There are a myriad of causes that may result in GI tract inflammation. Whether the cause is autoimmune, iatrogenic, ischemic, infectious, or idiopathic, the alimentary canal responds to injury in a limited number of ways. As a result, endoscopic and histologic evaluation of these patients may result in a great deal of frustration to both gastroenterologists and pathologists. Infections can be particularly challenging because (1) only a limited number of organisms provoke a specific endoscopic and/or histologic appearance and (2) whereas some organisms may be present on biopsies, the findings may be so subtle or organisms so few that they are missed easily if the reviewer is not performing a specific search for the culprit. To narrow the differential diagnosis, clinicians rely on a thorough clinical history and pertinent laboratory studies, whereas pathologists depend on identifying patterns of inflammation and tissue injury. Establishing definitive diagnoses requires an integrated and systematic approach that depends largely on an open dialogue between the gastroenterologist and pathologist. This review aims to illustrate some challenging entities that can be encountered in clinical practice, with a focus on sexually transmitted infection (STI) proctitis because world-wide outbreaks are being reported. The emphasis is on the topic of sexually transmitted infection (STI) proctitis because world-wide outbreaks are being reported. The United States is no exception, and we have identified several of these cases in recent years.

STIs

STIs represent an ever-increasing cause of GI tract inflammation. This discussion is limited to infectious proctitis, because it is predominantly in the rectum that STIs often are mistaken for other conditions, most notably inflammatory bowel disease (IBD). The bacterial pathogens implicated most frequently are Chlamydia trachomatis, Neisseria gonorrhoeae, and Treponema pallidum.

Proctitis is defined as inflammation involving, although not necessarily restricted to, the rectum. Causes of proctitis include IBD, radiation, diversion of the fecal stream (diversion colitis), ischemia, and sexually and non-sexually transmitted infections. The increased prevalence of infectious proctitis secondary to sexually transmitted pathogens has been widely documented in men who have sex with men (MSM). Although as many as 10% of women report having anal-receptive intercourse on a regular basis, sexually transmitted infectious proctitis is overlooked frequently in female patients. A review of proctitis in MSM implicated Neisseria as the causative organism in 30%, Chlamydia in 19%, herpes simplex virus in 16%, and Treponema in 2%. Patients with infectious proctitis are at higher risk for HIV infection because of shared risk factors. In addition, the presence of rectal inflammation facilitates the transmission of HIV.

Although there are no pathognomonic findings to definitively diagnose these infections on histologic grounds alone, there are morphologic clues that pathologists can
identify in order to suggest this as a diagnostic possibility and avoid misdiagnosis and mismanagement.

**CHLAMYDIAL PROCTITIS**

*Chlamydia trachomatis* serovars L1, L2, and L3 are the causative agents of lymphogranuloma venereum (LGV), an invasive infection that has tropism for the lymphatic system. Serovars D through K are typically responsible for cases of genital tract infection (urethritis, cervicitis) limited to the mucosal surfaces. An obligate intracellular gram-negative bacterium, this organism replicates inside membrane-bound vacuoles in endothelial and epithelial cells via a process that requires 2 morphologic forms, namely, the infectious but metabolically inactive elementary body and the noninfectious metabolically active reticulate body. In vitro studies have demonstrated a reversible persistent state for this organism, which is defined as “viable but non-cultivable chlamydiae,” characterized by large, abnormal, non-dividing reticulate bodies. This persistent, in vitro state may be triggered by several factors, namely, exposure of infected cells to penicillin, interferon-γ, nutrient–amino acid starvation, iron deprivation, and herpes virus infection. Whether this persistent state exists in vivo is unknown but certainly possible and could explain cases of reactivation in patients in whom infection resolved after antibiotic treatment (assuming re-exposure has been excluded). This is an interesting proposition, given that *Chlamydia* proctitis preferentially affects individuals infected with HIV, which induces production of several inflammatory cytokines, among them, interferon-γ.

Lymphogranuloma venereum proctitis outbreaks largely have been associated with serovar L2 (genovariant L2b) in Europe, Canada, and Australia. On the other hand, studies from Seattle and China were unable to identify LGV-associated serovars. Instead, the most prevalent genotypes in these groups were G, D, and J. Virulence factors responsible for the chronic inflammatory response are largely unknown. A *Clostridium difficile*–like cytotoxin has been demonstrated in vitro in *Chlamydia* serovar D but not in serovar L2. Recombination may play a role in the emergence of new, hypervirulent strains of *Chlamydia trachomatis*. For example, a unique recombinant strain of L2 and D strains (L2C) recently was isolated from the rectum of an MSM who presented with severe hemorrhagic proctitis. This particular strain is the only LGV strain that so far demonstrates an in vitro cytotoxic phenotype.

**Clinical presentation**

Although endemic to parts of Africa, Asia, the Caribbean and South America, LGV has been identified increasingly over the past decade among MSM in Western industrialized countries. From 67% to 100% of MSM with LGV infections also have concomitant HIV. The progression of LGV is divided into 3 stages. The primary stage occurs after an incubation of 3 to 30 days and presents as a painless, ulcerating papule at the inoculation site, which goes unnoticed by 58% of patients and resolves spontaneously. The secondary stage occurs several weeks later and is characterized by painful and typically unilateral inguinal and/or femoral lymphadenopathy. Lymphadenopathy is not, however, a sine qua non for LGV. Proctitis is common in the secondary stage, occurring in 96% of patients. LGV proctitis presents as rectal pain, tenesmus, bloody or purulent rectal discharge, and constipation, along with systemic symptoms such as fever and weight loss. Tertiary-stage LGV presents strictures, fistulas, and disfiguring lesions of the anogenital region. Non-LGV *Chlamydia* also can cause proctitis in individuals engaging in receptive anal intercourse. Although as many as half the patients may be asymptomatic, symptoms can include anorectal pain, tenesmus, mucosanguinous discharge, abdominal pain, constipation, and fever.

**Endoscopic appearance**

There is significant overlap in symptoms and morphology between *Chlamydia* proctitis and IBD. This mimicry extends to endoscopic appearance. On endoscopy, *Chlamydia* proctitis has protean manifestations (Figs. 1 A), with mucosal hyperemia, mucopurulent discharge, friability, and multiple ulcers; strictures may be seen in LGV-associated proctitis. Aside from the endoscopic resemblance to IBD, LGV proctitis also can present as a mass lesion, mimicking a neoplasm.

**Treatment**

Antimicrobial treatment cures LGV and prevents progression of tissue damage. First-line therapy consists of doxycycline 100 mg orally twice a day for 21 days. Alternative regimens are erythromycin 500 mg orally 4 times a day for 21 days or azithromycin 1 g daily for 21 days. Antibiotic regimens for non-LGV *Chlamydia* consist of doxycycline 100 mg twice daily for 7 days or a single dose of azithromycin 1 g given orally. All sexual partners of the patient during the 60 days before onset of symptoms should be tested for *Chlamydia* and offered treatment.

**SYPHILITIC PROCTITIS**

*T. pallidum*, a gram-negative, motile spirochete, is the causative agent of syphilis. Research on this organism is limited because this metabolically challenged bacterium obtains most necessary macromolecules from its host and cannot survive in vitro for more than a few generations. Despite its slow doubling time (30-33 hours) and oxygen and heat sensitivities, *T. pallidum* thrives in the human body, invading and disseminating to a wide variety of tissues. Latent or persistent infection in asymptomatic persons has been demonstrated in vivo. The organism’s lack of virulent factors (eg, cytotoxins) suggests
that tissue damage occurs as a result of the host immune response.

**Clinical presentation**

Primary anorectal syphilis presents 2 to 6 weeks after exposure as chancres, which are ulcerating papules that may be below or above the dentate line and heal spontaneously in 2 to 4 weeks. Although genital chancres are painless, anorectal chancres can be painful, may cause bleeding, and may resemble anal fissures. Syphilitic proctitis may occur without antecedent or concurrent anorectal chancres. Secondary syphilis occurs 6 to 8 weeks after the initial lesion heals and typically presents with a maculopapular rash involving the palms and soles, which may be accompanied by systemic symptoms such as fever, weight loss, and night sweats. In addition, condyloma latum, a wart-like lesion, may be seen near the site of the presenting chancre.

**Endoscopic appearance**

The great masquerade of syphilis assumes protean endoscopic appearances. Endoscopic findings are typically nonspecific (Fig. 1B), consisting of loss of the normal vascular pattern, ulcerations, frank ulcers, polyloid growths, and occasionally mass lesions, leading to mimicry of IBD, solitary rectal ulcers, rectal polyps, and rectal cancer. Co-infection with *Chlamydia* is common (Fig. 1C).

**Treatment**

Primary and secondary syphilis are treated with benzathine penicillin G, 2.4 million units given intramuscularly as a single dose. Individuals who are allergic to penicillin...
may be treated with either doxycycline 100 mg twice a day or tetracycline 500 mg 4 times a day, orally for 14 days.

**Histologic findings in chlamydial and syphilitic proctitis**

Although histologic features are indistinguishable for these 2 organisms, infection with 1 or both produces a pattern of inflammation that should raise suspicion in the astute observer, as recently characterized by Arnold et al\(^\text{51}\) and previously by others.\(^\text{52}\) The first low-power clue when confronted with one of these cases is the massive lymphoplasmacytic lamina propria expansion. Microscopic abnormalities are limited to the rectosigmoid colon and anal canal (Fig. 1D-F). One must remember that in the normal state, the rectum has few lamina propria inflammatory cells when compared with biopsy specimens from the right side of the colon (Fig. 2). When biopsy specimens from the more proximal colon are evaluated, they are normal or near normal. Histologic features associated with STI proctocolitis include (1) an intense lymphoplasmacytic and histiocytic expansion of the lamina propria with or without lymphoid aggregates; (2) mild-to-moderate active inflammation; (3) ulceration; (4) minimal basal plasmacytosis and crypt distortion; (5) rare granulomata; (6) rare Paneth cell metaplasia; (7) submucosal fibrosis with perivascular lymphoplasmacytic accentuation (submucosa often not included in superficial mucosal biopsies); (8) cases with squamous mucosa that may feature ulceration, hyperkeratosis, epithelial hyperplasia, and an underlying band-like pattern of lymphoplasmacytic and histiocytic inflammation (Fig. 3A,B); and (9) the so-called rectal tonsil or florid follicular hyperplasia sometimes reported in association with *Chlamydia* infection.\(^\text{53}\)

Although it may be tempting to call the pathologist to request a silver stain in suspicious cases, results may be misleading because the majority of cases have negative results, and background staining is a significant confounding factor. An immunohistochemical stain for *T. pallidum* immunostain.\(^\text{54}\) Our practice is to request results of ancillary studies as “non-contributory” instead of “negative” because the reader may erroneously interpret a negative stain result as definitive evidence of lack of infection. As of this writing, there is no commercially available *Chlamydia*-specific special stain or immunostain.

**Pitfalls, mimickers, and other considerations**

As with many inflammatory processes in the GI tract, these histologic findings are not specific, and an erroneous diagnosis may be rendered if the clinical context is not taken into account. Although the degree of architectural distortion is not significant in the majority of cases, basal lymphoplasmacytosis, mild crypt distortion, Paneth cell metaplasia, and/or the presence of granulomas may provoke concern for IBD. Biopsy specimens of untreated IBD typically show a higher degree of architectural distortion that is proportional to the degree of active inflammation (seen as cryptitis and crypt abscesses) (Fig. 4). Additionally, in patients with IBD, biopsy specimens from the more proximal colon may show a similar degree of inflammation and distortion. In STI proctitis, the histologic changes are limited to the rectum or rectosigmoid colon, thus, histologic overlap with ulcerative colitis can be problematic. Correlation with laboratory studies and sexual history is always required in the evaluation of STI proctitis versus IBD.

Syphilis involving the anal canal may provoke striking pseudoepitheliomatous hyperplasia in specimens containing squamous mucosa (Fig. 5). Any process (neoplastic [eg, granular cell tumor] or inflammatory) involving the connective tissue underneath squamous epithelium may incite dramatic hyperplasia and haphazard downward growth with “pointy” or “sawtooth” dermal papillae that may resemble squamous cell carcinoma to even the most experienced pathologist. In cases of pseudoepitheliomatous hyperplasia in the setting of STI, the epithelium lacks atypia and will be accompanied by a dramatic, eye-catching, band-like lymphoplasmacytic inflammatory infiltrate. Pathologists should have a high threshold to diagnose squamous cancer in the backdrop of such inflammation, even in the setting of a mass, because syphilis of the anal canal may present as a mass-like lesion endoscopically.\(^\text{51}\)

Both pathologists and gastroenterologists must be aware of the significant overlap between STI proctitis and IBD in order to avoid misdiagnosis and mismanagement. This need is underscored by documented reports such as that of Soni et al,\(^\text{54}\) in which 12 men with LGV proctitis were misdiagnosed and erroneously treated for IBD. All symptoms resolved after appropriate LGV-based treatment.
GONORROHEAL PROCTITIS

*N gonorrhoeae* is a gram-negative diplococcus that grows best at 35°C to 37°C in a medium containing 3% to 5% CO2. This bacterium has fimbriae on its outer surface, which may enhance virulence by facilitating attachment to human epithelial cells and by inhibiting phagocytosis. In addition, the organism inactivates secretory immunoglobulin (Ig) A via an IgA protease, and its outer membrane lipopolysaccharide has endotoxin activity, which plays a role in local and systemic toxicity and inflammation.65 Although classically associated with urethritis, cervicitis, pharyngitis, and conjunctivitis, *N gonorrhoeae* is also a known cause of proctitis.

Clinical presentation

*N gonorrhoeae* proctitis is typically encountered in men and women who practice anal-receptive intercourse. Anal-receptive intercourse is not, however, a requirement for gonococcal proctitis in women; approximately 50% of female patients with gonococcal proctitis develop rectal infections as a result of contiguous spread from the cervix.56 The prevalence in screening populations of MSM ranges from 4.5% to 6%, with higher prevalence reported in HIV or STI clinics.57,58 Nearly 85% of patients with rectal gonococcal infection are asymptomatic, with symptomatic patients demonstrating markedly higher bacterial loads and theoretically increased infectivity.58,59 A fourth of patients with rectal gonococcal infection are concurrently infected with *Chlamydia*.60 Gonococcal proctitis is also an independent risk factor for HIV.11 Gonococcal proctitis occurs 3 to 14 days after exposure and presents as perianal pain and pruritus, tenesmus, and mucopurulent or sanguinous discharge.56

Endoscopic findings

The endoscopic appearance is normal in the majority of infected patients.54 When abnormal, the findings are...
nonspecific and include mucosal erythema and edema and a thick, purulent discharge (Fig. 6A).

Treatment

If a purulent discharge is noted in the anorectum or if polymorphonuclear leukocytes are seen on Gram stain, empiric therapy for gonococcal proctitis should be initiated. The recommended regimen is ceftriaxone 250 mg given intramuscularly as a single dose, plus either azithromycin 1 g orally as a single dose or doxycycline 100 mg twice daily for 7 days. Patients with a cephalosporin allergy should be treated with azithromycin 2 g given orally as a single dose, followed by mandatory test-of-cure 1 week after completion of treatment.

Histologic findings

There is limited medical literature regarding the microscopic appearance of gonorrheal proctitis. McMillan and Lee report normal specimens in 18 patients (55%) with rectal gonorrhea versus 3 of 10 specimens (30%) in patients with rectal syphilis. A subsequent study similarly reported normal biopsy specimens in 3 of 57 specimens (57.9%) in patients with rectal gonorrhea. Abnormal biopsies in this setting show less striking inflammation than in cases of syphilis. One may see a mild-to-moderate increase in lamina propria lymphocytes and plasma cells with or without neutrophils within the crypts and the intestinal lumen. In approximately 5% of cases, the inflammatory infiltrate within the lamina propria is predominantly neutrophilic and superficial. Architectural distortion is not a feature of gonorrheal proctitis (Fig. 6B and C).

Pitfalls and/or mimickers

Regardless of whether or not the pathologist is aware of the clinical history, he or she is likely to report abnormal biopsies descriptively as active proctitis with or without a comment stating that this may represent an infectious process. The appearance may be similar to that seen in the setting of other, non–sexually transmitted bacterial infections (eg, *Salmonella*). Nuclear reactive changes and lamina propria hyalinization may be present, and, as a result, ischemic or radiation injury may enter the histologic differential diagnosis (Fig. 6B and C). From a pathologic standpoint, biopsies in this setting are unlikely to raise suspicion for IBD because changes of chronicity (crypt architectural distortion, lamina propria expansion, and basal lymphoplasmacytosis) are not a feature of this type of infection.

Both pathologists and clinicians must remember that over half of patients with rectal gonorrhea will have normal biopsy results. Additionally, histologic evidence of inflammation may be present in a subset of patients with a normal endoscopic impression. Hence, lack of histologic and/or endoscopic evidence of inflammation does not imply absence of infection.

Laboratory testing

Culture is the criterion standard for *Chlamydia* and gonorrhea testing, and it allows for antibiotic susceptibility testing in the face of emerging resistance. However, microbiologic culture is time consuming and expensive. In addition, culture has lower sensitivity when compared with the newer methodology of nucleic acid amplification testing (NAAT). A rectal swab for NAAT may be preferable over urine testing because 64% of gonococcal and 53% of chlamydial rectal infections are missed when MSM are screened only for urethral disease. Gonorrhea culture is still necessary because it allows for antibiotic susceptibility testing in the face of emerging resistance. Although neither gonorrhea nor *Chlamydia* NAAT is U.S. Food and Drug Administration (FDA) cleared for rectal or pharyngeal sites, the test has been validated and is offered by at least 2 large, commercial laboratories.

Rapid plasma reagin and Venereal Disease Research Laboratory (VDRL) tests are the screening tests for syphilis. Positive results must be confirmed with a fluorescent treponemal antibody-absorption (FTA-ABS) test. Non–treponemal test titers (rapid plasma reagin, VDRL) should be checked 6 months and 12 months after completion of therapy. A decline of titers by 4-fold over this period is indicative of treatment success. FTA-ABS should not be used to monitor response to treatment or assess the possibility of reinfection because these remain positive for the life of the patient. Sexual partners of index patients
who were exposed within 90 days of diagnosis should be treated presumptively for syphilis.40

WHIPPLE DISEASE

George Whipple described this multisystemic, malabsorptive disease in 1907.66 Eighty-five years after description of the eponymous disease, the causative organism, *Tropheryma whipplei*, was identified.52 Whipple disease is a rare condition, with an estimated worldwide incidence of 12 cases annually and a total of approximately 1000 cases reported to date.58,69 The disease primarily affects middle-aged, white men, with a male-to-female ratio of 8:1.70

Diagnostic tools

The organism’s 16S ribosomal RNA was sequenced in 1992, and phylogenetic analysis allowed classification of the organism as a gram-positive actinomycete.67 Its genome is reduced (less than 1,000,000 base pairs), with few genes associated with energy metabolism, and it lacks important biosynthetic pathways.71 The organism must, therefore, obtain some amino acids from the environment or host. The organism’s source in nature has not been elucidated yet.

Although the organism was successfully cultured in 2000,72 this technique is not widely available as a diagnostic tool, and tissue microscopic analysis with ancillary studies remains the mainstay of diagnosis. A sensitive and specific Whipple immunohistochemical stain is commercially available (Fig. 7A).73,74 Other tests include polymerase chain reaction (PCR) for 16S ribosomal RNA genes of *T. whipplei* and electron microscopy. Whipple immunohistochemistry, periodic acid-Schiff (PAS), and electron microscopy will not distinguish between viable and nonviable bacteria, which may persist within macrophage cytoplasm months after successful treatment.75,76 According to von Herbay et al,75 positive-to-negative PCR conversion in intestinal biopsy specimens occurs approximately within 1 year after initiation of therapy. PCR conversion in intestinal tissue is not indicative of systematic eradication because 3 of 24 patients in the von Herbay et al study experienced cerebral disease despite negative PCR results in intestinal biopsies.

Clinical presentation

Whipple disease presents in 2 stages, the prodromal stage and the steady-state stage, which are temporally separated on average by 6 years.69 The prodromal stage consists of nonspecific symptoms such as fever and arthritis; the steady-state stage presents with diarrhea and weight loss and may involve various organ systems, including the eye, heart, and nervous system.69,77 Immunosuppressive therapy can accelerate the progression to the steady-state stage and can precipitate GI and other symptoms of the disease.78-81 GI manifestations of classic Whipple disease include diarrhea, weight loss, occult intestinal bleeding, abdominal pain, abnormal liver chemistry test results, and ascites.82 Rheumatologic manifestations include intermittent migratory arthralgias and/or arthritis, which may be polyarticular or oligoarticular.77 Neurologic manifestations are found in up to 63% of patients with Whipple disease, and include cognitive changes, ophthalmoplegia, altered level of consciousness, psychiatric and personality disorders, motor disorders, ataxia, and seizures.69 Cardiac manifestations include pericarditis, myocarditis, culture-negative endocarditis, heart failure, and sudden death.83

Endoscopic findings

Laboratory test result abnormalities include increased sedimentation rates, thrombocytosis, and findings specific to involved organs.70 The requisite for diagnosis, however, remains demonstration of the causative organism in affected tissues.84 The tissue most often used to establish a diagnosis of Whipple’s disease is the small bowel, owing to its frequent involvement and ease of endoscopic biopsy. Endoscopic findings in Whipple’s disease include pale yellow, shaggy mucosa with patchy erythema and erosions.69,85 Mosaic-patterned and scalloped duodenal mucosa also have been described in Whipple’s disease, leading to misdiagnosis as celiac sprue.80 The use of narrow-band imaging and i-scan have been reported to aid in endoscopic diagnosis.85,87 Small-bowel capsule endoscopy may demonstrate erythema, edema, and a “salt and pepper” appearance, presumably because of intraepithelial abscesses.88,89 Because none of these endoscopic features are pathognomonic for Whipple’s disease, mucosal biopsies are essential in establishing the diagnosis.

Histologic findings

Small-bowel biopsies show classic Whipple’s disease histology in 63% to 90% of cases (Fig. 7B).74,90-92 Classic Whipple’s disease is characterized by (1) club-shaped, blunted, or broad villi; (2) lamina propria expanded by foamy, pink macrophages; (3) PAS–positive, diastase-resistant, globular, bacterial inclusions in macrophage cytoplasm (Fig. 7C); (4) bacterial inclusions that can be present extracellularly within the lamina propria, in epithelial cells, fibroblasts, endothelial cells, and smooth muscle; and (5) dilated lacteals and fat droplets that often are observed as a result of lymphatic obstruction and often are an eye-catching finding at initial low-power examination (Dr Whipple’s initial term for this disease was “intestinal lipodystrophy” based on these characteristic findings).

Pitfalls and/or mimickers

Pathologic diagnosis occasionally may be challenging because of several factors. First, foamy macrophage distribution may be patchy, and the diagnostic cells are sometimes found exclusively within the submucosa,73 which is
seldom present in endoscopic biopsy specimens. Second, biopsy specimens obtained after treatment may show a partial or complete histologic treatment effect, as recently described by Arnold et al.60 A partial histologic treatment effect may be seen as early as 6 months and as late as 18 months after initiation of therapy. Histologic examination in these cases reveals minimal villous blunting, with scattered collections of foamy macrophages and reduced PAS and Whipple immunohistochemical stain positivity. Cases with a complete histologic treatment effect may be encountered anywhere from 15.8 months to 138 months after initiation of therapy. These biopsy specimens show no significant pathologic changes on hematoxylin and eosin (H&E) staining except for rare macrophages within the deep mucosa. These macrophages are PAS negative but show focal positivity with Whipple immunohistochemical staining. Others have documented this macrophage “shift” from the upper mucosa to the deep mucosa in the after-treatment setting.73 Last, although most patients with Whipple’s disease present with intestinal manifestations, a minority of patients will have only extraintestinal disease localized to the lymph nodes, brain, heart, lung, uvea, or joints.92

Whipple’s disease may be similar to infection with *Mycobacterium avium* complex on H&E and PAS staining. *Mycobacterium avium* complex, however, is seen predominantly in immunocompromised patients, is not associated with dilated lacteals, is acid-fast stain positive, and is cultured easily in the microbiology laboratory.

Cases may be misdiagnosed as sarcoidosis because the clinical features overlap, and a minority of Whipple’s disease cases may present with nonnecrotizing granulomas on histology.20,93 The consequences of this gaffe may be significant because patients diagnosed with sarcoid undergo immunosuppressive therapy, the effects of which may precipitate or worsen Whipple’s disease manifestations.

**Treatment**

Untreated Whipple’s disease is uniformly fatal. The recommended treatment is streptomycin 1 g daily given in combination with penicillin G 1.2 million units daily or ceftriaxone 2 g daily for 2 weeks, followed by a 1- to 2-year course of oral trimethoprim 160 mg and sulfamethoxazole 800 mg twice daily.69

**SARCINA VENTRICULI**

*S ventriculi* was first described by Goodsir34 in 1842 in the “cases of chronic disease of the stomach associated with obstinate vomiting of acid, frothy, yeasty matters.” The chronic disease of the stomach in which *S ventriculi* was first identified was likely gastroparesis or gastric outlet obstruction, because it is in the context of these conditions that most *S ventriculi*–related illnesses have been reported.95

*S ventriculi* is a fastidious, anaerobic, gram-positive, sugar-fermenting bacterium. It thrives in acidic environments and ferments carbohydrates with production of ethyl alcohol and CO₂.96 The organism is ubiquitous in soil and has been isolated from the feces of healthy humans, mainly in association with a vegetarian diet.97 This bacterium has received some attention in the medical and veterinarian literature because of its association with cases of emphysematous gastritis.96,98-100 The precise mechanism of injury is uncertain, but in most human cases there is an underlying condition that hampers adequate gastric emptying (gastroparesis, gastric outlet obstruction).95,101 Carbohydrate stasis, along with the stomach’s acidic environment, may provide an ideal medium for *S ventriculi* growth. Although it is unlikely that *S ventriculi* initiates gastric injury in affected patients, its presence on biopsy material should be noted because it may be indicative of an underlying obstruction or motility abnormality.

**Clinical presentation**

Although *Sarcina* is traditionally thought of as a commensal organism that does not cause symptoms, it may be associated rarely with chronic nausea, dyspepsia, abdominal pain, gastric ulcers, emphysematous gastritis, and gastric perforation.98,101 Hence, when the organism is identified in the setting of these clinical features, treatment should be considered.
Endoscopic findings

The range of endoscopic presentations in patients with symptomatic *S. ventriculi* reflects the severity of disease and includes the presence of retained food or bezoar formation in the stomach, pyloric mass or stricture, gastritis, ulcer, and bile retention. Patients with emphysematous gastritis may present endoscopically with extensive inflammation and blackening of the gastric mucosa, with cobblestoning resulting from intramural air bubbles.

Histologic findings

Organisms are readily identified on H&E staining in packets of 4, 8, or more cells (up to 3 μm each), with characteristic flattening or molding in areas of contact with one another, with or without associated giant cells and food particles (Fig. 8A). Organisms usually are seen within the luminal surface, with no evidence of tissue reaction. Lam-Himlin et al\(^{101}\) reported the only human case series (\(n = 6\) specimens from \(5\) patients) to date and found no unifying theme in the background mucosa; biopsy results in their series were either normal (\(n = 2\)) or showed active or chronic duodenitis (\(n = 2\)) or gastric intestinal metaplasia (\(n = 2\)).

Pitfalls and/or mimickers

The main diagnostic consideration is with *Micrococcus* species. Although these are indetical in packets, they are much smaller (about 0.5 μm) and are arranged in much tighter clusters (Fig. 8B).

Treatment

Whether *Sarcina* should be treated when found incidentally in a clinically stable patient is not known. Given the reports of its presence in healthy individuals, however, it is reasonable to consider the organism as commensal in this clinical setting and forego antibiotic treatment. Because *S. ventriculi* is an acidophilic bacterium, there is at least a theoretical benefit of using a proton pump inhibitor as an adjunct to antibiotic therapy.\(^ {102}\)

**GIARDIASIS**

*Giardia lamblia*, also known as *G. intestinalis* or *G. duodenalis*, is a spore-common pathogen worldwide, with an incidence in developing countries of approximately 500,000 cases annually.\(^ {103}\) Nearly 20,000 new cases are reported annually in the United States.\(^ {104}\) Because ingestion of as few as 10 to 25 cysts can produce the disease in healthy volunteers, *Giardia* is a common cause of food and water-borne illness and can be transmitted from person to person via the fecal-oral route.\(^ {105}\) Wild mammals such as deer and beavers serve as a reservoir for *Giardia* and may contaminate surface or stream water; as a result, hikers who drink untreated stream or surface water are at risk for *Giardia* infection.\(^ {105,106}\) Returning travelers and refugees from developing countries are at risk for giardiasis.\(^ {107}\) Children, MSM, immunocompromised individuals, daycare workers, and patients with cystic fibrosis also are at increased risk for Giardiasis.\(^ {105,106-111}\)

*G. lamblia* is a noninvasive, flagellated protozoan that primarily affects the small intestine. This water-borne organism is transmitted in cyst form, and, once cysts are swallowed, gastric acid and intestinal proteases promote excystation into the trophozoite. The organism attaches to the epithelial surface via a ventral adhesion disk, but the exact mechanism by which *G. lamblia* produces human illness is unclear. Initial in vitro studies on canine epithelial cells failed to demonstrate alterations in epithelial integrity (intact occluding junctions) after infection and instead showed focal damage to the microvilli.\(^ {112,113}\) Subsequent in vitro studies on human colon and duodenum cell lines demonstrated reduced transepithelial electrical resistance associated with alterations and/or loss of cytoskeletal (F-actin and α-actinin) and tight junctional proteins (ZO-1 and claudin-1).\(^ {114-116}\) In animal models, CD4-positive T cells seem to mediate epithelial brush border injury and

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**Figure 8. Sarcina ventriculi.** A, Organisms are seen here in packets of 4, with characteristic flattening or molding in areas of contact with one another. B, A gram-positive, spherical bacterium, *Micrococcus*, is morphologically similar to *S. ventriculi* but is smaller and arranges in larger packets.
disaccharidase deficiency. Additionally, studies with human duodenal tissue show active epithelial chloride hypersecretion. Therefore, the diarrheal illness associated with giardiasis may result from a combination of both malabsorption and electrolyte hypersecretion.

**Clinical presentation**

*Giardia* infection may be asymptomatic or result in acute symptoms including diarrhea, steatorrhea, flatulence, nausea and vomiting, and fever. Chronic infection occurs in approximately half of infected individuals, and patients may present with loose stools, flatulence, malabsorption, and weight loss. In children, impaired growth and cognitive development can result from iron and micronutrient deficiencies. Clinically, chronic giardiasis may mimic IBS, inflammatory bowel disease, and celiac sprue.

**Endoscopic findings**

Because fully developed trophozoites are released in the proximal small bowel, endoscopic and histologic changes should be sought in this anatomic location (Fig. 9). Endoscopic findings may range from normal-appearing mucosa to such nonspecific findings as erythema, mucosal granularity, and nodular mucosa. The sensitivity of duodenal aspirates taken during upper endoscopy is low (20%), and its routine use for diagnosis of infection is of questionable value. In patients with a non-acidic gastric environment secondary to acid suppressive therapy, gastric surgery, duodenogastric reflux, *Helicobacter pylori* infection, and atrophic gastritis, giardiasis rarely may involve the stomach; in one such case, markedly erythematous antral mucosa with small, patchy, cotton-like lesions was described.

**Histologic findings**

Giardiasis typically is diagnosed via stool examination, fecal immunoassays, and/or tissue biopsy. Because organisms are not shed consistently in the stool, the Centers for Disease Control and Prevention (CDC) recommend the use of fecal immunoassays because of their increased sensitivity compared with conventional microscopy. If stool examination is relied on, testing of 3 stool samples is recommended before considering testing negative.

The organisms typically are found in duodenal biopsies (Fig. 10A and B), but in a minority of cases they can be identified in the gastric antrum, jejenum, terminal ileum, and colon. Duodenal mucosal architecture is intact in over 95% of cases. Biopsy specimens with mucosal histologic changes show varied and nonspecific findings including (1) mild villous blunting; (2) moderate-to-complete villous blunting, which has been reported in pediatric patients by some but not by others; (3) the presence of lymphoid follicles; (4) mild increases in the number of intraepithelial lymphocytes; (5) inflammatory expansion of the lamina propria by lymphocytes, plasma cells, and neutrophils; and (6) increased number of mucosal eosinophils sometimes seen in the pediatric setting.

Organism burden varies from case to case, and some biopsy specimens show only a few parasites within the luminal surface alongside intestinal villi. Because of this, and because mucosal architecture is completely normal in many cases, every pathologist should make it a habit to scan the luminal surface of small-intestine biopsy specimens as part of their systematic approach to these specimens. On H&E staining, trophozoites appear as pear-shaped structures cut along the long axis. *Giardia* trophozoites have 2 ovoid nuclei and 4 pairs of flagellae, but these structures often are difficult to identify on H&E staining. The organisms may be highlighted with Giemsa or trichrome special stains or a CD117 immunostain, but these stains are rarely necessary in daily practice.

**Pitfalls and/or mimickers and clinical considerations**

Abnormal biopsies in the setting of giardiasis may provoke concern for early celiac disease if the organisms are not readily identified. In both settings, patients may present with malabsorption, so correlation with the clinical setting and ancillary tests is imperative. Recurrent or persistent giardiasis should alert both pathologists and clinicians about the possibility of associated immunodeficiency or autoimmune disorders, namely, IgA deficiency, common variable immunodeficiency, autoimmune enteropathy, immunodysregulation, polyendocrinopathy, enteropathy, X-linked inheritance (IPEX syndrome), autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED syndrome), and X-linked agammaglobulinemia. In some instances, giardiasis may be the presenting sign in these disorders.
Although these immunodeficient states cannot be diagnosed based on histologic examination alone, there are clues that the pathologist may report on. For example, two thirds of biopsy specimens from patients with common variable immunodeficiency lack plasma cells, whereas goblet and/or Paneth cells may be absent in biopsy specimens from patients with autoimmune enteropathy.

**Treatment**

Tinidazole and nitazoxanide are FDA approved for treatment of *Giardia*. Metronidazole and albendazole, although not FDA approved for *Giardia*, have proven efficacy against the pathogen.

**SCHISTOSOMIASIS**

Schistosomes are trematode worms known to cause intravascular infestation in humans. *Schistosoma hematobium*, *S mansoni*, and *S japonicum* are species that most commonly infect humans. Schistosomiasis (also known as bilharzia), is endemic to South America, Southeast Asia, and Africa. Africa accounts for 90% of the annual global mortality attributed to schistosomiasis and for 84% of travel-related cases. In the United States, the disease is encountered primarily in expatriates from endemic areas, military personnel, missionaries, and volunteers.

Although *S mansoni* is most commonly associated with GI tract infection, all other *Schistosoma* species can infect the GI tract as well. *S hematobium* preferentially infects the genitourinary tract. Humans acquire the infection by swimming in contaminated fresh water. The cercarial form penetrates the human skin and becomes a schistosomula, which then travels via the portal blood flow to the liver, where it matures into the adult form and mates. The species with GI tract tropism migrate to mesenteric venules of the bowel and lay eggs that are shed in the stool. Eggs hatch in the water, releasing miracidia, which take shelter and develop inside snails. Snails then release cercariae into the water, and the cycle of infectivity begins again.

**Clinical presentation**

The clinical course of schistosomiasis parallels the life cycle of the pathogen. The initial penetration of the parasite into the skin may result in a self-limited but severe pruritus called cercarial dermatitis or swimmer's itch. Two to 12 weeks after entry of the parasite, the acute phase of schistosomiasis, known as Katayama syndrome, begins in parallel with the migratory phase of the parasite’s life cycle, when immune complexes form in response to deposition of parasite eggs in various tissues. Symptoms of Katayama syndrome include nocturnal fevers, myalgias, cough, headache, bloody or nonbloody diarrhea, and right upper quadrant pain; eosinophilia and diffuse pulmonary infiltrates are noted on diagnostic testing.

The chronic manifestations of schistosomiasis result from the immune response elicited by parasite eggs and the antigens they release and the resulting fibrosis and granuloma formation in the tissues where the eggs are embedded. The disease manifestations are most common in anatomic areas where egg burden is highest, namely the liver, GI tract, and genitourinary tract; other areas of disease involvement include the lungs, skin, adrenal glands, and brain. Granuloma formation in the GI tract results in ulceration, polyposis, and colorectal strictures; these structural changes manifest clinically as abdominal pain, diarrhea (bloody or non-bloody), and protein-losing enteropathy. Hepatomegaly resulting from granulomatous inflammation occurs early in the course of the disease; presinusoidal inflammation and fibrosis of the portal vein resulting in portal hypertension is a late manifestation of the disease and occurs in 4% to 8% of individuals with chronic infection and results in the characteristic sonographic and tomographic appearance.

**Endoscopic findings**

Although there is no pathognomonic endoscopic appearance of schistosomiasis, the endoscopic manifestations of
the disease are nonspecific and include ulcers, colitis, mass lesions, and strictures. These manifestations lend themselves to confusion with Crohn’s disease, ulcerative colitis, polyps, or cancer (Fig. 11A). In a study of 46 patients with schistosomiasis who underwent colonoscopy, findings were limited to the descending colon in 83% of patients and to the rectum and sigmoid colon in 63%. Most patients had chronic submucosal colitis characterized by pale mucosa, an abnormal mucosal vascular pattern, flat or raised yellowish nodules, and polyps or strictures. On upper endoscopy, changes secondary to portal hypertension may be seen.

Histologic features
Identification of parasite eggs in stool or urine with light microscopy remains the diagnostic criterion standard for schistosomiasis. Serology cannot distinguish between past exposure and active infection; however, it may be used to exclude the disease in an individual from an endemic region or confirm the diagnosis in returning travelers, who typically shed smaller numbers of eggs in the feces and may have falsely negative stool test results. PCR-based diagnostic tests are not commercially available but offer the possibility of sensitive and specific diagnosis in the near future. An antigen test has been developed, but it is not commercially available in the United States.

Eggs provoke sustained tissue injury with fibrosis, calcification, and granuloma formation with or without associated mucosal eosinophilia (Fig. 11B and C). A lateral spine is characteristic of *S. mansoni* eggs, whereas a terminal spine is seen with *S. haematobium*. *S. japonicum* has a minute or no terminal spine. An association between schistosomiasis and colon cancer has been suggested but is not well established.

**Pitfall**
In some cases, an inflammatory reaction is absent or minimal, and few organisms may be present in a given biopsy. Identification then rests on a thorough histologic examination and correlation with pertinent microbiologic cultures.

**Treatment**
All patients with schistosomal infection should undergo treatment. The CDC recommends 2 doses of praziquantel 20 mg/kg over the course of 1 day for a total dose of 40 mg/kg. *S. japonicum* requires a total dose of 60 mg/kg, which may be given in 3 divided doses. Repeat testing of urine or stool is recommended 1 month after treatment to confirm eradication (www.CDC.org).

**CRYPTOSPORIDIOSIS**
*Cryptosporidium* is a protozoan parasite that is a common cause of diarrheal illness in the United States, with 2.9 cases per 100,000 population reported in 2010.
bominis and C. parvum are the species most commonly implicated in infections in humans. Cryptosporidium can infect adults and children and immunocompetent as well as immunocompromised individuals. Cattle serve as a reservoir for the parasite, and water-borne outbreaks result from drinking water contaminated by manure. Prevalence of Cryptosporidium infection is higher among HIV-infected individuals. An intracellular, water-borne parasite, Cryptosporidium is notorious for its resistance to water disinfectant treatment except for ozone. Oocysts are swallowed and undergo excystation and release sporozoites, which then attach to and are enveloped by intestinal epithelial cell membranes where they divide inside parasitophorous vacuoles within the microvillous layer, outside of the cell's cytoplasm. They subsequently transform into characteristic round trophozoites. Female and male sexual forms fuse to form oocysts that are shed in the feces and into the environment.

As with Giardia, Cryptosporidium oocyst excretion is intermittent. The CDC recommends examination of at least 3 stool specimens before test results are considered negative. Immunoassay testing is available and is more sensitive than stool examination.

Clinical presentation
After a 7 to 10-day incubation period, diarrheal illness occurs, accompanied by abdominal cramps, vomiting, fever, and anorexia. The course is self-limited in immunocompetent hosts but is chronic in the setting of immunosuppression from HIV infection and is fulminating in patients with CD4 counts of <50, with fecal volumes of 2 L daily and increased mortality. In HIV-infected patients, Cryptosporidium may involve the biliary endothelium and cause periductal inflammation in the biliary tree. This inflammation results in HIV cholangiopathy, a disease characterized by papillary stenosis, long intrahepatic strictures, intrahepatic and extrahepatic sclerosing lesions and acalculous cholecystitis. Laboratory test evaluation demonstrates elevated alkaline phosphatase levels, with proportionally more modest transaminitis; jaundice is rare.

Endoscopic findings
Cryptosporidium organisms are most commonly identified in the duodenum. Endoscopic appearance of the duodenum in patients with Cryptosporidium infection is typically normal, because villous architecture does not change significantly in most cases. Case reports have described nodularity of the duodenum; whitish plaques; irregular, serrated appearance of the valvulae conniventes, with loss of mucosal folds and submucosal vasculature; and marked edema. Cholangiographic appearance in HIV cholangiopathy falls into 1 of 4 categories: papillary stenosis alone, papillary stenosis with sclerosing cholangitis, sclerosing cholangitis without papillary stenosis, and long extrahepatic stricture.

Histologic features
Diagnosis of Cryptosporidium is made based on identification of the pathogen in stool or tissue samples. Enzyme-linked immunosorbent assay tests have high sensitivity and can serve as an adjunct to microscopic evaluation of stool. PCR assays also demonstrate high sensitivity and specificity, but are not as widely available.

Cryptosporidium may infect any site of the GI tract, from the gastroesophageal junction to the anus. The esophagus is typically spared. Architectural and inflammatory changes as well as organism burden vary from case to case. When mucosal alterations are minimal, this is an easy diagnosis to miss because it requires examination of multiple fields at high power to identify spherical basophilic organisms with similar tinctorial quality as epithelial cell cytoplasm.

In the stomach, organisms are distributed in a patchy fashion and are typically seen at the luminal epithelial surface and within the gastric pits but rarely deep within the glands. They tend to localize to areas of histologic alterations, which are typically foci of reactive changes, with nuclear and nucleolar enlargement, loss of mucin, lymphocytes, plasma cells, activity, atrophy, intestinal metaplasia, and/or hyperplastic changes.

Duodenal biopsies produced the highest diagnostic yield in 1 study, with the histologic burden ranging from only a few organisms to over 50% of epithelial cells infected. At this site, the organisms are most commonly found within surface epithelial cells but also within crypt cells. Although villous architecture may be preserved in over 70% of cases, moderate-to-severe villous blunting may be evident and correlates with severity of infection. Other findings include nuclear and nucleolar enlargement, increased nuclear to cytoplasmic ratio, increased lamina propria, and intraepithelial lymphocytes, apoptotic bodies, crypt hyperplasia, and/or active inflammation. Although these inflammatory changes do not correlate with severity of infection, the presence of activity was associated with concurrent duodenal cytomeglovirus (CMV) infection in one study. In fact, the same study found that CMV was the most common GI additional pathogen, with 32% of the studied patients having histologic evidence of this viral infection.

Godwin found a similar association in his study of 15 cryptosporidiosis autopsy cases, with 8 of 15 patients having GI CMV.

When reviewing colon biopsy specimens, pathologists must keep in mind that some histologic findings may be
the reverse of those expected for the upper GI tract. For example, in the colon, organisms are more commonly identified within crypt epithelial cells and less often in association with surface epithelium (Fig. 12C). Similarly, reactive epithelial changes may be less obvious than those of the stomach and duodenum. Changes tend to be minimal and include mild, focal architectural distortion and foci of cryptitis.178 Apoptotic bodies may be prominent and correlate with intensity of infection. Although cellular apoptosis may be the direct result of infection, one must keep in mind that these patients often are taking medications that are toxic to the GI tract and may result in the same findings.178 Similarly, patients with GI tract CMV infection can display impressive epithelial apoptosis.

Pitfalls, mimickers, and other considerations

The main diagnostic pitfall in the setting of cryptosporidiosis is missing the organisms in a biopsy specimen with a low burden. Knowledge of the usual site where the organisms are typically identified may be helpful (surface in the upper GI tract vs crypts in the lower GI tract). As with Giardia, the best approach is to make this search part of a consistent systematic examination of endoscopic biopsy specimens.

Because the organisms’ tinctorial quality is similar to epithelial cell cytoplasm, one may overcall infection in cases of prominent surface globular fragments of mucin. In doubtful cases, one may highlight true organisms with a Giemsa stain (Fig. 12B). An immunohistochemical stain is commercially available.

Cryptosporidium may be mistaken for Cyclospora cayetanensis. They may be differentiated from one another based on size, because Cryptosporidium is smaller (2-5 μm) than Cyclospora (8-10 μm).

Finally, encountering a case of cryptosporidiosis should trigger a careful search for viral cytopathic changes of CMV because coinfection is common.

Treatment

Diarrheal illness caused by Cryptosporidium in the immunocompetent host is self-limited and does not require treatment in most cases. Patients with persistent diarrhea and oocyte shedding may be treated with nitazoxanide 500 mg twice daily for 3 days.185 Highly active antiretroviral therapy (HAART) is the treatment of choice for Cryptosporidium infection in HIV-infected individuals. The CDC recommends that nitazoxanide 500 to 1000 mg twice daily for 14 days be used in conjunction with HAART therapy.168,184 In patients with HIV cholangiopathy, HAART and nitazoxanide remain the cornerstones of treatment. Sphincterotomy should be performed in patients with papillary stenosis who present with abdominal pain or cholangitis.170

CONCLUSIONS

Infections affecting the GI tract are numerous, and an all-inclusive review is beyond the scope of this article. In this article we presented an overview of 6 infectious agents that may be misdiagnosed or altogether missed, especially if the clinical scenario is not taken into account at the time of histologic examination. A thorough clinical history that includes travel history, sexual practices, and associated conditions is as important as recognition of the patterns of inflammation associated with different organisms. An open dialogue between gastroenterologists and pathologists is crucial in order to diagnose these infections.

REFERENCES

Clues to uncommon infectious diagnoses Ali et al


1. Clinical features of chlamydial proctitis include
   a. Very painful papule at the inoculation site
   b. Rectal pain, tenesmus, purulent rectal discharge in 96% of patients in the secondary stage
   c. Perianal fistulas, when present, suggest Crohn’s disease and not LGV infection
   d. May present as a mass lesion on endoscopy, resembling a neoplasm

2. Classic histologic findings of syphilitic or chlamydial proctitis include
   a. intense lymphoplasmacytic and histiocytic expansion of the lamina propria
   b. marked crypt distortion and crypt abscesses
   c. multiple giant granulomas
   d. spiral shaped organisms consistent with spirochetes

True or False

3. Schistosomiasis mimics Crohn’s disease, the left colon is preferentially affected
4. Many patients with syphilitic or gonococcal proctitis are co-infected with chlamydia
5. Duodenal aspirates are superior to stool antigen tests to detect giardia.
6. Up to 50% of women can develop gonococcal proctitis without a history of rectal intercourse.
7. The diarrhea caused by Giardia is entirely due to malabsorption from the parasite’s coating of the small bowel mucosa.
8. The endoscopic appearance of syphilitic proctitis is diagnostic.
9. Cryptosporidium oocyst excretion is intermittent; at least 3 negative stool tests are needed to exclude infection
10. Typical small bowel histology in Whipple’s disease include pink foamy macrophages containing PAS positive, diastase resistant globular inclusions, dilated lacteals and fat droplets.
11. Cryptosporidia is often found in the surface epithelium of the small bowel, in contrast, when present in the colon, the organisms are found in the crypts
12. Endoscopic and histologic findings in gonococcal proctitis are usually mild and unimpressive.
13. S. ventriculi organism on a gastric biopsy resemble H. pylori
14. Silver staining is usually negative in biopsy specimens from syphilitic proctitis
15. There are no commercially available special stains that will accurately diagnose syphilitic or chlamydial proctitis on rectal biopsy.
16. Cryptosporidium only affects the small bowel and colon.