

Extraintestinal manifestations of inflammatory bowel disease in children

Koletić, Carolina Frances

Master's thesis / Diplomski rad

2014

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:737579>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-05-06**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



**UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE**

Carolina Koletic

**Extraintestinal Manifestations of
Inflammatory Bowel Disease in Children**

GRADUATE THESIS



Zagreb, 2014

This graduate thesis was made at the University of Zagreb School of Medicine mentored by Assistant professor Irena Senečić-Čala and was submitted for evaluation 2013/2014.

List of Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	mercaptopurine
AIH	autoimmune hepatitis
AZA	azathioprine
BMD	bone mineral density
CD	Crohn's Disease
EBV	Epstein Barr Virus
EIM	extraintestinal manifestations
EN	erythema nodosum
HLA	human leukocyte antigen
JCV	John Cunningham Virus
IBD	inflammatory bowel disease
IC	intermediate colitis
MCD	metastatic Crohn's disease
OFG	orofacial granulomatosis
PG	pyoderma gangrenosum
PSC	primary sclerosing cholangitis
TPMT	thiopurine methyltransferase
UC	ulcerative colitis

Table of Contents

I.	Abstract	1
II.	Introduction	2
III.	Pediatric Inflammatory Bowel Disease	
	A. Epidemiology	2
	B. Etiology	3
	C. Clinical Characteristics	4
	D. Diagnostics	6
	E. Treatment	8
IV.	Extraintestinal Manifestations in Pediatric Inflammatory Bowel Disease	
	A. Musculoskeletal Manifestations	9
	B. Oral Manifestations	11
	C. Hepatobiliary Manifestations	14
	D. Dermatological Manifestations	18
	E. Ophthalmological Manifestations	23
	F. Secondary Systemic Manifestations	24
V.	Conclusion	25
VI.	References	26
VII.	Biography	29

Abstract

Children with inflammatory bowel disease (IBD) have higher rates of extraintestinal manifestations (EIMs) than the adult IBD population.¹ It is believed that these manifestations are an extension of the autoimmune inflammatory pathology of IBD into organs of the body outside of the gastrointestinal system such as musculoskeletal, hepatobiliary, oral, dermatological, and ophthalmological systems. Secondary EIMs are systemic changes that result from inflammation of the gastrointestinal system. These include, weight loss and growth failure, anemia, and decrease in bone mineral density. EIMs can present before, during, or after gastrointestinal symptoms and may not necessarily be congruous with the severity of IBD flares. The goal of this review is to inform clinicians about the relationship between various EIMs and IBD in order to expedite diagnosis and treatment of IBD and its complications. This is especially important in the pediatric population where a delay in diagnosis affects patients' development and future health.

Key words: extraintestinal manifestation, inflammatory bowel disease, pediatrics

Introduction

The inflammatory bowel diseases (IBD) are comprised of the heterogeneous disorders Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis that all manifest as chronic inflammation of the gastrointestinal tract. For many patients, IBD does not only present with intestinal manifestations. Symptoms may manifest elsewhere in the gastrointestinal system such as oral and hepatic inflammation in addition to musculoskeletal, cutaneous, and ocular systems. Especially important in the pediatric population, gastrointestinal inflammation often results in malabsorption that may lead to constitutional symptoms such as growth failure, abnormal skeletal development, and anemia that often delay development and puberty. These symptoms in association with IBD are termed "extraintestinal manifestations" or EIM. In the adult IBD population, EIMs have a reported prevalence in the range between 6-42%. In the pediatric IBD population, this prevalence is much greater. The presentation of at least one EIM among pediatric IBD is 68%. According to one study, EIMs are present in 50% with UC and in 80% with CD.¹ In the management of pediatric IBD, it is necessary to recognize and address EIMs in addition to the gastrointestinal manifestations. Here we will discuss the presentation of EIM in the pediatric population with IBD. The first section presents current research and medical management of pediatric IBD. The second section presents a review of literature of common EIMs of pediatric IBD.

Pediatric Inflammatory Bowel Disease

Epidemiology

In the general IBD population, the peak incidence of IBD is in the third decade but about 25-30% of patients with CD and 20% of patients with UC present before the age of 20.² In the

pediatric population, the peak age of onset is during late adolescence, and 4% of the pediatric IBD is diagnosed before the age of 5.³ Overall, there has been an increase in the diagnoses of IBD in the past century. In a study that reviewed trends of incidence of pediatric IBD from 139 studies across 32 countries conducted from 1950 to 2009, 60% of studies reported an increase of incidence in CD and 65% reported no change in incidence in UC.⁴ These trends were also reflected in a recent 12-year study in Texas that showed an increase of incidence in CD but stability in incidence of UC. This study also noted that Caucasians had higher incidence (4.5/100,000) than African-American (1.83/100,000) or Hispanic (0.62/100,000), and that African-Americans had higher incidence of CD than UC.⁵

Etiology

Although the etiology of IBD has been studied for decades, we still have little understanding of the initiating factors of chronic inflammation of the intestines. We know that the etiology is likely multifactorial due to specific genetic predispositions and environmental exposures that affect the immune response to the intestinal epithelium. The pathological process includes a compromised intestinal epithelial barrier, microfloral invasion of the intestinal wall, and an exaggerated immune response.⁶

The hygiene hypothesis is thought to explain the increasing incidence of IBD around the world in past decades. This hypothesis comes from the observation that with the improvements of hygiene in the latter half of the 20th century, we have seen an increased prevalence of diseases of disturbed immune function such as allergies and autoimmune diseases. Multiple factors such as a lower exposure to *Helicobacter pylori* and helminthes, widespread use of antibiotics as well as increased hygiene and less crowding in households are implicated in altering the microflora to

which individuals are exposed. This suggests that interaction with certain microorganisms in the environment is integral to normal immune development.^{7,8}

Another hypothesis is that IBD presents as an appropriate immunological response to an unknown organism, antigen, or toxin.⁹ Studies have excluded organisms such as *Salmonella*, *Campylobacter jejuni*, *Clostridium difficile*, adenoviruses, rotaviruses, and mycoplasma as etiological infective agents, although they may have a role in triggering an increased immune response in an individual predisposed to IBD. Several studies and anecdotal evidence suggest that *Mycobacterium avium* subspecies *paratuberculosis* (MAP) may be a possible etiological agent for CD.¹⁰ A third possibility is that there is a structural anomaly of the intestinal wall that allows increased immune cell exposure to gut flora.⁹

CD is associated with increased Th1 T cell-mediated response that promotes production of pro-inflammatory cytokines interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α), IL-12 and IL-18, whereas UC is associated with atypical Natural Killer T cell and Th2 T cell-mediated response with production of the cytokines IL-5 and IL-13. Despite these differences, both CD and UC share similar end-stage inflammatory pathways of intestinal injury caused by interaction of immune cells, inflammatory mediators, intestinal epithelium, and microflora.^{11,12}

Clinical Characteristics

Symptoms that cause a high degree of suspicion of colitis are bloody stool, diarrhea, urgency and increased frequency of stooling, abdominal discomfort, and a presentation of anorexia and weight loss.¹³ Any one of these presenting symptoms may warrant consideration of colitis in a differential diagnosis. Clinical presentation, radiographic and endoscopic imaging and histological evaluation are able to distinguish 90% of cases as UC or CD. In about 10% of cases

diagnostic evaluation is inconclusive and a diagnosis of “indeterminate colitis” (IC) is given.¹⁴ Upon further progression of disease or follow-up diagnostic evaluation, about 90% of IC cases are able to be distinguished as UC or CD, but 10% of cases retain the diagnosis of IC.¹⁵

Gastrointestinal manifestations of UC by definition are limited to the large intestine. The natural progression of disease begins in the rectum and extends proximally in a continuous pattern along the colon. Extent of disease is measured by the extent of colon involved and the severity of inflammation of the mucosal layer. Pain in the left lower quadrant may reflect either distal disease that involves the rectum or rectosigmoid colon, or left-sided disease that involves the rectum, sigmoid, and descending colon. Pain extending to the entire abdomen may reflect pancolitis that involves the entire colon. In children with UC, 15-22% present with rectosigmoidal disease, 22-36% have left-sided disease, and 43-63% present with pancolitis.¹⁶ Inflammation of the colon is appreciated on colonoscopy characterized by hyperemia, edema, granularity with easy friability and superficial ulcerations limited to the mucosal layer. Islands of mucosal regeneration bulge up between the ulcers to form pseudopolyps. If the muscularis propria becomes exposed to the bacteria of colonic lumen, perforation and pericolic abscesses may form. Further involvement of the neural plexus in the muscularis propria causes dilation, edema and gangrene of the colon, termed toxic megacolon.¹⁷ Patients with UC are at higher risk for colon cancer. Proctocolectomy is preventative against colon cancer and curative for UC, yet requires a lifestyle change of managing a permanent stoma.¹⁸

Unlike UC that is limited to the colon, inflammatory lesions in CD may present anywhere along the gastrointestinal tract from the mouth to the anus, but most commonly affects the terminal ileum. Aphthous mouth ulcers and perianal disease (skin tags, fissures, abscesses, or fistulas) are specific symptoms of CD that are not seen in UC. CD lesions are classically discrete

“skip lesions” with unaffected healthy tissue between lesions, but may coalesce to create large lesions that resemble those of UC. Unlike UC, CD lesions can affect the entire thickness of bowel wall forming transmural noncaseating granulomas, fissures, strictures, and fistulas. Failure to thrive or weight loss is more likely to be the presenting symptom in CD (85%) than in UC (65%), but is present in a majority of cases in both types of IBD.¹⁹ CD refractory to medication may be treated with surgery, but unlike UC, resection is palliative and not curative because another part of the gastrointestinal tract may be affected after resection.¹⁷

A meta-analysis of 14 pediatric studies of 1153 children with CD found that 38% of cases had isolated ileal disease, 38% had both ileal and colonic disease, and 20% had isolated colonic disease.²⁰ In Mamula’s study of children 5 years of age and younger it was found that isolated ileal disease was less common (11% of cases) than among older children, and had higher involvement of the colon with mixed ileal and colonic disease in 59% of cases and isolated colonic disease in 30% of cases.²¹ Perianal disease is present in 11-18% of children with CD, but is more common among children under 5 years of age at 34% which is similar to that of the rate among the adult population (36-46%).²²

Diagnostics

Before diagnosing IBD, other more common causes of presenting symptoms such as bloody diarrhea or weight loss must be ruled out. First, a hemoccult stool test is performed to detect the presence of blood in stool. Further, stool cultures are taken to screen for common infectious gastroenteritis pathogens such as enteropathogenic *E. coli*, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Salmonella*, *Shigella*, *Entamoeba histolytica*, *Giardia lamblia*, *Dientamoeba fragilis*, *Mycobacterium tuberculosis*, *Clostridium difficile* in addition to ova and

parasites. Blood samples are also taken to evaluate degree of disease and differential diagnoses. A complete blood count with differential as well as a coagulation panel help assess possible anemia and bleeding tendency. Further, a comprehensive metabolic panel, liver enzymes and protein and albumin levels, gives information on the patient's nutritional status as well as liver function. Low levels of vitamin B12, folate, selenium and zinc also reflect the degree of malabsorption that may support a diagnosis of IBD. Blood markers of elevated erythrocyte sedimentation rate (ESR), fibrinogen and C-reactive protein (CRP) indicate present inflammation, and elevated orosomucoid is specific for CD. Further, increased levels of calprotectin in stool also indicates inflammation of the intestines.¹³

Locating affected regions of inflamed bowel by radiological imaging can be appreciated by thickening of luminal wall on abdominal ultrasound (US) or computed tomography (CT), but is most readily seen on magnetic resonance enterography (MRE) with contrast. In the pediatric population, MRE is the best radiographic imaging modality to detect small intestinal involvement but magnetic resonance (MR) colonoscopy as of yet has no role in diagnostics for pediatric IBD. The gold standard for diagnosis of IBD is gross inspection of the gastrointestinal tract upon endoscopy and colonoscopy with biopsy for histological evaluation. For the small bowel that cannot be seen by endoscopy or colonoscopy, wireless capsule endoscopy (WCE) is passed through the bowels to image the small intestine. Before administration of the WCE, patency capsules should be used to evaluate the risk of retention.⁶³ Further distinction between CD or UC may be elucidated by blood serology where elevated levels of ASCA (anti-*Saccharomyces cerevisiae* antibodies) suggest a diagnosis of CD and elevated levels of p-ANCA (perinuclear antineutrophil cytoplasmic antibody) suggest a diagnosis of UC, yet review of the literature suggest that these serological markers may not be reliable.⁶⁴ Since colonic involvement

is more likely in children with early onset, colonoscopy is indicated first. If negative then UC is unlikely and an upper-GI endoscopy is performed to search for lesions indicative of CD or any other pathology.

Treatment

Treatment for IBD is determined by the severity, location, and type of inflammation taking into account the age of the patient and presence of extraintestinal manifestations.

Presentation of acute flares of any severity is most effectively treated with a combination of bowel rest (supplemented with parental nutrition or clear fluids) as well as corticosteroid therapy to induce remission. Mild disease can often be controlled with the 5-aminosalicylic acid (5-ASA) anti-inflammatory agents such as sulfasalazine or mesalamine, as well as antibiotics such as metronidazole. For moderate disease, induction with bowel rest and corticosteroids is started with maintenance of immunomodulating agents such as azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate. These agents are antimetabolites and interfere in the replication of proliferating cells, such as autoimmune T-cells. For severe disease, induction and maintenance is most effective with biologic agents that have anti-TNF α properties such as infliximab, adalimumab, certolizumab, and natalizumab.

Side effects of these drugs are numerous and measures should be taken to prevent serious complications from these therapies. Folic acid should be supplemented in patients with IBD not only due to antimetabolic effects of IBD therapies but also due to malabsorption of vitamin B12 and folate. Anytime a patient is on high-dose steroids, it is recommended that a proton pump inhibitor be also administered to protect gastric mucosa. Before administering AZA or 6-MP, it is helpful to measure the thiopurine methyltransferase (TPMT) enzyme activity that indicates the

ability to prevent the build up of cytotoxic metabolites of 6-MP. Patients with low TPMT enzyme activity are at a higher risk for myelosuppression, bleeding, infection, and death at standard doses of AZA or 6MP, and therefore these agents are not used as therapy, or if necessary, only used at low-dose regimens.²³⁻²⁴ Before administering any immunosuppressing therapy, especially biologics, it is necessary to screen and treat any latent infections, specifically tuberculosis, EBV (Epstein Barr virus), and JCV (John Cunningham virus) to prevent activation of the infection. Further, it has been reported that concurrent therapy of AZA or 6-MP with a biologic therapy although effective in achieving remission in severe IBD, increases the risk of developing fatal hepatosplenic T-cell lymphoma. This occurs mostly in males after years of concurrent treatment, but can occur after just one administration of biologic therapy.²⁵

Extraintestinal Manifestations in Pediatric Inflammatory Bowel Disease

Musculoskeletal Manifestations

Arthritis is the most common extraintestinal manifestation in children with IBD occurring from 7-25% of cases.²⁶ It is more prevalent in the pediatric than the adult IBD population with a higher prevalence among females.^{16, 27} Arthritis occurs as noninfectious inflammation of joint synovium, seronegative for rheumatoid factor, antinuclear antibody, and LE factor.²⁸ Two patterns of arthritis present: peripheral and axial. Peripheral arthritis affects the joints of the extremities and presents as pauciarticular (type 1) or polyarticular (type 2). Both types of peripheral arthritis are more common in cases of CD (pauciarticular 6%, polyarticular 4%) than in cases of UC (pauciarticular 3.6%, polyarticular 2.5%).²⁹ Pauciarticular peripheral arthritis is the most common presentation of arthritis in children with IBD. By definition, it affects fewer than 5 joints, mostly large proximal joints such as hips, knees, elbows, and ankles, often

asymmetrically, and is self-limiting for 5 weeks at a time. 20-40% of patients have more than one episode of inflammation. Pauciarticular peripheral arthritis usually reflects the disease activity of IBD, but may present before gastrointestinal symptoms. It has a strong association with HLA-B27, HLA-B35, and HLA-DR. In contrast, polyarticular peripheral arthritis by definition affects more than 5 joints, mostly symmetric, bilateral, and distal in the hands and feet, and can last for an average of 3 years. Its course is independent of IBD and does not reflect gastrointestinal activity. Polyarticular peripheral arthritis is associated with uveitis and HLA-B4.¹ In Lindsley's study of 136 children with IBD, 17% had arthritis, whereas in Passo's study of 102 children with IBD, 12% had arthritis, mostly commonly pauciarticular arthritis with a majority presenting after onset of bowel symptoms.³⁰⁻³¹

Axial arthritis is less common than peripheral arthropathy, occurring from 3-25% of patients with IBD. Two types of axial arthritis present: isolated sacroiliitis and ankylosing spondylitis that affects the vertebral column as well as the sacroiliac joints. Ankylosing spondylitis occurs in 5-10% of patients with IBD, most of whom are young and have HLA-B27. Sacroiliitis in contrast has no association with HLA-B27.²⁹ Symptoms present as severe back pain and stiffness especially in the morning or after prolonged periods of rest. Because axial arthritis does not reflect gastrointestinal activity of IBD, treatment is usually directed against arthritis rather than IBD. Although NSAIDs are used to treat ankylosing spondylitis, in the presence of IBD, NSAIDs may exacerbate gastrointestinal disease. The drugs used to treat ankylosing spondylitis are similar to those used to treat IBD including disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine, mesalamine, immunosuppressants such as methotrexate, azathioprine, and biologic TNF- α antagonists with infliximab.¹

Oral Manifestations

Oral manifestations of IBD are more likely to present in the pediatric versus adult IBD population, in males, and in patients who have CD with involvement of proximal or perianal manifestations. Manifestations of IBD in the oral cavity may present as specific to either CD or UC, or non-specific lesions that are loosely associated with IBD. Lesions specific to CD include tag lesions, cobblestoning, mucogingivitis, linear ulcerations, and labial edema with fissures. Pyostomatitis vegetans is almost always associated with the diagnosis of IBD, notably more frequently in UC than in CD. Non-specific lesions include aphthous stomatitis, angular cheilitis, persistent submandibular lymphadenopathy, recurrent buccal abscesses, perioral erythema with scaling, and glossitis.³²

Specific CD lesions mostly affect the buccal mucosa, gingival, labial, vestibular and retromolar areas, usually sparing the palate, tongue and floor of the mouth. The most pathognomonic oral lesions of CD are oral tags and cobblestoned mucosa. Oral tags are epithelial folds found near the labial and buccal vestibules as well as the retromolar areas, and present upon histopathology with granulomas. Cobblestoned mucosa presents as firm, swollen micropapules with hyperplastic appearance of normal mucosal epithelium. In addition to being painful, these lesions may impair eating and speaking. Although oral tags and cobblestoning lesions do not correlate with intestinal CD activity, treatment may necessitate systemic therapy for CD if the lesions do not resolve with topical steroids. Mucogingivitis is also specific to CD presenting as edema, granulation, hyperplasia, and possible ulceration of the gingiva. It is treated similarly to oral tags and cobblestoning with topical steroids or systemic therapy for CD.³²

Deep linear ulcerations of the buccal mucosa are an oral manifestation of CD that are identical histologically to the fissuring ulcers of the intestines with noncaseating granulomas

characterized by epithelioid histiocytes, giant cells, and lymphocytes. Unlike oral tags and cobblestoning lesions, these ulcerating lesions are painful to the touch and to exposure to hot, acidic, or spicy foods. These ulcerations are linear, deep and persistent, unlike aphthous ulcers that are round, superficial, and heal within 1-2 weeks. Fissures and edema may also be present on the lips, and is treated similarly to deep ulcerations with topical tacrolimus and intra-lesion steroid injections.^{32,33}

Pyostomatosis vegetans (PV) is a rare oral manifestation far less common than any oral manifestation associated with CD. PV is specific to IBD, but more commonly present in UC than in CD. Males are more frequently affected than females (2:1-3:1), and adults are more frequently affected than children.

PV presents as multiple military white and yellow pustules scattered, clustered, or coalesced in a linear pattern, called “snail-track” ulcers, in an erythematous epithelium of the gingiva and lingual and buccal mucosa, sparing the tongue. Histological examination shows intra-epithelial and subepithelial microabscesses with infiltrates of neutrophils and eosinophils, hyperkeratosis, acanthosis and acantholysis. Unlike in pemphigus vulgaris, immunofluorescence shows no deposits of IgA, IgG, or C3 deposits in PV. PV is not associated with any infective microorganism, and its pathogenesis still eludes researchers. Because of similar histological findings, it is thought that PV is the oral equivalent to pyodermitis vegetans. The main laboratory finding in PV is peripheral eosinophilia which is present in 90% of cases. The differential diagnoses of PV include candidiasis, benign migratory glossitis, stomatitis areata migrans, and pemphigus vegetans that also present with neutrophilic and eosinophilic infiltrates.

Clinical presentation includes localized pain, enlarged and tender submandibular lymph nodes, and fever. About 10% of these patients also develop IBD associated arthritis of the

temporomandibular joint.³³ PV presentation may precede intestinal symptoms of UC, but mostly reflects the severity of intestinal UC. Systemic therapy for IBD therefore is usually needed to treat PV. The treatment of choice is systemic steroids because topical steroid and antiseptic mouthwashes are rarely effective. Azathioprine, sulfamethoxypyridazine, dapsone (second line in relapsing cases), cyclosporine A, biologics, and surgical colectomy are all effective options in treating PV and associated intestinal IBD.^{32, 33}

Differential diagnosis of oral manifestations include reactions to foreign bodies from dental procedures, infections, autoimmune diseases, drug reactions, nutritional deficiencies and malignancies. Most foreign bodies include dental amalgams and materials. Infections that cause oral ulceration or granulomas include candidiasis, histioplasmosis, cryptococcosis, paracoccidioidomycosis, blastomycosis, in addition to tuberculosis, leprosy, cat scratch disease, tertiary syphilis, and hepatic infections that have other prominent features that point to diagnosis. Autoimmune disease that may lead to similar oral manifestations include orofacial granulomatosis, Behcet's disease, Wegener's granulomatosis, oral sarcoidosis, bullous pemphigoid, erythema multiforme, and epidermolysis bullosa. Nutritional deficiencies from malnutrition or malabsorption of vitamin B, niacin, folate, zinc can cause stomatitis, aphthous ulcers, glossitis, cheilitis, and perioral dermatitis. Nutritional deficiencies can be side effects from immunosuppressant drugs frequently used to treat IBD such as methotrexate that causes folate deficiency and from sulfasalazine that causes both folate and niacin deficiency.

Orofacial granulomatosis (OFG) is a rare disease that presents with granulomatous cheilitis, chronic edema and fissuring of the lips, swelling of the jaw, and lesions of the gingiva and mucosa. Etiologically, OFG differs from oral manifestations of CD in that OFG is caused by infiltration of Th2 CD4+ lymphocytes whereas CD presents with infiltration of Th1 CD4

lymphocytes. Clinically, OFG may be identical to oral CD. Since oral CD can precede intestinal involvement, most diagnoses of OFG in children are found to be CD when intestinal inflammation presents months to years later.³²⁻³³

Hepatobiliary Manifestations

Patients with IBD are found to have increased risk of having primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH) potentiating complications of cirrhosis, hepatocellular carcinoma, and liver failure. Cholelithiasis is also presents as a hepatobiliary manifestation, but is uncommon in children. The incidence of cholelithiasis among patients with CD is about 14%. This is twice the incidence of patients with UC or in the general population without IBD.³⁴ The overlapping syndrome of PSC with concurrent AIH is more common in the pediatric population than the adult population with IBD. Often clinical symptoms are identical and a cholangiography is needed to distinguish PSC from AIH.³⁵ Some have proposed that PSC is a progression of disease from AIH or are manifestations of the same disease.^{36,37,38} Whereas more than 80% of cases of PSC is associated with IBD especially UC, about 16% of cases of AIH are associated with UC.³⁹ Among patients with concurrent AIH and UC, 42% presented with abnormal cholangiograms suggesting an overlapping diagnosis of PSC.

PSC is characterized by chronic inflammation and scarring of the biliary system causing obstruction and congestion of bile in the biliary tree. The lack of bile excretion presents with malabsorption of fat-soluble vitamins A, D, E, and K as well as jaundice and pruritus that reflect elevated levels of bilirubin. Liver damage due to congestion of bile may manifest as hepatomegaly, and ascites from portal hypertension and cause elevated liver enzymes.

Although the specific etiology of PSC is unknown, PSC is associated with various autoimmune diseases such as diabetes mellitus, autoimmune thyroid disease, celiac disease, rheumatoid arthritis. In fact, up to 25% of PSC cases versus 9% of IBD without PSC cases are associated with at least one other autoimmune disease. Interestingly in this study, the clinical presentation, outcome, and HLA alleles did not differ among groups of PSC cases with or without additional autoimmune diseases. In all cases of PSC, there was a significant association with HLA DRB1*03 compared to healthy individuals without PSC.⁴⁰ Other findings that suggest that PSC is an autoimmune disease are elevated immunoglobulins, infiltration of T-lymphocytes in portal tracts, as well as antibodies such as anti-mitochondrial antibodies (AMA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), smooth muscle antibodies (SMA), rheumatoid factor, anti-endothelial cell antibodies (AECA).⁴¹ These findings present in autoimmune diseases but have limited diagnostic value as they are not specific to PSC.

Diagnosis of PSC is made upon a biochemical profile showing cholestasis as well as characteristic strictures and dilation upon cholangiography in the absence of other causes of sclerosing cholangitis. In the biochemical profile, alkaline phosphatase (ALP) is usually elevated to two to three times normal values in addition to gamma-glutamyl transpeptidase (GGT) levels. When the biochemical and clinical findings suggest PSC but the cholangiogram is normal, a liver biopsy is necessary to diagnose small-duct PSC. Those with PSC are at increased risk for cholangiocarcinoma seen in 7-15% of patients with PSC, diagnosed at a mean age of 45 years with a very poor prognosis of mean survival of 6 months. Treatment for PSC is usually with immunosuppressants, antifibrotics, and biologic TNF- α antagonists. Ursodeoxycholic acid has been studied widely with limited efficacy in treating PSC but has shown to decrease rate of colorectal dysplasia in patients with PSC and IBD.⁴² Treatment of PSC with immunosuppressants

is most effective among the pediatric population with overlapping autoimmune disease such as with AIH.^{35, 43} Stenting and dilatation of strictured ducts provides clinical and prognostic benefits. The treatment of end stage liver disease is liver transplantation, which restores biliary function, but does not serve as a cure since PSC can also affect the liver transplant.

In adults with IBD, PSC is more common in UC, with a prevalence of 5% among patients with UC, and 3.6% among patients with CD. In adults who present with PSC, about 90% have concurrent IBD although intestinal symptoms may be mild.³⁷ Patients with PSC and concurrent UC are at higher risk for colorectal cancer than patients with UC without PSC. Therefore, it is prudent to perform a colonoscopy screening for IBD and colorectal cancer for all patients who present with PSC. Cases of PSC present twice as often in males than in females.

In a study done by Faubion et al. of 52 children with PSC, 43 (84%) also had IBD. Of those patients, the 36 who could be reviewed showed 89% diagnosed with UC and 11% diagnosed with CD. 4% of 36 had asymptomatic IBD. This shows that PSC without IBD is rare, but because IBD may often be asymptomatic, children presenting with PSC should be screened for IBD. Further, PSC may be a marker for long-standing extensive colitis. Interestingly, IBD associated with PSC often presents with pancolitis with rectal sparing, whereas UC without PSC usually involves the rectum. It was also noted that in patients who had undergone proctocolectomy with ileal pouch-anal anastomosis, those who had concurrent PSC were more likely to have pouchitis. It is important to recognize PSC in children with IBD to optimize therapy and prognosis.⁴⁴

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver with infiltration of mononuclear cells and elevated serum levels of autoantibodies, immunoglobulins, and transaminases. Types of AIH are categorized by the associated elevated autoantibodies that

predominate. Type 1 AIH is defined as AIH in the presence of smooth muscle antibodies (SMA) or antinuclear antibodies (ANA), or both. Type 2 AIH is defined as AIH in the presence of anti liver kidney microsomal type 1 antibody (anti-LKM-1). Type 3 AIH is defined as AIH in the absence of known antibodies. Type 1 AIH accounts for 60-70% of all AIH cases and can be present in both adults and children, whereas type 2 AIH presents mostly in childhood. Type 2 AIH presents more acutely and is associated with IgA deficiency. Both types 1 and 2 have similar clinical presentation, response to treatment, prognosis, family history of autoimmune disorders (40%) and association with additional autoimmune disorders (20%) and about three times more prevalent in females than in males. Further, both type of AIH in pediatrics have partial deficiency of HLA class III complement component C4. In northern Europe, HLA DR*0301 is present in both types of AIH, but HLA DR*0701 has a higher prevalence in type 2 AIH. HLA DR*1301 is associated with type 1 AIH in South American pediatric population as well as northern European pediatric PSC population.⁴⁵

Clinical presentation of AIH varies upon progression. 40% of cases present with an acute illness of non-specific symptoms of malaise, abdominal pain, nausea, vomiting, jaundice, that is common in type 2 AIH and can develop into acute hepatic failure with encephalopathy within a few weeks of onset. 25-40% of cases present with chronic illness of progressive fatigue, fluctuating headaches and jaundice, as well as loss of appetite and weight that can elude diagnosis for months to years. About 10% of cases show no signs of liver disease until fulminant liver failure. The first symptoms could be portal hypertension with ascites and esophageal variceal bleeding resulting in hematemesis, hepatosplenomegaly, increase bleeding tendency, diarrhea, and weight loss. Regardless of the progression of presentation, most children present with hepatosplenomegaly and cutaneous signs of chronic liver disease such as spider nevi,

palmar erythema, leukonychia, and striae. Differential diagnosis of AIH include PSC, viral hepatitis, and Wilson's disease.⁴⁵

AIH usually responds to immunosuppression. First line therapy is prednisolone at 2mg/kg/day at a maximum of 60mg/day. Azathioprine is usually added later, but is not first line as it can cause hepatotoxicity to children who are already severely jaundiced. If steroids or azathioprine do not induce remission, mycophenolate mofetil and calcineurin inhibitors such as cyclosporine A and tacrolimus are considered as third line therapies.^{46, 47, 48} Normalization of liver enzyme levels is achieved usually by 6 months for type 1 AIH and by 9 months for type 2 AIH. Disease activity can be monitored by measuring levels of autoantibodies and IgG. Relapses occur in 40% of cases and are more likely before and during puberty. Relapses usually are treated with an increased dose of steroids. Cessation of treatment is considered only after 3 years since diagnosis, if liver enzyme levels have been normal for at least one year, if liver biopsies show no inflammation, and if the patient is not going through puberty when relapse is likely to occur. Remission without therapy is achieved in about 20% of cases in type 1 AIH but not in type 2 AIH.⁴⁵ About 10% of patients require liver transplantation 10-15 years after diagnosis, but 90% have favorable outcomes with normal lifestyle regardless of their presenting clinical symptoms, laboratory, or histological findings.⁴⁹

Dermatological Manifestations

Skin manifestations in patients with IBD occur anywhere between 2-30% upon review of various studies. The most common skin manifestations are erythema nodosum (EN) and pyoderma gangrenosum (PG). Other cutaneous manifestations may be important red flags in diagnosing IBD. In addition to perianal disease that is frequent among patients with CD,

metastatic granulomatous tissue, while much rarer, is also specific for CD even in the absence of gastrointestinal manifestations. Nutritional deficiencies of zinc, vitamin B3, and vitamin C secondary to intestinal inflammation have reportedly caused acrodermatitis enteropathica, pellagra, and scurvy, respectively. These may be considered as manifestations of malabsorption secondary to intestinal inflammation^{50, 51} Psoriasis, Sweet's syndrome, Steven Johnson syndrome, erythema multiforme, erythema elevatum diutinum, epidermolysis bullosa acqista, polyarteritis nodosum, and alopecia have also been reported as dermatological manifestations in IBD.^{1, 50, 51}

Erythema nodosum presents as tender, inflamed, nonulcerative red nodules about 1-5 cm in diameter that are found most commonly on the limbs especially lower leg on the anterior tibial area, but can also affect the trunk. Upon microscopic examination, lesions are characterized by lympho-histiocytic infiltrate of the lower derma, defined as septal panniculitis. EN presents in various infections, diseases, and reactions to medications. Infections associated with EN include tuberculosis (TB), coccidioidomycosis, histoplasmosis, blastomycosis, and *Yersinia*. EN may also manifest in Behçet syndrome, and sarcoidosis and as a reaction to medications such as sulfonamides, iodides, bromides, and estrogens.⁵² EN is present in 4% of patients with IBD but has been reported in up to 15%.^{53,54} According to Veloso, EN was reported in 8% of CD patients and 3% of UC patients.⁵⁵ EN is strongly associated with CD, females, ocular and joint manifestations, as well as presentation of PG.⁵⁴ In some reports, EN is not associated with the severity of IBD manifestation in the intestines, but others reports that it reflects increased bowel inflammation.^{1, 54} Steroids, immunosuppressive therapy, potassium iodide, colchicine, hydroxychloroquine, and thalidomide have been used as therapy in the past but recently infliximab has been shown to be most effective in achieving rapid and complete resolution.^{53, 56}

Pyoderma gangrenosum develops first as an erythematous pustule that rapidly spreads and ulcerates with violaceous undermined borders that can cover an entire limb. Upon histological study, lesions show lymphocytic vasculitis peripherally, neutrophilic infiltration, and central abscess, yet the lesion is sterile. Direct immunofluorescence demonstrates immunoglobulin and complement deposits in vessels of the dermis. Lesions are usually found on the extensor surfaces of extremities, especially below the knee, are usually multiple, and are more prevalent in sites of trauma.⁵⁰ PG is reported in 0.5% to 5% of patients with IBD. About 50% of patients with PG are found to have UC. PG is strongly associated with black African origin, family history of UC, pancolitis, permanent stoma, eye involvement, and EN.⁵⁴ Conditions other than IBD associated with PG are myeloma, rheumatoid arthritis, and leukemia. Development of PG may occur before, during or after resolution of IBD symptoms. Resolution of mild PG can be achieved with local applications of corticosteroid, cromolyn sodium, 5-ASA. Other systemic agents used include sulfasalazine, dapsone, corticosteroid, immunomodulators (azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil). Most effective treatment for severe cases is infliximab.¹

In pediatric patients with CD, the incidence of perianal disease is 13-62%. Perianal disease includes perianal erythema, fissures, abscesses, and complex fistulas. In a study by Palder, 62% of 325 children with CD studied developed perianal disease. Of those, 51% presented with fissures, 35% with skin tags, 15% with fistulae, and 13% with perirectal abscesses.⁵⁷

Fissures are broad based tears in the skin near the anal opening. They are often found posteriorly and have undermined edges, with associated bleeding, discharge, and pruritus. Although anal fissures may be caused by the passing of hard stool not related to CD, in the

presence of CD, fissures are non-healing. Fissures reflect the activity of CD, and therefore, poor healing is seen with surgical attempts to suture the fissure. Most effective treatment is medical therapy with nitrate ointments and sitz baths.

Skin tags are benign fleshy lobes of skin surrounding the anal opening. They are often associated with fissures, but are rarely painful. Excision is usually not necessary and may even result in poor healing and recurrence of the skin tag.

Fistulae are patent tunnels that connect the rectum to perianal openings. Although various classifications are used to characterize perianal fistulae, the most common categories of classification are simple and complex fistulae. Simple fistulae are short tracts near the anal opening with no associated anal abscesses. Complex fistula may have longer tracts, branching, involvement of anal sphincters, with connections to the rectum above the anal sphincters and dermal openings farther away from the anus, and with associated abscesses. Fistulas are classically treated with setons that pull away surrounding tissue to allow drainage of the fistula. Historically, setons were pulled periodically to create a tract of healed scar tissue, but this has fallen out of favor due to damage to surrounding tissues that often leads to incontinence. Setons in conjunction with medical therapy such as antibiotics (metronidazole or ciprofloxacin), immunosuppressant's and biologics are the most effective therapy. Once the inflammatory process of CD is treated, the seton can be removed and the tissue is able to heal properly.

Abscesses are collections of pus that may present perianally (60%), ischiorectally (30%), submucosally (5%) and pelvirectally (5%). They usually appear as red swelling of the skin around the anus that may be firm or fluctuant, tense, and painful to the touch. They may present with purulent drainage from the anus or with systemic signs of fever, chills, and malaise. Abscesses are treated with incision and drainage, in addition to medical therapy used to treat

fistulas including antibiotics (metronidazole and ciprofloxacin), immunosuppressants and biologics. Sulfasalazine and 5-ASA have not been shown to be effective therapies.⁵⁸

Metastatic Crohn's disease (MCD), a term coined by Mountain⁵⁷ in 1970 was first described by Park et al.⁶⁰ in 1965 as noncaseating granulomatous involvement of skin noncontiguous from the gastrointestinal tract in a patient with Crohn's disease. These lesions can present as cutaneous ulcerations, plaques, papules, or nodules. Histological findings include multinucleated giant cells, noncaseating granulomas, perivascular lymphocytes, monocytes, and necrobiosis. These lesions can usually be found in skin folds such as the inframammary fold, on limbs, and external genitalia.^{51,61} 20% of MCD lesions present before intestinal manifestations of IBD which can make diagnosis challenging because genital manifestations may be erroneously attributed to a gynecological or urological disorder.⁶¹ For example, vulvar inflammation may be the only presenting sign of Crohn's disease.⁶¹ Therapy has included zinc, local and systemic steroids, and immunosuppressants.

Sweet syndrome is defined as acute febrile neutrophilic dermatosis that presents as tender erythematous plaques or nodules on the face, trunk and extremities. Histologically lesions reveal neutrophilic infiltrate with leukocytosis. A possible cause of Sweet syndrome is use of azathioprine in patients with CD, but resolution can be achieved with corticosteroids and metronidazole.¹

Ophthalmological Manifestations

Of patients with IBD, 1.6-4.6% of patients with UC and 3-6.3% of patients with CD have ophthalmological involvement. Of patients with CD, ocular involvement is associated with involvement of the colon rather than isolated ileal disease.¹ It is not clearly understood whether

the ocular manifestations are due to an immune-complex type hypersensitivity to a colonic antigen, cytotoxic antibodies, or delayed-type hypersensitivity. It is known that ocular manifestations often coexist with other EIMs especially arthritis and erythema nodosum, suggesting a common autoimmune mechanism. The most common ophthalmologic manifestations are episcleritis and uveitis, but also include scleritis, conjunctivitis, and rarer manifestations such as keratitis, retinitis, pars planitis, scleromalacia perforans, and optic neuritis.

Episcleritis is the inflammation of the episclera, the blood rich layer beneath the conjunctiva. Presentation involves acute redness of one or both eyes, with irritation, burning, and pain to palpation. Redness may be localized or diffuse around the eye, but usually spares the circum-limbal area. Unlike uveitis, episcleritis does not lead to loss of vision, photophobia, or pupillary changes. Episcleritis reflects the activity of IBD flare, and resolves with the treatment of the underlying IBD. For symptomatic relief, cool compresses and topical steroids may be used, but treatment of underlying IBD is necessary for complete resolution.⁶²

Uveitis is the inflammation of the vascular coat of the eye including the iris and ciliary body of the anterior chamber, and the vitreous, choroid and retina of the posterior chamber.⁶² Uveitis presents as a painful eye with visual blurring, photophobia, headache, and iridospasm. Ciliary flush or redness at the limbus that radiates outwards is characteristic of uveitis. Involvement of the ciliary body and iris of the anterior chamber alters pupillary response to light and presents as miosis. Visual acuity is altered when inflammation presents in the posterior chamber.^{1, 62} Uveitis does not reflect the gastrointestinal involvement of IBD, and therefore it is important to suspect IBD in patients who present with uveitis. HLA-B27 is strongly associated with uveitis, as well as with ankylosing spondylitis, suggesting a common underlying

autoimmune pathology. Diagnosis for both episcleritis and uveitis is with slit-lamp examination. Treatment for uveitis includes cycloplegics and topical steroids, and may necessitate systemic steroids or immunosuppressants.^{1, 62}

Secondary Systemic Manifestations

Weight loss with growth failure, anemia, as well as bone mineral density disturbances reflect the metabolic pathology of inflammatory of the gastrointestinal system in IBD.

Weight loss with growth failure is due to malnutrition and malabsorption in children with IBD. This may be due to too little oral intake due to fear of gastrointestinal exacerbation, nutrient malabsorption, or protein losing enteropathy. Impaired growth is more common in CD than in UC, but is common in both. Stawarski reported that 28% of children with UC and 80% of children with CD presented with growth delay. Insulin-like growth factor is decreased in both growth impaired and normally developed children with CD versus healthy controls, but studies have shown improvement of levels with nutritional restitution.²⁶ Frequent high dose corticosteroid regimens have been shown to affect type 1 collagen production that is required for linear growth, and therefore alternate-day regimens that have less impact on growth velocity are recommended especially in children.¹

Anemia is the most common hematological manifestation in IBD and according to Stawarski occurs in 5% of children with UC and 70% of children with CD.²⁶ Anemia is attributed to chronic blood loss, inadequate intake or absorption of vitamin B12 and other nutrients due to inflammation or resection, folate deficiency due to immunosuppressant therapy, or autoimmune hemolysis. Diagnosis is rapid upon routine blood tests. Therapy for anemia may just need vitamin supplementation or necessitate blood transfusion if symptomatic.¹

Decrease bone-mineral density (BMD) manifests due to malabsorption of calcium and vitamin D, hypogonadism, pubertal delay, low body mass index, corticosteroid exposure, and inflammatory cytokines involved in the IBD pathology. The spectrum of systemic skeletal disease is characterized by low bone density that leads to increased bone fragility and fracture. Measurement of BMD is presented as z-scores, or standard deviation scores in relation to reference values of healthy controls. Mild decrease in BMD is defined as a z-score of -1 to -2.5, whereas severe decrease of BMD, or osteoporosis is defined as a score lower than -2.5. Mild decrease in BMD is more prevalent in children with UC whereas severe decrease in BMD is predominant among children with CD. It is therefore recommended that children with IBD, especially those on high and frequent doses of steroids undergo bone densitometry every one to two years.¹

Conclusion

Inflammatory bowel disease can be a debilitating gastrointestinal disease but treating only gastrointestinal symptoms may be addressing only the tip of the iceberg of this disease. IBD is associated with many extraintestinal manifestations that can affect any organ in the body¹ and therefore it is important to understand IBD as a potentially systemic disease that requires systemic treatment of autoimmune disturbances. Further research is needed to elucidate the causative mechanisms of IBD as well as its associated EIMs. Currently, it is imperative for pediatricians to recognize symptoms in children that can be related to IBD to diagnose and treat the disease to prevent any delay in growth development and restoration to health.

References

1. Jose FA, Heyman MB. Extraintestinal manifestation of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2008 Feb;46(2):124-33. doi: 10.1097/MPG.0b013e318093f4b0.
2. Bernstein CN, Fried M, Krabshuis JH, et al. Inflammatory bowel disease: a global perspective. Global guidelines. World Gastroenterology Organization. 2009 Accessed at <http://www.worldgastroenterology.org/inflammatory-bowel-disease.html> Access date June 19, 2014.
3. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. *Inflamm Bowel Dis.* 2008; 14(S2): S9-11
4. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis.* 2011 Jan; 17(1): 423-39. doi: 10.1002/ibd.21349.
5. Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. *J Pediatr Gastroenterol Nutr.* 2010 Jan; 50 (1): 27-31. doi: 10.1097/MPG.0b013e3181b99baa.
6. Tsianos EV, Katsanos KH, Tsianos VE. Role of genetics in the diagnosis and prognosis of Crohn's disease. *World J of Gastroenterol.* 2012 Jan 14; 18(2): 105-118. doi:10.3748/wjg.v18.i2.105.
7. Koloski NA, Bret L, Radford-Smith G. Hygiene hypothesis in inflammatory bowel disease: A critical review of the literature. *World J Gastroenterol.* 2008 Jan 14; 14(2): 165-173.
8. Weinstock JV, Elliott DE. Helminths and the IBD hygiene hypothesis. *Inflamm Bowel Dis.* 2009 Jan; 15(1): 128-33. doi: 10.1002/ibd.20633.
9. Nielsen OH, Rask-Madsen J. Mediators of inflammation in chronic inflammatory bowel disease. *Scand J Gastroenterol Suppl.* 1996; 216: 149-59.
10. Comito D, Romano C. Dysbiosis in the Pathogenesis of Pediatric Inflammatory Bowel Diseases. *International Journal of Inflammation.* 2010 Feb; Article ID 687143, 7 pages; doi:10.1155/2012/687143
11. Monteleone G, Fina D, Caruso R, Pallone F. New mediators of immunity and inflammation in inflammatory bowel disease. *Curr Opin Gastroenterol.* 2006 Jul;22(4):361-4.
12. Fuss IJ et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical T_H2 response in ulcerative colitis. *J Clin Invest.* 2004 May;113(10): 1490-7.
13. Seidman EG, Caplan A. Special considerations in the diagnosis and management of inflammatory bowel disease in the pediatric age group. In: Targan SR, Shanahan F, Karp LC editors. *Inflammatory Bowel Disease: From Bench to Bedside*, 2nd ed. Great Britain: Kluwer Academic Publishers, 2003.
14. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol.* 2004 Jun; 57:1233-1244 doi: 10.1136/jcp.2003.015214
15. Sura SP, Ahmed A, Cheifetz AS, Moss AC. Characteristics of inflammatory bowel disease serology in patients with indeterminate colitis. *J Clin Gastroenterol.* 2014 Apr;48(4): 351-5. doi: 10.1097/MCG.0000000000000083.
16. Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin N Am.* 2003; 32: 967-995. doi:10.1016/S0889-8553(03)00046-3
17. Kumar V, Abbas AK, Aster JC. *Robbins Basic Pathology.* 8th ed. Saunders. 2007; 611-616.
18. Ekblom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer – a population-based study. *N Engl J Med.* 1990 Nov; 323: 1228-1233. DOI: 10.1056/NEJM199011013231802
19. Sartor RB, Sandborn W. *Kirsner's Inflammatory Bowel Diseases.* Saunders. 2004.
20. Barton JR, Ferguson A. Clinical features, morbidity and mortality of Scottish children with inflammatory bowel disease. *Q J Med* 1990;75:423–39.
21. Mamula P, Telega GW, Markowitz JE, Brown KA, Russo PA, Piccoli DA, et al. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002;97:2005–10.
22. Markowitz J, Daum F, Aiges H, Kahn E, Silverberg M, Fisher SE. Perianal disease in children and adolescents with Crohn's disease. *Gastroenterol* 1984;86:829–33.
23. Maddocks JL, Lennard L, Amess J, Amos R, Thomas RM. Azathioprine and severe bone marrow depression. *Lancet.* Jan 18 1986;1(8473):156.
24. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther.* Aug 1989;46(2):149-54.
25. Parakkal D, Sifuentes H, Semer R, Ehrenpreis ED.

- Hepatosplenic T-cell lymphom in patients receiving TNF- α inhibitor therapy: expanding the groups at risk. *Eur J Gastroenterol Hepatol*. 2011; 23:1150-1156.
26. Stawarsky A, Iwanczak B, Krzesiek E, Iwanczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease. *Pol Merkur Lekarski*. 2006 Jan; 20(115):22-5.
 27. Cardile S, Romano C. Current issues in pediatric inflammatory bowel disease- associated arthropathies. *World J Gastroenterol* 2014 Jan 7; 20(1):45-52.
 28. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications of inflammatory bowel diseases. *World J Gastroenterol*. 2006 Aug 14; 12(30): 4819-4831.
 29. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998; 42: 387-391
 30. Lindsley C, JG S. Arthritis associated with inflammatory bowel disease in children. *J Pediatr* 1974;86:76.
 31. Passo, MH, Fitzgerald JF, Brandt KD. Arthritis associated with inflammatory bowel disease in children. Relationship of joint disease to activity and severity of bowel lesion. *Dig Dis Sci*. 1986 May; 31(5): 492-7.
 32. Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: A review. *World J Gastroenterol*. 2013 Dec 14; 19(46): 8571-8579. doi:10.3748/wjg.v19.i46.8571
 33. Daley TD, Armstrong JE. Oral manifestations of gastrointestinal diseases. *Can J Gastroenterol* 2007; 21(4):241-244.
 34. Parente F, Pastore L, Bargiggia S, et al. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study. *Hepatology* 2007. 45(5):1267–1274
 35. Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study *Hepatology* 200; 33:544-553
 36. Abdo AA, Bain VG, Kichian K, Lee SS. Evolution of autoimmune hepatitis to primary sclerosing cholangitis: a sequential syndrome. *Hepatol* 2002; 36(6): 1393–1399.
 37. Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. *World J Gastroenterol*. 2008 Jan 21; 14(3): 331-337.
 38. Woodward J, Neuberger J. Autoimmune overlap syndromes. *Hepatology*. 2001; 33(4): 994-1002.
 39. Perdigoto R, Carpenter HA, Czaja AJ. Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. *J Hepatol* 1992; 14: 325-331
 40. Saarinen S, Olerup O, Broome U. Increased frequency of autoimmune diseases in patients with primary sclerosing cholangitis *Am J Gastroenterol* 2000 ; 95 : 3195-3199
 41. Hov JR, Boberg KM, Karlsen TH Autoantibodies in primary sclerosing cholangitis *World J Gastroenterol* 2008 ; 14 : 3781-3791
 42. Wiencke K, Boberg KM. Current consensus on the management of primary sclerosing cholangitis. *Clinics and Research in Hepatology and Gastroenterology*. 2011; 35:786-791.
 43. Boberg KM, Chapman RW, Hirschfield GM, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue *J Hepatol* 2011 ; 54 : 374-385
 44. Faubion WA, Loftus EV, Sandborne WJ, Freese DK, Perrault J. Pediatric “PSC-IBD”: A descriptive report of associated inflammatory bowel disease among pediatric patients with PSC. *J Ped Gastroenterol Nutr*. 2001 Sep; 33: 296-300.
 45. Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol*. 2008 Jun 7; 14(21); 3360-3367.
 46. Aqel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. *J Clin Gastroenterol*. 38(9), 805–809 (2004).
 47. Fernandes NF, Redeker AG, Vierling JM, Villamil FG, Fong TL. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. *Am J Gastroenterol*. 94(1), 241–248 (1999).
 48. Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J Hepatol*. 33(3), 371–375 (2000).
 49. Saadah OI, Smith AL, Hardikar W. Long-term outcome of autoimmune hepatitis in children. *J Gastroenterol Hepatol*. 16(11), 1297–1302 (2001)
 50. Hyams JS. Extraintestinal manifestations of inflammatory bowel disease in children. *J Ped Gastroenterol Nutr*. 1994; 19:7-21.
 51. Panackel C, John J, Krishnadas D, Vinayakumar K.

- Metastatic Crohn's disease of external genitalia. *Indian J Dermatol.* 2008; 53(3): 146–148. doi: 10.4103/0019-5154.43207
52. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol. & Hepatol.* 2011 Apr; 7(4): 235-241.
 53. Veloso FT. Extraintestinal manifestations of inflammatory bowel disease: Do they influence treatment and outcome? *World J Gastroenterol.* Jun 14, 2011; 17(22): 2702–2707. doi: [10.3748/wjg.v17.i22.2702](https://doi.org/10.3748/wjg.v17.i22.2702)
 54. Farhi D, Cosnes j, Zizi N, Chosidow O, Seksik P, Beaugerie L, Aractingi S, Khosrotehrani K. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine (Baltimore).* 2008 Sep; 87(5):281-93. doi: 10.1097/MD.0b013e318187cc9c.
 55. Veloso (2) FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol.* 1996 Jul; 23(1):29-34.
 56. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestation in inflammatory bowel disease. *World J Gastroenterol* 2005; 11(46):7227-7236.
 57. Palder SB, Shandling B, Bilik R, et al. Perianal complications of pediatric Crohn's disease. *J Pediatr Surg* 1991;26:513–5.
 58. de Zoeten EF, Pasternak BA, Mattei P, et al. Diagnosis and Treatment of Perianal Crohn Disease: NAPGHAN Clinical Report and Consensus Statement. *J Ped Gastroenterol Nutr.* 2013 Sep; 57(3): 401-412.
 59. Mountain JC. Cutaneous ulceration in Crohn's disease. *Gut.* Jan 1970; 11(1): 18–26.
 60. Parks AG, Morson BC, Pegum JS. Crohn's disease with cutaneous involvement. *Proc R Soc Med.* 1965; 58:241–242
 61. Corbett SL, Walsh CM, Spitzer RF, et al. Vulver inflammation as the only clinical manifestation of Crohn disease in an 8-year-old girl. *Pediatrics.* 2010 Jun; 125(6): e1518-22
 62. Mintz R, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. *Inflamm Bowel Dis.* 2004 Mar; 10(2): 135-9
 63. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Ped Gastroenterol Nutr.* 2014 Jun; 58(6): 795-806.
 64. Mokhtarifar A, Ganji A, Sadrneshin M, et al. Diagnostic value of ASCA and atypical p-ANCA in differential diagnosis of inflammatory bowel disease. *Middle East J of Digestive Dis* 2013 Apr; 5(2): 1-5.

Biography

Carolina Koletic was born and raised in Los Angeles California where she graduated high school and earned a Bachelors of Science in Anthropology at the University of California Los Angeles. During her college years, she became active in summer camps for children with diabetes. Her experiences in summer camp inspired her honors thesis on the socialization of young diabetes from novice to expert diabetics. After university, she worked for a year at Medtronic Diabetes where she helped patients gain access to insulin pump and diabetes medical equipment. In 2014, she completed her medical education at the University of Zagreb School of Medicine in Croatia. It was in Croatia where Carolina was inspired by young patients with inflammatory bowel disease who also presented with various other related symptoms that warranted attention. With the guidance of Assistant professor Irena Senečić-Čala, Carolina meticulously researched a wide scope of literature pertaining to inflammatory bowel disease in children to compile this literature review.