Published in final edited form as:

Curr Gastroenterol Rep. 2010 August ; 12(4): 249–258. doi:10.1007/s11894-010-0112-5.

Ileitis: When It Is Not Crohn's Disease

Steven DiLauro, MD¹ and Nancy F. Crum-Cianflone, MD, MPH^{2,3}

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 (ie, 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

Corresponding author: Nancy Crum-Cianflone, MD, MPH, Clinical Investigation Department (KCA), Naval Medical Center San Diego, 34800 Bob Wilson Drive, Suite. 5, San Diego, CA 92134-1005. nancy.crum@med.navy.mil, Phone: 619/532-8134/40; FAX: 619/532-8137.

Disclosure

The content of this publication is the sole responsibility of the authors and does not necessarily reflect the views or policies of the National Institutes of Health or the Department of Health and Human Services, the Department of Defense, or the Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government. This work is original and has not been published elsewhere.

Dr. Crum-Cianflone has received research funding from the National Institute of Allergy and Infectious Diseases. No other potential conflict of interest relevant to this article was reported.

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, pericolic 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 jejunioileum 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-*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 µm), and multiple in number (> 5 per section) [18].

***Mycobacterium avium-intracellulare* complex**

Disseminated *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 *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 *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 heterogeneous 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]. Gastrosopic 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 *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 typically 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}In -labeled leucocytes, increased fecal ^{111}In 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 pan-ulcerative 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

1. Matsumoto T, Iida M, Matsui T, et al. Endoscopic findings in *Yersinia enterocolitica* enterocolitis. *Gastrointest Endosc* 1990;36:583–587. [PubMed: 2279647]
2. Puylaert JB, Van der Zant FM, Mutsaers JA. Infectious ileocectitis caused by *Yersinia*, *Campylobacter*, and *Salmonella*: clinical, radiological and US findings. *Eur Radiol* 1997;7:3–9. [PubMed: 9000386]
3. Crum-Cianflone NF. Salmonellosis and the gastrointestinal tract: more than just peanut butter. *Curr Gastroenterol Rep* 2008;10:424–431. [PubMed: 18627657]
4. Balthazar EJ, Charles HW, Megibow AJ. *Salmonella* and *Shigella*-induced ileitis: CT findings in four patients. *J Comput Assist Tomogr* 1996;20:375–378. [PubMed: 8626893]
5. Lavalley C, Laufer B, Pepin J, et al. Fatal *Clostridium difficile* enteritis caused by the BI/NAP1/027 strain: a case series of ileal *C. difficile* infections. *Clin Microbiol Infect* 2009;15:1093–1099. [PubMed: 19681954]
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.

7. Benya EC, Sivit CJ, Quinones RR. Abdominal complications after bone marrow transplantation in children: sonographic and CT findings. *AJR Am J Roentgenol* 1993;161:1023–1027. [PubMed: 8273603]
8. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol* 2001;19:756–761. [PubMed: 11157028]
9. Leung VK, Law ST, Lam CW, et al. Intestinal tuberculosis in a regional hospital in Hong Kong: a 10-year experience. *Hong Kong Med J* 2006;12:264–271. [PubMed: 16912352]
10. Donoghue HD, Holton J. Intestinal tuberculosis. *Curr Opin Infect Dis* 2009;22:490–496. [PubMed: 19623062] This article is an excellent review of the epidemiology, presentation, diagnostic techniques, and management of intestinal TB.
11. Das K, Ghoshal UC, Dhali GK, et al. Crohn's disease in India: a multicenter study from a country where tuberculosis is endemic. *Dig Dis Sci* 2009;54:1099–1107. [PubMed: 18770037] This retrospective study describes the demographic and clinical parameters of 186 patients reported from 2000 to 2007 with Crohn's disease from India. It then considers the differentiation of Crohn's disease from intestinal TB.
12. Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J Gastroenterol* 2008;14:741–746. [PubMed: 18205265]
13. Ghoshal UC, Ghoshal U, Singh H, Tiwari S. Anti-*Saccharomyces cerevisiae* antibody is not useful to differentiate between Crohn's disease and intestinal tuberculosis in India. *J Postgrad Med* 2007;53:166–170. [PubMed: 17699989]
14. Boudiaf M, Zidi SH, Soyer P, et al. Tuberculous colitis mimicking Crohn's disease: utility of computed tomography in the differentiation. *Eur Radiol* 1998;8:1221–1223. [PubMed: 9724443]
15. Makharia GK, Srivastava S, Das P, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010;105:642–651. [PubMed: 20087333] This excellent study highlights certain features that are more common in Crohn's disease including blood in stool, involvement of the left side of the colon, and focally enhanced colitis. A score devised by the authors proved useful in differentiating between CD and intestinal TB.
16. Lee YJ, Yang SK, Byeon JS, et al. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. *Endoscopy* 2006;38:592–597. [PubMed: 16673312]
17. Uzunkoy A, Harma M, Harma M. Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature. *World J Gastroenterol* 2004;10:3647–3649. [PubMed: 15534923]
18. Pulimood AB, Ramakrishna BS, Kurian G, et al. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999;45:537–541. [PubMed: 10486361]
19. Gillin JS, Urmacher C, West R, Shike M. Disseminated *Mycobacterium avium-intracellulare* infection in acquired immunodeficiency mimicking Whipple's disease. *Gastroenterology* 1983;85:1187–1191. [PubMed: 6194041]
20. Nyberg DA, Federle MP, Jeffrey RB, et al. Abdominal CT findings of disseminated *Mycobacterium avium-intracellulare* in AIDS. *AJR Am J Roentgenol* 1985;145:297–299. [PubMed: 3875228]
21. Cintron JR, Del Pino A, Duarte B, Wood D. Abdominal actinomycosis. *Dis Colon Rectum* 1996;39:105–108. [PubMed: 8601346]
22. Harris LF, Kakani PR, Selah CE. Actinomycosis. Surgical aspects. *Am Surg* 1985;51:262–264. [PubMed: 3994166]
23. Bouree P, Paugam A, Petithory JC. Anisakidosis: report of 25 cases and review of the literature. *Comp Immunol Microbiol Infect Dis* 1995;18:75–84. [PubMed: 7621671]
24. Chamberlain RS, Atkins S, Saini N, White JC. Ileal perforation caused by cytomegalovirus infection in a critically ill adult. *J Clin Gastroenterol* 2000;30:432–435. [PubMed: 10875475]
25. Baroco AL, Oldfield EC. Gastrointestinal cytomegalovirus disease in the immunocompromised patient. *Curr Gastroenterol Rep* 2008;10:409–416. [PubMed: 18627655]

26. Kahi CJ, Wheat LJ, Allen SD, Sarosi GA. Gastrointestinal histoplasmosis. *Am J Gastroenterol* 2005;100:220–231. [PubMed: 15654803]
27. Cappell MS, Mandell W, Grimes MM, Neu HC. Gastrointestinal histoplasmosis. *Dig Dis Sci* 1988;33:353–360. [PubMed: 3277825]
28. Mielants H, Veys EM, De Vos M, et al. The evolution of spondyloarthropathies in relation to gut histology. I. Clinical aspects. *J Rheumatol* 1995;22:2266–2272. [PubMed: 8835560]
29. Mielants H, Veys EM, Cuvelier C, et al. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. *J Rheumatol* 1995;22:2273–2278. [PubMed: 8835561]
30. Passam FH, Diamantis ID, Perisinaki G, et al. Intestinal ischemia as the first manifestation of vasculitis. *Semin Arthritis Rheum* 2004;34:431–441. [PubMed: 15305242]
31. Karagozian R, Turbide C, Szilagyi A. Henoch-Schönlein purpura presenting with ileal involvement in an adult. *Dig Dis Sci* 2004;49:1722–1726. [PubMed: 15573933]
32. Byun JY, Ha HK, Yu SY, et al. CT features of systemic lupus erythematosus in patients with acute abdominal pain: emphasis on ischemic bowel disease. *Radiology* 1999;211:203–209. [PubMed: 10189472]
33. Cangemi JR, Picco MF. Intestinal ischemia in the elderly. *Gastroenterol Clin North Am* 2009;38:527–540. [PubMed: 19699412]
34. Hoeffel C, Crema MD, Belkacem A, et al. Multi-detector row CT: spectrum of diseases involving the ileocecal area. *Radiographics* 2006;26:1373–1390. [PubMed: 16973770]
35. Solem CA, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Small intestinal adenocarcinoma in Crohn's disease: a case-control study. *Inflamm Bowel Dis* 2004;10:32–35. [PubMed: 15058524]
36. Hsu EY, Feldman JM, Lichtenstein GR. Ileal carcinoid tumors stimulating Crohn's disease: incidence among 176 consecutive cases of ileal carcinoid. *Am J Gastroenterol* 1997;92:2062–2065. [PubMed: 9362193]
37. Allison MC, Howatson AG, Torrance CJ, et al. Gastrointestinal damage associated with the use of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1992;327:749–754. [PubMed: 1501650]
38. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005;3:55–59. [PubMed: 15645405]
39. Lang J, Price AB, Levi AJ, et al. Diaphragm disease: the pathology of non-steroidal anti-inflammatory drug induced small intestinal strictures. *J Clin Pathol* 1988;41:516–526. [PubMed: 3384981]
40. Sigthorsson G, Tibble J, Hayllar J, et al. Intestinal permeability and inflammation in patients on NSAIDs. *Gut* 1998;43:506–511. [PubMed: 9824578]
41. Tibble JA, Sigthorsson G, Foster R, et al. High prevalence of NSAID enteropathy as shown by a simple faecal test. *Gut* 1999;45:362–366. [PubMed: 10446103]
42. Hayashi Y, Yamamoto H, Taguchi H, et al. Nonsteroidal anti-inflammatory drug-induced small-bowel lesions identified by double-balloon endoscopy: endoscopic features of the lesions and endoscopic treatments for diaphragm disease. *J Gastroenterol* 2009;44 Suppl 19:57–63. [PubMed: 19148795] This is a retrospective case study of 18 patients illustrating the clinical features of NSAID enteropathy. Endoscopic balloon dilation therapy was safe and effective for diaphragm disease.
43. Gut lesions due to slow-release KCl tablets. *N Engl J Med* 1977;296:111–112.
44. Geltner D, Sternfeld M, Becker SA, Kori M. Gold-induced ileitis. *J Clin Gastroenterol* 1986;8:184–186. [PubMed: 3091675]
45. Daneshjoo R, J Talley N. Eosinophilic gastroenteritis. *Curr Gastroenterol Rep* 2002;4:366–372. [PubMed: 12228038]
46. Wedemeyer J, Vosskuhl K. Role of gastrointestinal eosinophils in inflammatory bowel disease and intestinal tumours. *Best Pract Res Clin Gastroenterol* 2008;22:537–549. [PubMed: 18492570]
47. Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. *Am J Gastroenterol* 2008;103:3184–3192. [PubMed: 18853979]
48. 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).

49. Haskell H, Andrews CW Jr, Reddy SI, et al. Pathologic features and clinical significance of "backwash" ileitis in ulcerative colitis. *Am J Surg Pathol* 2005;29:1472–1481. [PubMed: 16224214]
50. De Ceglie A, Bilardi C, Bianchi S, et al. Acute small bowel obstruction caused by endometriosis: a case report and review of the literature. *World J Gastroenterol* 2008;14:3430–3434. [PubMed: 18528943] The authors report an interesting case in which endometrial infiltration of the ileum caused acute obstruction requiring emergency surgery in a woman whose symptoms were not related to menses.
51. Cappell MS, Friedman D, Mikhail N. Endometriosis of the terminal ileum simulating the clinical, roentgenographic, and surgical findings in Crohn's disease. *Am J Gastroenterol* 1991;86:1057–1062. [PubMed: 1858741]

Table 1

Selected causes of ileitis

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

Backwash ileitis due to ulcerative colitis

Endometriosis

Radiation enteritis

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