

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on “**Inflammatory Bowel Disease.**” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedsCases.com/podcasts.

Inflammatory Bowel Disease

Developed by Katherine Pohoreski and Dr. Jason Silverman and reviewed by Dr. Hien Huynh for PedsCases.com.
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Introduction

Hello and welcome to PedsCases! My name is Katherine Pohoreski and I’m a fourth year medical student at the University of Alberta. This podcast was reviewed by Dr. Jason Silverman and Dr. Hien Huynh, pediatric gastroenterologists at the University of Alberta and the Stollery Children’s Hospital in Edmonton.

By the end of this podcast on Inflammatory Bowel Disease (IBD), we hope you will have achieved the following objectives:

1. Discuss the multifactorial etiology of IBD, an interplay between genetics, the immune system and the environment.
2. Describe the clinical presentation of IBD in the pediatric population.
3. Compare and contrast Crohn’s Disease and Ulcerative Colitis with respect to macroscopic and microscopic findings.
4. Review an approach to the diagnosis and management of IBD.

Let’s start with a case!

Case

You are a medical student in a Pediatric GI clinic, working with a staff gastroenterologist, and are about to see a new referral, Sarah. Your preceptor tells you that Sarah is a 13-year old female referred from her family physician for abdominal pain and recent hematochezia, or rectal bleeding. Based on the referral letter, Sarah is otherwise healthy, pre-menarchal, developmentally appropriate, and on no medications except for a vitamin D supplement.

You proceed to meet Sarah and her mother and gather a focused history. Her mother mentions that Sarah’s abdominal pain has been worsening over the last 3 months. It began as abdominal discomfort but now is crampy and localized more to the right lower quadrant. Sarah mentions that her abdominal pain seems to be worse around bowel

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movements. She has mild urgency when she has to pass a bowel movement, but denies tenesmus (feeling of incomplete evacuation) or any symptoms occurring at night, such as abdominal pain, waking from sleep for a bowel movement or nocturnal diarrhea. About a month ago, Sarah told her mother that there was blood mixed with her stool. She is now having about 4-6 loose bowel movements a day, classified as Bristol Type 5, with intermittent hematochezia. Sarah is not aware of any perianal irritation or skin tags. She also denies nausea, emesis and fevers. There has been no recent travel. Of note, there has been no significant weight loss, however Sarah has demonstrated decreased appetite, appears to be less energetic and has missed a few days of school due to feeling unwell over the past month. With knowledge about extra-intestinal manifestations of IBD in the back of your mind, you ask Sarah about any recent joint pain, sores in her mouth, skin rashes or lesions, or concerns with her vision, all of which she denies.

You move on to a physical exam. Sarah appears well and her abdomen is soft, non-distended with no obvious masses, and bowel sounds are present. Abdominal percussion is unremarkable. On palpation, you note that she is tender along the lower abdomen, with maximum discomfort on the right. Perianal exam reveals a small skin tag. Cardiac, respiratory, dermatologic and musculoskeletal exams are grossly normal.

Finally, you formulate a differential diagnosis and suspect inflammatory bowel disease, so what do you do next?

About Inflammatory Bowel Disease (IBD)

There are 3 subtypes of IBD: Crohn's disease, Ulcerative Colitis and IBD-unclassified (IBD-U).

Crohn's disease (CD) is the most common subtype of IBD diagnosed in children, compared to Ulcerative Colitis in adults. Crohn's disease causes inflammation that is generally transmural, with or without granuloma and it may affect any part of the gastrointestinal tract (which can be remembered as from "gum to bum"). Ulcerative colitis, in contrast, is characterized by superficial ulceration of the intestinal mucosa, usually limited to the rectum and colon. Finally, a diagnosis of IBD-U is given when patients present with a picture of chronic colitis with atypical features for UC, but without clear features of CD.

From a disease diagnosis and management perspective, it's very important to understand how these subtypes differ.

Epidemiology

Research has shown that the incidence of child-onset inflammatory bowel disease is rising worldwide, with Canada having amongst the highest incidence rates. Interestingly, a north-south gradient has been identified in pediatric Crohn's disease in the northern hemisphere. In Canada, a recent national study which utilized population based health administrative databases between 1999 and 2010 to study the epidemiology of pediatric

IBD, reported that the incidence had actually stabilized at 9.7/100 000 children, with the exception of a significant increase in younger children aged 0-5 years¹. The study analyzed trends in pediatric IBD in Alberta, Manitoba, Ontario, Quebec and Nova Scotia, and found similar incidences between provinces with the exception of a higher rate in Nova Scotia. Prevalence rates seem to be rising in Canada, with a reported value of 38.2/100 000 children during the study period. In general, IBD cases were predominantly Crohn's disease, with boys affected more than girls.

Etiology and Pathophysiology

Unfortunately, we don't know exactly what causes IBD, but we do know that there are multiple factors involved, with the disease etiology most likely involving an interplay between genetics, the immune system and the environment.

Genome Wide Association Studies (GWAS) have isolated >200 loci associated with IBD, with the majority identified within European ancestry populations, and the research is still growing². Some of these genes play a role in immunity, antigen sampling, and mucosal barrier function. For example, a gene on chromosome 16 called NOD2/CARD15 has 3 main polymorphisms that increase one's susceptibility to CD.

In UC, 10-15% of patients with this IBD subtype have a first-degree relative with IBD. The single greatest risk factor for developing CD is having a first degree relative with CD; siblings are known to have an average 5-10% lifetime risk, with twin studies showing up to a 45% risk.

Further hypotheses into IBD pathogenesis involve the immune system and a dysbiosis of the gut microbiota. Dysbiosis means an imbalance in the composition of our gut flora, which may mean less diversity or a shift in proportions of protective and pathogenic bacteria. An exaggerated immune response to this type of microbiome may occur in genetically susceptible individuals. In a normal host, GI inflammation will usually be self-limited, but in a genetically predisposed host an environmental trigger or injury could precipitate a chronic inflammatory cascade and subsequent tissue damage, as seen in IBD. Certain immune system components, such as helper T-cells (TH1 and TH17), have been found to play a role, by releasing pro-inflammatory cytokines and recruiting neutrophils. In UC, autoantibodies against epithelial proteins in the colon have been found to cross react with various sites of the body where we typically might find extra-intestinal manifestations, such as the biliary tract, skin, bone, and in the eye.

Other potential environmental influences for developing IBD include a low fiber and high fat diet, high simple sugar diet or highly processed diets including certain emulsifiers, antibiotic use in early childhood, and inadequate sunlight/vitamin D exposure. Dietary factors and lack of vitamin D are only specific to CD and, interestingly, an appendectomy before the age of 20 and passive smoking are actually protective against UC development as an adult.

Clinical Presentation

So how does a patient with IBD present?

Let's start with Crohn's. Abdominal pain, diarrhea and weight loss make up the "textbook" triad of presenting symptoms, but this constellation is only seen in about 25% of CD patients as symptoms will depend on the distribution of disease. It is more common for adults to present with this triad, while children are more likely to present with bloody diarrhea, a sign of significant colitis. Patients may have localized right lower quadrant pain, which anatomically represents the terminal ileum. Other symptoms or signs include perianal disease, growth retardation, delayed puberty, short stature, nausea or vomiting, and fatigue. Isolated abdominal pain, early satiety, or constipation and bloating are more atypical presentations that may be seen with small bowel disease. Finally, patients with Crohn's may have skin tags or fistulas on perianal exam.

UC patients are generally similar in presentation, with diarrhea, hematochezia and abdominal pain being the most common symptoms. Patients may notice streaks of blood or clots within the stool, more commonly in the morning, after eating or even nocturnally. Symptoms such as tenesmus (feeling of incomplete evacuation) and urgency are often associated, which are related to the presence of rectal inflammation. It's unusual to see linear growth abnormalities in a UC patient, but acute weight loss may be present. 10-15% of patients will present with more severe symptoms such as >6 diarrheal stools/day, tachycardia, and a diffusely tender abdomen representing acute fulminant disease.

Finally, IBD is known for its extraintestinal manifestations, which are conditions affecting mainly the skin, eyes, or joints. The etiology is unknown but it's hypothesized that cross-reacting antibodies play a role. Skin examples include erythema nodosum (painful, red, raised circular nodules), most commonly found over the tibia, and pyoderma gangrenosum, which are small painful, sterile pustules that can form an abscess. These are also seen on the lower extremities but are rare and less common than erythema nodosum. Oral ulcers (called aphthous stomatitis) may be present, more commonly in Crohn's. Eye findings can include episcleritis and uveitis, which are rare manifestations in kids. Musculoskeletal manifestations include joint issues like arthralgias or arthritis. The hepatobiliary system may also be involved, with Primary Sclerosing Cholangitis being an important disease association in UC to watch for, occurring in 3.5% of kids with UC. Autoimmune hepatitis occurs in <1% of kids with UC.

As you can see, IBD has significant effects on the body even outside the GI tract!

Back to the Case - Differential Diagnosis

Let's return to our case.

Sarah's presentation of bloody diarrhea is in keeping with IBD, but let's consider a broader differential diagnosis. When we think of lower GI bleeding, it's helpful to divide the differential in two ways: bloody diarrhea vs hematochezia without diarrhea. Within

the category of bloody diarrhea, we can consider inflammatory conditions such as IBD and infectious colitis, as well as rarer causes such as allergic or ischemic colitis. Celiac disease and Irritable Bowel Syndrome can present with diarrhea and abdominal pain, but should not cause blood in the stool. Now if Sarah were to present with hematochezia without diarrhea, we might think of other causes of bleeding such as hemorrhoids, anal fissures, polyps, or Meckel's diverticulum (if she were much younger). If rectal bleeding was accompanied with abdominal pain, we might think of a Henoch-Schonlein Purpura vasculitis (as abdominal pain and GI bleeding may present up to 1 week before the classic palpable purpuric rash), or if her presentation was more acute, you could think about intussusception (the telescoping of bowel into itself). Of note, intussusception is more common in younger children and might present with more obstructive symptoms like vomiting.

Keeping all this information in mind will help guide our investigations.

Diagnosis

Diagnosis of IBD is based on history, physical exam, labs, endoscopic evaluation, histology and imaging of the bowel, with endoscopy and biopsy being most important for definitive diagnosis.

Labs to help narrow the differential include CBC (to look for anemia), ESR and CRP (inflammatory markers), albumin (low in protein losing enteropathy), liver transaminases and GGT (which could be elevated). The etiology of microcytic anemia may be further defined with iron studies such as serum Fe, TIBC and ferritin.

We order fecal calprotectin, which is a highly sensitive, non-invasive test for detecting intestinal inflammation. Calprotectin is a protein found in stool that is initially released by neutrophils at sites of inflammation in the intestines. Keep in mind, this test won't help distinguish which type of IBD is present or the location of the disease. Other stool tests are important to rule out an enteric infection (bacterial or parasitic) prior to endoscopy. These include the "SECSY" bugs, such as *Salmonella*, *Enterohemorrhagic ecoli*, *Campylobacter*, *Shigella* and *Yersinia*. And don't forget about *Clostridium difficile*.

Other initial labs in the diagnostic work-up include a celiac screen (attG and IgA level).

Most importantly, keep in mind that normal labs do not exclude IBD!

We finally proceed with endoscopy (gastroscopy and colonoscopy). It's important to do both an upper and lower scope, as CD can be found anywhere from gum to bum. Biopsies are taken from multiple sites in the proximal GI tract, as well as the rectum, colon and distal ileum.

As for imaging modalities, we don't require them for a diagnosis; however, we do have several tools to further assess the extent of the disease. Capsule endoscopy can be used to detect disease involvement of the small bowel, but has a higher risk of capsule

impaction in CD. MR enterography can provide a cross-sectional view of the bowel to look for wall thickening or luminal narrowing and/or creeping fat, which are signs of inflammation, as well as bowel wall damage such as stricture, fistula, phlegmon and abscess. Pelvic MRI is useful for evaluating perianal involvement in CD, identifying a fistula or abscess. Interestingly, ultrasound is also a valuable screening tool in the preliminary work-up of IBD as it's a low cost, non-invasive method which can identify bowel wall inflammation or thickening or to rule out other organ etiology; however, it's important to keep in mind inter-observer variability.

Endoscopic Findings

The key macroscopic features of CD include skip lesions, which are patchy areas of disease that seem to “skip” over normal healthy bowel, and cobblestone mucosa, where the lining of the GI tract looks like cobblestones, indicating inflammation. We also see linear or serpentine ulceration, stenosis or stricturing of bowel and significant ileal inflammation. Aphthous ulcers in the mouth or perianal fistulas may be found. When we look microscopically, biopsies may show non-caseating granulomas and transmural inflammation. For example, European analysis cited that 43% of pediatric patients had granulomas upon histology at diagnosis of Crohn's disease³. Although reported rates of identified granulomas vary, they are identified in <50% of patients with Crohn's disease, so even though granulomas are more common in the pediatric population and are pathognomonic for Crohn's, they can't be relied upon for diagnosis.

In contrast, UC tends to be confined to the rectum and then extend proximally, leading to various extents of the disease such as proctitis, left-sided colitis, and pancolitis, based on how far the inflammation is found. It is not uncommon to see relative rectal sparing where inflammation in the rectum is less severe than other areas such as the sigmoid and cecal patch (an area of inflammation around the appendix opening surrounded by normal right colonic mucosa). Endoscopy may reveal inflamed mucosal surface, appearing erythematous with a loss of vascular pattern. With disease progression, surface ulcerations with scattered exudate may result and friable tissue may bleed with contact or spontaneously, in cases of very severe inflammation. Microscopically, we may see crypt abscesses and neutrophil infiltration.

Management

So how do we manage IBD once we have a diagnosis in hand?

The main goals of IBD therapy are to achieve and maintain remission and avoid complications, as we work to promote mucosal healing and prevent further intestinal damage. As you can imagine, the symptoms of IBD can be pretty painful, embarrassing and socially challenging, and many children just want to be able to return to a “normal” lifestyle. There are slight differences in managing Crohn's vs UC.

The first aspect in disease management of IBD is induction of remission for active disease, and in Crohn's this can be done using exclusive enteral nutrition (EEN) or corticosteroids (like prednisone). The efficacy of EEN almost matches that of steroids in

pediatric studies and EEN is also found to have higher rates of mucosal healing, but adherence can be challenging. Patients typically need to be on the same nutritional supplement (e.g. meal replacement drinks such as Ensure or other polymeric formula) for 6-8 weeks. As this can be difficult to tolerate, nasogastric (NG) tubes are sometimes required. Corticosteroids are effective in decreasing inflammation but it's important to keep in mind that with any medication comes potential adverse effects. Steroid therapy can lead to an increased risk of infection, weight gain, growth inhibition, mood changes and negative implications on bone health. In severe cases, biologics (eg. infliximab) or immunosuppressants (e.g. methotrexate) may also be required for induction. Some risks include infusion reactions in up to 10% of patients and opportunistic infections.

The second aspect of therapy involves maintenance of disease with immunosuppression. Options include methotrexate, biologics (anti-TNF agents) and adjuncts such as aminosalicylates or antibiotics for perianal disease.

When it comes to UC, we use similar management strategies with subtle differences. Firstly, nutritional therapy is not effective in this sub-type. Secondly, 5-Aminosalicylates, administered orally, can be effective in treating mild to moderate disease. Additionally, rectal 5-ASA therapy provided as enemas or suppositories, are often effective at controlling local inflammation such as in proctitis or distal colonic disease. The most significant difference is that UC has a potential cure if the disease is surgically resectable. Surgical candidates may undergo a restorative surgery by means of a colectomy with an ileal pouch anal anastomosis. Prognosis wise, 5-10% of UC patients will have continuous symptoms despite surgical therapy.

Surgical indications in patients with colitis (from Crohn's or UC) include failing medical treatment, persistent bleeding requiring multiple transfusions, perforation or toxic megacolon, or high risk of malignancy. The need for surgery in Crohn's disease usually results from complications relating to its transmural nature, such as stricturing, obstruction, perforation, abscess, or fistula formation. However, remember that surgery is not a curative treatment modality in Crohn's disease.

Don't forget - it's important to refer IBD patients for ophthalmic examinations to monitor for extra-intestinal eye findings. It's also important to offer IBD patients psychological support, as this is a chronic disorder which may not have a cure and IBD patients are at risk for developing social isolation, anxiety and depression. Imagine having a chronic disease with such a variable course, distressing and painful symptoms and potential treatment side effects. Peer and family supports and resources are available at local pediatric centres as well as nationally. Ensure that you refer families to trustworthy sources such as Crohn's Colitis Canada.

Case Resolution

Back to wrap up the case!

After your appropriate investigations, Sarah was found to have evidence of iron deficiency anemia, elevated inflammatory markers and a markedly elevated fecal calprotectin. On endoscopy and biopsy, skip lesions were identified throughout the colon and at the ileum, with transmural inflammation and non-caseating granulomas present. Her clinical picture and investigations are consistent with Crohn's disease and future therapy will include induction of remission with exclusive enteral nutrition or steroid therapy as well as maintenance with immunosuppression.

Take-Home Points

1. The clinical presentation of IBD is variable, with common presenting symptoms including abdominal pain, bloody diarrhea and weight loss. Extra-intestinal manifestations affecting the skin, eyes, and joints may be present on history and physical exam.
2. IBD has a multifactorial etiology which includes an interaction between genetic predisposition, the immune system and the environment.
3. The diagnosis of IBD involves a detailed history and physical exam, lab investigations to help narrow the differential diagnosis, and finally endoscopic evaluation to identify macroscopic and microscopic features. Remember that Crohn's disease is typically "gum to bum" with transmural inflammation, and Ulcerative colitis is a colonic disease with mucosal ulceration which begins distally at the rectum and progresses proximally.
4. The management of IBD typically includes induction of remission with exclusive enteral nutrition or steroids and maintenance with immunosuppressive therapy. Surgical management is reserved for resectable colon in Ulcerative colitis or for disease complications in Crohn's disease, such as strictures, obstruction, perforation, abscess, or fistula formation.

Thanks for joining! References are available within the podcast script.

References

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