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Extraintestinal Manifestations of IBD

DEVELOPED BY THE CROHN'S & COLITIS FOUNDATION'S NURSE & ADVANCED PRACTICE COMMITTEE

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Instructions

To begin, please use “Slide Show mode” to enable full interactivity of case and questions.

When you see words or phrases that are underlined, click on the underlined word for graphics, data, or explanations.

To return to the presentation, make sure you click back in the bottom right corner.

Not all cases of inflammatory bowel disease (IBD) present as bloody stools or diarrhea.

The presence of extraintestinal findings may raise concern and lead to the diagnosis of inflammatory bowel disease.

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Objectives

By the end of this presentation, the participant will be able to:

- Recognize several of the most common extraintestinal manifestations of inflammatory bowel disease (IBD).
- Identify the recommended evaluation (laboratory studies, imaging, referrals) for the pediatric patient presenting with extraintestinal manifestations of IBD.
- Identify current recommendations for treatment (management) of the pediatric patient presenting with extraintestinal manifestations of IBD.

Introduction/Background

K.O. is a 17-year-old female who presents to the pediatric GI clinic with a:

- six-month history of non-bloody diarrhea
- bruise-like rash on her lower extremities
- swollen perianal skin tags
- leg edema
- weight loss (10 pounds) in the past few months
- oral aphthous ulcers in the past 6 months

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Review of Systems (ROS)

General: fatigue, decreased appetite/early satiety, **weight loss**, no fever
Skin: **rash on legs**
Eyes: **vision changes, photophobia,** denies discharge
ENT: **mouth ulcers,** no bleeding gums
Respiratory: negative
Cardiovascular: negative
GU: **perianal skin tags**
GI: **diarrhea, nausea, vomiting, abdominal pain**
Musculoskeletal: joint pain, swollen ankles
Hematologic: negative
Neurologic: negative
Endocrine: negative
Psychosocial: negative

What additional information will be helpful?

- Family History
- Physical Exam
- What laboratory studies would you order and why?
- Previous Workup – none available

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Do you have red flags/cause for concern based on physical exam & review of systems?

- No concern – follow up in GI PRN
- Only minimal concern – no need to order further workup but return to clinic in 2–3 months to follow up
- Significant concern – requires further workup today
- Major concern indicating need for admission

What should be a part of your differential diagnosis?

- Peptic ulcer disease
- Celiac disease
- GI bleed
- Pancreatitis
- Infection
- Post viral gastroparesis
- Ulcerative colitis
- Crohn’s disease
- Lactose intolerance

Results of studies ordered

- Labs
- Esophagogastroduodenoscopy and colonoscopy with biopsies
- MRE

Diagnosis and Management

She was diagnosed with:

Ileocolonic Crohn's disease with upper tract involvement above the ligament of Treitz. Her disease is inflammatory. She has extraintestinal manifestations.

She has aphthous ulcers, episcleritis, peripheral arthritis, erythema nodosum, and psoriasis.

Medical management:

She was started on infliximab, which worked well for her.

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LET'S TALK ABOUT EXTRAINTESTINAL MANIFESTATIONS OF IBD.

Definition

The European Crohn's and Colitis Organization (2019) describes extraintestinal manifestations as:

> *"An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."*
>
> (Hedin et al., 2019, p. 542)

Many extraintestinal manifestations are related to the degree of gastrointestinal inflammation (disease activity). Others can occur independent of disease activity.

Some extraintestinal manifestations will improve with management of underlying disease, but others may need additional medical or procedural management. Referral to other subspecialists may be required.

Incidence

Extraintestinal manifestations occur in 5–50% of adult IBD patients.
(Cesa, 2022; Rogler et al., 2021; Garber & Regueiro, 2019; Greuter et al., 2017)

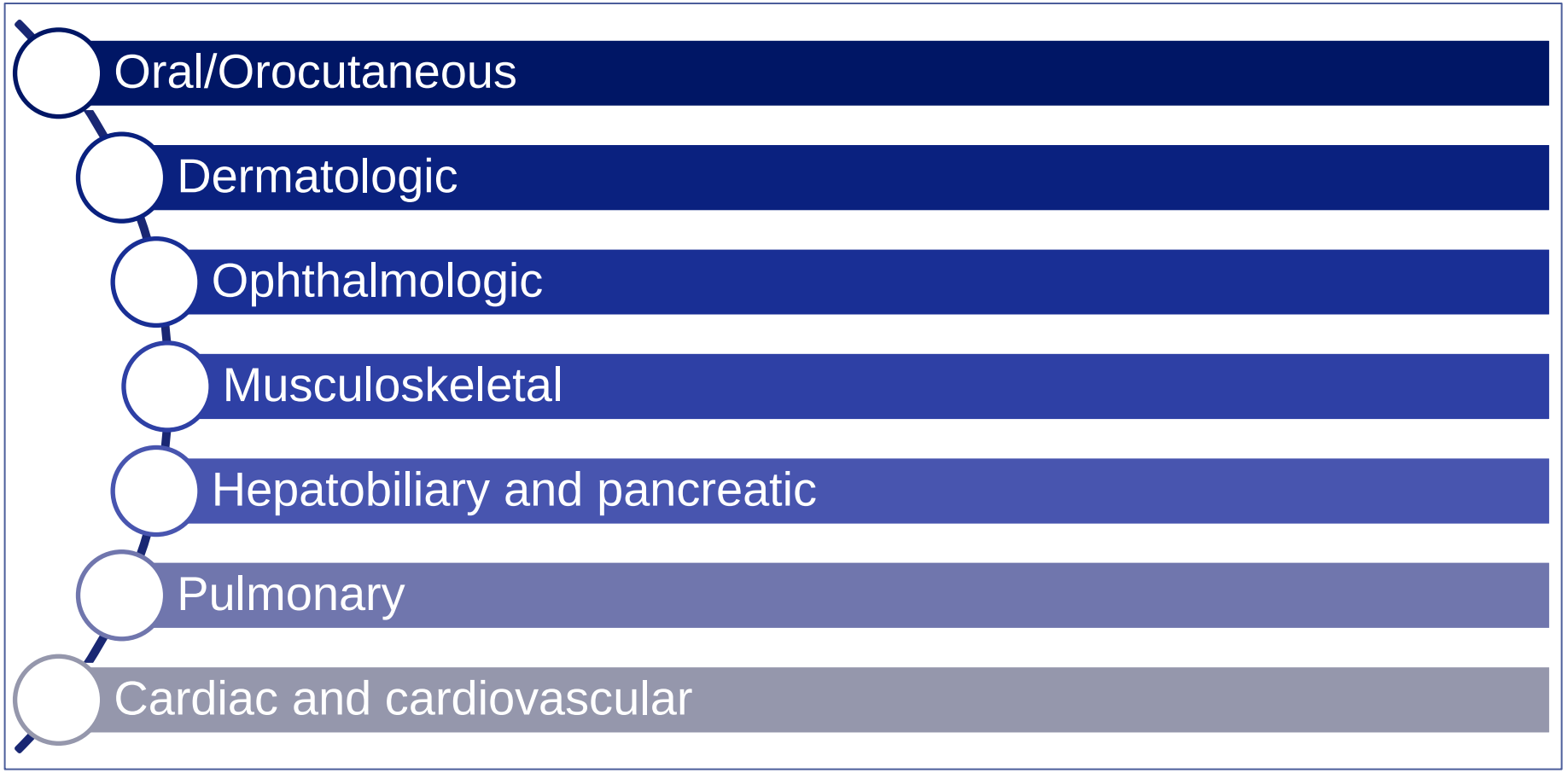
It is estimated that extraintestinal manifestations occur in ~30% of pediatric IBD patients. (Greuter et al., 2017; Rabizadeh & Oliva-Hemker, 2017)

Approximately 25% of extraintestinal manifestations occur prior to the development of gastrointestinal symptoms and the diagnosis of IBD.
(Rogler et al., 2021)

Studies suggest that the presence of one extraintestinal manifestation of IBD can increase the incidence of other extraintestinal manifestations over time. (Malik & Aurelio, 2022; Garber & Regueiro, 2019)

What are the most common extraintestinal manifestations of IBD?

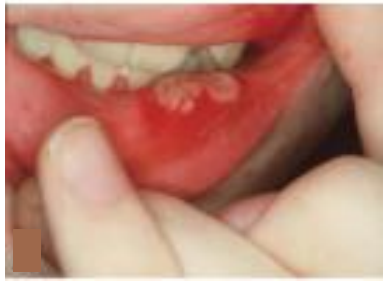
The most common extraintestinal manifestations of IBD are cutaneous, musculoskeletal, and ocular. Other body systems can be involved and include:



Oral/Orocutaneous

Oral and orocutaneous lesions are among the most common manifestations of IBD. They include:

Aphthous ulcers



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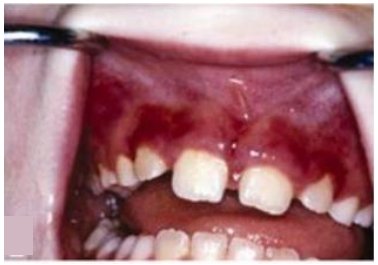
Mucogingovitis



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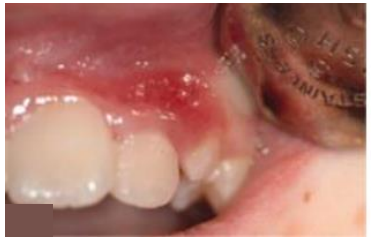
Pyostomatitis



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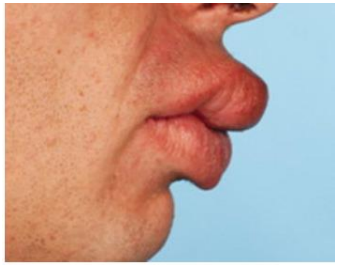
Oral facial granulomatosis

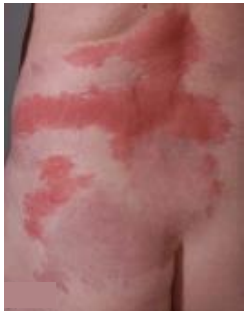
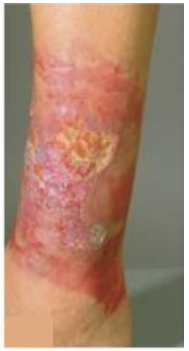
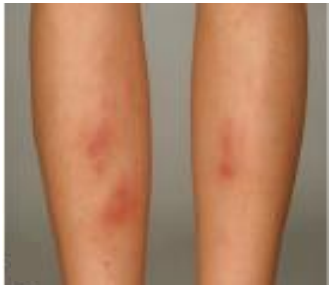
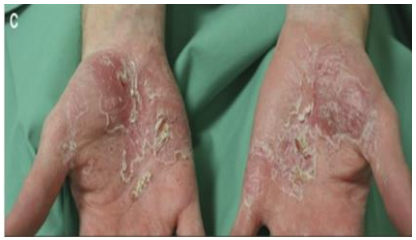


Adapted from: Campbell et al. *Inflammatory Bowel Diseases*, 2011; 17(10): 2109–2115

Back

Dermatologic

Cutaneous manifestations can occur in up to 15% of IBD patients. (Rogler et al., 2021)
They include:

Sweet syndrome	Pyoderma gangrenosum	Erythema nodosum	Psoriasis
			
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Ophthalmologic

Ocular manifestations can affect 2–5% of IBD patients. (Rogler et al., 2021) Ocular manifestations are the third most common extraintestinal manifestation of IBD. (Rogler et al., 2021)

They include:

- Episcleritis
- Scleritis
- Uveitis (chorioretinitis)

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Adapted from: Vavricka R. et al. *Inflammatory Bowel Diseases*, 2015; 21(8): 1982–1992 Last modified May 2020

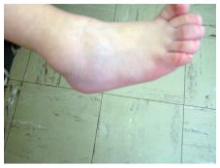
Adapted from: Shah et al. *Inflammatory Bowel Diseases*, 2021; 27(11): 1832–1838

Musculoskeletal

Musculoskeletal manifestations are the most common extraintestinal manifestations of IBD. (Bourikas & Papadakis, 2009) Can affect 40-46% of IBD patients. (Vavricka et al., 2015; Rogler, 2021)

They include:

- IBD-related arthralgia
- IBD-related arthritis
  - Peripheral arthropathies
    - Pauciarticular arthropathies
    - Polyarticular arthropathies
  - Axial arthropathies
    - Ankylosing spondylitis
    - Sacroiliitis
- Enthesitis
- Dactylitis



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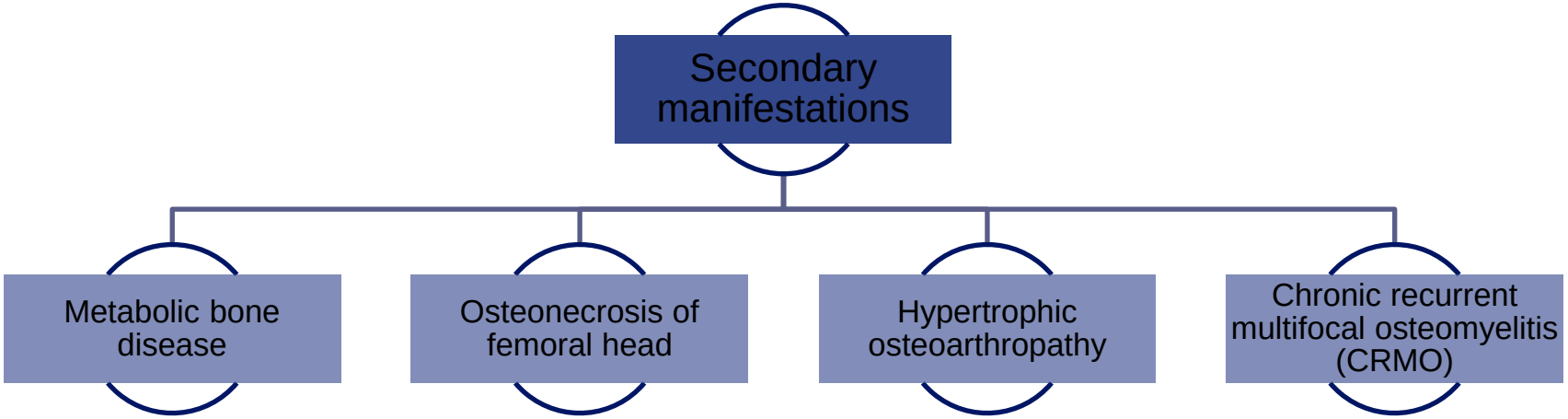
Musculoskeletal (secondary)

Secondary extraintestinal manifestations of IBD are often due to effects of medications, malabsorption, and chronic inflammation. (Garber & Regueiro, 2019)
They include:



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Hepatobiliary/pancreatic

Hepatobiliary disease can occur in 5–10% of pediatric IBD patients. (Ribizadeh & Oliva-Hemker, 2017) Pancreatic extraintestinal manifestations are rare. (Ribizadeh & Oliva-Hemker, 2017) Consider hepatobiliary disease in patients presenting with jaundice, pruritis, nausea/vomiting, or abnormal liver function tests. (Friedman et al., 2022)
Hepatobiliary and pancreatic extraintestinal manifestations include:

- Primary sclerosing cholangitis
- Autoimmune pancreatitis
- Autoimmune hepatitis

Secondary Manifestations

Gall stones

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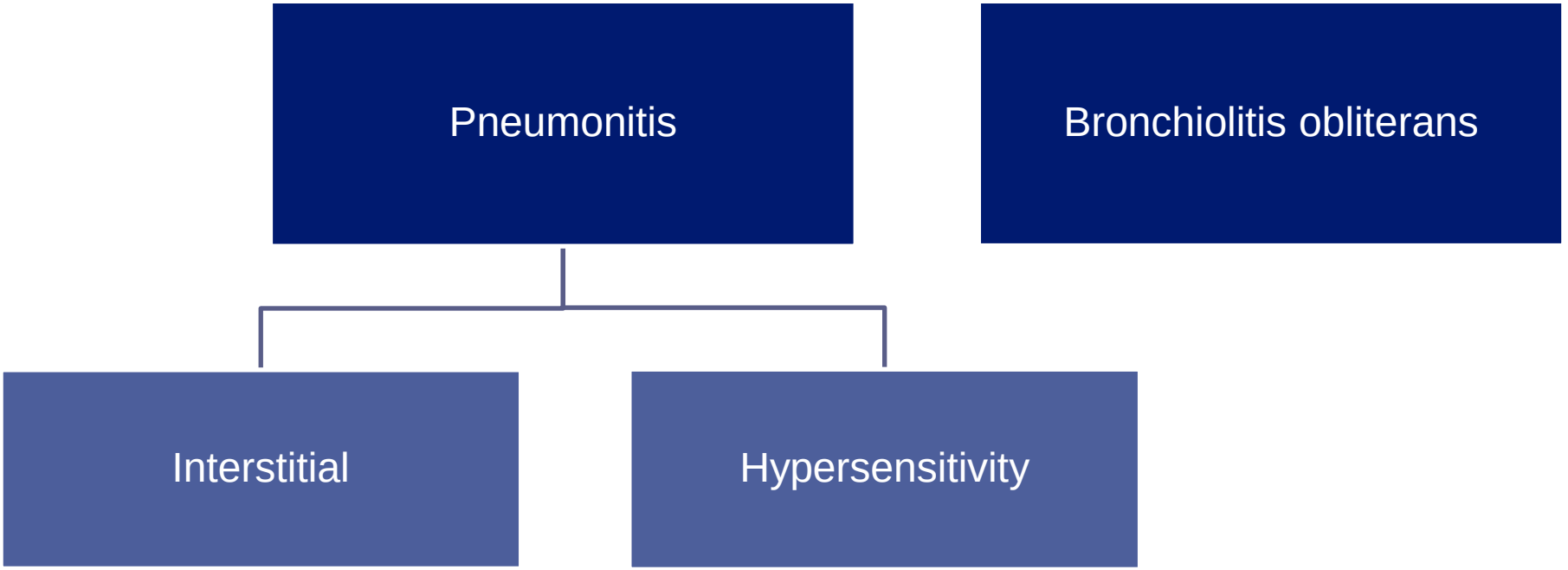
Pulmonary

Extraintestinal manifestations of IBD can affect the pulmonary airway as well as the lung parenchyma. (Garber & Regueiro, 2019) Common extraintestinal pulmonary manifestations include:



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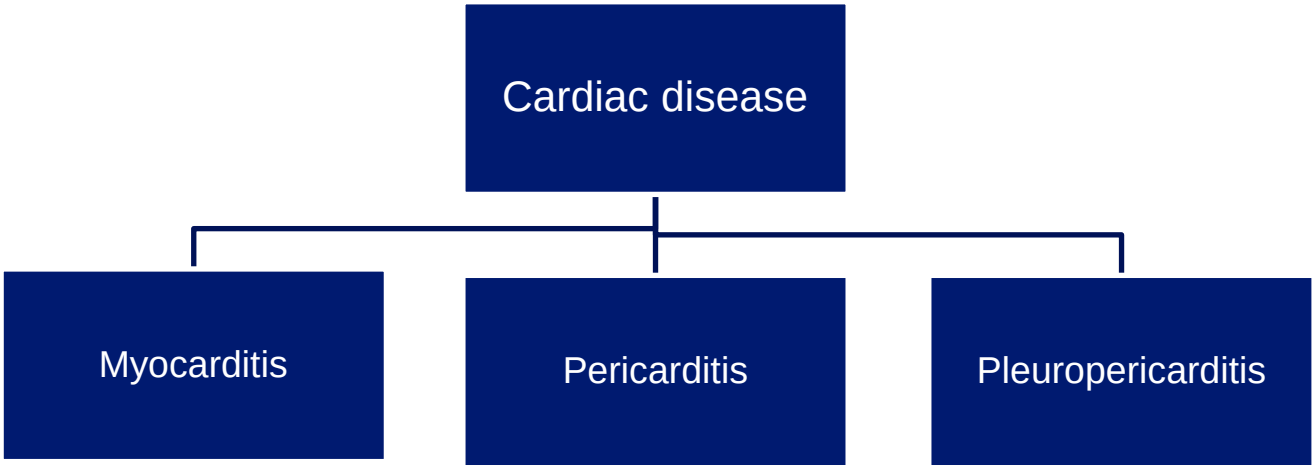
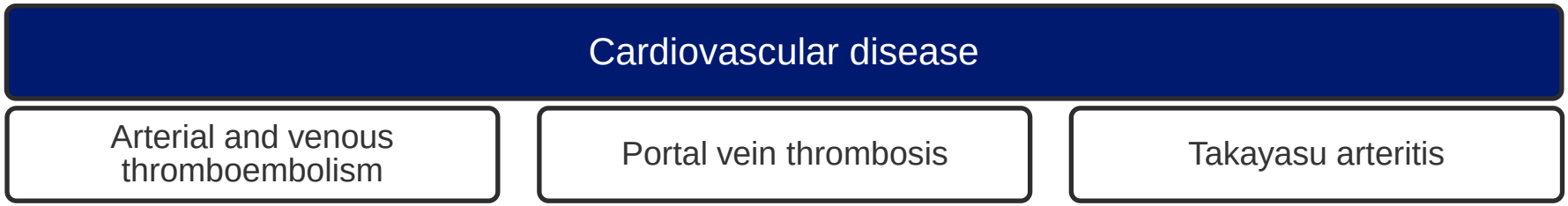
Cardiac and Cardiovascular

Cardiac and cardiovascular extraintestinal manifestations of IBD are uncommon in pediatrics. Occur in <1% of pediatric IBD patients. (Cesa et al., 2022) Can be immune mediated or associated with medications used to treat IBD. Consider in differential diagnosis in the IBD patient with cardiac symptoms when other etiologies have been ruled out. Cardiac and cardiovascular EIMs include:



Cardiovascular manifestations are more frequent in occurrence and include:



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Renal

Renal manifestations of IBD may be related to this chronic inflammatory disease or the medications used in IBD treatment. (Ambruzs & Larsen, 2018) Primary manifestations can result in renal insufficiency. Renal extraintestinal manifestations (Garber & Regueiro, 2019) include:

- Glomerulonephritis
- IgA nephropathy
- Tubulointerstitial nephritis
- Amyloidosis

Secondary manifestations

Kidney stones

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Hematologic

Hematologic extraintestinal manifestations are common in pediatric IBD. They can be found in more than 50% of pediatric IBD patients with active disease. (Ribizadeh & Oliva-Hemker, 2017)
They include:

- Anemia
- Thrombocytosis
- Leukocytosis

Secondary manifestations

- Leukopenia
- Venous thrombosis

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Endocrine

Endocrine-related extraintestinal manifestations of pediatric IBD are common. They are multifactorial and can be influenced by inflammation, nutritional deficits, malabsorption, metabolic changes, medications, glucocorticoid effects, and hormonal influences. (Setty et al., 2022)
The most common endocrine-related extraintestinal manifestations include:

- Metabolic bone disease
- Growth failure
- Pubertal delay
- Abnormal lipid and carbohydrate metabolism

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Neurologic

Neurologic extraintestinal manifestations of IBD can affect the central and/or peripheral nervous system. Etiology is often immune mediated, but can be caused by brain-gut dysregulation, medications, vascular, infectious or due to vitamin/mineral deficiencies. (Ferro et al., 2021)

- Peripheral nerve disorders
- Multiple sclerosis
- Optic neuritis
- Demyelinating disorder

Secondary manifestations

Multifocal leukoencephalopathy

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Extraintestinal Manifestation of IBD Summary

Extraintestinal manifestations (EIMs) can be found in almost every body system and affect approximately 1/3 of patients with IBD.

Not all EIMs are directly correlated to disease activity.

Some EIMs are secondary to complications from IBD (especially Crohn's disease).

Early detection and appropriate referral coordination with other subspecialists are critical for the care of your patients.

Thank you!

We hope you enjoyed this case.

Please complete a brief evaluation to provide us with feedback on this program: https://www.surveymonkey.com/s/ibdnurse

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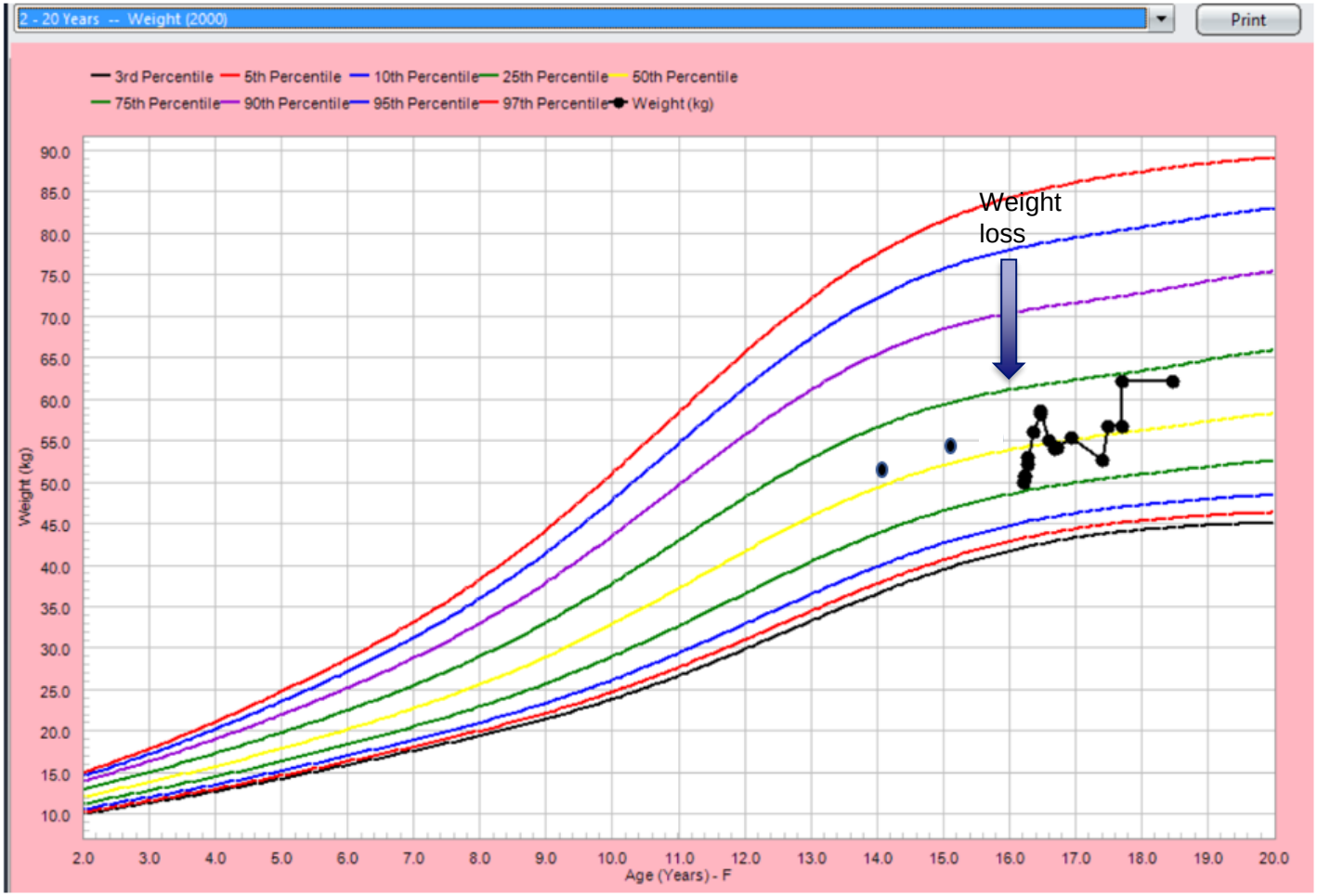
Growth Curve



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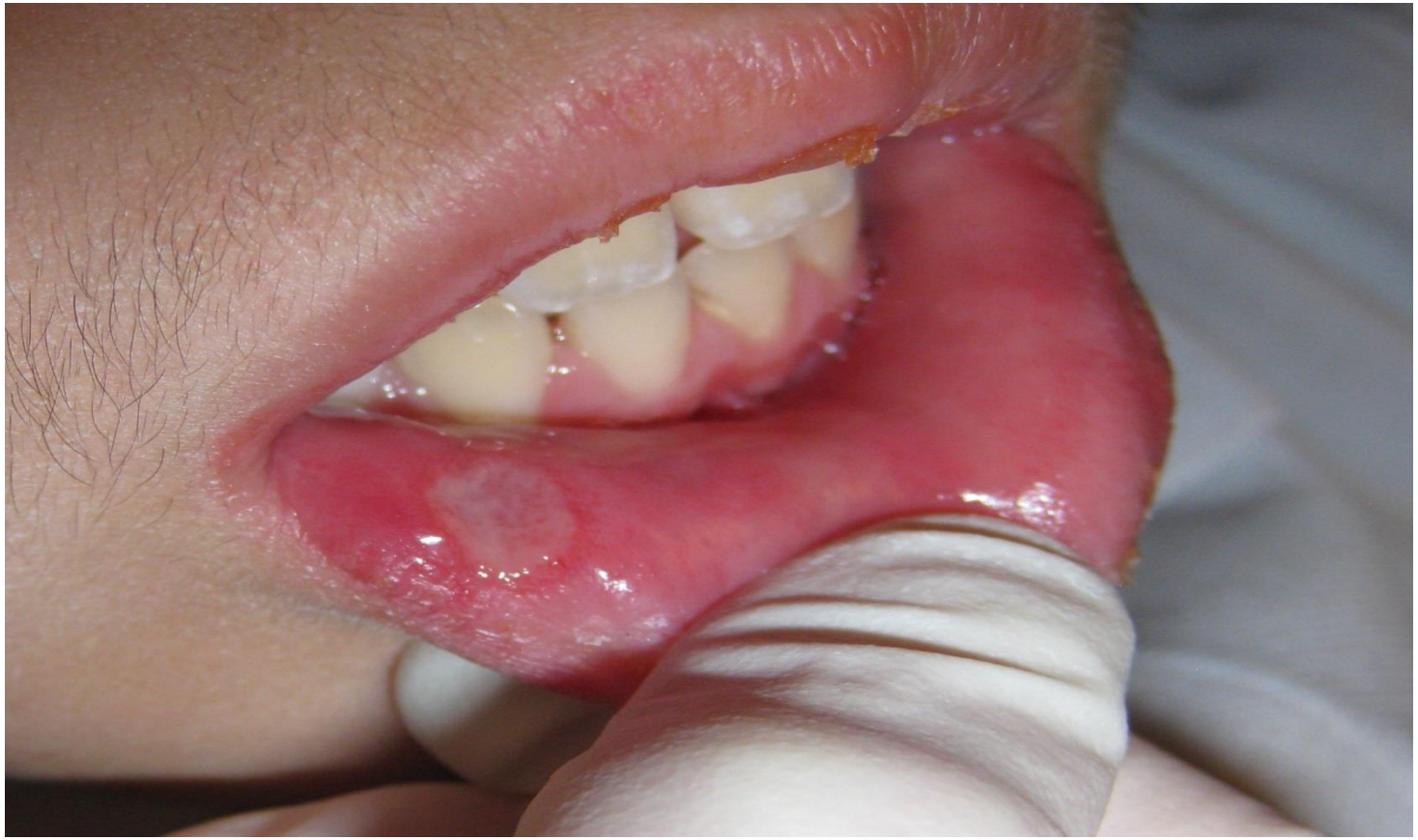
Oral Aphthous Ulcer



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Family History

- Maternal grandfather – Crohn’s disease, colonic polyps
- Maternal grandmother – hypothyroidism
- Mother – irritable bowel syndrome

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Physical Exam

General: alert, cooperative, no distress. **Edematous facies.**

HEENT: **localized area of redness at bulbar conjunctiva**. Non tender.

Mouth: MMM. **Ulcerations on erythematous base on hard and soft palate and buccal mucosa. Non-erythematous posterior pharynx but also with ulcers.**

Lungs: clear bilaterally.

Cardiovascular: regular rate and rhythm, no murmur.

Abdomen: soft, non-distended, no organomegaly, normal bowel sounds, no masses, **epigastric tenderness.**

Rectal: deferred with plan to scope.

Extremities: **tender erythematous LEs bilaterally. Decreased ROM of ankles with dorsal/plantar flexion. Tenderness with palpation at ankles bilaterally.**

Neurologic: alert and developmentally appropriate. Antalgic gait.

Skin: **tender, erythematous nodules on calf and anterior shins bilaterally**. No petechiae, no jaundice. **Dry, scaly rash with silver borders at hairline.**

What labs to order?

CBC	CMP	ESR/CRP	Stool studies
To evaluate anemia, infection	To evaluate liver enzymes, electrolytes, and hypoalbuminemia	To evaluate inflammation	(lactoferrin or calprotectin, occult blood, and stool culture) to evaluate for intestinal inflammation, blood, or infection

Based on her presentation, would also consider:

TIBC/Iron	To evaluate iron deficiency	
Ferritin	To evaluate iron stores. Ferritin may be falsely elevated as it is an acute phase reactant with inflammation	
Celiac Serology	To rule out fatigue and weight loss as result of celiac disease	
TSH/Free T4	To rule out fatigue and weight loss as a result of thyroid dysfunction	
Amylase/Lipase	To get baseline and rule out pancreatitis	
Other	Would consider laboratory studies to rule out :	Infectious cause of oral lesions and rash. Rheumatologic causes of joint pain.

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No Concern

Incorrect – Weight loss, fatigue, and mouth ulcers indicate an underlying gastrointestinal disease may be present. Workup should be ordered today in clinic.

Minimal Concern

Incorrect – There is recognizable need for ordering labs to make sure there is no anemia or electrolyte abnormalities and evaluate for elevated inflammatory markers.

Significant Concern

Correct – We need to move forward with urgent/not emergent workup to look for anemia, elevated inflammatory markers, hypoalbuminemia, or electrolyte abnormalities. We need to prevent growth failure and/or stunted growth by not allowing a chronic inflammatory process to progress without appropriate workup or treatment since patient presented with a 10-pound weight loss.

Major Concern

Incorrect – There are no emergent factors that we are aware of indicating need for admission to the hospital.

Peptic Ulcer Disease

Correct – Peptic ulcer disease may present with mouth sores, abdominal pain, and weight loss. Fatigue would be less likely.

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Celiac Disease

Correct – Celiac disease may present with weight loss, fatigue, and decreased appetite but less likely mouth sores.

GI Bleed

Incorrect – At this time, we have no evidence of anemia; there is no report of hematochezia or hematemesis.

Pancreatitis

Correct – However, less likely since pain is able to be ignored and there is no report of vomiting. There is value to obtaining a baseline lipase since pancreatitis can be a side effect of some IBD treatment.

Infection

Incorrect – Unlikely at this time; there is no report of fever or diarrhea. Although enterovirus or HSV infection can cause mouth sores, they do not usually last for 6 months without resolution or exacerbation of symptoms.

Post-Viral Gastroparesis

Correct – Can decrease gastric empty transit time and cause symptoms of early satiety, vomiting, decreased appetite, and weight loss, depending on the virus preceding the diagnosis.

Ulcerative Colitis (UC)

Correct & Incorrect - While UC is a form of IBD, it is limited to the colon and most times should not present with oral aphthous ulcers.

Crohn's Disease

Correct – Mouth sores can frequently be associated with inflammation anywhere in the gastrointestinal (GI) tract from the mouth to the anus.

Additionally, all other symptoms of weight loss, fatigue, and early satiety can be explained by a diagnosis of Crohn's disease.

Lactose Intolerance

Incorrect – While there may be a component of lactose intolerance, this is more likely to be secondary to a primary disease process, such as celiac disease or Crohn's disease.

NORMAL **ABNORMAL**

Laboratory Results

Complete Blood Count
- WBC 8.4
- RBC 4.1
- Hemoglobin **10.7**
- Hematocrit **33.0**
- MCV 80.4
- MCH 26.1
- MCHC 32.5
- RDW 15.3
- Platelet 387

Comprehensive Metabolic Panel
- Sodium 134
- Potassium 3.6
- Chloride 100
- Co2 27
- Calcium **8.0**
- Total Protein **6.0**
- Albumin **2.1**
- Total Bilirubin 0.5
- AST 12
- ALT 13
- Glucose **99**
- BUN 8
- Creatinine **0.7**

Other Labs
- Free T4 1.05
- TSH 1.57
- ANA negative
- Double stranded antibody negative
- SM negative
- HLA B51 negative
- HSV swab negative

Inflammatory Markers
- ESR **76** (<20)
- CRP **12.1** (<.80)
- Stool Calprotectin **319.5**

- Occult blood **+**
- Negative stool culture
- C. diff negative

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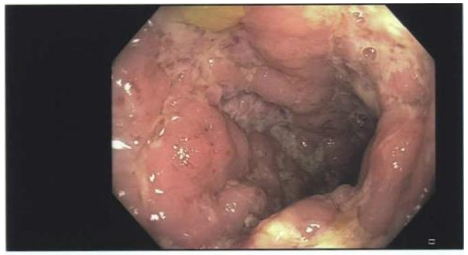
EGD/Colonoscopy

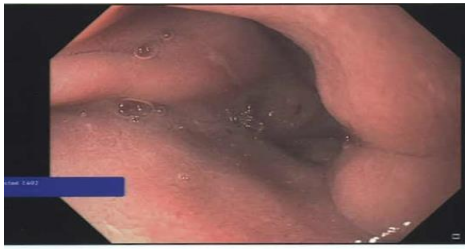
VISUAL EXAM:

Multiple **aphthous ulcers in distal esophagus, erosions and aphthous ulcers in duodenal bulb.**

Edematous TI; diffuse colitis with swelling, erythema, and aphthous ulcers with nodular mucosa in the transverse colon and cecum.



TERMINAL ILEUM



DUODENUM: 2ND PORTION

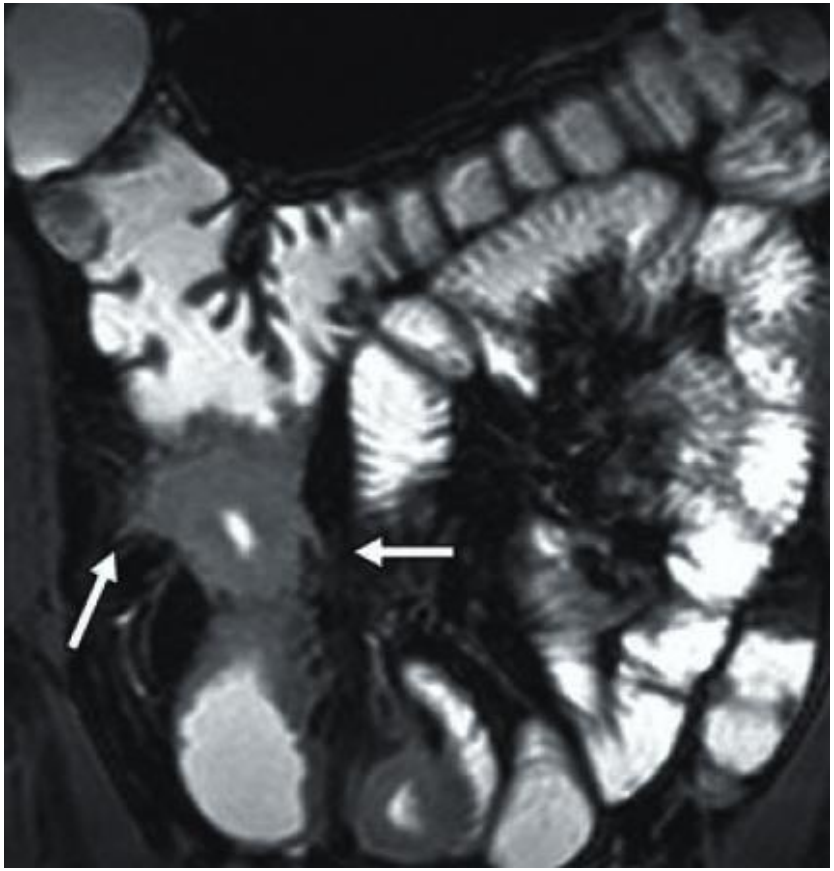
HISTOLOGY:

EGD: normal esophagus, **mild nonspecific gastritis and duodenitis**, negative for H. pylori.

Colonoscopy: **terminal ileum with chronic active ileitis with ulcers. Focal acute colitis in the cecum and ascending colon. Chronic colitis noted in the transverse, descending, rectosigmoid, and rectum with ulcerations**. No granulomas.

Magnetic Resonance Imaging (MRI)

MR enterography is a special type of magnetic resonance imaging (MRI) performed with a contrast material to produce detailed images of the small intestine. Provides intraluminal and extraluminal imaging for best decision making. This will evaluate extent of small intestinal involvement and identify any strictures.



K.O.'s MRE

1. Continuous **distal ileal bowel wall thickening and hyperemia**, compatible with a nonspecific infectious or inflammatory enteritis.
2. Question minimal **gastric antral and duodenal wall inflammation**.

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Oral/Orocutaneous

Aphthous ulcers are superficial ulcerations in the oral cavity. They can occur on the labia, buccal mucosa, tongue, and oropharynx. (Vavricka et al., 2015) Can be recurrent. The most common oral finding in IBD. May occur more frequently in CD than UC. Treatment: Treatment of underlying IBD, topical or oral corticosteroids, topical lidocaine. (Vavricka et al., 2015)

Periodontitis – Presents as gingival erythema, bleeding gums, and inflammation (gingivitis). Can progress to receding gumline and destruction of the boney structure of the mouth (periodontal disease) leading to tooth loss. Occurs more frequently in those with IBD than general population leading to concern for microbiome and oral CD as factors. (Rogler et al., 2021) More active during disease flares. May correlate with perianal disease. Treatment: Treatment of underlying disease and annual dental visits. Topical antiseptics and steroids. (Rogler et al., 2021)

Pyostomatitis vegetans – Presents as pustules or erosions in the oral cavity. Can be hemorrhagic. May have a cobblestone pattern. Can occur anywhere in the oral cavity. (Vavricka et al., 2015) Uncommon. May be seen more frequently in UC. Correlates with disease activities. (Rogler et al., 2021) Treatment: Antiseptic mouthwashes and steroids.

Oral facial granulomatosis (Melkersson-Rosenthal Syndrome) – Presents as swelling of the lips and face, gingival erythema and hyperplasia. May have mucosal tags, which, when biopsied, show evidence of granulomas. Treatment: Steroids and immune suppression. (Rogler et al., 2021)

Dermatologic

Sweet syndrome	An afebrile neutrophilic dermatosis. Rare. Presents as tender papulo-squamous exanthem or nodules on the extremities, trunk, or face. Can also have systemic features. Can correlate with IBD disease activity or precede diagnosis. Treatment topical or systemic steroids; anti-TNFs. (Rogler et al., 2021)
Pyoderma gangrenosum	Erythematous pustules/nodules. Can be solitary or numerous. Can rapidly spread causing deep ulcerations. Frequently seen on lower legs but can occur anywhere. Occurs in <2% of patients with IBD. Often confused with infection; but cultures are negative; biopsies may show neutrophilic proliferation. Seen more in long-standing UC but can be seen in CD. Related to disease activity. Treatment: Treatment of underlying IBD, steroids, cyclosporine, and immunosuppressives. (Vavricka et al., 2015)
Erythema nodosum	Raised and tender 1–5 cm diameter subcutaneous nodules. Often appear red to purple in color. Seen more frequently in CD but can occur in UC. Can be seen in other infections, malignancies, or other autoimmune diseases. Corresponds with disease activity. Can be self limited. Often improve with treatment of underlying IBD. (Peppercorn & Cheifetz, 2022) Can respond with symptomatic treatment with leg elevation, analgesics, and compression stockings.
Psoriasis	A chronic inflammatory condition of the skin characterized by erythematous patches with greyish, scaly boarders. Immune mediated. Can be associated with IBD, develop following treatment with biologic therapy (anti-TNF), or occur independent of IBD. Treatment: Topical therapies and biologics. (Peppercorn et al., 2022)
Hidradenitis suppurativa	An inflammatory condition that can be associated with IBD and consists of painful deep-seated indurated nodules and abscesses effecting the sweat glands of the axilla, groin, perianal area, and perineum. Treatment: Skin hygiene, topical therapies, oral medications, biologics, and surgical interventions. (Peppercorn et al., 2022)

Ophthalmologic

Episcleritis and uveitis are the most common ocular manifestations of IBD. (Vavricka et al., 2015)
Often associated with other extraintestinal manifestations.

Episcleritis	Presents with localized eye redness, irritation, and burning due to inflammation of the episcleral (the clear layer that covers the sclera). Most common. **Does not impair vision.** Treatment: Treat underlying IBD. Topical corticosteroids can be used if no improvement. Correlates with disease activity. (Vavricka et al., 2015; Rogler et al., 2021; Peppercorn et al., 2022)
Scleritis	Inflammation of the sclera. Presents as eye redness, severe pain and burning. Can be serious and associated with vision changes, requiring urgent ophthalmology referral to assess for retinal detachment and optic nerve swelling. **Can result in vision loss.** Correlates with disease activity. (Vavricka et al., 2015; Rogler et al., 2021; Peppercorn et al., 2022).
Uveitis (chorioretinitis)	Uveitis is independent of disease activity. Can precede diagnosis of IBD. Initial treatment: Patching, pupil dilatation, and topical or systemic steroids. May require immunosuppression and anti-TNF. (Vavricka et al., 2015; Rogler et al., 2021; Peppercorn et al., 2022)
	Anterior Uveitis – Inflammation of the iris and ciliary bodies. Presents as eye pain, headache, photophobia, blurred vision, or decreased vision acuity. Posterior Uveitis can be painless but with complaints of floaters and/or vision loss. Requires slit lamp exam. (Vavricka et al., 2015; Rogler et al., 2021; Peppercorn et al., 2022)
	If not treated promptly, Uveitis can lead to iris atrophy, synechiae, pigment deposits, glaucoma, cataracts, optic nerve dysfunction, retinal detachment, and permanent loss of vision. **Requires urgent referral.** (Peppercorn et al., 2022)

Ophthalmologic

Ophthalmology referral is recommended for those with symptoms of, or findings suggestive of, episcleritis or uveitis as well as those on long-term steroids. (Rufo, 2022)

Immediate ophthalmologic referral for:

Vision changes, stabbing pain with photophobia, fixed pupil(s), headache and nausea, corneal opacity, or ciliary flush. (Peppercorn et al., 2022)

Musculoskeletal

IBD-RELATED ARTHRALGIA: Joint pain without inflammation

IBD-RELATED ARTHRITIS: joint pain and inflammation; affects 16–33% of children and adolescents with IBD. (Rabizadeh & Oliva-Hemker, 2017) Often involves large joints. More common in CD than UC; can present prior to or after diagnosis of IBD.

They include peripheral or axial arthropathies. (Vavricka et al., 2015)

Peripheral arthropathies more frequently reported in CD. Presents with redness, swelling, and decreased ROM.
Categorized as:
- Pauciarticular
- Polyarticular

Pauciarticular arthropathies effect <5 joints.
Primarily involves knees, elbows, and/or hips. Asymmetric. Can be acute and self limiting. Can precede diagnosis of IBD. Associated with disease flares. Worsens with disease activity. Can be associated with other extraintestinal manifestations. Treatment: Management of underlying bowel inflammation.

Polyarticular arthropathies effect >5 joints.
Often effects bones of the hands, wrists, and fingers. Other joints can be affected. Symmetric. Chronic. Can have recurrent flares independent of disease activity. Can be migratory. Treatment: Sulfasalazine, steroids, anti-TNF.

(Vavricka et al., 2015)

Axial arthropathies involves the axial spine and sacroiliac joints. Can be accompanied by synovitis.

Ankylosing spondylitis
Progressive arthropathy effecting the spine. Leads to fusion of the spine. Associated with UC and HLA B27 antigen. Effects <2%. Symptoms: Back stiffness, pain, and stooped posture as well and peripheral joint complaints. Treatment: May respond to ASA, steroids, anti TNF.

Sacroiliitis
Not associated with HLA B27 antigen. Occurs in 10–52% of patients. Can be asymptomatic. Incidental finding on imaging studies (bone scans or CTE or MRE). Treatment: Anti-TNF, PT, and exercise program. (Vavricka et al., 2015)

Enthesitis – Inflammation at the insertion site of tendons, ligaments into the bones. (Inman, 2022) Examples include: Achilles tendinitis and plantar fasciitis. Occurs in 1 in 5 pediatric IBD patients.
Dactylitis – Swollen digits.

Musculoskeletal Secondary Manifestations

Metabolic bone disease

Bone demineralization can be due to malnutrition, malabsorption and/or steroids. May also be influenced by growth/nutritional failure, pubertal delay and sedentary lifestyle. (Rufo, 2022)

Categorized as:

Normal bone density z score	(+1 to -1 SD)
Risk for Low Bone Density	(-1 to -2.5 SD)
Low Bone Density	(≤-2.5 SD)

Treatment: Treat underlying IBD; provide nutritional support; vitamin D and calcium supplementation; limit use of steroids; encourage weight-bearing exercises; endocrinology referral if needed. (Rufo, 2022)

Osteonecrosis of femoral head

Infarction of the head of the femur causing cellular necrosis. Associated with chronic steroid use. Presents with hip or knee pain. (Inman, 2022)

Hypertrophic osteoarthropathy

Abnormal accumulation of skin and bone tissue at distal digits thought to be due to increased blood flow and connective tissue growth secondary to circulating cytokines. Resembles clubbing. Can be associated with arthralgias and joint fusion. (Krugh & Vaidya, 2021)

Chronic recurrent multifocal osteomyelitis (CRMO)

Rare. (Setty et al., 2022) Recurrent multifocal aseptic inflammation affecting long bones and clavicles (osteomyelitis).

Hepatobiliary/Pancreatic Disease

Consider hepatobiliary disease in patients presenting with jaundice, pruritis, nausea/vomiting, or abnormal liver function tests. (Friedman et al., 2022)

Primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH)	Chronic and often progressive cholestatic disease characterized by inflammation and stricturing of bile ducts. Primarily associated with ulcerative colitis and increases risk of colon cancer for IBD patients with concurrent PSC. (Friedman et al., 2022)
	30–70% of IBD patients with PSC also have concurrent clinical symptoms, biochemical, and histological findings consistent with autoimmune hepatitis. (Setty et al., 2022)
	PSC occurs independent of disease activity.
	Prevalence of PSC is up to 5% with UC, rare in CD; AIH rare (<1%).
	Order ERCP and possible dilation, will likely require liver transplant within 10–12 years.
Autoimmune pancreatitis (AIP)	Rare, but type 2 AIP can be associated with IBD (most commonly UC). Consider in patients presenting with painless jaundice and abdominal pain or if pancreatic mass noted on imaging. (Whitcomb, 2022). Not typically associated with disease activity or medications. Monitor pancreatic enzymes.
Gallstones	Increased risk for development for patients with ileal Crohn's disease. Treatment may include cholecystectomy, if symptomatic. (Friedman et al., 2022)

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Pulmonary

Pneumonitis	Interstitial – Symptoms include acute onset of dyspnea with crackles on exam. Imaging may reveal diffuse ground glass or reticular opacities. (Weinberger et al., 2021)
	Drug reaction – Common recognized complication of sulfasalazine and 5-ASA usage (most common with sulfasalazine). Symptoms include cough with crackles on exam, eosinophilia may also be appreciated. (Weinberger et al., 2021)
Bronchiolitis obliterans	Small airway injury which can occur secondary to an inflammatory reaction from IBD and/or sulfasalazine. Symptoms include dyspnea and cough, which is sometimes productive. This is typically not acute and is progressive over weeks to months and will eventually result in respiratory failure. (King et al., 2022)

Cardiac Disease

Myocarditis	Inflammation of the heart muscle (myocardium). Etiology can be infectious and autoimmune, due to hypersensitivity reaction or exposures to toxins. Symptoms range from flu-like symptoms, fever, chest pain, tachycardia, difficulty breathing, and fatigue to cardiogenic shock and heart failure. (Cesa et al., 2022)
Pericarditis	Inflammation of the sac around the heart (pericardium). Etiology includes: Infection, autoimmune, trauma, surgery, metabolic, or medication induced (ASA, thiopurines, methotrexate, mesalamine, and adalimumab). (Cesa et al., 2022) Symptoms include: Sharp pleuritic pain, which worsens when supine, SOB, palpitations, and fatigue. Physical exam may show muffled heart sounds, tachycardia, and friction rub. (Cesa et al., 2022)
Pleuro-pericarditis	Inflammation of the of the pericardium and pleura. Symptoms include: Chest pain, tachycardia, dyspnea, and shoulder pain. (Cesa et al., 2022)

Treatment includes: Prompt diagnosis; treatment of inflammation (often requires steroids); and prevention of recurrence. May require avoidance of suspected causative medication.

Cardiovascular disease

Cardiovascular manifestations are associated with active IBD. Thought to be due to hypercoagulability caused by genetic predisposition, systemic inflammation, platelet abnormalities, stasis, prolonged immobilization, dehydration, and estrogen-containing OCP. These include:

Venous thromboembolism (VTE)	Can occur in 1–2% of hospitalized children and adolescents with active IBD. Commonly occurs in lower extremities or cerebral veins. Deep venous thromboembolism (DVT) is one of the most common in occurrence. (Ribizadeh & Oliva-Hemker, 2017) VTE/DVT can lead to cerebral vascular accident (CVA) and/or pulmonary embolism (PE). (Setty et al., 2022)
	Preventative measures: Treatment of IBD, hydration, mobilization, and embolic stockings.
	Treatment: Anticoagulation.
Portal vein thrombosis/embolism	Rare in occurrence. Can present as an acute onset of severe abdominal pain, distention, and ileus. Can be life threatening.
Takayasu arteritis	A chronic inflammatory granulomatous vasculitis effecting large vessels (aorta and its main branches). It has been associated with IBD. It is rare in occurrence. Can lead to stenosis, occlusions, dilations, and aneurysms. (de Almeida Martins et al., 2021) Can present as persistent fever, weight loss, heart murmur, and tachycardia in a patient with IBD that is non-respondent with IBD treatment.

Renal

Glomerulonephritis – Commonly presents with hematuria, proteinuria, edema, and hypertension due to glomerular injury due to inflammation. (Niaudet, 2020)	IgA nephropathy	Renal complication that can lead to ESRD (higher incidence in patients with Crohn's). (Hayashi et al., 2021)
	Tubulointerstitial nephritis	Kidney injury, potentially irreversible, that can lead to ESRD.
		Has been associated with the usage of 5-ASA. (Vasanth et al., 2016)
Amyloidosis	Rare complication of IBD, more often with Crohn's. Most commonly associated with renal disease; but can also be associated with hepatic amyloidosis.	
	Consider with patients with diarrhea, weight loss, GI bleeding. (Camilleri, 2020)	

Secondary effects	
• **Kidney stones**	Can result from steatorrhea diarrhea, dehydration, and metabolic acidosis. (Peppercorn et al., 2022)

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Hematologic

Anemia – Most common hematologic complication, affecting up to 1/3 of IBD patients, often resulting from iron, vitamin B12, or folate deficiencies. Can result from chronic blood loss in GI tract or anemia of chronic illness. (Ribizadeh & Oliva-Hemker, 2017)

Thrombocytosis – Can be reactive due to IDA or inflammation from IBD. Both inflammation and IDA predispose a patient to thrombocytosis. May also be a marker of disease activity.

Leukocytosis – Often correlates to disease activity. Can also be a consequence of corticosteroid, azathioprine, and 6-MP use.

Secondary effects

- **Leukopenia** – Well-recognized potential side effect from the use of thiopurine medications. Pretreatment testing of *NUDT15* and *TPMT* genotyping can be helpful to identify patients at higher risk for leukopenia, as well as regular laboratory monitoring for all patients on these medications. Consider lowering dose of medication and monitoring clinical symptoms and labs closely vs. discontinuing if leukopenia noted.
- **Venous thrombosis** – Incidence ranges from 1–3%. Typically presents as a deep vein thrombosis or pulmonary embolism.

Endocrine

Metabolic bone disease	Osteoporosis common (prevalence of 18–42% of patients) due to many factors, such as corticosteroid use, inflammation, dietary restrictions, malabsorption, and possible hypogonadism. Monitor clinically at each visit for risk of fracture (advanced age, low BMI, chronic steroid use, hx of fractures, and cigarette or alcohol use). If at higher risk, DXA study of spine and hip is warranted. Consider yearly exams to monitor, possibly more frequently for high-risk patients. Treatment includes vitamin D/calcium supplementation, minimizing glucocorticoid use, and referral to endocrinology. (Rosen, 2021)
Growth failure	Common EIM, especially with Crohn's disease. Potential causes include chronic inflammation, undernutrition, pubertal delay, and steroid use. (Teitelbaum, 2022)
Pubertal delay	Onset of puberty more than 2–3 standard deviations above the mean time for the general population (approx. age 12–13 years for females and 13–14 years for males). Maximize IBD management and nutrition therapy for growth concerns and pubertal delay and refer to endocrinology. (Teitelbaum, 2022)
Abnormal metabolism and/or absorption	Fat maldigestion is uncommon but can occur in patients with Crohn's who have extensive mucosal disease, liver dysfunction, extensive small bowel resections, or enteroenteric fistulas. There may be a higher prevalence of lactose intolerance in IBD population. Capillary leaks due to chronic inflammation are primary reason for low serum albumin (most often seen in Crohn's). (Setty et al., 2022)

Management includes close monitoring of growth trends at every visit. Optimizing nutrition (may need to consider enteral nutrition) and biologic therapies have been shown to be effective treatments to maximize linear growth. (Rosen, 2021)

Neurologic

Peripheral nerve disorders	Very rare. Polyneuropathies seem to be more associated with Crohn's. Important to rule out neuropathy from metronidazole in these patients. (Hoffman & Kruis, 2004)
Multiple sclerosis	Several cases have demonstrated coexisting MS and IBD, primarily associated with Crohn's. Possible genetic predisposition. (Hoffman & Kruis, 2004)
Optic neuritis	Demyelinating inflammation or degeneration of the optic nerve, which can lead to loss of vision. Ocular IBD EIM ranges from 1–43% and optic neuritis is thought to be present in about 4% of those patients. Symptoms include eye pain, vision changes, and possible headaches. Consider STAT referral to ophthalmology. (Hsieh, 2021; Boyd, 2022)
Demyelinating disorder	Guillain-Barre may have a higher incidence associated with ulcerative colitis. (Hoffman & Kruis, 2004)

Secondary

- Multifocal leukoencephalopathy

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