1	0
Vibrio vulnificus	0	0	0	0
Aeromonas hydrophila	0	0	1	0
Coxiella burnetii	0	0	1	0
Francisella novicida	0	0	0	0
Brucella spp.	0	0	1	0
Other *Clostridium* spp.	0	0	2	0
EPEC	0	0	4	0
Enterococcus faecalis	0	0	2	0
Other bacteria	5	1	67	1
Subtotal	272	46	6078	52
Chemicals and Toxins				
Scombroid toxin/histamine	14	2	43	0
Ciguatoxin	13	2	48	0
Mycotoxins	2	0	6	0
Puffer fish tetrodotoxin	0	0	1	0
Paralytic shellfish poison	0	0	2	0
Pesticides	0	0	6	0
Amnesic shellfish poison	0	0	0	0
Other chemicals	6	1	40	0
Subtotal	37	6	146	1
Parasitic				
Cryptosporidium	2	0	26	0
Trichinella	1	0	5	0
Cyclospora	1	0	62	1
Giardia	0	0	2	0
Subtotal	5	1	94	1

Continued

TABLE 101.1 Mean Annual Foodborne Disease Outbreaks and Outbreak-Associated Illnesses and Hospitalizations by Etiology (Confirmed and Suspected)[a]—Foodborne Disease Outbreak Surveillance System, United States, 2009–2015—cont'd

	OUTBREAKS		OUTBREAK-ASSOCIATED ILLNESSES	
ETIOLOGY	**Total**	**%**	**Total**	**%**
Viral				
Norovirus	267	46	5291	45
Hepatitis A	2	0	37	0
Sapovirus	1	0	19	0
Rotavirus	0	0	12	0
Astrovirus	0	0	3	0
Other	0	0	4	0
Subtotal	271	46	5366	46
Single, Multiple, and Unknown Etiologies				
Single etiology[b]	585	71	11,684	81
Multiple etiologies[c]	12	1	285	2
Unknown etiology[d]	226	27	2451	17
TOTAL	823	100	14,420	100

[a]Guidelines for reporting agencies are to consider an etiology confirmed if it meets confirmation criteria (https://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/confirming_diagnosis.html); otherwise, it is considered suspected. If more than one etiology is reported and at least two etiologies are confirmed, the outbreak is considered a confirmed multiple-etiology outbreak; otherwise, it is considered suspected. Agents that are not listed in confirmation criteria or that are not known to cause illness are sometimes reported as confirmed or suspected etiologies.
[b]The denominator for the etiology percentages is the single etiology total. The denominator for the single etiology, multiple etiologies, and unknown etiology categories is the total. Because of rounding, numbers may not add up to the single etiology total or the total.
[c]If at least two etiologies are confirmed in an outbreak, it is considered a confirmed multiple etiology outbreak; otherwise, it is considered a suspected multiple etiology outbreak.
[d]An etiologic agent was not confirmed or suspected based on clinical, laboratory, or epidemiologic information.
EAEC, Enteroaggregative *Escherichia coli;* EPEC, enteropathogenic *E. coli;* ETEC, enterotoxigenic *E. coli;* STEC, Shiga toxin–producing *E. coli.*
Modified from Dewey-Mattia D, Manikonda K, Hall AJ, et al. Surveillance for Foodborne Disease Outbreaks—United States, 2009-2015. MMWR Surveill Summ. *2018;67:1–11.*

common food exposure. A foodborne disease outbreak should be considered when an acute illness, especially one with gastrointestinal or neurologic manifestations, affects two or more people who shared a common meal. The following section divides acute foodborne diseases into a variety of syndromes based on acute signs and symptoms and typical time of onset after consumption of contaminated food. Agents most likely responsible for each syndrome are described. The incubation period in an individual illness is usually unknown, but it is often apparent in the context of the outbreak setting.

Foodborne Syndromes Caused by Microbial Agents or Their Toxins

Nausea and Vomiting Lasting Less Than 24 Hours

The major etiologic considerations are *Staphylococcus aureus* and *Bacillus cereus* (see Chapters 194 and 208). These diseases are caused by preformed enterotoxins and have a short incubation period of 1 to 8 hours. Another clue to the cause of staphylococcal and emetic *B. cereus* illnesses is that their duration is typically less than 24 hours[18,19] and often less than 12 hours.[20,21] Staphylococcal food poisoning is characterized by vomiting (87% of cases), diarrhea (89%), and abdominal cramps (72%); fever is uncommon (9%).[22] Staphylococci responsible for food poisoning produce one or more serologically distinct enterotoxins (SEA through SEV, excluding SEF), but not all cause vomiting.[18] All of these toxins are highly heat resistant and withstand ordinary cooking. They are very resistant to proteolytic enzymes and therefore pass through the stomach intact. Strains producing SEA alone account for most reported outbreaks of staphylococcal food poisoning in the United States.[20,23] In studies of rhesus monkeys, a smaller dose of SEA compared with doses of SEB, SEC, and SED was required to produce emesis.[24] The mechanisms by which enterotoxins lead to emesis may involve vagus nerve stimulation.[18]

Rarely, other enterotoxigenic coagulase-positive staphylococcal species have been implicated in outbreaks.[18] Although enterotoxigenic coagulase-negative staphylococci exist, very few reports have associated these strains with foodborne disease outbreaks.[25,26]

B. cereus strains can cause two types of food poisoning syndromes, one with an incubation period of 0.5 to 6 hours (short-incubation emetic syndrome) and a second with an incubation period of 8 to 16 hours (long-incubation diarrheal syndrome).[19] The emetic syndrome is characterized by vomiting (100% of cases), abdominal cramps (100%), and, less frequently, diarrhea (33%).[19,21] The emetic toxin is cereulide, a peptide resistant to heat and proteolysis; it is stable at pH 2 to 11. Cereulide stimulates the vagus afferent nerve by binding to the 5-hydroxytryptamine-3 receptor.[27] Rarely, fulminant liver failure may develop via impairment of fatty acid oxidation caused by the toxicity of cereulide to mitochondria.[19]

Norovirus illness is characterized by acute onset of vomiting, nonbloody diarrhea, or both, accompanied by nausea and abdominal pain. Fever occurs in about 40% of patients, is usually low grade, and lasts for less than 24 hours. Symptoms usually resolve in 2 to 3 days, but 12% of patients require medical care, and 1.5% are hospitalized for rehydration.[28,29] Noroviruses are the most common foodborne pathogens (see Chapter 176). They were estimated to cause 5.5 million foodborne illnesses per year in the United States in 2006.[2] Even more cases of acute gastroenteritis are caused by nonfoodborne transmission of noroviruses, directly from one person to another or by fomite contamination.[30] The median incubation period reported in foodborne norovirus outbreaks is 33 hours.[28] A group of related viruses in the Caliciviridae family, most notably the sapoviruses (see Chapter 176), can cause similar illness.[31]

Watery Diarrhea Without Fever Lasting 1 to 2 Days

The major etiologic considerations for this enterotoxin-mediated syndrome are *Clostridium perfringens* type A and *B. cereus.* In *C. perfringens* type A food poisoning the most common symptoms are diarrhea (91%) and abdominal cramps (73%); only 14% of patients

TABLE 101.2 Estimated Annual Number of Illnesses Caused by Pathogens That Can Be Transmitted Through Food in the United States

DISEASE OR AGENT	TOTAL NO. OF ILLNESSES	TOTAL NO. OF DOMESTICALLY ACQUIRED FOODBORNE ILLNESSES	PERCENT HOSPITALIZED	PERCENT DIED
Bacterial				
Bacillus cereus	—[a]	63,400	0.4	0
Brucella spp.	2003	839	55	0.9
Campylobacter spp.	1,322,137	845,024	17.1	0.1
Clostridium botulinum	—[a]	55	82.6	17.3
Clostridium perfringens	—[a]	965,958	0.6	<0.1
STEC O157	96,534	63,153	46.2	0.5
STEC non-O157	168,698	112,752	12.8	0.3
ETEC	—[a]	17,894	0.8	0
Other diarrheogenic *Escherichia coli*	39,871	11,982	0.8	0
Listeria monocytogenes	1662	1607	94.0	15.9
Mycobacterium bovis	208	60	55	4.7
Nontyphoidal *Salmonella*	1,229,007	1,027,561	27.2	0.5
Salmonella serotype Typhi	5752	1821	75.7	0
Shigella spp.	494,908	131,254	20.2	0.1
Staphylococcus aureus	—[a]	241,148	6.4	<0.1
Streptococcus spp.	—[a]	11,217	0.2	0
Toxigenic *Vibrio cholerae*	277	84	43.1	0
Vibrio parahaemolyticus	44,950	34,664	22.5	0.9
Vibrio vulnificus	207	96	91.3	34.8
Other *Vibrio* spp.	34,585	17,564	37.1	3.7
Yersinia enterocolitica	116,716	97,656	34.4	2.0
Parasitic				
Cryptosporidium parvum	748,123	57,616	25.0	0.3
Cyclospora cayetanensis	19,808	11,407	6.5	0
Giardia intestinalis	1,221,564	76,840	8.8	0.1
Toxoplasma gondii	173,995	86,686	2.6	0.2
Trichinella spp.	132	156	24.3	0.2
Viral				
Astrovirus	3,090,384	15,433	0.4	<0.1
Hepatitis A	35,769	1566	31.5	2.4
Norovirus	20,865,958	5,461,731	0.03	<0.1
Rotavirus	3,090,384	15,433	1.7	<0.1
Sapovirus	3,090,384	15,433	0.4	<0.1
SUBTOTAL	37,220,098	9,388,075		
Unspecified Agents[b]		38,400,000	0.2	<0.1
TOTAL		47,788,075		

[a]Recent estimates are not available.
[b]Includes known agents with insufficient data to estimate agent-specific illness, known agents not yet recognized as causing foodborne illness, substances known to be in food but of unproven pathogenicity, and unknown agents.
ETEC, Enterotoxigenic *Escherichia coli; STEC,* Shiga toxin–producing *E. coli*.
Modified from Scallan E, Griffin PM, Angulo FJ, et al. Foodborne illness acquired in the United States—unspecified agents. Emerg Infect Dis. *2011;17:16–22; and Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens.* Emerg Infect Dis. *2011;17:7–15.*

experience vomiting, and only 5% report fever.[22,32] In contrast to staphylococcal food poisoning and emetic *B. cereus* disease, which are caused by preformed enterotoxins, *C. perfringens* (see Chapter 246) food poisoning is caused by toxins produced in vivo, accounting for a longer incubation period of 9 to 12 hours.[22] *C. perfringens* can produce at least 11 toxins in addition to *C. perfringens* enterotoxin (CPE). Toxinotype A strains always produce α toxin, and strains that result in gastrointestinal illness also express CPE, which is produced as the ingested vegetative cells sporulate within the intestine.[33] The toxin binds to the apical membrane of epithelial tight junctions in the small intestines, triggering formation of pores through which influx and efflux of water, ions, and other small molecules may lead to diarrhea and cytotoxicity.[34]

B. cereus strains that cause a similar long-incubation syndrome including diarrhea (96%), abdominal cramps (75%), sometimes vomiting (33%), and rarely fever[21] elaborate either separately or together two three-component enterotoxins (hemolysin BL and nonhemolytic enterotoxin). A single-protein enterotoxin (CytK) has also been described.[19,27] *B. cereus* diarrheal toxins can be detected in foods, but it has been postulated that the disease is also caused by ingested vegetative cells that produce enterotoxin within the host's intestinal tract. It is possible that both modes of infectivity coexist.

Although these illnesses last longer than staphylococcal and emetic *B. cereus* food poisoning, symptoms usually resolve within 24 to 48 hours.[19,35] However, some *B. cereus* illnesses last several days,[27,36] and in one outbreak attributed to *B. cereus*, some patients had bloody diarrhea, and three died.[37] In an outbreak of *C. perfringens* type A infections, severe necrotizing colitis developed in patients with a history of chronic, likely medication-induced, constipation.[38] A foodborne infection, fatal in about 20% of patients, is caused by *C. perfringens* type C in people with low protein intake; the disease is rare outside of Papua New Guinea, where it is sometimes called pigbel.[35,39]

Watery Diarrhea and Abdominal Cramps Lasting More Than 2 Days

The major etiologic considerations for this syndrome are enterotoxigenic strains of *E. coli* (ETEC) and *Vibrio parahaemolyticus*. Enterotoxins expressed in vivo are responsible for illness caused by ETEC[40] and by cholera toxin–producing strains of *Vibrio cholerae*.[41] Diarrhea caused by ETEC lasts a median of 6 days, often accompanied by abdominal cramping for the full duration of illness.[42] In one ETEC outbreak, uncommon symptoms included vomiting (13% of cases) and fever (19%).[42]

In the United States, many *Vibrio* spp. including *V. cholerae* cause a diarrheal syndrome; outbreaks are uncommon, but cases are reported every year.[43] The virulence factors of *V. parahaemolyticus* include both secreted toxins and effector proteins delivered directly into the cytoplasm of the host cell via type III secretion systems.[44] The median duration of diarrhea caused by *V. parahaemolyticus* is 6 days; most patients have abdominal cramping (89%), half have vomiting or fever, and 29% have bloody diarrhea.[45] Epidemic cholera, caused by cholera toxin–producing strains of *V. cholerae* O1 and O139, manifests as a profuse, watery diarrhea accompanied by muscular cramps. *V. cholerae* O141 and O75 can also produce cholera toxin and cause a similar syndrome (see Chapter 215).[46]

Diarrhea, Abdominal Cramps, and Fever

The major etiologic considerations for this syndrome are nontyphoidal *Salmonella, Shigella,* and *Vibrio* spp., especially *V. parahaemolyticus* (see Chapters 214, 215, 223, and 224).[45,47–50] *Campylobacter jejuni,* STEC, and *Yersinia enterocolitica* should also be considered and typically have a longer incubation period; also, fever is less common with STEC (see Chapters 98, 216, and 229A). Norovirus does not consistently cause fever but should be considered. These pathogens, with the exception of norovirus, can cause an inflammatory diarrhea, some by invading the intestinal epithelium and some by damaging it via secreted cytotoxins.[44,51] Bloody diarrhea and vomiting may occur in varying proportions. These illnesses usually resolve within 2 to 7 days.[47]

Nontyphoidal *Salmonella* is the most common bacterial cause of foodborne illnesses and outbreaks in the United States.[2,52] The median incubation period is 6 to 48 hours. However, *C. jejuni,* with a typical incubation period of 2 to 4 days, is the most common bacterial cause of gastroenteritis including both foodborne and nonfoodborne routes of transmission.[2]

Infrequent outbreaks of diarrhea with fever caused by *Listeria monocytogenes* (see Chapter 206) have been reported among previously healthy people.[53–55] This syndrome is characterized by frequent watery diarrhea, fever, abdominal cramps, headache, and myalgias, with a median incubation period of 20 to 31 hours.

Although febrile diarrhea is the most common presentation of *Y. enterocolitica* (see Chapter 229B) infection in young children,[56–58] in older children and adults the illness may manifest as either a diarrheal illness or without diarrhea as a pseudoappendicular syndrome; as ileocecitis, consisting of abdominal pain (resembling that of appendicitis); fever; leukocytosis; and, in some patients, nausea and vomiting.[59] Joint pain (see "Postinfection Syndromes"), beginning about 1 week after onset of diarrhea, is more common in adults.[59] Sore throat and rash can affect patients of all ages. The median duration of diarrhea is 2 weeks, but other symptoms may last longer.[60] *Campylobacter* and *Salmonella* can also cause an ileocecitis that mimics appendicitis.

Bloody Diarrhea With Minimal Fever

The distinctive syndrome of hemorrhagic colitis has been linked to STEC, most often serogroup O157 (see Chapter 224).[61] These strains produce one or both types of Shiga toxins (Shiga toxin 1 or 2). Shiga toxins, also referred to as verotoxins, are cytotoxins that damage vascular endothelial cells in target organs such as the gut and kidney.[62] Strains that produce Shiga toxin 2 are more virulent than strains that produce both Shiga toxin 1 and 2.[63] To cause disease, STEC must also possess additional virulence factors including factors that lead to adherence to the intestinal epithelium.[62] The illness is characterized by severe abdominal cramping and diarrhea, which is initially watery but may quickly become grossly bloody.[61,64] About one-third of patients report a short-lived low-grade fever that typically resolves before seeking medical attention.[61,65] Most patients fully recover within 7 days.[61] However, overall 6% (15% in children <5 years of age) of patients develop hemolytic-uremic syndrome (HUS), which is typically diagnosed about 1 week after the beginning of the diarrheal illness, when the diarrhea is resolving.[66] The fatality rate for HUS is 3% in children younger than 5 years of age and 33% in adults 60 years of age or older. For most age groups, deaths in patients without HUS are rare, but 2% of adults 60 years old or older with only hemorrhagic colitis die.[66] Non-O157 STEC are diverse in their virulence properties, causing illness ranging from uncomplicated watery diarrhea to hemorrhagic colitis and HUS. Outbreaks reported in the United States have involved serogroups O26, O103, O111, O121, O145, and O104 (serotype O104:H21, but not O104:H4).[67]

Persistent Diarrhea Lasting 2 or More Weeks

Parasites including *Cryptosporidium, Giardia,* and *Cyclospora* are the most common causes of persistent (lasting ≥14 days) foodborne diarrhea (see Chapters 279, 282, and 283). In the mid-1990s outbreaks of cyclosporiasis linked to various types of imported fresh produce were recognized in the United States.[68] The incubation period averages about 1 week (range, about 2 days to 2 or more weeks), and the most common symptom is watery diarrhea. Other common symptoms include anorexia, weight loss, abdominal cramps, nausea, and body aches. Vomiting and low-grade fever may occur. Untreated illness can last for weeks or months, with a remitting-relapsing course and prolonged fatigue.[68]

A distinctive chronic watery diarrhea, known as Brainerd diarrhea, was first described in people who had consumed raw milk.[69] After a mean incubation period of 15 days, affected individuals developed acute watery diarrhea with marked urgency and abdominal cramping. Diarrhea persisted for more than a year in 75% of patients. Several restaurant-associated outbreaks and a cruise ship–associated outbreak of a similar illness have suggested that water also transmits the agent, which has not been identified.[70–73]

Cranial Nerve Palsies and Descending Paralysis

Botulism should be strongly suspected in anyone with acute onset of symmetrical cranial nerve palsies. In some patients, illness progresses to symmetrical descending flaccid paralysis that may result in respiratory arrest (see Chapter 245). Among patients with botulism, 98% report at least one of the following symptoms: dysphagia, blurred vision, slurred speech, double vision, and change in the sound of the voice.[74] Paralysis may coincide with or be preceded by nausea in 42%, vomiting in 33%, and diarrhea in 16%.[74] Botulism is usually caused by one of four immunologically distinct, heat-labile protein neurotoxins—botulinum toxins A, B, E, and rarely F.[75] The toxins irreversibly block acetylcholine release at the neuromuscular junction. Nerve endings regenerate slowly, so recovery typically takes weeks to months[75] but is longer for some patients.[76] Foodborne botulism results from ingestion of preformed toxin. The syndromes of infant botulism and adult intestinal colonization result from ingestion of spores, with subsequent toxin production in vivo.[75,77] Clinical suspicion is important for correct diagnosis of botulism.[78]

Systemic Illness

Some foodborne diseases manifest mainly as invasive infections in immunocompromised patients. Invasive listeriosis typically affects pregnant women, fetuses, and individuals with compromised cellular immunity (see Chapter 206). In pregnant women, infection may be asymptomatic or manifest as a mild flulike illness; 20% of pregnancies in infected women end in miscarriage.[79] Neonatal listeriosis is acquired in utero or at birth and manifests as either early-onset sepsis during the first several days of life or as late-onset meningitis during the first several weeks after birth; the neonatal fatality rate is approximately 20% to 30%.[80] In elderly and immunocompromised persons, listeriosis causes meningitis, sepsis, and focal infections.[80] The median incubation period is 11 days, and 90% of cases occur within 28 days of exposure.[81]

Vibrio vulnificus can cause septicemia after ingestion of contaminated food, typically raw oysters (see Chapter 215). This severe syndrome, often accompanied by bullous skin lesions (Fig. 101.1), is seen almost exclusively in patients with impaired immunity, especially patients with chronic liver disease including cirrhosis, alcoholic liver disease, and hepatitis.[82] The association with liver disease may be related to portal hypertension, resulting in reduced hepatic phagocytic function, elevated serum iron levels that promote growth of *V. vulnificus,* or achlorhydria. The overall mortality rate is approximately 15% to 30% and varies by the timeliness of antibiotic administration.[43,49,83–86]

Occasionally, other *Vibrio* spp. including *V. parahaemolyticus* and strains of *V. cholerae* that do not produce cholera toxin cause septicemia.[44,87] Nontyphoidal *Salmonella* can cause bacteremia and focal infections, often in patients at the extremes of age or in patients with sickle cell anemia, inflammatory bowel disease, or an immunocompromising condition.[88] *Campylobacter* spp., particularly *Campylobacter fetus,* may cause systemic infection, especially in patients with immunocompromising conditions.[89]

Consumption of foods contaminated with *Toxoplasma gondii* oocysts excreted from cats or meats containing tissue cysts can cause different manifestations of toxoplasmosis depending on the host (see Chapter 278).[90] In healthy children and adults, up to 90% of infections are asymptomatic, but the remainder lead to nontender, nonsuppurative lymphadenopathy lasting weeks to months or chorioretinitis. Fever, malaise, night sweats, myalgias, sore throat, maculopapular rash, and hepatosplenomegaly may occur; other manifestations (e.g., disseminated disease, pneumonitis, hepatitis, encephalitis, myocarditis, and myositis) are rare. Both asymptomatic and symptomatic acute infections lead to latent infections that can reactivate into life-threatening central nervous system infections if a person later becomes immunocompromised. The manifestations of congenitally acquired toxoplasmosis include subclinical infection (which may reactivate during childhood or adulthood), a diverse array of abnormalities at birth (e.g., hydrocephalus, cerebral calcifications, chorioretinitis, thrombocytopenia, and anemia), and perinatal death.[90]

Several species of *Trichinella* roundworms cause trichinellosis in humans, who are only accidental hosts, when raw or undercooked pork or wild game meat contaminated with larvae is consumed (see Chapter 287). The signs and symptoms depend partly on number of larvae ingested and the person's immunity. Gastrointestinal symptoms such as nausea, diarrhea, vomiting, and abdominal cramps may develop 24 to 48 hours after ingestion, corresponding to the enteral phase of infection. This may be followed by a constellation of signs and symptoms including fever, myalgias, periorbital or facial edema, headache, or eosinophilia lasting up to several weeks to months, corresponding to the parenteral phase of infection.[91]

Other infectious agents and diseases with primary symptoms outside the gastrointestinal tract and neurologic system that can be transmitted by foods include (with a food vehicle example) group A β-hemolytic streptococci (cold egg-containing salads),[92] typhoid fever (raw produce exposed to human sewage or foods contaminated by asymptomatic human carriers),[93] brucellosis (goat's milk cheese), anthrax (meat), tuberculosis (raw milk), Q fever (raw milk), hepatitis A (shellfish or raw produce), various trematode infections (fish and aquatic invertebrates),[94] anisakiasis (fish), and cysticercosis (foods contaminated by *Taenia solium* eggs shed in feces of persons with pork tapeworms).

FIG. 101.1 Hemorrhagic bullae of the leg secondary to *Vibrio vulnificus* infection. *(From Millet CR, Halpern AV, Reboli A, et al. Bacterial diseases. In: Bolognia JL, Jorizzo JL, Schaffer JV, et al, eds.* Dermatology. *3rd ed. Philadelphia: Mosby; 2012:1187–1220.)*

Postinfection Syndromes

Although arthropathy has been reported after various enteric infections, most experts agree that the term *reactive arthritis* should be applied only to infections caused by *Salmonella, Yersinia, Campylobacter,* or *Shigella*.[95] Reactive arthritis can occur as part of the triad of aseptic inflammatory polyarthritis, urethritis, and conjunctivitis described by Reiter. Attack rates of reactive arthritis after salmonellosis vary from 1.2% in studies using more objective case definitions to 14% to 29% in studies using more subjective case definitions.[95] Although associations between HLA-B27 positivity and reactive arthritis have been identified, the association may exist only for patients with more severe joint or extraarticular involvement. In studies consisting of mostly mild cases, no associations with HLA-B27 were found.[95]

Worldwide, approximately 20% to 40% of Guillain-Barré syndrome cases have been attributed to recent *C. jejuni* infection (see Chapter 216).[96] When preceding diarrheal illness is reported, it typically occurs 1 to 3 weeks before the onset of neurologic symptoms.[97] In contrast to botulism, this syndrome is usually manifested by an ascending paralysis accompanied by sensory findings and abnormal nerve conduction velocity.

Several enteric pathogens including *Campylobacter*, STEC, *Salmonella, Shigella, Giardia,* and norovirus may lead to the development of postinfectious irritable bowel syndrome or other functional gastrointestinal disorders.[98,99]

Foodborne Syndromes Caused by Nonbacterial Toxins

A description of all nonbacterial toxins that can cause foodborne illness is beyond the scope of this chapter. Illness caused by natural substances found in staple fruits and vegetables, spices, medicinal herbs and oils, and mycotoxins (other than those in mushrooms) are not covered.[100] Likewise, food allergies[101] and illnesses caused by additives,[100] methylmercury,[102] or niacin are not covered.[103]

Nausea, Vomiting, and Abdominal Cramps Associated With Heavy Metal Ingestion

Heavy metals including copper, zinc, tin, and cadmium have caused foodborne outbreaks.[104–109] Latency periods for symptom onset most often range from 5 to 15 minutes after ingestion of contaminated beverages but can be longer with contaminated foods.[110] Nausea, vomiting, and abdominal cramps result from direct irritation of the gastric and intestinal mucosa and usually resolve within 2 to 3 hours if minor amounts are ingested. Progression to serious illness and death is possible if larger amounts are consumed.

Histamine Reaction After Eating Seafood

Histamine fish poisoning (scombroid poisoning) is characterized by symptoms resembling those of a histamine reaction. Symptoms typically begin within 1 hour of eating contaminated seafood. Flushing, rash, diarrhea, headache, perioral paresthesias, palpitations, sweating, pruritus, abdominal cramps, nausea, and vomiting are common. In severe cases, urticaria bronchospasm may also occur.[111] Histamine can accumulate in fish flesh that has a high concentration of histidine if postmortem spoilage occurs from inadequate refrigeration. Marine bacteria catalyze the decarboxylation of histidine to heat-stable histamine. Symptoms usually resolve within 24 hours. In contrast to seafood allergies, scombroid fish poisonings have a very high attack rate.[112]

Paresthesias After Eating Shellfish

Two types of shellfish poisoning manifest with paresthesias: paralytic (PSP) and neurotoxic (NSP). Mild PSP is characterized by paresthesias of the mouth, lips, face, and extremities. Larger intoxications progress rapidly to include headache, vomiting, diarrhea, dyspnea, dysphagia, muscle weakness or frank paralysis, ataxia, and respiratory insufficiency or failure.[111,113] The disease is caused by saxitoxins produced by certain dinoflagellates. Bivalve mollusks and some fish feed on these dinoflagellates; the toxins are concentrated in their flesh. Saxitoxin is heat stable and blocks the propagation of nerve and muscle action potentials by interfering with sodium channel permeability. Patients typically recover in hours to a few days.[98]

The features of NSP are similar to the features of PSP, although they are less severe. Reverse temperature perception may occur.[111,113] Brevetoxins produced by certain dinoflagellates are responsible. Brevetoxins cause an influx of sodium into nerve and muscle cells, leading to continuous activation causing paralysis and fatigue.[113] Symptoms typically resolve within 48 hours.[111]

Gastrointestinal, Neurologic, and Cardiovascular Symptoms After Eating Fish

Ciguatera fish poisoning (Table 101.3) is caused by ingestion of reef fish (e.g., barracuda, amberjack, grouper, and red snapper) and is commonly seen in tropical coastal regions.[114,115] Illness usually begins within 6 to 24 hours after eating the contaminated fish and is characterized by a broad array of neurologic, gastrointestinal, and cardiovascular symptoms including facial, perioral, and extremity paresthesias, hot and cold temperature sensation reversal, metallic taste, headache, dizziness, nausea, vomiting, bradycardia, and hypotension.[114] In severe cases, respiratory distress and death may occur. Gastrointestinal and

TABLE 101.3 Etiology of Foodborne Disease Outbreaks by Commonly Implicated Foods, Peak Season, and Geographic Predilection

ETIOLOGY	COMMONLY IMPLICATED FOODS	PEAK SEASON(S)	GEOGRAPHIC PREDILECTION
Bacterial			
Salmonella	Beef, poultry, eggs, dairy products, produce	Summer, fall	None
Staphylococcus aureus	Ham, poultry, salads, sandwiches, unpasteurized dairy products in some countries (e.g., France)	Summer	None
Campylobacter jejuni	Poultry, produce, unpasteurized (raw) milk and dairy products	Spring, summer	None
Clostridium botulinum	Home-canned vegetables, preserved fish, honey (infants)	Summer, fall	Type E common in Alaska
Clostridium perfringens	Beef, poultry, gravy	Fall, winter, spring	None
Shigella	Cold foods contaminated by food handler	Summer	None
Vibrio parahaemolyticus	Shellfish	Spring, summer, fall	Coastal states
Bacillus cereus	Fried rice, meats, vegetables		None
Yersinia enterocolitica	Pork, chitterlings	Winter	Unknown
Vibrio cholerae O1	Shellfish		Tropical, Gulf Coast, Latin America
Vibrio cholerae non-O1	Shellfish		Tropical, Gulf Coast
STEC	Ground beef, raw produce unpasteurized milk	Summer, fall	Northern United States
Viral			
Noroviruses	Salads, shellfish	Winter	None
Parasitic			
Toxoplasma gondii	Undercooked meat, raw shellfish, produce		None
Trichinella	Game meat, less commonly pork in United States		None
Cyclospora cayetanensis	Imported fresh produce	Spring, summer	None
Cryptosporidium	Unpasteurized apple cider	Summer	Northern United States
Giardia	Raw produce and a variety of other foods	Summer	Northern United States
Chemical			
Ciguatera	Barracuda, snapper, amberjack, grouper		Tropical reefs
Histamine fish poisoning (scombroid)	Tuna, mackerel, bonito, skipjack, mahi-mahi		Coastal areas
Shellfish poisoning	Shellfish		Coastal areas
Mushroom poisoning	Mushrooms	Spring, fall	Temperate
Heavy metals	Acidic beverages		None

STEC, Shiga toxin–producing *Escherichia coli.*

cardiovascular symptoms resolve in a few days, but neurologic symptoms can last for weeks or years.[111,116]

Ciguatoxins are lipid-soluble, heat-stable dinoflagellate toxins that open voltage-sensitive sodium channels in neuromuscular junctions. The dinoflagellates are consumed by small fish, which are then consumed by carnivorous fish where the toxins concentrate. Some dinoflagellates that produce ciguatoxins also produce maitotoxin. Although maitotoxin opens cell membrane calcium channels, its role in ciguatera is uncertain given its water-soluble nature.[111,116]

Rapid Paralysis After Eating Puffer Fish

Puffer fish poisoning, caused by tetrodotoxin, is rare outside of East Asia, but an outbreak in the United States resulted from fish transported in a suitcase. Rapid ascending paralysis occurs, and 14% of patients die.[111] Patients may be conscious while paralyzed.

Diarrhea and Chills Within 12 Hours After Eating Shellfish

Outbreaks of diarrhetic shellfish poisoning have been reported throughout the world including in the United States.[117,118] Diarrhea follows ingestion of filter-feeding bivalve mollusks such as mussels and scallops that contain okadaic acid produced by certain dinoflagellates. Symptoms, which can include diarrhea, chills, and vomiting, usually occur within a few hours and resolve within 3 days.[111,113] Outbreaks of azaspiracid shellfish poisoning, causing a similar syndrome, have been reported in Europe.[113]

Diarrhea, Abdominal Cramps, Memory Loss, and Disorientation After Eating Shellfish

Rare outbreaks of amnesic shellfish poisoning have been reported. Gastrointestinal symptoms, which typically occur within 24 hours of consumption, predominate in individuals younger than 40 years of age. Neurologic symptoms including headache, visual disturbances, cranial nerve palsies, anterograde amnesia, coma, and death, are more common in individuals older than 50 years of age and typically occur within 48 hours of consumption. The illness is caused by the toxin domoic acid, which is produced by certain dinoflagellates and concentrated in shellfish.[111,113]

Abdominal Cramps, Vomiting, and Diarrhea Followed by Hepatorenal Failure

Mushrooms containing cyclopeptides (amatoxins and phallotoxins) are responsible for greater than 90% of all deaths resulting from mushroom poisoning (Table 101.4). The most common implicated mushrooms are *Amanita phalloides* and *Amanita virosa*.[119] The illness is biphasic. Severe abdominal cramps, vomiting, and severe diarrhea manifest acutely and usually resolve within 12 to 24 hours. The patient then remains well for 12 to 24 hours. Two to 4 days after ingestion, hepatic and renal failure supervene. The mortality rate in adults is about 10% to 30%.[119,120] A similar syndrome occurs after ingestion of mushrooms containing gyromitrin. Although renal failure is not a feature, hemolysis, seizures, and coma may occur.[121]

Amanita smithiana mushrooms contain toxins that cause nausea, vomiting, and sometimes diarrhea 4 to 11 hours after ingestion; renal failure may develop 4 to 6 days after ingestion.[122] *Cortinarius* spp. containing orellanine cause nausea, vomiting, and diarrhea 6 to 48 hours after ingestion; renal injury may develop 2 days to 3 weeks after exposure.[121]

Miscellaneous Other Mushroom Poisoning Syndromes With Onset Within 2 Hours

Several syndromes may occur after ingestion of toxic mushrooms; identification of the syndromes is more important than knowing the associated species (see Table 101.4).[119,121,122] Species containing ibotenic acid and muscimol cause an illness that mimics alcohol intoxication and is characterized by confusion, restlessness, and visual disturbances, followed by lethargy; symptoms usually resolve within 12 hours. Muscarine-containing mushrooms cause parasympathetic hyperactivity (e.g., salivation, lacrimation, diaphoresis, blurred vision, abdominal cramps, diarrhea). Some patients experience miosis, bradycardia, and bronchospasm. Symptoms usually resolve within 24 hours. Species containing psilocybin cause hallucinations and behavior changes, which usually resolve within 8 hours. Mushrooms containing a disulfiram-like substance, coprine, cause headache, flushing, paresthesias, vomiting, and tachycardia if alcohol is consumed within 72 hours after ingestion. Species containing allenic norleucine cause gastrointestinal symptoms (e.g., anorexia, nausea, vomiting, diarrhea) within 30 minutes to 12 hours after ingestion. Progression to liver injury and acute renal failure typically occurs 4 to 6 days after ingestion. A variety of mushrooms can cause typically mild gastrointestinal irritation.[121]

TABLE 101.4 Mushroom Poisoning Syndromes, Commonly Implicated Mushrooms, and Associated Toxins

SYNDROME	COMMONLY IMPLICATED MUSHROOMS	TOXINS
Short Incubation		
Delirium, restlessness	*Amanita muscaria, Amanita pantherina*	Ibotenic acid, muscimol
Parasympathetic hyperactivity	*Inocybe* spp., *Clitocybe* spp., *Boletus* spp.	Muscarine
Hallucinations, somnolence, dysphoria	*Psilocybe* spp., *Panaeolus* spp., *Conocybe* spp.	Psilocybin
Disulfiram reaction	*Coprinus atramentarius*	Coprine
Gastroenteritis	Many	Various uncharacterized irritants
Long Incubation		
Gastroenteritis, hepatorenal failure	*Amanita phalloides, Amanita virosa,* and other *Amanita* spp.; *Galerina, Cortinarius,* and *Lepiota* spp.	Cyclopeptides (i.e., amatoxins, phallotoxins)
Gastroenteritis, muscle cramping, hepatic failure, hemolysis, seizures, coma	*Gyromitra* spp.	Gyromitrin
Gastroenteritis, acute renal failure (temporary)	*Amanita smithiana*	Allenic norleucine
Gastroenteritis, acute renal failure (often irreversible)	*Cortinarius* spp.	Orellanine

EPIDEMIOLOGY

Additional clues to the cause of a foodborne illness may be found when the illness occurs as part of an outbreak. Clinicians and public health officials can consider the type of food implicated and the outbreak setting in the context of typical epidemiologic characteristics associated with foodborne pathogen outbreaks (see Table 101.3).

Foods

Outbreaks of staphylococcal food poisoning are associated with foods of high protein content. In the United States, the foods most frequently implicated include ham, poultry, beef, potato and egg salads, pasta dishes, and sandwiches, which are thought to be contaminated during preparation by a food handler.[22] In the classic staphylococcal foodborne outbreak, a food handler's hand has a purulent skin lesion, but this is true in only a minority of outbreaks. In countries with high consumption of unpasteurized cheese such as France, dairy products are the most common vehicles. The udders of dairy animals, especially animals with mastitis, are one source.[123] In contrast, outbreaks of emetic *B. cereus* food poisoning are most often associated with starchy foods, especially rice, that have been cooked and held warm for extended periods, during which heat-resistant spores can germinate into vegetative cells that multiply and produce toxin.[19,27]

C. perfringens outbreaks usually occur after the ingestion of meat (especially beef and poultry) that has not been cooked or stored properly.[32]

Organisms have been isolated from raw meat, poultry, and fish. Outbreaks are more likely to occur when these items are held between 15°C (59°F) and 50°C (122°F) after cooking, allowing spores to germinate and vegetative cells to rapidly multiply.[33,35] *B. cereus* strains that cause the diarrheal syndrome are frequently associated with proteinaceous meat, dairy, and vegetable dishes.[27] One large *B. cereus* diarrheal outbreak was attributed to barbecued pork that was unrefrigerated for 18 hours after cooking[124]; another outbreak was traced to a meal delivery service in which food was held at and above room temperature for an extended period.[125]

E. coli O157 outbreaks were initially recognized mostly after consumption of undercooked ground beef, and this remains the most commonly recognized source in the United States. However, outbreak investigations have implicated a broad range of foods through laboratory, epidemiologic, and traceback evidence including leafy greens, apple cider, alfalfa sprouts, venison, salami, cookie dough, and flour.[12,126,127] Healthy cattle commonly carry *E. coli* O157 in their intestines and excrete it in manure, which may be used to fertilize fields; this organism is not commonly found in other food animals. Produce may become contaminated with *E. coli* O157 through environmental contamination by feces (from cattle or other animals such as feral swine or deer)[128,129] or by use of water in processing that has been contaminated with fecal matter. Outbreaks of non-O157 STEC infections have been associated with a range of food vehicles.

Nontyphoidal *Salmonella* is carried in the intestines of many animals including wild reptiles, amphibians, birds, and mammals as well as most food production animals. Consequently it is common in the environment and food chain, leading to potential contamination of many types of foods. Outbreaks have been associated with contaminated poultry, beef, fish, egg, dairy products, produce, juice, peanut butter, chocolate, cereals, and frozen processed foods. *Salmonella* serotype Enteritidis, common in poultry flocks, can internally contaminate shell eggs through an ovarian infection in the hen.[130] In the United States in the years 1998–2008, eggs and poultry were the predominant sources in outbreaks caused by *Salmonella* serotype Enteritidis[131]; these foods are also the dominant sources of sporadic infections of this serotype.[132,133]

Illnesses caused by *E. coli* O157:H7, other STEC, *Salmonella, Campylobacter, Brucella, Listeria,* and *Shigella* have been associated with consumption of raw milk. Despite these risks, raw milk is still legally sold in many states. From 1993 to 2006, 73 foodborne disease outbreaks caused by nonpasteurized milk or cheese were reported to the CDC, accounting for 1571 illnesses, 202 hospitalizations, and 2 deaths; 75% of these outbreaks occurred in the 21 states that permitted sale of nonpasteurized dairy products.[134]

Shigella outbreaks are most often associated with cool, moist foods consumed raw or that require handling after cooking such as lettuce-based salads, potato and egg salads, salsas, dips, and oysters.[135] The organism is carried by humans, not animals. Many foodborne *Shigella* outbreaks are associated with restaurants and are usually attributable to ill food workers.[135] Less than half of *Shigella* infections are estimated to be acquired through food; most are transmitted person to person directly or via fomites. The major food source for *Campylobacter* infection is poultry. Foodborne illness occurs from consumption of undercooked poultry and from consumption of other foods, especially produce, cross-contaminated from poultry in the kitchen or earlier in the farm-to-table continuum. Cattle also carry *Campylobacter,* and unpasteurized dairy products are a source.[136]

Listeriosis outbreaks have been traced to delicatessen meats, frankfurters, soft cheeses (e.g., queso fresco), and produce.[137] Delicatessen meats and frankfurters, which previously had caused large outbreaks of infections, have been infrequently implicated in outbreaks occurring since 2005, probably because of several regulatory initiatives.[138] In the United States, raw produce including raw sprouts (2008), precut celery in chicken salad (2010), whole cantaloupe (2011), and lettuce (2015–16) has been recognized as the source of listeriosis outbreaks.[138–141]

Vibrio outbreaks are rarely identified in the United States and have been caused by *V. parahaemolyticus,* toxigenic *V. cholerae,* and *Vibrio mimicus,* usually associated with the ingestion of shellfish.[45,50,87,142] Sporadic foodborne cases of *Vibrio* illness are also typically linked to ingestion of shellfish, especially oysters.[87] Toxigenic strains of *V. cholerae* have been acquired from domestically grown shellfish. Crabs transported in travelers' luggage have caused cholera.[143]

Y. enterocolitica infections are much less commonly diagnosed in the United States than in some European countries.[56,144,145] However, the use of CIDT syndrome panels is increasing detection. Outbreaks occur occasionally and have been associated with consumption of pork products and contaminated milk; produce has been implicated less frequently.[57,58,146–148] Fewer infections attributable to cross-contamination from the preparation of pork chitterlings in the household now appear.[57,144]

Although diarrhea caused by ETEC is usually thought to be acquired primarily through exposures encountered during travel outside developed countries or on cruise ships,[149,150] outbreaks caused by ETEC do occur in the United States and are most commonly associated with foods that require extensive handling to prepare and are often served cold such as seafood, fresh produce, herbs, or salads.[151–155] Foodborne ETEC infections are typically associated with a breech in hygiene and sanitation during food production, transport, or preparation.[156]

Clostridium botulinum spores can germinate into cells that can grow and produce toxins only in foods that provide an anaerobic environment, a pH of less than 4.5, low salt and sugar content, and a temperature of 4° to 121°C.[75] Foodborne botulism outbreaks have been associated with home-canned vegetables, fruits, fish, and alcohol made illegally in correctional institutions.[157–159] Additional vehicles have included baked potatoes, sautéed onions, and commercial chopped garlic in oil lacking a growth inhibitor.[160] Outbreaks caused by bottled carrot juice in 2006 and canned chili sauce in 2007 were the first related to commercial products in almost 20 years.[161,162] Honey is a recognized source of *C. botulinum* spores in infant botulism; therefore parents are advised to not feed honey to infants younger than 1 year old.[77]

In norovirus outbreaks, food is most often contaminated by a food handler; contamination can also occur directly with human fecal matter at the source of production such as shellfish caught in sewage-contaminated waters or produce irrigated with water contaminated by sewage.[28] Foods that require handling without subsequent cooking are typically implicated, including sandwiches, leafy vegetables, fruits, and shellfish.[28] In one large multistate outbreak, steamed shellfish from the Gulf Coast were implicated. These were probably contaminated by ill oystermen, who, lacking toilet facilities on their oyster boats, defecated and vomited directly into shallow oyster beds.[163]

Cyclospora infection results from ingestion of mature (infective) oocysts in contaminated food or water. Cyclosporiasis is endemic in various tropical and subtropical regions. Outbreaks of cyclosporiasis in the United States have been linked to multiple types of imported fresh produce including raspberries, basil, mesclun lettuce, and snow peas.[68,164] Detection of *Cyclospora* infections has increased markedly in recent years, at least partly due to improved detection.[165]

Foodborne toxoplasmosis is acquired through consumption of undercooked meat (especially pork, lamb, and game meat) that contains tissue cysts or uncooked foods (primarily fruits and vegetables, but also raw shellfish) contaminated with oocysts originating from cat feces.[166] Free-range organically raised meats, which are growing in popularity, may be more likely to be contaminated.[166] Trichinellosis caused by consumption of contaminated pork still occurs infrequently in the United States. However, largely because of improvements in swine husbandry in the past several decades as well as efforts to educate consumers on cooking pork thoroughly to kill any *Trichinella* larvae present, the most frequent source of trichinellosis cases and outbreaks in the United States has shifted from commercial pork to wild game meat, especially bear meat.[167]

Outbreaks of heavy metal poisoning are most often associated with acidic beverages such as tea, lemonade, fruit punch, and carbonated drinks that have been stored in corroded metallic containers for periods sufficient to leach the metallic ions from the container.[104–108,110]

Although histamine, or scombroid, fish poisoning is named after the Scombroidae family, which includes fish such as tuna, mackerel, bonito, and skipjack, many nonscombroid fish including, but not limited to, mahi-mahi, bluefish, and escolar can also cause histamine fish poisoning.[111,112,168,169] Ciguatera fish poisoning is associated with consumption of many different large reef-dwelling carnivorous fish including barracuda, red snapper, amberjack, and grouper caught between 35° north and

south of the equator.[111] Shellfish poisonings mostly occur after ingestion of bivalve mollusks, most often oysters, clams, mussels, and scallops.[113] However, cases of PSP in Florida have followed consumption of local puffer fish.[170]

The possibility that foodborne illness could be the result of an intentional contamination should also be considered. An outbreak of salmonellosis in Oregon in 1984 involved 751 people who ate or worked at 10 area restaurants. Epidemiologic investigation determined that illness was associated with eating from salad bars. A subsequent criminal investigation revealed that members of a religious commune had deliberately contaminated the salad bars.[171] In 1996 an outbreak of *Shigella dysenteriae* type 2 infections affecting 12 people was caused by consumption of deliberately contaminated muffins.[172] In 2003 ground beef was intentionally contaminated with nicotine at a supermarket.[173]

Nonfoodborne Transmission

The evaluation of a suspected foodborne outbreak may reveal other modes of transmission including consumption of water (drinking or recreational)[174,175] or contact with infected animals[176] or persons.[30]

Some pathogens incriminated in waterborne disease outbreaks are different from those most often responsible for foodborne disease. *Giardia* is a frequently recognized pathogen in outbreaks associated with drinking water including several large outbreaks traced to municipal water supplies.[177–179] Foodborne giardiasis outbreaks in the United States are rare and are usually caused by infected food handlers.[180] Giardiasis is characterized by diarrhea, nausea, abdominal pain, bloating, flatulence, and occasionally malabsorption. The incubation period is typically 1 to 2 weeks, and the duration of illness may be several weeks or occasionally longer. *Cryptosporidium* is the most common infectious cause of outbreaks caused by contaminated recreational water intended for swimming.[175] *Cryptosporidium* outbreaks caused by contaminated food and a massive outbreak caused by contaminated drinking water have occurred.[180,181] Norovirus spreads easily and can cause large outbreaks through contaminated food, water, and environments; most transmission occurs from person-to-person.[182–187] Other waterborne outbreaks have been caused by *E. coli* O157:H7,[188,189] *Shigella,*[190] hepatitis A,[191] *Salmonella* serotype Typhi,[192] nontyphoidal *Salmonella,*[193] ETEC,[194] *C. jejuni,*[136,195–197] *Toxoplasma,*[198] and *V. cholerae.*

Vulnerable Populations

Some people are more susceptible than others to acquiring a foodborne infection or to experiencing more severe illness.[199] Most host factors associated with increased risk are related to inadequate immune response. Immune-related factors include, but are not limited to, age younger than 5 years, age 65 years or older, primary immunodeficiencies, pregnancy, human immunodeficiency virus (HIV) infection, leukemia, immunosuppressive medications (e.g., chemotherapy, corticosteroids, agents used to treat autoimmune conditions), diabetes, and nutritional deficiencies.[199] Individuals with excessive iron stores, such as patients with cirrhosis and hemochromatosis, are more susceptible to infection with foodborne pathogens that grow more rapidly in the presence of iron.[199] The protection against foodborne infections conferred by gastric acid is reduced in persons who consume antacids (especially proton pump inhibitors), large volumes of liquid, or fatty foods.[199] The increasing average age and accompanying chronic illnesses in many countries means that more of the population has a heightened susceptibility to severe foodborne infections.

People with compromised immunity caused by HIV infection have higher reported rates of salmonellosis, campylobacteriosis, shigellosis, invasive listeriosis, and cyclosporiasis than persons not infected with HIV.[200,201] Most of these infections are more likely to be severe, recurrent, or persistent in such patients.[200,201] This may result from multiple aspects of host-pathogen interaction such as a lower dose needed to cause illness among these susceptible individuals owing to differences in innate, humoral, and cellular immunity. Rates of cryptosporidiosis have decreased since the advent of highly active antiretroviral therapy.

People who consume unpasteurized (raw) milk are at increased risk of acquiring foodborne infections. Immigrant and refugee populations may have certain customs that involve consumption of raw, undercooked, or fermented food.[202] Severe mushroom poisonings have occurred among immigrants who mistook poisonous mushrooms as safe mushrooms from their place of origin.[119]

Seasonality

Illnesses caused by *S. aureus, Salmonella, Shigella*, *C. jejuni, Vibrio* spp., STEC, *Giardia,* and *Cryptosporidium* are most common during the summer months. Similarly, shellfish-associated *Vibrio* infections peak during warmer months and are closely related to the temperature of the water in the oyster beds.[203] Illnesses caused by *C. perfringens* occur throughout the year but least often during the summer months.[32] Among black children in the United States, *Y. enterocolitica* infections have occurred primarily after winter holidays at which pork chitterlings are served. However, likely related to education efforts, decreased contamination of chitterlings, or both, the winter seasonality of these infections in black children diminished considerably during 2000–09. *Y. enterocolitica* infections occur throughout the year for other demographic groups.[144] The use of CIDTs has markedly increased detections of *Yersinia.*[165] Although transmitted year-round, winter is the season of peak norovirus activity, which provides additional opportunity for foodborne contamination with this pathogen.[29]

With a few exceptions, chemical food poisoning occurs throughout the year. Shellfish poisonings and ciguatera occur in association with harmful algal blooms such as a red tide. These blooms can occur at any time of the year but may be more common in late summer and fall in Florida. Mushroom poisoning is most common in the spring, late summer, and fall.

Geographic Location

The geographic setting may also provide a clue to the cause of foodborne disease. For unexplained reasons, *E. coli* O157 infections and outbreaks in the United States are more common in the northern states bordering Canada.[126,204,205] In Germany, areas of higher frequency of human *E. coli* O157 and some non-O157 STEC infections are those with higher cattle density.[206]

V. parahaemolyticus outbreaks in the United States are most frequently reported from coastal states (Gulf Coast, Atlantic, and Pacific).[45] Cases of toxigenic and nontoxigenic *V. cholerae* infection have been most often reported from the Gulf Coast of the United States.[87] Type E botulism is most common in Alaska due to consumption of fermented marine animals among Alaskan Natives.[207]

Most ciguatera fish poisoning outbreaks in the United States have been reported from the Caribbean, Florida, or Hawaii.[208] Travelers who return from these areas with the characteristic syndrome should be questioned regarding fish consumption. Transport of fish from endemic areas has caused outbreaks in nonendemic locations.[209,210] PSP and NSP outbreaks occur more frequently in coastal areas.

Globalization and centralization of the world's food supply has led to increased detection of multistate and multinational outbreaks.[15] Seemingly isolated illnesses within a geographic area may actually be part of a larger multistate or multinational outbreak.

Epidemiologic Assessment

If an outbreak of foodborne disease is suspected, public health authorities should be contacted so that it can be investigated. Investigating the outbreak is important to identify and rapidly control the source. Sometimes a common epidemiologic characteristic or meal shared by all or most patients is identified. Other outbreaks are the result of a widely distributed contaminated food, so cases may be dispersed across a broad geographic area. Ordering appropriate laboratory testing on patients is critical to identifying clusters of related cases by subtype-based surveillance.[211] In addition to identifying related strains among patients who may have shared a common exposure, subtype-based surveillance can match isolates from patients to isolates from foods or establishments.

After a food source for the infections is identified and the outbreak is halted, the investigation turns to the question of how contamination is likely to have occurred. Steps of food preparation, holding temperatures, and hygienic circumstances in the kitchen are assessed. Investigation into the sources of food ingredients may lead to assessments of the originating farm or processing plant. These assessments can result in

changes in regulatory guidance and industry practices that prevent future illnesses.

LABORATORY DIAGNOSIS

Most diarrheal illnesses do not require diagnostic testing. Guidelines exist that describe clinical presentations that should prompt stool testing in patients with diarrhea including, but not limited to, fever, bloody diarrhea, sepsis, and illness in people with certain high-risk conditions.[212] Blood cultures should be obtained from infants with sepsis or suspected enteric fever, patients with systemic manifestations of infection, patients with immunocompromising or other high-risk conditions, and patients with possible exposure to a person with suspected enteric fever.[212] Bacterial infections that are identified by culture-independent diagnostic tests and are subject to public health reporting rules should prompt culture. With culture, an isolate can be obtained and subtyped, which aids in outbreak detection; isolates can also be tested for antimicrobial susceptibility, which may change management.

Because some pathogens require specific culture media, culture conditions, or stains, diagnosis may depend on the skill of the clinician or laboratory. Some bacterial foodborne pathogens are not readily identified from cultures alone (e.g., diarrheogenic *E. coli* other than *E. coli* O157 such as non-O157 STEC and ETEC).[156,213] In addition, clinical laboratories in general do not have the capacity to test for norovirus. Therefore to identify some etiologies, human specimens must be sent to reference laboratories. Reference laboratories can identify non-O157 STEC isolates from Shiga toxin–positive specimens received from clinical laboratories,[213] identify other diarrheogenic *E. coli* (e.g., ETEC, EAEC, enteropathogenic *E. coli*, and enteroinvasive *E. coli*) by detection of virulence genes or toxins that define specific pathotypes, and identify norovirus by polymerase chain reaction (PCR).[214]

Newer commercially available molecular diagnostic assays such as assays that use multiplex PCR to simultaneously detect and distinguish between multiple enteric pathogens including several undetectable by traditional methods (e.g., ETEC, norovirus) are now widely available in the clinical setting.[215,216] These multipathogen assays can yield results within several hours. Because of the multipathogen nature of these newer molecular tests, they are likely to increase the number of illnesses for which two or more enteric pathogens are identified. Over time, this may improve understanding of pathogen interactions. However, it will become increasingly important to interpret positive results in a clinical context because some potential pathogens detected may not be causing illness.[215–217] Despite the clinical advantages of CIDTs (speed, number of detectable pathogens, and possibly lower cost), they are unable to provide information that is sometimes essential for patient care and public health purposes. Therefore bacterial culture remains necessary for antimicrobial susceptibility testing and for pathogen subtyping that aids outbreak detection and investigation. In the future, metagenomics methods may allow for subtyping and resistance testing of pathogens directly from stool specimens.

Diagnosis in Foodborne Outbreaks

In the context of a possible outbreak, determining an etiology is always important for identification of additional cases and for investigation into the possible sources of infection. To confirm the etiologic agent in outbreaks, appropriate specimens (e.g., stool or vomitus) should be tested from multiple patients. Specimen types vary by etiologic agent, and proper specimen collection and transport are important for successful diagnosis[218]; guidance is available at https://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/specimen-collection.html. In addition, as guided by epidemiologic findings, outbreak investigators may examine samples from leftover food, the food preparation environment, and food handlers. Food specimens must be sent to food microbiology laboratories that can detect bacterial or nonbacterial toxins and chemicals.

The identification, investigation, and confirmation of foodborne outbreaks of bacterial etiology have been aided greatly by standardized pulsed-field gel electrophoresis (PFGE) and whole-genome sequencing (WGS) methods in public health laboratories in the United States and Canada that are part of a subtyping network called PulseNet.[211] Bacterial isolates received from clinical laboratories that are routinely subtyped by PFGE include *E. coli* O157 and other STEC, *Salmonella, V. cholerae,* and *C. botulinum. Campylobacter, Shigella,* and other *Vibrio* spp. are sometimes subtyped. *L. monocytogenes* is routinely subtyped by WGS. Other pathogens may be subtyped by PFGE or WGS to confirm an outbreak. PulseNet is growing internationally, which will enable better detection of outbreaks on an international scale.

Specific Considerations About Important Pathogens

Staphylococcus aureus

Staphylococcal food poisoning is usually diagnosed clinically. Outbreaks of staphylococcal food poisoning can be confirmed by isolation of *S. aureus* of the same phage type pattern from vomitus or feces of two or more ill people or from both patient and food samples or by detection of enterotoxin or the isolation of greater than 10^5 organisms per gram in epidemiologically implicated food.[219] However, because *S. aureus* (but not the enterotoxins they produce) is heat sensitive, it is often difficult to isolate the organism from heat-treated foods. The identification of specific *S. aureus* enterotoxins (SEA through SEE) in food is accomplished most commonly by reverse passive latex agglutination or enzyme-linked immunosorbent assay platforms, which are available commercially. The tests distinguish SEA through SEE and are useful for identifying the types of enterotoxins involved in foodborne outbreaks. More recently, mass spectrometry has been used to quantify enterotoxins in foods. Although PCR detection alone of enterotoxin genes directly from contaminated foods and specimens cannot be used to confirm staphylococcal food poisoning, it can confirm isolation and direct toxin testing results.

Bacillus cereus

B. cereus food poisoning is also usually a clinical diagnosis. Outbreaks may be documented by isolating organisms from the feces of two or more ill people who shared the same meal or by isolating 10^5 or more *B. cereus* organisms per gram of incriminated food. Because nontoxigenic *B. cereus* is commonly found in foods, testing for enterotoxin genes in several isolates is advised. Molecular subtyping (e.g., by multilocus sequence typing,[220] plasmid analysis, or serotyping[221]) may be of value in confirming that isolates were derived from a common source because 14% of healthy adults have been reported to have transient gastrointestinal colonization with *B. cereus.*[222] Commercial immunoassays are available for two of the diarrheogenic enterotoxins of *B. cereus*.[19] A wild boar sperm assay has proven to be a simple and effective way to screen for cereulide-producing *B. cereus* isolates.[223] PCR assays that detect the *ces* gene (cereulide) in emetic strains have been developed.[224]

Clostridium perfringens

C. perfringens are part of the normal microbiota in many people. In addition, because less than 5% of *C. perfringens* type A strains produce CPE,[34] toxin assessment is needed to confirm a diagnosis. A reverse passive agglutination kit for detection of CPE directly from stools is commercially available. PCR can detect the *cpe* gene, but detection may not indicate expression of the protein. Therefore, detection of toxin in stool is the best indicator of infection. *C. perfringens* outbreaks can be confirmed by detection of enterotoxin or isolation of 10^6 organisms per gram of stool from two or more ill patients or by the isolation of 10^5 organisms per gram in epidemiologically implicated food.[225] Molecular subtyping can confirm that the same strains are present in both implicated foods and patients.[35] Because both heat-sensitive and heat-resistant strains of *C. perfringens* type A have been implicated in food poisoning, selective isolation procedures involving heat treatment of food and fecal specimens should not be used.

Classic Bacterial Enteropathogens

STEC (including *E. coli* O157), *Salmonella, Shigella, C. jejuni, Vibrio,* and *Y. enterocolitica* outbreaks may be detected by isolation of the organisms from the feces of ill people. However, pathogens identified as part of a routine stool culture typically include only *Salmonella, Shigella, Campylobacter,* and sometimes *E. coli* O157. To identify other bacterial pathogens in culture, the clinical laboratory needs to be notified so that special media can be used.[88] Culture-independent diagnostic

tests may also detect these organisms and are now routinely used to diagnose STEC infection. However, the tests usually do not identify species and subtypes. Culture is needed for antimicrobial susceptibility testing and for molecular subtyping (e.g., by PFGE or WGS, which are used to identify outbreaks). Infection with STEC O157 can be diagnosed by isolating sorbitol-negative *E. coli* from stools of ill patients on selective and differential media such as sorbitol-MacConkey and confirming the serogroup as O157 and then either confirming the H7 antigen, the detection of Shiga toxin, or the presence of *stx* genes that encode for the expression of the toxin. Non-O157 STEC can be identified by demonstration of Shiga toxin in stool by enzyme immunoassay or *stx* genes in stool by PCR at the clinical laboratory, with subsequent isolation of the organism by culture at a reference laboratory. In the United States, isolates of *E. coli* O157 or Shiga toxin–positive broth cultures should be forwarded to a public health laboratory for full characterization and PFGE or WGS subtyping.[213] Although immunoassays for detection of *Campylobacter* in stool are available, the accuracy of these tests varies considerably.[226] Testing of sera, especially paired serum from the acute and convalescent phases of illness, may be helpful in confirming the diagnosis of patients in outbreaks of STEC, cholera, and typhoid fever.

Botulism

Patients with suspected botulism should be treated before the diagnosis is confirmed. Tests that can help narrow the differential diagnosis include lumbar puncture (a high cerebrospinal fluid protein level is suggestive of Guillain-Barré syndrome and Miller Fisher syndrome, a variant of Guillain-Barré syndrome, which can be confused with botulism), the Tensilon test (to diagnose myasthenia gravis), and electromyography (findings of neuromuscular junction blockade, normal axonal conduction, and potentiation with rapid repetitive stimulation are suggestive of botulism).[75] Botulism may be confirmed by the demonstration of botulinum toxin in serum, gastric secretions, stool, or the incriminated food by the mouse neutralization test or by the isolation of *C. botulinum* from stool or the incriminated food; these tests can be arranged through contact with state health departments.[75] Laboratory confirmation by testing of clinical specimens can be obtained in about 70% to 75% of botulism cases.[227,228]

Protozoa

Physicians should specifically request testing for *Cyclospora* and *Cryptosporidium,* if indicated, because these pathogens are not typically detected via routine ova and parasite examination and require specialized techniques. *Cyclospora cayetanensis, Cryptosporidium,* and *Giardia* are included on the BioFire FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT).[165,229] PCR assays are available for *Cyclospora*.[230] Cryptosporidiosis can be diagnosed by microscopy, PCR, or enzyme immunoassays.[231,232] Toxoplasmosis can be diagnosed by both serology and PCR.[90] Trichinellosis is diagnosed by serologic testing and, less frequently, by muscle biopsy. Additional information on the diagnosis of parasitic infections can be found at https://www.cdc.gov/dpdx/diagnosticprocedures/index.html and in Chapters 278, 279, 282, 283, and 287.

Heavy Metals

Outbreaks caused by heavy metals may be documented by demonstration of the metal in the incriminated food or stool specimens from ill patients. Marine toxin syndromes are diagnosed by clinical presentation and history of seafood consumption in the preceding 24 hours; diagnostic tests are not available in the clinical setting.[111,233] However, detection of toxin in implicated foods or certain clinical samples may be possible in coordination with the health department. Mushroom poisonings should be diagnosed by clinical suspicion and may be confirmed either by the identification of the responsible toxin in gastric contents, blood, urine, or fecal specimens or by the identification of the mushroom by a mycologist.[119]

Unknown or Rare Causes

About one-third of the reported foodborne disease outbreaks in the United States are of unknown etiology.[52] In many cases, appropriate diagnostic procedures are not conducted, or specimens are not collected in a timely manner, not transported properly, or are transported under suboptimal conditions. Many of these unknown outbreaks may be due to typical agents.[234] In others, no agent is identified despite testing, raising the possibility that etiologic agents not routinely tested for are responsible; possibilities include ETEC, EAEC, and sapovirus. The frequency of outbreaks of unknown etiology may decrease as molecular methods that can detect a wider array of pathogens become increasingly available.

Rare instances of enterococci and gram-negative rods (e.g., *Aeromonas hydrophila, Klebsiella, Enterobacter, Proteus, Citrobacter,* and *Pseudomonas*) have been reported as causes of foodborne outbreaks. However, because these organisms may be present in foods without causing illness and may be part of the normal human fecal flora, documenting their role in foodborne disease outbreaks is difficult.

THERAPY

Supportive measures are the mainstay of therapy for most foodborne illnesses. In any diarrheal illness, gastrointestinal fluid losses should be replaced. Usually any over-the-counter oral rehydration solution is sufficient; for severe dehydration, intravenous hydration may be required.[235] Early intravenous hydration may reduce the risk of oligoanuric HUS in patients with STEC O157 infection[236]; patients who develop HUS frequently require blood transfusions.[61] Antiemetics and antimotility agents offer symptomatic relief in adults, although the latter are contraindicated in patients with high fever, bloody diarrhea, or fecal leukocytes indicative of inflammatory diarrhea. Antiemetics and antimotility agents are usually not recommended for children. Supportive intensive care is essential in the management of botulism; access to mechanical ventilation greatly reduces the mortality rate.[75] The most lethal foodborne diseases are botulism, invasive listeriosis (affecting neonates, elderly adults, and immunocompromised patients), *V. vulnificus* infection (in patients with liver disease), paralytic shellfish poisoning, and long-incubation mushroom poisoning. With other pathogens, fatalities most often occur in elderly or immunocompromised patients.

Most bacterial diarrheal illnesses are self-limited and do not require antimicrobial therapy in healthy hosts who are not at the extremes of age. Empirical antimicrobial therapy may be indicated for infants; immunocompetent patients with fever, abdominal pain, bloody diarrhea, and bacillary dysentery presumptively due to *Shigella;* patients with recent international travel and fever or signs of sepsis; immunocompromised patients with severe illness and bloody diarrhea; and patients with suspected enteric fever.[212] In adults with indications for antibiotic therapy, a fluoroquinolone or azithromycin is recommended. In children, a third-generation cephalosporin may be given for infants <3 months old and for children with neurologic involvement; azithromycin is an alternative choice in children.[212] Selection of empirical antimicrobial therapy should depend on local susceptibility patterns and travel history, and therapy should be modified or discontinued when a clinically plausible organism is identified. Antibiotic treatment of nontyphoidal *Salmonella* gastroenteritis may increase the risk of long-term carriage.[237] Antibiotic treatment of STEC O157 infections may increase the risk of HUS.[238] Antibiotics are of no value in the management of staphylococcal, *C. perfringens,* and *B. cereus* food poisoning. Antimicrobial agents are lifesaving in invasive salmonellosis, invasive listeriosis, *Vibrio* septicemia, and typhoid fever. Azithromycin, doxycycline, and tetracycline shorten both the duration of choleric diarrhea and the excretion of toxigenic *V. cholerae* O1 and are first-line agents (in combination with rehydration) in patients with moderate-to-severe illness. Most diarrheal illness caused by *Campylobacter* and *Shigella* is self-limited. Early treatment of *Campylobacter* infection with fluoroquinolones, erythromycin, or azithromycin can shorten the duration of illness. However, domestically acquired fluoroquinolone-resistant *Campylobacter* infections emerged after the approval of these agents for use in poultry. Antibiotic treatment of shigellosis is recommended for patients with severe infections, patients with dysentery, or patients who are immunocompromised. Antimicrobial susceptibility testing of *Shigella* isolates is important, as resistance is common, and isolates are increasingly found that have reduced susceptibility to ciprofloxacin or azithromycin. Antimicrobial agents are also used to treat parasitic infections. More information on treating parasitic infections can be found at www.cdc.gov/parasites.

Resistant strains can complicate treatment and are associated with a greater risk of invasive infection and hospitalization.[239] Asymptomatic *Salmonella* infection may become clinically apparent when an unrelated condition is treated with an antimicrobial agent to which the *Salmonella* organism is resistant; such treatment also lowers the infectious dose.[240] The proportion of resistant isolates varies widely by serotype. *Salmonella* serotype Typhimurium resistant to multiple antibiotics emerged globally, particularly in Europe and the United States, in the 1990s.[241,242] An emerging monophasic variant of *Salmonella* serotype Typhimurium, serotype I 4,[5],12:i:-, has emerged; 59% of isolates reported to National Antimicrobial Resistance Monitoring System (NARMS) national surveillance in 2015 were resistant to ampicillin, streptomycin, sulfonamides, and tetracycline.[243]

Salmonella serotype Newport resistant to amoxicillin-clavulanate, ampicillin, ceftriaxone, chloramphenicol, streptomycin, sulfonamides, and tetracycline and with decreased susceptibility to ceftriaxone emerged in the United States in the early 2000s. It is associated with consumption of undercooked ground beef.[244] The proportion of *Salmonella* serotype Newport isolates with this resistance pattern tested in NARMS increased from none in 1996 to a peak of 25% in 2001, and it declined to 4.7% in 2015.[243] However, other resistance patterns are emerging. From 1996 through 2015 in NARMS surveillance, the percentage of *Salmonella* isolates resistant to ceftriaxone increased from 0.2% to 2.7%, and the percentage with nonsusceptibility to ciprofloxacin increased from 0.4% to 5.8%.[243] The emergence of these multidrug-resistant *Salmonella* organisms was probably related to agricultural uses of antimicrobials. This highlights the interconnected pool of pathogens between animal reservoirs and people and underlines the need for prudent use of antimicrobials in both sectors and of a One Health approach (https://www.cdc.gov/onehealth/index.html).

Medical care providers who suspect botulism should implement close observation and supportive care and immediately call their state health department's emergency 24-hour telephone number. The state health department will contact the CDC to arrange a clinical consultation by telephone and, if indicated, release of botulinum antitoxin. Management of botulism is discussed in Chapter 245.

Patients with paralytic shellfish poisoning and some patients with ciguatera may require ventilatory support, usually for only a few days. Although case reports and unblinded randomized studies have suggested that intravenous mannitol may ameliorate the acute neurologic symptoms of ciguatera, a double-blind randomized trial showed no benefit.[245] Case reports have suggested that amitriptyline and tocainide may improve persistent dysesthesias.[233] Therapy is otherwise supportive; no antitoxins are available. If not contraindicated by the presence of ileus, enemas or cathartics may be administered in an effort to remove unabsorbed toxin from the intestinal tract. Because of the severe dysesthesias associated with ciguatera, analgesics may also be required. Scombroid poisoning may be treated with a combination of H1 and H2 antihistamines. In severe cases with bronchospasm, epinephrine may be required.[246]

Therapy for short-incubation types of mushroom poisoning is primarily supportive. Patients with severe parasympathetic hyperactivity caused by muscarine poisoning may be treated with atropine.[121] Therapy for cyclopeptide poisonings includes cathartics to remove unabsorbed toxin in the minority of patents who present before the onset of severe gastrointestinal symptoms and many additional unproven measures.[119] Pyridoxine is indicated for treatment of neurologic manifestations of gyromitrin poisonings.[121]

Therapy for acute heavy metal poisoning is supportive. Emesis should be induced if it does not occur spontaneously. Antiemetics are contraindicated because retention of the toxic ions in the gut and subsequent systemic absorption may result. In severe cases of heavy metal toxicity, use of specific antidotes may be considered, but that is rarely necessary.

SURVEILLANCE

Surveillance of enteric diseases has four objectives: (1) individual case investigation for localized disease-control activities; (2) outbreak detection to protect the population and to identify gaps in control measures; (3) assessment of disease burden and trends to prioritize and assess impact of control measures; and (4) microbiologic characterization of infectious agents to improve understanding of their epidemiology, antimicrobial resistance, and virulence factors.[226] State public health laws determine reportable conditions for each state and who is responsible for reporting. State public health officials voluntarily submit data to the CDC for nationwide surveillance.

Laboratory-based surveillance, which relies on reports of test results from public health laboratories, has proven especially valuable for surveillance of foodborne diseases because of information gleaned from subtyping. For *Salmonella, Shigella,* STEC, and *Listeria,* clinical laboratories should send isolates to a reference laboratory for serotyping and molecular subtyping by PFGE or WGS. In the United States, all state public health laboratories participate in PulseNet.[211] Similarly, many US public health laboratories, as part of CaliciNet, can perform genetic sequencing of PCR products to link multiple norovirus cases to environmental sources.[247]

Although knowing the specific serotype, PFGE pattern, or WGS characteristics is rarely important in the management of a single case, this or other subtyping information is essential to the investigation of many outbreaks and is fundamental to the recognition of multistate outbreaks. This means that a diagnostic culture is of benefit not only to the patient but also to society as a whole. The use of culture-independent methods such as enzyme immunoassay or PCR that do not yield isolates that can be subtyped is increasing.[226] Until culture-independent diagnostic tests are developed that provide subtype information, it is important to reflexively culture any specimen that tests positive by a culture-independent test so that the public health functions of laboratory-based surveillance are not impaired. Culture-independent methods also do not provide information about antimicrobial susceptibility.

Efforts are underway to develop new diagnostic methods that serve both clinical and public health needs. One approach is metagenomics, the sequencing of all the genetic material in a stool sample. Although this technology has not reached a stage that is useful for routine diagnostic testing or surveillance, it was used in a retrospective study of an STEC outbreak.[248,249]

A report of illness in a single person who has attended a daycare center, family gathering, or other setting often leads to discovery of an outbreak. Outbreaks can be apparent even before the causative agent is known, and early investigation can control a source. This means that the astute clinician or microbiologist who calls the public health department epidemiologist to discuss a case plays an important role in the control of foodborne and other diseases.

PREVENTION

Monitoring of food production systems is increasingly important as the global food supply becomes more interconnected, centralized, and preprocessed for the convenience of the consumer. Prevention of foodborne disease depends on careful handling of animals, raw products, and processed foods all the way from the farm to the table and on practices that reduce or eliminate contamination in food.

Much foodborne disease can be prevented if food is selected, prepared, and stored properly. In large kitchens and in homes, careful cooking and storage are necessary to kill pathogens and to prevent their growth when food is contaminated after cooking. Bacterial pathogens grow in food at temperatures ranging from 40°F to 140°F; growth may be prevented if cold food is adequately refrigerated and hot food is held at temperatures higher than 140°F before serving. Although thorough cooking of food just before consumption eliminates the risk of many illnesses, protection against staphylococcal food poisoning is not provided because the staphylococcal enterotoxins are heat stable. Particular care in handling and cooking of raw poultry, beef, pork, shellfish, and eggs is important to prevent many foodborne diseases. Contamination in the kitchen may occur if cooked foods or ready-to-eat foods come in contact with raw foods of animal origin or with equipment such as knives and cutting boards. Poor personal hygiene by food handlers frequently contributes to norovirus, *Staphylococcus, Shigella,* and hepatitis A outbreaks.

Because they serve high-risk populations, the kitchens of hospitals and nursing homes must pay particular attention to food safety.[250] For example, routine use of pasteurized eggs instead of shell eggs for recipes

TABLE 101.5 Control and Prevention of Foodborne Diseases

General Recommendations for All People

- Thoroughly cook raw food from animal sources such as beef, pork, poultry, fish, and eggs to temperatures that eliminate most pathogens.[a]
- Wash raw fruits and vegetables before eating.
- Keep uncooked meats separate from fruits, vegetables, cooked foods, and ready-to-eat foods.
- Do not thaw meat, poultry, or fish on the counter (instead, thaw in a refrigerator, in cold water, or in a microwave oven).
- Wash hands before, during, and after preparing food and before eating food.
- Wash knives, other utensils, and cutting boards after handling uncooked foods.
- Keep refrigerators set to <40°F and freezers set to 0°F or lower, and verify with a thermometer.
- Refrigerate perishable foods within 2 hours (or within 1 hour if left out at temperatures >90°F).
- Read and follow all cooking and storage instructions on food product packaging. This is especially important for foods prepared in microwave ovens because these ovens heat foods unevenly. Even foods that appear ready to eat may require thorough cooking.
- Persons with diarrhea or vomiting possibly caused by an infectious agent should not prepare foods for others.
- Keep all animals including reptiles and amphibians away from surfaces where foods or drinks are prepared.
- Do not drink unpasteurized (raw) milk or eat foods made from unpasteurized milk. (Exception: hard cheeses made from raw milk that have been aged >60 days are generally safe to eat.)
- Do not eat home-canned foods that were not known to be adequately heat processed during canning.

Recommendations for People at High Risk Such as Pregnant Women and People With Weakened Immune Systems in Addition to Above Recommendations

Measures to Prevent a Variety of Bacterial Infections

- Do not eat uncooked sprouts.
- Do not drink prepackaged juice or juice-containing beverages that have not been processed to reduce or eliminate microbial contamination (e.g., by pasteurization).

Listeriosis Prevention Measures

- Do not eat soft cheeses such as feta, Brie, and Camembert; blue-veined cheeses; and Mexican-style cheeses such as queso blanco, queso fresco, and panela unless the package has a label that clearly states that the cheese is made from pasteurized milk. Be aware that certain soft cheeses made from pasteurized milk such as queso fresco have also caused *Listeria* infections, most likely because they were contaminated during cheese-making.
- Do not eat refrigerated pâtés or meat spreads. Canned or shelf-stable pâtés and meat spreads are safe to eat.
- Do not eat refrigerated smoked seafood unless it is contained in a cooked dish such as a casserole. Refrigerated smoked seafood such as salmon, trout, whitefish, cod, tuna, and mackerel is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky." The fish is found in the refrigerator section or sold at delicatessen counters of grocery stores and delicatessens. Canned or shelf-stable smoked seafood is safe to eat.
- Do not eat hot dogs, luncheon meats, or delicatessen meats unless they are reheated until steaming hot.
- Avoid getting fluid from hot-dog packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and delicatessen meats.

Salmonellosis Prevention Measures

- Use pasteurized eggs.

Vibriosis, Toxoplasmosis, and Norovirus Prevention Measures

- Do not eat raw or lightly steamed oysters, clams, or other raw shellfish (especially important for patients with liver disease).

[a]Poultry: 165°F (73.9°C); ground meats: 160°F (71.1°C); intact cuts of beef, pork, ham, veal, and lamb: 145°F (62.8°C) and allow to rest for at least 3 minutes before eating; fish and shellfish: 145°F (62.8°C); egg dishes: 160°F (71.1°C).
More food safety information can be found at www.foodsafety.gov/keep/index.html.

that pool large numbers of eggs may prevent salmonellosis.[251,252] Low microbial (or neutropenic) diets are advised for some especially vulnerable patients.[199,250] Some foods pose such high risk of infection that they should be avoided by even healthy nonhospitalized persons; these include raw milk (which can transmit *Salmonella, C. jejuni,* STEC, and *Mycobacterium tuberculosis*)[134] and inadequately heat-processed home-canned foods (botulism).

Except for scombroid fish poisoning, food-handling errors resulting in chemical intoxication are different from errors leading to bacterial outbreaks. Heavy metal poisoning occurs when acidic beverages are stored in defective metallic containers. Ciguatera and shellfish poisoning occur when seafood are obtained from unsafe sources; seafood containing the toxins appear and taste normal, and cooking does not provide protection because the toxins are heat stable. Scombroid fish poisoning can be prevented through refrigeration of raw fish.[112]

The role of the clinician goes beyond that of diagnosis and treatment to prevention. This means educating patients or caregivers, especially for patients more vulnerable to foodborne disease (e.g., infants, pregnant women, older adults, and immunocompromised persons) about food safety measures. Such patients may choose to avoid high-risk foods, and everyone can benefit from following good food-handling practices (Table 101.5).

Clinicians and microbiologists have an important role in the detection of outbreaks, and rapid investigation of outbreaks can identify the source and trigger actions such as recalls or policy changes to prevent additional illnesses. Obtaining appropriate diagnostic tests for foodborne pathogens and reporting them to public health authorities are key to outbreak detection efforts. There are well-documented outbreaks of botulism,[253] salmonellosis,[254] and *E. coli* O157:H7[255] in which recognition and reporting of the initial illness could have prevented many subsequent cases.

Diagnosing and reporting of illnesses with the potential for intrafamilial spread or for spread within institutions such as daycare centers (e.g., shigellosis, *E. coli* O157:H7 infection) can prevent secondary transmission.[256] Public health authorities may exclude food handlers, recreational water staff, healthcare providers, and individuals who work in or attend schools or daycare centers from working or attending until symptoms or diagnostic tests indicate that the transmission risk is sufficiently reduced.[212] Clinicians should counsel patients with diarrhea on practicing hand hygiene and to avoid swimming, water-related activities, and sexual contact while symptomatic.

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The complete reference list is available online at Expert Consult.

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102 Tropical Sprue and Environmental Enteric Dysfunction

Honorine D. Ward and Christine A. Wanke

SHORT VIEW SUMMARY

Definition
- Tropical sprue: Syndrome of diarrhea, malabsorption of at least two distinct nutrients, abnormal duodenal histopathology, and weight loss.
- Environmental enteric dysfunction (EED): Incompletely understood syndrome of gut mucosal inflammation, reduced intestinal absorption, and increased permeability, associated with environmental contamination, altered gut microbiota, and stunting in young children in resource-limited countries.

Epidemiology
- Sprue: Most frequent in Asia and the Caribbean islands, more frequent in adults than children; occurs in long-term travelers to endemic regions.
- EED: occurs throughout the resource-limited world.

Microbiology
- Sprue and EED: No single agent has been associated with a causal role, but small bowel overgrowth is common.

Diagnosis
- Sprue: Presence of an appropriate clinical syndrome (persistent diarrhea, malabsorption of at least two distinct nutrients, weight loss) with consistent findings on small bowel series or upper endoscopy. Response to folate and tetracycline ultimately confirms the diagnosis.
- EED: A number of potential biomarkers of EED have been investigated but there is no single biomarker that is diagnostic of EED.

Therapy
- Sprue: Removal from area of risk, treatment with folate and tetracycline.
- EED: No definitive effective treatment as yet. Ongoing trials involve nutritional supplements, water and sanitation interventions, and immunomodulators.

Prevention
- Sprue and EED: Good hygienic practices.

Tropical sprue, also called *postinfectious tropical malabsorption,* and environmental enteric dysfunction (EED) are both syndromes of enigmatic origin. Although there is substantial overlap between these two illnesses, there are also distinct features.

Tropical Sprue

Tropical sprue has been recognized since the 2nd or 3rd century AD, when Aretaeus of Cappadocia reported on "The Coeliac Affection," and was described in India in the Charaka Samhita.[1] The first mention of sprue in the modern medical literature was in 1747, when Hillary emigrated from England to Barbados and published his observations on a prolonged tropical diarrheal disease in native islanders. The English term *sprue* is an adaptation from the Dutch *sprouw,* which was originally used to refer to persistent diarrheal disease in Holland (possibly celiac disease). The term *sprue* first was used in 1880 by Manson for the persistent wasting diarrhea that occurred in tropical countries.[2] Knowledge about the cause or pathogenesis of sprue did not advance significantly until investigations were begun after recognized outbreaks during World War II. The distinction between celiac sprue and tropical sprue was not clear until the early 1970s. The distinction between sprue and EED is only just now occurring.

Environmental Enteric Dysfunction

What has been previously called tropical or environmental enteropathy[3] is currently referred to as *environmental enteric dysfunction*, indicating that there are functional deficits associated with the histopathologic changes of enteropathy, which include small intestine villous blunting or atrophy, crypt hyperplasia, and lymphocytic infiltration of the lamina propria.[4–7] Currently, this poorly understood acquired syndrome affects young children as well as adults in resource-limited areas of the world.[8–10] The functional defects include increased intestinal permeability or impaired gut barrier function, malabsorption, intestinal injury and repair, immune activation, and chronic mucosal and systemic inflammation.[4,7,9]

Although widespread efforts to decrease the global impact of childhood diarrhea—including oral rehydration, zinc supplementation, exclusive breastfeeding, vaccines to prevent enteric infections, and public health strategies to implement these interventions—have resulted in a radical reduction in the number of deaths due to childhood diarrhea,[9] there has not been a concurrent decrease in the rates of stunting in the resource-limited world. These data suggest that repeated diarrheal episodes and enteric infections themselves may not be contributing to impaired linear growth in these children, but rather that this may be the outcome of a chronic inflammatory state of the small intestine.[9]

EXPOSURES/EPIDEMIOLOGY

Tropical Sprue

Although sprue is considered a disease of tropical locales, there are distinct geographic areas of risk within the tropics. Tropical sprue has been identified most readily in Asia and the Caribbean islands, and there are isolated areas of particular risk within both hemispheres.[11,12] It is seen in northern South America, including Venezuela and Colombia, but rarely in Central America or Mexico. Currently, it remains on the Indian subcontinent, from the Himalayas to the south, but is less common than previously, and it has been recognized in Myanmar and the Philippines.[13–15] An illness consistent with sprue has been documented in patients who had undergone renal transplantation in Asia.[16] Infrequent cases of tropical sprue were documented in Africa until the 1970s; cases have been recognized in Rhodesia (now Zimbabwe) and South Africa.[17] There may be endemic foci of tropical sprue in the Middle East as well.[18]

In contrast to other endemic diarrheal illnesses in the tropical world, tropical sprue is a disease mainly of adults. Children are believed to be relatively spared, although disease has been documented in all age groups. Tropical sprue is rare in very young children; this may represent a beneficial effect of breastfeeding. In studies of family outbreaks of tropical sprue in South India, even older children developed disease at a significantly lower rate than adults.[19] The reasons underlying these observations are not known. Persistent diarrhea develops in children more commonly in parts of the world where the environment is contaminated more heavily with microbes that are potentially disease-causing.[20] Tropical sprue may be one of the causes of prolonged diarrhea and wasting in this age group as well, but studies such as small bowel intubation and cultures or biopsy have shown conflicting results, relating small bowel colonization with persistent diarrhea.

Some patterns of disease expression are of particular interest in tropical sprue. There are clear epidemics of the disease, which have

been documented best in families and villages in South India.[19] There have been descriptions of "sprue houses," in which successive tenants have developed disease. Such an epidemic pattern suggests an underlying infectious (transmissible) cause.

There have been seasonal variations in the frequency of outbreaks of tropical sprue as well. At an American military base in the Philippines,[15] an increased rate of mild tropical sprue in the setting of an increased rate of diarrheal disease was seen more often from March to July than at other times of the year for at least 4 years. In these outbreaks, sprue occurred in American military personnel and their dependents, who were eating a high-calorie, Western-style diet. This seasonal variation also lends credence to the possibility of an underlying infectious cause.

Tropical sprue occurs in expatriates living in endemic areas. Tropical enteropathy has been described in Peace Corps volunteers and has occurred sporadically in travelers.[21] Generally, tropical sprue develops in an expatriate who has lived for a prolonged time (6 months to 1 year) in an endemic area.[22] Rare cases also have been described in short-term travelers. Tropical sprue is also recognized in immigrants who leave endemic areas. Classical sprue appears to be less frequent than it was previously.

Environmental Enteric Dysfunction

Because the diagnosis of EED is less refined, the epidemiology of EED is correspondingly less well -understood. EED appears more frequently in children than does sprue, and children are at risk whenever they reside in regions where hygiene is less feasible.

EED is prevalent in low- and middle-income countries of the world with poor access to clean water, sanitation, and hygiene (WaSH) and fecal environmental contamination.[23] These include countries in sub-Saharan Africa, South Asia, and South America. Children below the age of 5 years as well as adults are affected.

CLINICAL FEATURES

Tropical Sprue

The classic clinical features of tropical sprue are nonspecific and simply reflect the symptoms of malabsorption. Changes in hygiene, increased access to medical care, and improved access to clean water supplies may all be altering the frequency and severity of malabsorption. Currently, the diagnosis of sprue often is made when the presentation is still quite subtle compared with the severe disease that was the more common presentation in the past. Malabsorptive symptoms include prolonged diarrhea, abdominal cramping, and anorexia, with or without nausea and secondary weight loss. Other associated but less common symptoms, also related to the malabsorption of specific nutrients and subsequent malnutrition or micronutrient deficiencies, may include peripheral edema, glossitis, stomatitis, and dermatitis.[24,25] Fever may occur at the onset of sprue-related diarrhea (especially in Asia). Although the presence of fever has been suggested as a means to distinguish Caribbean from Asian sprue, this distinction has not been observed consistently. Fever rarely persists for the course of disease.

Many patients can pinpoint the onset of disease. Tropical sprue rarely has an insidious onset and far more often is associated with an obvious acute episode of diarrhea that then becomes prolonged. Because the current definition of tropical sprue implies that the function of the gut was normal before the development of the disease, most typically, the diarrhea has an acute onset; however, the distinction between normal and abnormal bowel habits often may not be so clear.

Patients describe crampy abdominal pain; multiple soft or loose stools daily, often with mucus; and exacerbation of symptoms with food consumption. Patients may also complain of nausea and bloating that lead to decreased appetite and decreased oral intake. Malabsorption of specific nutrients may lead to the development of other manifestations,[26] including lactose intolerance or anemia. Anemia may convert from macrocytic to microcytic anemia. Impaired absorption of calcium, vitamin D, and magnesium also may occur, with resulting osteopenia.[27]

Environmental Enteric Dysfunction

EED can be subclinical or associated with diarrhea, enteric infections, linear growth faltering leading to stunting, and physical and cognitive impairments.[7,9] There is no single clinical feature that is specific for EED.

PATHOGENESIS

Tropical Sprue

There is a strong presumption that tropical sprue is caused by an enteric infection, perhaps in individuals predisposed by a nutritional deficiency. The facts lending support to this theory include the following: (1) often, the prolonged episode of tropical sprue is initiated by an episode of acute diarrheal disease; (2) there is an epidemic and seasonal nature to the epidemiology of the disease, as noted; and (3) the disease responds most often to treatment with antibiotics with or without nutritional supplements. Nevertheless, the precise nature of the infection(s) that lead to development of tropical sprue is less clear.

Multiple studies in Asia and the Caribbean islands have shown small bowel bacterial overgrowth in patients with tropical sprue.[21,28,29] Although some bacteria normally live in the upper small bowel of healthy persons, the organisms isolated from this region of the gut in healthy asymptomatic individuals are most often gram-positive. Streptococci, staphylococci, and lactobacilli are among the common isolates, and these are present in small numbers. In the distal small bowel, the cecum, and the colon, anaerobes and facultative gram-negative organisms predominate in normal persons. Small bowel cultures from travelers with tropical sprue show increased numbers of gram-negative rods, including *Alcaligenes, Enterobacter aerogenes,* and *Hafnia* spp. In small bowel cultures from persons with tropical sprue who were native to India, Haiti, or Puerto Rico, *Klebsiella, Escherichia coli,* and *Enterobacter cloacae* were the most common organisms. Carefully done studies in South Africa and India documented similar organisms in similar concentrations in the small bowel of asymptomatic control patients and in patients with tropical sprue, suggesting that environmental contamination may predispose to increased small bowel microbial populations.[21,28,29] In another series of patients from India, the number of organisms found in the small bowel of tropical sprue patients was the same as that found in the small bowel of healthy controls, but the types of organisms isolated varied.[28] Other organisms, especially *Enterobacter* and *Veillonella,* were isolated more frequently from the small bowel of patients with tropical sprue than from healthy controls.[30] However, the presence of particular organisms does not prove any causal effect, and all of these studies were conducted before the era of sequence-based analyses or molecular diagnostics (such as Biofire) of bacterial populations rather than relying on culture alone, which underrepresents fastidious organisms.

Gram-negative organisms isolated from the small bowel of tropical sprue patients in Haiti were found to have a secretory effect on intestinal cells, presumably by toxin production; however, these toxins have not been characterized by current methods. Other studies have further suggested that enteroaggregative *E. coli* are associated with malnutrition, with or without persistent diarrhea, and with intestinal inflammation and cytokine production.[31] In addition to its association with persistent diarrhea in children in tropical developing areas, enteroaggregative *E. coli* in patients with acquired immunodeficiency syndrome is associated with persistent diarrhea that improves with antimicrobial therapy.[32,33] Although the traditional definition of tropical sprue excludes patients with diarrhea on the basis of recognized pathogens, it is possible that improvements in diagnostic techniques, such as multiplex molecular diagnostics,[34] would permit the identification of organisms that are or have been associated with tropical sprue but previously were not able to be isolated or identified. Whether tropical sprue is distinct from EED is not clear. One possibility is that these syndromes may exist at the ends of the spectrum of a single disease, with sprue being the more advanced and symptomatic form of the more frequently asymptomatic EED.[1] Sequence-based microbial identification is another example of a significantly more sensitive technique that may be beneficial in elucidating intestinal microbiota as it contributes to the pathogenesis of tropical sprue and may clarify the relationship toEED.[1,35]

The concept that small bowel overgrowth, as it occurs spontaneously in a certain segment of the population in resource-limited countries or after an acute enteric infection, may precipitate a series of intestinal insults that proceed to full-blown tropical sprue in susceptible persons represents an attractive hypothesis for the cause of tropical sprue. The predisposition for progression from intestinal insult to tropical sprue is less easy to explain. Malnutrition, whether generalized or presenting as specific micronutrient deficiencies, may be a predisposing factor, but

is neither necessary nor sufficient, as shown by the occurrence of tropical sprue in apparently well-nourished military personnel and their dependents. Small bowel overgrowth may alter intestinal transit time and promote further overgrowth and intestinal stasis, but it cannot explain the initial colonization that induces the episode.

In vitro data suggest that small bowel colonization by *E. coli* may be increased by low levels of cytokines, as might be expected in chronic parasitic infections in resource-limited settings. As noted, certain organisms, such as enteroaggregative *E. coli,* can alter the intestinal environment by the induction of intestinal proinflammatory cytokines and intestinal inflammation.[36] There has been no genetic predisposition noted for tropical sprue as there has been for celiac sprue, and the inflammatory cytokine profile in the lymphocytes of the small bowel in patients with tropical sprue has not been described.

The processes that control the normal bacterial colonization of the small bowel are not well understood; the forces that may disrupt these normal processes to permit abnormal colonization are even less well understood. Some factors that can affect the normal small bowel colonization process include gastric acidity, which controls the entry of viable organisms into the small bowel, and intestinal mucin glycoprotein, which contains receptors for, and specifically binds, a variety of bacteria within the small bowel lumen.[37]

Bacterial binding to mucin is presumed to promote clearance of pathogenic organisms as a protection of the small bowel, but it may promote colonization by nonpathogenic organisms or promote small bowel colonization by pathogens when the mucin is damaged by malnutrition, an inflammatory process, or bacterial proteases or mucinases. Loss of the protective mucin layer in tropical sprue is suggested by evidence that the bacteria visualized are often associated tightly within the mucosa rather than being free within the intestinal lumen.[2] Damage to the protective mucin layer may also permit epithelial cell damage by other small bowel microbes and their toxins. The presence of free bile acids within the upper small bowel can alter intestinal bacterial growth rates and colonization, but bile acid concentrations have not been abnormal in patients with tropical sprue, and the bacterial organisms that have been cultured from patients with tropical sprue are not organisms that typically alter bile salt metabolism.[38]

Intestinal immunologic dysfunction has been suggested as a factor that might predispose to abnormal bacterial colonization in tropical sprue. Patients with deficiencies of secretory immunoglobulin (Ig) A are subject to more frequent and severe bouts of enteric infections. In addition to secretory IgA, lymphoid tissue is present throughout the small bowel focally in Peyer patches and diffusely as mucosal lymphocytes. When small bowel lymphocytes were characterized in patients with tropical sprue and in control patients with irritable bowel syndrome in southern India, there was no difference in the number of IgA-producing, IgG-producing, or IgM-producing lymphocytes between the two groups.[39,40] Patients with sprue had increased numbers of lymphocytes in the crypt epithelium, with a higher percentage of immunoblasts and a higher mitotic index.[41] These data can be interpreted as evidence that lymphoid activation occurs in tropical sprue, but that it is probably a secondary response to inciting microbes, rather than being the inciting process itself.

It has also been postulated that dietary fat might play a role in tropical sprue. Similar to the permissive effect of protein ingestion in the pathogenesis of pig-bel, the intake of long-chain fatty acids has been studied as a potential causative factor for tropical sprue.[42] The seasonal epidemic occurrence of tropical sprue in Puerto Rico immediately follows a traditional holiday feast of pork, which is rich in long-chain fatty acids.[43] There are several mechanisms whereby these long-chain fatty acids might contribute to the production of clinical tropical sprue. Long-chain fatty acids can alter intestinal motility and delay intestinal transit time. Plasma levels of enteroglucagon and motilin are increased significantly in patients with tropical sprue; motilin slows gastric emptying, and enteroglucagon slows intestinal transit.[44] Studies have also demonstrated abnormalities in peptide YY and neurotensin after infusion of fat in some patients with sprue, which may contribute to altered motility and bacterial overgrowth.[45] Intubation studies have shown that intestinal infusions of fat increase plasma enteroglucagon levels and decrease intestinal motor activity. Fat within the gut lumen also inhibits the mucosal sodium-potassium fluxes and the magnesium

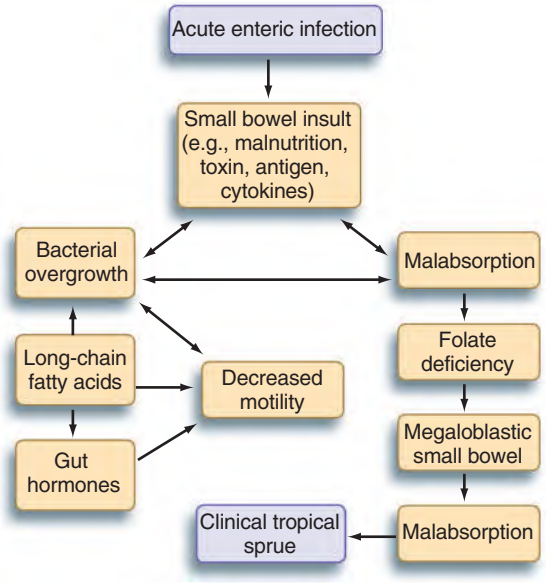

FIG. 102.1 Proposed pathogenesis of tropical sprue. The complex vicious cycle of small bowel insult that results in bacterial overgrowth and malabsorption, as well as further small bowel damage by luminal long-chain fatty acids and dysregulation of intestinal hormones, may promote disease in susceptible persons after an acute enteric infection.

adenosine triphosphatases, which can contribute to malabsorption of water and electrolytes in the intestine and raise the pH of the mucosal microenvironment.[42,46]

The elevated mucosal pH produced by intestinal fats also has been associated with increased growth of gram-negative bacteria in the lumen of the small bowel, and a switch to a high-fat diet has been associated with alterations in the intestinal microbiota.[24,47]

The elevation of mucosal pH and the presence of fatty acids within the lumen of the gut also may impair the ability of the intestine to absorb folate; folate deficiency may potentiate the intestinal dysfunction that precedes it.[48] Folate deficiency leads to a decreased number of gut epithelial cells, as assessed by DNA concentrations, and to villous atrophy. Additional structural alterations are seen in the intestine with folate deficiency, including crypt hypertrophy, villous blunting, and megaloblastic changes in the epithelial cells. These changes are nonspecific and are similar to those seen with vitamin B_{12} deficiency, celiac disease, or tropical sprue. Functionally, the folate-deficient gut is less efficient in absorbing water, electrolytes, and carbohydrates than the normal small bowel.[49] It is likely that whatever the initial insult to the gut may be in tropical sprue, the resulting folate malabsorption and deficiency contribute to the further pathogenesis of disease (Fig. 102.1).

Exocrine pancreatic insufficiency has been documented in patients with tropical sprue by the indirect pancreolauryl test.[50]

INTESTINAL ABNORMALITIES

Tropical Sprue

Although the secretory and malabsorptive syndrome seen in tropical sprue suggests preferential damage to the small bowel, functional abnormalities are seen in the large bowel as well. Functional changes in the small bowel mirror the morphologic changes seen and are most prominent in the ileum and jejunum. In tropical sprue, the jejunum is in a net secretory state, with active secretion of water, sodium, and chloride[51]; however, glucose-linked absorption remains intact, as it does for many other secretory infectious diarrheal syndromes.[52] In tropical sprue, there also is malabsorption of bile acids and vitamin B_{12} in the ileum. Bile acid malabsorption leads to fat malabsorption and malabsorption of the fat-soluble vitamins D, A, K, and E. Brush border enzymes are decreased functionally and are less efficient in digesting and absorbing disaccharides, such as lactose.[53,54] Xylose, glucose, and folate malabsorption occur, as does malabsorption of minerals such as calcium and