Ileitis: When It Is Not Crohn’s Disease

Steven DiLauro, MD and Nancy F. Crum-Cianflone, MD, MPH
1Division of Gastroenterology, Scripps Hospital, San Diego, CA
2Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, MD
3Division of Infectious Disease, Naval Medical Center San Diego, San Diego, CA

Abstract

Ileitis, or inflammation of the ileum, is often caused by Crohn’s disease. However, ileitis may be caused by a wide variety of other diseases. These include infectious diseases, spondyloarthropathies, vasculitides, ischemia, neoplasms, medication-induced, eosinophilic enteritis, and others. The clinical presentation of ileitis may vary from an acute and self-limited form of right lower quadrant pain and/or diarrhea, as in the majority of cases of bacterial ileitis, but some conditions (i.e., vasculitis or Mycobacterium tuberculosis) follow a chronic and debilitating course complicated by obstructive symptoms, hemorrhage, and/or extraintestinal manifestations. Ileitis associated with spondylarthropathy or nonsteroidal anti-inflammatory drugs is typically subclinical and often escapes detection unless further testing is warranted by symptoms. In a minority of patients with long-standing Crohn’s ileitis, the recrudescence of symptoms may represent a neoplasm involving the ileum. Distinguishing between the various forms of ileitis remains a test of clinical acumen. The diagnosis of the specific etiology is suggested by a detailed history and physical examination, laboratory testing, and ileocolonoscopy and/or radiologic data.

Keywords
Ileitis; Crohn’s disease; Infectious ileitis; Yersinia; Salmonella; Clostridium difficile; Typhlitis; Mycobacterium tuberculosis; Mycobacterium avium; actinomycosis; Anisakiasis; Cytomegalovirus; Histoplasmosis; Spondyloarthropathies; Vasculitis; Ischemia; Neoplasms; Drug-induced; NSAID enteropathy; Eosinophilic enteritis; Sarcoidosis; Amyloidosis; Backwash ileitis

Introduction

Ileitis, defined as inflammation of the ileum, is classically caused by Crohn’s disease (CD). However, a wide variety of diseases may be associated with ileitis. These include infectious...
diseases, spondyloarthropathies, vasculitides, ischemia, neoplasms, drug-related, eosinophilic enteritis, sarcoidosis, amyloidosis, and a variety of other conditions (Table 1). The diagnosis of the specific cause of ileitis is of paramount importance because misdiagnosis may result in delays or errors in patient management. This review describes each of these entities and provides a concise description of the differentiating characteristics from those of CD.

**Infectious Ileitis**

**Yersinia**

*Yersinia enterocolitica* and *Yersinia pseudotuberculosis* are acquired by ingestion of contaminated food (eg, raw vegetables, milk products, and raw pork intestines [chitterlings]) or water. Less often, acquisition occurs from contact with infected wild or domestic animals. Enterocolitis is the most common clinical manifestation and is characterized by diarrhea, low-grade fever, and abdominal pain lasting 1 to 3 weeks. Vomiting occurs in 15% to 40% of cases. Severe *Yersinia* infections may cause ileal perforation and rectal bleeding. Other manifestations include reactive polyarthritis (especially among HLA-B27–positive patients) and septicemia with metastatic complications (especially among immunosuppressed patients or those with iron overload). Clinical illness results from the organism penetrating the mucosa and invading the underlying intestinal lymphoid tissue, particularly Peyer’s patches.

Diagnosis is by stool culture. Radiographically, a thickened and nodular mucosal pattern in the terminal ileum is seen. In contrast to CD, fistula formation and fibrotic stenosis are not observed. Endoscopic features of *Yersinia* include aphthoid lesions of the cecum and terminal ileum with round or oval elevations with ulcerations. The ulcers are mostly uniform in size and shape, in contrast to CD [1].

*Yersinia* can also lead to mesenteric adenitis with terminal ileitis mimicking acute appendicitis, which most commonly occurs in older children and adults. Presentation is right lower quadrant pain with fever, whereas diarrhea is absent or mild. Symptoms may lead to an unnecessary appendectomy; surgery discloses a normal appendix, edematous thickening of the ileum and cecum, and enlarged mesenteric lymph nodes. Sonographic or CT examination may provide clues to the diagnosis: (sub)mucosal bowel wall thickening with enlarged mesenteric lymph nodes [2]. By contrast, ileocecal CD usually has transmural inflammation giving rise to inflamed, noncompressible fat surrounding the ileum.

**Salmonella**

Nontyphoidal *Salmonella*, the most commonly identified cause of foodborne illness in the United States, occurs after ingestion of contaminated food products of animal origin (eg, eggs, dairy products, poultry, or ground meat). Other food items (ie, unpasteurized orange juice and peanut butter) and exposure to exotic pets have also been implicated [3]. Unlike nontyphoidal *Salmonella*, enteric fever (*Salmonella typhi* and *Salmonella paratyphi*) is transmitted person-to-person.

*Salmonella* infections most often cause self-limited acute gastroenteritis, but may cause bacteremia, vascular infections, and/or a chronic carrier state. Because *Salmonella* can affect the regional mesenteric lymph nodes, adenitis and terminal ileitis may occur, mimicking acute appendicitis. The CT findings of *Salmonella* ileitis include circumferential and homogenous thickening of the terminal ileum wall spanning a 10- to 15-cm segment [4]. Differentiating other causes of ileitis, including CD, may be problematic on CT scan or endoscopy; biopsy is useful, showing acute ileitis. The definite diagnosis of *Salmonella* is based on culture.
Clostridium difficile

*Clostridium difficile* typically causes antibiotic-associated colitis. Small-bowel infections are rare, but well-described [5,6••]. Ileal *C. difficile* infection caused by hypervirulent BI/NAP1/027 strains has been reported [5]. Cases may occur after colectomy and present with low-grade fevers, abdominal or pelvic pain, and increased ileostomy output [6••]. Diagnosis is by visualizing pseudomembranes and/or stool studies showing toxin-producing organisms.

Typhlitis—Typhlitis (from the Greek word “typhlon” or cecum) is an acute, life-threatening inflammatory condition of the cecum and ascending colon that may also affect the terminal ileum. It most often occurs in patients with immunocompromising conditions. The exact pathogenesis is unknown, but probably involves damaged mucosa (from chemotherapy, radiation therapy, and/or leukemic infiltration), profound neutropenia, impaired host defenses, and possibly ischemia.

Clinically, it manifests as right lower quadrant pain, fever, nausea, vomiting, bloody diarrhea, and/or evidence of peritoneal inflammation. Early diagnosis is important, because without treatment the inflammatory process can progress rapidly to transmural necrosis with subsequent perforation.

The diagnosis is suggested by finding a thickened bowel wall involving the ileocecal region in an immunosuppressed or neutropenic patient. CT or ultrasound findings include cecal and terminal ileal wall thickening, often with decreased attenuation suggesting edema, pericolonic fluid collection or fat stranding, pneumatosis coli, and intramural low-attenuation regions indicative of edema or necrosis [7]. The degree of bowel wall thickening typically correlates with the severity of disease [8]. Endoscopy during pancytopenia is usually contraindicated. Histologic examination of surgically removed bowel shows mononuclear infiltrates and a variety of bacteria and fungi invading the affected bowel wall.

Mycobacterium tuberculosis

Extrapulmonary tuberculosis (EPTB) accounts for about 20% of cases in immunocompetent patients and 50% of cases in HIV-positive individuals; intestinal TB (ITB) is the sixth most prevalent form of EPTB. Bovine TB (*Mycobacterium bovis*), caused by contaminated dairy products, is a rare cause of ITB that exists where pasteurization practices are lacking.

ITB develops most commonly after ingesting infected sputum in cases of active pulmonary TB. Prior to effective therapy, up to 70% of TB cases developed ITB via this route. Other routes include hematogenous spread or contiguous spread from adjacent organs. The ileocecal area and jejunileum are the most common sites involved because of high densities of lymphoid aggregates and physiologic stasis. In studies, the ileocecal region has been involved in about 90% of ITB cases [9].

ITB is thought to arise by the same pathophysiologic sequence as pulmonary TB; initial infection of macrophages followed by multiplication, subsequent caseation necrosis, and host inflammatory response. The intestinal lesions can be ulcerative (most common), hypertrophic or ulcerohypertrophic, or fibrous. With chronic inflammation, the ileal wall may become stenotic or fibrotic with stricture formation or may form masses (tuberculomas) leading to intestinal obstruction or perforation. Rarely, ITB presents with malabsorption and a protein-losing enteropathy.

Symptoms include fever, night sweats, abdominal pain, a palpable mass, altered bowel habits, and/or bleeding [10••,11•]. Because symptoms are nonspecific and about 70% of ITB cases have a normal chest radiograph, clinicians must have a high suspicion for diagnosis.
Several disease processes, as described in this review, resemble TB ileitis. A notoriously difficult dilemma is to differentiate ITB from CD, especially in geographic regions where both diseases are prevalent. Features that favor ITB are high fevers in the absence of an intra-abdominal abscess, lack of perianal disease, and shorter duration of symptoms [12]. Serologic tests such as anti-\textit{Saccharomyces cerevisiae} antibodies (ASCA) do not reliably discriminate between ITB and CD [13].

Contrast-enhanced CT, MRI, and ultrasound may aid in differentiating ITB from CD. Findings supportive of ITB in the ileocecal region include asymmetric wall thickening and enlarged necrotic lymph nodes [14]. In CD, wall thickening is usually symmetric and concentric, with fibrofatty proliferation of the mesentery known as “creeping fat.”

Endoscopic features of ITB are similar to CD; both may have ulcerations, pseudopolyps, luminal narrowing, strictures, and nodularity of the ileocecal valve [15••]. As in CD, ITB may involve any part of the gastrointestinal (GI) tract but the esophagus, stomach, rectosigmoid, and anal canal are much less commonly affected. In a recent study, clinical parameters more common in CD were anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance that involved fewer than four segments; a patulous ileocecal valve, transverse ulcers, and pseudopolyps were observed more frequently in patients with ITB [16].

It can be challenging to diagnose ITB on endoscopic biopsy. The typical caseating granulomas and acid-fast bacilli (AFB) stained by Ziehl-Neelsen are present in less than 30% of cases. PCR may provide a rapid diagnosis, but endoscopic biopsy material has sensitivities of only 40% to 75% [17]. A positive TB culture remains the gold standard, but diagnosis may be delayed (3–8 weeks). Apart from finding AFB, differentiating ITB and CD can be difficult. Histologic features encountered more frequently in ITB are granulomas that are confluent, larger (> 200 \mu m), and multiple in number (> 5 per section) [18].

\textbf{Mycobacterium avium-intracellulare complex}

Disseminated \textit{Mycobacterium avium-intracellulare} complex (MAC) occurs predominantly in persons with AIDS or immunosuppressing conditions. The bacteria are acquired by ingestion or inhalation with intestinal localization as a consequence of direct inoculation, shedding from the lungs, or hematogenous spread. The main symptoms (diarrhea, malabsorption, and fever) resemble Whipple’s clinically [19]. MAC infections are also called pseudo-Whipple disease because of diffuse mucosal fold thickening in the jejunum and histiocytic aggregates that stain positive with periodic acid–Schiff (PAS).

MAC also mimics CD with terminal ileitis. Distinguishing features of MAC are diffuse granulomatous involvement of the terminal ileum, positive stain and culture for MAC, and response to antimycobacterial therapy. Barium examination often demonstrates a separation of small bowel segments caused by mesenteric lymphadenopathy. In terms of deciphering \textit{M. tuberculosis} and MAC infections radiographically, diffuse jejunal wall thickening and enlarged soft-tissue attenuating lymph nodes with hepatosplenomegaly suggest disseminated MAC infection, whereas focal abdominal lesions with low-attenuating lymph nodes suggest \textit{M. tuberculosis} [20].

Diagnosis is suggested by the clinical and radiographic features discussed previously. Isolation of MAC from the blood or another sterile site (eg, lymph node, bone marrow, liver, spleen) establishes the diagnosis. MAC in the stool alone does not make the diagnosis because it may be a colonizer.
**Actinomycosis**—Actinomycosis is a chronic bacterial infection caused by a heterogenous group of anaerobic gram-positive bacteria. It is characterized by contiguous spread, suppurative and granulomatous inflammation, and formation of multiple abscesses and fistulous sinus tracts that may discharge sulfur granules. The three main clinical forms of this disease are cervicofacial, thoracic, and abdominopelvic, with the abdominopelvic form accounting for 10% to 20% of cases.

Because the bacteria are normal microflora of the GI tract and are not virulent, injury (from trauma, surgery, or foreign body ingestion) to the mucosa is required to cause disease. The ileocecal region is most commonly involved, perhaps because of physiologic stasis. Symptoms follow an indolent course with right lower abdominal pain, mass, and/or fever. Contrast-enhanced CT imaging reveals an infiltrative mass invading surrounding tissues with focal areas of decreased attenuation [21]. Lymphadenopathy is uncommon. Because symptoms and signs are nonspecific, the diagnosis is usually delayed with only 10% of cases diagnosed preoperatively [22].

**Anisakiasis**—GI anisakiasis is acquired after ingestion of raw marine fish or squid infested with larvae of the roundworm *Anisakis simplex* (herring worm) or *Pseudoterranova decipiens* (cod worm). Anisakiasis is most common in Japan, but also occurs in the United States. Symptoms include violent and relatively acute epigastric or abdominal pain caused by penetration of larvae through the stomach or lower small intestine mucosa, especially the ileum. Nausea, vomiting, and fever may occur. Symptoms begin within 48 hours of ingestion, and quickly self-resolve or become chronic. Chronic infection may provoke an eosinophilic granulomatous response in the ileocecal region, causing masses with obstruction, or may produce nonspecific abdominal symptoms. Cases may mimic appendicitis or regional enteritis. Barium studies show narrowing of the intestinal lumen in areas with mucosal inflammation or occasionally a filling defect, suggesting a worm. Upper endoscopy may reveal edematous mucosa with ulcerations and a thin, stringlike worm penetrating the gastric wall [23]. Gastroscopic removal of worms often hastens symptom resolution.

**Cytomegalovirus**—Cytomegalovirus (CMV) infection of the GI tract most frequently causes esophageal ulcers and colitis, whereas small bowel involvement occurs in only 4% of GI cases [24]. Disease usually occurs in immunosuppressed patients, including those with AIDS or transplant recipients. Of note, AIDS patients with CMV often have concurrent infections (eg, MAC). Symptoms include fever, abdominal pain, watery diarrhea, or bleeding. Endoscopic findings include erosions, ulceration, and mucosal hemorrhage; a mass lesion may also occur. The prototypical ulceration has a well-defined, punched-out appearance. The pathogenesis involves ischemic mucosal injury secondary to infection of the vascular endothelial cells. The diagnosis is by demonstration of typical CMV inclusion bodies by routine histologic examination, culture, staining for CMV antigen, or DNA [25].

**Histoplasmosis**—*Histoplasma capsulatum* is a dimorphic fungus that exists in mold form in soil contaminated with bird or bat droppings, and transforms to yeast form when inhaled. Infection is usually asymptomatic or results in a self-limited respiratory illness. GI involvement occurs in 70% to 90% of those with disseminated histoplasmosis as determined by autopsy studies, and may be misdiagnosed as inflammatory bowel disease (IBD) or malignancy. Dissemination to the GI tract occurs via the reticuloendothelial system by tissue macrophages that accumulate in lymphoid aggregates and Peyer’s patches. This likely explains why the terminal ileum is commonly affected [26]. Symptoms include diarrhea, weight loss, fever, and/or abdominal pain. Patients may also have GI bleeding, bowel perforation, or obstruction from ileocecal masses or enlarged retroperitoneal lymph nodes. Hepatomegaly and/or splenomegaly occur in 30% to 100% of cases.
Lesions on endoscopy or laparotomy range from segmental or continuous superficial mucosal ulcerations with erythema or edema, to deep ulcers with or without frank perforation [27]. Intraabdominal lymphadenopathy is seen on CT in two thirds of patients. Diagnosis is by positive fungal culture or tissue biopsy showing diffuse lymphohistiocytic infiltrates in the mucosa and submucosa. Gomori methenamine or Grocott silver stains demonstrate \textit{H. capsulatum} organisms, which appear as 2-µ to 4-µ round, budding yeast.

**Ileitis Associated with Spondyloarthropathies**

Spondyloarthropathies (SpA) are characterized by inflammation of axial joints, asymmetric oligoarthritis, and enthesitis. SpA include ankylosing spondylitis (AS), reactive arthritis, arthritis associated with IBD and psoriasis, and undifferentiated SpA. SpA are associated with extra-articular manifestations, including uveitis and genital, skin, and inflammatory gut lesions. Inflammatory gut lesions occur in up to two thirds of patients and usually affect the terminal ileum. In most cases, however, inflammation is subclinical and escapes detection unless colonoscopic biopsy is warranted by symptoms. The histologic appearance of lesions is either acute or chronic, and is not related to disease duration. The acute form is mainly seen in patients with reactive arthritis and mimics bacterial ileitis (preserved architecture and neutrophil dominance). The chronic form is more prevalent in AS and undifferentiated SpA, and may be indistinguishable from CD (disturbed mucosal architecture, irregular and blunted villi, distorted crypts, and lymphocyte dominant). In some cases, aphthoid ulcers and sarcoidlike granulomas are present [28,29].

Distinguishing ileitis of SpA and CD can be difficult. The main distinctions are that SpA does not usually cause radiologically detectable abnormalities of the terminal ileum and most patients have asymptomatic gut inflammation. HLA-B27 testing may be helpful and is positive in more than 80% of cases of AS versus 10% to 35% of CD patients. In most cases of CD, intestinal symptoms precede or coincide with the joint manifestations. However, patients with SpA may develop GI symptoms after the appearance of joint symptoms. Finally, the pattern of joint involvement may be a distinguishing feature.

In SpA, a relationship exists between gut and joint findings: chronic GI lesions are associated with more advanced sacroiliitis, spondylitis, and peripheral arthritis [28]. Remission of articular inflammation correlates with disappearance of gut inflammation, whereas the persistence of joint inflammation is mostly associated with the persistence of gut inflammation.

**Vasculitides**

Vasculitides that are primary to the intestine or occur secondary to systemic vasculitis represent a rare cause of ileitis. The most common vasculitides with GI involvement include the medium-sized vessel vasculitides of systemic lupus erythematosus and polyarteritis nodosa, and the small vessel vasculitides of Henoch-Schönlein purpura (HSP) and Behçet's disease. Visceral vasculitis presents with abdominal pain, nausea, vomiting, diarrhea, and GI bleeding. Small-vessel or leukocytoclastic vasculitis is characterized by mucosal ischemia, whereas vasculitis involving medium-size or larger vessels may more likely result in transmural involvement, leading to peritoneal findings or perforation. Other serious complications include obstruction, protein-losing enteropathy, and intussusception. Moreover, patients with acquired antiphospholipid antibodies and systemic lupus erythematosus or related disorders are at increased risk for mesenteric artery thrombosis and subsequent bowel infarction [30].

Among the vasculitides, HSP deserves mention. HSP is an IgA-mediated vasculitis associated with palpable purpura predominantly on the lower extremities and buttocks.
accompanied by arthralgias, abdominal pain, and occasionally nephritis. HSP is rare in adults as compared to children (90% of patients are < 10 years old). Common GI presentations are colicky right lower quadrant pain and GI bleeding. In 10% to 15% of patients, GI symptoms precede cutaneous lesions by ≥ 4 weeks. Induction of IgA in the abundant Peyer patches may be involved in the pathogenesis of ileitis and subsequent spread to other involved sites (skin and kidney) because of antigen mimicry. The endoscopic findings in the ileum may be dramatic, with marked mucosal congestion, hemorrhagic necrosis, and ulceration consistent with ischemia [31]. Classic IgA deposition and leukocytoclastic vasculitis in cutaneous, renal, or bowel tissue confirms the diagnosis. As for CD, in a small number of cases, cutaneous leukocytoclastic vasculitis has been reported; however, the skin manifestations are most commonly erythema nodosum and pyoderma gangrenosum.

Diagnosing vasculitis is typically based on evidence of generalized disease activity elsewhere. For example, although mucocutaneous manifestations are common in CD, the recurrent and severe aphthous stomatitis and genital ulcers observed in Behçet’s are a notable feature of this form of vasculitis. Plain radiographic studies may reveal nondiagnostic findings such as segmental bowel dilation, air-fluid levels, “thumbprinting” or narrowing of the lumen, and pseudoobstruction. Contrast-enhanced CT may show engorgement of mesenteric vessels (comb sign), multisegmental areas of symmetric bowel thickening (> 3 mm), abnormal bowel-wall enhancement (a double halo or target sign), and ascites [32]. These findings are also seen in CD; however, the presence of creeping fat of the mesentery, small mesenteric lymph nodes, and complications of CD, including abscess, fistula, and/or perianal disease, are differentiating features.

**Ischemia**

Other conditions aside from vasculitis cause ischemic ileitis. An important cause is nonocclusive mesenteric ischemia (NOMI) as a result of splanchnic hypoperfusion and vasospasm observed predominantly in elderly patients with atherosclerotic vascular disease in the setting of low-flow states (eg, shock, heart failure, drugs such as cocaine). The microvasculature is patent in NOMI, but blood flow is inadequate to meet intestinal tissue demands. Because the ileocolic branches are the longest branches of the superior mesenteric artery, the ileocecal region is most susceptible to ischemia from poor perfusion [33].

Early diagnosis is difficult because of the nonspecific symptoms (abdominal pain, nausea, vomiting, and ileus). Contrast-enhanced CT reveals patent mesenteric vessels and bowel wall thickening. Ileocolonoscopy reveals segmental distribution with a clear boundary between the injured and uninvolved region. Lesions range from marked edematous mucosa with loss of clear vascular vessel pattern or having a dusky pattern to scattered discrete ulcerations and friability [33].

**Small-Bowel Neoplasms**

The mucosa of the small intestine encompasses about 90% of the luminal surface area of the digestive system, but accounts for only 2% of GI malignant neoplasms. Neoplastic processes with a propensity for the ileum are adenocarcinoma, lymphoma, and carcinoid tumor. Small-bowel neoplasms may occur sporadically, in association with genetic diseases (familial adenomatous polyposis coli, hereditary nonpolyposis colorectal cancer, or Peutz–Jeghers syndrome), or in association with chronic intestinal inflammatory disorders (CD or celiac sprue).

The diagnosis is often made late because of their uncommon occurrence and nonspecific symptoms. The CT appearance of ileal adenocarcinoma is an annular and constricting lesion
involving a short segment of bowel. For patients with carcinoid, CT reveals an ill-defined spiculated mass with a stellate pattern containing calcification. Lymphoma most commonly manifests as single or multiple segmental areas of markedly thickened (1.5–7 cm) circumferential thickening, or may ulcerate with formation of a fistulous tract to adjacent bowel loops, mimicking CD [34].

The risk of GI cancer is elevated in patients with IBD (eg, 60-fold higher compared to the general population). Small-bowel adenocarcinoma complicating CD is predominantly seen in men, in patients with excluded bowel loops, and at the distal ileum in an area of active disease [35]. Carcinoid tumors have also been described in association with CD, and these cases tend to be malignant and have a worse prognosis [36]. Ileal carcinoid tumor should be suspected in elderly CD patients presenting with obstructive symptoms. In general, the presence of suspected ileal CD refractory to medical therapy should alert clinicians to the possibility of a small-bowel neoplasm. When technically feasible, ileoscopy with biopsy may help distinguish between the two and guide early diagnosis and treatment.

**Drug-Related Ileitis**

**Nonsteroidal anti-inflammatory drugs**

Although the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in the stomach and duodenum are well established, only recently were NSAIDs shown to cause small-bowel injury (NSAID enteropathy). An autopsy study detected small-intestine ulcers in 8.4% and mucosal breaks in 55% of patients who recently used NSAIDs compared to 0.6% and 7%, respectively, in nonusers [37]. In a video capsule endoscopy (VCE) study, 71% of long-term NSAID users had jejunal or ileal mucosal injury [38]. Virtually all classes of NSAIDs that block both cyclooxygenase (COX)-1 and COX-2 have been implicated. Whether COX-2–selective inhibitors cause similar effects is unclear. In an attempt to decrease gastroduodenal side effects of NSAIDs, the use of extended-release or enteric-coated formulations may have shifted the damage to the distal small intestine and colon. Hold-up of pills at the ileocecal valve, partially because of the inhibition of prostaglandin that suppresses normal propagation, may lead to ileitis.

The pathogenesis involves a combination of biochemical events that compromise enterocyte integrity and increase intestinal permeability. These include COX-1 inhibition (restricts mucosal blood flow), COX-2 inhibition (through an unknown immunomodulatory mechanism), and the topical effects of NSAIDs (disrupt membrane phospholipids and uncouple mitochondrial oxidative phosphorylation). This increased permeability allows exposure to luminal substances (eg, bacteria, intraluminal toxins, bile acids), thereby leading to inflammation.

Although NSAID-related inflammation by itself rarely has clinical consequences, in some patients, it may induce erosions or ulceration, protein-losing enteropathy, or occasionally bleeding, perforation, strictures, or obstruction. A type of stricture known as “diaphragm disease” is characteristic, if not pathognomonic, for NSAID-induced damage. These diaphragms are numerous, thin-walled, concentric, septate-like mucosal projections that narrow the intestinal lumen to pinhole size. They are characterized histologically by prominent submucosal fibrosis without evidence of vascular involvement [39]. The adjacent mucosa between diaphragms is usually normal. As a potential cause of subacute obstruction, these strictures are difficult to diagnose because they may appear as exaggerated plica circularis.

Several indirect diagnostic tests indicating NSAID-induced inflammation and increased permeability are available, but are nonspecific and abnormal in a variety of other conditions.
However, these methods show that long-term NSAID use is associated with enhanced migration of $^{111}$indium-labeled leucocytes, increased fecal $^{111}$indium secretion, and increased fecal calprotectin shedding in more than 50% of patients [40,41]. Diagnosis may also be made using direct methods such as VCE, ileocolonoscopy, and balloon enteroscopy. Regarding these modalities, NSAID enteropathy involving the ileum is suspected in patients with a history of NSAID use, findings of erosion, ulcer, and/or typical diaphragm-like strictures, clinical improvement in symptoms and/or endoscopic findings by cessation of NSAID use (except for diaphragm disease), and after exclusion of other causes [42•]. Differentiating NSAID-induced versus CD ileitis may be complicated by the fact that the two entities may coexist, or that NSAIDs can flare CD. Helpful distinguishing features are that CD classically causes long, thick inflammatory strictures rather than thin fibrotic diaphragms and that ulcers are often deeper, longitudinal, and more irregular than the sharply demarcated lesions of NSAID enteropathy.

Other causes of drug-related ileitis

Potassium chloride (KCL) tablets are a rare cause of ileitis. In the 1960s, cases of small-intestinal ulceration were attributed to the use of enteric-coated KCL [43]. In 1965, this form of the drug was withdrawn from the market; the incidence was greatly diminished, but not eliminated, with the development of slow-release formulations. The clinical presentation, diagnosis, and management are identical to NSAID-induced ileitis.

Parenteral gold therapy has also been associated with enterocolitis, with edema and ulceration limited to the ileum [44]. This rare complication is most commonly seen in women and can occur shortly after starting therapy for rheumatoid arthritis. Other drugs that may cause ileitis include oral contraceptives, ergotamine, digoxin, and enteric-coated hydrochlorothiazide with potassium.

Infiltrative Causes of Ileitis

Eosinophilic gastroenteritis

Eosinophilic gastroenteritis (EG) is a rare disorder characterized by prominent eosinophilic infiltration of the GI tract in the absence of known causes of eosinophilia (eg, parasitic infection, malignancy, and drug reaction). EG commonly involves the stomach and small intestine, but occasionally causes diffuse colonic involvement.

Although the etiology is unknown, a personal or family history of food allergies and atopic disorders is present in 50% to 70% of cases. The proposed pathogenesis is alteration in the mucosal integrity, resulting in localization of various antigens in the gut wall, thereby inducing tissue and blood eosinophilia [45].

Clinical features vary depending on the layer(s) and extent of bowel involved with eosinophilic infiltration (mucosa, muscle, and/or subserosa). Small-bowel EG may present with abdominal pain, diarrhea, or malabsorption. Ileal strictures and bowel obstruction may occur with muscle layer involvement, and eosinophilic ascites manifests if the serosa is affected. Patients may have peripheral eosinophilia or elevated serum IgE levels.

Radiographic changes are variable, but may show bowel wall thickening, obstruction, or ascites. Definitive diagnosis requires histologic confirmation of eosinophilic infiltration in tissue obtained on endoscopy or surgery. The endoscopic findings vary from normal mucosa to mild erythema, nodularity, and frank ulceration. Diffuse enteritis with complete loss of villi, submucosal edema, and fibrosis may be present. Multiple biopsies are required because of the patchy nature of the disease, and full-thickness surgical biopsies may be necessary if disease is confined to the muscle layer [45]. CD can usually be differentiated by the typical
architectural distortion that is not found in EG. Rarely, CD is associated with peripheral eosinophilia and/or an eosinophil-rich tissue infiltrate [46].

Sarcoidosis

Sarcoidosis is a chronic, multisystemic, granulomatous disease most commonly involving the lung, lymph nodes, spleen, and skin. Clinically recognizable GI involvement occurs in 0.1% to 0.9% of patients, although the incidence of subclinical disease may be higher. The stomach is the most common portion of the GI tract involved, whereas the small bowel is the least common. About 50% of the cases of small-bowel disease occur in the context of generalized disease, with symptoms of nonbloody diarrhea and colicky abdominal pain. Weight loss, anorexia, low-grade fever, and weakness may be present [47]. In patients with sarcoidosis and suspected ileitis, ileocolonoscopy with biopsy revealing noncaseating granulomas containing multinucleated giant cells is nearly diagnostic. Proper interpretation of ileal biopsies is crucial because mycobacterial infections, histoplasmosis, CD, and lymphoma are granulomatous conditions that mimic sarcoidosis.

Amyloidosis

Amyloidosis is characterized by the extracellular deposition of protein in an abnormal fibrillar form. Several different types of amyloidosis exist, each defined by the identity of their respective fibril precursor protein. The three main types are primary, secondary, and dialysis-related amyloidosis. Primary amyloidosis is associated with plasma cell dyscrasias, and secondary amyloidosis is associated with inflammatory, infectious, and neoplastic diseases. Amyloid deposition in the GI tract is greatest in the small bowel and results from either mucosal or neuromuscular infiltration. Most patients have subclinical disease; bleeding (from vascular friability or mucosal lesions), intestinal dysmotility, malabsorption (related to mucosal infiltration or bacterial overgrowth), or protein-losing enteropathy may occur [48••]. Endoscopic findings include a fine granular appearance, polypoid protrusions, erosions, ulcerations, mucosal friability, and thickening of the wall. Rarely, tumor-forming deposits called amyloidoma localized to the small intestine are found, mimicking adenocarcinoma. Biopsies of the affected organ, fat, or rectum reveal amyloid deposits that stain with Congo red, producing a pathognomonic red-green birefringence under cross-polarized light microscopy.

Other Causes

Backwash ileitis

Backwash ileitis (BWI) refers to inflammation in the distal few centimeters of terminal ileum in patients with ulcerative colitis [49]. Ileitis is caused by reflux of colonic contents, and when present, may raise the differential diagnosis of CD. In general, the severity of ileal inflammation parallels the severity of colonic activity, being more common with pancolitis and cecal involvement. Associations with an aggressive disease course, primary sclerosing cholangitis, and following subtotal colectomy for ulcerative colitis have been reported. Definite diagnostic criteria for BWI have not been determined, but it should be restricted to an active enteritis that involves the ileum in a contiguous pattern from the cecum and has a similar or greater degree of inflammation. Distinguishing Crohn’s ileocolitis from pancolicetative colitis with BWI is otherwise straightforward when granulomas are present on histology or aphthous ulcers, cobblestoning, and skip lesions are seen endoscopically, but can be a clinical challenge when these features are absent.

Endometriosis

Endometriosis is defined by the presence of endometrium outside the uterus, and most commonly involves nulliparous women 25 to 45 years of age. Disease occurs from
retrograde menstruation of endometrial tissue implanted on the serosa of abdominal organs (implantation theory) and/or by transformation of pluripotential peritoneal mesothelium (coelomic metaplasia theory). Although the rectosigmoid colon is the most common site (85% of cases), the ileum is involved in 1% to 7% of patients [50•]. Ileal endometriosis presents most commonly with intermittent obstruction, constipation, or vague abdominal and/or pelvic pain. In some individuals, the predominant complaints of right lower quadrant pain, diarrhea, and/or fever may mimic CD. Endometriotic tissue in the ileum may undergo cyclic hormonal changes, with periodic hemorrhage. When the muscularis propria is involved, there is marked muscular hypertrophy and a fibrotic reaction in bowel wall, leading to an appearance of an extrinsic mass effect or segmental narrowing. On tissue biopsy, if only the mucosa is sampled, the typical lesions in the muscularis propria may be missed. In this regard, radiographic imaging can be helpful. In indeterminate cases, diagnostic laparoscopy is recommended [51].

Conclusions

Ileitis may present acutely with right lower quadrant pain and/or diarrhea, or with chronic obstructive symptoms and bleeding. Although CD often is the etiology of ileitis, many conditions can involve the ileum, including infections localizing in the distal ileum due to the presence of Peyer’s patches and physiologic stasis. Beyond infections, systemic disorders including spondyloarthropathies, vasculitides, ischemia, and amyloidosis as well as medications may lead to ileal inflammation. The diagnosis of the cause of ileitis is of paramount importance because misdiagnosis may result in critical delays or errors in management. The specific diagnosis is suggested by the clinical disease course, presence of other systemic manifestations, appearance of imaging and endoscopic findings, and histologic results.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance


6. Causey MW, Spencer MP, Steele SR. Clostridium difficile enteritis after colectomy. Am Surg 2009;75:1203–1206. [PubMed: 19999913] This article reviews the current available literature on C. difficile enteritis by presenting three cases occurring after colectomy. The authors emphasize the importance of recognizing this potentially serious condition in postoperative colectomy patients who present with low-grade fevers, abdominal or pelvic pain, and increased ileostomy output.


45. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol 2008;103:776–787. [PubMed: 18076735] This article provides a comprehensive overview of amyloidosis and small bowel involvement. The authors emphasize the need for a high index of
clinical suspicion for this rare diagnosis in certain high-risk groups (ie, patients with chronic inflammatory diseases, certain infections, or malignancy, and patients with renal disease on dialysis).


### Table 1

**Selected causes of ileitis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Yersinia</em> spp.</td>
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<td></td>
<td><em>Salmonella</em> spp.</td>
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<tr>
<td></td>
<td><em>Clostridium difficile</em></td>
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<tr>
<td></td>
<td>Typhlitis</td>
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<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td></td>
<td><em>Mycobacterium avium</em></td>
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<td></td>
<td>Actinomycosis</td>
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<td></td>
<td>Anisakiasis</td>
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<td></td>
<td>Cytomegalovirus</td>
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<td></td>
<td><em>Histoplasma capsulatum</em></td>
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<tr>
<td><strong>Spondyloarthropathies</strong></td>
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<tr>
<td></td>
<td>Ankylosing spondylitis</td>
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<tr>
<td></td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td></td>
<td>Arthritis associated with inflammatory bowel disease</td>
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<tr>
<td></td>
<td>Psoriasis with arthritis</td>
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<tr>
<td></td>
<td>Undifferentiated spondylarthropathy</td>
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<tr>
<td><strong>Vascular</strong></td>
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<td></td>
<td>Vasculitides</td>
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<td></td>
<td>Systemic lupus erythematosus</td>
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<td></td>
<td>Polyarteritis nodosa</td>
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<td></td>
<td>Henoch-Schönlein purpura</td>
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<td></td>
<td>Behçet's disease</td>
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<td></td>
<td>Other vasculitides: Churg-Strauss syndrome, rheumatoid arthritis vasculitis,</td>
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<tr>
<td></td>
<td>Wegener granulomatosis, lymphomatoid granulomatosis, giant-cell</td>
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<tr>
<td></td>
<td>arteritis, Takayasu arteritis, thromboangiitis obliterans</td>
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<tr>
<td><strong>Ischemia</strong></td>
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<tr>
<td><strong>Small-bowel neoplasms</strong></td>
<td></td>
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<tr>
<td></td>
<td>Cecal or small-bowel (ileal) adenocarcinoma</td>
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<tr>
<td></td>
<td>Lymphoma</td>
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<tr>
<td></td>
<td>Carcinoid tumor</td>
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<tr>
<td></td>
<td>Lymphosarcoma</td>
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<td></td>
<td>Metastatic cancer</td>
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<tr>
<td><strong>Drug-related</strong></td>
<td></td>
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<td></td>
<td>NSAID enteropathy</td>
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<td></td>
<td>Other drugs: KCL tablets, parenteral gold therapy, oral contraceptives,</td>
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<tr>
<td></td>
<td>ergotamine, digoxin, diuretics, antihypertensives</td>
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<tr>
<td><strong>Infiltrative</strong></td>
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<tr>
<td></td>
<td>Eosinophilic enteritis</td>
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<td></td>
<td>Sarcoidosis</td>
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<td></td>
<td>Amyloidosis</td>
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<tr>
<td><strong>Other causes</strong></td>
<td></td>
</tr>
</tbody>
</table>
Backwash ileitis due to ulcerative colitis
Endometriosis
Radiation enteritis

KCL—potassium chloride; NSAID—nonsteroidal anti-inflammatory drugs.