Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults

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INTRODUCTION

Inflammatory bowel disease (IBD) is comprised of two major disorders: ulcerative colitis (UC) and Crohn disease (CD). UC affects the colon and is characterized by inflammation of the mucosal layer. CD is characterized by transmural inflammation and may involve any portion of luminal gastrointestinal tract, from the oral cavity to the perianal area. Patterns of disease distribution include the following:

- Approximately 80 percent of patients have small bowel involvement, usually in the distal ileum, with one-third of patients having ileitis exclusively.
- Approximately 50 percent of patients have ileocolitis, which refers to involvement of both the ileum and colon.
- Approximately 20 percent have disease limited to the colon. In contrast to rectal involvement in patients with ulcerative colitis, one-half of CD patients with colitis have sparing of the rectum.
- Approximately one-third of patients have perianal disease.
- Approximately 5 to 15 percent have involvement of the mouth or gastroduodenal area, while fewer patients have involvement of the esophagus and proximal small bowel.

Crohn disease can be classified based on age of onset, disease location, and disease behavior

(eg, stricturing), and the Montreal classification is commonly used for epidemiologic and population-based studies (table 1) [1]. (See "Definitions, epidemiology, and risk factors for inflammatory bowel disease in adults".)

This topic will review the clinical manifestations, diagnosis, and prognosis of CD in adults. The pathogenesis of IBD is discussed separately. (See "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease".)

Management of patients with CD including assessment of disease activity, severity and risk, is discussed separately:

- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)
- (See "Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease".)
- (See "Management of Crohn disease after surgical resection".)
- (See "Perianal Crohn disease".)
- (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

CLINICAL FEATURES

Patient presentation — Patients with CD can have symptoms for many years prior to diagnosis or they may present acutely [2,3].

Cardinal symptoms — The cardinal symptoms of CD include abdominal pain, diarrhea (with or without gross bleeding), fatigue, and weight loss [4]:

- **Abdominal pain** – Crampy abdominal pain is a common manifestation of CD, regardless of disease distribution:
  - A patient with disease limited to the distal ileum frequently presents with right lower quadrant pain.
  - The transmural nature of the inflammatory process results in fibrotic strictures. These strictures often lead to repeated episodes of abdominal pain and small bowel obstruction, or less commonly colonic obstruction.
  - Some patients have no symptoms of CD until luminal narrowing causes abdominal pain and early signs of obstruction (fewer bowel movements).

- **Diarrhea** – Diarrhea is a common presentation, but bowel symptoms often fluctuate over a long period of time [5]. A history of persistent but intermittent diarrhea without gross blood but with other features of IBD (eg, skin, eye, or joint problems) suggests the diagnosis of CD. Diarrhea associated with CD may have multiple causes including:

  - Excessive fluid secretion and impaired fluid absorption by inflamed small or large bowel
  - Bile salt malabsorption due to an inflamed terminal ileum
  - Steatorrhea related to loss of bile salts
  - Enteroenteric fistulas causing bypass of portions of absorptive surface area

  Stools frequently contain microscopic blood (eg, positive guaiac or immunochemical test); however, some patients with CD with predominantly colonic involvement may have grossly bloody stools.

- **Systemic symptoms** – Fatigue is a common feature of CD. Weight loss is often related to decreased oral intake because patients with obstructing segments of bowel feel better when they do not eat. Weight loss may also be related to malabsorption.

  Fever occurs less frequently and may be due to the inflammatory process itself or may be the result of intestinal perforation complicated by an intra-abdominal abscess. (See 'Features of transmural inflammation' below.)

Features of transmural inflammation — Transmural bowel inflammation of CD is associated with sinus tracts that may lead to fistulas and phlegmon formation:

- **Fistulas** – Transmural inflammation is associated with sinus tracts that may penetrate the serosa and give rise to fistulas. Penetration of the bowel wall most often presents as an indolent process and not as the acute onset of severe abdominal pain. (See "Overview of gastrointestinal tract perforation", section on 'Clinical features'.)

  Fistulas are tracts or communications that connect two epithelial-lined organs. For example, fistulas may connect the intestine to bladder (enterovesical), to skin (enterocutaneous), to bowel (enteroenteric), or to the vagina (enterovaginal).

  The clinical manifestation of the fistula depends upon the area of involvement adjacent to the diseased bowel segment:

  - Enteroenteric fistulas may be asymptomatic or present as a palpable mass
  - Enterovesical fistulas lead to recurrent urinary tract infections, often with multiple organisms, and to pneumaturia

- Fistulas to the retroperitoneum may lead to psoas abscesses or ureteral obstruction with hydronephrosis
- Enterovaginal fistulas may present with passage of gas or feces through the vagina
- Enterocutaneous fistulas can cause bowel contents to drain to the surface of the skin

In a population-based study of 169 patients with CD, 12 patients (7 percent) had evidence of a fistula of any type at least 30 days prior to the diagnosis of CD [6].

- **Phlegmon/abscess –** All sinus tracts do not lead to fistulas, but may present as a phlegmon, (ie, a walled-off inflammatory mass without bacterial infection) that may be palpated on physical examination of the abdomen. Ileal involvement is suggested by a mass in the right lower quadrant.

  Some sinus tracts lead to abscess formation and an acute presentation of localized peritonitis with fever, abdominal pain, and tenderness.

- **Perianal disease** – Symptoms and signs related to perianal disease may occur in up to 40 percent of patients during the course of CD. For example, patients with perianal fistula may present with perianal pain and drainage, while patients with perianal abscess present with perianal pain, fever, and purulent discharge. The evaluation and management of perianal CD is discussed separately. (See "Perianal Crohn disease".)

Other gastrointestinal features — The clinical manifestations of other sites of gastrointestinal involvement in CD are variable and occur less frequently than ileocolonic involvement. Examples include:

- Oral involvement may present with aphthous ulcers or pain in the mouth and gums.
- Esophageal involvement may present with odynophagia or dysphagia.
- Gastroduodenal involvement is seen in up to 15 percent of patients and may present with upper abdominal pain, nausea, and/or postprandial vomiting [7]. The clinical features of gastroduodenal CD may be similar to those of peptic ulcer disease or gastric outlet obstruction.

  The distal antrum of the stomach and duodenum are the most commonly affected upper gastrointestinal (GI) sites in patients with CD. Some patients have limited upper GI involvement and may be asymptomatic, while other patients with persistent symptoms have deep ulcerations and longer segments of intestinal involvement. (See "Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease", section on 'Gastroduodenal disease'.)

Malabsorption — Patients with small bowel CD and bile salt malabsorption may present with watery diarrhea and steatorrhea that can lead to protein calorie malnutrition, hypocalcemia, vitamin deficiency (eg, vitamin B12), and metabolic bone disease. (See "Approach to the adult patient with suspected malabsorption" and 'Extraintestinal manifestations' below.)

Small bowel disease involving greater than 100 cm of terminal ileum usually results in severe impairment of the enterohepatic circulation of bile salts such that the liver's ability to upregulate de novo bile acid synthesis is inadequate to meet normal physiologic needs for bile production, resulting in fat malabsorption. (See "Overview of nutrient absorption and etiopathogenesis of malabsorption", section on 'Etiopathogenesis of malabsorption'.)

Shorter segments of terminal ileal disease (ie, <100 cm) may result in chronic diarrhea, even though it may not result in fat malabsorption, since the bile acids that are not absorbed in the small intestine may stimulate water and electrolyte secretion in the colon (which is called "cholerrheic diarrhea").

Extraintestinal manifestations — Extraintestinal manifestations of CD are generally related to inflammatory disease activity and include (table 2) [8]:

- **Arthritis or arthropathy** – Primarily involving large joints in approximately 20 percent of patients without synovial destruction, arthritis is the most common extraintestinal manifestation. Central or axial arthritis, such as sacroiliitis, or ankylosing spondylitis, may also occur. An undifferentiated spondyloarthropathy or ankylosing spondylitis may be the presenting manifestation of CD. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases".)

- **Eye involvement** – Eye manifestations occur in approximately 5 percent of patients and include uveitis, iritis, and episcleritis (picture 1A-B). (See "Dermatologic and ocular manifestations of inflammatory bowel disease".)

- **Skin disorders** – Dermatologic manifestations occur in approximately 10 percent of patients and include erythema nodosum and pyoderma gangrenosum (picture 2A-C). Rarely, vulvar involvement of CD may manifest as pain, edema, erythema, and ulceration [9]. (See "Vulvar lesions: Differential diagnosis based on morphology", section on 'Crohn disease'.)

- **Primary sclerosing cholangitis** – Primary sclerosing cholangitis typically occurs in approximately 5 percent of patients with CD, who are often asymptomatic but have an elevated serum alkaline phosphatase concentration. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis".)

- **Other hepatobiliary involvement –** Hepatobiliary disorders in patients with CD are often related to IBD medications rather than the disease itself. However, conditions such as pyogenic liver abscess are rarely seen in association with CD. (See "Overview of hepatobiliary disorders in patients with inflammatory bowel disease".)

- **Secondary amyloidosis –** Secondary amyloidosis is very rare but may lead to renal failure and other organ system involvement [10]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

- **Renal stones** – Calcium oxalate and uric acid kidney stones can result from steatorrhea and diarrhea [11]. Uric acid stones can result from dehydration and metabolic acidosis. (See "Risk factors for calcium stones in adults" and "Uric acid nephrolithiasis".)

- **Bone loss -** Metabolic bone disease may occur as a result of glucocorticoid use and impaired vitamin D and calcium absorption [12,13]. (See "Metabolic bone disease in inflammatory bowel disease".)

- **Pulmonary involvement** – Pulmonary manifestations of IBD include bronchiectasis, chronic bronchitis, interstitial lung disease, bronchiolitis obliterans with organizing pneumonia, sarcoidosis, necrobiotic lung nodules, and pulmonary infiltrates with eosinophilia syndrome. (See "Pulmonary complications of inflammatory bowel disease", section on 'Primary respiratory involvement'.)

Physical examination — Physical examination may be normal or show nonspecific signs (eg, weight loss) suggestive of CD. More specific findings include perianal skin tags, sinus tracts, and abdominal tenderness or palpable abdominal mass (typically in the right lower quadrant).

Laboratory findings — Routine laboratory tests may be normal or they may reveal anemia, an elevated white blood cell count, an elevated C-reactive protein, electrolyte abnormalities, iron deficiency, vitamin B12 deficiency, and vitamin D deficiency.

Stool inflammatory markers (fecal calprotectin or lactoferrin) may be elevated due to intestinal inflammation [14]. (See 'Stool inflammatory markers' below.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis associated with CD is broad and varies with the site of involvement and the chronicity of the clinical presentation (eg, abdominal pain, diarrhea, weight loss):

- **Infectious colitis** – For patients with diarrhea (especially with acute symptoms), stool

studies are performed to evaluate for enteric pathogens (ie, *Shigella*, *Salmonella*, *Campylobacter*, *Escherichia coli* O157:H7, *Yersinia*, *Clostridioides* (formerly *Clostridium*) *difficile* infection, parasites, and amebiasis. (See "Approach to the adult with acute diarrhea in resource-rich settings".)

In immunocompromised patients, cytomegalovirus infection can mimic CD. (See "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'Gastrointestinal manifestations'.)

In patients with primarily small bowel involvement, *Yersinia* can cause an acute ileitis that is difficult to distinguish endoscopically from acute Crohn ileitis. Both tuberculosis and amebiasis can mimic CD of the ileum and cecum. (See "Giardiasis: Epidemiology, clinical manifestations, and diagnosis" and "Causes of acute infectious diarrhea and other foodborne illnesses in resource-rich settings".)

- **Ulcerative colitis** – When CD involves the colon, it must be distinguished from UC because management of these disorders can differ. Clinical features that suggest CD include (see "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Differential diagnosis'):

  - Small bowel involvement
  - Normal appearing rectal mucosa (ie, rectal sparing) (see 'Ileocolonoscopy' below)
  - Stools without gross blood
  - Perianal disease
  - Focal or segmental disease distribution rather than continuous involvement

  For some patients with IBD, the distinction between CD and UC cannot be made; such patients are referred to as having indeterminate colitis. Some patients may initially be diagnosed with ulcerative colitis or CD but it evolves with time to the other diagnosis. One report suggested that an evolution to a diagnosis of CD was more likely in patients initially diagnosed with ulcerative colitis who presented with non-bloody diarrhea or weight loss [15].

- **Diverticular colitis** – Diverticular colitis is characterized by inflammation in the interdiverticular mucosa without involvement of the diverticular orifices. In contrast, in patients with IBD and diverticulosis, the inflammation involves the colonic area harboring diverticula, as well as the diverticular orifices [16]. (See "Segmental colitis associated with diverticulosis", section on 'Diagnosis'.)

- **Celiac disease –** Celiac disease is a small bowel disorder characterized by mucosal

inflammation and villous atrophy which occur in response to dietary gluten. Patients with celiac disease may present with gastrointestinal symptoms that are similar to CD (eg, diarrhea, weight loss). Serologic evaluation (ie, tissue transglutaminase-IgA antibody) is typically performed to detect celiac disease in adults. The clinical manifestations and diagnosis of celiac disease are presented separately. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults" and "Diagnosis of celiac disease in adults".)

- **Irritable bowel syndrome –** Gastrointestinal symptoms such as diarrhea and abdominal pain are common to both IBS and IBD. However, patients with IBS do not have abnormal laboratory studies such as fecal calprotectin or C-reactive protein and do not have mucosal inflammation on ileocolonoscopy. (See 'Stool inflammatory markers' below and 'Laboratory studies' below.)

- **Lactose intolerance –** Intolerance to lactose-containing foods (primarily dairy products) is a common problem and the diagnosis may be initially confused with CD. Clinical symptoms of lactose intolerance include diarrhea, abdominal pain, and flatulence after ingestion of milk or milk-containing products. (See "Lactose intolerance: Clinical manifestations, diagnosis, and management".)

- **Other disorders –** Because of the segmental nature of CD, patients with a variety of disorders may have similar presenting symptoms and imaging studies. These include appendicitis, diverticulitis, ischemic colitis, and a perforating or obstructing bowel cancer.

  The clinical presentation of common variable immunodeficiency (CVID) can also resemble CD (eg, diarrhea, weight loss), and the diagnosis of CVID is discussed separately. (See "Clinical manifestations, epidemiology, and diagnosis of common variable immunodeficiency in adults", section on 'Gastrointestinal disease'.)

DIAGNOSTIC EVALUATION

Goals — Goals of the diagnostic evaluation for a patient with suspected CD are to exclude other causes for symptoms, establish the diagnosis of CD, and determine the severity of disease. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Assessing disease activity, severity and risk'.)

The diagnosis of CD may be suspected in patients with compatible clinical features, including symptoms (eg, right lower quadrant abdominal pain, chronic intermittent diarrhea, fatigue, weight loss) and laboratory tests (eg, anemia, vitamin B12 deficiency, vitamin D deficiency).

The diagnosis of CD is established on the basis of radiologic, endoscopic, and/or histologic findings that demonstrate segmental and transmural inflammation of the luminal gastrointestinal tract in a patient with compatible clinical presentation (eg, abdominal pain, chronic intermittent diarrhea). Laboratory testing is complementary in assessing the severity and complications of CD, but does not establish the diagnosis.

Approach to testing — The typical workup for most patients in whom CD is suspected includes:

- Laboratory studies including blood tests and, for patients with diarrhea, stool studies. (See 'Laboratory studies' below.)
- Small bowel imaging (usually magnetic resonance enterography [MRE] where available). (See 'Small bowel imaging' below.)
- Colonoscopy with intubation of the terminal ileum, including mucosal biopsies. (See 'Ileocolonoscopy' below.)

Laboratory studies — Laboratory testing is complementary and useful for assessing disease complications, while no single laboratory test can establish the diagnosis of CD [4].

Blood tests — Blood tests for patients in whom the diagnosis is suspected include:

- Complete blood count
- Blood chemistry including electrolytes, renal function tests, liver biochemical and function tests, and blood glucose
- Serum iron, vitamin D, and vitamin B12 levels
- C-reactive protein (CRP)

Serum CRP is an acute phase reactant that rises with inflammatory activity and is seen in some patients with IBD [17,18]. Elevated levels of CRP may help differentiate patients with IBD from those with symptoms caused by other disorders (eg, irritable bowel syndrome) [17,19-21]. CRP levels are reported to correlate with CD activity [22,23]. The use of laboratory testing for pretreatment evaluation and for monitoring patients with CD who have achieved clinical remission with medical therapy is discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Assessing disease activity, severity and risk' and "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Monitoring during remission'.)

Stool studies

Testing for enteric pathogens — For patients with diarrhea, a stool specimen is sent for culture, examination for ova and parasites, and for those with risk factors (eg, recent antibiotic use), *Clostridioides* (formerly *Clostridium*) *difficile* toxin. The epidemiology, clinical manifestations and diagnosis of *Clostridioides* (formerly *Clostridium*) *difficile* infection is discussed in more detail separately. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology" and "Clostridioides (formerly Clostridium) difficile infection in adults: Clinical manifestations and diagnosis".).

Stool inflammatory markers — Although tests for fecal calprotectin or lactoferrin are not used routinely to diagnose Crohn disease, they may help to differentiate patients with intestinal inflammation from patients with functional bowel disease [4,24-26]. While calprotectin is used more commonly by some clinicians, lactoferrin is an acceptable alternative [26,27]. (See "Approach to the adult with chronic diarrhea in resource-rich settings", section on 'General laboratory tests'.)

In selected patients (eg, those in whom it is difficult to distinguish Crohn disease from functional bowel disease), we measure fecal calprotectin instead of proceeding directly to ileocolonoscopy. If fecal calprotectin is normal, a diagnosis of IBD is unlikely. If fecal calprotectin level is above the reference range, we proceed with ileocolonoscopy and biopsy to confirm the diagnosis of IBD.

In a meta-analysis of eight studies including 1062 participants (565 patients with IBD [confirmed by endoscopy], 259 patients with IBS and 238 healthy controls), which evaluated the performance of fecal calprotectin in distinguishing between IBD and IBS, patients with a fecal calprotectin level of <40 microg/g had a 1 percent chance or less of having IBD [26]. In a separate analysis of two studies in the same systematic review (541 participants [275 patients with IBD, 168 patients with IBS and 98 healthy controls]), patients with a fecal lactoferrin level of <10microg/g had a 2 percent chance or less of having IBD. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults", section on 'Laboratory testing'.)

In an earlier meta-analysis that included six studies with 670 adult patients, the presence of fecal calprotectin was 93 percent sensitive and 96 percent specific for identifying patients with IBD [14], using ileocolonoscopy with histology as the reference standard.

We also measure fecal calprotectin when evaluating a patient with established Crohn disease who had achieved clinical remission but who now presents with symptoms of a disease flare (eg, abdominal pain, diarrhea). In this setting, some clinicians may initiate treatment based on

clinical evaluation, but we obtain objective testing (eg, stool markers, laboratory studies) prior to initiating immunosuppressive therapy.

The use of fecal calprotectin for pretreatment evaluation and for monitoring disease activity in patients with IBD is discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Management of Crohn disease after surgical resection", section on 'Postoperative monitoring'.)

Endoscopy

Ileocolonoscopy — Colonoscopy with intubation of the terminal ileum (including mucosal biopsies) is performed for the evaluation of suspected ileocolonic CD. Endoscopic features include focal ulcerations adjacent to areas of normal appearing mucosa along with nodular mucosal changes that result in a cobblestone appearance (picture 3). (See "Endoscopic diagnosis of inflammatory bowel disease", section on 'Endoscopic findings in Crohn disease'.)

Skip areas of involvement are typical with segments of normal-appearing bowel interrupted by large areas of disease. Pseudopolyps (hypertrophied masses of mucous membrane resembling polyps) may also be present. Normal appearing rectal mucosa (ie, rectal sparing) is common in CD. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Induction of remission'.)

During colonoscopy, biopsies are obtained from the right colon, left colon, and rectum even if endoscopically normal in appearance to assess for histologic evidence of inflammation. The histologic findings include focal ulcerations and acute and chronic inflammation. These findings are usually confirmatory rather than diagnostic.

Granulomas may be noted in up to 30 percent of patients with CD and this histologic finding supports but is not required to establish the diagnosis (picture 4) [4].

Other endoscopic examinations

- **Upper endoscopy** – Upper endoscopy with biopsies of the stomach and small bowel is performed in patients with suspected CD and upper gastrointestinal symptoms (eg, dyspepsia, early satiety, nausea, emesis). Endoscopic findings consistent with CD include esophageal ulceration, gastric inflammation, and duodenal ulceration and/or inflammation.

- **Video capsule endoscopy** – Video capsule endoscopy ([VCE] or wireless video endoscopy), provides an alternative method for visualizing the small bowel mucosa but without radiation exposure. It may detect suggestive lesions (eg, small bowel ulcerations) not visible by other small bowel studies (picture 5). VCE should not be performed in

patients with a suspected intestinal stricture since the capsule may not be able to pass through the stricture, thus requiring surgical or endoscopic removal. (See "Overview of deep small bowel enteroscopy".)

The use and diagnostic accuracy of VCE are presented separately. (See "Wireless video capsule endoscopy".)

Imaging

Small bowel imaging — Small bowel imaging is performed as part of the diagnostic evaluation for patients with suspected CD, because much of the small bowel is not accessible by direct endoscopic visualization, and small bowel imaging also demonstrates disease distribution and extent.

We perform magnetic resonance imaging with small bowel enterography (MRE) for most patients because it avoids radiation and has comparable diagnostic accuracy to computed tomography with small bowel enterography (CTE) [28,29]. Patient evaluation prior to magnetic resonance imaging (MRI) with contrast is discussed separately. (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging" and "Patient evaluation for metallic or electrical implants, devices, or foreign bodies before magnetic resonance imaging".)

MRI with enterography (using a neutral contrast agent to distend the small bowel) demonstrates bowel inflammation, complications (eg, stricturing disease and enteric fistula), and disease distribution and extent [30-32]. MRE features of small bowel inflammation include increased bowel wall enhancement and wall thickness, hyperintensity (possibly reflecting edema), and mucosal lesions (eg, ulcers).

The sensitivity of MRE with contrast for detecting inflammation associated with CD is >90 percent [29,33]. In one study, 44 patients with ileal or ileocolonic CD underwent MRE, CTE, and ileocolonoscopy for measurement of disease activity and detection of CD-related complications [34]. Both CTE and MRE demonstrated similar accuracy for disease location, wall thickening and enhancement, enlarged lymph nodes, and involvement of perivisceral fat, but MRE demonstrated higher accuracy in the detection of strictures (0.95 versus 0.91). In per-segment analysis, as compared with CTE, MRE was more accurate in the detection of ileal wall enhancement (0.88 versus 0.81).

Alternatives to MRE for small bowel imaging include:

- CTE – CTE (with a neutral contrast similar to MRE) is useful for detecting small bowel inflammation and complications (eg, such as intraabdominal abscesses (image 1)), and

has a sensitivity of approximately 90 percent [28,35].

- Upper gastrointestinal series with small bowel follow through – Upper gastrointestinal series with small bowel follow through involves ingestion of a barium solution with subsequent radiologic imaging of the small intestine. Typical features of small bowel CD include narrowing of the lumen with nodularity and ulceration, a "string" sign when luminal narrowing becomes more advanced or with severe spasm, a cobblestone appearance, fistulas and abscess formation, and separation of bowel loops, a manifestation of transmural inflammation with bowel wall thickening (image 2A-E). Antral narrowing and segmental stricturing of the duodenum are suggestive of gastroduodenal CD (image 3A-B).

  While barium studies were traditionally part of the evaluation for patients with suspected CD, cross sectional imaging (eg, MRE, CTE) is used more commonly because of greater diagnostic accuracy. In a study of 40 patients with suspected CD, CTE had higher sensitivity compared with small bowel follow through (83 versus 65 percent) [35].

Other diagnostic imaging

- Alternatives to colonoscopy – Colonoscopy is the preferred study for evaluation of the large bowel, while barium enema or computed tomography (CT) colonography are less desirable alternatives because the colon and ileum are not directly visualized and mucosal biopsies cannot be obtained. However, an alternative to optical colonoscopy may be indicated when it cannot be completed for technical reasons (eg, nonobstructing colonic stricture). (See "Overview of computed tomographic colonography".)

  For example, air-contrast barium enema may detect aphthous ulcers and can document the extent of disease and the location and severity of colonic strictures. Sacculations may be seen in patients with chronic involvement (image 4A-B). It may also reveal small perforations with fistula tracts.

- Perianal and pelvic imaging – MRI of the pelvis is used to detect perianal fistula and define the fistula tract (image 5 and image 6). The evaluation of a patient with suspected CD and perianal fistula and/or abscess is presented separately. (See "Perianal Crohn disease" and "The role of imaging tests in the evaluation of anal abscesses and fistulas".)

- Investigational methods – Crohn disease activity can be assessed with multispectral optoacoustic tomography (MSOT), a transabdominal imaging technique that detects bowel wall inflammation by quantifying surrogate markers such as hemoglobin-dependent tissue perfusion [36]. MSOT uses the excitation of short-pulsed laser light with near-infrared wavelengths to induce the photoacoustic effect in targeted tissues, which results in sound

waves generated by thermoelastic expansion [37]. In a preliminary study using endoscopy as the reference standard in 44 patients with CD, MSOT parameters (ie, total hemoglobin, oxygenated hemoglobin and deoxygenated hemoglobin) successfully distinguished active versus nonactive disease. Results were similar using histology as the reference standard in 42 patients [36]. Although not yet available for use in practice and further validation is needed, this technique holds promise for future clinical application.

Risks associated with imaging — Risks associated with imaging studies include:

- Ionizing radiation – Many examinations (eg, radiographs, CT scans, and fluoroscopic barium studies) expose patients to ionizing radiation, which is associated with an increased risk of malignancy. In one study, the radiation exposure from radiographic studies over a five-year period was assessed in 371 patients with CD [38]. The mean cumulative radiation exposure over five years was 14 milli-Sieverts (mSv), with a range of 0 to 303 mSv. The median cumulative radiation exposure was lower, at 3 mSv. While the majority of patients had a cumulative exposure of less than 50 mSv (a cutoff used by some investigators to identify patients at high risk of complications from radiation exposure), 27 patients (7 percent) had a cumulative exposure of more than 50 mSv. The risks associated with radiation exposure have contributed to increased utilization of alternative imaging techniques that do not require ionizing radiation (eg, MRI), especially in children and young adults [38,39]. (See "Radiation-related risks of imaging" and "Clinical presentation and diagnosis of inflammatory bowel disease in children", section on 'Imaging'.)

- Gadolinium retention – For patients who have MRI with gadolinium contrast, a small portion of the gadolinium remains in the body for an undetermined duration, and the long-term effects are unknown. Concerns about gadolinium retention are discussed separately (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging".)

PROGNOSIS

Disease course — For many patients with CD, symptoms are chronic and intermittent, but the disease course can vary. Some patients may have a continuous and progressive course of active disease, while approximately 20 percent of patients experience prolonged remission after initial presentation [40,41].

Chronic bowel inflammation can lead to complications such as strictures, fistula, or abscess. A population-based cohort study showed that the risk of developing intestinal complications

among patients with inflammatory CD was 50 percent at 20 years after diagnosis, and ileal involvement was associated with a shorter time interval to onset of complications [42].

Risk factors for progressive disease include [43,44]:

- Age <40 years
- Tobacco use
- Perianal or rectal involvement
- Glucocorticoid-requiring disease

Risk of surgery — Many patients with CD ultimately require surgical intervention. Although advances in medical therapy have coincided with lower rates of surgical resection in patients with CD, surgery is often required in the setting of bowel obstruction, abscesses, perforation, or refractory disease. The 10-year risk of surgical resection for CD is nearly 50 percent [45]. (See "Operative management of Crohn disease of the small bowel, colon, and rectum".)

The management of patients with CD after surgical resection and the risk factors for disease recurrence are presented separately. (See "Management of Crohn disease after surgical resection".)

Cancer risk — The risk of colorectal cancer in longstanding CD involving the colon is probably comparable to UC [46-48]. However, not all studies reached these conclusions and thus the magnitude of risk in patients with CD remains unsettled. These issues, including surveillance for dysplasia, are presented separately. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Crohn disease'.)

Increases in incidence of squamous cell carcinoma of the anus and skin, adenocarcinoma of the small bowel, duodenal neoplasia, testicular cancer, and leukemia have all been reported in CD, although the strength of these associations is unclear [49]. In a retrospective population-based cohort study that included 3348 patients with IBD and no prior cancer history, both the overall cancer risk and the risk of colon cancer was not increased [50]. However, patients with CD had a higher risk of hematologic malignancies (standardized incidence ratios 14, 95% CI 6.7-25.9).

In addition, patients receiving thiopurine therapy for IBD had an increased risk of developing lymphoproliferative disorders [51,52]. Analyses of lymphoma risk in patients receiving biologic agents directed against tumor necrosis factor-alpha are confounded by concomitant use of immunosuppressive agents in most of these patients. The risk of lymphoma, including

hepatosplenic T-cell lymphoma, is discussed separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease", section on 'Lymphoma' and "Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease", section on 'Hepatosplenic T-cell lymphoma'.)

Mortality — Patients with CD may have a slightly higher overall mortality compared with the general population. In a meta-analysis of 35 studies, the standardized mortality ratio (an approximation of the risk of death compared to the general population) was 1.38 (95% CI 1.23-1.55) [53].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Crohn disease in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Crohn disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- IBD is comprised of two major disorders: UC and CD. UC affects the colon and is

characterized by inflammation of the mucosal layer. CD is characterized by transmural inflammation and may involve any portion of gastrointestinal tract, from the oral cavity to the perianal area. (See 'Introduction' above.)

- The cardinal symptoms of CD include crampy abdominal pain, chronic intermittent diarrhea (with or without gross bleeding), fatigue, and weight loss. The duration of symptoms suggestive of CD is variable. Some patients may present years after the onset of symptoms, while others may present acutely. (See 'Clinical features' above.)

- Transmural bowel inflammation of CD is associated with sinus tracts that may lead to intestinal or perianal fistulas, phlegmon, or abscess. (See 'Features of transmural inflammation' above.)

- Extraintestinal manifestations, such as arthritis or arthropathy, eye and skin disorders, biliary tract involvement, and kidney stones, may occur and are generally related to inflammatory disease activity. (See 'Extraintestinal manifestations' above.)

- Goals of the diagnostic evaluation of a patient with suspected CD are to exclude other causes for symptoms, establish the diagnosis of CD, and determine the severity of the disease. The diagnosis of CD may be suspected in patients with compatible clinical features including symptoms (eg, right lower quadrant abdominal pain, chronic intermittent diarrhea, fatigue, weight loss) and laboratory tests (eg, anemia, vitamin B12 deficiency, vitamin D deficiency). (See 'Goals' above.)

  The diagnosis of CD is established on the basis of radiologic, endoscopic, and/or histologic findings that demonstrate segmental and transmural inflammation of the luminal gastrointestinal tract in a patient with compatible clinical presentation (eg, abdominal pain, chronic intermittent diarrhea). Laboratory testing is complementary in assessing the severity and complications of CD, but does not establish the diagnosis.

- The initial workup for patients in whom CD is suspected typically includes (see 'Approach to testing' above):

  - Laboratory studies including blood tests and, for patients with diarrhea, stool studies (see 'Laboratory studies' above)

  - Small bowel imaging (usually magnetic resonance enterography where available) (see 'Imaging' above)

  - Colonoscopy with intubation of the terminal ileum, including mucosal biopsies (see 'Ileocolonoscopy' above)

- For many patients with CD, symptoms are chronic and intermittent, but the disease course is variable. Some patients may have a continuous and progressive course of active disease, while approximately 20 percent of patients experience prolonged remission after initial presentation. (See 'Prognosis' above.)

  Many patients with CD ultimately require surgical intervention. Although advances in medical therapy have coincided with lower rates of surgical resection in patients with CD, surgery is often required in the setting of bowel obstruction, abscesses, perforation, or refractory disease. The management of patients with CD after surgical resection and the risk factors for disease recurrence are presented separately. (See "Management of Crohn disease after surgical resection".)

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Topic 4070 Version 42.0

GRAPHICS

Montreal classification for Crohn disease

Age at diagnosis
A1 below 16 years
A2 between 17 and 40 years
A3 above 40 years
Location
L1 ileal
L2 colonic
L3 ileocolonic
L4 isolated upper disease*
Behavior
B1 nonstricturing, nonpenetrating
B2 stricturing
B3 penetrating
p perianal disease modifier¶

* L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present.
¶ "p" is added to B1-B3 when concomitant perianal disease is present.

Graphic 86283 Version 8.0

Extraintestinal manifestations of inflammatory bowel disease

Common extraintestinal manifestations
Musculoskeletal
Arthritis – Colitic type, ankylosing spondylitis, isolated joint involvement such as sacroiliitis.
Hypertrophic osteoarthropathy – Clubbing, periostitis, metastatic Crohn disease.
Miscellaneous – Osteoporosis, aseptic necrosis, polymyositis, osteomalacia.
Skin and mouth
Reactive lesions – Erythema nodosum, pyoderma gangrenosum, aphthous ulcers, vesiculopustular eruption, cutaneous vasculitis, neutrophilic dermatosis, metastatic Crohn disease, epidermolysis bullosa acquisita.
Specific lesions – Fissures and fistulas, oral Crohn disease, drug rashes.
Nutritional deficiency – Acrodermatitis enteropathica (zinc), purpura (vitamins C and K), glossitis (vitamin B), hair loss and brittle nail (protein).
Associated diseases – Vitiligo, psoriasis, amyloidosis, epidermolysis bullosa acquisita.
Hepatobiliary
Specific complications – PSC and bile duct carcinoma, small duct PSC, cholelithiasis.
Associated inflammation – Autoimmune chronic active hepatitis, pericholangitis, portal fibrosis and cirrhosis, granuloma in Crohn disease.
Metabolic – Fatty liver, gallstones associated with ileal Crohn disease.
Ocular
Uveitis iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease, retrobulbar neuritis, Crohn keratopathy.
Metabolic
Growth retardation in children and adolescents, delayed sexual maturation.
Less common extraintestinal manifestations
Blood and vascular
Anemia due to iron, folate, or vitamin B12 deficiency or autoimmune hemolytic anemia, anemia of chronic disease, thrombocytopenic purpura; leukocytosis and thrombocytosis; thrombophlebitis and thromboembolism, arteritis and arterial occlusion, polyarteritis nodosa, Takayasu arteritis, cutaneous vasculitis, anticardiolipin antibody, hyposplenism.
Renal and genitourinary tract
Urinary calculi (oxalate stones in ileal disease), local extension of Crohn disease involving ureter or bladder, amyloidosis, drug-related nephrotoxicity.
Renal tubular damage with increased urinary excretion of various enzymes (eg, beta N-acetyl-D-glucosaminidase).
Neurologic
Up to 3% of patients may have non-iatrogenic neurologic involvement, including peripheral neuropathy, myelopathy, vestibular dysfunction, pseudotumor cerebri, myasthenia gravis, and cerebrovascular disorders. Incidence equal in ulcerative colitis and Crohn disease. These disorders usually appear 5 to 6 years after the onset of inflammatory bowel disease and are frequently associated with other extraintestinal manifestations.
Airway and parenchymal lung disease
Pulmonary fibrosis, vasculitis, bronchitis, necrobiotic nodules, acute laryngotracheitis, interstitial lung disease, sarcoidosis. Abnormal pulmonary function tests without clinical symptoms are common (up to 50% of cases).

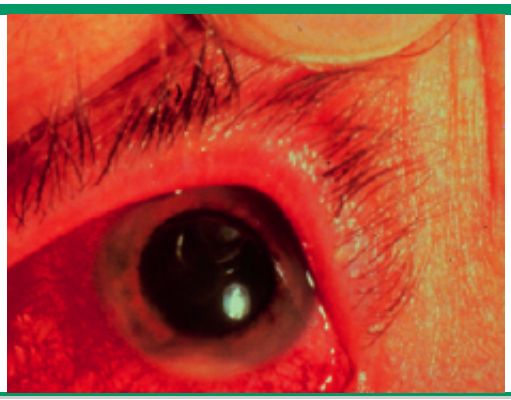
Cardiac
Pericarditis, myocarditis, endocarditis, and heart block – More common in ulcerative colitis than in Crohn disease; cardiomyopathy, cardiac failure due to anti-TNF therapy.
Pericarditis may also occur from sulfasalazine/5-aminosalicylates.
Pancreas
Acute pancreatitis – More common in Crohn disease than in ulcerative colitis. Risk factors include 6-mercaptopurine and 5-aminosalicylate therapy, duodenal Crohn disease.
Autoimmune
Drug-induced lupus and autoimmune diseases secondary to anti-TNF-alpha therapy.
Positive ANA, anti-double-stranded DNA, cutaneous and systemic manifestations of lupus.

PSC: primary sclerosing cholangitis; TNF: tumor necrosis factor; ANA: antinuclear antibody.

Modified from: Das KM. Relationship of extraintestinal involvements in inflammatory bowel disease: New insights into autoimmune pathogenesis. Dig Dis Sci 1999; 44:1.

Graphic 81867 Version 11.0

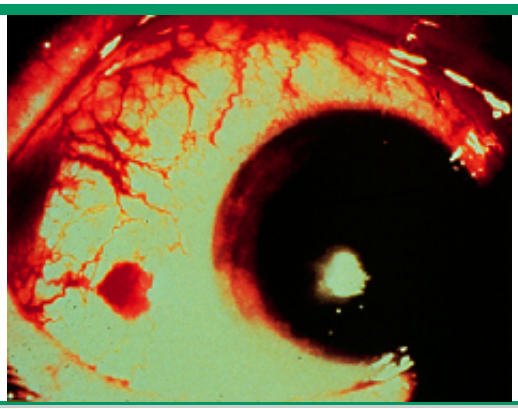
Anterior uveitis in a patient with inflammatory bowel disease



Anterior uveitis in a patient with inflammatory bowel disease is characterized by injection of the conjunctiva and opacity in the anterior chamber.

Graphic 75384 Version 5.0

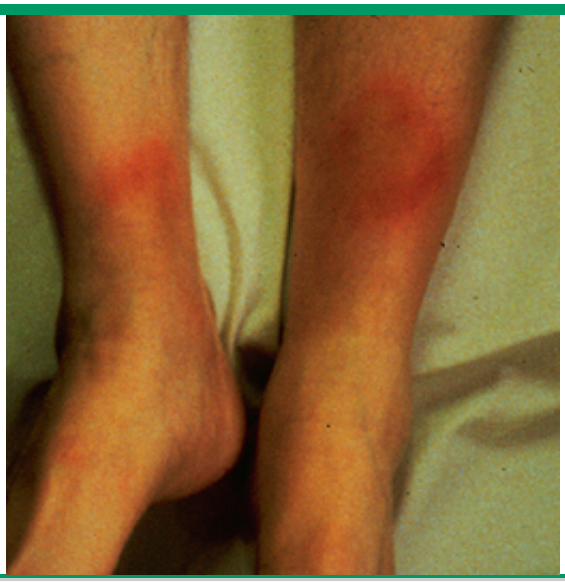
Episcleritis



Patient with episcleritis associated with inflammatory bowel disease showing the characteristic injection of the ciliary vessels.

Graphic 70384 Version 4.0

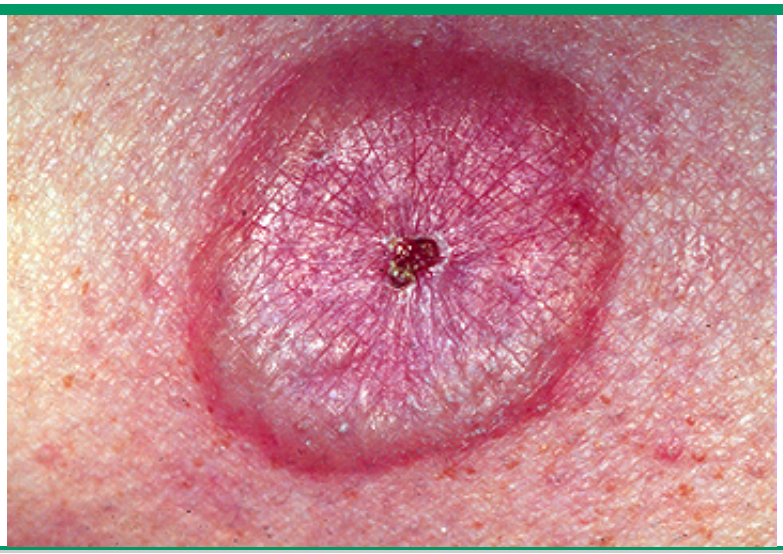
Erythema nodosum



Patient with inflammatory bowel disease with red nodular areas on the shins which are characteristic of erythema nodosum.

Graphic 71344 Version 3.0

Pyoderma gangrenosum

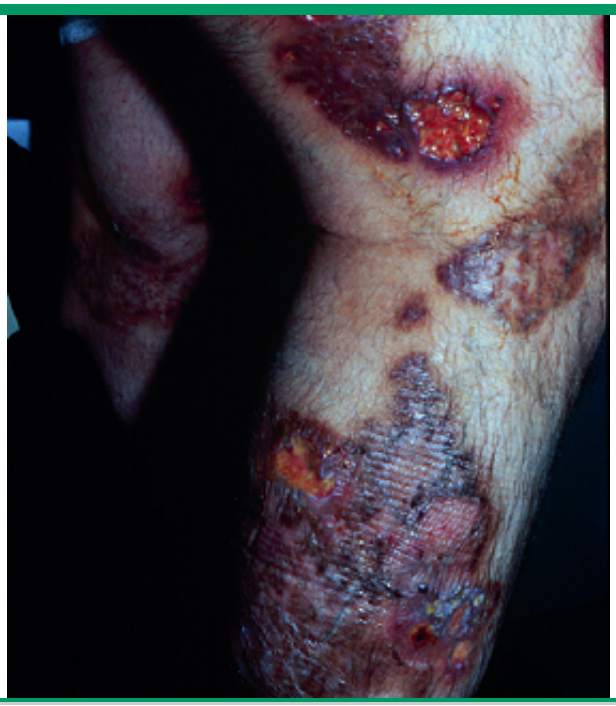


Early lesion in pyoderma gangrenosum presenting as a pustular and violaceous plaque with incipient breakdown.

Courtesy of Cynthia Magro, MD.

Graphic 53733 Version 1.0

Pyoderma gangrenosum

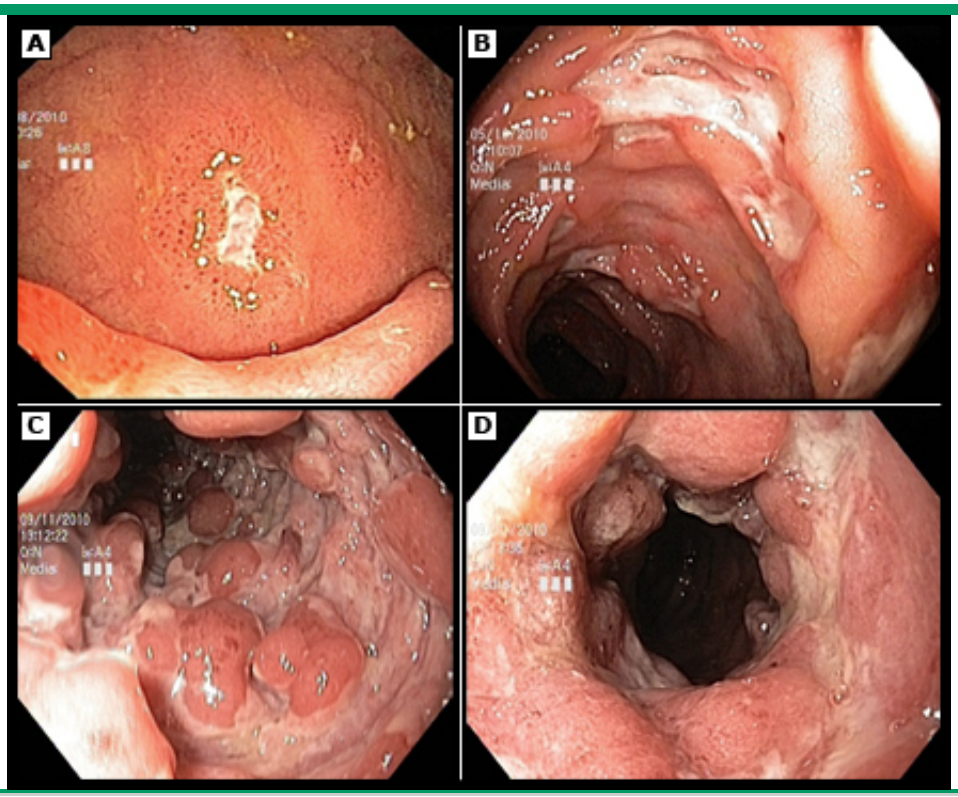


Multiple active and healing lesions of pyoderma gangrenosum with cribriform scarring in patient with inflammatory bowel disease.

Courtesy of Samuel Moschella, MD.

Graphic 52528 Version 1.0

Endoscopic findings in Crohn disease

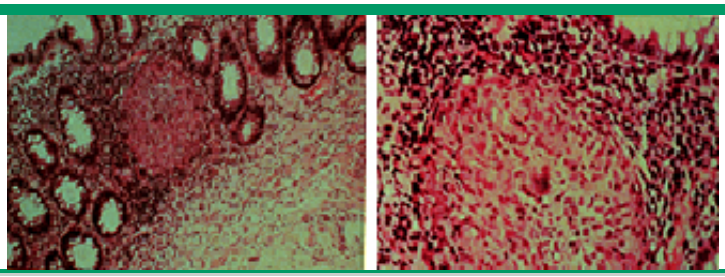


The dominant endoscopic feature in Crohn disease is the presence of ulcerations. Endoscopic findings in Crohn disease include: aphthous ulcers, which are the earliest lesions seen in Crohn disease (panel A); large ulcers interspersed with normal mucosa, which are typical for the segmental distribution of Crohn disease (panel B); a cobblestone appearance that is characterized by nodular thickening, with linear or serpiginous ulcers (panel C); and strictures due to fibrosis (panel D).

Courtesy of Paul Rutgeerts, MD, PhD, FRCP.

Graphic 74646 Version 2.0

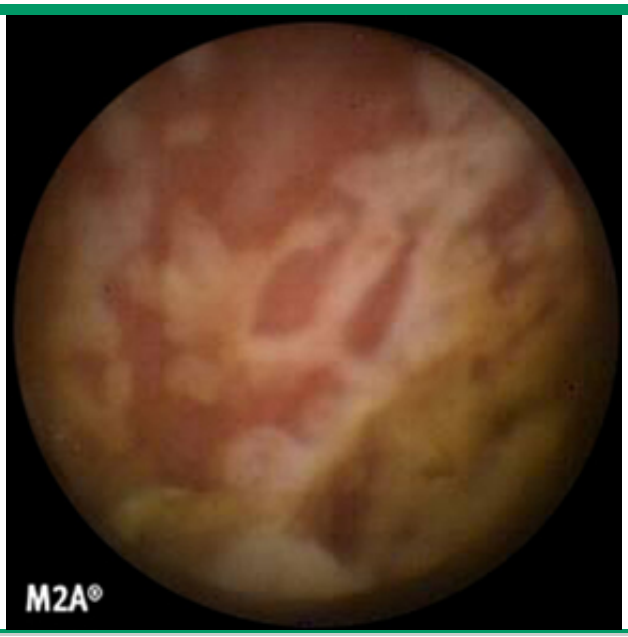
Typical granuloma of Crohn disease



Light micrographs showing a granulomatous lesion that is diagnostic of Crohn disease. Low and high power views show a central giant cell surrounded by epitheliod cells and rimmed by lymphocytes.

Graphic 81744 Version 4.0

Crohn disease

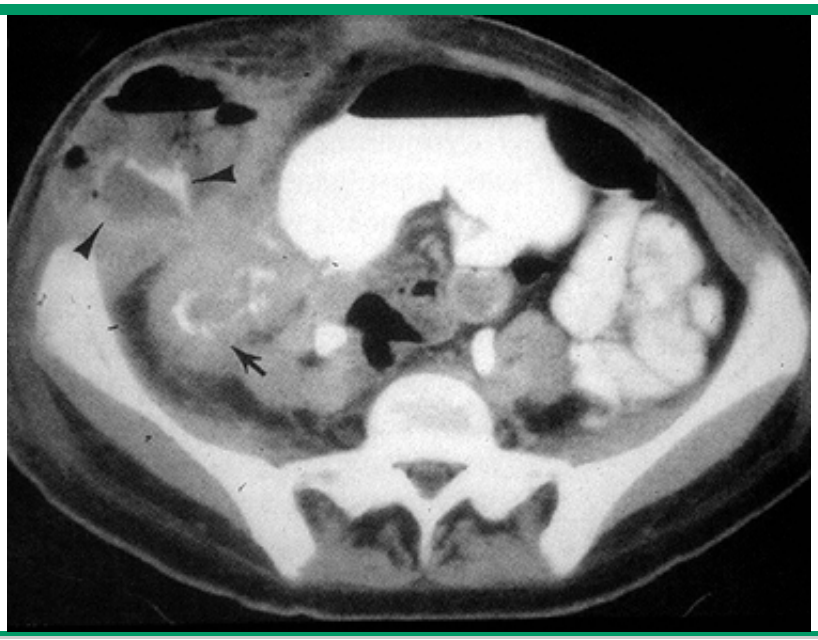


Small bowel ulceration as seen during capsule endoscopy.

Courtesy of Given Imaging, Inc.

Graphic 76042 Version 3.0

Right lower quadrant abscess in Crohn disease

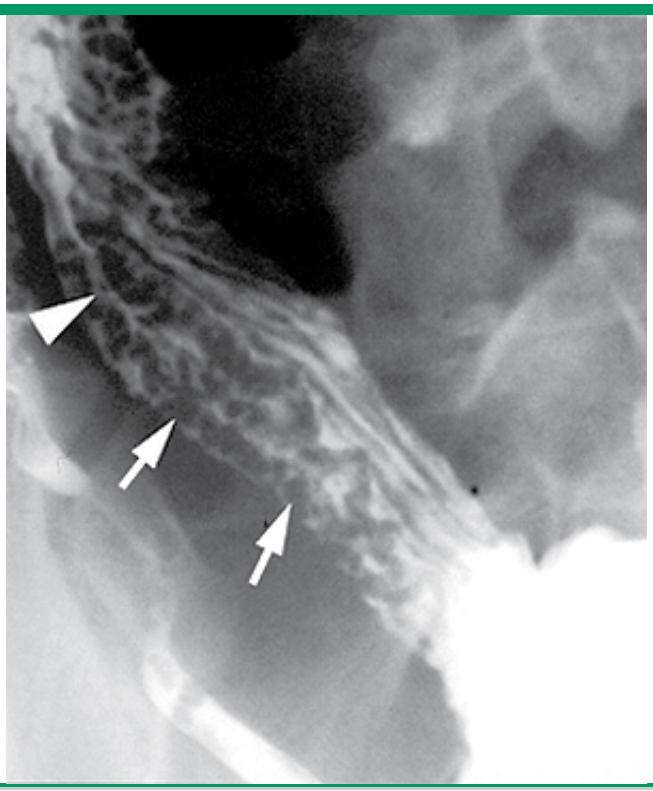


Single axial CT scan of the lower abdomen demonstrates an abscess (arrowheads) extending from the markedly thickened and inflamed terminal ileum (arrow). The presence of contrast material within the abscess confirms a communication with the adjacent ileum.

Courtesy of Norman Joffe, MD.

Graphic 72882 Version 3.0

Crohn disease

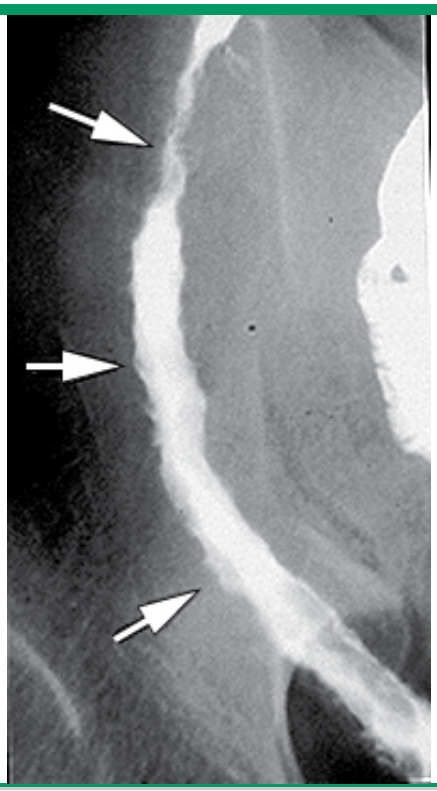


Small bowel follow through examination demonstrates nodular filling defects arising on thickened folds in the terminal ileum (arrows). These features are characteristic of Crohn disease.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 67391 Version 3.0

String sign in Crohn disease

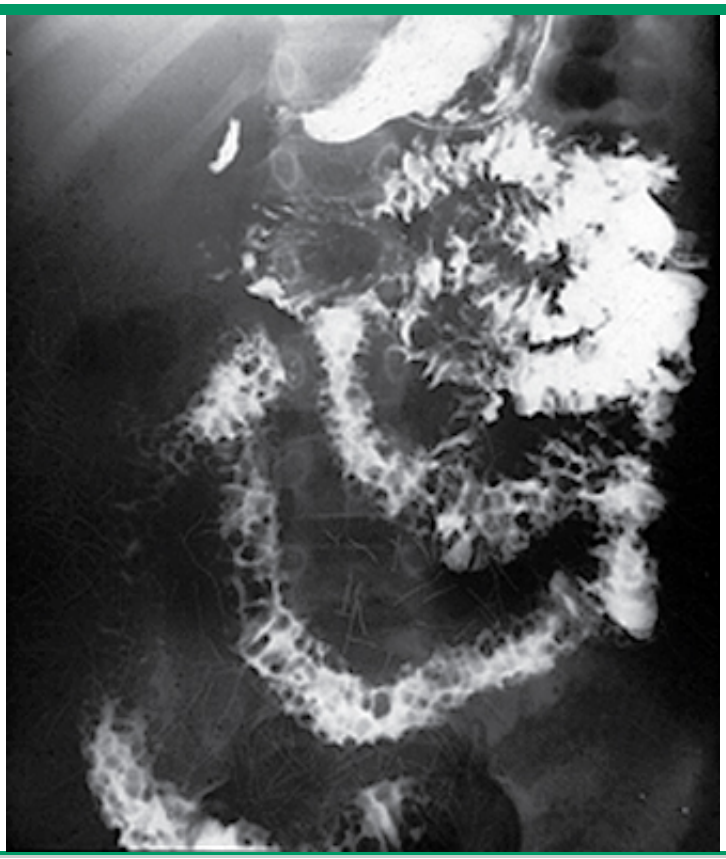


Small bowel follow through study shows marked narrowing, irregularity and ulceration in the distal ileum (arrows) in a patient with Crohn disease.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 80832 Version 4.0

Cobblestone appearance in Crohn disease

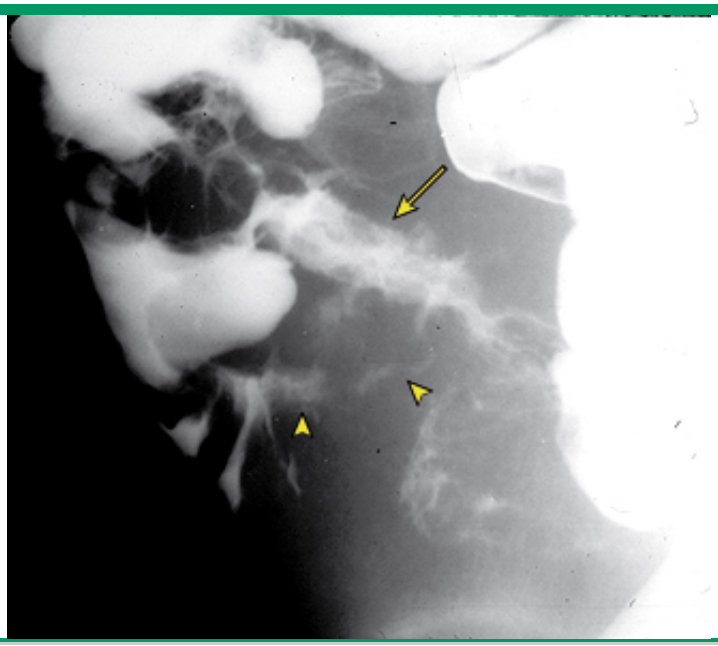


Small bowel follow through study demonstrates diffuse thickening of the small bowel mucosa in a patient with Crohn disease. The cobblestone appearance is produced by barium being dispersed between the edematous inflamed mucosa.

Courtesy of Norman Joffe, MD.

Graphic 81129 Version 3.0

Ileocecal fistulae in Crohn disease

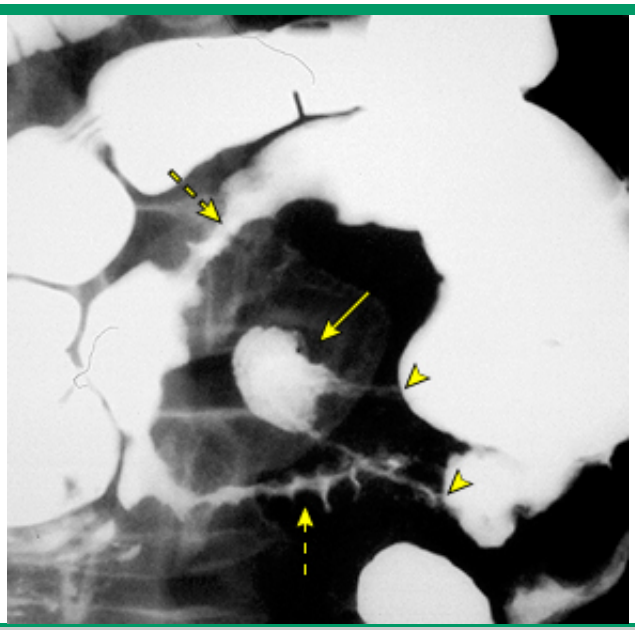


Small bowel follow through examination demonstrates nodular thickening of the terminal ileal mucosal folds in a patient with Crohn disease (arrow). Several fistulae extend from the terminal ileum to the adjacent cecum (arrowheads).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 57661 Version 4.0

Crohn disease with abscess and fistulae

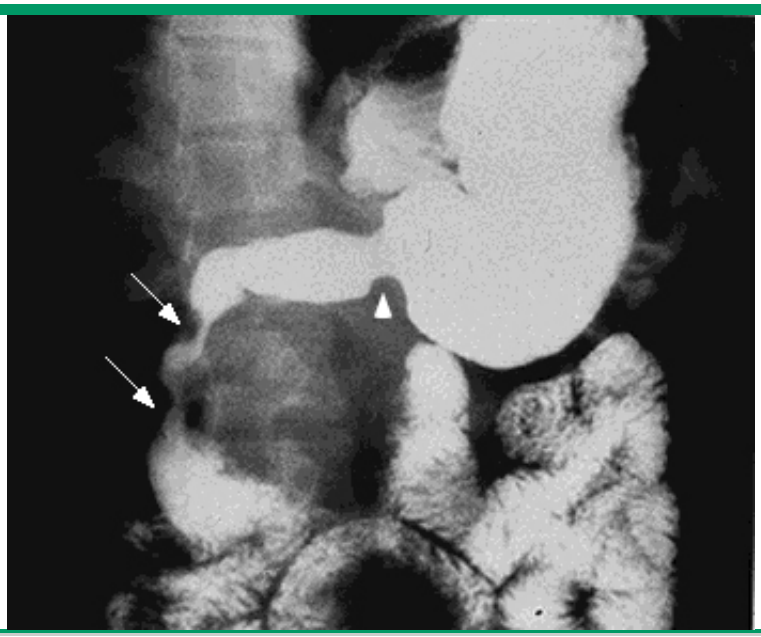


Small bowel follow through study demonstrates an abscess cavity (arrow) with fistulae connecting the cavity to the adjacent small bowel (arrowheads). Note the marked thickening of the inflamed mucosal folds (dashed arrows).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 53956 Version 4.0

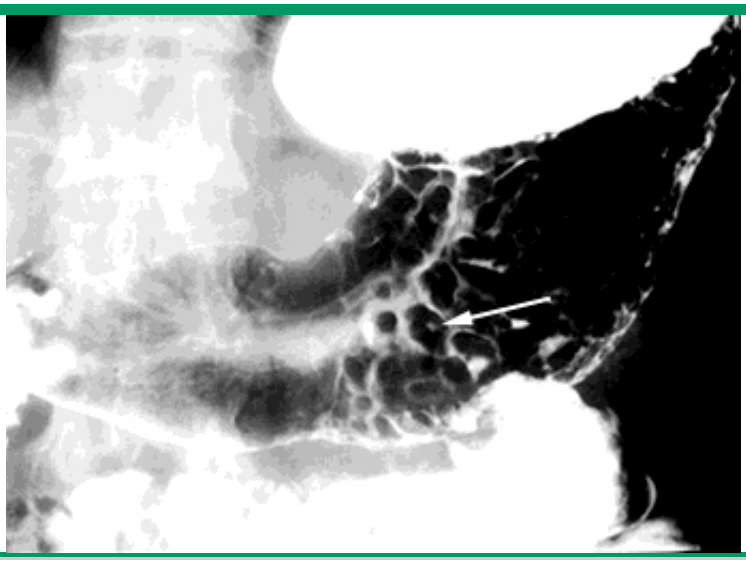
Crohn disease of the upper gastrointestinal tract



Upper gastrointestinal series in a patient with gastroduodenal Crohn disease shows antral narrowing (small arrow) and two duodenal strictures (large arrows).

Graphic 77013 Version 6.0

Crohn disease of the stomach

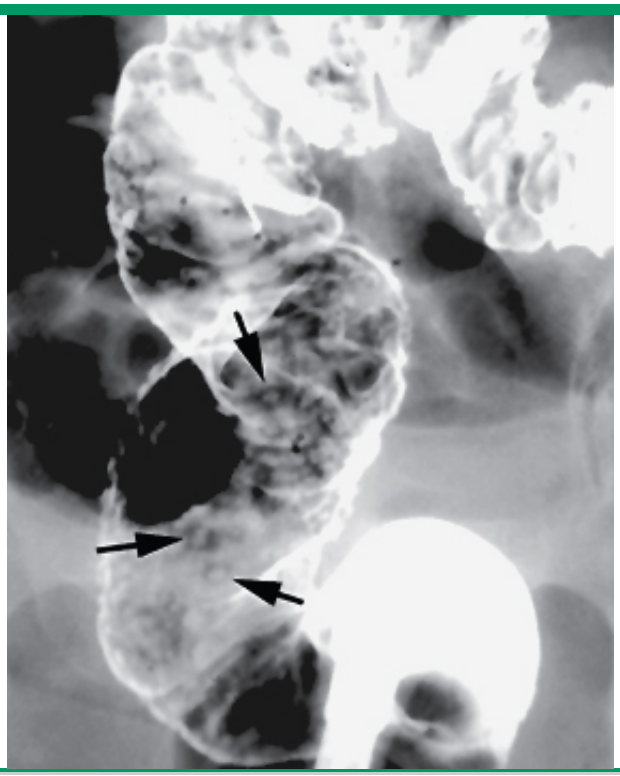


This upper gastrointestinal series, performed in a young man with known Crohn disease of the terminal ileum, shows numerous rounded filling defects in the stomach produced by edematous mucosa. In some of these areas, small central collections of barium are demonstrated (arrow), resulting from superficial erosions. These features are suggestive of Crohn disease, but may also be seen in patients with peptic ulcer disease and in those with viral gastritis.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 78617 Version 4.0

Aphthoid ulcers in Crohn disease

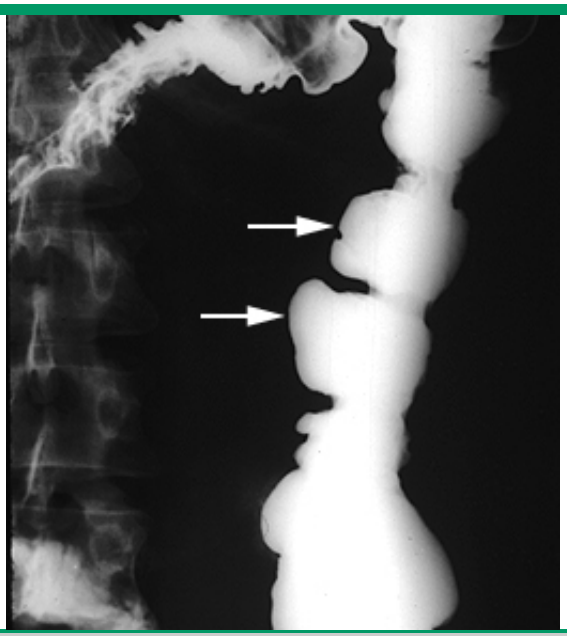


Double contrast barium enema demonstrates small aphthoid ulcers in a patient with early Crohn disease of the colon (arrows). Barium has collected in the superficial erosions, which are surrounded by edematous mucosa. These small erosions, less typically seen in ulcerative colitis, are the precursors of larger discrete ulcers, fistulae, and sinus tracts.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 52610 Version 5.0

Chronic Crohn colitis

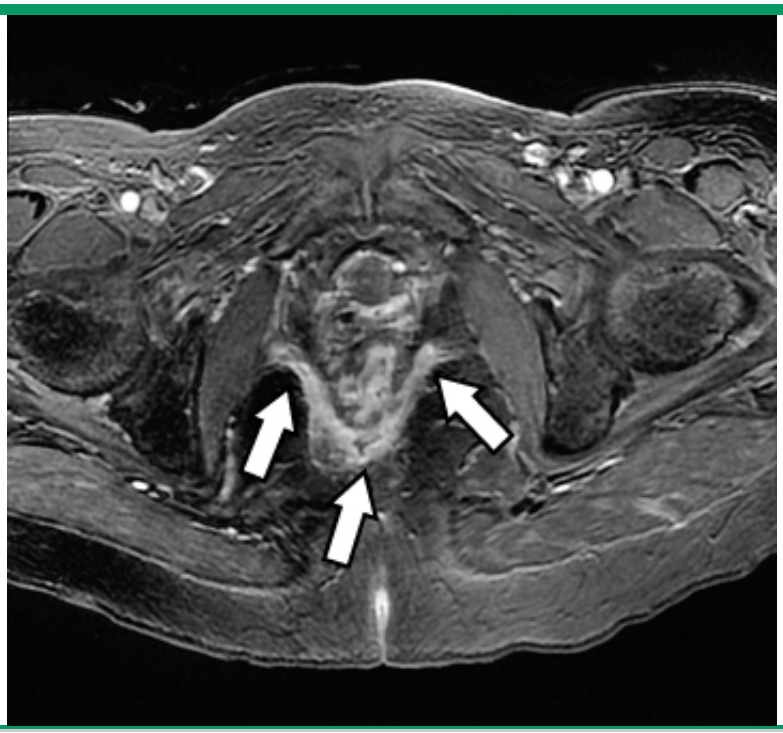


Barium enema demonstrates sacculations along the medial border of the ascending colon (arrows) produced by scarring and fibrosis in a patient with Crohn disease.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 75400 Version 4.0

Perianal fistulas in Crohn disease

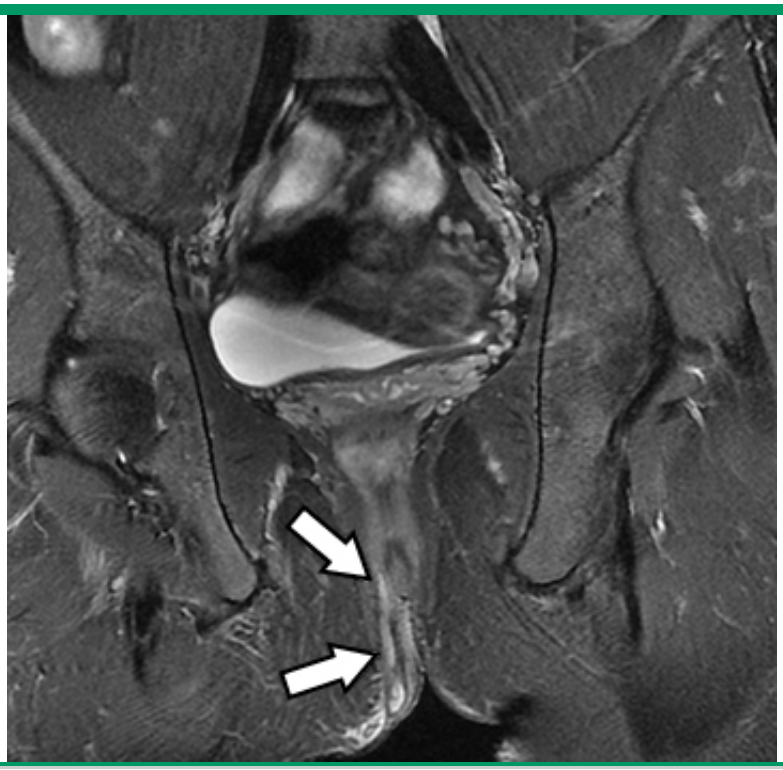


T2-weighted axial magnetic resonance imaging (MRI) study showing perianal fistulas (arrows) in a patient with Crohn disease.

Courtesy of Jonathan Kruskal, MD.

Graphic 72435 Version 5.0

Perianal fistulas in Crohn disease



T2-weighted coronal magnetic resonance imaging (MRI) study showing a perianal fistula (arrows) in a patient with Crohn disease.

Courtesy of Jonathan Kruskal, MD.

Graphic 50476 Version 5.0

Contributor Disclosures

Mark A Peppercorn, MD Nothing to disclose **Sunanda V Kane, MD, MSPH** Grant/Research/Clinical Trial Support: Crohn's and Colitis Foundation [IBD]. Consultant/Advisory Boards: Samsung Bioepis [IBD (infliximab biosimilar)]. Other Financial Interest: ABIM [Gastroenterology]; American college of Gastroenterology; Sherman Foundation [IBD]. **Paul Rutgeerts, MD, PhD, FRCP** Consultant/Advisory Boards: Johnson & Johnson; MSD; UCB; AbbVie; Takeda; Genentech; Bristol-Myers Squibb; Tillotts Pharma; Parexel; Quintiles; Robarts; Amgen/Medimmune/AstraZeneca. **Kristen M Robson, MD, MBA, FACG** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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