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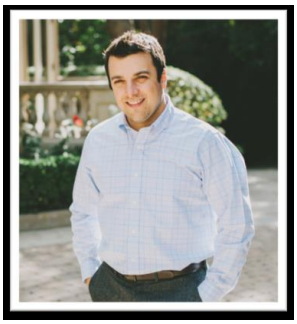

Pediatric Inflammatory Bowel Disease - Updates in Screening, Diagnosis and Treatment

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Inflammatory bowel disease is classically comprised of two major disorders: Crohn's disease and ulcerative colitis (UC). Crohn's disease is defined as having a penetrating phenotype (i.e. deep ulcers, abscesses, fistula formation) and affecting the entire gastrointestinal tract – from the mouth to the anus, with frequent involvement of the small bowel. Ulcerative colitis, on the other hand, is typically confined to the colon and affects only the superficial mucosal layers. However, in many in cases, patients "do not read the textbook" and indeed a significant number of patients present initially with indeterminate colitis which displays features of both Crohn's and UC. Furthermore, as our understanding of inflammatory bowel disease grows we are beginning to understand IBD as a spectrum of disease with significant phenotypic heterogeneity.

Our current understanding of the pathophysiology of IBD is that it is an **altered host-immune response to otherwise commensal bacteria in a genetically susceptible individual**. Recent large scale genomic studies have identified common mutations in patients with IBD – most often those mutations involve genes important for innate/adaptive immunity (e.g. cytokines, T/B-cell function etc.) and epithelial barrier function (i.e. tight junctions between cells)[1]. The gut is an important player in the development of our immune system by constantly sampling antigens from our environment through its interaction with the intestinal milieu. The genetic alterations in patients with IBD result in sampling errors - friendly bacteria are recognized as pathogenic and pathogenic are recognized as innocuous. The result is dysbiosis, inflammation and infection.

Interestingly, the incidence of IBD has increased steadily over the past three decades. This may be partly due to improved diagnostic tools (improved biomarkers, endoscopic techniques, imaging and histopathology). However, even when controlled for these factors the annual incidence continues to rise[2]. One theory that explains the rise in autoimmune illness over the past several decades has been dubbed the 'hygiene hypothesis'. The theory postulates that reduced childhood exposure to infectious agents over the past few generations (through advancements in sanitation and overuse of antibiotics) has led to a loss of symbiotic intestinal microorganisms and parasites which previously played an important role in the natural development of the human immune system. The result is a paradigm shift in immune development in favor of the production of autoimmune and allergic immune mediators[3]. The theory is supported by older epidemiologic data that described IBD as a 'Western' disease. However, more recent data suggests that IBD *does*

occur in developing or underdeveloped nations but it's diagnosis is simply being missed early in life due to poor access to healthcare[4].

Children with IBD typically present in late childhood or adolescence. Recently, there has been increased recognition of early-onset IBD (<10 years-old) and very-early onset IBD (<5 years-old). Typically, children will present with one or more of the following features:

1) Unexplained recurrent fever
2) Diarrhea, loose or bloody/hemoccult positive stool
3) Abdominal pain
4) Growth failure (decreased height/weight velocity), delayed puberty

In my experience, the presence of three (and perhaps even two) of these symptoms together should be considered IBD until proven otherwise. Occasionally, IBD may cause extra-intestinal manifestations including oral ulcers, perianal skin tags, arthritis/arthralgia, unexplained recurrent rash or jaundice/hepatitis.

Diagnosis of IBD is classically made on the basis of blood/stool tests, radiologic, endoscopic and histologic findings. CBC often reveals a normal WBC count which goes against an infectious etiology while hemoglobin counts are often low in the face of ongoing rectal bleeding. Blood and stool tests should include biochemical markers of inflammation including ESR, CRP and fecal calprotectin. A fecal calprotectin cut-off of 200 has ~90% validity in differentiating IBD versus IBS (irritable bowel syndrome – which is entirely different and much less insidious)[5]. Macronutrient (i.e. albumin) and micronutrients deficiencies (e.g. iron, folate, vitamin D, B12, zinc) are often seen in patients with small bowel disease, as absorption may be affected by long standing inflammation.

In the past, the imaging test of choice was the upper GI series with small bowel follow-through. However, advances in MRI have made MRE (magnetic resonance enterography) the test of choice due to the avoidance of radiation, high resolution smalll bowel images and improved evaluation of extraintestinal findings (e.g. fistula, abscess)[6]. However, small children will often not tolerate MRI.

Capsule endoscopy is increasingly used in adults and older children to evaluate small bowel disease and may play an important role in treatment decisions.

Endoscopy should be performed in all patients with suspected IBD, even in the absence of clear lower gastrointestinal symptoms such as bloody stool. Pathology may clinch a diagnosis and may help differentiate between autoimmune disorders such as IBD, allergic disease or infectious etiologies. Endoscopy is also paramount in staging disease and guides therapy. Endoscopy is performed in children under anesthesiologist-administered propofol or general anesthesia. This approach improves patient comfort and increases the likelihood of complete endoscopic examination. The short-term complication rate in children undergoing colonoscopy for a variety of indications is ~1% and is significantly higher in patients with intravenous sedation alone[7].

The treatment for IBD has rapidly evolved over the past 20 years. Prior to the turn of the century, the mainstay of treatment for the induction of remission of IBD has been steroids. Even to this day, steroids remains the most commonly used drug for treatment for moderate to severe IBD. However, purine analogues, or immodulatory drugs, and biologic agents have been used as

"steroid-sparing" agents. Among the biologic agents, anti-TNF (Remicaid, Humira and others) have shown tremendous results in both inducing and maintaining steroid-free remission in children with IBD. However, no medication is without risks – reports of lymphoma while on concomitant immunosuppressive medications has been reported[8]. Importantly, no such cases have been reported when biologics are given as monotherapy. The 5-ASAs, including mesalamine, are aspirin derivatives and can be thought of as topical anti-inflammatories for mild-to-moderate cases of IBD. 5-ASAs are commonly packaged in *enteric coatings* that are *pH*-dependent. The coatings exploit the *pH* progression in the GI tract and are designed to target specific regions of the GI tract that may be more affected or inflamed. Surprisingly, probiotics have been shown to be of limited help with induction of remission and often play more adjunctive role in maintaining remission[9]. A testament to the fact that it is our immune system that shapes our microbiome - not vice versa.

Lastly, nutrition is paramount in patients with IBD. Both polymeric and elemental formula supplementation has been shown to improve outcomes in patient with IBD flare. The thought is that formulas are low-antigen (i.e. sterile) and can reduce inflammation, allow the gut to reestablish a healthy microbiome and erase caloric and vitamin deficits. In fact, exclusive enteral nutrition (EEN) for 8-12 weeks has been shown to induce remission for mild-to-moderate Crohn's disease. That is to say that a diet composed exclusively of a liquid elemental or polymeric formula can achieve the same effect as steroids and other immunomodulatory drugs. The challenge, obviously, is having a child adhere to the exclusive liquid formula diet for a 8-12 weeks. Children often require nasogastric feedings for induction of remission using EEN therapy. The physical and psychosocial hurdles is usually too great for both the family and child to bear. However, EEN is first line therapy in many centers across Europe and several across the US including CHOP[10,11]. More recent literature suggests that even supplementation with elemental or polymeric formulas for significant caloric supplementation can speed up recovery in patients with IBD flare[12]. Furthermore, supplementation of N-3 fatty acids (fish oil), short-chain fatty acids may have some benefit in decreasing inflammation and dependence on steroids[13].

IBD is certainly a complicated spectrum of disease with variable presentation and often challenging diagnosis. Prompt recognition of signs and symptoms is important in preventing long term sequale including growth failure. However, as our understanding of IBD grows, so do our diagnostic tools and treatment modalities. Nutrition is sure to play an increasingly important role - not only in maintaining growth in children suffering from IBD but as a steroid sparing agent for induction of remission.

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