Viral								
Measles	Measles virus							+
Rubella	Rubella virus							+
Infectious mononucleosis	Epstein-Barr virus							+
Cytomegalovirus mononucleosis	Cytomegalovirus							+
Dengue fever	Dengue virus							+
West Nile fever	West Nile virus							+
Lassa fever	Lassa fever virus							+
Oropharyngeal herpes infection	HSV type 1	+	±					+
Genital herpes infection	HSV type 2	+						
Primary HHV-6 infection	HHV-6	+						
Primary HHV-7 infection	HHV-7	+						
Cowpox	Cowpox virus	+	±					
Pharyngoconjunctival fever	Adenovirus (types 3 and 7)	+	+					
Epidemic keratoconjunctivitis	Adenovirus (types 8 and 19)	+						
AIDS, AIDS-related complex	Human immunodeficiency virus							+
Protozoan								
Kala-azar	*Leishmania donovani*							+
African trypanosomiasis	*Trypanosoma brucei*				+			+
Chagas disease	*Trypanosoma cruzi*						+	+
Toxoplasmosis	*Toxoplasma gondii*	+					+	+
Helminthic								
Filariasis	*Wuchereria bancrofti* *Brugia malayi*	+ +						+ +
Loiasis	*Loa loa*			+				
Onchocerciasis	*Onchocerca volvulus*			+				

+, Present; ±, rare; *AIDS,* acquired immunodeficiency syndrome; *HHV,* human herpesvirus; *HSV,* herpes simplex virus.

cultures, which yield uniformly positive results in the septicemic phase of plague, as well as cultures and stained smears of carefully obtained bubo aspirates. Appropriate treatment (see later) should be instituted immediately, before results of cultures become available, if bubonic plague is suspected. Miscellaneous causes of inguinal buboes include cat-scratch disease, group A streptococci superimposed on chronic lymphadenopathy in homosexual men,[116] and melioidosis.[117]

Generalized Lymphadenitis Associated With Systemic Infections

Widespread nonsuppurative lymphadenitis is a common feature of a variety of disseminated bloodstream infections and generally reflects the presence of the invading microorganism in the nodes. Generalized lymphadenopathy is a feature, for example, of secondary syphilis, HIV infection, infectious mononucleosis, acute toxoplasmosis, leptospirosis, and miliary TB, and, considered broadly, may occur in a variety of infections due to bacterial, rickettsial, chlamydial, spirochetal, viral, protozoal, and helminthic agents (see Table 95.1). Generalized lymphadenitis due to *Bartonella* infection has been observed in HIV-infected individuals,[99] sometimes associated with hemophagocytic lymphohistiocytosis.[118] Leishmanial lymphadenitis has been documented by fine-needle aspiration cytology in an HIV-infected patient.[119] In immunocompromised hosts, particularly after organ transplantation, Epstein-Barr virus infection may evolve into a lymphoproliferative disorder (posttransplantation lymphoproliferative disorder) that requires modulation of immunosuppressive therapy and possible rituximab administration[120,121] (see Chapter 138).

Recurrent Lymphadenitis

Periodic Fever, Aphthous Ulcers, Pharyngitis, and Adenitis Syndrome

There are several periodic fever syndromes that possess well-defined genetic defects or readily identifiable laboratory abnormalities in addition to distinctive patterns of illness. Lymph node involvement is generally not a prominent feature of these diseases. However, recurrent cervical lymphadenitis is a prominent feature of periodic fever, aphthous ulcers, pharyngitis, and adenitis syndrome (PFAPA)[122] (Marshall syndrome), a disease of unknown etiology but possibly associated with interleukin (IL)-1β receptor polymorphisms[123] or regulators of the NLRP3 (NOD-like receptor family, pyrin domain–containing 3) inflammasome, such as CARB-8.[124] This syndrome, which has its onset primarily, but not exclusively, in young children, is recognized by roughly monthly sudden bouts of high fever associated with oropharyngeal involvement (aphthous ulcers, pharyngitis) and cervical adenitis and has an incidence of roughly 2.3 per 10,000.[122] Adult onset of PFAPA shares the same clinical features as the more typical childhood-onset syndrome.[125] Febrile episodes are accompanied by leukocytosis and elevation of the erythrocyte sedimentation rate. Patients become entirely well after 4 to 5 days of fever and remain asymptomatic, with normal laboratory studies until the next bout of fever. The syndrome persists for an average of 4 to 5 years. The acute febrile symptomatic episodes can be promptly aborted by single doses of prednisone (1–2 mg/kg).[122] Colchicine, cimetidine, and IL-1 inhibitors such as anakinra may be effective second-line therapies.[126] The evidence that tonsillectomy induces permanent remission of symptoms in nearly all cases is increasingly robust, with remission rates greater than 95% commonly reported.[127] Excised tonsillar tissue from PFAPA patients show changes in nodal germinal center size, but this does not explain the efficacy of tonsillectomy in this population.[128]

Filarial Lymphangitis

Recurrent inguinal lymphadenitis, accompanied by lymphangitis, is a common problem in individuals with bancroftian filariasis. These acute inflammatory episodes (acute filarial lymphangitis) are thought to reflect the death of adult filariae with elicitation of a brisk host response but at times may represent bacterial infection that complicates adult worm-induced lymphectasia (see later).[129]

Etiologic Agents and Differential Diagnosis

It is helpful for purposes of the differential diagnosis to consider infective lymphadenitis in several categories (see Table 95.1): (1) regional lymphadenopathy, (2) regional lymphadenopathy with breakdown of nodes, (3) inguinal bubo formation, (4) ulceroglandular syndrome, (5) oculoglandular syndrome, and (6) generalized lymphadenopathy.

In distinguishing among the causes of fluctuant cervical lymphadenitis, the history and disease tempo may suggest a streptococcal (preceding tonsillitis) or staphylococcal process (recent facial or neck infection), or more indolent TB (previous exposure to TB) or cat-scratch disease (exposure to cat) as the causative disorder. In recent years an increasing fraction of reported suppurative cervical adenitis episodes is caused by *S. aureus; S. aureus* was recovered in approximately 40% to 50% of cases (two-thirds methicillin sensitive, one-third methicillin resistant), whereas group A streptococci were recovered in only approximately 15% to 20% of cases; 20% to 30% of cases were culture negative.[9,10] A subacute clinical course with little fever and a normal leukocyte count would be more consistent with cat-scratch disease or mycobacterial involvement. Sinus tract formation suggests infection due to *M. tuberculosis* or a nontuberculous mycobacterium. Gram-stained and Ziehl-Neelsen smears and culture (including cultures for mycobacteria) of material aspirated or drained from suppurating nodes provide a diagnosis in approximately two-thirds of such cases of cervical lymphadenitis. Further information may be provided by skin tests (PPD) or IFN-γ release assays,[130] or both; serologic tests (anti–streptolysin O and anti–DNase B antibody titers); histologic examination (e.g., caseation necrosis suggesting mycobacterial infection or bimorphic appearance suggesting cat-scratch disease); and molecular diagnostic tests, such as PCR (if available) of an excised node when culture of aspirated material is unrevealing. Surgical exploration affords both diagnosis and therapy of suppurative lymphadenitis. Fine-needle cytologic diagnosis is often effective for the diagnosis of *M. tuberculosis* infection, and in many centers with procedural and cytologic expertise, this procedure is initially used in the evaluation of subacute nonsuppurative lymphadenitis.[131] Simple incision and drainage are satisfactory for bacterial or *B. henselae* lymphadenitis. Complete excisional biopsy is preferred when exploring mycobacterial adenitis to reduce the risk of poor wound healing, unsightly scar formation, and relapse[88–91]; thus the presenting clinical features must guide surgical strategy.

A variety of noninfectious processes may resemble unilateral cervical lymphadenitis. Lymphoma may be suggested by the indolent course of cat-scratch disease. Kawasaki disease (acute febrile mucocutaneous lymph node syndrome), a vasculitic process of unknown etiology almost exclusively affecting infants and young children, is characterized by nonsuppurative cervical lymphadenopathy (also see Chapter 297).[132–134,135] The age of the patient, extended febrile course, conjunctival injection, polymorphic erythematous rash, and subsequent acral desquamation strongly suggest the diagnosis. In some patients unilateral lymphadenitis may precede mucocutaneous manifestations and make diagnosis more difficult by initially suggesting bacterial involvement.[136,137] A variety of additional clinical (uveitis, hydrops of the gallbladder) and laboratory findings (sterile pyuria, inflammatory synovitis, aseptic meningitis, hypoalbuminemia, thrombocytosis, elevated erythrocyte sedimentation rate, and C-reactive protein) may also be present and support the diagnosis.[132] Cases of Kawasaki disease, in both "classic" and "incomplete" forms, have been rarely reported in adults.[138]

An additional benign disorder of lymph nodes, histiocytic necrotizing lymphadenitis or Kikuchi-Fujimoto disease, was first reported in Japan 40 years ago but is now widely observed.[139,140,141,142] Clinical features consist of localized, sometimes tender cervical lymphadenopathy, often with an upper respiratory prodrome and associated in some patients with fever or rash. Most cases occur in women, commonly younger than 40 years. The involved nodes are usually rubbery or firm, discrete, and often modest in size, but occasionally they can exceed 4 cm in diameter.[139] Although 75% of patients have unilateral cervical adenopathy, bilateral disease and involvement of other nodal regions can occur. CT imaging frequently demonstrates involvement of multiple lymph nodes.[143] On occasion, patients present with generalized lymphadenopathy, and, rarely, hepatosplenomegaly occurs.[140] Less frequent symptoms include nausea, vomiting, weight loss, and night sweats, suggesting the diagnosis of lymphoma. Mild leukopenia is generally present; lymphocytosis may suggest infectious mononucleosis. The illness does not respond to antibiotics, but it usually resolves spontaneously within 1 or 2 months,[141] although recurrences are seen. Histologically, surgical biopsy specimens may be erroneously interpreted as lymphoma, but the principal findings

are those of focal or confluent nodules (composed of crescentic histiocytes, plasmacytoid monocytes, immunoblasts, and karyorrhectic debris) combined with patchy areas of coagulative necrosis. Neutrophils are few or absent. Diagnosis can be made in many cases by fine-needle aspiration cytology,[1,144] although the cytologic findings may overlap with other conditions, particularly TB, and specimens should be submitted for mycobacterial studies and cytologic examination.[145] Histologically, the lymph node appearance in systemic lupus erythematosus is similar to that in Kikuchi disease, but hematoxylin bodies are characteristic of the former. Serologic studies (antinuclear antibody and anti–double-stranded DNA antibody titers) help to distinguish between these processes. Although a viral origin is suspected based on the clinical features, serologic, ultrastructural, and molecular biologic studies have failed to identify consistently a specific agent.[139]

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is another benign process that produces extensive, painless lymphadenopathy in the cervical areas, primarily in adolescents and young adults with a mean age at onset of 20 years.[146] It represents a heterogenous disorder, with acquired mutations in cell activation pathways seen in some individuals.[147] It is often accompanied by fever, neutrophilic leukocytosis, and polyclonal hypergammaglobulinemia. Histologically, there is extensive proliferation of histiocyte-like cells within the sinuses of the involved lymph nodes.[146] The etiology is unknown, and the prognosis is favorable. Spontaneous remission may occur in half of all patients. Excision of lymph nodes associated with obstructive complications or administration of glucocorticoid therapy can be considered in selected patients.[147]

Kimura disease, a pruritic infiltrative eosinophilic process of soft tissue associated with hyperimmunoglobulin E, seen predominantly in men, often presents with painless regional lymphadenopathy, most commonly involving cervical lymph nodes, although generalized lymphadenopathy may develop. The soft tissue and laboratory findings (eosinophilia and elevated immunoglobulin [Ig]E) and cytologic abnormalities on fine-needle aspiration all contribute to confirm the diagnosis.[148,149]

Bronchial cleft cysts and cystic hygromas may be mistaken for cervical lymphadenitis, particularly if infected; thyroglossal duct cysts may suggest infected submental nodes. Infections of these congenital structures must be considered, particularly if a patient presents with a history of recurrent bacterial cervical adenitis. Lymphoepithelial cysts, indolent lesions of the salivary glands (usually the parotid) occurring in HIV-infected patients, may mimic preauricular lymphadenopathy or suggest Sjögren syndrome.[150] Submaxillary sialadenitis or salivary gland tumors may mimic submandibular lymphadenitis. Bimanual (intraoral and submandibular) palpation can be helpful in distinguishing between these processes.

Isolated inguinal lymphadenitis or bubo formation in the adult suggests venereal disease (syphilis, LGV, chancroid). Distinctive associated primary lesions are usually features of syphilis and chancroid but not of LGV, but in some individuals a syphilitic chancre may not be visible because of vaginal, cervical, or rectal inoculation. The inguinal adenopathy of primary syphilis consists of painless, firm, discrete, movable nodes without erythema of the overlying skin. The nodes do not suppurate, whereas spontaneous rupture of the buboes of LGV and chancroid may occur. The groove sign, reflecting lymphadenopathy proximal and distal to the inguinal ligament, is suggestive of LGV. The buboes of chancroid are characteristically painful. Axillary, cervical, and inguinal buboes may occur with plague and tularemia. In plague an inguinal location is common. The geographic locale and a history of animal exposure are important clues to the diagnosis. Inguinal and femoral nodes can be involved in cat-scratch disease, although much less frequently than axillary or cervical nodes, and this diagnosis should be considered if only limited toxicity or fever is present.

Generalized lymphadenopathy is frequently a manifestation of disseminated infection (see Table 95.1). Clues may be provided by the age of the patient and the presence of a characteristic rash (childhood exanthems, secondary syphilis), geographic factors (dengue, filariasis, localized *Leishmania* lymphadenitis[119,151] histoplasmosis), occupation and dietary history (brucellosis, toxoplasmosis); exposure to animals and their excreta (e.g., standing water [leptospirosis]), and the presence of atypical lymphocytes (infectious mononucleosis, cytomegalovirus [CMV] infection, acute toxoplasmosis, HIV). Diagnosis of toxoplasmic lymphadenitis in the immunocompetent patient is based primarily on serologic testing,[152,153] although sometimes a lymph node biopsy is performed because of initial concern for lymphoma. A negative result on the Sabin-Feldman dye test or on a comparable test for *Toxoplasma* IgG antibody (indirect immunofluorescence, passive hemagglutination, or enzyme-linked immunosorbent assay [ELISA]) practically excludes the diagnosis. Laboratory diagnosis of acute toxoplasmic lymphadenitis can be made by seroconversion from a negative to a positive result on IgG antibody testing, by demonstration of a fourfold increase in titers over 3 weeks, or by single Sabin-Feldman dye titers of 1:1024 or greater after 3 months of symptoms.[154] With toxoplasmosis the results of the ELISA are positive for IgM antibodies within the first 3 months of infection in most patients. A panel of serologic responses (dye test, IgM, IgA, IgE ELISA, and IgG avidity testing based on preferential binding to acetone versus formalin-fixed tachyzoites) helps to define recent infection and thus may avoid excisional biopsy.[152] High-avidity IgG responses suggest long-standing and likely prior incidental toxoplasmosis infection and encourage tissue biopsy for new-onset lymphadenopathy.[154] In endemic areas generalized nonsuppurative (and, rarely, suppurative) lymphadenopathy occurs in typhoid fever.[155]

Widespread suppurative infections of lymph nodes occur as a result of the microbicidal defect characteristic of neutrophils and monocytes in patients with chronic granulomatous disease. Recurrent infections (involving the skin, bones, lungs, liver, as well as lymph nodes) beginning in childhood and typically due to *S. aureus* and certain gram-negative bacilli (*Escherichia coli,* salmonellae, *Serratia marcescens*) or a variety of rare bacteria suggest the diagnosis. Focal suppurative lymphadenitis can also be seen in patients lacking early complement factors C1r or C3.

Widespread lymphadenopathy may be a feature of many noninfectious diseases, particularly infiltrative processes such as lymphoma and reticuloendothelioses. Miscellaneous noninfectious processes producing prominent peripheral lymphadenopathy include rheumatoid arthritis and adverse reactions after prolonged use of phenytoin. A rare form of regional lymphadenopathy, showing sinus histiocytosis (with the cells seen to contain metal granules or polyethylene) histologically, can be the result of wear-induced debris from an adjacent metallic prosthesis.[156,157] Similarly, enlarged regional lymph nodes (showing noncaseating granulomas containing silicone or histiocytic necrotizing lymphadenitis[158–160]) have been described draining areas in which a silicone mammary prosthesis[158,159] or a Silastic joint prosthesis[160] had been inserted previously. These lymph nodes may be ^{18}F-FDG avid by PET-CT scanning and erroneously suggest metastatic disease.[161]

Generalized Lymphadenopathy With Acquired Immunodeficiency Syndrome

HIV-infected patients may have generalized lymphadenopathy reflecting progressive primary HIV infection[61,162] (see Chapter 122). These immunosuppressed individuals are also at risk for lymph node involvement with opportunistic infection or neoplastic disease (particularly Kaposi sarcoma and a number of lymphoproliferative processes[162]). Commonly encountered opportunistic pathogens have included CMV, *M. avium-intracellulare, M. tuberculosis* (in high-incidence regions), rarely *Bartonella,* and/or fungal pathogens, such as *C. neoformans* or rarely *P. jirovecii*. Histoplasmosis may occur in endemic areas, and dual infections[60] or mixed infectious and neoplastic diseases are occasionally seen. Generalized mycobacterial lymphadenitis usually shows a few poorly formed or no granulomas and a prominent histiocytic reaction. Large clusters (globi) of acid-fast bacilli are present within the cytoplasm of histiocytes. Kaposi sarcoma in patients with AIDS may follow the pattern of generalized lymph node involvement and a fulminant course with mucosal and visceral lesions.[163] Multicentric Castleman disease and a variety of B- and T-cell lymphomas may present with lymphadenopathy in HIV-infected individuals, reflecting HIV-induced immunosuppression and resultant Epstein-Barr virus and HHV-8/Kaposi sarcoma–associated herpes virus–driven lymphocyte proliferation.[162]

Lymphadenopathy occurs in 50% to 75% of patients with primary HIV infection who present with an acute illness approximately 3 to 6 weeks after initial exposure to HIV.[164] These patients frequently experience a heterophile-negative mononucleosis-like syndrome consisting of fever, malaise, myalgias, headaches, sore throat, diarrhea,

leukopenia, thrombocytopenia, and a maculopapular rash. After the acute clinical illness subsides, lymphadenopathy may remain as persistent generalized lymphadenopathy, involving at least several extrainguinal sites, of at least 3 months' duration. This progressive lymphadenopathy early in the course of this infection may be the result of an active immune response against HIV in the affected lymph nodes.[165] The nodes are a prominent site of HIV replication and may regress somewhat in the first year or two after infection. The nodes are generally discrete and nontender; suppuration does not occur. In addition to characteristic cytologic findings,[61] immunohistochemical staining for p24 antigen expression will confirm HIV lymphadenitis in biopsy specimens of patients not thought to be at risk of HIV infection or who decline HIV testing.[166]

Presumptive Treatment of Lymphadenitis

Initial treatment of infective lymphadenitis requires some narrowing of the diagnostic possibilities (see Table 95.1). Localized pyogenic lymphadenitis generally responds well to early antibiotic treatment. When cervical lymphadenitis has clearly developed from a pharyngeal or periodontal portal, initial treatment of mild-to-moderate illness in nontoxic patients with penicillin is appropriate. Penicillin V (500 mg) administered orally every 6 hours or amoxicillin (500 mg) every 8 hours for 2 weeks in older children and adults is usually adequate. When the risk factors for cervical lymphadenitis are unclear, initial broader-spectrum coverage targeted for possible *S. aureus* infection is appropriate (see later). Macrolide therapy—azithromycin (5 mg/kg/day after a 10-mg/kg loading dose) or clindamycin (300 mg orally three times daily or 30 mg/kg/day in three divided doses for children)—is an alternative for patients allergic to penicillin, although resistance to macrolides among streptococci is known and may be striking in certain communities.[167,168] Nauseated patients with early or mild disease may receive initial parenteral therapy with daily ceftriaxone to ensure effective therapy before transitioning to oral therapy. In patients who are more acutely ill, high-dose penicillin G or broader-spectrum coverage, such as parenteral ampicillin-sulbactam or clindamycin (to cover possible β-lactamase–producing oral pathogens) administered parenterally, is indicated.

Pyogenic lymphadenitis complicating skin infections may be of staphylococcal or streptococcal etiology; gram-negative infections in competent hosts are extremely rare.[9,10] In communities with low rates of methicillin-resistant *S. aureus* (MRSA) infections, a penicillinase-resistant penicillin (e.g., dicloxacillin), a first-generation cephalosporin (e.g., cephalexin, given 0.5 g orally every 6 hours for the older child or an adult), or amoxicillin-clavulanic acid (875 mg orally twice daily) may be considered for nontoxic outpatients with mild-to-moderate infection. The current epidemic of community-acquired MRSA[9,10,169] has made empirical antibiotic management problematic. Trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline are generally effective against community-acquired MRSA isolates in vitro, but there are limited data regarding their clinical efficacy in this situation. Fluoroquinolones are no longer reliably efficacious against methicillin-susceptible *S. aureus* or MRSA in vitro,[9] and moreover, resistance can emerge readily when staphylococcal infections are treated with fluoroquinolones as monotherapy.[170] Macrolide resistance is common; clindamycin, although effective against clindamycin-susceptible MRSA strains, has variable resistance rates in different communities that may approach 50% in some settings, making linezolid, which is expensive and often unavailable, the only remaining reliable oral agent available. Thus patients will frequently require hospitalization and administration of vancomycin if they fail to respond to oral therapy. The recovery of a MRSA isolate by blood culture, node aspirate, or even nasal culture for susceptibility testing is thus helpful with regard to antibiotic therapy strategy.

In the more acutely ill patient, intravenous (IV) administration of vancomycin should be used. Failure to show improvement or progression to suppuration is an indication for imaging by ultrasonography or CT and consideration for percutaneous needle aspiration (for bacteriologic diagnosis and treatment) or surgical drainage. Many patients who present with acute suppurative lymphadenitis lack a history of focal infection; in these individuals antistaphylococcal therapy is appropriate. Surgical exploration before the evolution of frank suppuration is associated with difficult dissection and recovery of little, if any, purulent material. Hence exploration is usually reserved for clear-cut suppurative adenitis manifested by palpable fluctuance or the demonstration of necrotic nodes by cross-sectional imaging in the setting of continued fever and toxicity. In some centers needle aspiration is performed rather than open surgical drainage, with favorable clinical outcomes and avoidance of open surgery.[171] Recovery of MRSA at the time of a drainage procedure is invaluable to guide appropriate postoperative antibiotic therapy, particularly when considering a transition to oral therapy after initial improvement with parenteral therapy.

For cat-scratch disease, usually a self-limited process resolving in 2 to 4 months, treatment is principally symptomatic (see Chapter 234). If the nodes become fluctuant, aspiration is appropriate for both relief of pain and bacteriologic diagnosis. A limited number of strains of *B. henselae* from cases of cat-scratch disease that have been studied show in vitro susceptibility to a variety of antimicrobial agents, particularly to macrolides, ciprofloxacin, penicillins, and doxycycline.[172] In a retrospective review of antimicrobial treatment of several hundred patients with cat-scratch disease, clinical efficacy (58%–87%) was attributed to four drugs (in increasing order): TMP-SMX, gentamicin, ciprofloxacin, and rifampin.[173] Azithromycin has also been used to treat *B. henselae* lymphadenitis[174]; the intracellular concentration of this agent may offer a therapeutic advantage over other macrolides, but clinical trials comparing these agents are not available. In general the efficacy of antibiotic therapy in competent hosts seems limited[172]; therapy may be reasonable in patients with more severe or extranodal cat-scratch disease. Oral corticosteroids have been used in individuals with *B. henselae* lymphadenitis[175] or hepatosplenic infection refractory to antibiotic therapy. Bacillary angiomatosis and bacillary peliosis hepatitis, infections in patients with AIDS that are due to *B. henselae* or closely related Bartonellaceae spp., appear to respond to prolonged antimicrobial therapy with erythromycin, doxycycline, or rifampin.[172] Similarly, bartonellosis in solid-organ transplant recipients has responded to a variety of antibiotic regimens.[176]

If the diagnosis of bubonic plague is suspected, antibiotic treatment should be instituted promptly. Streptomycin (1 g intramuscularly [IM] every 12 hours in adults), alone or in combination with tetracycline (0.5 g orally every 6 hours in adults) or doxycycline (0.1 g orally every 12 hours in adults), is the preferred antibiotic therapy, and treatment is continued for 10 days. If streptomycin is not readily available, IV gentamicin should be considered, although clinical experience is more limited (see Chapter 229).[121,177]

LYMPHANGITIS

Lymphangitis is an inflammation of lymphatic channels, usually in the subcutaneous tissues. It occurs either as an acute process of bacterial origin or as a chronic process of mycotic, mycobacterial, or filarial etiology.

Pathologic Changes and Pathogenesis

The visible red streaking in acute lymphangitis stems from inflammation in the walls (and surrounding tissue spaces) of dilated lymphatic channels. Lymphatic obstruction often occurs on healing, sometimes resulting in persistent lymphedema. Cutaneous lymphatic sporotrichosis, a form of chronic lymphangitis, produces a combined suppurative and granulomatous response.

Clinical Findings

Acute Lymphangitis

Acute lymphangitis develops when a superficial dermal infection, commonly on an extremity, is not contained locally but spreads along lymphatic channels. Such infections are most often due to group A streptococci (and on occasion streptococci of other groups and, rarely, to *S. aureus* or *Pasteurella multocida* after a cat bite). Systemic manifestations may develop rapidly before evidence of infection becomes apparent at the site of inoculation of organisms, and they may be more prominent than might be anticipated based on local pain and erythema. Red linear streaks, a few millimeters to several centimeters in width, extend from the initial site of infection toward the regional lymph nodes, which are enlarged and tender. Peripheral edema of the involved extremity often

occurs. The time course of this type of infection can be accelerated from initial lesion to lymphangitis to complicating bacteremia in 24 to 48 hours. On occasion, there are recurrent episodes of lymphangitis, with the initial episode causing some degree of chronic lymphedema, in turn predisposing to another episode. Rarely, elephantiasis nostras verrucosa, a temperate-zone (nonfilarial) form of progressive lymphatic obstruction of a lower limb, can follow recurrent episodes of streptococcal lymphangitis. With each episode, further localized edema occurs, eventuating in grotesque enlargement of the extremity due to permanent solid edema, fibrosis of dermis and subcutaneous tissues, and verrucous pachydermia.[178] The peripheral white blood cell count is commonly increased. The etiologic agent sometimes can be identified on Gram-stained smears and cultures obtained from the initial lesion. Blood cultures also may reveal the causative organism.

Acute lymphangitis or lymphadenitis, usually involving the lower extremities, is a feature of filariasis due to *Wuchereria bancrofti* (and sometimes to *Brugia malayi*).[129,179] These mosquito-borne diseases are endemic to Africa, Southeast Asia and the Pacific, and tropical South America. The acute form of disease is characterized by recurrent episodes of headache, backache, lymphangitis, lymphadenitis, epididymitis, and orchitis. Bancroftian lymphangitis may involve the breast, with a clinical appearance suggesting carcinoma.[180] Fever is uncommon. The adult filariae reside in lymphatics and lymph nodes and discharge microfilariae into the bloodstream. With prolonged exposure in an endemic area, chronic lymphatic obstruction can develop with elephantiasis of the skin and scrotum.[180] In this setting recurrent episodes of lymphangitis (dermatolymphangioadenitis) may be the result of both the parasitic infestation and superimposed streptococcal infections (to which the chronic lymphedema predisposes).[129,181] The presence of microfilarial intracellular rickettsiae *(Wolbachia)* may help drive the ongoing host inflammatory response with resultant tissue injury.[179] Conventional serologic tests for bancroftian filariasis have limited specificity due to cross-reactivity with other filaria and even helminths. A rapid-format, immunochromatography filariasis card test is now widely used for the diagnosis of bancroftian filariasis.[182] Lymph node or lymphatic vessel biopsy may occasionally be necessary for diagnosis but is avoided if possible to minimize further lymphatic injury of the affected limb.

Chronic Granulomatous Lymphangitis

Unlike acute lymphangitis, chronic granulomatous lymphangitis is an indolent process associated with little pain or systemic evidence of infection and is most commonly due to sporotrichosis[183] (see Chapter 259), although a rather wide range of pathogens has been associated with this syndrome.[184] Minor trauma (e.g., from a barberry or rosebush thorn) inoculates *Sporothrix schenckii* (present on some plants and in gardeners' sphagnum moss) into the skin of a gardener's hand or finger. An erythematous subcutaneous nodule (often becoming fluctuant) or a chancriform ulcer subsequently develops at the site of inoculation. The lesion does not respond to local treatment or administration of common antibacterial agents. Slowly, multiple subcutaneous nodules appear and extend proximally along the course of regional lymphatics, which become thickened. Other infections producing a sporotrichoid pattern are described as nodular lymphangitis[185] and lymphocutaneous syndrome.[186]

Cutaneous infection ("swimming pool granuloma") with *Mycobacterium marinum,* an atypical mycobacterium that grows optimally at 25°C to 32°C and is found in swimming pools and fish tanks, produces a chronic nodular, verrucous, or ulcerative lesion at the site of an abrasion, usually about the knees or elbows. The lesion is usually solitary, but on occasion new lesions develop proximally, as in sporotrichosis. Multiple sporotrichoid lesions have occurred occasionally in infections due to *Nocardia brasiliensis* and in rare infections due to *Mycobacterium kansasii, Mycobacterium chelonae*, and *Nocardia asteroides.* Even rarer causes of nodular lymphangitis include leishmaniasis,[186] staphylococcal lymphangitis,[186,187] botryomycosis, and tularemia.[184,186] A rare but most troublesome process is localized granulomatous lymphangitis of the penile and scrotal skin with resulting chronic edema of the genital area. It may be associated with LGV, granuloma inguinale, Milroy disease, self-inflicted trauma, Melkersson-Rosenthal syndrome, or Crohn disease, or it may be idiopathic.[188] Penile edema can be an initial manifestation of Crohn disease or can develop as a late complication of well-established gastrointestinal disease.

Pseudolymphangitis

Exogenous liquid chemical agents that drain along the skin may produce localized linear inflammatory reactions and mimic superficial lymphangitis. When the provoking agent is directly toxic, the etiology of the rash is obvious. However, certain plant products can serve as photosensitizing agents, and the history of initial contact may not be recalled by the patient. In particular, lime rinds and juice contain several coumarin moieties that can provoke phytophotodermatitis.[189]

Etiologic Agents

In the United States acute lymphangitis is most commonly due to group A streptococci, and chronic lymphangitis is usually caused by *S. schenckii.* Other infectious agents occasionally produce lymphangitis (Table 95.2).

Differential Diagnosis

The combination of a peripheral infection or traumatic lesion and the acute onset of fever with proximal red linear streaks directed toward regional lymph nodes are diagnostic of acute lymphangitis. In the legs thrombophlebitis may produce linear areas of tender erythema, but the absence of an initiating lesion and tender regional adenopathy is helpful in distinguishing it from lymphangitis. It is important to note that, on occasion, severe lymphangitis may be complicated by the development of secondary thrombophlebitis. A history of rat bite and the subsequent development of lymphangitis suggest *Streptobacillus moniliformis* infection. Filariasis is a consideration when an appropriate geographic history is obtained. Sporotrichosis is considered when chronic ulcerative lymphangitis develops in a person working with plants, soil, or timbers. *M. marinum* is suggested as the etiologic agent when sporotrichoid lesions develop in a person who has been around brackish water environments, swimming pools, and fish tanks. In the absence of successful culture of draining purulent material, tissue biopsy for extensive

TABLE 95.2 Causes of Lymphangitis

CLINICAL FORM	ETIOLOGIC AGENT	RELATIVE FREQUENCY AS CAUSE OF LYMPHANGITIS
Acute	Group A streptococci	Common
	Staphylococcus aureus	Occasional
	Pasteurella multocida	Occasional
	Streptobacillus moniliformis (rat-bite fever)	Rare
	Wuchereria bancrofti; Brugia malayi (filariasis)	Rare (only in immigrants from endemic areas)
Chronic	*Sporothrix schenckii* (sporotrichosis)	Occasional
	Mycobacterium marinum (swimming pool granuloma)	Occasional
	Mycobacterium kansasii	Rare
	Nocardia brasiliensis	Rare
	W. bancrofti; B. malayi	Rare (only in immigrants from endemic areas)
	Nocardia asteroides	Very rare
	Mycobacterium chelonae	Very rare
	S. aureus (botryomycosis)	Very rare
	Leishmania brasiliensis or *Leishmania mexicana*	Very rare
	Francisella tularensis	Very rare

microbiologic (routine, fungal, mycobacterial), molecular (PCR), and histologic evaluation are important for confirming a specific etiology and initiating targeted therapy.

Presumptive Therapy

Penicillin therapy is the recommended initial treatment for acute lymphangitis. Prompt empirical therapy is crucial because disease progression may be quite rapid. Mild-to-moderate disease may be managed in an outpatient setting for nontoxic, reliable patients. In moderate cases an initial dose of IM ceftriaxone (1 g) may be administered, followed by high-dose oral therapy with penicillin V or amoxicillin (500 mg every 6 hours) if close monitoring is possible. Oral dicloxacillin or cephalexin (500 mg every 6 hours) is commonly given if there is concern regarding a possible staphylococcal etiology, but staphylococcal infections generally have a somewhat more indolent course, often with local suppuration at the primary site of infection with adjoining cellulitis, rather than rapidly progressive lymphangitis. If MRSA is prevalent in the community, consideration of methicillin-resistant staphylococcal infection should lead to appropriate therapy as discussed previously. More acutely ill patients, particularly those in whom bacteremia may have developed, should be hospitalized and given parenteral aqueous penicillin G (e.g., 2 million units every 4–6 hours) or ceftriaxone (2 g IV daily). If a possible staphylococcal etiology is suspected, vancomycin (1 g every 12 hours) should be initially administered to hospitalized patients.

The initial treatment of presumptive lymphocutaneous sporotrichosis is itraconazole; a saturated solution of potassium iodide is also effective (see Chapter 259).[183,190] If sporotrichoid *M. marinum* infection is suspected, the diagnosis should be confirmed by demonstration of acid-fast bacilli and isolation of the organism at 30°C on appropriate media. Localized swimming pool granulomas are often treated by limited surgical excision. Chemotherapy is reserved for more extensive and sporotrichoid forms of infection. Based on limited data, monotherapy with doxycycline or clarithromycin has been suggested; combination therapy (rifampin with ethambutol and TMP-SMX or doxycycline-clarithromycin) in more severe disease is recommended (see Chapter 252).[191,192] Chronic lymphedema, a complication of recurrent lymphangitis, has been treated primarily in the past with elevation and elastic hosiery. Newer and more successful methods to increase lymph drainage for problematic patients have recently been developed and include remedial exercises, manual massage, multilayered bandage wrapping, and intermittent pneumatic compression massage.[193] Individuals with frequent episodes of recurrent cellulitis occurring in the setting of chronic lymphedema may benefit from chronic suppressive therapy with penicillin (e.g., 250 mg orally twice daily).

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The complete reference list is available online at Expert Consult.

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J Gastrointestinal Infections and Food Poisoning

96 Syndromes of Enteric Infection

Regina C. LaRocque and Jason B. Harris

SHORT VIEW SUMMARY

- Gastrointestinal (GI) infections are an important cause of morbidity and mortality worldwide.
- GI infections may manifest with acute vomiting, acute watery diarrhea, bloody diarrhea (dysentery), persistent diarrhea, or enteric fever. Most pathogens may cause more than one syndrome.
- GI infections in adults are usually uncomplicated. Complicated GI infections are associated with certain clinical features, epidemiologic risk factors, and host determinants.
- Although a microbiologic diagnosis is not necessary for most GI infections, diagnostic testing is important for the management of severe disease and may also have public health implications, particularly in recognizing outbreaks.
- Rehydration is the mainstay of treatment for most GI infections, and the role of antimicrobial and other therapies varies depending on the specific pathogen and clinical scenario.

Gastrointestinal (GI) infections have a range of clinical manifestations and can result from infection with viruses, bacteria, protozoa, or parasites. Symptoms of gastroenteritis relate to infection at the mucosal surface, to direct microbial invasion of the gut, and/or to the effect of microbial toxins on GI mucosal cells or on the central or enteric nervous systems. Systemic symptoms may occur in association with GI infection as a result of microbial dissemination via the bloodstream, the systemic effects of toxins produced in the GI tract, and/or the host inflammatory response to the infection. Enteric pathogens are frequently transmitted through contaminated food or water, and some pathogens with low infectious doses may spread from person to person. These pathogens may cause outbreaks of local and international significance and are among the leading causes of childhood morbidity and mortality, particularly in populations with limited access to safe water or adequate sanitation. Travel and the globalization of the food supply are important factors in the global dissemination of enteric infections.

Most GI infections due to common bacterial and viral causes are self-limited, with symptoms resolving in a normal host usually within 7 days. In such cases a specific microbiologic diagnosis is not necessary unless the disease is more severe or is part of an outbreak. An array of diagnostic and therapeutic strategies is available for GI infections, and these need to be applied in clinical scenarios in which they will yield the most benefit to the patient. The emergence of multidrug-resistant enteric pathogens, such as nontyphoidal *Salmonella, Shigella,* and *Vibrio cholerae,* and the increasing frequency and severity of nosocomial *Clostridioides difficile* (formerly *Clostridium difficile*) infection underscore the need for optimal, cost-effective approaches to the diagnosis, management, and control of enteric infections.

The term *gastroenteritis* is applied to syndromes of diarrhea or vomiting. *Diarrhea* is commonly defined as three or more loose stools in a 24-hour period[1]; it is considered *acute* when the duration is 14 days or less and *persistent* when the duration is 14 days or longer. Causative organisms differ significantly between gastroenteritis that is *community acquired* and that which is *nosocomial.* A broader spectrum of organisms may cause enteric infection in the immunocompromised host, and clinical manifestations may be more severe and more prolonged in such individuals.

OCCURRENCE AND SCOPE OF GASTROINTESTINAL INFECTIONS

Diarrhea is an important cause of morbidity and mortality worldwide, particularly in children living in areas without adequate access to safe water and sanitation. The Global Burden of Disease Study found that diarrhea was the ninth leading cause of death globally in 2015 and was responsible for 8.6% of deaths among children younger than 5 years.[2] The greatest impact of diarrheal illness is among children younger than 5 years in low- and middle-income countries, where diarrhea is the second most common cause of death beyond the neonatal period.[2,3] Death rates from diarrhea have declined over the past decade with improvements in sanitation, more widespread use of oral rehydration solution, and the introduction of rotavirus vaccination programs. Nevertheless, diarrheal disease continues to cause significant morbidity, with nearly 1.7 billion cases of childhood diarrheal disease globally every year.[4,5]

Diarrhea has a complex interplay with nutritional status among children. Undernutrition, particularly micronutrient deficiency, increases susceptibility to acute infectious diarrhea and predisposes to more prolonged episodes of diarrheal illness. Conversely, diarrheal disease may exacerbate nutritional deficiencies in several ways. Overall caloric demands are increased during acute diarrheal illness. Gut injury causes malabsorption, and anorexia and altered eating habits may also affect caloric intake. In parts of the world where body stores of vitamin A are low, children with acute or persistent diarrhea can quickly develop complications of vitamin A deficiency, including xerophthalmia.

Repeated episodes of diarrheal illness are associated with deficits in the physical and cognitive development of children. A multivariate analysis of longitudinal data from five developing countries found that the odds of stunting at 2 years increased with each diarrheal episode and with each day of diarrhea.[6] Early childhood diarrhea has also been associated with subsequent impairments in cognitive development and school performance.[7,8] Thus, the overall health impact of diarrheal disease

in children may be even greater than is suggested by incidence and mortality data alone.

OCCURRENCE AND SCOPE OF GASTROINTESTINAL INFECTIONS IN HIGH-INCOME COUNTRIES

Approximately 179 million cases of acute gastroenteritis occur in the United States each year.[9] Although gastroenteritis is most often an uncomplicated illness, outbreaks of acute gastroenteritis are, nonetheless, an important public health concern; 10,756 outbreaks of gastroenteritis due to presumed person-to-person spread or environmental contamination occurred in the United States in 2009–13.[9] Closed and semiclosed communities, including schools, residential facilities, and cruise ships, are important settings for such outbreaks. Norovirus, which is highly contagious and robust in surviving on surfaces, is the most common etiologic agent associated with outbreaks of acute gastroenteritis and the leading cause of medically attended acute gastroenteritis in the United States.[9–11] Other reported causes of outbreaks of acute gastroenteritis transmitted by person-to-person contact in the United States include *Shigella,* Shiga toxin–producing *Escherichia coli* (STEC, also known as enterohemorrhagic *E. coli*), and rotavirus. Historically, rotavirus has been the most common cause of acute gastroenteritis among infants and young children; pediatric rotavirus vaccination was broadly recommended in the United States in 2006,[12] and pediatric diarrheal hospitalizations and medical expenditures have declined sharply since then.[13,14]

Outbreaks of foodborne gastroenteritis are also common, even in high-income countries. The Centers for Disease Control and Prevention (CDC) estimates that there are 9.4 million illnesses, 59,961 hospitalizations, and 1351 deaths due to foodborne disease annually in the United States.[15] Among the most important pathogen-food combinations in terms of disease burden are *Campylobacter* (poultry), *Toxoplasma gondii* (pork), *Listeria monocytogenes* (delicatessen meats and dairy), and *Salmonella enterica* (poultry).[16] Norovirus may spread by consumption of contaminated food and water, as well as by airborne droplets of vomitus and fomite contamination.[17–20] Multinational epidemics can highlight the global significance and economic impact of foodborne GI infections. In 2011, a multinational outbreak of STEC O104:H4, transmitted via contaminated bean sprouts, was centered in northern Germany and affected nearly 4000 individuals, with 53 deaths.[21–23] The cost of this outbreak in material and human losses was estimated to be more than 2 billion US dollars.

Gastroenteritis is also a common nosocomial infection in the developed world, and the causative organisms are distinct from those of diarrhea in the community. *C. difficile* is the predominant cause of nosocomial diarrhea among adults in the United States,[24] but other bacterial pathogens, including *Klebsiella oxytoca*[25] and toxin-producing strains of *Clostridium perfringens,*[26] have also occasionally been associated with nosocomial diarrhea. Outbreaks of norovirus are common in health care settings, and illness can be more prolonged in hospitalized individuals.[27]

PATHOGENS ASSOCIATED WITH GASTROINTESTINAL INFECTIONS

GI infections can result from infection with viruses, bacteria, protozoa, or parasites (Table 96.1). Most of the agents of GI infection can cause more than one syndrome of enteric infection. Precise data regarding the incidence of enteric pathogens responsible for diarrheal illness are often limited. For example, the microbiologic etiology was unknown in 31% of outbreaks of acute gastroenteritis transmitted by person-to-person spread in the United States in 2009–13.[9] When active surveillance is performed, norovirus has been identified as the most common cause of medically attended acute GI illness in the United States.[28,29] The CDC's Foodborne Diseases Active Surveillance Network (FoodNet) monitors cases of nine laboratory-diagnosed enteric organisms reported from 10 US sites; in 2013–16, nontyphoidal *Salmonella*, *Campylobacter,* and *Shigella* were the three leading pathogens identified, with *Listeria* being associated with the highest number of deaths.[30]

The spectrum of causative pathogens in resource-limited areas is different than in high-income countries. Using a combination of culture-based and quantitative molecular diagnostic testing methods, the Global Enteric Multicenter Study (GEMS), a large case-control study of diarrhea in children in Africa and Asia, identified that most attributable cases of moderate-to-severe diarrhea were due to six pathogens: *Shigella* spp., rotavirus, adenovirus 40/41, enterotoxigenic *E. coli* (ETEC), *Cryptosporidium* spp., and *Campylobacter* spp.[31,32] In addition, in settings where there is a high burden of enteric disease in children, concomitant infection with multiple pathogens is common.[32,33] For example, Bangladeshi infants with diarrheal illness had an average 5.6 pathogens detected versus 4.3 pathogens detected in control samples.[33]

ENVIRONMENTAL RISK FACTORS FOR GASTROINTESTINAL INFECTION

Environmental factors play an important role in the epidemiology of gastroenteritis. Most important, exposure to contaminated food and/or water plays a key role in the transmission of most GI pathogens; lower-income countries that lack sanitation infrastructure and access to safe water consequently have the highest rates of diarrhea-associated morbidity and mortality.

International travel is one important risk factor for GI infection in developed countries. Traveler's diarrhea is the most common travel-related infectious illness and occurs in up to 40% of travelers to regions of Asia, Africa, and Latin America. Among US travelers, the majority of cases of traveler's diarrhea occur in individuals returning from Latin America and the Caribbean, but risk is greatest after travel to Africa.[34] A variety of organisms may cause traveler's diarrhea (see Table 96.1), although ETEC strains are the most common cause overall. *Campylobacter,* nontyphoidal *Salmonella,* and *Shigella* are the pathogens that are most commonly identified when microbiologic evaluation is performed.[34]

Consumption of contaminated food remains an important risk factor for the acquisition of enteric infection. Fruits, vegetable row crops, beef, sprouts, and seeded vegetables were the most commonly implicated foods in 120 multistate foodborne outbreaks in the United States from 2010–14.[31,35] Ill food handlers are also important sources for foodborne outbreaks, particularly due to norovirus and other pathogens easily transmitted by person-to-person contact. The US Food and Drug Administration Food Code requires no bare-hand contact with ready-to-eat foods, but a failure to maintain proper personal hygiene has been observed in as many as 76% of restaurants.[36] *Campylobacter, Salmonella,* and STEC are zoonotic infections, and consequently food prepared from infected animals may be contaminated when sold to consumers. In contrast, humans are the only natural host for *Shigella* and norovirus, so food may be contaminated during preparation or by an infected food service worker.

GI infections exhibit a seasonal pattern in both temperate and tropical climates. Enteric infections in temperate climates may occur during the winter when individuals tend to congregate together indoors. The wintertime predominance of norovirus infection is so marked that it has been called "winter-vomiting disease." Foodborne outbreaks occur more commonly during summer months.[37] In tropical areas, such as Bangladesh, there are distinct summer peaks of GI illness, and seasonal flooding may play a role in facilitating the transmission of organisms.[38]

Behavioral and environmental factors also play a role in the spread of nosocomial diarrhea. Spores of *C. difficile* often contaminate hospital environments and the hands of health care workers. These spores are resistant to alcohol-based disinfectants and can survive on environmental surfaces for as long as 6 months. Spores are resistant to gastric acid and can easily spread from one patient to another on the hands of health care workers or from contaminated surfaces in the room of an infected patient, even after they have been discharged.[24]

HOST FACTORS IN GASTROINTESTINAL INFECTION

Host factors are important in determining which individuals become ill after exposure to an enteric pathogen.

Age

The epidemiology and clinical manifestations of enteric infection vary with age, with young children and the elderly usually being susceptible

TABLE 96.1 Common Gastrointestinal Pathogens and Their Key Epidemiologic Features

ORGANISM	KEY EPIDEMIOLOGIC FEATURES
Viruses	
Adenovirus	Serotypes 40/41 among the leading causes of infantile gastroenteritis globally
Astrovirus	Outbreaks in closed populations
Norovirus	Most common cause of medically attended gastroenteritis in United States: winter vomiting illness; environmentally hardy
Rotavirus	Most common global cause of gastroenteritis in young children, particularly in settings without rotavirus vaccination
Sapovirus	Mainly affects infants and toddlers
Bacteria	
Aeromonas spp.	Widely distributed in aquatic environments; may cause diarrhea or extraintestinal infection
Bacillus cereus	Vomiting illness; rare fatal cases with hepatic necrosis; testing for toxin available
Campylobacter jejuni	Associated with poultry; common cause of traveler's diarrhea in Asia; associated with postinfectious arthritis and Guillain-Barré syndrome
Clostridioides difficile	Leading cause of mortality from gastrointestinal infection in United States
Clostridium botulinum	Vomiting illness due to preformed toxin ingestion; infant botulism due to germination of spores presents with progressive weakness
Enteroaggregative *Escherichia coli*	Persistent diarrhea in young children, associated with malnutrition
Enterohemorrhagic *E. coli* (STEC)	Associated with hemolytic-uremic syndrome in children
Enteroinvasive *E. coli*	Associated with dysentery
Enteropathogenic *E. coli*	Acute watery diarrhea
Enterotoxigenic *E. coli*	Most common cause of traveler's diarrhea
Listeria	Associated with raw dairy products; pregnancy complications with systemic illness
Nontyphoidal *Salmonella* spp.	Intestinal carriage can be prolonged
Plesiomonas shigelloides	May cause watery diarrhea, dysentery, or extraintestinal infection
Shigella spp.	Most common global cause of dysentery
Staphylococcus aureus	Vomiting due to preformed staphylococcal enterotoxin ingestion
Vibrio cholerae	Outbreaks of watery diarrhea associated with lack of sanitation and humanitarian crises
Vibrio parahaemolyticus	Associated with shellfish consumption
Yersinia enterocolitica	Zoonosis; able to grow in refrigerated food; associated with postinfectious polyarthritis
Yersinia pseudotuberculosis	Appendicitis-like syndrome
Protozoa	
Cryptosporidium hominis/parvum	Major cause of childhood diarrheal in children in low-income countries
Cyclospora cayetanensis	Opportunistic infection; associated with foodborne outbreaks
Cystoisospora belli	Tropical and subtropical areas; opportunistic infection
Entamoeba histolytica	May cause liver abscess
Giardia lamblia	Associated with drinking from contaminated streams
Microsporidium	Ubiquitous in the environment; opportunistic infection
Parasites	
Anisakis simplex	Vomiting illness after consuming raw fish

STEC, Shiga toxin–producing enterohemorrhagic *E. coli* (original, alternative definition of enterohemorrhagic *E. coli*).

to the most severe complications. Globally, children younger than 5 years suffer the greatest morbidity and mortality from GI infection. Participants in the GEMS in sub-Saharan Africa and South Asia experienced 20 episodes of moderate-to-severe diarrhea in the first 2 years of life.[39] The elevated risk for children in this age range can be attributed to the loss of maternal antibodies and the discontinuation of breastfeeding, which is highly protective against diarrheal disease.[40] High rates of antibiotic use in the first 2 years of life may also play a role in elevating this risk through alterations in the intestinal microbiome.[41] Breastfeeding protects against GI pathogens via a number of mechanisms. Human milk glycans function as soluble receptors that inhibit pathogens from adhering to their target receptors on the intestinal mucosa.[42] Breast milk also contains high levels of secretory immunoglobulin A (IgA), which plays a crucial role in mucosal immunity, and breastfeeding reduces exposure to contaminated foods and ensures adequate nutrition for infants. In large part because of its protective effects against GI infection, World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life if the mother is not infected with human immunodeficiency virus (HIV).[43]

Numerous GI pathogens have higher attack rates in young children. Rotavirus causes nearly uniform infection in the first or second year of life in unvaccinated populations. ETEC, enteropathogenic *E. coli* (EPEC), and STEC, *Shigella, Salmonella, Campylobacter jejuni,* and *Giardia lamblia* also have higher attack rates among children than adults. For *C. jejuni,* there is a distinct second peak in incidence in young adulthood that is not fully understood but may relate to food preparation habits.[44]

Older individuals are also more susceptible to complications of enteric infection.[45] In the United States the highest death rates for *Salmonella*

are among individuals age 65 years or older.[15,46,47] Advanced age is a risk factor for the development of and death from C. *difficile*–associated disease.[48] Critically ill elderly patients are 68% more likely to experience 30-day mortality from *C. difficile*–associated disease than younger individuals.[49] A dramatic progressive increase in the risk for invasive listeriosis occurs between 45 and 84 years of age.[50] Norovirus gastroenteritis is typically mild in healthy adults, but more severe outcomes can occur in the institutionalized elderly.[11] Rotavirus outbreaks may also occur among the elderly in residential facilities, with considerable morbidity.[51] These age-dependent changes in the incidence and severity of enteric disease may relate to immune senescence, alterations in the gut microbiota, or environmental and behavioral factors, including more frequent antibiotic use.

Gastric Acidity and Physical Barriers

The acidic pH of the stomach is an important barrier to enteric pathogens. Gastric acidity is found in nearly all vertebrates, and the preservation of this highly energy-consuming process across species reflects its biologic importance. Experimental studies have shown that bacteria instilled into the intact human stomach at a pH of 4.0 are killed within 15 minutes but remain viable in the achlorhydric stomach for at least 1 hour.[52] Many bacteria capable of causing GI disease, such as *Yersinia enterocolitica* and *Helicobacter pylori,* have developed an acid tolerance response that is activated under conditions of low pH to protect the organism from gastric acidity. Impaired acid secretion increases both the frequency and the severity of infection with a number of enteric pathogens.[53] Patients taking histamine type 2 (H2) blockers or proton pump inhibitors, which induce blockade of gastric acid, are more susceptible to infection with *V. cholerae,*[54] nontyphoidal *Salmonella,*[55] *C. jejuni,*[56] *Listeria,*[57] and some strains of *E. coli.*[53]

Intestinal motility is another important line of defense against invasion of the gut by microorganisms. Normal peristalsis helps to maintain the enteric microbiota and to clear pathogenic bacteria from the small intestine. A placebo-controlled trial in men with shigellosis demonstrated increased duration of fever and prolonged shedding of organisms in the stool among individuals treated with diphenoxylate hydrochloride with atropine (Lomotil).[58] Patients treated with opiates for mild *Salmonella* gastroenteritis may develop bacteremia, and case reports suggest that complications of *Campylobacter, Entamoeba histolytica,* and *C. difficile* enteritis are more common in individuals who have received antimotility agents or who have underlying gastric motility disorders.[59–61]

Intestinal Microbiome

The human intestinal tract contains a complex microbial community of approximately 100 trillion cells, which exceeds the number of human cells by a factor of 10. The intestinal microbiome plays an important role in maintaining human health, including influencing the development of innate and adaptive immunity, providing nutrients and vitamins, and maintaining epithelial integrity.[62,63] The intestinal microbiome also prevents colonization and infection by GI pathogens. Specifically, the intestinal microbiome may compete with pathogenic organisms for nutrients, for specific niches within the intestine, or for intestinal binding sites; it also may defend against pathogens by maintaining a low luminal pH or by producing compounds that are inhibitory to pathogens.

The intestinal microbiome varies by numerous factors, including age, location in the intestine, geographic region of the world, host genetic factors, nutritional status, and prior antimicrobial exposures, among others. A perturbation of the intestinal microbiota is also evident after enteric infection and its treatment. For instance, the fecal communities in patients with recurrent *C. difficile*–associated disease are markedly less diverse than those of control subjects or those with a first episode of *C. difficile*–associated disease.[64]

Immunocompromise

Immunocompromised individuals are at higher risk for acquiring GI infections and may have more severe disease if infected.[65] Immunocompromised individuals may also experience prolonged excretion of enteric pathogens, including *Salmonella, Campylobacter,* and *Shigella.* Organisms that cause symptomatic infection less commonly in healthy hosts, such as *Mycobacterium avium* complex, cytomegalovirus, microsporidia, and *Cyclospora cayetanensis,* may cause disease in immunocompromised hosts. *Strongyloides stercoralis* can cause hyperinfection and severe illness in immunocompromised patients.[66] More severe and prolonged norovirus infection occurs in individuals with congenital immunodeficiency, organ transplant, cancer chemotherapy, and infection with HIV.[67]

Genetic Determinants

The study of human genes that influence susceptibility to enteric infection is still in its infancy, but a number of notable associations have been made that shed light on the pathogenesis of intestinal infection and inflammation. For instance, the neutrophil chemotactic factor interleukin-8 (IL-8), produced by macrophages and epithelial cells, is central to the pathogenesis of several bacterial enteric infections. A common variant in the IL-8 promoter is associated with an increased risk for severe infection with *C. difficile*[68] and enteroaggregative *E. coli*[69] and an elevated risk for gastric cancer associated with *H. pylori* infection.[70] These associations suggest a particular role for an exaggerated inflammatory response in the pathogenesis of these diseases. Similarly, individuals with the O blood group are at an increased risk for severe *V. cholerae* infection,[71] as well as for diarrhea after norovirus infection.[72] Norovirus and rotavirus also recognize and bind to histo–blood group antigens, and variants in genes controlling the expression of histo–blood group antigens on gut surface epithelium are associated with risk of infection.[73,74] These associations underscore the important role of blood group glycoconjugates in binding directly to enteric pathogens or their toxins.

Nutritional Status

Underlying malnutrition is a major risk factor for diarrheal illness, particularly among children in the developing world.[75] The risk for diarrhea associated with malnutrition may be pathogen specific. In a prospective study of 289 Bangladeshi children between the ages of 2 and 5 years, the risk for diarrheal illness with ETEC, *E. histolytica,* and *Cryptosporidium* was significantly higher among malnourished children; this was not the case for multiple other enteric pathogens that were evaluated.[76] Malnourished children with diarrhea in Ghana were frequently coinfected with enteroaggregative *E. coli* and *Cryptosporidium.*[77]

MICROBIAL FACTORS IN GASTROINTESTINAL INFECTION

A number of microbial factors allow pathogenic microorganisms to colonize and cause infection of the human GI tract. In bacteria, genes required for colonization and infection are often carried on laterally transferred genetic elements, such as virulence plasmids, transposons, or bacteriophage, or on pathogenicity islands in the bacterial chromosome. Pathogenic bacteria produce and secrete a number of proteins that modulate their interaction with the host. In gram-negative bacterial pathogens, proteins must be secreted across both the inner and outer membranes; and for a subset of proteins that act within host cells, these proteins must also enter the host cell. A variety of protein secretion systems have been identified in gram-negative bacteria for these purposes, and these have been described as types I to VI. Proteins secreted by the type I, III, IV, and VI secretion systems are taken in a single step from inside the bacterial cell to the outside; in the type II and V systems, proteins are first transported across the inner membrane into the periplasmic space by the general secretion pathway shared by all bacteria and then exported across the outer membrane in a separate step by the additional protein secretion system. Type III, IV, and VI secretion systems deliver their secreted proteins from the bacterial cytoplasm across both bacterial membranes and the host cell membrane, directly into the host cytoplasm to affect host cell physiology. Among these protein secretion systems, type III protein secretion is one of the most commonly used by bacterial pathogens that cause GI infection.[78] Pathogens have a variety of strategies to survive and replicate in the GI tract, including nutrient acquisition, production of proteases that cleave the human adaptive immune protein IgA1, and the ability to be motile and to manifest chemotaxis toward intestinal epithelial surfaces. Many pathogens are capable of sensing environmental signals that indicate they are in the human GI tract and to use these signals

to trigger coordinated regulation of a set of virulence genes termed a *virulence regulon* to cause infection.[79,80]

Infection of the GI tract involves several steps in pathogenesis, including adherence/attachment to the GI mucosa, cellular invasion, production of exotoxins, changes in epithelial cell physiology, loss of brush border digestive enzymes, and/or cell death. The net result of these can be increased intestinal motility, net fluid secretion, influx of inflammatory cells, and/or intestinal hemorrhage, with the clinical manifestations of gastroenteritis.

Inoculum Size

The inoculum of microorganisms needed to produce infection can vary widely across organisms and between different hosts. The median infective dose (ID_{50}) represents the inoculum required to infect 50% of a population. The ID_{50} is influenced strongly by gastric acidity because many organisms are susceptible to killing by gastric acid. Some organisms have a very low ID_{50} because they are resistant to killing by gastric acid.[81,82] These organisms include *E. coli* and *Shigella,* the cyst forms of certain parasites, including *Cryptosporidium, G. lamblia,* and *E. histolytica,* and norovirus.[11] The ID_{50} of these pathogens may be as low as 10 to 100 organisms, cysts, or viral particles; such low infectious doses may facilitate direct person-to-person spread and influence the epidemiology of these infections.[83] Most agents that infect the GI tract have an intermediate ID_{50}, generally in the range of 10^3 to 10^8 microorganisms. Other organisms, such as *Yersinia,* have a higher ID_{50}, such as 10^{10} or more. Other factors that may influence the ID_{50} include intestinal motility, prior immunity to that pathogen, and the presence of normal intestinal microbiota. Notably, infection still occurs in a smaller subset of individuals exposed to considerably lower doses than the $ID_{50,}$ and this can result in a substantial burden of disease for enteric pathogens that are widely distributed.

Adherence/Attachment

Adherence to host cell surfaces is essential to the pathogenesis of diarrheal disease. Interaction of bacterial surface proteins with host cell glycolipid, glycoprotein, or protein receptors conveys tissue and species specificity to this binding.

Pili (or fimbriae) are one of the more common mechanisms used by bacteria to adhere to the GI mucosa.[84] These are surface appendages made up of repeated polymers of a protein called pilin. Other proteins may coat the tip of the structure and confer additional specificity of binding. Examples of fimbrial adhesins in diarrheal pathogens include the bundle-forming pilus (Bfp) of EPEC[85] and the colonization factor antigens of ETEC.[86] Some bacteria may also use nonfimbrial adhesins in the outer membrane to bind to epithelial surfaces or intercellular matrix materials, such as fibronectin. The Bfp of EPEC produces a pattern of localized adherence on GI mucosal cells; other pathogenic *E. coli* produce different patterns of adherence, such as the aggregative adherence of enteroaggregative *E. coli.*[87] This property can be mediated by multiple adherence factors.

Some bacterial pilus structures, such as the toxin-coregulated pilus (TcpA) of *V. cholerae,*[88] mediate cell-cell interactions between bacteria to create microcolonies on the GI surface, rather than binding to a specific intestinal receptor.

EPEC and STEC produce an intimate interaction with the surface of GI epithelial cells termed an *attaching-effacing lesion;* these adherent bacteria remain on the outside of the cell surface but are intimately attached through a coordinated series of steps that involves a type III protein secretion system.[89] All of the genes involved in inducing the attaching-effacing lesion in EPEC and STEC are encoded in a pathogenicity island termed the *locus of enterocyte effacement.*[90]

The VP1 protein on the surface of human norovirus strains binds to complex carbohydrates of the histo–blood group antigen system on GI epithelial cells to initiate infection of the cell.[11]

Invasion

Certain enteropathogenic bacteria invade into intestinal epithelial cells or traffic through them to the underlying submucosal space as part of the pathogenic process.[79] Epithelial invasion often occurs preferentially through specific microfold (M) cells in the intestinal mucosa, and this provides access to the submucosal space and the basolateral surface of the epithelial cells, from where bacteria can either enter the epithelial cell or be taken up by macrophages or interact with the submucosal lymphoid system. Many of the invasion strategies used by bacteria, including those used by *Salmonella, Shigella,* and *Yersinia,* involve a type III secretion system similar to that of EPEC and STEC.

For example, *Salmonella* uses a type III secretion system encoded on *Salmonella* pathogenicity island-1 to induce reorganization of host cell actin under the adherent bacterium, to ruffle the host cell membrane, and to cause engulfment and ingestion of the bacterium via macropinocytosis.[91] The organisms can then live and replicate in specialized phagosomal vacuoles that are able to prevent phagolysosomal fusion and acidification.[92]

Shigella accesses the basolateral surface of intestinal epithelial cells by uptake into and transcytosis of M cells, then uptake into epithelial cells, mediated by a type III protein secretion system encoded on a virulence plasmid.[93,94] Once within the intestinal epithelial cell, *Shigella* lyses the vacuolar membrane to escape into the cell cytoplasm. In the cytoplasm it replicates intracellularly and catalyzes polymerization of host cell actin at one pole of the bacterium, to move within cells and to spread directly from one epithelial cell to another.[95]

The host responses to attachment and intracellular invasion by enteric pathogens may lead to the release of proinflammatory cytokines, such as IL-8 and others, and these may mediate influx of inflammatory cells into the GI mucosa, as well as symptoms of disease.

Toxins

A number of pathogenic bacteria produce protein exotoxins (Table 96.2), and several of these have an A (enzymatically active)–B (binding) motif. These exotoxins bind to specific receptors on eukaryotic cells, are internalized and catalyze specific enzymatic activities within the cell, and lead to alterations in cell physiology with secretion of fluid and electrolytes (enterotoxins) or cell death (cytotoxins) or both. Other exotoxins (neurotoxins) of enteric bacterial pathogens act directly on the central or enteric nervous systems rather than the GI mucosal cells.[96]

Neurotoxins

Toxins of pathogenic bacteria in the GI tract with direct neurotoxicity are often ingested preformed. For instance, *Staphylococcus aureus* produces a potent enterotoxin that acts on the central autonomic nervous system, leading to an acute upper GI syndrome characterized primarily by vomiting.[97] A similar emetic neurotoxin is produced by *Bacillus cereus,* particularly when the organism grows in contaminated fried rice.[98] Symptoms of both of these toxin-mediated illnesses generally occur 1 to 6 hours after ingestion of the preformed toxin. *B. cereus* and *C. perfringens* can also produce enterotoxins that produce primarily a diarrheal illness with an incubation period of 8 to 16 hours.[26,99] Neurotoxins are also present in certain seafood, such as the agents of paralytic shellfish poisoning and ciguatera toxins.[100] Last, botulinum toxin, produced by *Clostridium botulinum* and other clostridial species,

TABLE 96.2 Enteric Bacterial Toxins

TOXIN TYPE	TOXIN-PRODUCING BACTERIA	TOXIN NAME, IF RELEVANT
Neurotoxin	*Staphylococcus aureus* *Bacillus cereus* *Clostridium botulinum*	Enterotoxin B Emetic toxin Botulinum toxin
Enterotoxin	*Vibrio cholerae* Enterotoxigenic *Escherichia coli* *Clostridium perfringens*	Cholera toxin Heat-labile toxin, heat-stable toxin Enterotoxin
Cytotoxin	*Shigella dysenteriae* type I Enterohemorrhagic *E. coli* *Vibrio parahaemolyticus* *Campylobacter jejuni* *Clostridioides difficile* *Bacteroides fragilis* *Clostridium perfringens*	Shiga toxin Shiga toxins 1 and 2 Thermostable direct hemolysin Cytolethal distending toxin Toxin A, toxin B *B. fragilis* toxin Alpha toxin

prevents release of acetylcholine from the presynaptic vesicle of the neuromuscular junction, leading to the clinical syndrome of botulism with paralysis.[101]

Enterotoxins

A number of pathogenic bacteria produce enterotoxins that act directly on GI mucosal cells to stimulate net fluid secretion. The prototypical example of this class is cholera toxin, which is an A_1-B_5 protein enterotoxin that is exported out of the bacterial cell by a type II protein secretion system.[102] The B pentamer binds to the enterocyte surface receptor GM1 monosialoganglioside. The A subunit is then nicked by a protease and reduced, and a portion of the A subunit enters the eukaryotic cell cytoplasm, where it catalyzes adenosine diphosphate ribosylation of an arginine residue on the Gsα subunit of adenylate cyclase, leading to increased intracellular cyclic adenosine monophosphate and net fluid secretion through the apical chloride channels of the epithelial cell.[103] The genes for the A and B subunits of cholera toxin are encoded together on a bacteriophage that inserts itself into the chromosome of pathogenic strains of *V. cholerae.*[104]

ETEC produces a heat-labile enterotoxin that is very similar to cholera toxin, both in protein sequence as well as in mechanism of action.[86] Strains of ETEC may also produce a heat-stable enterotoxin that is secreted extracellularly and binds and activates intestinal guanylate cyclase in the cell membrane of intestinal epithelial cells. Heat-stable enterotoxin acts as a homologue of the peptide guanylin, an endogenous peptide made by small intestinal villus cells that regulates normal intestinal secretion by stimulating intracellular cyclic guanosine monophosphate production.[105]

Cytotoxins

One example of a potent cytotoxin produced by enteric pathogens is the Shiga toxin family of proteins produced by *Shigella dysenteriae* type 1 and by strains of STEC; these are A_1-B_5 protein toxins.[106] The B pentamer binds toxin to a receptor on the cell surface, globotriaosylceramide (Gb3); the toxin is then internalized and undergoes retrograde transport to the endoplasmic reticulum and the nuclear membrane.[107] The A subunit is nicked by a protease, reduced, and enters the cytoplasm, where it cleaves a specific adenine residue from the 28S ribosomal RNA in the 60S ribosomal subunit, inhibiting protein synthesis and causing cell death.[108] This toxin family specifically targets endothelial cells that are rich in the Gb3 receptor, causing vascular damage, bloody diarrhea, and, in some cases, the hemolytic-uremic syndrome (HUS).[109]

A number of bacterial enteric pathogens, including *C. jejuni* and some strains of *E. coli,* produce a cytolethal distending toxin.[110] This toxin produces cell cycle arrest, leading to cytoplasmic distention and cell death.

Toxigenic strains of *C. difficile* encode two protein exotoxins—toxin A and toxin B; the genes encoding these two toxins are located near each other on a pathogenicity island.[111] Toxin A binds to a specific receptor on the brush border of the intestinal epithelium, a glycoprotein with an α-linked galactose; the intestinal receptor in humans for toxin B is less well characterized. After binding to the appropriate receptors, the toxins are internalized, where they act within the eukaryotic cell to covalently modify proteins in the Rho subfamily, a group of low-molecular-weight guanosine triphosphate–binding proteins involved in regulation of the actin cytoskeleton.[112] This is followed by disaggregation of polymerized actin, opening of tight junctions between cells, cell rounding, and subsequent cell death.

The protozoal parasite *E. histolytica* is able to lyse phagocytic cells after direct contact by release of a protozoal phospholipase A and pore-forming peptides.[113] The action of these toxins leads to direct cell death of responding phagocytic cells.

MAJOR CLINICAL SYNDROMES

GI infection may manifest as reasonably distinct clinical syndromes, including acute vomiting, acute watery diarrhea, profuse watery diarrhea, invasive or bloody diarrhea (dysentery), persistent diarrhea, and enteric fever (Table 96.3). This classification scheme is useful in considering the etiology, pathogenesis, and management of each type of illness. However, there is much overlap, and organisms that cause bloody diarrhea, for example, may also manifest as watery diarrhea.

Acute Vomiting

Acute vomiting illnesses are frequently caused by noroviruses or by bacterial food poisoning. Norovirus gastroenteritis is typically mild in healthy adults, but hospitalization and death from norovirus gastroenteritis are more common with genogroup II genotype 4 infection and in young children, the elderly, and the immunocompromised.[11,114] Bacterial food poisoning results from the ingestion of preformed toxins elaborated outside the host; these illnesses have short incubation periods (1–6 hours) and generally last less than 12 hours. Toxin-producing staphylococci can multiply at a wide range of temperatures; organisms consequently have the opportunity to reproduce in food that is left to cool slowly or that remains at room temperature after cooking. *B. cereus* can produce a food poisoning syndrome with a short incubation period (the emetic form, mediated by a staphylococcal type of neurotoxin) or a longer incubation period of 8 to 16 hours (the diarrheal form, mediated by an enterotoxin resembling *E. coli* heat-labile toxin). Microbiologic

TABLE 96.3 Clinical Syndromes Associated With Community-Acquired Gastrointestinal Infection

CLINICAL SYNDROME	SIGNS AND SYMPTOMS	PATHOGENIC MECHANISM	EXAMPLE PATHOGENS
Acute watery diarrhea[a]	Loose stools, often with mucus but not blood Occasional vomiting and anorexia Low-grade fever Malaise	Local infection in the gut	Norovirus genogroups I, II, and IV, enteric adenovirus types 40 and 41, rotavirus, enterotoxigenic *Escherichia coli,* enteropathogenic *E. coli, Cryptosporidium, Clostridium perfringens, Bacillus cereus*
Dysentery (acute bloody diarrhea)	Loose stools with gross blood and mucus Fever Abdominal cramps and, in some cases, tenesmus May be clinically toxic	Local invasion of the gut	*Shigella,* enteroinvasive *E. coli, Campylobacter jejuni, Entamoeba histolytica,* nontyphoidal *Salmonella, Yersinia enterocolitica, Aeromonas, Plesiomonas, Clostridioides difficile*
Profuse purging	Copious watery stools resembling "rice water" Low-grade fever Overt signs of dehydration	Toxin mediated	*Vibrio cholerae* O1 and O139, enterotoxigenic *E. coli*
Persistent diarrhea	Similar to acute diarrhea, but symptoms persist for at least 14 days	Local infection in the gut and/or immune compromise of host	*Giardia lamblia, Cryptosporidium hominis/parvum, Cystoisospora belli, Cyclospora cayetanensis,* enteropathogenic *E. coli,* enteroaggregative *E. coli*
Acute vomiting	Sudden onset of nausea and vomiting Little or no diarrhea	Local infection in the gut or intoxication	Norovirus, food poisoning due to *Staphylococcus aureus, Bacillus cereus*
Enteric fever	Fever Lymphadenopathy	Local invasion of the gut with systemic spread	*Salmonella enterica* serovar Typhi, *S. enterica* serovar Paratyphi A, B, or C

[a]Etiologic agents that can cause dysentery can also cause acute watery diarrhea.

methods are rarely used to confirm a specific cause of bacterial food poisoning, although it is possible to do so if necessary for an epidemiologic investigation.

Acute Watery Diarrhea

Most bacterial and nonbacterial enteric pathogens cause acute watery diarrhea, and consequently this syndrome is not characteristic of any single organism. Common causes include rotavirus in infants, particularly those who have not been vaccinated, ETEC in older children and adults, and norovirus. Norovirus is now the most common cause of acute GI illness in both children and adults in the United States.[10] Enteric adenoviruses 40 and 41 may cause acute watery diarrhea, particularly in children younger than 5 years.[115,116] *V. cholerae* infection should be considered when diarrheal purging is profuse, particularly with a characteristic rice-water appearance, or when otherwise healthy older children and adults die of watery diarrhea. The enterotoxin of *C. perfringens* causes moderately severe abdominal cramps and watery diarrhea; heat-resistant spores of *C. perfringens* can survive in inadequately cooked meat, poultry, or legumes.

In most cases of acute watery diarrhea a specific microbiologic diagnosis is not necessary. Treatment should be focused on fluid repletion, and antibiotics are not indicated except in situations in which they may shorten the duration of the illness. An example of this is epidemic *V. cholerae* infection, in which antibiotics for moderate or severe illness shorten symptoms and may play a role in optimizing case management.[117] It is also useful to distinguish cholera from other causes of acute watery diarrhea because cholera may affect large communities, necessitating initiation of a rapid response to improve the water supply and sanitation systems.[102]

Diarrhea With Fever

Invasive diarrhea, or dysentery, is suggested by the presence of blood or mucus or both in fecal matter and is most often the result of inflammation of the small bowel or colon in response to invasive bacterial infection. Fecal leukocytes are often detectable by direct microscopy. Fever usually accompanies invasive diarrhea, also resulting from the pronounced mucosal inflammatory response. Major causes of bloody diarrhea in the United States include *Shigella, C. jejuni,* nontyphoidal *Salmonella,* and STEC (often without fever). Other organisms that may cause dysentery include *Aeromonas, Plesiomonas,* noncholera vibrios, *Y. enterocolitica,* and *E. histolytica.*

HUS, characterized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia, may result from infection with STEC or with *S. dysenteriae* serotype 1. This syndrome has a mortality rate of 3% to 5% and is the leading cause of renal failure in childhood in the United States.[118] Disease results from the effects of Shiga toxin, absorbed systemically from the gut, on the renal endothelium. Certain antibacterial drugs increase the induction of phage-mediated Shiga toxin production and may increase the risk for development of HUS.

Persistent Diarrhea

Diarrhea lasting for more than 2 weeks is classified as persistent or chronic diarrhea. In some cases persistent diarrhea is associated with infection with enteroaggregative *E. coli* or parasitic infections, such as *Cryptosporidium hominis/parvum, Cystoisospora belli,* or *C. cayetanensis.* However, many cases of persistent diarrhea are triggered by a previous episode of acute gastroenteritis, and diarrhea is perpetuated by an inability to restore normal resorptive capacity after intestinal injury. Persistent diarrhea is associated with malnutrition and chronic enteropathy and should also raise suspicion for underlying illnesses, such as HIV infection; in HIV-infected persons, unexplained persistent diarrhea constitutes an acquired immunodeficiency syndrome–defining illness. Brainerd diarrhea is a persistent, severe, watery diarrheal illness that has been recognized in outbreaks, and that presumably occurs sporadically, but an etiologic agent has yet to be identified.[119]

Enteric Fever

Enteric fever is a febrile illness that follows systemic spread of *S. enterica* after local invasion of the gut.[120] Typhoid fever results from infection with *S. enterica* serovar Typhi, and paratyphoid fever results from infection with *S. enterica* serovar Paratyphi A, B, or C. All are characterized predominantly by persistent fever, but hepatosplenomegaly, abdominal pain, and neuropsychiatric symptoms may also occur. Perforation of the distal ileum, related to congested Peyer patches, is a potentially serious complication.

Complications of Acute Enteric Infection

Complications during an episode of acute gastroenteritis may manifest within the GI tract, such as the syndrome of pseudoappendicitis or exacerbation of underlying inflammatory bowel disease, or manifest outside the GI tract, owing to bacteremic spread of the organism or systemic action of a bacterial toxin, such as HUS (Table 96.4). Five to 10 percent of hospitalized children younger than 15 years with *Shigella* infection will experience a seizure.[121] Complications of gastroenteritis may also occur at some time after the acute illness, often the result of immunologic response to the infection. This latter category includes a postinfectious reactive arthritis seen in a small fraction of patients after infection with *Campylobacter, Shigella flexneri,* nontyphoidal *Salmonella, Yersinia,* and occasionally STEC; this syndrome occurs almost exclusively in individuals who are human leukocyte antigen–B27 positive.[122] Another example is the Guillain-Barré syndrome, seen after infection with *C. jejuni,* as a result of antibodies cross-reactive with GM1 ganglioside or with GQ1b (producing the Miller Fisher variant of Guillain-Barré syndrome).[123,124]

Asymptomatic Passage of Enteropathogens

Enteric pathogens may be excreted by individuals without symptoms of diarrhea, and there are host and microbial explanations for this phenomenon.[125] First, some enteric pathogens may be excreted asymptomatically for weeks after recovery from an acute diarrheal illness. Enteric pathogens associated with extended excretion after an episode

TABLE 96.4 Complications That May Accompany or Follow an Episode of Acute Diarrheal Illness

COMPLICATION	COMMONLY ASSOCIATED BACTERIAL AGENT(S)	COMMENT
Bacteremia	Nontyphoidal *Salmonella enterica, Campylobacter fetus, Shigella* spp.	Particular concern in HIV-infected individuals
Seizure	*Shigella* spp.	Particularly in children
Chronic diarrhea		Occurs in ≈1% of travelers with acute diarrhea Causes may include lactase deficiency, small bowel bacterial overgrowth, and malabsorption syndromes
Initial presentation or exacerbation of inflammatory bowel disease	All bacterial pathogens, including *Clostridioides difficile*	
Irritable bowel syndrome		May follow infection with many bacterial pathogens
Reactive arthritis (formerly Reiter syndrome)	*Shigella, Salmonella, Campylobacter, Yersinia,* STEC, *C. difficile*	Particularly likely after infection with invasive organisms and in patients who are HLA-B27 positive
Hemolytic-uremic syndrome	Shiga toxin–producing bacteria (*Shigella dysenteriae* type I and STEC)	Characterized by hemolytic anemia, thrombocytopenia, and renal failure
Guillain-Barré syndrome	*Campylobacter jejuni*	Cross-reactive antibodies to GM1 or GQ1b gangliosides

HIV, Human immunodeficiency virus; *HLA,* human leukocyte antigen; *STEC,* Shiga toxin–producing *E. coli.*

of acute diarrhea include nontyphoidal *Salmonella, C. jejuni,* norovirus, and, uncommonly, *Shigella.*[126] A host with preexisting immunity may also asymptomatically excrete an enteric pathogen after ingestion. Some individuals, owing to age or genotype, are inherently less susceptible to symptomatic or severe diarrheal infection with certain pathogens, as exemplified by the relationship between ABO blood group and *V. cholerae* and norovirus infection. Similarly, healthy infants frequently carry toxigenic strains of *C. difficile* without evidence of disease.[24]

DIAGNOSTIC APPROACH TO ENTERIC INFECTIONS

A thorough history and physical examination should be the first step in evaluating the patient with a GI illness. The history should focus on recent travel, specific items in the diet, animal and other epidemiologic exposures, recent and current medications, and underlying medical conditions, particularly immunosuppressive conditions. The nature of the symptoms (vomiting, type of diarrhea—watery, mucus, or blood—and the presence of fever or other systemic symptoms) should also be explored. The clinician should be aware of any relevant ongoing outbreaks in the community or in the patient's travel destinations. A directed physical examination is important and should focus on vital signs (particularly fever and orthostasis), volume status, abdominal tenderness, complications outside the GI tract, and the sensorium.

For purposes of directing the diagnostic evaluation, diarrheal illness can be divided into community-acquired/traveler's diarrhea, nosocomial diarrhea, and persistent diarrhea (Fig. 96.1). Most cases of community-acquired or traveler's diarrhea are mild and self-limited, and a specific microbiologic diagnosis usually is not necessary.[127] However, the presence of fever or blood in the stool should prompt evaluation of a fecal specimen for commonly associated pathogens, including *Salmonella, Shigella, Campylobacter,* STEC, and, in the case of appropriate epidemiologic exposure, *E. histolytica.* Testing for *C. difficile* should also be considered if there is a history of recent antibiotic use or if other testing is negative. Nosocomial diarrhea is a common complication in hospitalized patients. *C. difficile* is by far the most common infectious cause of nosocomial diarrhea, with 10% to 20% of patients becoming colonized with this organism during hospitalization.[24,128] Other causes of antibiotic-associated nosocomial diarrhea, including cytotoxic *K. oxytoca,* enterotoxin-producing *C. perfringens,* and potentially *S. aureus,* are rare and not readily diagnosed. Of importance, most cases of diarrhea in the hospitalized patient are noninfectious and are due to medications, enteral feeding, or underlying illness.[129] Persistent diarrhea, particularly in the immunocompromised host, should prompt consideration of a distinct array of organisms, including parasites (*Giardia, C. hominis/parvum, C. belli, C. cayetanensis,* microsporidia) and *M. avium* complex. In transplant patients, cytomegalovirus and GI viruses, such as rotavirus, adenovirus, and norovirus, should be considered, as well as parasites and bacteria that are typically associated with community-acquired diarrhea.

Most laboratories are able to culture for *Salmonella, Shigella,* and *Campylobacter* and to test for *C. difficile* and STEC. Consultation with the laboratory and use of special media may be required if other pathogens, such as *Yersinia* or *Vibrio,* are suspected. Culture-independent diagnostic tests for diarrheal pathogens are increasingly available but are limited by their lack of antibiotic susceptibility data.[130] The failure to obtain clinical isolates also hampers the ability of public health officials to perform surveillance activities and detect outbreaks.[30] The specimen of choice for laboratory testing is a loose stool that takes the shape of the container. Multiple stool specimens are rarely indicated for the detection of stool pathogens. In a study of 1256 adult patients who submitted more than one specimen, the enteric pathogen was detected

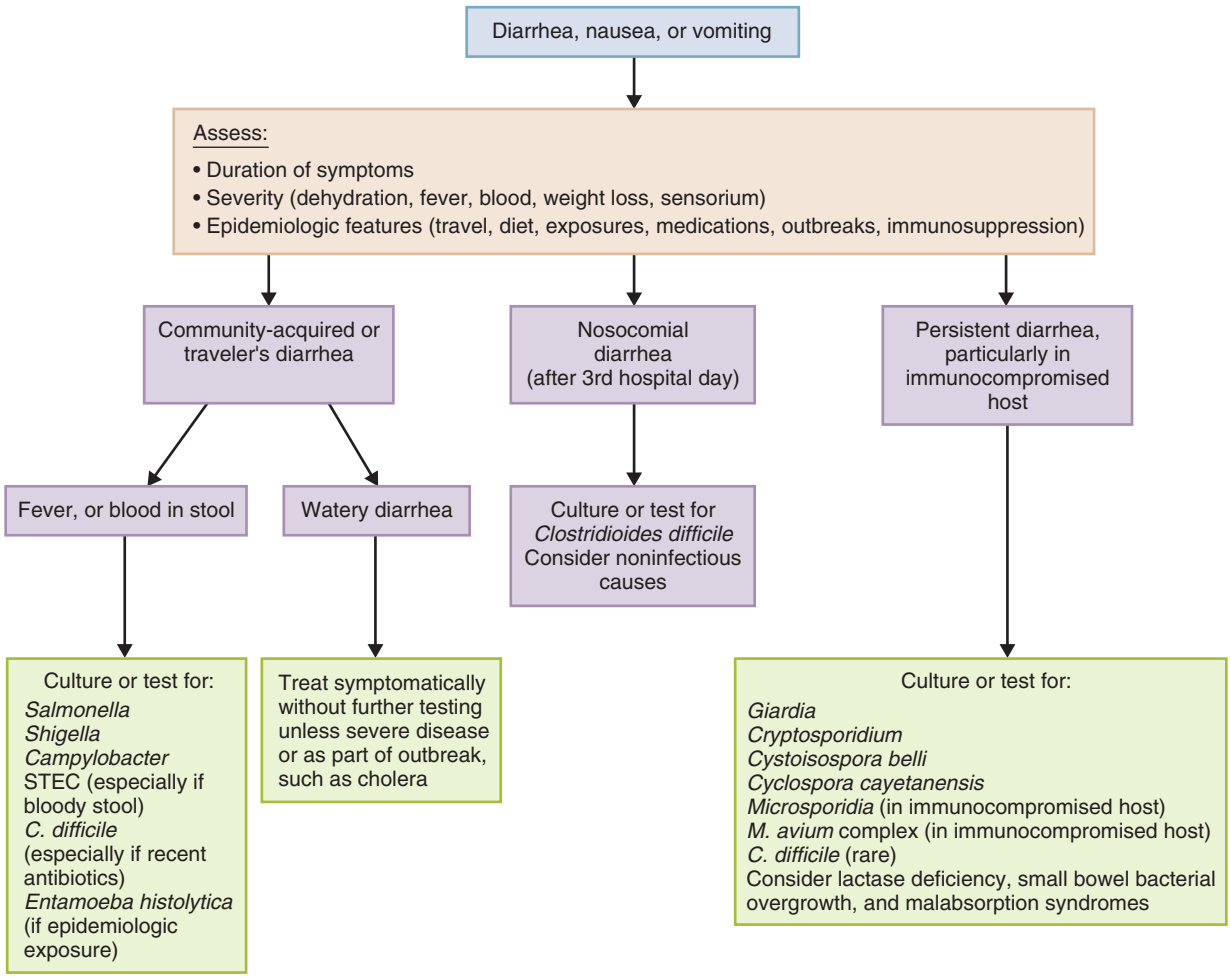

FIG. 96.1 Approach to diagnosis of infectious diarrhea. *STEC,* Shiga toxin–producing *Escherichia coli.*

in the first sample 87% to 94% of the time, with the second specimen increasing the detection rate to 98%.[131] In pediatric patients the first specimen detects 98% of the identifiable enteric pathogens.[132] Thus one sample for children and a second for selected adult patients are generally sufficient. Rectal swabs are less sensitive than stool specimens and are not recommended in adults, but in symptomatic pediatric patients, rectal swabs and stool culture are equivalent in the ability to detect fecal pathogens.[133,134] Given that most community-acquired gastroenteritis has an incubation period of less than 3 days, evaluation in a hospitalized patient after the third hospital day can be focused on nosocomial pathogens alone.[135]

THERAPY FOR ENTERIC INFECTIONS

Rehydration is the mainstay of treatment of GI infection. In the vast majority of cases dehydration can be effectively treated with oral rehydration salts (ORS).[136] A reduced-osmolarity ORS solution, containing 75 mEq/L of sodium and 75 mmol/L of glucose, is officially recommended by WHO and the United Nations Children's Fund for this purpose. A diet of easily digestible food is commonly recommended for those with diarrhea, and randomized studies support the continuation of feeding in children.[137] Adults with severe dehydration should receive intravenous fluids. Lactated Ringer solution or lactated Ringer solution with 5% dextrose is preferred, but normal saline can also be used. Disadvantages of normal saline are that it does not contain potassium to correct losses or a base to correct acidosis.

The role of antimicrobial therapy for acute bacterial gastroenteritis depends on the pathogen (Table 96.5). For some pathogens, antimicrobial therapy has been shown in randomized, controlled trials to reduce the duration of symptoms and complications, as for infection with *Shigella,*[138] *V. cholerae,*[102] and ETEC,[139] and antibiotics are recommended for moderate or severe illness. For other pathogens, such as *Campylobacter,* trials show only a modest reduction in duration of symptoms of 1.3 days, and antibiotics are recommended only for those with severe illness or risk factors for severe illness, such as the elderly, pregnant women, or the immunocompromised.[140] Antimicrobial therapy for patients with nontyphoidal *Salmonella* infection has no significant effect on the length of illness and may prolong carriage of the organism in the stool[141]; therefore antibiotics should not be given except in particularly severe illness, in patients older than 50 years (who are at risk for a mycotic aneurysm from bacteremic seeding of preexisting atherosclerotic plaque), in infants younger than 12 months (who are at risk for *Salmonella* meningitis), in individuals with cardiac or joint prostheses at risk for bacteremic seeding, in pregnant women near term, and in the immunocompromised. Last, therapy for STEC infection has no effect on the duration or severity of symptoms in most individuals, and there is a risk that certain antimicrobial agents may increase the risk for HUS through induction of Shiga toxin, particularly in children younger than 10 years. Therefore antimicrobial agents should generally be avoided for this infection, particularly for children.[142,143]

Antimicrobial resistance in enteric pathogens, particularly in the developing world, is increasingly common and complicates clinical treatment and the management of diarrheal outbreaks.[144,145] Multidrug resistance has been identified in nontyphoidal *Salmonella, Shigella* spp., and *V. cholerae.*[146–149] If antimicrobial treatment is indicated for a diarrheal disease, the choice of agent should be based on recent local susceptibility testing. Misuse and overuse of antibiotics in the treatment of diarrheal diseases has played an important role in the development of drug resistance. Use of antibiotics in farm animals has also contributed to antimicrobial resistance in human infection. Identical strains of antibiotic-resistant pathogens have been demonstrated in both infected humans and the farm animals that were the source of those infections.[150] This suggests that antibiotic use in farm animals meant for human consumption should be restricted to treatment of specific infections in those animals and not for growth promotion.

Antimotility agents may aggravate disease due to invasive organisms if not given with effective antibiotics, and they may increase absorption of Shiga toxin in STEC infection, increasing the risk for HUS. Antimotility agents should therefore be avoided in those with suspected or documented infection with STEC and should be given only along with antibiotics in patients with bloody diarrhea or fever.[151,152] Antimotility agents are considered safe for use in individuals with traveler's diarrhea.[153]

TABLE 96.5 Antimicrobial Therapy for Bacterial Gastroenteritis

USEFULNESS OF ANTIBIOTICS	EXAMPLE ORGANISMS
Antibiotics have demonstrated benefit in RCTs and are indicated for patients with moderate-to-severe disease.	*Shigella* spp., enteroinvasive *Escherichia coli,* enterotoxigenic *E. coli* *Vibrio cholerae, Aeromonas, Plesiomonas*
Antibiotics have demonstrated only modest benefit in RCTs and are indicated only for patients with severe or prolonged illness, or in abnormal hosts.	*Campylobacter jejuni*
Antibiotics have demonstrated no clear benefit in RCTs and may prolong excretion of organisms. Antibiotics should be used in selected circumstances (see text).	Nontyphoidal *Salmonella* spp.
Antibiotics have demonstrated no clear benefit in RCTs and in some studies, particularly in children, may increase risk for complications such as hemolytic-uremic syndrome.	Shiga toxin–producing *E. coli*

RCTs, Randomized controlled trials.

PREVENTION AND CONTROL OF ENTERIC INFECTIONS

Acute diarrheal diseases can be prevented with a variety of measures focused on limiting the spread of organisms within the community and from person to person. Because diarrheal diseases spread by a fecal-oral route, hand washing is considered a key barrier to the transmission of enteric pathogens. A systematic review and meta-analysis of studies from the developing world and from US and Australian child care settings estimated that hand washing with soap reduces the risk for diarrheal diseases by 42% to 47%.[154] Globally, more than 1 billion people lack access to improved drinking water supplies. Strategies to improve the microbial quality of drinking water can be applied at the source or in the household. Water-source strategies include protected wells, bore holes, or public tap stands; household strategies include improved water storage or approaches for treating water, such as chlorination, solar disinfection, filtration, or combined flocculation and disinfection. Although randomized studies are few, interventions to improve the microbial quality of drinking water are likely effective in preventing diarrhea.[155]

Many community-acquired bacterial GI infections are foodborne. Reduction of such illnesses depends on monitoring of food sources for bacterial contamination and removal from the market when such contamination is detected. Food should be appropriately refrigerated to prevent bacterial multiplication and cooked to recommended temperatures to ensure killing of any existing bacteria. Food preparers should wash hands after handling any uncooked food products, after cleaning surfaces where food is prepared, and after defecation. Ill food preparers should be kept out of work until symptoms of a diarrheal illness have resolved and, in some cases, stool cultures for the pathogen have become negative.

There are three GI infections for which vaccines have shown efficacy and are approved for use. A pentavalent rotavirus vaccine was recommended for routine use in infants in the United States in 2006, with three doses given at 2, 4, and 6 months, respectively.[12] A monovalent rotavirus vaccine was recommended as an alternative in 2008, with two doses given at 2 and 4 months. As described earlier, this vaccine has had a substantial impact on the morbidity associated with rotavirus infection in children in the United States.[13]

For cholera, there are two killed whole-cell oral cholera vaccines that are internationally licensed and prequalified by WHO. One is a monovalent *V. cholerae* O1 vaccine, supplemented with the B subunit of cholera toxin (manufactured as Dukoral [Valneva; Solna, Sweden]), and the second is a bivalent *V. cholerae* O1 and O139 vaccine without

supplemental B subunit (manufactured as either Shanchol or Euvichol [SBL Vaccines; Shantha Biotec, Hyderabad, India]). The creation of a WHO global cholera vaccine stockpile in 2013 derived from the lower-cost bivalent vaccine has led to increasing use of killed oral cholera vaccines globally, whereas the monovalent vaccine has been used primarily in travelers from high-income countries. A recent meta-analysis demonstrated that these vaccines have an effectiveness of 75% over 2 years when administered in a two-dose schedule but provide substantially less protection in children younger than 5 years.[20,102] In addition to these two killed whole-cell vaccines, a live-attenuated monovalent oral cholera vaccine, CVD 103-HgR (manufactured as Vaxchora [PaxVax; Redwood City, CA]), is licensed in the United States and currently recommended for adult travelers to cholera endemic areas.[156]

There are two current approaches to typhoid vaccination: an oral, live-attenuated Ty21a vaccine, which is given in three doses and produces approximately 50% protective efficacy over the subsequent 3 years, and a parenteral Vi (virulence) polysaccharide vaccine, which is given in one dose and produces approximately 60% protective efficacy over the subsequent 2 years.[157,158]

A number of vaccines for GI infections are being developed or may be available in the near future. A norovirus vaccine consisting of virus-like particles given intranasally has shown evidence of protective efficacy after subsequent challenge with wild-type norovirus.[159] An *S. enterica* serovar Typhi vaccine, in which the Vi polysaccharide is conjugated to a protein carrier, improves efficacy over the polysaccharide vaccine alone but is not yet manufactured or available for clinical use.[17]

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The complete reference list is available online at Expert Consult.

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97 Esophagitis

Paul S. Graman

SHORT VIEW SUMMARY

Definition
- Inflammation of the esophagus, of noninfectious or infectious etiology

Epidemiology
- Gastroesophageal reflux disease is the most common cause. Esophageal infections occur predominantly in patients with impaired immunity, particularly those with acquired immunodeficiency syndrome or receiving cancer chemotherapy. Immunocompetent persons are occasionally affected.

Microbiology
- *Candida* spp., herpes simplex virus (HSV), and cytomegalovirus (CMV) are most common.

Diagnosis
- Endoscopy and biopsy for immunohistopathology and cultures; polymerase chain reaction for HSV

Therapy (see Table 97.2)
- *Candida:* fluconazole, itraconazole, amphotericin lipid formulations, voriconazole, echinocandins
- HSV: acyclovir or valacyclovir, famciclovir; foscarnet for acyclovir-resistant HSV
- CMV: ganciclovir, valganciclovir, or foscarnet
- Aphthous ulceration (in acquired immunodeficiency syndrome): prednisone, thalidomide

Prevention
- Recipients of allogeneic hematologic stem cell transplants who are neutropenic commonly receive antiviral and antifungal prophylaxis.

Esophagitis, or inflammation of the esophagus, is most often caused by noninfectious conditions, of which gastroesophageal reflux disease is the most common. Eosinophilic esophagitis, in which eosinophils infiltrate the mucosa, is increasingly recognized and associated with food allergy. Esophageal infection occurs predominantly in patients in whom immunity is impaired as a result of cancer chemotherapy, transplantation, or human immunodeficiency virus (HIV) infection and occasionally in persons who are otherwise healthy. *Candida albicans,* cytomegalovirus (CMV), and herpes simplex virus (HSV) are the leading etiologic agents of esophageal infection. Among patients with HIV infection, aphthous ulceration of the esophagus is a well-recognized entity. Acute HIV infection may also be a direct cause of esophageal ulceration.[1] Various other fungal, viral, mycobacterial, and parasitic agents have been shown to cause esophagitis on rare occasion. Pill-induced esophagitis resulting from local mucosal injury has been attributed to almost 100 different drugs, particularly if they are ingested without water or in the supine position; antibiotics and antiviral agents are implicated in 50% of such cases.[2,3] Infectious and noninfectious causes of esophagitis are listed in Table 97.1. Multiple concomitant causes of esophagitis are common in patients who are significantly immunosuppressed or critically ill.[4]

CLINICAL MANIFESTATIONS

Most patients with esophagitis present with odynophagia (pain on swallowing) or dysphagia, described as difficulty swallowing or a sense of obstruction that is substernal, epigastric, or in the throat. Liquids are often better tolerated than solids such as meats, which may worsen both odynophagia and dysphagia. Pain may be exacerbated by the ingestion of acidic liquids and by eructation. Ulcerative esophagitis is characterized primarily by odynophagia, which can be severe, at times to the point of limiting oral intake and resulting in weight loss and dehydration. Spontaneous substernal pain or burning sensation may also occur intermittently, unrelated to swallowing. Gastrointestinal (GI) bleeding is rarely the initial manifestation of esophagitis, but it does occur.[5] Among patients evaluated for nausea and vomiting or abdominal pain, endoscopically proven esophagitis may be present in the absence of specific esophageal symptoms. Weight loss and anemia are observed presenting signs of *Candida* esophagitis in older patients.[6] In one review, odynophagia or dysphagia was absent in 21% to 41% of patients with documented esophagitis caused by *Candida* spp., HSV, CMV, or, in rare cases, *Mycobacterium tuberculosis.*[7] Fever accompanied esophagitis in 20% of patients with CMV or mycobacterial infection but was less common among those with *Candida* or HSV infection. Nausea and vomiting were most common (42%) in patients with CMV esophagitis, which possibly reflects the fact that CMV infection is seldom confined to the esophagus. Oral lesions frequently provide clues to the diagnosis of esophagitis, particularly in patients with acquired immunodeficiency syndrome (AIDS). Oral thrush is seen in most patients with esophageal candidiasis and AIDS.[8] The finding of oropharyngeal candidiasis in a patient with esophageal symptoms and AIDS has a positive predictive value of 70% or greater for esophageal involvement.[4,9–11,12] Similarly, oropharyngeal vesicles or ulcerations may suggest, but do not prove, concomitant esophageal HSV or aphthous ulceration in a symptomatic patient.

SPECIFIC ETIOLOGIC AGENTS

Candida Esophagitis

C. albicans is the predominant pathogen of esophagitis. Non-*albicans* species of *Candida,* including *Candida tropicalis, Candida parapsilosis, Candida krusei,* and *Candida glabrata,* are implicated less often but may play a greater role as a result of selective pressure among patients who have received antifungal agents.[13,14] Small numbers of *C. albicans* are part of the normal oral microbiota; esophageal colonization may be present in up to 20% of the population,[15] particularly in patients treated with histamine type 2 blockers.[16] Colonization is the initial process in which superficial adherence and proliferation of organisms remain confined to the superficial mucosa, without penetration or inflammation of the epithelium. Colonization progresses to infection if systemic and local defenses are inadequate for preventing invasion into deeper epithelial layers; pseudohyphae are present at the advancing margin of tissue involvement. On endoscopic examination the esophagus appears hyperemic with discrete, yellow-white mucosal plaques that are firmly

TABLE 97.1 Etiology of Esophagitis

COMMON	RARE
Infectious	
Candidiasis	*Mycobacterium tuberculosis*[80,81]
Cytomegalovirus	*Mycobacterium avium complex*[9,76]
Herpes simplex virus	*Cryptococcus neoformans*[4,82]
HIV infection, acute	*Histoplasma capsulatum*[77] *Actinomyces*[78,79] *Saccharomyces cerevisiae* *Cryptosporidium* *Pneumocystis jirovecii*[74] Varicella-zoster virus[83,84] Epstein-Barr virus[75] Human papillomavirus
Noninfectious	
Gastroesophageal reflux	Ingestion of corrosives (e.g., lye)
Mucositis resulting from cancer chemotherapy Mucositis resulting from radiation therapy	Local mucositis from tablets or capsules[2,3] (e.g., doxycycline, tetracycline, clindamycin, penicillin, rifampin, zidovudine, dideoxycytidine [ddC, zalcitabine], nelfinavir)
Aphthous ulcers	
Eosinophilic esophagitis caused by food allergy	
Nonsteroidal antiinflammatory drugs	
Bone resorption inhibitors (e.g., alendronate)	

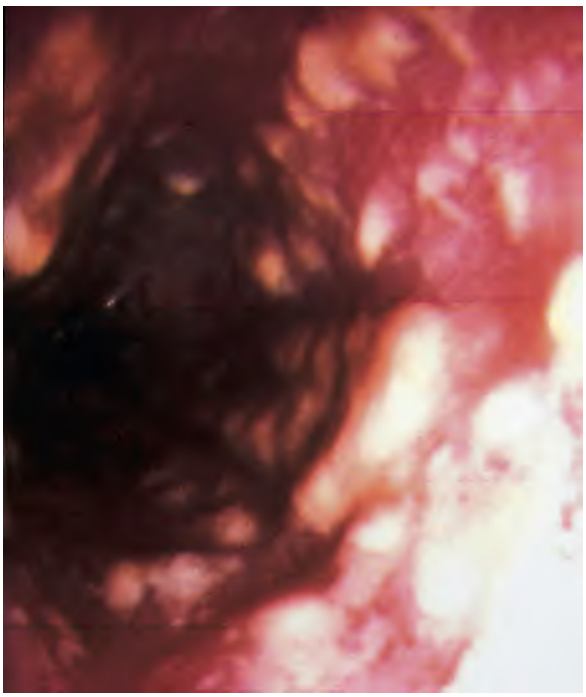

FIG. 97.1 Endoscopic appearance of esophageal candidiasis, with typical white plaques and nodules, in a patient with multiple myeloma. *(Courtesy Dr. Arthur DeCross, Rochester, NY.)*

adherent and, when removed, reveal an underlying rough and friable surface (Fig. 97.1). Lesions are most frequently located in the distal third of the esophagus. Disease may progress to involve large confluent plaques, ulceration, luminal narrowing, strictures, and necrosis.[2,17] Perforation of the esophagus is a rare complication of necrotizing esophagitis that may necessitate surgical intervention.[18]

Systemic host factors predisposing to esophageal candidiasis include acute[19] and advanced HIV infection, diabetes mellitus, leukemia and lymphoma, broad-spectrum antimicrobial therapy, antineoplastic therapy, corticosteroid therapy, and bone marrow or solid-organ transplantation. In addition to immune dysfunction, contributing local factors are those that impair esophageal motility (e.g., systemic sclerosis, achalasia, esophageal webs or rings, obstructing esophageal cancer) and conditions that result in mucosal injury (e.g., reflux, HSV esophagitis). Esophageal symptoms occur in up to half of all patients with AIDS,[9,20] and *Candida* accounts for 50% or greater of these cases.[4,12] Porro and colleagues[11] documented esophageal candidiasis in 48% of patients with AIDS who were admitted to a hospital, although 40% of those infected reported no esophageal symptoms. Transplant recipients, many of whom receive routine antifungal prophylaxis, appear less susceptible to *Candida* esophagitis, which developed in 5 (2.2%) of 224 renal transplant recipients,[21] 12 (2.2%) of 547 solid-organ transplant recipients,[22] and none of 304 cardiac transplant recipients.[23] Among symptomatic bone marrow transplant recipients, esophageal infection was diagnosed in 21 of 46 endoscopic examinations, but *Candida* accounted for only 5 of the 21 infections, the remainder being caused by CMV, HSV, or both.[24]

Diagnosis

Accurate diagnosis of esophageal candidiasis is established by endoscopy with directed brushings and biopsies. The characteristic gross appearance of candidiasis is suggestive but occasionally misleading, inasmuch as white exudative lesions may also be visualized with HSV or CMV infection or pill esophagitis. Brushings of exudative lesions and ulcer craters are obtained with a sheathed cytology brush, smeared onto slides, and submitted for calcofluor white, silver, or Gram stain. Biopsies of lesions and the edges of ulcers are submitted for histopathologic examination and for viral culture to identify CMV and HSV. Masses of yeast and pseudohyphae seen in tissue or brushings are diagnostic of *Candida* infection. Fungal cultures are not generally helpful except to identify the pathogen in cases of fungal esophagitis that are refractory to treatment. Blind brushing of the esophagus via a nasogastric tube has been advocated as an alternative to endoscopy in patients with HIV infection and suspected esophagitis; in one study, this technique was 96% sensitive and 87% specific for the diagnosis of candidiasis.[10]

Radiology

Radiologic contrast studies are of limited diagnostic value and are seldom performed in patients with esophagitis. Although focal or confluent plaques or a diffuse, "shaggy" appearance is characteristic of candidiasis on esophagography (Fig. 97.2), the examination result may be normal in some patients, and visualized abnormalities such as plaques, ulcerations, fistulas, or masses are often nonspecific; concurrent infections are likely to be missed.[5,25] Radiographic studies may be useful if endoscopy is unavailable. Computed tomographic scanning may demonstrate thickening of the esophageal wall in patients with esophagitis, but this finding is neither sensitive nor specific for infection.[26]

Cytomegalovirus Esophagitis

CMV esophagitis occurs most often in patients with AIDS or severe immunosuppression. CMV was an esophageal pathogen or copathogen in 33 (30%) of 110 patients with HIV infection and esophageal symptoms[4] and in 7 (33%) of 21 symptomatic recipients of bone marrow transplants.[24] Rare cases in immunocompetent hosts have been reported.[27] Symptoms are indistinguishable from those associated with *Candida* or HSV esophagitis. The endoscopic appearance of CMV esophagitis is typified by large (>10 cm^2), shallow, "punched-out" ulcers, solitary or multiple in number, located in the middle to distal part of the esophagus.[28] The ulcer margins are distinct, and the intervening mucosa appears relatively normal. Isolation of CMV in culture is not diagnostic because virus harbored in blood or saliva may contaminate esophageal specimens. Conversely, culture is not positive in all actual cases. Histopathologic examination is the most reliable diagnostic method when mucosal and submucosal biopsy samples are obtained from the ulcer edge and ulcer

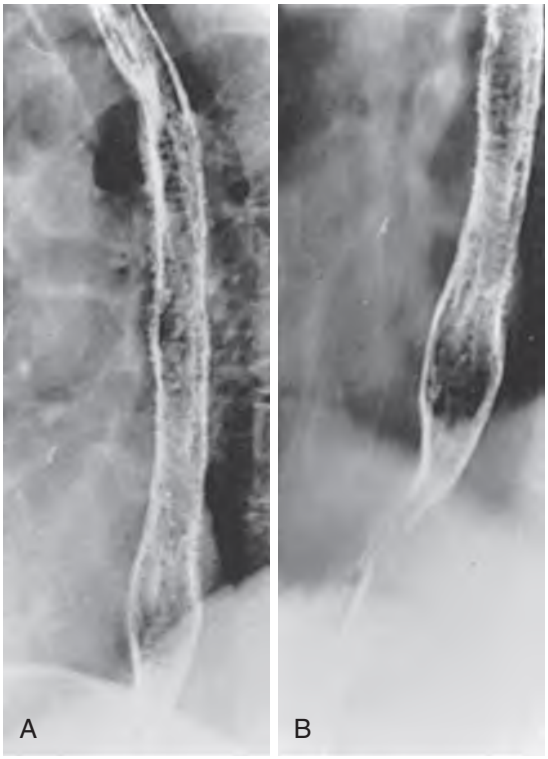

FIG. 97.2 (A and B) Barium contrast esophagograms of *Candida* esophagitis, revealing marked irregularity of the esophagus as a result of multiple plaques in a patient with acquired immunodeficiency syndrome and severe odynophagia. *(From Polis M. Esophagitis. In: Mandell GL, Bennett JE, Dolin R, eds.* Principles and Practice of Infectious Diseases. *4th ed. New York: Churchill Livingstone; 1995:962–965.)*

base; routine hematoxylin and eosin staining demonstrates enlarged endothelial cells or fibroblasts containing large, dense intranuclear inclusions.[28] Multiple biopsies increase the yield for diagnosis of CMV.[29] Immunohistochemical and direct fluorescent staining techniques, highly specific for CMV and HSV, are also useful in establishing these diagnoses. Coinfections of the esophagus are common in patients with CMV; concomitant candidiasis (73%) and HSV (12%) have been reported among these patients.[4]

Herpes Simplex Virus Esophagitis

HSV esophagitis is usually identified in patients with AIDS or other significant immunosuppressive conditions, although cases in healthy adults also occur. Of 23 patients with HSV esophagitis reported by McBane and Gross,[30] 7 (30%) had hematologic malignancies, 4 (17%) had received chemotherapy or irradiation for solid tumors, 8 (35%) had been treated with immunosuppressive agents for nonmalignant conditions, and 1 was otherwise healthy. HSV esophagitis accounts for 6% to 16% of HIV-infected patients with esophageal symptoms.[20] In a series of 21 bone marrow transplant recipients with esophagitis, HSV was identified in 48%.[24] Fifty-six cases of HSV esophagitis have been described in immunocompetent hosts, predominantly men, in whom the infection is typically self-limited.[31–33] Odynophagia, chest pain, fever, and dysphagia are the most common initial symptoms; clinically significant GI bleeding occurs in 5% to 10%.[33,34] Esophageal rupture is a rare complication. Oral, labial, or cutaneous HSV is clinically evident in only 19% to 38% of cases.[31,34]

Diagnosis

Typical lesions of HSV esophagitis appear endoscopically as multiple, small, superficial ulcers in the distal third of the esophagus; larger confluent ulcers, pseudomembranes, or diffusely denuded epithelium may be seen as the infection progresses (Fig. 97.3). "Volcano ulcers" may have raised margins around the central crater. Vesicles are rarely

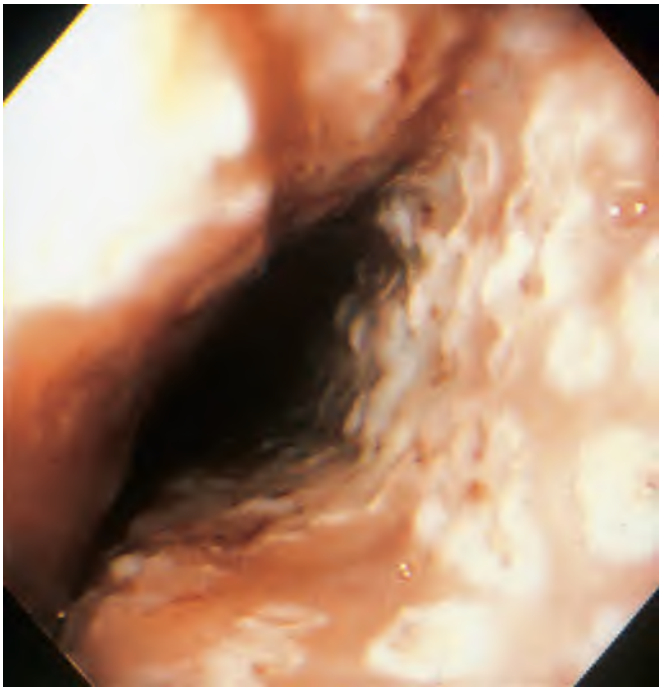

FIG. 97.3 Herpes simplex esophagitis, characterized by numerous small ulcerations, in an immunocompetent adult with fever and odynophagia. *(Courtesy Dr. Charles Michalko, Rochester, NY.)*

visualized. Double-contrast esophagography demonstrates ulcerative irregularities that are not specific or diagnostic. Viral culture of brushing or biopsy samples is positive for type 1 HSV (HSV-1) in most, but not all, cases; HSV-2 has rarely been implicated.[34,35] Quantitative polymerase chain reaction (PCR) for HSV-1 in biopsy specimens is highly sensitive (95%) and reasonably specific (73%) compared with histopathology and immunohistochemistry and may aid in diagnosis.[36] Histologic examination may reveal characteristic ballooning degeneration, multinucleated giant cells, and prominent intranuclear Cowdry type-A inclusion bodies in 55% to 70% of biopsy specimens. Superficial candidal invasion of HSV ulcers is often seen on biopsy. Several cases of HSV esophagitis have been reported in immunocompetent individuals with preexisting eosinophilic esophagitis.[37]

Aphthous (Idiopathic) Ulceration of the Esophagus

Aphthous, or idiopathic, ulceration, an important variant of esophagitis in patients with advanced HIV infection, accounts for approximately 5% of patients with AIDS who have esophagitis.[4,9] No specific cause is evident in 40% of patients with AIDS and esophageal ulceration,[38] and painful ulcers are often present in the oropharynx as well.[39] Esophageal ulceration has also been described in patients with acute HIV infection who present initially with odynophagia, and some authorities believe that detection of HIV virions by electron microscopy in the margins of these ulcers may indicate a direct pathogenic role for HIV itself.[1] Others, having detected HIV nucleic acid by in situ hybridization or PCR in the esophageal mucosa of up to 80% of patients with AIDS and idiopathic ulceration or with specific etiologic diagnoses (*Candida*, CMV, or HSV esophagitis), have concluded that HIV is not a primary pathogen in ulcerative disease.[12,40] Unrecognized other infectious agents may contribute to the pathogenesis of these idiopathic ulcerations.

MANAGEMENT OF ESOPHAGEAL INFECTION

General Considerations in Therapy

Specific therapies for infectious causes of esophagitis are listed in Table 97.2. The approach to diagnosis and therapy in a particular patient often depends on the presence of underlying disease and the severity of immunosuppression (Table 97.3).

Patients receiving cancer chemotherapy may experience severe mucositis with odynophagia that is clinically indistinguishable from fungal or viral esophagitis. Oropharyngeal candidiasis is highly predictive of esophageal candidiasis in patients with cancer, particularly in patients with mucositis after chemotherapy.[41] Diagnostic endoscopy should be pursued whenever possible, but in practice the procedure is frequently deferred because of bleeding, severe pain, mucosal friability, or critical illness; empirical therapy for *Candida* and HSV infection is appropriate in the interim period, particularly if oral thrush or mucocutaneous HSV lesions are clinically evident or if cultures are positive. Patients with fever and neutropenia (<100 neutrophils/mm^3) are usually treated empirically with systemic antifungal agents (amphotericin B, lipid formulations of amphotericin, voriconazole, caspofungin, or other echinocandins) in doses sufficient to treat either esophageal or disseminated candidiasis. Intravenous (IV) acyclovir is often administered in this acute setting if HSV stomatitis or labialis is present or if esophageal symptoms are severe. Recipients of allogeneic bone marrow transplants who are neutropenic commonly receive antiviral prophylaxis until engraftment occurs. Esophageal infections in recipients of bone marrow transplants usually begin more than 40 days after transplantation, and neutrophil counts are usually within the normal range at that time; CMV and HSV infections are at least as common as *Candida* infections in this group of patients, and treatment should be guided by the results of endoscopic diagnosis.[24] Similarly, treatment of esophagitis in recipients of solid-organ transplants or in immunocompetent hosts should be guided by endoscopic appearance, culture data, and histopathologic findings. Tacrolimus and cyclosporine levels may be elevated and should be monitored in transplant recipients who are receiving concomitant fluconazole, voriconazole, or itraconazole.

TABLE 97.2 Treatment of Esophagitis

CAUSE	USUAL TREATMENT (ADULT DOSE)	ALTERNATIVE DRUGS
Candida	Fluconazole, 200–400 mg/day PO for 14–21 days; for patients unable to tolerate PO therapy, IV fluconazole, 400 mg/day or an echinocandin is recommended; maintenance suppressive therapy may be necessary in AIDS (fluconazole, 100–200 mg 3 times weekly PO)[46]	Itraconazole oral suspension, 200 mg/day PO Voriconazole,[64] 200 mg bid PO[a] Amphotericin B, 0.3–0.7 mg/kg/day IV for 7 days Caspofungin, 50 mg/day IV after 70–mg loading dose[a] Micafungin, 150 mg/day IV Anidulafungin, 200 mg/day IV[46]
Herpes simplex virus	Acyclovir, 5 mg/kg IV q8h for 7–14 days or 400 mg 5 times daily PO for 14–21 days *or* valacyclovir, 1 g PO tid for 14–21 days[b]; maintenance suppressive therapy may be necessary in AIDS	Famciclovir, 500 mg bid PO for 14–21 days (not for acyclovir-resistant infection) Foscarnet, 90 mg/kg q12h IV for 7–14 days (used for acyclovir-resistant infection)
Cytomegalovirus	Ganciclovir, 5 mg/kg IV q12h for 14–21 days; maintenance suppressive therapy usually is necessary in AIDS (ganciclovir, 5 mg/kg/day IV 7 days/wk or 6 mg/kg/day IV 5 days/wk)	Foscarnet, 90 mg/kg q12h IV for 14–21 days; suppression with foscarnet, 90–120 mg/kg/day IV Valganciclovir, 900 mg bid PO for treatment, and 900 mg qd for maintenance/suppression[b]
Aphthous ulceration (in AIDS)	Prednisone,[57] 40 mg/day PO for 14 days, then taper	Thalidomide,[58,85] 200 mg/day PO[b]

[a]Amphotericin, echinocandins, and voriconazole are indicated for severe or refractory esophageal candidiasis.
[b]Not approved by the US Food and Drug Administration for this indication.
AIDS, Acquired immunodeficiency syndrome; *bid,* twice daily; *IV,* intravenous.

Esophagitis in Patients With Acquired Immunodeficiency Syndrome

Before the introduction of antiretroviral therapy (ART), esophageal symptoms occurred in 40% to 50% of patients with AIDS at some point in the course of the disease and often had a significant effect on nutritional status and overall morbidity.[5,9,20] The incidence of esophagitis has declined dramatically since the advent of ART; however, cases of opportunistic infection of the esophagus continue to occur in patients in whom antiretroviral therapy fails because of drug resistance or noncompliance.[42–44,45] The frequencies of various causes are shown in Table 97.3, and treatment regimens are listed in Table 97.2. *Candida* esophagitis is the most common type; it is treated empirically with oral fluconazole[46] in symptomatic patients, particularly if oropharyngeal candidiasis is also observed. The presence of oral thrush is predictive of esophageal involvement in greater than 70% of such cases.[4,9–11,12,47] Itraconazole solution is comparable to fluconazole,[48] but itraconazole capsules are erratically absorbed and are less effective.[49] For patients who cannot tolerate oral therapy, IV fluconazole or an echinocandin is recommended.[46] Complete symptomatic response can be expected in greater than 80% of patients treated empirically, usually within 1 week. If the patient has no response to empirical azole therapy within 14 to 21 days, endoscopy should be performed to establish a diagnosis.[46,50] Among patients in whom empirical azole therapy for esophageal symptoms has failed, endoscopy demonstrates ulceration of the esophagus in 62% to 77%, attributable most often to CMV infection (32%–40%), aphthous disease (27%–32%), or HSV infection (5%–8%).[51,52] Early endoscopy is appropriate in patients with severe symptoms or GI bleeding.

A viral cause is identified in approximately one-third of cases, often in association with candidiasis. Empirical antiviral therapy for CMV or HSV is discouraged. Patients with CMV esophagitis confirmed by culture or histopathologic examination are treated with ganciclovir, 5 mg/kg IV every 12 hours. Although no trials have been conducted to test the efficacy of valganciclovir in CMV esophagitis, Centers for Disease Control and Prevention, National Institutes of Health, and Infectious Diseases Society of America guidelines state that patients may be switched to valganciclovir 900 mg orally every 12 hours once they can tolerate oral therapy.[53] Cases refractory to ganciclovir may

TABLE 97.3 Causes of Esophagitis in Symptomatic Patients With Underlying Disease

CAUSE	AIDS[4,9,12] (*N* = 183)	BONE MARROW TRANSPLANTATION[24] (*N* = 39)	SOLID-ORGAN TRANSPLANTATION[23,86] (*N* = 88)
Candida alone	38%	10%	3%
Candida + other	22%	3%	—
Cytomegalovirus	21%	26%	6%
Herpes simplex virus	11%	26%	7%
Aphthous ulceration	4%	—	—
Kaposi sarcoma	7%	—	—

[a]Patients on whom upper endoscopy was performed to evaluate odynophagia, dysphagia, epigastric pain, nausea and vomiting, or gastrointestinal bleeding.
AIDS, Acquired immunodeficiency syndrome.

respond to foscarnet, 90 mg/kg IV every 12 hours. A partial or complete response to induction therapy is observed in 75% to 85% of patients treated with either ganciclovir or foscarnet,[54–56] but relapses are common with or without maintenance therapy. Documented HSV esophagitis is usually treated with IV acyclovir initially in severe cases; therapy may be continued with oral acyclovir, valacyclovir, or famciclovir. Complete resolution is reported in 70% of patients treated with acyclovir, but relapse occurs in 15% of patients with HSV esophagitis within 4 months.[34] If acyclovir therapy has failed because of resistance, no response to ganciclovir is expected, and foscarnet should be given.

Aphthous ulceration of the esophagus has been ameliorated with a regimen of prednisone, 40 mg daily for 2 weeks, in greater than 90% of cases.[57] A placebo-controlled trial demonstrated complete healing of AIDS-associated oropharyngeal aphthous ulcers in 55% of 29 patients treated with thalidomide, 200 mg daily for 1 month, in comparison with only 7% of patients who received placebo.[58] In a similar randomized study of 24 HIV-infected patients with biopsy-confirmed aphthous ulceration of the esophagus, the same regimen of thalidomide resulted in complete healing at 4 weeks in 73% of treated subjects, in comparison with 23% of placebo recipients ($P = .033$).[59] In a series of 12 patients with idiopathic esophageal ulceration, 92% experienced complete resolution of symptoms with this treatment regimen.[60] Use of these therapies should be considered for patients with esophageal ulcerations not attributable to specific pathogens. Thalidomide in lower dosages of 100 mg three times per week was not effective in preventing recurrences of oral and esophageal aphthous ulcers in HIV-infected patients.[59] Zidovudine, zalcitabine (ddC), and nelfinavir capsules may also cause esophageal ulceration; patients should be advised to take these and all oral medications in the upright position and with sufficient water.

Approximately 5% of endoscopically proven cases of *Candida* esophagitis are refractory to fluconazole therapy because of either acquisition of a resistant strain or gradual emergence of resistance over time. Refractory candidiasis—most common in patients with advanced AIDS, a $CD4^+$ T-cell count lower than $50/mm^3$, and long-term exposure to azole antifungal agents—is an indicator of poor disease prognosis.[61] Patients unresponsive to fluconazole, 200 mg daily for 2 weeks, may respond to higher doses, at least transiently; 50% to 60% of such patients have responded to itraconazole oral solution, 200 mg daily.[61,62] Chronic prophylaxis with itraconazole is associated with reduced susceptibility to itraconazole and cross-resistance to fluconazole.[63] Oral voriconazole has demonstrated efficacy equivalent to that of fluconazole in treatment of esophageal candidiasis; voriconazole may be effective in management of fluconazole-refractory cases.[64] Oral posaconazole has yielded clinical responses in 74% of patients with esophageal candidiasis refractory to fluconazole or itraconazole.[65] The newer agent isavuconazole has also shown efficacy equivalent to fluconazole in treatment of uncomplicated esophageal candidiasis.[67] Echinocandins are usually effective but are associated with higher relapse rates than seen with fluconazole, and higher doses of echinocandins are recommended for esophagitis than for candidemia.[46] Caspofungin has proved as efficacious as fluconazole or amphotericin B, including good responses in cases refractory to fluconazole; however, response rates to either amphotericin or caspofungin are reduced in patients for whom fluconazole previously failed, probably because these patients have more severe immunosuppression.[68,69] Micafungin and anidulafungin have also proved as effective as fluconazole.[70,71] Emergence of resistance to echinocandins during echinocandin therapy has been reported.[72,73] Parenteral amphotericin has been reserved for patients in whom other therapies fail; doses of 15 to 20 mg daily are often sufficient. Relapse rates are higher with refractory candidiasis, and maintenance therapy is almost always required. ART is critical in such patients and must be optimized. To reduce the risk of refractory disease, continuous antifungal prophylaxis should be avoided in most patients with AIDS who have mucosal candidiasis unless recurrences are particularly frequent or severe.[61]

Various other pathogens have caused rare cases of esophagitis in patients with AIDS, including *Pneumocystis jirovecii,*[74] Epstein-Barr virus,[75] *Mycobacterium avium* complex,[9,76] *Histoplasma capsulatum,*[77] *Cryptococcus neoformans,*[4] *Cryptosporidium, Actinomyces,*[78,79] *Trichomonas,* human papillomavirus, and *Saccharomyces.* Therapy is the same as for infections with these agents at other sites. Kaposi sarcoma involving the esophagus has been documented in up to 7% of patients with AIDS who have esophageal symptoms.[4,9,12] As opportunistic infections have decreased in frequency, gastroesophageal reflux disease is relatively more common as a cause of esophagitis among patients with HIV infection.[45]

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The complete reference list is available online at Expert Consult.

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98 Diarrhea With Little or No Fever

Luther A. Bartelt and Richard L. Guerrant

SHORT VIEW SUMMARY

Definition

- A diverse group of pathogens cause acute and chronic forms of gastroenteritis that occur in both pediatric and adult patients. These diseases have the unifying characteristic of being predominantly clinically *noninflammatory* (typically without dysentery and with little or no fever) in nature.

Epidemiology

- Noninflammatory gastroenteritides are among the most common infections of humans. As a group, they are second in incidence only to viral upper respiratory infections.
- Most cases of these diseases are not tracked or reported, but they are estimated to affect tens of millions of people or more worldwide each year.
- There are baseline endemic sporadic and seasonal rates as well as epidemic outbreaks of most forms of these infections.
- The rates of infection and etiologic agents vary according to age, climate, and geography. In addition, there are differences in these parameters observed for place of acquisition (e.g., community-acquired vs. health care facility–acquired infections or travel-associated infections).

Microbiology

- Viruses including members of the rotavirus, norovirus, adenovirus, and astrovirus genera are the cause of most cases of noninflammatory gastroenteritis.
- Among the bacterial causes of this syndrome, certain pathogenic strains of *Escherichia coli* and some serotypes of cholera and noncholera *Vibrio* spp. are particularly noteworthy.
- Certain protozoan types of parasites can cause a predominantly noninflammatory type of gastroenteritis and include members of the *Cryptosporidium, Giardia, Cystoisospora,* and *Cyclospora* genera.
- Although many of the etiologic agents are similar, there are also some important differences between the endemic and epidemic causes of noninflammatory gastroenteritis in resource-limited countries compared with resource-abundant countries.
- Neonatal nursery–associated and nosocomial outbreaks of this syndrome differ from community outbreaks.
- The number of potential infectious agents is much greater in immunocompromised hosts compared with immunocompetent hosts.

Diagnosis

- The typical clinical syndrome consists of varying degrees of watery diarrhea with or without nausea and vomiting, often in combination with abdominal discomfort. Fevers when present are typically low-grade. Myalgias and arthralgias or other systemic symptoms can occur but are frequently absent.
- Most cases of this syndrome, regardless of etiology, are self-limited, and no specific pathogen is identified. The duration may be prolonged in immunocompromised and malnourished hosts.
- In certain instances such as epidemics, health care–associated outbreaks, foodborne cases, cases in immunocompromised hosts, and cases associated with international travel, an etiologic agent should be identified by culture, immunoassay, or molecular diagnostic assay.

Therapy

- Adequate replacement of fluids and electrolytes is the mainstay of treatment for all forms of gastroenteritis.
- In most cases, specific antimicrobial therapy is unnecessary. However, in severe forms or select populations or situations, specific antiviral, antibacterial, or antiparasitic treatment may be beneficial. When used, the choice of antimicrobial therapy should be guided by the identification of a specific pathogen.
- There are increasing reports of emerging multidrug resistance among Enterobacteriaceae (*Campylobacter, Shigella,* and *Salmonella* spp.) members of this group.

Prevention

- Adequate sanitation for the local water supply and food processing and distribution systems helps to prevent many forms of endemic, community-acquired noninflammatory gastroenteritis.
- Personal protective equipment such as gloves, hand hygiene with soap and water, and patient education are used in health care settings to reduce nosocomial spread.
- Although there has been considerable interest in developing effective vaccination or immunization schemes for many of these infectious agents, only vaccines for rotavirus are currently available for general use.

Gastroenteritis is one of the most common infectious disease syndromes. An estimated 2.4 billion episodes occur worldwide each year,[a] with children younger than 5 years old living in resource-limited settings accounting for nearly 1 billion of these infections and more than 500,000 deaths yearly.[b] Despite decreasing global mortality rates, the collective morbidities due to these infections in resource-limited settings remain significant.[5,6,7,9] Also, the emergence of *Clostridiodes difficile* (formerly *Clostridium difficile*) has been associated with increasing diarrhea-associated mortality in the United States and other resource-abundant countries. Despite considerable morbidity and mortality, most episodes of acute gastroenteritis are self-limited. In most cases there is no clinically recognizable inflammatory process (i.e., fever or dysentery),[11,12] suggesting viral, toxigenic bacterial, or noninvasive parasitic etiologies.[c] With the notable exceptions of profuse purging (*cholera gravis*) as a potentially fatal manifestation of *Vibrio cholerae* and diarrhea persisting for greater than 2 weeks due to parasitic causes, clinical symptoms rarely indicate a specific etiology in an afebrile patient. Fever can accompany many etiologies of gastroenteritis; the absence of fever or blood in the stool, or both, diminishes the likelihood of an invasive bacterial or amebic process and the urgency to treat (see Chapter 99). Local and seasonal prevalence, outbreaks, host factors (e.g., age and immune compromise), antibiotic use, and the environment (varying across industrialized and nonindustrialized, and community and health care environments), influence the likelihood of the attributable pathogen.[6,7,9,10] Fluid and electrolyte replacement appropriate to the severity of illness is the

[a]References 1, 2, 3, 4–6, 7, 8, 9, 10.
[b]References 3, 4, 5, 6, 8, 9.
[c]References 1, 2, 4, 5, 6, 7, 8, 9, 10.

mainstay of treatment. Pathogen-directed diagnostic tests should guide antimicrobial therapy when indicated.

EPIDEMIOLOGY OF ACUTE NONINFLAMMATORY DIARRHEA

Despite declining global incidence, a broad group of gastrointestinal pathogens remains that cause typically self-limited, watery diarrhea with or without nausea and vomiting, often accompanied by other abdominal complaints. Collectively, in 2015 these pathogens caused more than 1.3 million deaths globally, were the ninth leading cause of death for all ages, and were the fourth leading cause of death in children less than 5 years of age.[3] Pathogen-attributable burden varies geographically and throughout the human life span and is largely influenced by economic indicators and rotavirus vaccine availability.[3,9] The burden of gastrointestinal infections is overwhelmingly skewed toward young children in resource-limited countries, particularly children with malnutrition. Therefore diarrhea-related mortality in children less than 5 years old is almost exclusive to regions of sub-Saharan Africa and South Asia.[3] In contrast, pediatric gastroenteritis in the United States is seldom fatal. However, total diarrhea-attributable mortality across all ages in the United States increased by 36.8% from 2005 to 2015, largely due to the emergence of health care–associated and antibiotic-associated *C. difficile* diarrhea, which disproportionally affects older adults. In the United States there are an estimated 179 million outpatient visits and nearly 500,000 hospitalizations due to foodborne or waterborne gastroenteritis per year.[13]

COMMUNITY-ACQUIRED DIARRHEA

Acute Pediatric Diarrhea

The rapid decline of infant mortality rates during the 20th century coincided with increased availability of piped water and chlorination systems. In areas of the world that continue to have unsafe water and sanitation, gastroenteritis remains a major cause of infant mortality.[3] The highest attack rate of diarrhea occurs at the time of weaning (weanling diarrhea), usually between 6 and 24 months of age.[14,15] The increased susceptibility of a recently weaned infant is related to several factors.[16] First, human breast milk appears to convey a level of resistance to some gastrointestinal pathogens and may protect an infant who is still breastfeeding.[17–21] In contrast, in resource-limited settings, weaning and complementary foods are often prepared under conditions of poor hygiene and are frequently found to be contaminated with large numbers of potential diarrheal pathogens.[22,23] Children may also ingest soil contaminated with diarrheogenic bacteria.[24] Finally, undernutrition can influence pathogen-attributable diarrhea risk.[25–28]

Early childhood diarrhea, regardless of etiology, often manifests as acute, watery, noninflammatory diarrhea. Cases are sporadic, but there are seasonal patterns, often peaking in the summer months in resource-limited settings.[9] In a well-nourished infant, the disease is usually short-lived and resolves within 2 to 3 days with adequate hydration.[15,29] Diarrhea in a malnourished child tends to persist or to recur and is often much more severe.

Early childhood diarrhea has been most commonly associated with rotaviruses[29–31] and enterotoxigenic *Escherichia coli* (ETEC).[32,33,34] Use of molecular diagnostics in longitudinal and case-control studies has refined these pathogen-attributable estimates across multiple global regions.[5,6,9,35] Using quantitative polymerase chain reaction (PCR) methods, up to 90% of moderate-to-severe acute diarrheal episodes were pathogen-attributable in low-income–to–middle-income settings.[6] Rotavirus is the most common global etiology of severe acute watery diarrhea.[6,9,35] Other viruses, predominately norovirus GII and adenovirus types 40 and 41, and to a lesser extent sapovirus and astrovirus, are significant contributors, especially where rotavirus vaccine is established.[6,9,35] Cases due to *Shigella* spp. slightly outnumber cases caused by heat-stable enterotoxin-producing ETEC (ST-ETEC).[6,9,35] These studies have also revealed the emerging importance of previously difficult to detect or noncultivable pathogens such as *Campylobacter* spp. and the protozoan *Cryptosporidium*. In some settings, *Cryptosporidium* is second only to viral etiologies and, together with rotavirus and *Shigella* spp., may combine to account for more than 50% of diarrhea-attributable mortality in children less than 5 years of age.[5,35] Although these studies have clarified the major drivers of early childhood diarrhea at the population level, the clinical application of these tools for individual cases is more challenging. First, molecular diagnostics are seldom available. Second, 40% or more of diarrheal stools may harbor two or more pathogens simultaneously.[6]

Diarrhea Caused by Rotavirus

Rotaviruses are the most common cause of severe diarrhea in infants and young children (see Chapter 150).[35–38,39] Worldwide, rotaviruses cause more than 100 million cases of gastroenteritis and up to 240,000 deaths each year in children younger than 5 years old.[3,37,40] Of these rotavirus-induced deaths, more than 90% occur in children residing in low-income or middle-income countries.[40] Although most adults have antibody to rotaviruses that may be protective, unvaccinated children younger than 2 years are highly susceptible to rotavirus diarrhea.[37]

In the United States few deaths are attributable to rotavirus infection; however, before inclusion of rotavirus vaccine in childhood immunization programs, almost every child had been infected by the age of 5 years, and rotavirus-induced gastroenteritis caused about 400,000 physician encounters, almost 200,000 emergency department visits, and about 70,000 hospitalizations each year.[37] Since routine vaccination began in 2008, rotavirus-related diarrhea has declined by 62% to 71%, and hospitalization for all-cause gastroenteritis has declined by 31% to 33%.[41,42] Infection occurs more frequently in the winter or in cooler, dry months[29,30,43–50] than in the summer months.[9,51]

There are five major rotavirus serotypes, A through E, with group A strains further subdivided based on the combination of G (the VP7 glycoprotein) and P (the VP4 protease-cleaved protein) types.[37,38,52–56] Worldwide, five serotypes (G1 through G4 and G9) predominate.[37,38,52–54,57] A particular strain (the number in brackets indicates the genotype), P1B[4]G2, is associated with a more severe form of infection in children.[58,59] Such epidemiologic information was important in designing rotavirus vaccines. Before rotavirus vaccination in the United States, six rotavirus strains were most commonly found: G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G9P[6].[54–57,60,61] In the postvaccine era, G3P[8] was predominant through 2011 and has since been replaced by G12P[8]. Vaccine-derived strains occur in 0.6% to 3.4% of cases.[62] Recent outbreaks of milder illness have been associated with more unusual serotypes, for example, strain G8P[8], which affected vaccinated and nonvaccinated individuals equally.[63]

Rotavirus diarrhea is usually mild, without high-grade fever, and is often associated with vomiting; however, clinical syndromes range from asymptomatic carriage to severe gastroenteritis with profound dehydration, shock, and death.[29,30,36,37,64] Serious complications of rotavirus gastroenteritis include necrotizing enterocolitis in neonates.[60,65,66] Severe cases are more common in resource-limited settings,[37,65] and among severely immunocompromised patients. Large symptomatic outbreaks of moderately severe rotavirus diarrhea can occur. Although outbreaks are geographically distinct, they are often caused by the same rotavirus strain.

The diagnosis of rotavirus diarrhea is established with the use of a variety of molecular assays designed to detect virus-specific antigens, antibodies, or nucleic acids in feces of infected patients.[67–70] Rotaviruses can also be cultured directly from stool samples, although this method is time-consuming, expensive, and limited primarily to research-based laboratories.

The human rotaviruses are nonenveloped RNA viruses of approximately 70 nm belonging to the Reoviridae family.[37,52,53] The major rotavirus-mediated effects on the host include disruption of intestinal epithelial cell brush-border enzymes, cytotoxicity, and alteration of the enteral nervous system.[38,39,71–73] Normal columnar epithelium at the villus tips is replaced by irregular cuboidal, cryptlike cells, leading to multiple defects in fluid and electrolyte regulation. Many of these effects are believed to be mediated by a calcium ion–dependent enterotoxin.

The loss of absorptive villus tip cells may be responsible for the fluid imbalance and nutritional impact of rotavirus infections. The degree of microvillus damage roughly parallels the severity of diarrhea and dehydration.[74] Certain patients with rotavirus gastroenteritis also exhibit extraintestinal symptoms in association with detectable antigenemia and viremia, supporting a systemic phase to this infection.[75–78]

Oral or intravenous rehydration is the cornerstone of therapy for rotavirus gastroenteritis. No definitive antiviral therapy is established for rotavirus infection; however, the antiparasitic drug nitazoxanide was shown in randomized, controlled studies to shorten the duration of illness in children and adults with symptomatic rotavirus diarrhea.[79,80] Adjuvant probiotic use may reduce repeated diarrhea episodes and promote intestinal function after rotavirus infection,[81] but the role of specific probiotics regarding duration and severity of illness across different populations requires further investigation.[82]

Because of the great global burden of childhood rotavirus gastroenteritis, significant multinational efforts have been directed toward the development of a safe and effective rotavirus vaccine. The first rotavirus vaccine approved for use in the United States was the rhesus-human reassortant rotavirus tetravalent vaccine (RotaShield; Wyeth-Lederle, Madison, NJ). It was approved and released in 1998 for use in infants. Despite high efficacy, the vaccine was removed less than 1 year later because of concerns about possible cases of intussusception in vaccinated infants.[83,84] After the withdrawal of the rhesus-human reassortant rotavirus tetravalent vaccine, two new rotavirus vaccines became licensed and approved for use in infants in the United States:[37,53,85,86] first, a live oral pentavalent rotavirus vaccine (RotaTeq; Merck Vaccines, Whitehouse Station, NJ) comprising bovine-human recombinant strains in 2006,[37,85,86,87] followed by a monovalent human rotavirus vaccine (Rotarix; GlaxoSmithKline, London, United Kingdom) derived from an attenuated P1A[8]G1 rotavirus strain in 2008.[37,85,86,87–89] Both are administered starting between 6 and 14 weeks of age in a three-dose (pentavalent rotavirus vaccine) or two-dose (human rotavirus vaccine) schedule and are highly efficacious. No significant increased risk of intestinal intussusception has been observed to date. Neither vaccine should be administered to infants with severe combined immunodeficiency syndrome[90]; however, despite a theoretical risk of transmission of vaccine-derived strains within a household, living with an immunosuppressed patient is not an absolute contraindication.[91]

Routine rotavirus vaccination has dramatically reduced rotavirus-diarrhea in the United States, and use of the rotavirus vaccine has been estimated to have saved $1.2 billion in annual health care costs associated with acute gastroenteritis.[42] Rotavirus vaccine is now available in more than 90 countries; however, vaccine efficacy varies geographically and is lower in resource-limited countries where the bulk of rotavirus infections still occur.[3] Among the potential reasons for decreased rotavirus efficacy is as yet poorly understood differences in mucosal immune responses in children in these settings, particularly children with evidence of undernutrition, and possibly differences in intestinal microbial ecology or the presence of high maternal antirotavirus immunoglobulin A, or both. A parenterally administered P2-VP8-P[8] subunit vaccine appears to be safe and immunogenic.[92]

Acute Nausea and Vomiting (Winter Vomiting Disease)

The syndrome of acute nausea and vomiting (intestinal flu, viral gastroenteritis, or what had been called *winter vomiting disease*) sometimes with low-grade fever commonly occurs in winter months in temperate climates.[93,94] Although this syndrome overlaps with rotavirus-associated infantile gastroenteritis, rotaviruses are relatively uncommon causes of winter vomiting disease in older children and adults. The Cleveland family studies of Dingle and coworkers[95] showed gastrointestinal illnesses were most common between the ages of 1 and 10 years, when approximately two illnesses occurred per person per year. Illnesses peaked from November through February, with June being the month of lowest frequency. Most illnesses lasted 1 to 3 days; 20% occurred with respiratory symptoms, and 20% involved only diarrhea.

Illnesses tended to occur in one of two patterns: (1) a mild afebrile illness with watery diarrhea or (2) a more severe febrile illness with vomiting, headache, and constitutional symptoms. Although etiologic agents were rarely identified, these two patterns of illness also developed among volunteers who ingested filtrates prepared from the feces of ill patients.[96–98] Studies done in Charlottesville, Virginia, confirmed this pattern of wintertime gastroenteritis including clustering in families, highest attack rates in children, and absence of identifiable etiologic agents in most cases despite the application of techniques for virologic and enterotoxin studies.[99,100]

Caliciviruses are now recognized as the etiologies of many cases of gastroenteritis occurring in winter months. The Caliciviridae family comprises four genera:[101,102] *Norovirus, Sapovirus, Lagovirus*, and *Vesivirus* (see Chapter 176). Viruses belonging to *Norovirus* (from *Nor*walk) and *Sapovirus* (from *Sap*poro) genera are currently the most common causative agents for viral gastroenteritis in humans.[101,102,103,104,105] Noroviruses and sapoviruses may predominate as causes of early childhood diarrhea in rotavirus-vaccinated populations.[6,7,35,106] Noroviruses, in particular, cause major outbreaks, especially in older children and adults (see Chapter 176). Immunocompromised patients can develop chronic norovirus infection lasting for months or years (see "Diarrhea in Immunocompromised Patients").[107]

Norovirus

Norovirus accounts for more than one-third of the outbreaks of nonbacterial gastroenteritis in the United States.[108,109] Initially these viruses were referred to as Norwalk-like viruses. Their individual names were originally derived from the site of origin of each particular outbreak and included Norwalk,[110,111,112] Hawaii,[113] Snow Mountain,[114] Taunton, and W agents.[115] Person-to-person spread is common, and secondary attack rates can be high.

Norovirus outbreaks have been observed in a wide variety of settings[116,117] including hospitals,[118] extended-care facilities,[119] child care centers,[120] cruise ships,[121] refugee centers associated with natural disasters (e.g., Hurricane Katrina[122]), and military combat areas including Afghanistan[123] and Iraq.[124] Several genotypes are known to infect humans[103,116,117]; in recent years, newly identified variant strains of norovirus genotype GII.4 have caused outbreaks worldwide[125–127] including in the United States, United Kingdom, Europe, New Zealand, and Australia.

The pathophysiologic features of norovirus gastroenteritis parallel features of rotavirus in several respects.[101,102,103,117] Each type is essentially noninflammatory and causes villus disruption and transient brush-border enzyme deficiencies in the upper small intestine, without any alteration in adenylate cyclase activity.[54,128,129] This enteropathy can be severe in patients with underlying immunocompromise, especially patients with common variable immunodeficiency.[130] The roles of enzyme deficiencies, malabsorption of xylose and lactose, and an increase in intestinal bacteria during norovirus illness remain unclear.[128,131]

Sapovirus

Global studies on etiology of pediatric diarrhea in low-income–to–middle-income countries have unmasked a greater burden of sapovirus diarrhea than previously recognized.[6,7] Sapovirus was the second most common all-cause etiology of diarrhea in the community setting,[7] and cumulative incidence may exceed 80% by 2 years of age.[132] Sapoviruses were initially called typical human caliciviruses or Sapporo-like viruses after the prototype strain found in an outbreak in Sapporo, Japan, in 1982. Similar to norovirus, diverse sapovirus genogroups and genotypes cause infections in humans. Repeated infections are typically due to different genotypes, suggesting immunity is genotype-specific.[132] Sapovirus symptoms overlap with norovirus symptoms. Similar to norovirus, sapovirus can cause outbreaks in long-term care facilities, but fewer laboratories specifically test for sapovirus. Sapovirus should be considered if the cause for an outbreak is otherwise unexplained.[133] Sapovirus also occurs as a coinfection with other pathogens.

Diarrhea Caused by Astrovirus, Adenovirus, and Other Possible Viral Etiologies

Several other groups of viral pathogens have been identified in endemic and epidemic gastroenteritis (Table 98.1) including[36,67,134–136] (1) other types of caliciviruses with characteristic, "chalice-like" surface; (2) astroviruses, with a five- or six-pointed starlike surface structure[137]; (3) enteric adenoviruses (especially serotypes 40 and 41)[6,138]; and (4) human enteric coronaviruses,[139,140] as well as other miscellaneous or less well-characterized viral agents. More detailed discussions of these agents may be found in Chapters 142, 155, 172, 174, 177, and 178.

TABLE 98.1 Viral Pathogens Causing Gastroenteritis

ESTABLISHED PATHOGENS	LIKELY AND EMERGING PATHOGENS
Adenoviruses (enteric types)	Bocaviruses
Astroviruses	Coronaviruses
Caliciviruses (including noroviruses and sapoviruses)	Enteroviruses (various)
Rotaviruses groups A–C	Picobirnaviruses, picornaviruses
Cytomegalovirus	Pestiviruses
	Toroviruses

Data from references 36, 60, 67, 104, 105, 116, 120, 135, 137, 149, 393, and 394.

Astroviruses are among the most common causes of pediatric viral gastroenteritis.[141–144] Astrovirus occasionally occurs in association with other enteric pathogens; in these cases the illness is more severe and protracted.[143] After rotavirus, adenovirus 40/41 was the most common viral etiology of moderate-to-severe acute diarrhea in children in low-income settings and the third most common cause overall.[6] In a case-control study in China, adenovirus serotype 3 was also associated with diarrhea, whereas asymptomatic detection of other serotypes (1, 2, 5, 6, 31, and 56) were more common in healthy children.[145]

Vomiting and diarrhea can also manifest during infections with respiratory viruses. Human coronaviruses are known respiratory pathogens that can be isolated from intestinal tissues and stools.[139,140,146] Enteric coronaviruses have clear pathology in animals (i.e., transmissible gastroenteritis in pigs), and all four of the human coronaviruses (HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43) have been detected in cases of acute gastroenteritis. However, codetection with other common viruses such as rotavirus and norovirus is frequent, and the role of human coronavirus as a primary etiology of diarrhea is likely minor.[146] Up to 10% to 20% of children with seasonal influenza present with diarrhea, although this is uncommon in adults. Diarrhea may be more prominent with Asian avian influenza A (H5N1) infection.[147]

Bocaviruses,[148] pestiviruses,[149] toroviruses,[150,151] and picobirnaviruses[152] are becoming better recognized as pathogens in children and adults, but their roles in causing diarrheal illnesses are uncertain. Similarly, although enteroviruses may cause systemic illnesses, their role as diarrheal pathogens is minimal. Unbiased viral metagenomics approaches have further identified sequences of obscure viruses in diarrheal stools that require further clarification.[153] In addition, a hallmark characteristic of the 2014 Ebola virus disease epidemic caused by *Zaire ebolavirus* (EBOV) in West Africa was nausea and abdominal pain, with voluminous vomiting and diarrhea that led to life-threatening cholera-like gastrointestinal volume losses through unclear mechanisms.[154,155]

Nucleic acid–based assays (e.g., reverse-transcriptase PCR) of stool specimens, either pathogen-specific or as part of multipathogen panels, are the standard method of gastrointestinal virus detection. Rotavirus-specific and norovirus-specific reverse-transcriptase PCR is also available. In the typical outpatient clinical situation, norovirus-specific diagnostic tests are rarely performed because results of this assay do not alter management of the illness.

Cryptosporidiosis

Cryptosporidium is another cause of acute, noninflammatory diarrhea, second only to viruses in some countries.[6,9,156] Sporadic cryptosporidiosis typically occurs through direct exposure to either infected people or animals. Outbreaks occur via contaminated food, drinking water, or recreational water including swimming pools.[d] Of the more than 20 species of this tiny coccidian intracellular protozoal parasite, two, *C. parvum* and *C. hominis,* cause the majority of human disease.[161–165] Cryptosporidiosis is commonly asymptomatic or mild in normal hosts and usually results from waterborne outbreaks, often related to contaminated drinking water or public swimming pools.[161–165] However, infection can be severe in infants and toddlers, accounting for >200,000 deaths per year.[166] Malnourished children and immunocompromised hosts, especially patients with advanced human immunodeficiency virus (HIV) infection, can manifest severe diarrhea.[e] *Cryptosporidium*, either with or without diarrhea, in some children can also contribute to the development of malnutrition.[169]

Cryptosporidium causes a secretory form of diarrhea associated with dysregulated intestinal absorption that may be less responsive to oral rehydration than other diarrhea etiologies. In addition to gastroenteritis, biliary infection with cholangitis has been reported. The pathogenesis of cryptosporidiosis is incompletely understood; the organism primarily alters villus structure and function.[162,170,171] No specific enterotoxin has been identified. Diagnosis depends on identification of oocysts in stool specimens by standard light microscopy, immunofluorescence assays, or nucleic acid–based molecular tests.[165,172–174] In addition to supportive care, nitazoxanide has been shown to be moderately successful in various patients with cryptosporidiosis. Data are inconclusive regarding universally recommended duration of therapy, especially in immunocompromised patients.[175–177,178,179] Alternative therapeutic agents for immunosuppressed patients include combinations of paromomycin and azithromycin. Novel drugs such as bumped-kinase inhibitors and pyrazolopyridine KDU731 appeared highly effective in preclinical studies.[180,181] Despite resurging interest, vaccine development remains in early stages, in part because determinants of host immunity are poorly understood.

Diarrhea Due to Enteropathogenic Bacteria

Several diarrheogenic *E. coli* pathotypes (ETEC, enteroaggregative *E. coli* [EAEC], enteropathogenic *E. coli* [EPEC], enteroinvasive *E. coli* [EIEC], and Shiga toxin–producing *E. coli* [STEC]), *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., and both *V. cholerae* and non-cholera *Vibrio* spp.) can cause noninflammatory diarrhea. *Shigella* spp. and ETEC are the most common bacterial etiologies of acute gastroenteritis worldwide.[35] Either may be associated with low-grade fever.[6,9] The inflammatory manifestations of these bacterial gastroenteritides are discussed in greater detail in Chapter 99. Among typically noninflammatory bacterial etiologies, ETEC and *V. cholerae* account for 6% to 17% of diarrhea-attributable mortality in children younger than 5 years of age.[3]

The greatest risk for ETEC diarrhea is between age 12 and 24 months.[35] Antibody directed against the heat-labile enterotoxin (LT) of *E. coli* in human colostrum may account for lower burden of ETEC in infancy.[17,18,182] Diarrhea produced by LT shares the adenylate cyclase–activating mechanism with cholera toxin.[183,184,185,186,187] Certain strains of *Klebsiella, Citrobacter,* and *Aeromonas* produce an LT-like toxin and may cause a small percentage of diarrheal disease in children.[188]

EAEC, although frequently subclinical, is among the most commonly identified enteropathogens. EAEC infection is nearly universal in children in resource-limited settings. Despite no clear association with diarrhea, EAEC, even in the absence of diarrhea, is associated with growth impairment,[189] particularly when found as a coinfection with LT-ETEC, EPEC, and *Campylobacter* spp.[189,190] Similarly, independent of diarrhea, cumulative and diverse pathogen exposures are associated with growth impairment in the first 2 years of life; these findings highlight the substantial potential cost of early-life gastrointestinal infection in low-resource settings (see Chapter 102).[191,192]

Diarrhea in Adults

In resource-abundant settings, acute gastroenteritis in adults is most often caused by noroviruses.[f] Less common viruses in adults include rotaviruses,[62,195,196] adenoviruses, and coxsackieviruses. *C. difficile* and its potential for recurrence is of increasing concern in patients with recent antibiotic use (see Chapters 99 and 243).[197] Bacterial gastroenteritides such as nontyphoidal *Salmonella* spp. are important causes of foodborne diarrhea outbreaks, often with fever (see Chapter 99). In addition, several agents of food poisoning such as *Clostridium perfringens, Bacillus cereus,* and *Staphylococcus aureus* commonly cause diarrheal syndromes in adults (see Chapter 101).

[d]References 157, 158, 159, 160, 161, and 162.

[e]References 157, 159, 160, 161, 162, 166, 167, and 168.

[f]References 103, 111, 117, 127, 193, and 194.

In adults living in resource-limited settings, several pathogens are known to cause sporadic noninflammatory diarrhea, but none has had as much historical impact or notoriety as *V. cholerae,* causing cholera.[198,199] Cholera has long been endemic in South Asia. With the increased infection-to-case ratio of El Tor cholera, the current seventh pandemic swept most of the continents of the Eastern Hemisphere including Asia, Africa, and the Mediterranean portions of Europe in the 1960s.[200] Rare isolated cases occurred in the United States[201,202] and Europe related to contaminated mineral water[203] and to undercooked shellfish.[204,205] Beginning in Madras, India, in late 1992 and rapidly spreading to Calcutta and Bangladesh in 1993, a new strain of non-O1 *V. cholerae*—O139, called Bengal—caused epidemic cholera gravis.[206–210] Most recently, natural disasters and social conflict have preceded large outbreaks including the introduction of *V. cholerae* into previously cholera-free Haiti following the devastating earthquake in 2010 and more than 750,000 cases in conflict-stricken Yemen beginning in 2016 that is still ongoing.

Severe, watery diarrhea in a patient residing in or having recently traveled to an endemic area should raise suspicion of cholera. The disease can be so fulminant as to cause hypovolemic shock and death from the outpouring of fluid into the upper portion of the small bowel before the first diarrheal stool occurs.[211] As discussed in detail in Chapter 214, the entire dehydrating syndrome of cholera appears to be related to the activation of intestinal adenylate cyclase by the potent cholera enterotoxin.[183,184,212,213] To make the diagnosis bacteriologically, stool specimens should be cultured onto thiosulfate citrate bile salts sucrose agar. Of prime importance in therapy is fluid replacement, accomplished either intravenously with isotonic fluids or orally with glucose-electrolyte solutions.

Patients from whom *V. cholerae* cannot be isolated may have a cholera-like syndrome caused by certain strains of ETEC. In 1956, De and associates[214] demonstrated that *E. coli* isolated from adults and children with this syndrome caused fluid accumulation similar to that seen with *V. cholerae* infection in ligated rabbit ileal loops. In the early 1960s Trabulsi,[215] working in São Paulo, Brazil, reported similar findings with toxigenic *E. coli.* Various investigators then demonstrated that acute undifferentiated diarrhea in adults was caused by ETEC strains that usually were not of the classically recognized pathogenic serotypes.[216,217,218,219] The toxic material present in the culture filtrate of these *E. coli* strains was demonstrated to be heat labile and nondialyzable. Subsequent studies demonstrated two types of enterotoxin produced by ETEC—LT and heat-stable enterotoxin (ST).[220] LT activates adenylate cyclase[185,186,187] and is antigenically and mechanistically similar to cholera toxin in many ways. In contrast, ST activates guanylate cyclase,[221–223] has an earlier onset of action,[220] has greater tissue specificity,[223] and has a much lower molecular weight than LT.[224]

Several studies have shown that ETEC strains producing LT only, ST only, or LT plus ST are associated with episodes of diarrhea in adults.[8] Adults in resource-limited settings who carry LT-producing *E. coli* are often asymptomatic.[225,226] In contrast, ST-producing strains are significantly associated with diarrheal disease. Diarrhea due to ETEC is less common in the United States.[43,99]

Diarrhea in Immunocompromised Patients

Patients With HIV Infection

Patients with HIV infection often develop or present with diarrhea. With increased access to antiretroviral therapy (ART), the incidence of infectious diarrhea among HIV-infected patients decreased markedly.[227–229] However, among HIV-infected patients in the United States meeting criteria for acquired immunodeficiency syndrome (AIDS), 30% to 60% present with diarrhea,[157,228,230–233,234,235] and this figure can reach 95% in parts of Africa or Haiti.[234] In many patients with advanced HIV infection and immunocompromise, diarrhea becomes prolonged, causes severe malnutrition, predisposes to other types of serious infections, and can be life threatening. In addition, symptomatic management of chronic diarrhea in such patients poses major difficulties. The importance of the interactions of HIV with the components of the intestinal immune system in modulating systemic HIV infection has come to light in recent years.[236–238]

TABLE 98.2 Possible Enteric Pathogens in Patients With Acquired Immunodeficiency Syndrome

PATHOGEN	% WITH DIARRHEA (*n* = 181)	% WITH NO DIARRHEA (*n* = 28)
Cytomegalovirus	12–45	15
Cryptosporidium	14–30	0
Microsporidia	7.5–33	0
Entamoeba histolytica	0–15	0
Giardia lamblia	2–15	5
Salmonella spp.	0–15	0
Campylobacter spp.	2–11	8
Shigella spp.	5–10	0
Clostridiodes difficile (formerly *Clostridium difficile*) toxin	6–7	0
Vibrio parahaemolyticus	4	0
Mycobacterium spp.	2–25	0
Cystoisospora belli	2–6	0
Cyclospora	0–11	0
Blastocystis hominis	2–15	16
Candida albicans	6–53	24
Herpes simplex	5–18	40
Chlamydia trachomatis	11	13
Strongyloides	0–6	0
Intestinal spirochetes	11	11
One or more pathogens	55–86	39

Data from references 242–246, 248–252, and 255–266.

Although some investigators have reported an enteropathy without identifiable infectious pathogens[239,240] or with primary HIV infection of enterochromaffin cells in the bowel mucosal crypts and lamina propria,[241] others have reported one or more enteric pathogens in 55% to 85% of patients with AIDS and diarrhea.[235,242,243] As shown in Table 98.2, the leading agents found in these patients are *Cryptosporidium,* cytomegalovirus (CMV), microsporidia, *Entamoeba histolytica, Giardia lamblia, Salmonella, Campylobacter, Shigella, C. difficile, Vibrio parahaemolyticus,* and *Mycobacterium* spp.[242–246,247] *Cyclospora* and *Cystoisospora belli* also cause persistent diarrhea in patients with AIDS.[235,248–250] *Pneumocystis jirovecii* infection can occasionally involve the intestinal tract.[251] Men with HIV who have sex with men are at increased risk of *G. lamblia, E. histolytica, Campylobacter jejuni, Shigella, Chlamydia trachomatis, C. difficile*, (with proctitis) *Neisseria gonorrhoeae,* herpes simplex virus, or *Treponema pallidum.*[252]

Although eradicative treatment may be difficult, most patients respond to specific antimicrobial or antiparasitic therapy and ART, emphasizing the need to identify an etiologic agent whenever possible.[179,253] The antiviral agent ganciclovir often controls intestinal CMV,[254,255] and most bacterial and parasitic infections can be treated with the expectation of some improvement. *Cryptosporidium,* which infects 3% to 21% of patients with AIDS in the United States, can be found in 50% of patients with AIDS and diarrhea in Africa and Haiti.[157,158,159,160,234] *Cryptosporidium*-mediated biliary infection occurs in this patient population as well. Similarly, certain microsporidia organisms, such as *Encephalitozoon intestinalis* or *Enterocytozoon bieneusi,* can cause persistent and severe diarrhea in HIV-infected individuals. *Cryptosporidium* and microsporidial infections are associated with villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes, and D-xylose malabsorption.[244]

The same acid-fast stain that detects *Cryptosporidium* or *Mycobacterium* in fecal specimens may also reveal *C. belli* and *Cyclospora* in approximately 2% of patients with AIDS with diarrhea in the United States and in 15% of patients in Africa.[234,235,249,250,256] Nontyphoidal *Salmonella* infections occur with an estimated 20-fold increase in

frequency and with increased severity in patients with AIDS.[257–260] Enteric viruses also are associated with diarrhea in HIV-infected individuals. In one study, astrovirus, picobirnavirus, calicivirus, and adenovirus were found in 6% to 12% of HIV-positive patients with diarrhea.[261] In addition, ART regimens can cause diarrhea, often complicating the workup of an HIV-infected patient with persistent diarrhea.[229,262,263]

Several practical algorithmic approaches to the diagnosis and management of diarrhea in HIV-infected patients have been published.[231,232,235] These strategies favor the use of early, noninvasive stool studies and practical empirical treatment trials, followed by more invasive tests (e.g., endoscopy with biopsy) for patients with refractory or more severe presentations. ART has decreased the incidence of several important opportunistic infections including certain causes of gastroenteritis. Of particular note, there has been a dramatic decline in the incidence of tissue-invasive infections caused by CMV gastrointestinal disease.[255,264,265] An effort to judiciously adhere to safe food and water guidelines in higher-risk patients can significantly help in preventing many of these serious enteric infections.[266]

Patients With Solid-Organ Transplants and Others Receiving Immunosuppressants

Chemotherapy for malignancy, autoimmune disease, and especially antirejection medications following solid-organ transplantation (SOT) or hematopoietic cell transplantation (HCT) increase risk of serious enteric infections.[267,268] Frequent encounters with the health care system, prolonged hospitalizations, and antimicrobials contribute to high rates of *C. difficile* infection (CDI) in these populations. Transplantation of any organ is associated with increased risk of CDI. CDI occurs in 9% to 13% of patients following HCT and up to 20% following SOT.[268] Hospital-onset CDI after SOT can prolong hospitalization and is associated with allograft dysfunction.[269]

In addition to CDI, several other bacteria, viruses, and parasites can cause diarrhea after SOT or HCT. Viral infections are common in this population and can result in long-term shedding, particularly in cases of norovirus.[107] There is less seasonal variation in norovirus infections in immunocompromised hosts, and these infections manifest with more prolonged symptoms and viral shedding than infections in immunocompetent hosts. Up to one-third of these patients have diarrhea persisting for 2 weeks or longer, and shedding has been reported beyond a year.[270] Symptoms may occur at lower levels of viral genome copies per gram of stool. Prolonged viral shedding in these patients is associated with an increased diversity of genomic variants in an infected individual.[271] The pathogenicity of these divergent variants is unclear, and therefore the clinical significance of continued norovirus detection over prolonged periods of time in patients with mild symptoms is uncertain. Flattening of the villus border and loss of villin colocalizes with viral particles on duodenal biopsy specimens, but other histologic changes described in chronic norovirus infections in immunocompromised patients (edema, cellular debris, and metaplasia) are nonspecific and overlap with noninfectious etiologies of enteritis in these patients.[272] No specific therapy is available. Combinations of oral immunoglobulins, nitazoxanide,[273] and decreasing immunosuppressive therapy[274] may benefit some patients, but results are inconsistent.

CMV enteritis should be considered in the differential diagnosis of diarrhea following transplantation, especially in donor-recipient mismatch cases. CMV enteritis often occurs in the absence of peripheral viremia, and direct intestinal sampling is recommended to rule out this condition. Diarrhea may also be a presenting symptom of disseminated adenovirus in transplant recipients. Reduction of immunosuppression is part of management for any infectious diarrhea in this population. Ganciclovir is effective treatment for most cases of CMV enteritis; however, options for adenovirus are more limited. Brincidofovir, a prodrug of cidofovir, is conjugated to a lipid to enhance intracellular delivery with lower plasma concentrations and less renal toxicity than cidofovir. This drug has been prescribed on a compassionate use basis for disseminated adenovirus infection in this population, but efficacy data are lacking, and diarrhea itself may be a significant side effect of brincidofovir.

Cryptosporidiosis can also be severe in these patients and may mimic graft-versus-host disease on endoscopy and intestinal biopsy. The clinical presentation of these infectious etiologies overlaps with medication side effects, especially mycophenolate and chemotherapy, which cause direct epithelial cell injury.[269]

TRAVEL-ASSOCIATED DIARRHEA (TURISTA)

Whether it "arouses one from bed with a start at 4 a.m. for a record-breaking race to the bathroom to begin a staccato ballet"[275] or produces the poetry of the psalmist ("I am poured out like water … my heart like wax is melted in the midst of my bowels"[276]), traveler's diarrhea has a major impact each year on the 300 million to 500 million international travelers and probably on the distribution of well over $100 billion in international tourism receipts.[277,278]

Diarrhea is the most common and among the most disconcerting illnesses that threaten the traveler.[279,280–285] North American and northern European travelers appear to be at greatest risk when they travel to Latin America, southern Europe, Africa, or Asia.[286–290] Most symptoms of traveler's diarrhea begin 5 to 15 days after arrival, although a range from 3 to 31 days has been noted.[256,279,291–296] The illness is typically manifested by malaise, anorexia, and abdominal cramps followed by the sudden onset of watery diarrhea. Nausea and vomiting occur in 10% to 25% of cases. The diarrhea is usually noninflammatory, although a low-grade fever is present approximately one-third of the time. The duration is usually 1 to 5 days, but up to 50% of patients have illness that continues 5 to 10 days and sometimes beyond.

The attack rate for traveler's diarrhea varies from 5% to 50%, depending on the destination and duration of the trip. Destinations with increased risk for acquiring traveler's diarrhea include portions of Africa and Asia (including India), and certain areas of Central and South America.[279,296,297] The attack rate also appears to decrease with age after 25 years, an observation that may reflect different habits and exposures rather than inherent susceptibility.[275,289] Expatriate residents living in certain countries appear to be at some level of persistent risk for diarrhea of infectious causes; for instance, an attack rate of 49% per month is observed during the first 2 years of residence in Nepal.[298]

For many years, the etiology of turista was an enigma; only infrequently had parasites or bacteria, such as amebas, *Giardia, Salmonella,* or *Shigella,* been identified, and viral studies had failed to elucidate significant causes. The first suggestion that an infectious process was likely came from the effective reduction in the attack rate achieved by the use of prophylactic antimicrobial agents.[291,296,299,300] Studies by Kean[275] suggested that certain EPEC serotypes may be involved in up to one-third of the cases. The involvement of *E. coli* was further confirmed in an outbreak of traveler's diarrhea among British troops in Aden, where *E. coli* O148 was identified in 54% of the British troops with diarrhea.[292]

Later studies demonstrated ETEC in approximately 50% (range, 5%–75%) of cases of traveler's diarrhea in Latin America, Africa, and Asia (Table 98.3).[301–303] The attack rate ranged from 20% to 100% (median, 52%–54%) (see Table 98.3).[279,297,300,304] ETEC was almost never present before travel, and such organisms were acquired by only 12.6% of fellow travelers who did not become ill.[256,294,295] ETEC producing LT, ST, or both can cause traveler's diarrhea (Table 98.4). In some areas, EAEC is a major cause (see Chapter 218).[279,303]

A number of other microbial agents have also been identified in small subsets of patients with traveler's diarrhea. *Salmonella, Shigella, Campylobacter, Vibrio,* and *Aeromonas* spp. are increasingly recognized in travelers with diarrhea.[304,306–308] Pathogen-specific prevalence appears to vary by destination. *Campylobacter* was present in 25% to 35% of cases during travel to South Asia and 15% to 25% of cases related to travel in Southeast Asia, but accounted for less than 5% of cases from Africa or Latin America.[279] In US military personnel deployed to Southeast Asia, *Campylobacter* spp. were detected in 35% and nontyphoidal *Salmonella* in 23% of cases of diarrhea.[306] In Thailand, *Campylobacter* was the most common etiology (28%) of pathogen-attributable diarrhea cases.[308] *Shigella* accounted for 5% to 15% of cases from Latin America, Africa, and South Asia and was less frequent in travelers to Southeast Asia.[279] *Salmonella* infections were more common during travel to Africa and Southeast Asia than to South Asia or Latin America.[279] *V. cholerae* is rarely a problem for most US travelers, but infection can occur among military personnel or relief workers in endemic cholera locales.[289,308,309] Single-dose live lyophilized CVD 103-HgR (Vaxchora)

oral cholera vaccine is approved for travel to areas with active cholera transmission.

Rotavirus or calicivirus infections have been described in 0% to 36% of cases but were often found in association with either bacterial or parasitic pathogens.[310] Noroviruses in particular have been implicated in several large outbreaks of gastroenteritis or diarrhea on large cruise ships.[311–313] In many respects, however, cruise ship–associated outbreaks of gastroenteritis share more epidemiologic characteristics with institution-associated gastroenteritis than with classic traveler's diarrhea.

Intestinal protozoa also may be important causes of traveler's diarrhea. Agents such as *C. parvum, Cyclospora cayetanensis, G. lamblia,* and various microsporidia should be considered in the workup of subacute or chronic noninflammatory diarrhea in returned international travelers.[314–316] In the GeoSentinel Surveillance Network global database of 2902 unwell travelers seeking medical care, parasitic etiologies (predominantly *G. lamblia* [27%], *E. histolytica* [14%]) accounted for 65% of chronic diarrhea cases, whereas bacteria (*Campylobacter* [13%], *Shigella* [6%]) were identified in 31% and viruses (hepatitis A and hepatitis E) were identified in only 3%. *G. lamblia* was the most commonly identified pathogen regardless of travel destination[317] Other protozoal parasites such as *Blastocystis hominis* can be commonly identified in the stools of persons traveling to developing countries. However, it has been difficult to ascertain whether these organisms actually cause disease or are merely commensal.[318–320] A subset of patients have persistent diarrhea for which no infectious agent can be implicated. Chronic idiopathic diarrhea (see "Brainerd Diarrhea") has been reported to occur in a few small travel-related outbreaks[321–324] and may cause prolonged diarrhea in sporadic cases.

In contrast to the frequent identification of potential etiologic agents among travelers to tropical areas who develop diarrhea, travelers to temperate areas often develop a mild syndrome of diarrhea for which no infectious cause can be identified.[325] Environmentally distributed *Cryptosporidium* and *Giardia* and oocysts are hardy in temperate regions, have zoonotic reservoirs in these regions, and are relatively tolerant to chlorination. Travelers to certain areas such as Russia and national parks in the United States who drink unfiltered or unboiled water may therefore be susceptible to development of the more insidious watery diarrhea seen with giardiasis or cryptosporidiosis.[326–329] Strongyloidiasis acquired during travel may cause noninflammatory diarrhea, abdominal pain, and eosinophilia.[330]

Several other potentially serious infections manifested initially by diarrhea or abdominal pain may be acquired by travelers. Malaria may begin as gastroenteritis with nausea, vomiting, diarrhea, or abdominal pain in 30% to 50% of cases.[331] The physician should also remember to consider typhoid fever and other infections that may be manifested with a typhoidal pattern including plague, melioidosis, typhus, and arboviral hemorrhagic fevers.[331,332]

The desire to control the bothersome problem of diarrhea in travelers has led to a variety of medications used for management.[275] Commonly used remedies, such as diphenoxylate-atropine (Lomotil) and kaolin-pectin suspension, were found to have little or no efficacy in most studies.[333] Lomotil and other antimotility agents may actually worsen the illness in inflammatory processes such as shigellosis.[334] Bismuth subsalicylate (Pepto-Bismol) was shown to inhibit enterotoxin activity in experimental animal models,[335] and it has been recommended for symptomatic therapy as well as prophylaxis.[334,336,337] As in any type of diarrheal illness, the mainstay of therapy is adequate hydration with an oral glucose-electrolyte or sucrose-electrolyte solution.

Prevention of traveler's diarrhea should be directed toward reducing the consumption of infectious agents in food and water. Foods that are handled but not cooked (e.g., salads, raw vegetables) are high-risk foods.[279,280,281] Bottled, noncarbonated water cannot be considered safe because outbreaks of cholera[203] have been traced to bottled water, and typhoid fever[339,340] has been traced to other bottled beverages. Care in eating and drinking may reduce one's risk, even in highly endemic areas, to less than 15%.[338,341,342]

The efficacy of prophylactic antimicrobial agents has been documented in several studies.[291,296,343–345] The increased risk of acquiring a more severe infection (e.g., salmonellosis), the risk of drug side effects (e.g., photosensitivity in the tropics), and the emergence of drug-resistant organisms[347] should preclude the widespread use of antibiotic prophylaxis at this time.[348] Because treatment regimens that combine loperamide with an antibiotic are rapidly effective in controlling traveler's diarrhea (<10 hours), most experts consider prophylactic therapy only for travelers with special issues such as individuals with a high risk of infection and individuals for whom it is important to remain disease-free during the trip.[349,350]

Empirical self-treatment of traveler's diarrhea with a fluoroquinolone such as ciprofloxacin or levofloxacin for 1 to 3 days or a single dose of

TABLE 98.3 Etiology of Acute Traveler's Diarrhea in Three Locales

CHARACTERISTIC	LATIN AMERICA	AFRICA	ASIA
Duration of stay (days)	21 (2–42)	28 (28–35)	(28–42)
Attack rate (%)	52 (21–100)	54 (36–62)	(39–57)
Organism (%)			
No bacterial pathogen	28	—	35
Bacterial pathogen	72	—	80
Enterotoxigenic *Escherichia coli*	46 (28–72)	36 (31–75)	15 (5–25)
Enteroaggregative *Escherichia coli*	30 (25–35)	<5	17 (15–25)
Shigella	5 (0–30)	5 (0–15)	5 (4–15)
Salmonella	<5	10 (5–15)	10 (5–15)
Campylobacter jejuni	<5	<5	15 (2–35)
Vibrio parahaemolyticus	—	—	7 (1–13)
Rotavirus	23 (0–36)	10 (5–15)	5 (0–15)
Norovirus	10	—	3
Protozoa (*Giardia, Cryptosporidium, Entamoeba histolytica,* others)[b]	7	<5	11

[a]Values shown are median (range) from multiple studies.[278,279,300,303,305,352,444]
[b]Parasitic etiology may increase to 65% among returned travelers seeking medical care.[317]

TABLE 98.4 Frequency of Enterotoxigenic *Escherichia coli* in Association With Traveler's Diarrhea in Latin America, Africa, and Asia

FEATURE	REPORTED FREQUENCY (%) Gastroenterologists in Mexico[293]	Peace Corps Volunteers in Kenya[294]	Yale Glee Club in Latin America[295]	Japanese Travelers Returning to Tokyo From India, Southeast Asia, Orient[304]	Total
Illness attack rate	49% in 16 days	69% in 5 wk	74% in 1 mo	—	
Type of enterotoxin					
LT only	16	33	25	4.8	21
LT and ST	16	15	12.5	11.8	38
ST only	9.8	2	19	13.6	41
% of ill patients with ETEC	41 (21/51 cases)	52 (14/27 cases)	56 (9/16 cases)	32 (270/843 cases)	33.5

ETEC, Enterotoxigenic *Escherichia coli; LT,* heat-labile; *ST,* heat-stable.

1000 mg of azithromycin, can significantly reduce the duration and severity of the disease (see Chapters 318 and 319).[279,280,281,304,351–353] Therapy with trimethoprim-sulfamethoxazole had traditionally been suggested for children, but because of resistance, most experts currently recommend the use of a macrolide such as azithromycin.[279,280,281,354] Fluoroquinolone resistance has emerged among all bacterial etiologies. *Campylobacter* spp. resistant to quinolones is of special concern for travelers to many areas of the world, most notably Thailand and other parts of Southeast Asia.[355–358] Nearly 90% of *Campylobacter* diarrhea cases in US military personnel deployed to Southeast Asia were resistant to ciprofloxacin.[306] Resistance to quinolones has also increased among ETEC and EAEC strains, especially strains from India and sub-Saharan Africa. Extended-spectrum β-lactamase ETEC and EAEC strains expressing $bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-27}}$ genes are emerging.[307] Fluoroquinolone drugs are contraindicated in pregnant women[279,280,281,350,352] and in children younger than 16 years. Also, US Food and Drug Administration black box warnings exist for arthropathy, neuropathy, tendinopathy, and central nervous system side effects associated with fluoroquinolones.[359] The adverse reactions associated with quinolones combined with increasing resistance have made azithromycin the preferred first choice for empirical self-treatment of traveler's diarrhea in many individuals. Resistance to azithromycin among ETEC and EAEC, however, is greater than 25% in parts of Southeast Asia, India, and Africa. Rifaximin, a nonabsorbable relative of rifampin, is useful for treatment of less severe cases of traveler's diarrhea in the absence of fever. Levofloxacin, azithromycin, and rifaximin in combination with loperamide have similar efficacies of 91% and 96% cure at 48 and 72 hours, respectively.[360] Because of ongoing changing resistance patterns among bacterial etiologies of traveler's diarrhea, pretravel counseling, empirical acute treatment, and posttravel diagnostic and treatment recommendations should consider up-to-date reported susceptibility patterns that are specific to geographic destinations, such as can be found at the Centers for Disease Control and Prevention website (cdc.gov/travel). The benefits of treatment also need to be weighed against risk of acquisition of colonization with extended-spectrum β-lactamase–producing Enterobacteriaceae during travel and increased susceptibility to pathogens after the antibiotic course is over but before the microbiome has recovered; antibiotics are not recommended for cases of mild traveler's diarrhea for these reasons.

DIARRHEA IN INSTITUTIONS

Institutions provide unique settings that promote the acquisition of certain enteric pathogens. As with diarrhea in patients with AIDS and traveler's diarrhea, many cases of institution-acquired diarrhea are noninflammatory. Given the rise *C. difficile*–associated disease (CDAD), new-onset diarrhea in patients in the hospital or long-term care facilities should prompt stool immunoassay or PCR assaying for the presence of *C. difficile* toxins.

Epidemic Nosocomial Diarrhea in Newborns

Epidemic nosocomial neonatal diarrhea has long been recognized as a potentially serious problem with mortality rates of 24% to 50%.[362,363] The unusual susceptibility of newborns to this syndrome may be explained by their underdeveloped intestinal microbiota or lack of specific immunity. Prematurity or congenital cardiac or pulmonary disease complicates this situation. The consequences of diarrhea in newborns are unusually severe, partially because they have poorly developed homeostatic mechanisms with limited water and electrolyte reserves. Crowded conditions in newborn nurseries promote nosocomial transmission.[364] In addition, delays in recognizing a nursery outbreak may occur because infants may not develop diarrhea until after they have been discharged from the hospital.

The onset of illness is often insidious, with the development of listlessness, irritability, and poor feeding over a period of 3 to 6 days.[363,365,366] Vomiting and fever are infrequent, and the stools tend to be watery; yellow-green in color; and usually without mucus, pus, or blood.[367,368] Early signs such as failure to gain weight or a slight weight loss and abdominal distention may be subtle. The disease may progress to more severe signs of dehydration and shock with depressed sensorium, drowsiness, coma, sunken eyes, circumoral cyanosis, and grayish discoloration of the skin. Shock without hyperpnea often occurs in this setting despite the development of severe acidosis. Poorly nourished infants may develop severe hypokalemia, hyponatremic dehydration, or paradoxical edema. Appropriate antibiotic therapy must be tailored to the specific sensitivity pattern of the organism isolated.[367]

The typical illness usually lasts 5 to 15 days, but persistence or relapse may occur over the course of several weeks after the initial onset of symptoms. Complications may include otitis media, pneumonia, bacteremia, peritonitis, and renal vein or cerebral sinus thrombosis. Several potentially life-threatening processes may mimic this infantile diarrhea syndrome. So-called parenteral diarrhea refers to the well-recognized but poorly understood tendency for systemic infections or localized infections elsewhere (e.g., otitis, meningitis) to be manifested clinically with diarrhea. Likewise, a strangulated hernia, intussusception, or torsion of an ovary or testis may be manifested by abdominal pain or diarrhea.

Epidemic diarrhea among hospitalized newborns has been commonly associated with certain enteropathogenic serotypes of *Escherichia coli* (EPEC). In many areas such as South Africa and southern Brazil, EPEC organisms are also among the most common causes of sporadic diarrhea in infants and young children, especially during the summer months.[369–371] Up to 20% of cases of endemic childhood diarrheal illness, even in temperate, more developed areas of the world such as England and Canada, are also known to be caused by EPEC organisms.[369,370]

The association of a certain strain of *E. coli* with infantile diarrhea was first demonstrated by slide agglutination by Bray and Beavan[372] in 1945 and reported in further detail in 1948. Excluding certain invasive serotypes (see Table 99.2 in Chapter 99), there are now at least 14 classically recognized EPEC *E. coli* serotypes including O111-K58 (α), O55-K59 (β), O127-K63, O128-K67, O26-B6, O86-K61, O119-K69, O125-K70, O126-K71, O20-B7, and O44-K74. Additional serotypes recognized as causes of epidemic infantile diarrhea include O114,[362,373,374] O142,[364,375] and O158.[376] The mechanism by which most EPEC organisms cause disease involves a complex set of attachment and effacement traits, as detailed in Chapter 96. Although most are not invasive and do not produce conventionally recognized LT or ST enterotoxins, these organisms are capable of causing diarrheal disease in human volunteers, from whom the organism can be reisolated and in whom an antibody response can be documented.[365,377]

In addition to EPEC organisms, certain enterohemorrhagic (EHEC) and enterotoxigenic (ETEC) strains of *E. coli* have caused outbreaks of diarrhea in infants. *E. coli* O157-H7 and other EHEC strains have been associated with a syndrome of hemorrhagic diarrhea with only minimal inflammation and mild severity. Most EHEC organisms secrete a Shiga-like toxin, and certain strains of EHEC have also been associated with outbreaks and sporadic cases of hemorrhagic diarrhea that are more severe and can include a form of hemolytic-uremic syndrome.[378–380,381–383]

Diarrheogenic *E. coli* serotypes are not the only bacterial causes of epidemic infantile diarrhea. For example, an outbreak of diarrheal illness was described in which multiple serotypes of different organisms (*E. coli, Klebsiella,* and *Citrobacter*) were found to be transiently enterotoxigenic.[384] This observation suggests the transmission of enterotoxigenic potential between susceptible strains, likely by certain plasmids[385] or by bacteriophages.[386] Another report of sporadic diarrhea in infants and children in Africa showed that several enteric organisms other than *E. coli* may produce an enterotoxin under certain conditions.[32] This finding is relevant to other situations as well, as typified by an outbreak of watery diarrhea occurring on a cruise ship and found to be caused by enterotoxigenic strains of *E. coli* as well as *Klebsiella* spp. and *Citrobacter* spp.[387] Many other well-known bacterial causes of diarrhea such as shigellosis[388] and epidemic salmonellosis may also spread readily in the newborn nursery.[389,390] Viral causes of epidemic infantile diarrhea include, but are not limited to, specific types of echoviruses,[391] coxsackieviruses,[392] adenoviruses,[393] and rotaviruses.[36,37,394–397]

Hospitals

Nosocomial diarrhea is among the most common nosocomial outbreaks reported to the Centers for Disease Control and Prevention.[398,399] Nosocomial diarrhea appears to be a significant factor predisposing to other nosocomial infections such as urinary tract infections.[400] Overall

rates range from 2.3 to 4.1 illnesses per 100 admissions on pediatric wards[399,401] and from 7.7 per 100 admissions to 41% of adults hospitalized in intensive care units.[399,402,403]

C. difficile remains the most common, most serious, and most costly infectious cause of nosocomial diarrhea in hospitalized patients[404–406] and ranks among the most commonly reported hospital-acquired pathogens.[407] In particular, CDAD is an important emerging nosocomial infection worldwide, especially among elderly hospitalized patients and patients occupying beds in surgical wards or intensive care units.[406,408–410] Most sporadic and outbreak cases of CDAD appear to be caused by exposure to contaminated environmental surfaces rather than direct contact with an index case.[411–413]

Other enteric pathogens are occasionally identified in outbreaks of nosocomial diarrhea. *Klebsiella oxytoca* can produce a toxin that inhibits DNA synthesis and, similar *C. difficile,* causes diarrhea and sometimes hemorrhagic colitis associated with recent antibiotic use. Enterotoxin-producing methicillin-resistant *S. aureus* has been implicated as a rare cause of antibiotic-associated diarrhea.[403] Salmonella is a common cause in reported outbreaks of nosocomial gastroenteritis and may rarely cause pseudomembranous colitis after antibiotic exposure. *Cryptosporidium* may be associated with cases of nosocomial diarrhea involving chronically ill, pediatric, and elderly patients as well as HIV-infected patients and other immunocompromised patients.[414] In young children and in immunocompromised hosts, viral agents (rotaviruses, adenoviruses, coxsackieviruses, and others) are often found.[268,401] In addition, there has been a newfound appreciation for the roles of certain viruses (e.g., norovirus, rotaviruses, adenoviruses, coxsackieviruses, and others) as causes of nosocomial diarrhea, especially in neonates, children, and patients in intensive care units.[335,403,415,416]

Long-Term Care Facilities

Diarrheal illnesses constitute a significant problem in extended-care facilities for elderly patients. A conservative estimate based on passively reported illness rates is that one-third of patients in long-term care facilities experience diarrhea each year.[417–419] CDAD remains a common and important cause of diarrhea in these facilities.[361,420,421] Sporadic cases and epidemic outbreaks of CDAD have been reported in many types of long-term care facilities. In other instances, viral causes of gastroenteritis or diarrhea have been identified in certain outbreaks occurring in these settings. The frequency of potentially transmissible enteric pathogens emphasizes the importance of careful hand washing in situations in which hygiene is often difficult.

Daycare Centers

Another special institutional setting in which hygiene is difficult and enteric infections are increasingly appreciated is daycare centers. Numerous outbreaks have been reported in association with viruses, bacteria, or parasites. The most common etiologic agents in infants and children younger than 2 years are rotaviruses, whereas older toddlers have been more likely to acquire *G. lamblia.*[422] Newer diagnostic tests based on immunoassays and reverse-transcriptase PCR have been used to detect additional agents such as astrovirus in many diarrhea outbreaks in daycare centers.[423,424] A clinical syndrome of prolonged noninflammatory diarrhea may be associated with *Cryptosporidium* in daycare centers.[425–427] Outbreaks of inflammatory diarrhea caused by *Shigella, Campylobacter,* and *C. difficile* have also been reported.[301,302]

TREATMENT OF ACUTE NONINFLAMMATORY DIARRHEA

Treatment of diarrhea from any cause in adults and children consists primarily of rehydration.[253] If glucose or sucrose accompanies oral isotonic fluid, the coupled absorption of sodium and water is often sufficient to replace fluid loss.[428] Bismuth subsalicylate may reduce enterotoxin action,[429] and if there is no significant febrile or inflammatory process, low doses of antimotility agents may offer some relief with minimal risk in adults. Some studies also suggest that novel analogues of glutamine may be beneficial in reducing the severity and extent of symptoms associated with certain forms of infectious diarrhea.[430] The potential utility of probiotic compounds for the treatment of various forms of diarrhea has also garnered attention. The current data are not sufficient to issue a general recommendation on the use of probiotics for the management of infectious diarrhea (see Chapter 3).[431–436]

There is interest in the roles of various micronutrients in the management of diarrheal disease, especially in young children residing in underdeveloped areas.[436,437] Several agents have been examined, but the strongest support has emerged relating to zinc supplementation. Several randomized, controlled international studies as well as a Cochrane Database Review found a beneficial effect of oral zinc supplementation in the prevention and management of a variety of infectious forms of diarrhea, especially in children.[438,439,440,441]

Chronic Noninflammatory Diarrhea

Syndromes of chronic noninflammatory diarrhea of infectious etiology include giardiasis, tropical sprue–like syndromes, syndromes of bacterial overgrowth, and *Cryptosporidium* or *C. belli* infection (especially in immunocompromised hosts).[234,241,442,443] In a patient with weight loss, malaise, and watery or fatty stools, giardiasis or some other cause of a malabsorption syndrome should be suspected. This syndrome may also be associated with hypocalcemia; with iron or folate deficiency anemia; or with deficiency of vitamin D, vitamin K, or protein.

Giardiasis is endemic throughout most the world but still may often go undiagnosed for weeks of illness.[161,163,444,445–447] Transmission is through water or food during outbreaks and by direct person-to-person contact. Clinical syndromes range in severity from asymptomatic infection to severe, persistent diarrhea associated with anorexia, weight loss, and malnutrition.[161] Current immunoassays and molecular tests have markedly improved diagnostic sensitivity.[161,163] Recommended therapy classically included metronidazole, with a reported 70% cure rate.[445] More recently, tinidazole and nitazoxanide have shown improved efficacy for treatment and are associated with far fewer side effects than standard courses of metronidazole (see Chapters 28 and 42).[448]

Other infectious agents of chronic noninflammatory diarrhea include *Cryptosporidium, C. belli,* and *Cyclospora.* Each of these agents can be identified by standard stool analyses using ova and parasite testing combined with specific immunoassay as needed. Of note, *Cyclospora* was identified as the etiologic agent causing a large, multistate outbreak of gastroenteritis in 2013 in the United States.[449] *Cyclospora* infection is treated with trimethoprim-sulfamethoxazole.[250,444]

Bacterial Overgrowth Syndromes

Many syndromes have been described in which impaired absorption was attributed to abnormal bacterial colonization in the upper small intestine.[443] Whether these organisms are pathogens or part of the normal intestinal microbiota abnormally distributed is unclear at the present time.

Normally the upper portion of the small bowel is relatively sparsely populated, with less than 10^5 organisms/mL; these are predominantly facultative gram-positive organisms (diphtheroids, streptococci, and lactobacilli).[450] The organisms most often incriminated in bacterial overgrowth syndromes in the small bowel are aerobic enteric coliforms (members of the family Enterobacteriaceae), anaerobic gram-negative fecal flora (*Bacteroides* and other genera), and miscellaneous other organisms such as *Plesiomonas shigelloides*.[451]

Bacterial colonization in the upper part of the small bowel may be associated with malabsorption or chronic diarrhea in the absence of significant histopathologic changes. Small bowel overgrowth is usually associated with a predisposing bowel abnormality, such as achlorhydria (from gastritis, pernicious anemia, or gastric surgery), blind-loop syndromes, cholangitis, impaired motility (scleroderma, diabetic neuropathy, vagotomy), surgery, strictures, diverticula, or radiation damage.[452,453] Protein, folate, or vitamin B_{12} deficiency may also render the bowel more susceptible to microbial colonization and injury.[450,454] An episode of acute infectious diarrhea may be the initiating event in the establishment of small bowel colonization and chronic diarrhea.[450,455,456] Lindenbaum and colleagues[457] described spruelike morphologic changes in the upper portion of the small bowel in association with increased numbers of bacteria and malabsorption among Peace Corps volunteers living in Pakistan.

Small intestinal bacterial overgrowth may causes malabsorption through bacterial binding (e.g., vitamin B_{12}) or utilization (e.g.,

carbohydrates) of nutrients, deconjugation of bile salts by bacteria such as enterococci and anaerobes,[458] or the toxic effects of bacterial products such as fatty acids or amines.[450] *E. coli* strains that lack other recognized virulence traits but colonize the bowel were shown to cause prolonged diarrhea in a rabbit model,[459] with an associated impairment in water and electrolyte absorption and disaccharidase activity.[460]

The approach to a patient with suspected bacterial overgrowth as a cause of malabsorption or chronic diarrhea should include quantitative aerobic and anaerobic cultures of the upper small bowel contents, obtained by intubation or string passage. Because the critical number of organisms appears to be approximately 10^5/mL, semiquantitative estimates from a Gram stain (analogous to the urine Gram stain) may also prove valuable. In addition, the ^{14}C-glycocholic acid breath test for bacterial deconjugation of bile salts has been shown to be helpful for diagnosis in some patients.[461]

Patients with symptomatic bacterial overgrowth are potential candidates for antibiotic therapy, especially if a predisposing condition such as achlorhydria, scleroderma, or diabetes is present. Depending on the results of quantitative cultures of upper small bowel aspirates, therapy may need to be directed against anaerobes as well as aerobic coliform organisms.[450,455]

Brainerd Diarrhea

Brainerd diarrhea is a clinical syndrome of chronic, self-limited, idiopathic diarrhea lasting for >4 weeks and up to several months.[462] Symptoms often occur with an acute onset, but an infectious etiology is not found, and other noninfectious causes are also absent. Stool frequency ranges from 5 to 25 bowel movements per day and fecal electrolyte and osmolality testing are consistent with secretory diarrhea.[462] Cases can be sporadic without evidence of household clustering; however, outbreaks including the first description of the entity in Brainerd, Minnesota, in 1983 also occur.[324] Travel and consumption of untreated water or unpasteurized milk have been associated with this entity, but infectious, chemical, or other toxins have not been identified as etiologies.[322,463] Although symptoms often are prolonged, recovery is nearly universal. Relapse or progression to chronic sequelae suggests an alternative diagnosis such as lymphocytic colitis, collagenous colitis, malignancy, or drug reactions.

Other Noninfectious Mimics of Gastroenteritis

Acute noninflammatory diarrhea may be a consequence of several noninfectious processes. Exposures to antibiotics and other medications are common causes of noninfectious diarrhea, and although diarrhea is typically mild, it can result in additional costs related to diarrhea workups and medication nonadherence, and in some cases necessitate a change in therapy. As with agents that effect an osmotic diuresis, nonabsorbable agents such as sorbitol may cause diarrhea if consumed in excess. Heavy metal poisoning (i.e., arsenic, tin, iron, cadmium, mercury, or lead) is often associated with diarrhea, probably as a result of toxic effects on the mucosal epithelium.

Endocrine causes of diarrhea that may share the adenylate cyclase–activating mechanism with enterotoxins include non–beta-islet cell tumors, medullary carcinoma of the thyroid, carcinoid tumors, and others that are associated with increased serum levels of prostaglandins or vasoactive intestinal polypeptide.[464] Patients with thyrotoxicosis or adrenal or parathyroid insufficiency may have diarrhea. Congenital and acquired enzyme deficiencies include lactase deficiency and pancreatic or biliary insufficiency, in which inadequately degraded or absorbed nutrients may promote an osmotic diarrhea. In a child who has diarrhea and edema, hypertension, or petechiae, hemolytic-uremic syndrome with or without enterohemorrhagic *E. coli* O157-H7 should be suspected. Patients with dermatitis herpetiformis may also have diarrhea that may respond to sulfone or sulfapyridine therapy or to a gluten-free diet.

Noninfectious causes should also be considered in the differential diagnosis of chronic noninflammatory diarrhea. Examples include congenital deficiency syndromes and food allergies, certain neoplastic and endocrine processes, and less well-understood functional disorders. Causative disorders to be considered in the first two categories are milk allergies, disaccharidase deficiencies, gluten enteropathy, acrodermatitis enteropathica, β-lipoprotein deficiency, familial hyperchloremic alkalosis (congenital chloridorrhea), Leiner disease, and Wiskott-Aldrich syndrome. Neoplastic and endocrine causes of diarrhea include carcinoid tumors, Werner syndrome (multiple endocrine adenomatosis), Zollinger-Ellison syndrome (gastrinoma), pancreatic cholera syndromes, medullary carcinoma of the thyroid, and thyrotoxicosis. Patients with partial mechanical bowel obstruction or pellagra may also have chronic diarrhea. Milder forms of inflammatory bowel disease and irritable bowel disease including postinfectious subtypes can also be associated with a variety of types of chronic diarrhea. Although a thorough search for an infectious cause of any form of chronic diarrhea is usually warranted, most often the specific diagnosis of one of these etiologies requires referral to a gastroenterologist.

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99 Acute Dysentery Syndromes (Diarrhea With Fever)

Aldo A.M. Lima, Cirle A. Warren, and Richard L. Guerrant

SHORT VIEW SUMMARY

Definition

- Diarrhea associated with fever is typically seen in acute and chronic inflammatory enteritides that are caused by several specific infectious agents.

Epidemiology and Clinical Signals and Symptoms

- Acute dysenteric syndromes can be caused by any of several diverse pathogens, depending on exposures. *Campylobacter, Shigella,* and *Salmonella* are often febrile illnesses (with or without bloody stools) acquired in settings of suboptimal sanitation or food handling, as can be enterohemorrhagic *Escherichia coli* (EHEC), but with less likelihood of fever. *Shigella* can be spread person-to-person by low inocula, and recent antibiotic or hospital exposure makes *Clostridioides difficile* (formerly *Clostridium difficile*) more likely.
- The bacterial enteric pathogens most associated with illnesses in children younger than 5 years in the United States are nontyphoidal *Salmonella*, followed by *Campylobacter* spp., *Yersinia enterocolitica,* and *E. coli* O157. In developing countries norovirus GII, rotavirus, *Campylobacter* spp., astrovirus, and *Cryptosporidium* spp. have the highest attributable burdens of diarrhea in the first year of life. In the second year of life the major pathogens were *Campylobacter* spp., norovirus GII, rotavirus, astrovirus, *Shigella* spp., and *Campylobacter* spp., and *Shigella* spp. were primarily associated with bloody diarrhea, and fever and vomiting were associated with rotavirus and vomiting with norovirus GII.
- Venereal exposure, particularly among men who have sex with men, may implicate gonococci, herpes simplex virus, *Chlamydia trachomatis*, or *Treponema pallidum* as a cause of proctitis, or *Campylobacter, Shigella, C. trachomatis* (lymphogranuloma venereum serotypes), or *C. difficile* as a cause of colitis.
- A history of antibiotic intake, colonic instrumentation, and/or recent admission to a health care facility would strongly suggest *C. difficile* infection (CDI).

Microbiology

- Genomic studies of *Shigella* spp. have indicated that *Shigella* and enteroinvasive *E. coli* are derived from multiple origins of *E. coli* and form a single pathovar.
- The cause of a recent outbreak of bloody diarrhea and severe hemolytic-uremic syndrome, unlike prior EHEC strains that had exhibited enteropathogenic *E. coli* traits of attachment and effacement, was a Shiga toxin–producing enteroaggregative *E. coli* strain.
- *Campylobacter* spp. have a small genome (1.6–2.0 megabytes) and can cause both intestinal and systemic infections.
- The primary virulence factors that are known to cause disease in CDI are the two large toxins: *C. difficile* toxin (Tcd)A, or toxin A (308 kilodaltons [kDa]), and TcdB, or toxin B (270 kDa), although TcdB may be more clinically relevant than TcdA.
- *Vibrio parahaemolyticus* has been recognized since 1950 in Japan and is a cause of seafood poisoning.
- *Salmonella* flagellin is regulated by the *fliC* gene, which is the major ligand for Toll-like receptor 5, nucleotide oligomerization domain-like receptors, and interleukin-1b–converting enzyme (ICE) protease-activating factor (IPAF) protein.

Diagnosis

- Any of the previously mentioned microorganisms may cause an acute dysentery syndrome with blood and pus in the stool.
- Examination for leukocytes or for fecal lactoferrin may suggest intestinal inflammation, even if blood is not present in the stool on gross examination.
- Recent approaches using multiple pathogen nucleic acid amplification tests for simultaneous detection of several enteropathogens hold promise, with high accuracy, sensitivity, and specificity and being potentially suited for surveillance or clinical purposes.

Therapy and Prevention

- Because there are many etiologic agents, the treatment and prevention rely on each specific cause of acute and chronic inflammatory enteritides, which are viewed in more detail in this chapter. Although *Shigella* and perhaps *Campylobacter* durations of infection and symptoms may be reduced by antimicrobials to which they are susceptible, antibiotics may also be indicated for systemic *Salmonella* infections for which foreign intravascular material or prostheses or severe atherosclerosis may pose increased risk. Some antimicrobials may worsen EHEC toxin production and illness severity.

DEFINITION

Diarrhea associated with fever typically suggests an acute inflammatory enteritis caused by one of several specific infectious agents. However, noninflammatory enteritides caused by viral or other agents may also present with diarrhea and fever. This chapter will address bacteria and amebic colitis as potential major causes of this syndrome. Viral and other parasitic etiologies will be addressed in another chapter. The acute inflammatory enteritides include several specific, distal, small bowel, and colonic infections, such as those caused by *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., and enteroinvasive *Escherichia coli* (EIEC), as well as the syndromes of necrotizing enteritis (NE) and antibiotic-associated pseudomembranous enterocolitis (*Clostridioides difficile* [formerly *Clostridium difficile*]). Several other infectious agents cause chronic enteric inflammatory processes that may result in syndromes of abdominal pain, weight loss, diarrhea, or malabsorption. These involve disease processes such as gastrointestinal (GI) mycoses; mycobacterioses; bacterial infections, such as those caused by enteropathogenic *E. coli* (EPEC), EIEC, enterotoxigenic (enterohemorrhagic [EHEC]), and enteroaggregative *E. coli* (EAEC); and syphilis.

EPIDEMIOLOGY

Syndromes of acute dysentery with fecal blood and pus have been well recognized since the days of Hippocrates. Dysentery is defined as frequent small bowel movements accompanied by blood and mucus, with tenesmus or pain on defecation. This syndrome, with or without fever, implies an inflammatory invasion of the colonic mucosa resulting from bacterial, cytotoxic, or parasitic destruction.

The pathologic changes of inflammatory colitis range from a superficial intense exudative inflammatory process involving the colonic mucosa, as seen in infection by shigellae or invasive *E. coli* organisms,

to deeper, penetrating, flask-shaped ulcers with undermined edges, as seen in amebic dysentery. The pathogenesis of the inflammatory colitides may involve cytotoxic products of shigellae,[1] certain *E. coli* strains,[2] clostridia, or other organisms.

The epidemiologic patterns of acute dysenteric syndromes are influenced by the unusually low inoculum for infection required by organisms such as shigellae or amebas. As few as 100 shigellae or 10 cysts of enteric parasites, such as *Entamoeba coli* or *Giardia lamblia,* have been found to result in infection in adult volunteers.[3,4] In consequence, there is a substantial risk of person-to-person spread in daycare centers,[5] institutions, or other areas where nonhygienic conditions may allow direct fecal-oral spread. The cysts of parasites such as *Entamoeba histolytica* or *Balantidium coli* often resist chlorination and therefore may cause waterborne outbreaks of dysenteric illnesses. Saltwater or seafood exposure should lead to consideration of *Vibrio parahaemolyticus* as a potential cause of inflammatory colitis or of watery diarrhea, and farm or domestic animal exposure might lead to consideration of nontyphoid *Salmonella* spp., *Campylobacter jejuni* or *Campylobacter coli*, or *Yersinia enterocolitica.* A study in children younger than 5 years in the United States found nontyphoid *Salmonella*, followed by *Campylobacter, Y. enterocolitica,* and *E. coli* O157, were the most common bacterial enteric pathogens associated with illnesses.[6] When typhoid fever is present with diarrhea in an endemic area, the diarrhea is often inflammatory, with many fecal polymorphonuclear or mononuclear leukocytes seen on microscopic examination.[7] A recent multisite birth cohort study (Malnutrition and Enteric Disease Study [MAL-ED]) showed that norovirus GII, rotavirus, *Campylobacter* spp., astrovirus, and *Cryptosporidium* spp. exhibited the highest attributable burdens of diarrhea in the first year of life. In the second year of life the major pathogens were *Campylobacter* spp., norovirus GII, rotavirus, astrovirus, and *Shigella* spp.[8] *Campylobacter* spp. and EIEC were associated with dysentery. Rotavirus and *Shigella* spp. were associated with fever, whereas rotavirus and norovirus GII were most associated with vomiting. A history of travel to areas of poor sanitation may implicate any of the aforementioned pathogens. Finally, venereal exposure, particularly among men who have sex with men, may implicate gonococci, herpes simplex virus, *Chlamydia trachomatis* (including lymphogranuloma venereum serotypes), or *Treponema pallidum* as a cause of proctitis, or *Campylobacter, Shigella, E. histolytica*, or *C. difficile* as a cause of colitis.[9] A history of antibiotic intake and/or recent admission to a health care facility would strongly suggest *C. difficile* infection (CDI), although community-acquired infection has been recognized as well.

Although not grossly inflammatory, the still enigmatic Brainerd diarrhea syndrome, which has been associated with raw milk or unchlorinated water consumption in several outbreaks, may involve some proximal colonic lymphocytic infiltration.[10,11]

The potential causes of acute dysentery are listed in Table 99.1.

TABLE 99.1 Differential Diagnosis of Acute Bacterial Dysentery and Inflammatory Enterocolitis

Specific Infectious Processes
Bacillary dysentery (*Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii;* invasive *Escherichia coli*)
Campylobacteriosis *(Campylobacter jejuni)*
Amebic dysentery *(Entamoeba histolytica)*
Ciliary dysentery *(Balantidium coli)*
Vibriosis *(Vibrio parahaemolyticus)*
Salmonellosis (*Salmonella enterica* serovar Typhimurium)
Typhoid fever (*Salmonella enterica* serovar Typhi)
Enteric fever (*Salmonella enterica* serovar Choleraesuis, *Salmonella enterica* serovar Paratyphi)
Yersiniosis *(Yersinia enterocolitica)*
Proctitis
Gonococcal *(Neisseria gonorrhoeae)*
Herpetic (herpes simplex virus)
Chlamydial *(Chlamydia trachomatis)*
Syphilitic *(Treponema pallidum)*
Other Syndromes
Necrotizing enterocolitis of the newborn
Enteritis necroticans
Pseudomembranous enterocolitis or *Clostridioides difficile* (formerly *Clostridium difficile*) colitis without overt pseudomembranes (*C. difficile*)
Diverticulitis
Typhlitis
Chronic Inflammatory Processes
Enteropathogenic and enteroaggregative *E. coli*
Syphilis
Gastrointestinal tuberculosis
Gastrointestinal mycosis (including *Basidiobolus ranarum*)
Parasitic enteritis
Syndromes Without Known Infectious Cause
Idiopathic ulcerative colitis
Crohn disease
Radiation enteritis
Ischemic colitis
Allergic enteritis
Brainerd diarrhea

MICROBIOLOGY AND PATHOGENESIS OF THE MAJOR CAUSES OF ACUTE DYSENTERIC SYNDROMES

Shigella spp. and Enteroinvasive *Escherichia coli*

Bacillary dysentery is caused by *Shigella* spp. and EIEC. It is estimated that *Shigella* spp. (see Chapter 224) infect more than 200 million people and cause 650,000 deaths each year worldwide.[12] The four *Shigella* species are classified in subgroups A to D—*Shigella dysenteriae, Shigella flexneri, Shigella sonnei*, and *Shigella boydii*, respectively. Genomic studies of *Shigella* spp. have indicated that *Shigella* and EIEC are derived from multiple origins of *E. coli* and form a single pathovar.[13] *S. dysenteriae* is capable of elaborating a potent toxin with enterotoxic, cytotoxic, and neurotoxic properties (Shiga toxin).[13] *S. dysenteriae* is responsible for severe and epidemic disease, and *Shigella boydii* is mostly seen in the Indian subcontinent. *S. flexneri* and *S. sonnei* are the most common species around the world.[14] Shigellae are facultative intracellular pathogens and may cause acute bloody dysentery with high fever and systemic manifestations of malaise, headache, and abdominal pain. The incubation period ranges from 6 hours to 9 days but is usually less than 72 hours. *Shigella* spp. are the most common cause of bloody diarrhea in children, and the syndrome may be particularly severe in poorly nourished children.[14]

Despite the intense superficial destructive process in the colonic epithelium that typifies acute shigellosis, bacteremia and disseminated infection are relatively rare.[15] *S. flexneri* invades and causes inflammatory destruction of the human colonic epithelium. The cell and tissue invasion results from a type III secretion system that delivers effector protein into target eukaryotic cells.[16] Acute shigellosis by *S. dysenteriae* type 1 induces apoptotic cell death in rectal tissues associated with increased production of Fas/Fas ligand, perforin, caspase-1, and caspase-3 but reduced production of B-cell lymphoma 2 (Bcl-2) and interleukin-2 (IL-2).[17] *Shigella* infection, especially with *S. dysenteriae* type 1, is associated with enteric protein loss that ceases after appropriate antimicrobial therapy.[18] This protein loss may contribute to increased susceptibility to secondary infections or growth stunting.[19,20] A complication of severe shigellosis in childhood is a hemolytic-uremic syndrome (HUS), which may be associated with a leukemoid reaction, pseudomembranous colitis, circulating immune complexes, and circulating endotoxin, usually in the absence of demonstrable bacteremia.[21]

Intestinal obstruction, which occurs in about 3% of patients, is a poor prognostic sign, not infrequently associated with death or the development of HUS.[22] Other, more common extraintestinal manifestations of shigellosis are headache, meningismus, and occasionally seizures, especially in children.[23] These findings may be attributable to a neurotoxin that has been demonstrated with *S. dysenteriae* type 1[1,24] but may be seen with any *Shigella* infection. A serious arthritis similar to that seen in reactive arthritis has been described in up to 10% of patients 2 to 5 weeks after the dysenteric illness that characteristically occurs in patients