Inflammatory Bowel Disease=IBD
(Crohn disease=CD and ulcerative colitis=UC)

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A bimodal distribution :

- early onset at ١٠-٢٠ years of age
- a second, smaller peak at ٥٠-٨٠ years of age.

- The most common time of onset of IBD = **preadolescent/adolescent** era and **young adulthood**.

- # ٢٥% of patients present before ٢٠ years of age.

IBD may be classified according to age at onset:

- pediatric onset (<١٧ years)
- early onset (<١٠ years)
- very early onset (<٦ years)
- Infant/toddler onset (٠-٢ years),
- neonatal onset IBD (<٢٨ days)

- incidence of **P- IBD** is **rising** (greatest rates = among young children).
- **VEO-IBD** accounts for up to ١٥% of **P- IBD** (prevalence of ١٤/١٠٠’٠٠٠ children).
- # ١% of children with IBD are diagnosed before the age of ٢ years.

- **Genetics**, the immune system, the microbiome, and environmental factors are involved in the **pathogenesis** of IBD.

- Risk of IBD in family members of an affected person = ۷-۳۰%;

- a child whose parents both have IBD has a >۳۵% chance of acquiring the disorder.
- Relatives of a patient with UC have a greater risk of **acquiring** UC than CD, whereas relatives of a patient with CD have a greater risk of acquiring CD than UC.
- two diseases can occur in the same family.

- risk of occurrence of IBD among relatives of patients with **CD** is somewhat > **UC**.

- higher chance in monozygotic >dizygotic.
- concordance rate in twins is higher in CD(٣۶%) than in UC(١۶%).

Genetic disorders that have been associated with IBD include :

- Turner syndrome,
- Hermansky-Pudlak syndrome,
- GSD Ib,
- various immunodeficiency disorders.
- The first IBD gene, NOD٢, was identified through association mapping

Table 382.1 Selection of Most Important Genes Associated with Inflammatory Bowel Disease and the Most Commonly Associated Physiologic Functions and Pathways

	GENE NAME	ASSOCIATED DISEASE	GENE FUNCTION AND ASSOCIATED PATHWAYS	PHYSIOLOGIC FUNCTION
NOD2	Nucleotide-binding oligomerization domain- containing protein 2	Crohn disease	Bacterial recognition and response, NFκB activation and autophagy and apoptosis	Innate mucosal defense
IL10	IL-10	Crohn disease	Antiinflammatory cytokine, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RA	IL-10 receptor A	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RB	IL-10 receptor B	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL23R	IL-23 receptor	Crohn disease and ulcerative colitis	Immune regulation, proinflammatory pathways—JAK-STAT regulation	IL-23/T helper 17
TKY2	Tyrosine kinase 2	Crohn disease and ulcerative colitis	Inflammatory pathway signaling (IL-10 and -6, etc.) through intracellular activity	IL-23/T helper 17
IRGM	Immunity-related GTPase M	Crohn disease	Autophagy and apoptosis in cells infected with bacteria	Autophagy
ATG16L1	Autophagy-related 16 like 1	Crohn disease	Autophagy and apoptotic pathways	Autophagy
SLC22A4	Solute carrier family 22 member 4	Crohn disease	Cellular antioxidant transporter	Solute transporters
CCL2	C-C motif chemokine ligand 2	Crohn disease	Cytokine involved in chemotaxis for monocytes	Immune cell recruitment
CARD9	Caspase recruitment domain family member 9	Crohn disease and ulcerative colitis	Apoptosis regulation and NFκB pathway activation	Oxidative stress
IL2	IL-2	Ulcerative colitis	Cytokine involved in immune cell activation	T-cell regulation
MUC19	Mucin 19	Crohn disease and ulcerative colitis	Gel-forming mucin protein	Epithelial barrier

IL, Interleukin; JAK-STAT, Janus kinase-signal transducers and activators of transcription; NFκB, nuclear factor κ-light chain enhancer of activated B cells.
From Ashton JJ, Ennis S, Beattie RM. Early-onset paediatric inflammatory bowel disease. *Lancet*. 2017;1:147–158. Table 1.

environmental factors

- **Gut microbiota** increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome.
- Evidence includes association between **IBD** and **residence in** **or** **immigration** to **industrialized** nations, a **Western diet**,
- **increased** use of **antibiotics** at a younger age,
- high rates of vaccination,
- **less exposure** to microbes at a **young age**.
-
- Some environmental factors are disease specific; for example, **cigarette smoking** is a risk factor for **CD** (but paradoxically protects against **UC**).

Table 382.2 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50–75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for intestinal cancers	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

- It is **not possible** to make a definitive diagnosis in #١٠% of patients with **chronic colitis**; this disorder is called **indeterminate colitis**.

- This is particularly true for **the youngest patients**, because CD in this patient population can more often manifest as exclusively colonic inflammation, mimicking **UC**.

Extraintestinal manifestations

- occur slightly **more commonly with CD** than with UC.

Poor growth is seen in ١٥-٤٠% of children with CD at diagnosis.

- Decrease in height velocity occurs in nearly ٩٠% of patients with CD diagnosed in childhood or adolescence.
-
- The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, **correlates with activity** of the bowel disease.

- Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease,
- whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis **do not correlate with** intestinal disease.

Table 382.3 Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL
Peripheral arthritis
Granulomatous monoarthritis
Granulomatous synovitis
Rheumatoid arthritis
Sacroiliitis
Ankylosing spondylitis
Digital clubbing and hypertrophic osteoarthropathy
Periostitis
Osteoporosis, osteomalacia
Rhabdomyolysis
Pelvic osteomyelitis
Chronic recurrent multifocal osteomyelitis (CRMO)
Relapsing polychondritis

SKIN AND MUCOUS MEMBRANES
Oral lesions
Orofacial granulomatosis
Cheilitis
Aphthous stomatitis, glossitis
Granulomatous oral Crohn disease
Inflammatory hyperplasia fissures and cobblestone mucosa
Peristomatitis vegetans

DERMATOLOGIC
Erythema nodosum
Pyoderma gangrenosum
Sweet syndrome
Metastatic Crohn disease
Psoriasis
Epidermolysis bullosa acquisita
Perianal skin tags
Polyarteritis nodosa
Melanoma and nonmelanoma skin cancers

OCULAR
Conjunctivitis
Uveitis, iritis
Episcleritis
Scleritis
Retrobulbar neuritis
Chorioretinitis with retinal detachment
Crohn keratopathy

HEMATOLOGIC/ONCOLOGIC
Anemia: iron deficiency (blood loss)
Vitamin B_{12} (ileal disease or resection, bacterial overgrowth, folate deficiency)
Anemia of chronic inflammation
Anaphylactoid purpura (Crohn disease)
Hyposplenism
Autoimmune hemolytic anemia
Coagulation abnormalities
Increased activation of coagulation factors
Activated fibrinolysis
Anticardiolipin antibody
Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions and pulmonary embolism
Systemic lymphoma (nonenteric)

RENAL AND GENITOURINARY
Metabolic
- Urinary crystal formation (nephrolithiasis, uric acid, oxalate)

Hypokalemic nephropathy
Inflammation
- Retroperitoneal abscess
- Fibrosis with ureteral obstruction
- Fistula formation

Glomerulitis
Membrane nephritis
Renal amyloidosis, nephrotic syndrome

PANCREATITIS
Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Ampullary Crohn disease
Granulomatous pancreatitis
Decreased pancreatic exocrine function
Sclerosing cholangitis with pancreatitis

HEPATOBILIARY
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis (pericholangitis)
Carcinoma of the bile ducts
Fatty infiltration of the liver
Cholelithiasis

Scleritis
Retrobulbar neuritis
Chorioretinitis with retinal detachment
Crohn keratopathy
Posterior segment abnormalities
Retinal vascular disease
Idiopathic orbital inflammation (orbital pseudotumor)

BRONCHOPULMONARY

Chronic bronchitis with bronchiectasis
Chronic bronchitis with neutrophilic infiltrates
Fibrosing alveolitis
Pulmonary vasculitis
Small airway disease and bronchiolitis obliterans
Eosinophilic lung disease
Granulomatous lung disease
Tracheal obstruction

CARDIAC

Pleuropericarditis
Cardiomyopathy
Endocarditis
Myocarditis

MALNUTRITION

Decreased intake of food
- Inflammatory bowel disease
- Dietary restriction

Malabsorption
- Inflammatory bowel disease
- Bowel resection
- Bile salt depletion
- Bacterial overgrowth

Intestinal losses
- Electrolytes
- Minerals
- Nutrients

Increased caloric needs
- Inflammation
- Fever

Small duct primary sclerosing cholangitis (pericholangitis)
Carcinoma of the bile ducts
Fatty infiltration of the liver
Cholelithiasis
Autoimmune hepatitis

ENDOCRINE AND METABOLIC

Growth failure, delayed sexual maturation
Thyroiditis
Osteoporosis, osteomalacia

NEUROLOGIC

Peripheral neuropathy
Meningitis
Vestibular dysfunction
Idiopathic intracranial hypertension (Pseudotumor cerebri)
Cerebral vasculitis
Migraine

Modified from Kugathasan S. Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004.p. 285.

Arthritis occurs in three patterns:

- ١-- **migratory peripheral** arthritis involving primarily large joints, The peripheral arthritis of IBD tends to be **nondestructive**.

- ٢-- **ankylosing spondylitis**,

Ankylosing spondylitis begins in the **third decade** and occurs most commonly in patients with **UC** +**HLA-B٢٧** .(low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected).

- ٣- **Isolated sacroiliitis** is usually asymptomatic but is common when a careful search is performed.

- Glomerulonephritis,
- uveitis,
- a hypercoagulable state
- Cerebral thromboembolic disease has been described in children with IBD.

Ulcerative colitis:

- localized to the colon and spares UGI tract.
- Disease usually begins in the rectum and extends proximally for a variable distance.
- # ٥٠-٨٠% of **pediatric** patients have **extensive colitis**; **adults** more commonly have distal disease.
-
- **Ulcerative proctitis** is **less likely** to be associated with **systemic manifestations**, although it may be **less** responsive to treatment than more diffuse disease.
- # **٣٠%** of children who present with UC experience **proximal spread** of the disease.

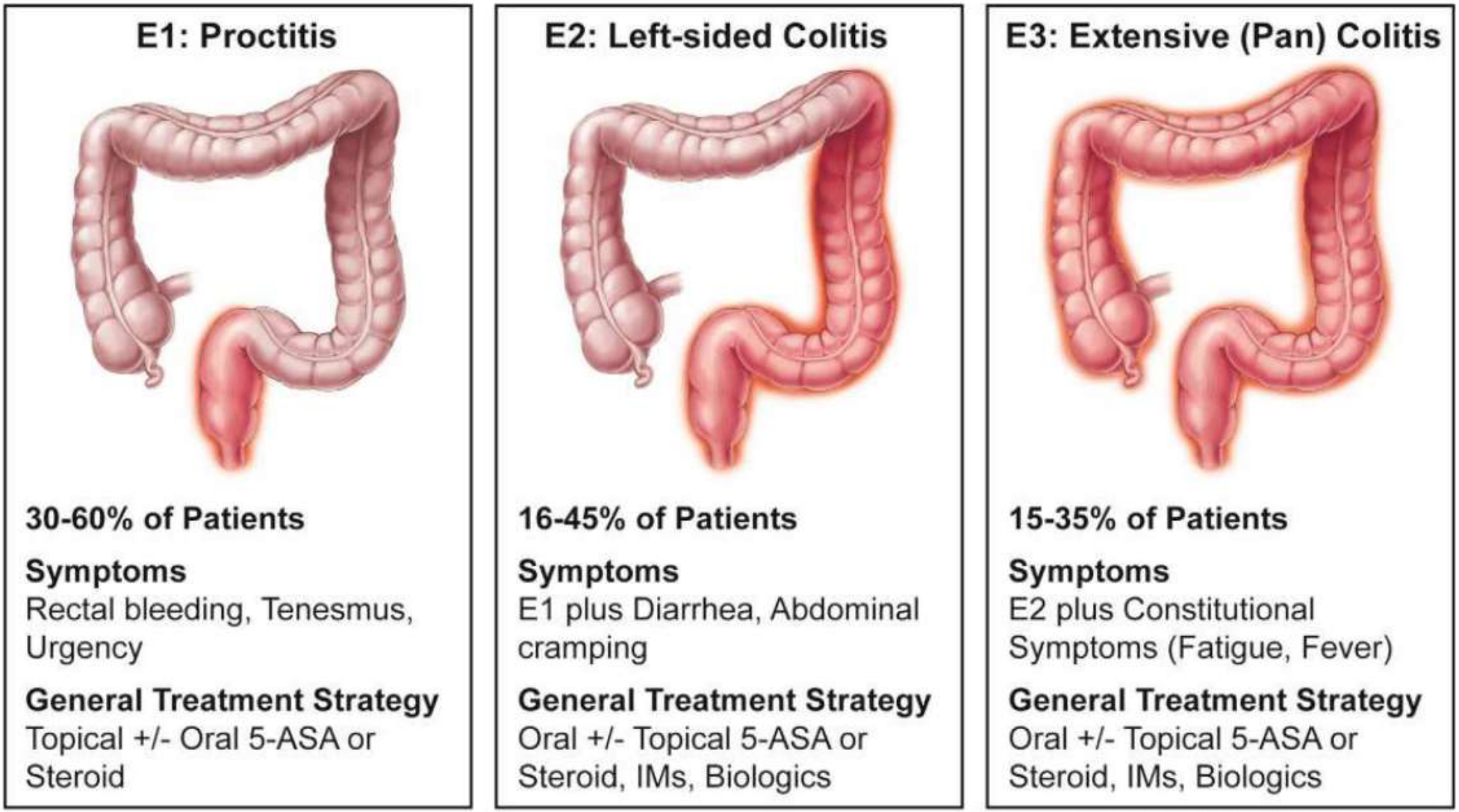


Fig. 382.2 Ulcerative colitis phenotypes by Montreal Classification. Symptoms and treatment strategy can differ based on extent of disease. 5-ASA, 5-Aminosalicylate; IM, immunomodulator. *(Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)*

- UC has rarely been noted to present in infancy (Missed diagnosis with CMA).
- Incidence of UC has increased but not to the extent of the increase in CD ; incidence varies with country of origin.
- **Men** are slightly more likely to acquire **UC** than are **women**; the reverse is true for **CD**.

CLINICAL MANIFESTATIONS:

- Blood, mucus, and pus in the stool as well as **diarrhea** are **typical** presentation of UC.
- **Constipation** may be observed in those with **proctitis**.
-
- Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common.
-
- The mode of onset ranges from **insidious with gradual** progression of symptoms to **acute and fulminant** (Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than ٥ bloody stools /day for ٥ days).
- **Chronicity** is an important part of the diagnosis (difficult to know if a patient has a course ١-٢ weeks of symptoms).
- Anorexia, weight loss, and growth failure may be present, although these complications are more typical of CD.

Table 382.4 Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): four stools per day, minimum signs of systemic symptoms
- S3 (severe): six or more bloody stools per day, pulse rate of ≥90 beats/min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, Extent; S, severity.

From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. *Lancet*. 2012;380: 1606–1616. Panel 2.

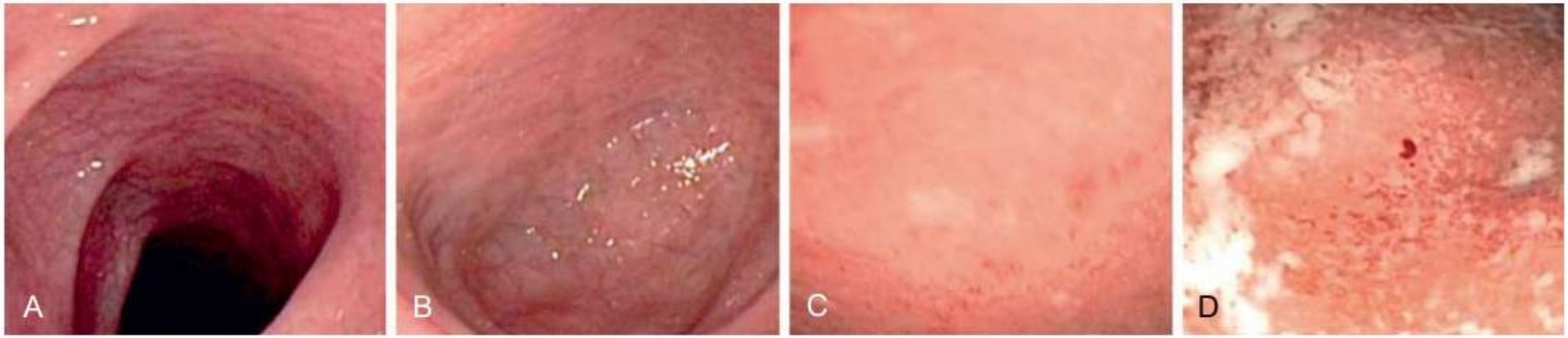


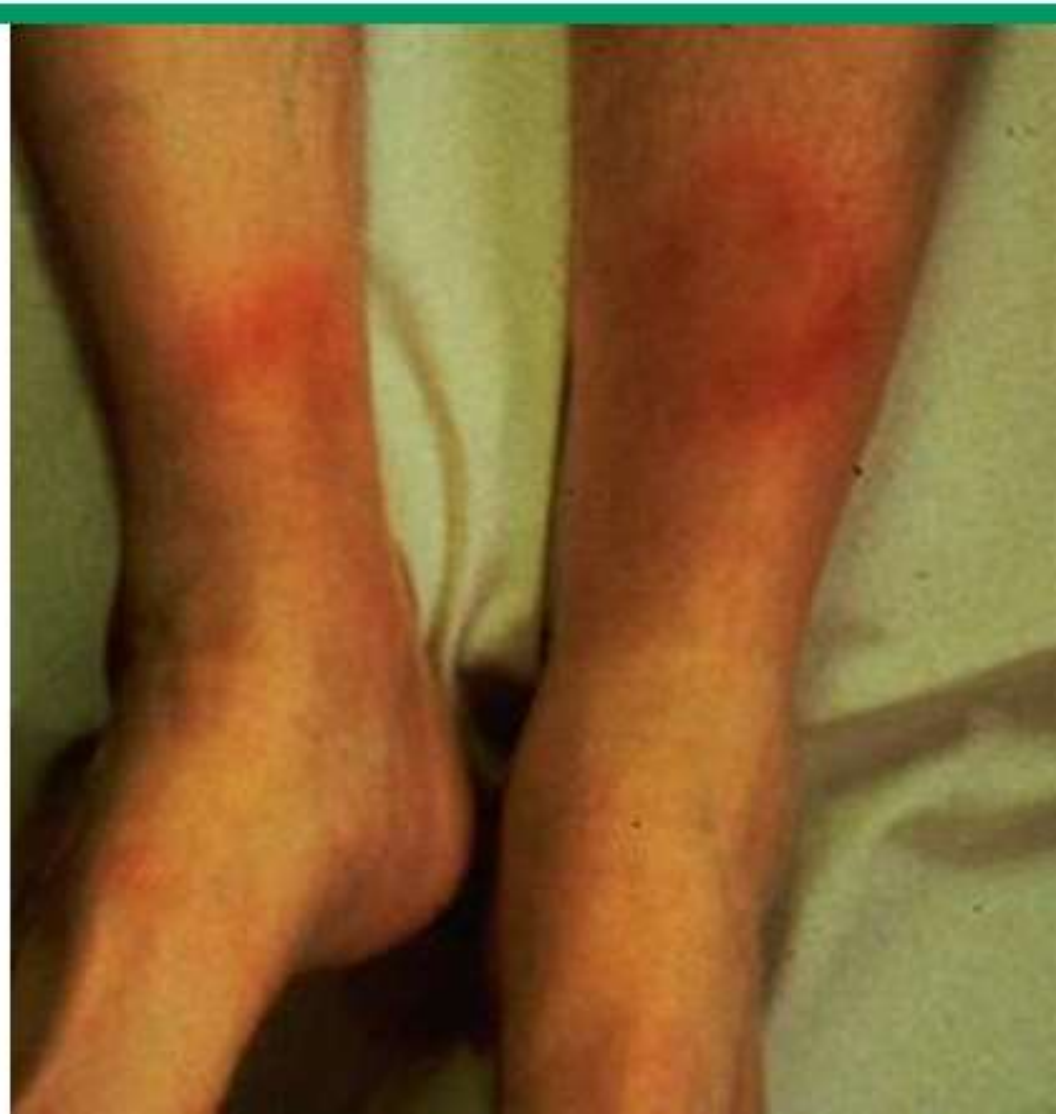
Fig. 382.1 Mayo endoscopic score for ulcerative colitis. **A,** Score 0 = normal; endoscopic remission. **B,** Score 1 = mild; erythema, decreased vascular pattern, mild friability. **C,** Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. **D,** Score 3 = severe; spontaneous bleeding, ulceration. *(Images courtesy Elena Ricart. From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. 2012;380:1606–1616. Fig. 2, p. 1610.)*

Table 382.7 Pediatric Ulcerative Colitis Activity Index

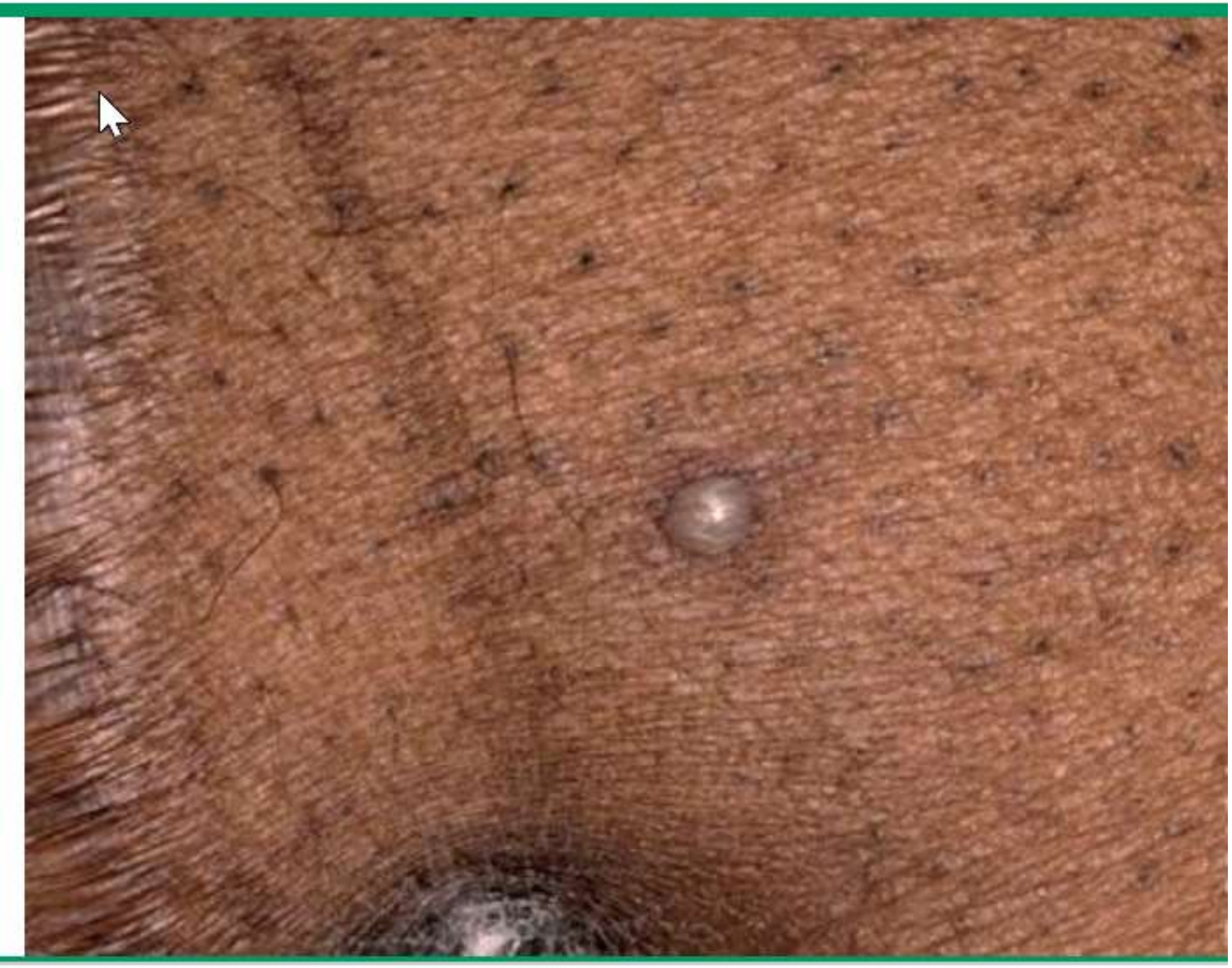
ITEM	POINTS
(1) ABDOMINAL PAIN	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) RECTAL BLEEDING	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) STOOL CONSISTENCY OF MOST STOOLS	
Formed	0
Partially formed	5
Completely unformed	10
(4) NUMBER OF STOOLS PER 24 HR	
0-2	0
3-5	5
6-8	10
>8	15
(5) NOCTURNAL STOOLS (ANY EPISODE CAUSING WAKENING)	
No	0
Yes	10
(6) ACTIVITY LEVEL	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

Extraintestinal manifestations that tend to occur more commonly with UC than with CD include:

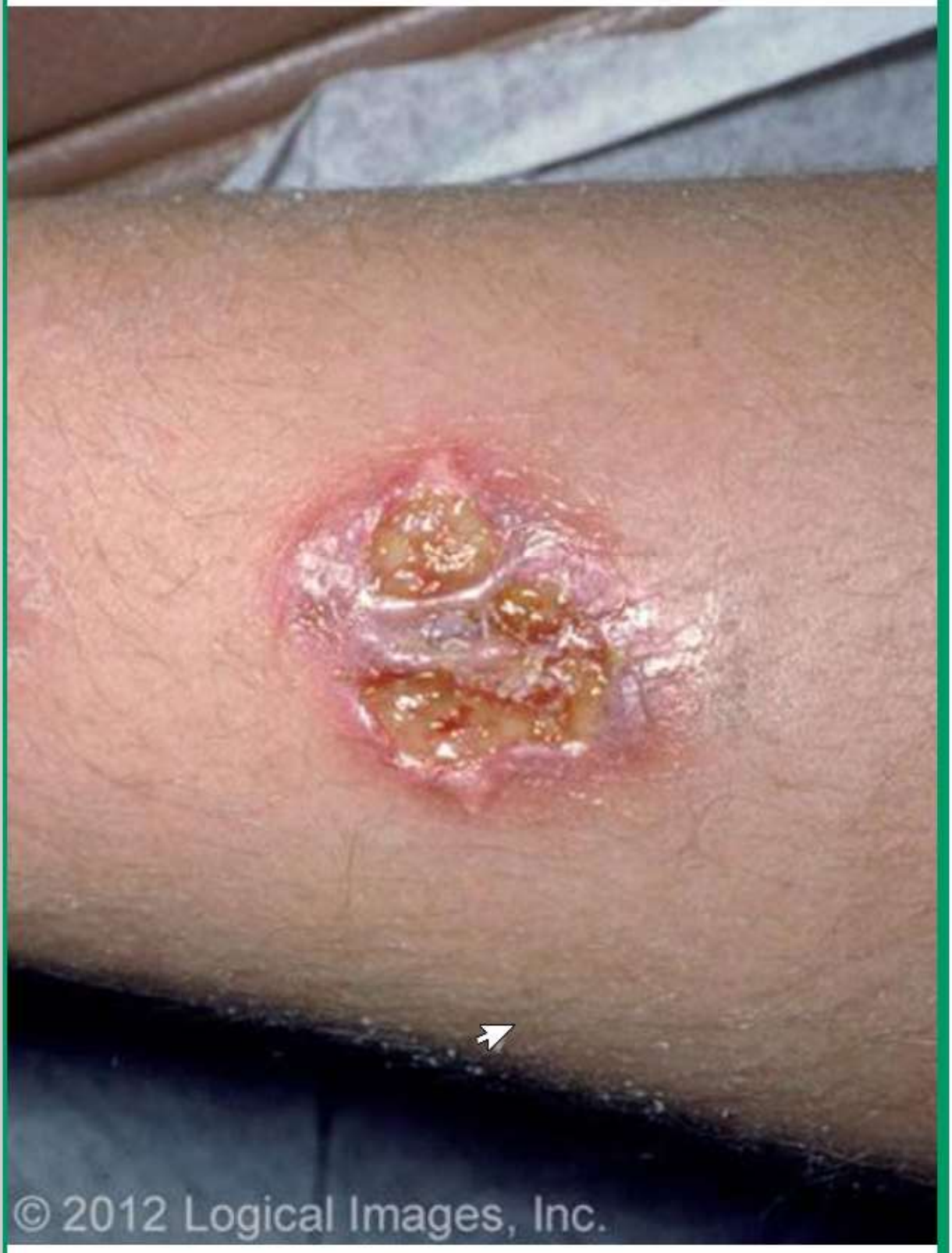
- pyoderma gangrenosum,
- sclerosing cholangitis,
- chronic active hepatitis,
- ankylosing spondylitis.
- **Iron deficiency** can result from **chronic blood loss** as well as **decreased intake**.
- **Folate deficiency** is unusual but may be accentuated in children treated with **sulfasalazine** (interferes with **folate absorption**).
- **anemia of chronic disease** (Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis).
- **Secondary amenorrhea** is common during periods of **active disease**



red nodular areas on the shins which are characteristic of erythema nodosum.



early lesion of pyoderma gangrenosum.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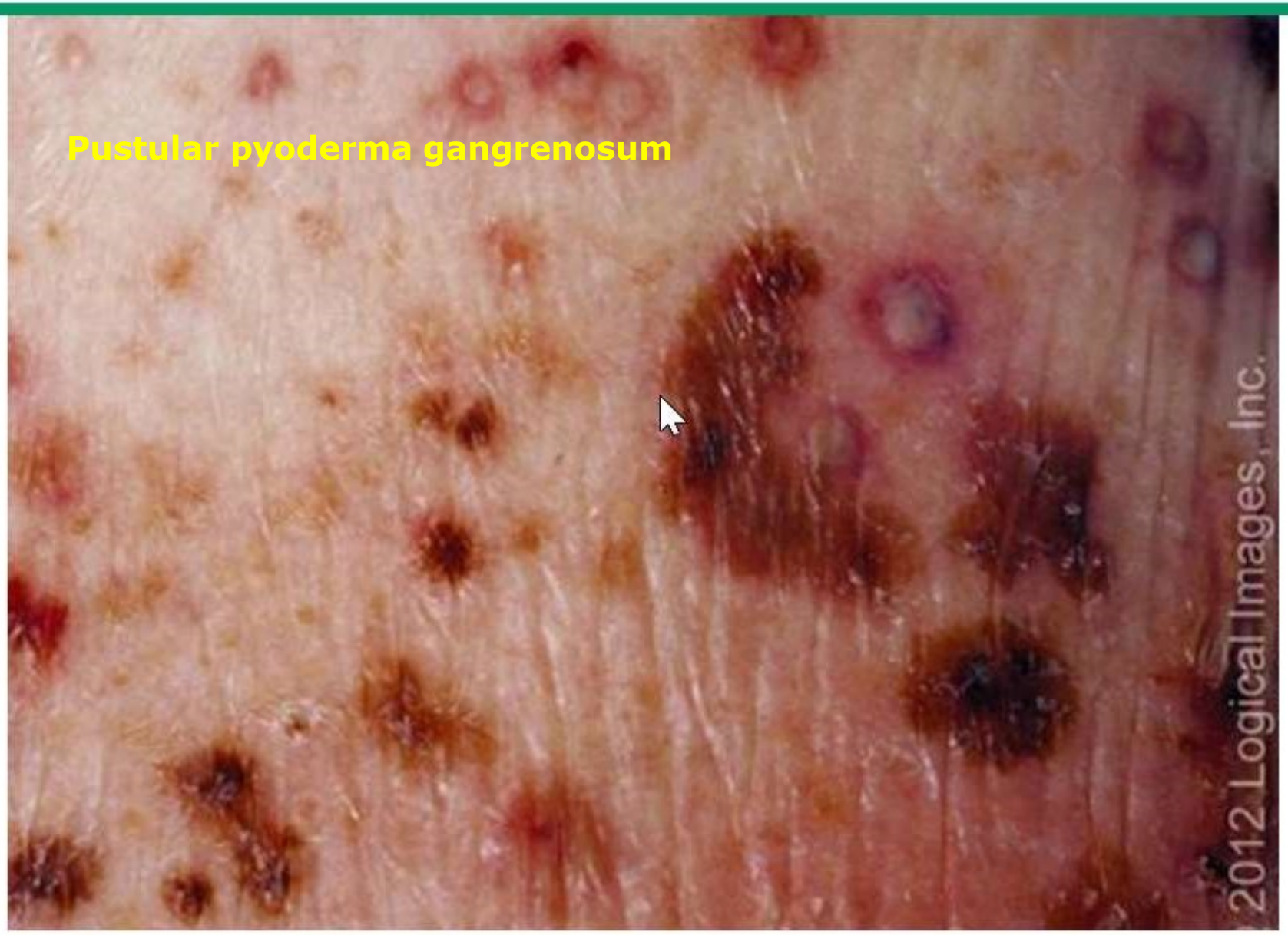
Bullous pyoderma gangrenosum


Pustular pyoderma gangrenosum
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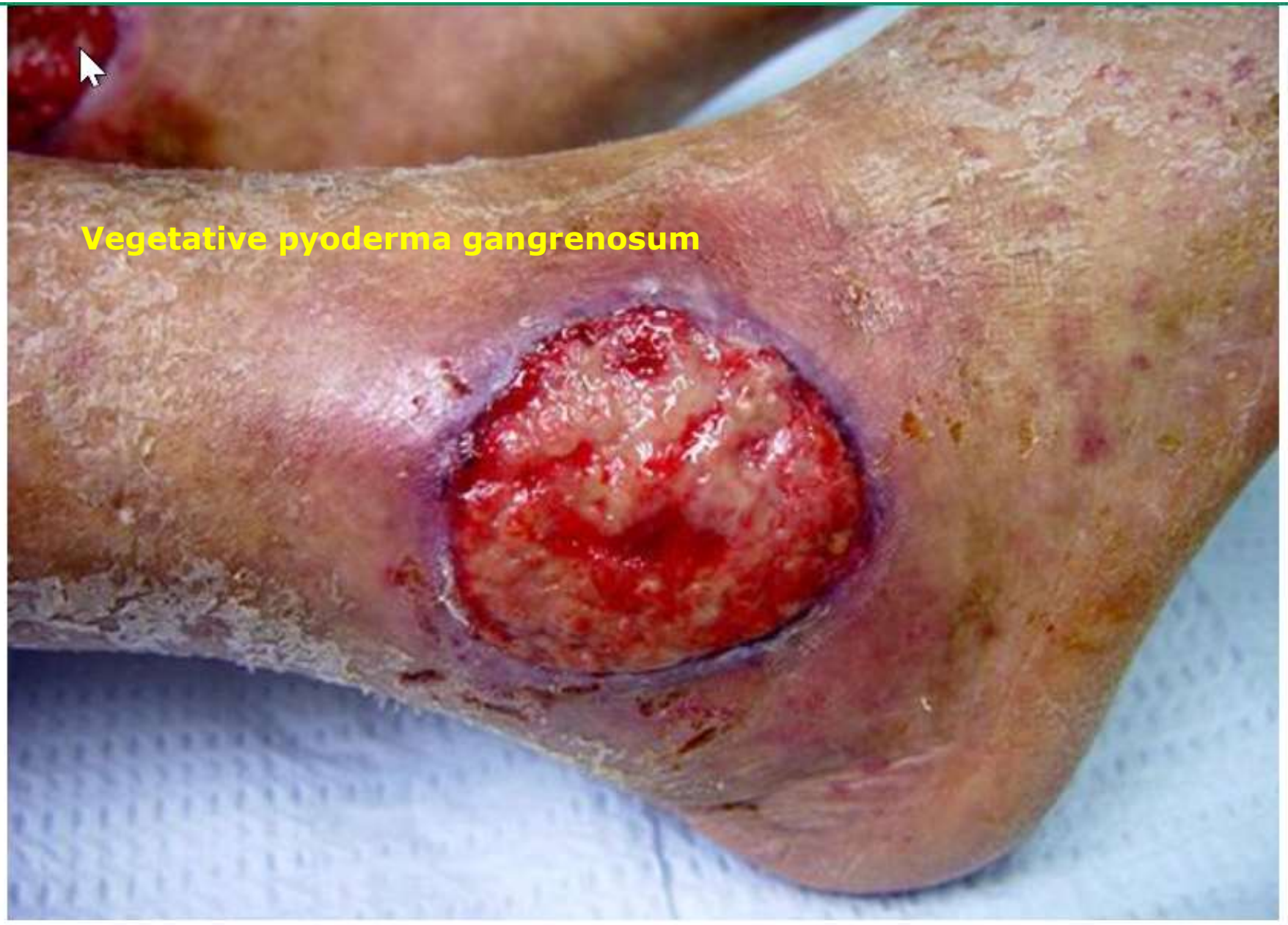
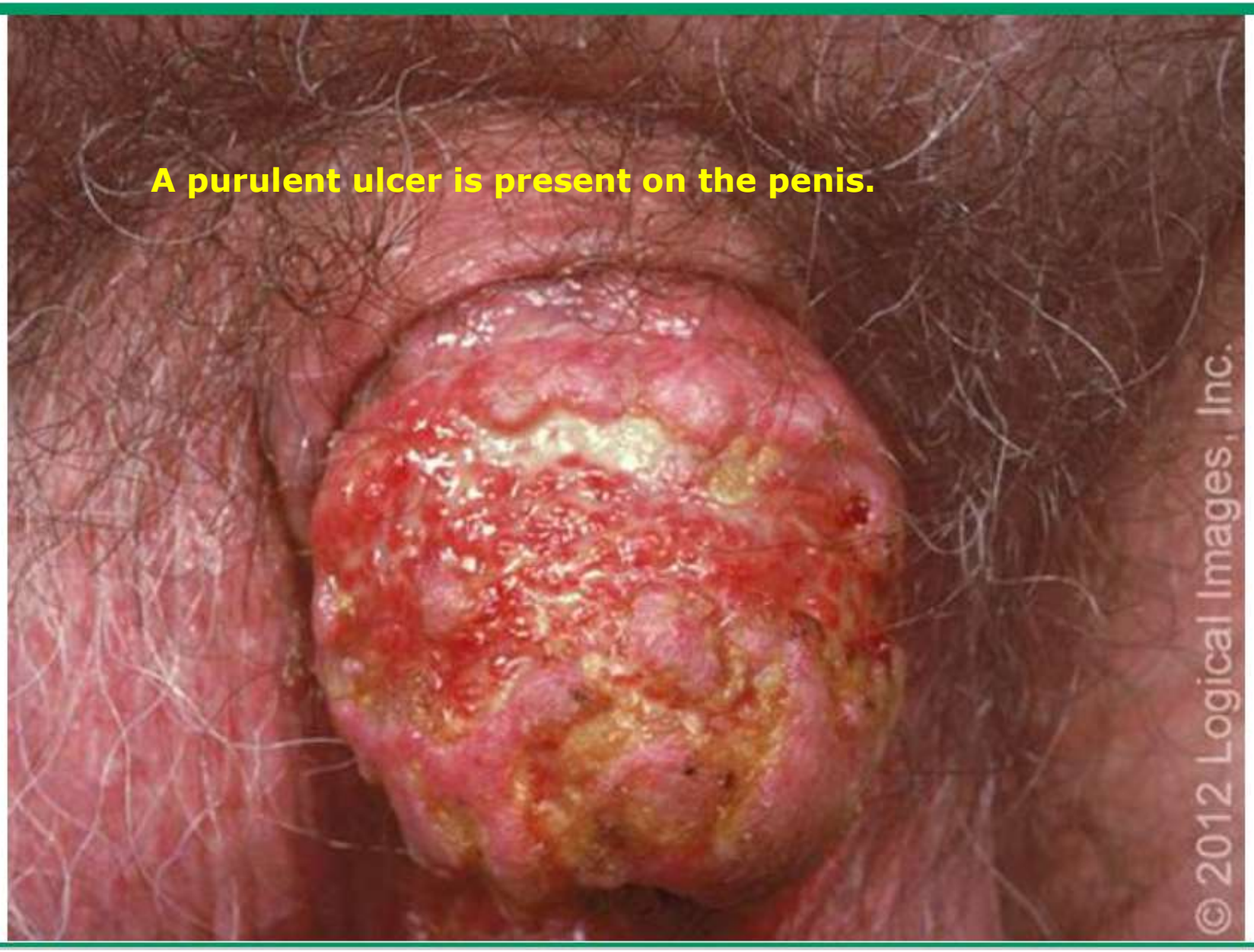

Vegetative pyoderma gangrenosum


Peristomal pyoderma gangrenosum is caused by an inflammatory process that produces severe and painful skin ulcerations.


A purulent ulcer is present on the penis.
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DIFFERENTIAL DIAGNOSIS

- Allergic colitis,
- Crohn colitis.
- Infectious colitis,
- Every child with a new diagnosis of UC should have stool cultured for enteric pathogens, stool evaluation for C. difficile, ova and parasites, and perhaps serologic studies for amebae .
- CMV infection can mimic UC or be associated with an exacerbation of existing disease, usually in immunocompromised patients.
- At the onset, the colitis of HUS may be identical to that of early UC.
- Although IgA vasculitis (Henoch-Schönlein purpura) can manifest as abdominal pain and bloody stools, it is not usually associated with colitis.
- Behçet disease can be distinguished by its typical features .
- Other considerations are radiation proctitis,
- viral colitis in immunocompromised patients,
- ischemic colitis.
- Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with UC.

Table 382.5 Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
Salmonella	Watery → bloody diarrhea, food-borne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium* tuberculosis Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	As in *Cryptosporidium*		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

Table 382.6 Chronic Inflammatory Bowel–Like Intestinal Disorders Including Monogenic Diseases

INFECTION (SEE TABLE 382.5)
AIDS-Associated
Toxin
Immune–Inflammatory
Severe combined immunodeficiency diseases
Agammaglobulinemia
Chronic granulomatous disease
Wiskott-Aldrich syndrome
Common variable immunodeficiency diseases
Acquired immunodeficiency states
Dietary protein enterocolitis
Autoimmune polyendocrine syndrome type 1
Behçet disease
Lymphoid nodular hyperplasia
Eosinophilic gastroenteritis
Omenn syndrome
Graft-versus-host disease
IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes
Interleukin-10 signaling defects
Autoimmune enteropathy*
Microscopic colitis
Hyperimmunoglobulin M syndrome
Hyperimmunoglobulin E syndromes
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase $C\gamma_2$ defects
IL10RA pathogenic variant
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2 (*XIAP* gene)
Congenital neutropenias
TRIM22 pathogenic variant
Leukocyte adhesion deficiency 1
NLRC4 pathogenic variants

VASCULAR–ISCHEMIC DISORDERS
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis

OTHER
Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Kindler syndrome
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome

*May be the same as IPEX.

diagnosis of UC:

- Typical presentation in absence of an identifiable specific cause .
-
- anemia (either iron deficiency or the anemia of chronic disease)
- hypoalbuminemia.
- Although ESR **and** CRP are often elevated, (may be normal even with fulminant colitis)
- An elevated WBC is usually seen only with more severe colitis.
- Fecal calprotectin levels are usually elevated (a **more** sensitive and specific marker of **GI inflammation**).
- Barium enema is **suggestive** but **not diagnostic** of acute (Fig. ٣٨٢/٣) or chronic burned-out disease
- A barium enema is **contraindicated** in the setting of a potential toxic megacolon.

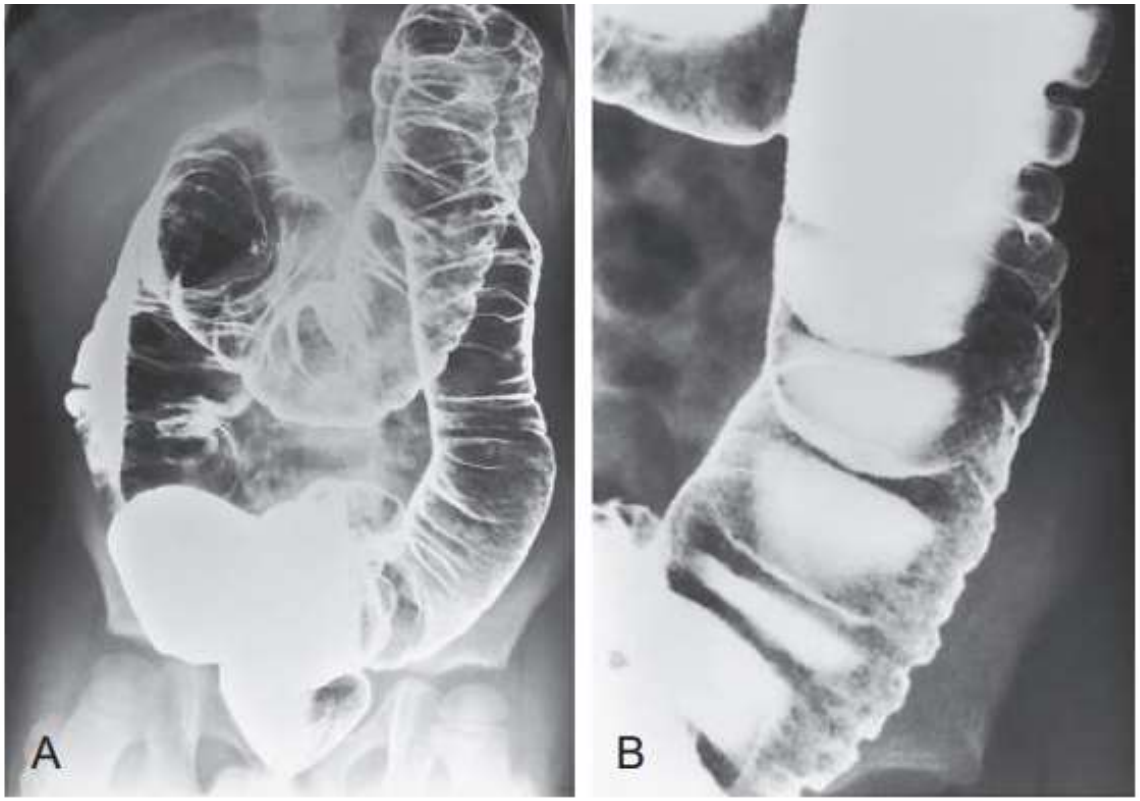


Fig. 382.3 Ulcerative colitis. Double-contrast barium enema in a 5-yr-old child who had had intermittent intestinal and extraintestinal symptoms since the age of 3 yr. **A,** Small ulcerations are distributed uniformly about the colonic circumference and continuously from the rectum to the proximal transverse colon. This pattern of involvement is typical of ulcerative colitis. **B,** In this coned view of the sigmoid in the same patient, small ulcerations are represented by fine spiculation of the colonic contour in tangent and by fine stippling of the colon surface en face. *(From Hoffman AD. The child with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediatric Radiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 260.)*

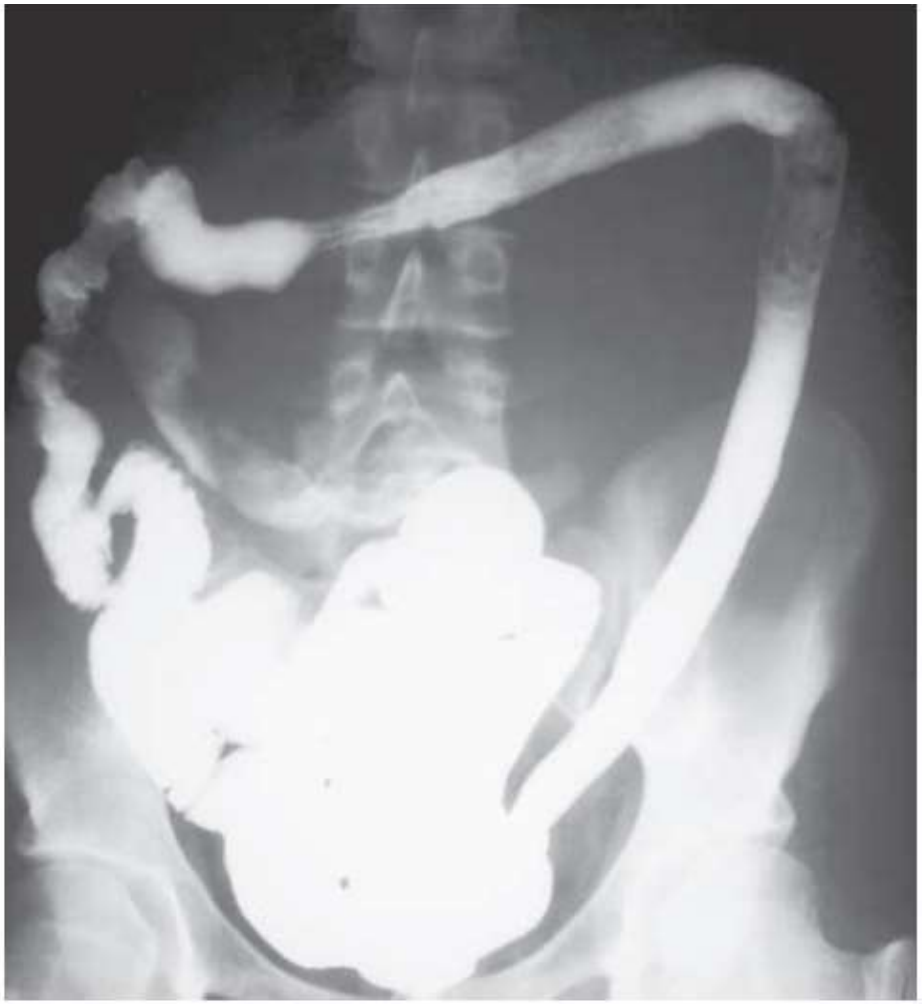


Fig. 382.4 Ulcerative colitis: late changes. This single-contrast bariu
nema shows the late changes of ulcerative colitis in a 15-yr-old chil
he colon is featureless, reduced in caliber, and shortened. Dilation
ne terminal ileum (backwash ileitis) is present. *(From Hoffman AD. T*
hild with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediat
adiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 262.)

- A perinuclear antineutrophil cytoplasmic antibody (**P-ANCA**:a marker of genetically controlled immunoregulatory disturbance) is found in # ٧٠% of patients with **UC** compared with <٢٠% **CD** .
- # ٥٥% of those with **CD** are positive for anti-Saccharomyces cerevisiae antibody(**ASCA**)
-

- Flexible **sigmoidoscopy** = confirm the **diagnosis**;
- **colonoscopy** can evaluate the **extent of disease** and **R/O Crohn colitis** .
- A colonoscopy **should not** be performed when **fulminant colitis** is **suspected** (of the risk of provoking **toxic megacolon** or a **perforation** during the procedure.

- Degree of colitis can be evaluated by the gross appearance of the mucosa.
- **Biopsy** of involved bowel demonstrates:
- evidence of **acute and chronic mucosal inflammation**.
- cryptitis,
- crypt abscesses,
- separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion,
- branching of crypts (not seen in infectious colitis).
- Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggest Crohn disease.

Perianal disease

- Except for *mild local irritation* or **anal fissures** associated with diarrhea, should make the clinician think of CD.
- Plain radiographs of the abdomen : loss of haustral markings in an air-filled colon or marked dilation with toxic megacolon.
- With severe colitis, the colon may become dilated; a diameter of >۶ cm, determined radiographically, in an adult suggests toxic megacolon.
- If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an UGI series with SBFT and then look at delayed films of the colon.
- **Small bowel ultrasonography** is another option for evaluation of small intestinal inflammation.
- CT and MR enterography allow for even higher resolution images of the small intestine.
- A **barium enema** is **contraindicated** in the setting of a **potential toxic megacolon**.

TREATMENT

- A **medical cure** for ulcerative colitis **is not** available;

Aims :

- controlling symptoms
- reducing the risk of recurrence,
- minimizing steroid exposure.
-
- ١--**mild or mild to moderate colitis** is **an ASA**.
- **Sulfasalazine** (sulfur +٥-ASA). This linkage prevents absorption of medication in UGI tract, allowing it to reach the colon, where the two components are separated by bacterial cleavage.
- Dose of sulfasalazine is ٣٠-١٠٠ mg/kg/٢٤ hr(divided into two to four doses),<٢-٤ g/٢٤ hr.
- **Hypersensitivity to sulfa** component is major side effect of sulfasalazine and occurs in ١٠-٢٠% .
- Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated ٥-ASA preparations (mesalamine, ٥٠-١٠٠ mg/kg/day; balsalazide ٢/٢٥- ٦/٧٥ g/day).
- Medication be **continued even** when the disorder is **in remission**.
- These medications might also modestly **decrease** the lifetime risk of **colon cancer**

- # ٥% of patients have an **allergic reaction** to ٥-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from **symptoms of a flare of UC**.
- ٥-ASA can also be given in **enema** **or** **suppository** form and is especially useful for **proctitis**.
- **Hydrocortisone enemas** are used to treat proctitis as well(probably not as effective).
- **A combination** of **oral** **and** **rectal** **٥-ASA** as well as **rectal** **monotherapy** has been shown to be **more effective** than **just** **oral** ٥-ASA for **distal colitis**.
- **Extended release budesonide** may also **induce remission** in mild to moderate UC..
- **Rectal preparations of budesonide** are also available

- **Probiotics** are effective in **adults** for **maintenance of remission** for UC.

- **The most promising role** for probiotics has been to **prevent pouchitis**, a common complication following colectomy and IPAA surgery.
- --٢- Children with **moderate to severe pancolitis** or **unresponsive** colitis **to ٥-ASA** therapy should be treated with **corticosteroids**, most commonly **oral prednisone**.
- Prednisone is ١-٢ mg/kg/٢٤ hr (٤٠-٦٠ mg maximum dose).
-
- Steroids are considered an effective medication for acute flares, but they **are not appropriate maintenance medications** because of loss of effect and side effects, including poor growth, adrenal suppression, cataracts, osteopenia, aseptic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects

- For a hospitalized patient with persistence of symptoms despite **intravenous steroid** treatment for **٣-٥ days**, **escalation of therapy** or **surgical options** should be considered.
- The validated pediatric ulcerative colitis activity index can be used to help determine current disease severity based on clinical factors and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table ٣٨٢/٧)

Table 382.7 Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) ABDOMINAL PAIN	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) RECTAL BLEEDING	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) STOOL CONSISTENCY OF MOST STOOLS	
Formed	0
Partially formed	5
Completely unformed	10
(4) NUMBER OF STOOLS PER 24 HR	
0-2	0
3-5	5
6-8	10
>8	15
(5) NOCTURNAL STOOLS (ANY EPISODE CAUSING WAKENING)	
No	0
Yes	10
(6) ACTIVITY LEVEL	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

- With medical management, most children are in remission within ٣ months; however, ٥-١٠% continue to have symptoms unresponsive to treatment beyond ٦ months.
- ٣-- Many children with disease requiring frequent corticosteroid therapy are started on **immunomodulators** such as azathioprine (٢/٠-٢/٥ mg/kg/day) or ٦-MP(١-١/٥ mg/kg/ day).
- **Not appropriate** choice in a patient who is **nonresponsive to steroids** with acute severe colitis because of longer onset of action.
- **Lymphoproliferative** disorders are associated with thiopurine use.

- ٤--**Infliximab and adalimumab**, which are a fully human monoclonal antibody to tumor necrosis factor (TNF)-α, are effective for **induction** and **maintenance** therapy in children and adults with moderate to severe disease.
- TNF blocking agents are associated with an increased risk of infection (particularly TB) and malignancies (lymphoma, leukemia).

other agents that are approved for adults UC :

- vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract,
- ustekinumab, a monoclonal antibody against interleukins (ILs) ١٢ and ٢٣.
- tofacitinib and upadacitinib; oral Janus kinase inhibitors;
- ozanimod, a sphingosine ١-phosphate receptor modulator that leads to peripheral lymphocyte sequestration.
- A specific combination of three to four broad-spectrum oral antibiotics given over ٢-٣ weeks may be effective in treating severe pediatric ulcerative colitis refractory to other therapies, but it is being further studied in children

Surgical:

Colectomy is performed for:

- ١- intractable disease,
- ٢- complications of therapy,
- ٣- fulminant disease that is unresponsive to medical management.

- **No clear benefit** of the use of **TPN** or a **continuous enteral elemental diet** in the treatment of **severe UC** has been noted.
- Nevertheless, parenteral nutrition is used if **oral intake is insufficient** so that the patient will be nutritionally ready for surgery if medical management fails.
- With **any medical treatment** for UC, the clinician should always **weigh the risk** of the medication or therapy against the **fact** that colitis can be successfully treated surgically
- ٤-Detection of significant dysplasia on biopsy would prompt colectomy

- Surgical treatment for intractable or fulminant colitis is **total colectomy**.

- major complication of this operation **is pouchitis**, which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever.
- Pouchitis is seen in ٣٠-٤٠% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin.
- Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy

Support:

- Psychosocial support is an important part of therapy for this disorder.
- Patient and family support from a social worker or family counselor.
- Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

PROGNOSIS:

- is marked by **remissions and exacerbations**.
- Most children with this disorder respond initially to medical management.
- Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods.
- An occasional child with mild onset, however, experiences intractable symptoms later.

- After treatment of initial symptoms, # ٥% of children with UC have a prolonged remission (longer than ٣ years).
- **#٢٥%** of children presenting with **severe UC** require **colectomy within ٥ years** of diagnosis, compared with **only ٥%** of those presenting with **mild disease**.
- It is important to consider the possibility of **enteric infection** with **recurrent symptoms**, specifically **Clostridium difficile**; these infections can **mimic** a **flare-up** or **actually provoke** a **recurrence**.
- The use of **NSAIDs** drugs is considered by some to **predispose to exacerbation**

- **risk of colon cancer** begins to increase after ٨-١٠ years of disease and can then **increase** by **٠/٥-١% per year**.
-
- **Proctitis** alone is associated with virtually **no increase in risk** over the general population.
- Because colon cancer is usually preceded by changes of **mucosal dysplasia**, UC for > ٨-١٠ years be **screened** with **colonoscopy and biopsies** **every ١-٢ years**.
- Although this is the **current standard** of practice, it **is not clear** if morbidity and mortality are changed by **this approach**.
- Two competing concerns about this plan of management remain unresolved.

١- The original studies may have overestimated the risk of colon cancer;

٢- screening for dysplasia might not be adequate for preventing colon cancer in UC.

- **Crohn Disease** (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

- Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table ٣٨٢/٢).
- The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas).
- Although inflammation in UC is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often transmural.

Table 382.2 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50–75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for intestinal cancers	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

- Pediatric CD is more likely to have extensive anatomic involvement.

At initial presentation:

- more than ٥٠% of patients have ileocolitis,
- ٢٠% have exclusively colonic disease
- UGI involvement (esophagus, stomach, duodenum) is seen in up to ٣٠% of children.
- Isolated small bowel disease is much less common in the pediatric population compared to adults.
- Isolated colonic disease is common in children younger than ٨ years of age and may be indistinguishable from UC.
- Anatomic location of disease tends to extend over time in children.
- CD tends to have a bimodal age distribution, with the first peak beginning in the teenage years.
- Incidence of CD has been increasing.
- In USA (incidence of pediatric CD= ٤٫٥٦/١٠٠٬٠٠٠ and Prevalence is ٤٣/١٠٠٬٠٠٠ children).

CLINICAL MANIFESTATIONS CD:

can be characterized as :

- inflammatory,
- Stricturing
- penetrating.

- Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostenosis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping).
- Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Figs. ٣٨٢/٥ and ٣٨٢/٦)

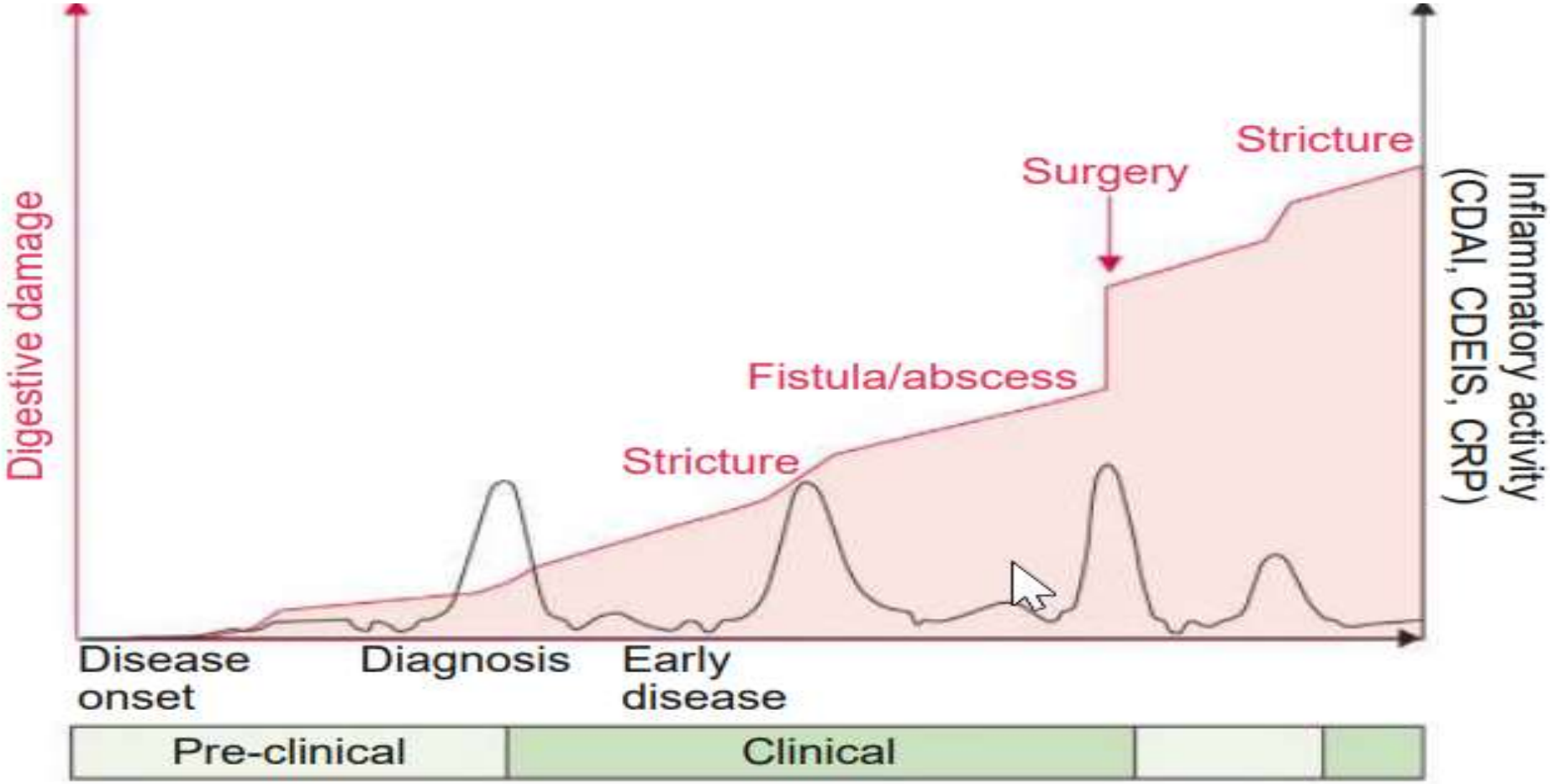
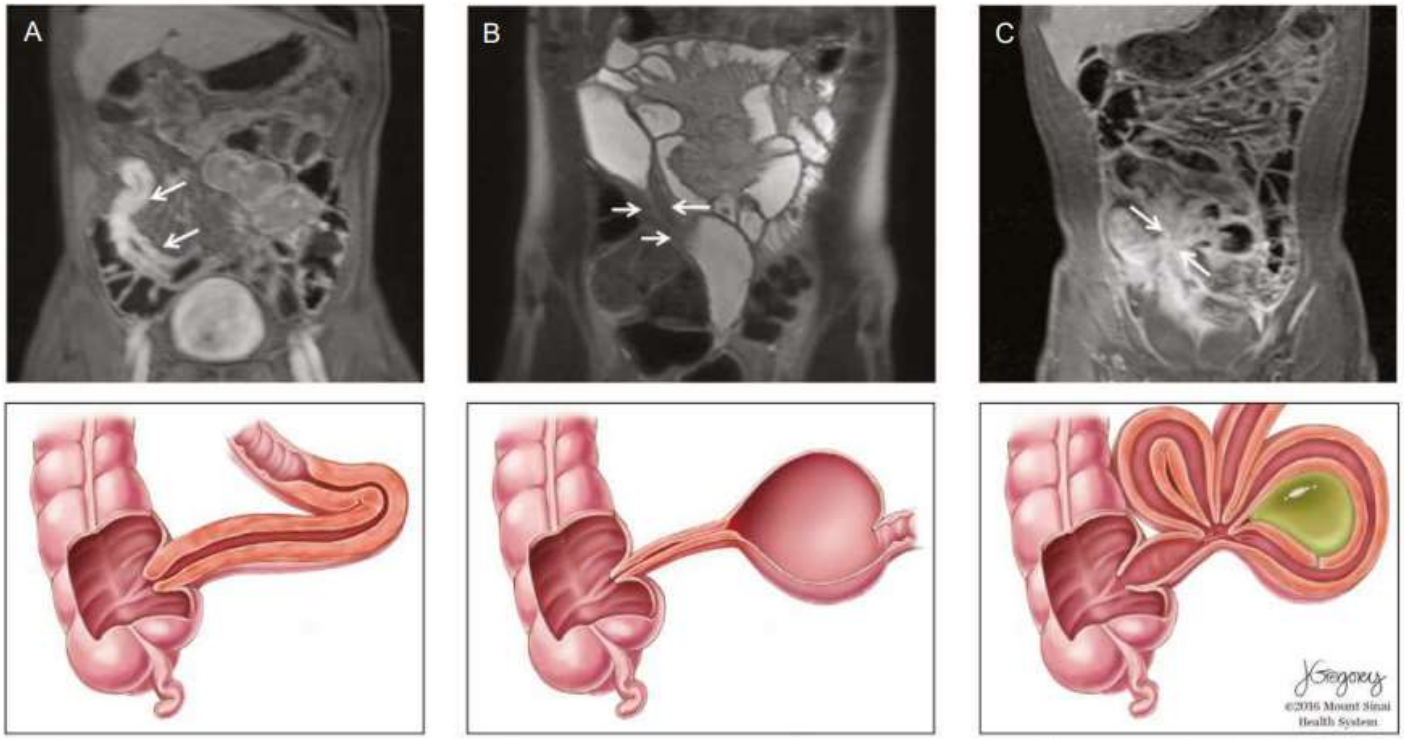


Fig. 382.5 The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn disease. CDAI, Crohn disease activity index; CDEIS, Crohn disease of endoscopic severity; CRP, C-reactive protein. *(From Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–1602. Fig. 5, p. 1596.)*



- Diarrhea
- Abdominal pain
- Weight loss
- Low-grade fever
- Fatigue
- Growth retardation
- Malnourishment

- Postprandial pain
- Bloating
- Nausea and vomiting
- Occlusion/subocclusion

- Symptoms depend on the location of fistulae
- Enterourinary fistula: fecaluria, pneumaturia, recurrent UTI
- Rectovaginal fistula: dispareunia, stool discharge through the vagina
- Enteroenteric fistula: asymptomatic, abdominal abscesses

Fig. 382.6 Behavior of Crohn disease (CD) as per Montreal classification represented in MR enterography (MRE) and illustrated with typical symptoms. **A**, T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows mural thickening and enhancement in the distal ileum *(arrows)* in a patient with active CD. **B**, T2 weighted MRE imaging shows a narrowed luminal segment with thickened wall and upstream dilation *(arrows)*, suggesting the presence of a stricture. **C**, T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows multiple converging enhancing loops of small bowel suggestive of enteroenteric fistulas *(arrows)*. Lower illustration shows a deep and transmural fissure or ulcer leading to the formation of an abscess. UTI, Urinary tract infection. *(Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)*

- Systemic signs and symptoms are more common in CD than in UC.
- Fever, malaise, and easy fatigability are common.
- Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by ١ or ٢ years and is at least twice as likely to occur with Crohn disease as with ulcerative colitis.
- Children can present with growth failure as the only manifestation of CD.
- Decreased height velocity occurs in about ٨٨% of prepubertal patients diagnosed with CD, and this often precedes GI symptoms.
- Causes of growth failure include inadequate caloric intake (anorexia, partial obstruction-related pain), suboptimal absorption or excessive loss of nutrients, the effects of chronic inflammation on bone metabolism and appetite, and the use of corticosteroids during treatment.
- Primary or secondary amenorrhea and pubertal delay are common.
- In contrast to UC, perianal disease is common (tag, fistula, deep fissure, abscess).
- Gastric or duodenal involvement may be associated with recurrent vomiting and epigastric pain.
- Partial small bowel obstruction, usually secondary to narrowing of the bowel lumen from inflammation or stricture, can cause symptoms of cramping abdominal pain (especially with meals), borborygmus, and intermittent abdominal distention (Fig. ٣٨٢/٧).
- Stricture should be suspected if the child notes relief of symptoms in association with a sudden sensation of gurgling of intestinal contents through a localized region of the abdomen

- Penetrating disease is demonstrated by fistula formation.
- Enteroenteric or enterocolonic fistulas (between segments of bowel) are often asymptomatic but can contribute to malabsorption if they have high output or result in bacterial overgrowth.
- Enterovesical fistulas (between bowel and urinary bladder) originate from ileum or sigmoid colon and appear as signs of urinary infection, pneumaturia, or fecaluria.
- Enterovaginal fistulas originate from the rectum, cause feculent vaginal drainage, and are difficult to manage.
- Enterocutaneous fistulas (between bowel and abdominal skin) often are caused by prior surgical anastomoses with leakage.
- Intraabdominal abscess may be associated with fever and pain but might have relatively few symptoms.
- Hepatic or splenic abscess can occur with or without a local fistula.
- Anorectal abscesses often originate immediately above the anus at the crypts of Morgagni.
- The patterns of perianal fistulas are complex because of the different tissue planes.
- Perianal abscess is usually painful, but perianal fistulas tend to produce fewer symptoms than anticipated.
- Purulent drainage is commonly associated with perianal fistulas.
- Psoas abscess secondary to intestinal fistula can present as hip pain, decreased hip extension (psoas sign), and fever.

Extraintestinal manifestations

- occur more commonly with CD than with UC ; include
- oral aphthous ulcers,
- peripheral arthritis,
- erythema nodosum,
- digital clubbing,
- episcleritis,
- venous thrombosis,
- pulmonary disease,
- renal stones (uric acid, oxalate),
- gallstones. Any of the extraintestinal disorders described in the section on IBD can occur with Crohn disease (see Table ٣٨٢/٣). The peripheral arthritis is nondeforming. The occurrence of extraintestinal manifestations usually correlates with the presence of colitis.
- Metastatic Crohn disease is most often cutaneous, presenting with noncaseating granulomas in a location that is not contiguous with an active penetrating lesion; it may resemble erythema nodosum

- Extensive involvement of small bowel, especially in association with surgical resection, can lead to short bowel syndrome, which is rare in children.
- Complications of terminal ileal dysfunction or resection include bile acid malabsorption with secondary diarrhea and vitamin B_{12} malabsorption, with possible resultant deficiency.
- Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk of renal stones secondary to ileal inflammation.
- The risk of cholelithiasis is also increased secondary to bile acid depletion.

- A disorder with this diversity of manifestations can have a major impact on an affected child’s lifestyle.
- Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, havin

DIFFERENTIAL DIAGNOSIS

- ١-infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables ٣٨٢/٥ and ٣٨٢/٦; Table ٣٨٢/٨).
- . Yersinia can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are more likely to be mistaken for ulcerative colitis than for Crohn disease.
- Celiac disease and Giardia infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy.
- GI tuberculosis is rare but can mimic Crohn disease.
- Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease.
- Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular filling defects of the bowel without ulceration or narrowing of the lumen.
- Bowel lymphoma is much less common in children than is Crohn disease.
- Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease.
- Lymphoid nodular hyperplasia of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis.
- Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Growth failure may be the only manifestation of Crohn disease; other disorders such as:

- growth hormone deficiency,
- gluten-sensitive enteropathy (celiac disease),
- Turner syndrome,
- anorexia nervosa
- If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made.
- Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder.
- Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease.
- Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease.
- Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table ۳۸۲/۶).

DIAGNOSIS:

- ١-variety of symptom combinations (see Fig. ٣٨٢/٦). Only ٢٥% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only ٢٥% have GI bleeding
- ٢- laboratory studies,
- ٣- endoscopic
- ٤- radiologic findings
- ٥- ruling out specific entities that mimic Crohn disease,

- Children with Crohn disease often appear:
- chronically ill.
- weight loss and growth failure
- often malnourished.
- The earliest sign of growth failure is decreased height velocity, which can be present in up to ٨٨% of prepubertal patients with Crohn disease and typically precedes symptoms.
- Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea.
- There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic.
- Large anal skin tags (١-٣ cm in diameter) or perianal fistulas with purulent drainage suggest Crohn disease.
- Digital clubbing, findings of arthritis, and skin manifestations may be present.

CBC:

- anemia (commonly), often **IDA** ,
- thrombocytosis.
- ESR and CRP often elevated, (may be unremarkable).
- Hypoajbuminemia (small bowel inflammation or PLE).
- Fecal calprotectin and lactoferrin are more sensitive and specific markers of bowel inflammation as compared to serologic parameters, and these are often elevated.
- Multiple serologic, immune, and genetic markers can also be abnormal, although the best utilization of these remains to be determined.

- EGD and ileocolonoscopy +BX
- Findings on biopsy may be only nonspecific chronic inflammatory changes. Noncaseating granulomas, similar to those of sarcoidosis, are the most characteristic histologic findings, although often they are not present.
- Transmural inflammation is also characteristic but can be identified only in surgical specimens.

- radiologic studies(SBFT): may be normal or might demonstrate findings of partial small bowel obstruction or thumbprinting of the colon wall (Fig. ٣٨٢/٨).
- An upper GI contrast study with small bowel follow-through might show aphthous ulceration and thickened, nodular folds as well as narrowing or stricturing of the lumen. Linear ulcers can give a cobblestone appearance to the mucosal surface. Bowel loops are often separated as a result of thickening of bowel wall and mesentery (Fig. ٣٨٢/٩). Other manifestations on radiographic studies that suggest more severe Crohn disease are fistulas between bowel (enteroenteric or enterocolonic), sinus tracts, and strictures (see Fig. ٣٨٢/٧).

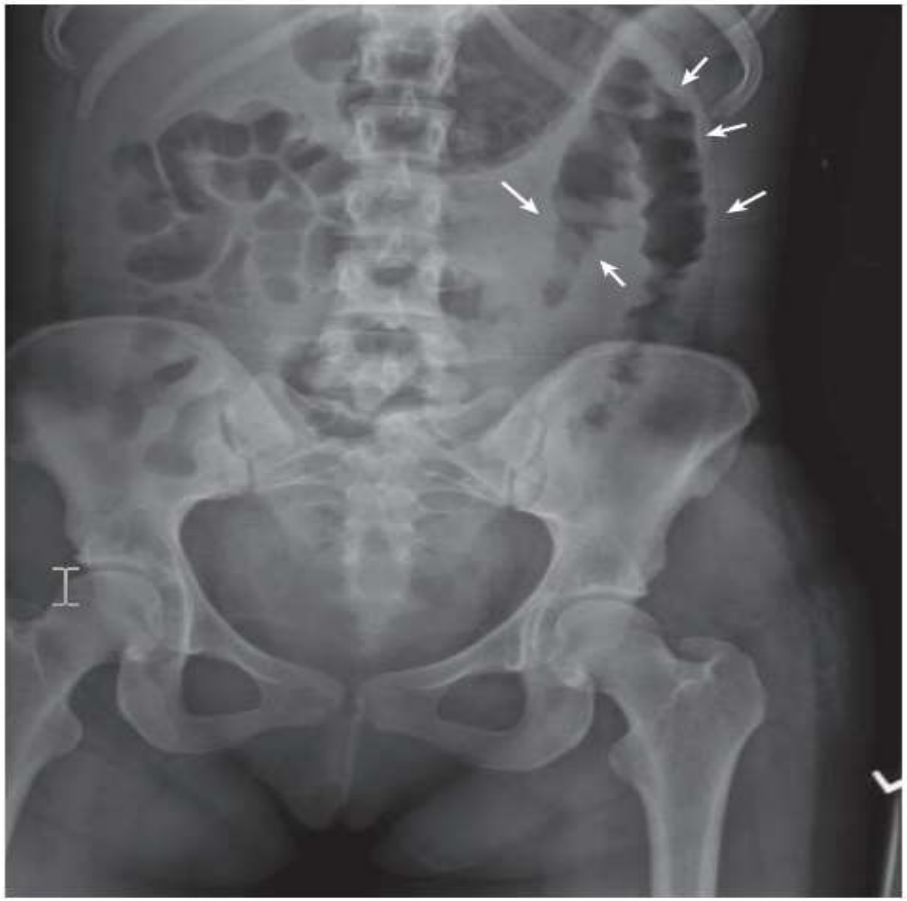


Fig. 382.8 A 19-yr-old patient who presented with bloody stools and later diagnosed with inflammatory bowel disease. Abdominal radiograph at presentation showed classic thumbprinting involving the distal transverse colon, splenic flexure, and descending colon *(arrows)* representing submucosal edema seen in colitis. *(Images from Department of Radiology, Children's Hospital of Philadelphia.)*

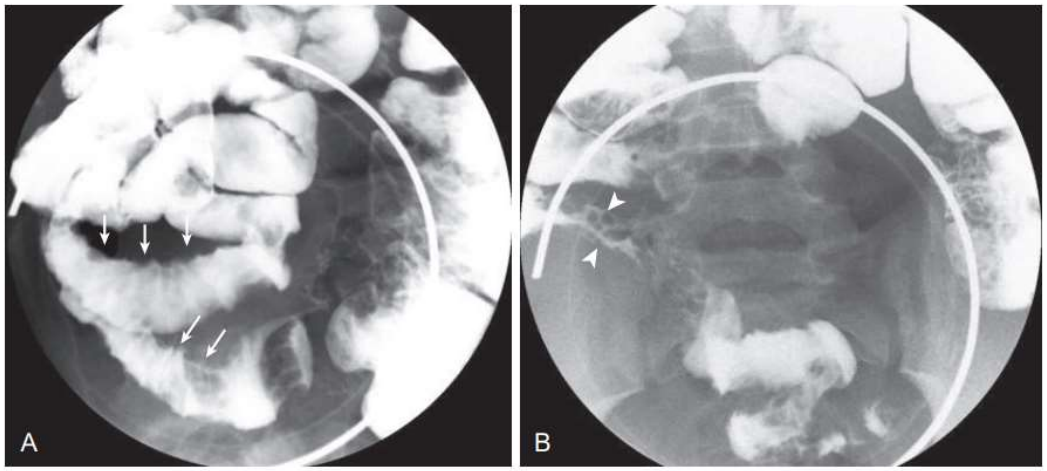


Fig. 382.9 A 12-yr-old child with weight loss and bloody stools diagnosed with Crohn disease. Small bowel follow-through barium examination showed the classic features of Crohn disease. **A,** Mucosal thickening, irregularity *(arrows)*. **B,** Nodularity, "cobblestoning" *(arrowheads)* of the terminal ileum and distal ileal loops. There was also separation of the bowel loops due to fatty proliferation of the mesentery. *(Images from Department of Radiology, Children's Hospital of Philadelphia.)*

- An upper GI contrast examination with small bowel follow-through has typically been the study of choice for imaging of the small bowel, but CT and MR enterography as well as small bowel ultrasonography are more often performed (Fig. ٣٨٢/١٠). MR and ultrasound have the advantage of not exposing the patient to ionizing radiation. CT and MR enterography can also assess for extraluminal findings such as intraabdominal abscess. MR of the pelvis is also useful for delineating the extent of perianal involvement. PET/MRI studies are also helpful in identifying areas of active intestinal and extraintestinal inflammation (Fig. ٣٨٢/١١).

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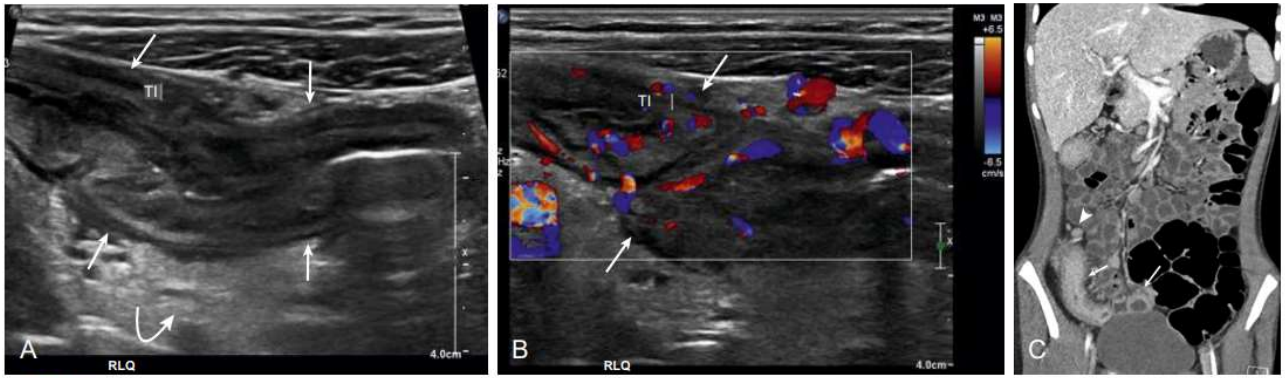

Fig. 382.10 An 11-yr-old child who presented with abdominal pain, weight loss, leukocytosis, and elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP). The patient underwent an initial bowel ultrasound and then CT enterography with assistance from Child Life mitigating use of sedation. Sagittal **(A)** grayscale and color Doppler **(B)** ultrasound images showed markedly thickened abnormal hyperemic terminal ileum *(straight arrows)* and surrounding thickened echogenic mesentery *(curved arrow)* indicative of active inflammation, **C**, Coronal image from a contrast-enhanced CT enterography showed correlating abnormal enhancing and thickened distal and terminal ileum *(arrows)* with enlarged reactive adjacent lymph nodes *(arrowhead)*. *(Images from Department of Radiology, Children's Hospital of Philadelphia.)*

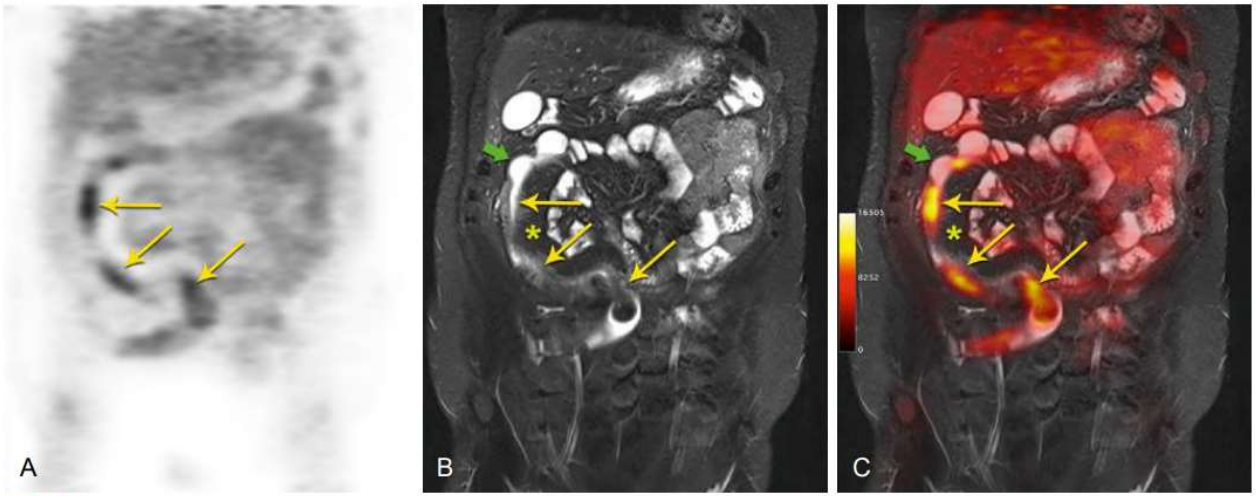

Fig. 382.11 Crohn disease, coexistence of active and chronic changes. Coronal PET **(A)**, coronal STIR MRI **(B)**, and fused PET/MRI **(C)**. Discontinuous areas of active inflammation *(arrows)* demonstrate increased focal FDG uptake, bowel wall thickening, and edema. Note adjacent fibrofatty proliferation *(asterisk)* and pseudosacculations indicative of the chronicity of the process. *(From Furtado FS, Suarez-Weiss KE, Amorim BJ, et al. Gastrointestinal imaging. In Catalano A (ed). Clinical PET/MRI. London: Elsevier, 2023. Fig 14.15.)*

Video capsule endoscopy :

- for evaluation of the small bowel (mucosal inflammation or ulceration that might not have been detected by traditional imaging).
- is contraindicated in the presence of stricturing disease, as surgical intervention would be required to remove a video capsule that is unable to pass through the bowel because a stricture.
- If there is concern for stricturing disease, a patency capsule can be swallowed before video capsule endoscopy to assess for passage through the GI tract

TREATMENT of CD:

- cannot be cured by medical or surgical therapy.
- The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing

Medical

- depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess).
- Traditionally, a step-up treatment paradigm has been used in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medications, or for steroid dependence.
- A top-down approach has also been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease-modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course.
- This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. Improvements in remission and growth have been shown using a top-down approach in pediatrics, and this treatment approach is being increasingly used among children.

۵-Aminosalicylates

- For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (۵۰-۱۰۰ mg/kg/day, maximum ۳-۴ g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active ۵-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.

Antibiotics/Probiotics

- Antibiotics such as metronidazole (۵ mg/kg/dose three times per day, up to ۲۵۰ mg three times per day) are used for infectious complications and are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued). Additionally, at low doses antibiotics may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.

Corticosteroids

- Corticosteroids are used for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, ١-٢ mg/kg/day, by mouth [PO], maximum ٤٠-٦٠ mg).
- The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops, and steroids do not change disease course or promote healing of mucosa.
- A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic firstpass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: ٩ mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause fewer steroidrelated side effects.

Immunomodulators

- Approximately ٧٠% of patients require escalation of medical therapy within the first year of pediatric Crohn disease diagnosis.
- Immunomodulators such as azathioprine (٢/٠-٢/٥ mg/kg/day) or ٦-mercaptopurine (١/٠-١/٥ mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent.
- Because a beneficial effect of these drugs can be delayed for ٣-٤ months after starting therapy, they are not helpful acutely.
- The early use of these agents can decrease cumulative prednisone dosages over the first ١-٢ years of therapy.
- Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine S-methyltransferase) can affect response rates and potential toxicity.
- Lymphoproliferative disorders have developed from thiopurine use in patients with IBD.
- Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate

- is another immunomodulator that is effective in the treatment of Crohn disease and has been shown to improve height velocity in the first year of administration.
- The advantages of this medication include once-weekly dosing by either a subcutaneous or oral route (١٥ mg/m٢, adult dose ٢٥ mg weekly) and a more rapid onset of action (٦-٨ weeks) than azathioprine or ٦-mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron before methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis.
- The immunomodulators are effective for the treatment of perianal fistulas.

Biologic Therapy

- Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease. Infliximab, a chimeric monoclonal antibody to TNF-α, is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid, and it is initially given as three infusions over a ٦-week period (٠, ٢, and ٦ weeks), followed by maintenance dosing beginning every ٨ weeks. The durability of response to infliximab is variable, and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level before an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test or gamma interferon test for tuberculosis should be done before starting infliximab.

Adalimumab

- a subcutaneously administered, fully humanized monoclonal antibody against TNF-α, is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children.
- After a loading dose, this is typically administered once every ٢ weeks, although dose escalation is sometimes required with this medication

Vedolizumab

- a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, is approved for Crohn disease .
- Like infliximab, vedolizumab is initially given as three infusions over a ٦-week period followed by maintenance dosing beginning every ٨ weeks.
- However, the onset of action for vedolizumab is slower compared to infliximab and adalimumab. Therefore concomitant therapies may be needed until response is demonstrated. Dose escalation to every ٤ weeks may be necessary in some patients with loss of response, but it is being further studied

Ustekinumab

- a monoclonal antibody against both IL-١٢ and IL-٢٣, is also approved for treatment of chronically active moderate to severe Crohn disease in adults.
- A loading dose is given intravenously followed by maintenance dosing administered subcutaneously every ٨ weeks

Risankizumab,

- a monoclonal antibody against IL-٢٣A, has demonstrated efficacy for induction and remission maintenance in adults.

Enteral Nutritional Therapy

- Exclusive enteral nutritional therapy, whereby all of a patient's calories are delivered via formula, is an effective primary as well as adjunctive treatment.
- The enteral nutritional approach is as rapid in onset and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation.
- Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula.
- A novel approach where ٨٠-٩٠% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal.
- High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation

Surgical:

- Surgical therapy should be reserved for very specific indications.
- Recurrence rate after bowel resection is high (>٥٠% by ٥ years); the risk of requiring additional surgery increases with each operation.
- Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome.

Surgery is the treatment of choice for:

- ١- localized disease of small bowel or colon that is unresponsive to medical treatment,
- ٢-bowel perforation,
- ٣- fibrosed stricture with symptomatic partial small bowel obstruction,
- ٤- intractable bleeding.
- ٥- Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful.

- Perianal abscess often requires drainage unless it drains spontaneously.
- In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged

- The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents, such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

- Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

Support

- Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease.
- Social support is an important component of the management of Crohn disease.
- Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate.
- Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues.
- Patients who are socially “connected” fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation has local chapters throughout the United States and supports several regional camps for children with Crohn disease.

PROGNOSIS

- Crohn disease is a chronic disorder that is associated with high morbidity but low mortality.
- Symptoms tend to recur despite treatment and often without apparent explanation.
- Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs.
- Up to ١٥% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth.
- Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids.
- Dual-energy x-ray absorptiometry can help identify patients at risk for developing osteopenia.
- Steroid-sparing agents, weight-bearing exercise, and improved nutrition, including supplementation with vitamin D and calcium, can improve bone mineralization.
- Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis

- The region of bowel involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intraabdominal or retroperitoneal abscess.
- Most patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high.
- Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously.
- An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation.
- The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after ٨-١٠ years of colonic disease is indicated.
- Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

Very Early Onset Inflammatory Bowel Disease

IBD may be classified according to age at onset:

- pediatric onset (<١٧ years)
- early onset (<١٠ years)
- very early onset (<٦ years)
- Infant/toddler onset (٠-٢ years),
- neonatal onset IBD (<٢٨ days)

- incidence of pediatric IBD is rising with the greatest rates of increase occurring among young children.
- VEO-IBD) accounts for up to ١٥% of pediatric-onset IBD (prevalence of ١٤/١٠٠٬٠٠٠ children).
- # ١% of children with IBD are diagnosed before the age of ٢ years.

- **IBD** is a complex disorder(genetics, the immune system, the microbiome, and environmental factors), but VEO-IBD is more likely to have a **monogenic cause** .
-
- **Genetic testing** has led to the identification of novel genetic pathways linked to the development of VEO-IBD.
- Many of these pathways contain genes associated with PD (see Tables ۳۸۲/۱ and ۳۸۲/۶; Table ۳۸۲/۹).
- **Family history** of IBD among first-degree relatives occurs more frequently in children diagnosed at a younger age.
- # ۴۴% of children diagnosed with UC < ۲ years will have a first-degree relative with IBD compared with ۱۹% of older children with IBD

VEO-IBD:

- a higher likelihood for extensive colonic involvement
- a greater tendency for a more aggressive disease course
- refractory to conventional therapies.
- Severe perirectal disease can be present and is often associated with monogenic forms of VEO-IBD, including those caused by IL-١٠ receptor pathogenic variants.
- Table ٣٨٢/٩ Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings DEFECTS GENE DEFECT EXTRAINTESTINAL IMMUN

- In addition to intestinal symptoms, there may be associated manifestations of the specific monogenetic disorder (Fig. ٣٨٢/١٢).

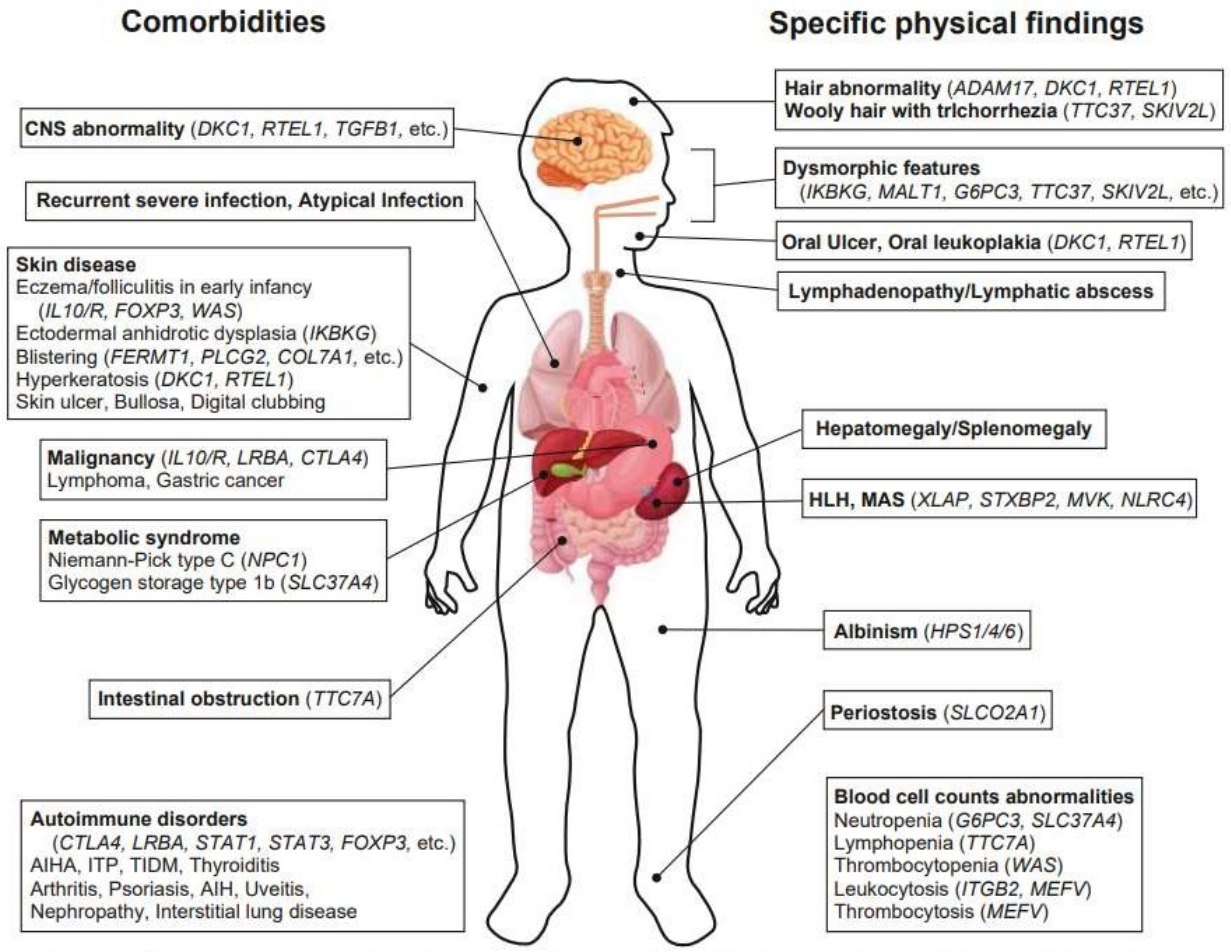

Fig. 382.12 Key indicators of monogenic IBD in clinical practice. Showing physical findings and comorbidities of which physicians should be aware at the initial physical examination and during follow-up. *(Modified from Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. Front Pediatr. 2021;8:Article 618918. Fig. 1C.)*

- Diagnosis of IBD is ultimately confirmed by upper endoscopy and ileocolonoscopy.
- Classic histologic findings of IBD can be seen, although atypical findings, such as the presence of extensive epithelial apoptosis, could indicate the presence of monogenic disease.
- Most children with VEO-IBD will have isolated colonic inflammation on ileocolonoscopy. However, the inflammation can be extensive and involve the entire colon making it challenging to differentiate between Crohn disease and ulcerative colitis;
- # ١١-٢٢% VEO-IBD = indeterminate colitis.
- # ٦٠% of VEO-IBD = UC at diagnosis.
- because children with VEO-IBD are more likely to have disease extension over time, a number of patients felt to have **indeterminate** colitis or UC at diagnosis may eventually be reclassified as having CD later in life.
- As CT or MR enterography may not be tolerated in a young child, small bowel ultrasonography is an alternative imaging modality in VEO-IBD

differential diagnosis of VEO-IBD:

- ١- similar to older children and adults including infectious and allergic colitis (see Table ٣٨٢/٥).
- ٢- However, primary immunodeficiencies, such as chronic granulomatous disease, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome and immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, are higher on the differential (see Tables ٣٨٢/٦ and ٣٨٢/٩).
- Therefore immunologic evaluation is a critical component of diagnosis and management (Table ٣٨٢/١٠).
- History of autoimmunity, atypical infections, recurrent infections, skin disorders, and/or hair abnormalities could indicate an underlying immunodeficiency. Laboratory evaluation could include dihydrorhodamine cytometric testing, quantitative immunoglobulins, vaccine titers, as well as testing of B- and T-cell function.
- More targeted immunologic testing is guided by clinical history. Genetic testing modalities, such as whole exome sequencing, are helpful in identifying rare monogenic pathways responsible for development of the disease.

- A multidisciplinary team approach at a center experienced in VEO-IBD can be helpful in formulating an individualized treatment plan.
- Younger children are more likely to fail conventional therapies, such as ۵-ASA, immunomodulators, and biologics, and require surgical intervention.
- Surgical decisions must be made with caution in very young children as disease extension from the colon to the small intestine can occur with time. More extensive and severe disease at presentation could explain the higher rates of treatment failure among younger children. However, other children may fail conventional therapies if the inflammation is being driven by a monogenic disease process that is not targeted by conventional therapies. Therefore for children with an underlying primary immunodeficiency or a novel monogenic disease process, the specific disease pathway involved may influence treatment choices. In some cases, bone marrow transplantation may be a necessary treatment for the underlying disease process

Table 382.9 Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings—cont'd

DEFECTS	GENE DEFECT	EXTRAINTESTINAL IMMUNE, HEMATOLOGIC, OR SOMATIC MANIFESTATIONS	LABORATORY FINDINGS AND FUNCTIONAL EVALUATION
HYPERINFLAMMATORY DISORDERS			
XIAP	*BIRC4*	Perianal fistula, recurrent HLH, EBV, and CMV infections, hypogammaglobinemia	Markedly elevated IL-18 Decreased or absent XIAP protein expression by flow
NLRC4 GOF variant	*NLRC4*	Recurrent macrophage activation, rash	Markedly elevated IL-18
Mevalonate kinase deficiency	*MVK*	Recurrent fever, rash, abdominal pain and emesis	Elevated inflammatory markers Elevated IgD Elevated urine mevalonate
Familial Mediterranean fever	*MEFV*	Recurrent fever, abdominal pain, arthralgia, peritonitis	Elevated inflammatory markers
Familial HLH type 5	*STXBP2*	HLH, hypogammaglobinemia, sensorineural hearing loss	Marked elevated ferritin and sIL-2R Decreased CD107a degranulation
Hermansky-Pudlak syndrome	*HPS1* *HPS4* *HPS6*	Partial albinism, bleeding tendency, recurrent infection and immunodeficiency	Decreased CD107a degranulation
DEFECTS IN EPITHELIAL BARRIER FUNCTION			
TTC7A deficiency	*TTC7A*	Varying degree of intestinal atresia, T-cell immune defect and recurrent infections	Mild to severe T-cell immune deficiency Hypogammaglobinemia
X-linked ectodermal immunodeficiency (NEMO deficiency)	*IKBKG*	Varying degree of ectodermal dysplasia, conical teeth, sparse and brittle hair, recurrent bacterial, viral and mycobacterial infections	Hypogammaglobinemia Decreased class switched memory B cells
ADAM17 deficiency	*ADAM17*	Neonatal inflammatory skin and bowel disease, generalized pustular rash	Normal T-cell and B-cell numbers
Dystrophic epidermolysis bullosa	*COL7A1*	Blistering disorder primarily affect the hands, feet, knees, and elbows	Unremarkable immune findings
Kindler syndrome	*FERMT1*	Acral skin blistering, photosensitivity, progressive poikiloderma, and diffuse cutaneous atrophy	Eosinophilia
ISOLATED OR COMBINED T-CELL AND B-CELL IMMUNE DEFECTS			
X-linked agammaglobulinemia	*BTK*	Recurrent sinopulmonary infection	Absent B cells in peripheral blood Absent plasma cells in tissue Decreased class switched memory B cells
Common variable immune defect (CVID)		Heterogeneous group of defects with sinopulmonary infections, autoimmunity, lymphoproliferation, and variable T-cell immune defect	Hypogammaglobinemia Variable T-cell lymphopenia
X-linked hyper IgM (CD40L)	*CD40L*	Sclerosing cholangitis, Cryptosporidium diarrhea and Pneumocystis infection	Elevated or normal IgM, neutropenia Absent class switched memory B cells
Wiskott-Aldrich syndrome	*WAS*	Eczema, recurrent infection, autoimmunity, vasculitis	Microthrombocytopenia Variable lymphopenia, low IgM Decreased WAS protein
Leaky SCID or Omenn	*RAG1, RAG2* *IL-7Ra* *IL-2RG*	Generalized erythroderma, hepatosplenomegaly, lymphadenopathy	Eosinophilia T-cell lymphopenia Decreased naive T cells

*STAT3 signaling following IL-6 and IL-10 will only identify IL-10R A and B defects; it will not identify IL-10 deficiency.
†*Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Aspergillus,* and *Candida.*
IPEX, Immune dysfunction, polyendocrinopathy, enteropathy, X-linked; Treg, regulatory T cell; CMV, cytomegalovirus; EBV, Epstein-Barr virus; NK, natural killer; GOF, gain of function; IL, interleukin; CGD, chronic granulomatous disease; HLH, hemophagocytic lymphohistiocytosis; SCID, severe combined immune deficiency.
From Chandrakasan S, Venkateswaran S, Kugathasan S. Nonclassic inflammatory bowel disease in young infants – immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and other disorders. *Pediatr Clin N Am.* 2017;64:139–160. Table 2.

Table 382.10 Functional Analysis

FUNCTIONAL SCREENING CONSIDERED

- Immunoglobulins (IgG, IgM, IgA, IgD, IgE)
- Lymphocyte subsets by flow
- Antibody to vaccines
- TRECs
- DHR-123
- Cytokine assay (serum cytokine level during flare)

TARGETED FUNCTIONAL ANALYSIS *(RECOMMENDED)*

GENE	FUNCTIONAL ANALYSIS
IL10RA	IL-10-induced STAT3 phosphorylation by flow cytometry or immunoblotting
IL10RB	
NCF1	Neutrophil oxidative burst study, DHR-123 test
NCF2	
CYBA	
CYBB	
*NCF4**	Neutrophil oxidative burst study
CYBC1	
TTC7A	Immunohistochemistry-TTC7A, apoptosis
WAS	WASP expression by flow cytometry
XIAP	XIAP expression by flow cytometry TNF, IL-8, and MCP-1 expression in response to MDP stimulation
SLCO2A1	Immunohistochemistry-SLCO2A1
NPC1	Filipin staining of cultured skin fibroblasts
SLC37A4	G6Pase enzyme activity in Liver tissue (non-frozen)
MVK	Increased urine mevalonic acid when fever
TNFAIP3	A20 expression by immunoblotting RT-PCR using total RNA
CTLA4	CTLA-4 expression within stimulated Treg cells by flow cytometry
LRBA	LRBA expression in response to PHA stimulation by flow cytometry
FOXP3	FOXP3 expression by flow cytometry
STAT1(GOF)	CD25 expression by flow cytometry
STAT3(GOF)	STAT3 reporter luciferase assay under basal or stimulated condition (IL-6/growth hormone) in cell lines SOCS3 expression levels under basal or stimulated condition (IL-21) in EBV-transformed patient cell lines

*The production of ROS in phagocyte is normal and need to examine the bacterial killing activity.

TREC, T-cell receptor excision circles; DHR-123, dihydrorhodamine 123; WASP, Wiskott-Aldrich syndrome protein; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein; MDP, muramyl dipeptide; RT-PCR, real-time reverse transcription polymerase chain reaction, TNF, tumor necrosis factor; Treg, regulatory T cell; PHA, phytohemagglutinin; SOCS3, suppressor of cytokine signaling 3; EBV, Epstein-Barr virus; ROS, reactive oxygen species.

From Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. *Front Pediatr.* 2021;8:Article 618918. Table 1A.