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REVIEW

Inflammatory bowel disease in children: current trends

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Abstract Once considered rare in the East, inflammatory bowel disease (IBD) is now recognized to be an emerging entity in that region. East or West, the clinical features of and treatment options for IBD are the same, but it is possible that the exact pathogeneses or the initiating events differ. In this review, existing knowledge of IBD and new discoveries in the epidemiology, genetics and treatment of IBD are discussed in detail. The diagnosis and management of IBD in children has changed dramatically over the last decade, mainly due to increased awareness, the availability of newer diagnostic modalities such as MRI and video capsule endoscopy, and newer, more powerful treatments such as biologics. It is hoped that the combination of innovative research and advances in drug discoveries will change the natural history of IBD and make a major difference in children who are suffering from this unfortunate lifelong chronic inflammatory disorder.

Keywords Epidemiology · Crohn's disease · IBD · Children

Introduction

Amongst the various chronic gastrointestinal inflammatory conditions prevalent in the Western world, Crohn's disease (CD) and ulcerative colitis (UC)—the two clinical subtypes of inflammatory bowel disease (IBD)—are the two most common. Once considered rare in the Eastern world, IBD is now recognized as one of the emerging entities, and is drawing a lot of attention among medical communities in Far Eastern countries and South-East Asian nations. East or West, the clinical features and treatment options are the same, but it is still to be seen if the pathogeneses differ. In this article, we will discuss the existing knowledge of IBD and examine new discoveries in epidemiology, genetics and treatment options for IBD. We will also devote particular attention to studies that have been published from the Eastern world.

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Epidemiology

Although a diagnosis of IBD can be made at any age, about one in every four new diagnoses of IBD are made before the age of 20 years. Population-based studies suggest that IBD is unevenly distributed throughout the world, with the highest disease rates occurring in Western or industrialized countries. Although the true impact of IBD in children is not entirely known, we estimate that about 100,000 children are suffering from IBD in North America at any given time [1]. There are differences in the descriptive epidemiology of IBD when pediatric IBD is compared with adult-onset IBD. While CD and UC occur with equal distribution in adults, there are three CD occurrences for each new UC case in pediatric age groups [1]. In adult IBD there is an equal ratio of male to female disease, or perhaps more women withthe disease. In contrast, prepubertal males seem to be more affected with pediatric CD, with a male preponderance of 1.5:1 [2]. There is currently no molecular explanation as to why children with IBD differ from adults in regard to CD:UC gender ratio.

Epidemiology: differences between the West and East

IBD was traditionally considered to be a disease of the Western world. The incidence and prevalence rates of IBD were much lower in Eastern countries. However, emerging data have shown a rising trend of IBD in Eastern countries. The epidemiological changes that are occurring seem to go hand in hand with the socioeconomic development of Eastern, and particularly Asian, countries. Though changes in lifestyle and diet, host genetic factors, migration-related changes in genetic susceptibility, urbanization, and environmental changes may be relevant attributes, it is still unclear which specific factors are responsible for this rising trend. The pathogenesis of IBD is incompletely understood and numerous hypotheses have been proposed.

Over the years, epidemiological studies have investigated IBD in immigrant populations. Immigration provides an opportunity to study the correlation between environmental factors and disease outcome. The migrant population adopts the lifestyle, dietary and social practices of the host community. Such factors may have an impact on diseases in the migrant population. Consequently, the study of migrants can be useful in the evaluation of etiological factors related to the disease. A retrospective epidemiological study of UC performed in Leicestershire from 1972 to 1989 showed that migrants had a significantly higher incidence of UC than indigenous Europeans in that area [3].

Earlier clinical observations suggested that children born of Indian parentage, but who were living in the United Kingdom and in Canada, suffered more from UC than children of other ethnic groups. Montgomery et al. [4] found that Young Asians who were born in Britain are at a significantly higher risk of developing IBD than the indigenous European population. Small case series studies from Korea [5, 6], Thailand [7], Taiwan [8] and Hong-Kong [9] also suggest a rising incidence of IBD among children, although the incidence is much lower than in Western countries. In 1986, Yao et al. [10] estimated the prevalence and incidence of patients with CD in Japan to be approximately 2.9 and 0.6 per 100,000, but this had increased to 13.5 and 1.2 in 1998. This suggests that, as in the Western world, there was continuous increase in the incidence and prevalence of CD over the decade in Japan.

Etiology and pathogenesis; environmental, genetic and microbial factors

IBD encompasses two clinical subtypes: UC and CD. They are closely related yet distinct diseases. The etiology underlying IBD is considered to be complex, although significant advances have been made over the last decade. IBD appears to be multifactorial in origin. The well-documented increase in the incidence and prevalence of IBD is part of a worldwide emergence of chronic autoimmune and inflammatory diseases, a phenomenon closely linked to social and economic development. Initially noted in Northern Europe and North America, this increase has now been documented in the rest of Europe, Japan and South America, and most recently in the Asia–Pacific region [11]. The "hygiene hypothesis" postulates that there has been a fundamental lifestyle change from one with high to one with low microbial exposure [12]. This may provide an explanation for the higher frequency of IBD. Exposure to fewer microbial antigens early in life would lead to a less robust immune system that is ill-prepared to tackle challenges later on in life, when immune responses would be unable to eliminate offending agents, resulting in chronic inflammation. Numerous other environmental factors and stimuli are considered risk factors for IBD, including smoking, diet (junk food), drugs, geography and social status, increased stress, enteric flora, altered intestinal permeability, and appendectomy [11, 13].

Recent research also shows that heritable factors have more influence in IBD than in schizophrenia, asthma, and essential hypertension [14]. Numerous family, twin, and phenotype concordance studies and the discovery of many susceptibility genes strongly support the concept that IBD is highly heritable [15, 16]. A positive family history is a well-known identifiable risk factor for the development of IBD. Basic science research is growing in leaps and bounds, and with the advent of newer techniques such as genome-wide association studies (GWAS), which employs high-density single-nucleotide polymorphism (SNP) array technology, the investigation of newer areas in this field has been made possible. To date, this method of broad, unbiased screening for the contributions of common genetic variations to disease susceptibility has provided as many as 40 susceptibility loci in CD and over 17 loci in UC. However, the most surprising finding was that the vast majority of the new gene discoveries were common to both CD and UC, further reinforcing our belief that CD and UC stem from same pathogenesis but have differing clinical spectra.

The search for infectious agents as a cause of IBD has been popular for many years. However, a multitude of studies have failed to confirm the presence of infectious agents by histological examination, culture of tissue homogenates, genomic identification, and serum antibodies. More recently, an entero-adhesive/invasive strain of *E. coli* has been described as being associated with ileal CD, but its potential etiological role remains unclear. Evidence continues to accumulate that the indigenous commensal gut flora are the target for the chronic immune response in IBD. The majority of IBD patients show

enhanced immunological reactivity against gut bacterial antigens. The discovery that CD is associated with mutations of the *NOD2/CARD15* gene, whose product is a bacteria-sensing cytoplasmic protein, suggests that the ability of the immune system to recognize the gut flora in a normal manner may be genetically altered in IBD. Almost all GWAS have been performed exclusively in Caucasians of European origin. When performed in non-Caucasians, replication studies did not result in associations previously found in Caucasians, indicating that different genetic determinants may determine IBD in different ancestral populations. Interestingly, a GWAS of a Japanese population revealed a novel genetic susceptibility locus, TNFSF15 [17].

Clinical presentation: intestinal manifestations

Crohn's disease and UC are both chronic, inflammatory diseases of the gastrointestinal tract with periods of remission and exacerbation. Although related, UC and CD are distinct entities. UC is chronic inflammation involving only the mucosa of the colon, the inflammation being continuous, starting in the rectum and extending proximally to varying extents. CD is characterized by transmural inflammation. It is not localized to the colon and can be found anywhere in the GI tract, from mouth to anus. Colonic CD can be differentiated from UC by the fact that the inflammatory process is patchy in CD. The terminal ileum is the most common site of CD; however, about 60% of pediatric patients have ileocolonic involvement, while 20–30% have isolated colonic disease [2]. If there is oral or perianal involvement, then CD is more likely.

Location, chronicity, and severity of abdominal pain may help determine if it is IBD-related or functional abdominal pain. Abdominal pain in CD can wake the child at night, can cause decreased appetite, and—in the case of ileocecal disease—can be localized to the RLQ. Odynophagia/dysphagia can be seen in esophageal CD, which occurs in approximately 10% of CD patients [18]. Diarrhea is seen commonly in UC (70–90%). It is seen in CD 65–75% of the time and can be intermittent, depending on the location of disease [19]. Distal colonic disease can cause tenesmus and urgency. Gross blood is usually seen with colonic involvement and may or may not be associated with abdominal pain. Nocturnal stooling is also common in colonic disease. Between 50 and 90% of UC patients present with rectal bleeding and 20–60% in CD [19].

Weight loss is a major problem in CD; over 80% of patients have some degree of weight loss at presentation [20]. Many children have decreased appetite/intake and decreased nutritional absorption. Growth failure is a critical concern in childhood-onset IBD. For unknown reasons, growth failure is more pronounced in boys than girls [20]. Growth impairment can be the only presenting sign of CD, even before GI symptoms manifest [21]. However, the etiology of growth failure is multifactorial; likely reasons are nutritional deficits, increased nutrient losses, malabsorption, increased metabolic demands and medications. Several alterations in the pattern of puberty among pediatric patients with IBD has been seen. Delayed puberty affects twice as many patients with CD compared to UC. Average age of menarche in healthy adolescents is 12.8; however, one study found that more than one half of females with CD had menarche delayed to age 16 if the disease started before puberty. Duration of puberty might also be prolonged in patients due to frequent relapses of the disease during puberty [22]. When evaluating a patient for delayed growth and puberty, bone age radiography can aid in determining if they will have time to catch up in those areas.

Perianal or perirectal disease is present in CD but is not a feature of UC. Perianal disease can include multiple large anal tags, perirectal abscesses, nonhealing deep fissures, and fistulas. Perianal disease is painful when there is abscess formation. One-third of patients will develop a perianal fistula or abscess at some point in their disease course. Approximately 80% of fistulas seen in CD are perianal/perirectal.

Extra-intestinal manifestations

Inflammatory bowel disease is not a single organ disease but a systemic disease with many "extra"-intestinal features. Between 25 and 30% of patients will exhibit some extra-intestinal manifestations (EIM) during their lifetimes [23]. These cause varying degrees of morbidity and mortality in IBD patients. The exact etiology of these conditions is unknown, but autoimmune reactions to bacteria, induction of immune complexes and inflammatory response, and genetic factors have all been postulated. EIM can correlate with GI symptoms, but some will be present even in remission. The most common EIM will be covered here.

An EIM commonly seen for IBD in adults and children is joint inflammation. Up to 25% of IBD patients are affected by arthralgias/arthritis, and 20–40% patients have more than one episode [24]. Joint manifestations in IBD can be axial or peripheral in form. The axial form includes ankylosing spondylitis and sacroiliitis. Asymptomatic sacroiliitis can be found in 10–52% of patients and is usually revealed by bone scans [24]. Ankylosing spondylitis occurs in <2% of patients and is also associated with HLA-B27 positivity [25].

Cutaneous manifestations can be classified into three principal groups: granulomatous, reactive, and secondary

to nutritional deficiency. Skin involvement has been described in 10–15% of patients with IBD [23]. The two most common cutaneous manifestations of IBD are erythema nodosum and pyoderma gangrenosum, which are reactive in nature.

The most common ocular manifestations of IBD are episcleritis and uveitis. Ocular manifestations occur in approximately 1% of patients with IBD [25]. These are seen more frequently in CD patients with colonic disease. Acute anterior uveitis is an ophthalmologic emergency and requires prompt intervention. Patients with IBD can also develop eye disease, like cataracts and glaucoma, secondary to drug complications.

Bone disease has been increasingly studied since the recognition that up to 40% of adult IBD patients have osteoporosis. In one study, the relative risk for fractures in adult IBD patients was 1.4 compared to the general population [26]. This is extremely important in the pediatric population, since this is the time of skeletal growth and maturation. Multiple factors could contribute to the decreased bone mass density (BMD) in these patients, including medications, inflammatory responses, decreased physical activity and nutritional deficiencies from poor intake and malabsorption.

Oral aphthous stomatitis is seen in at least 5–10% of patients with UC and 20–30% of those with CD [27]. The most common serious hepatobiliary complication among pediatric patients is primary sclerosing cholangitis (PSC), a disorder of both the intrahepatic and the extrahepatic bile ducts. It is estimated that 3.5% of UC patients will develop cholangitis [25]. PSC should be suspected in an IBD patient with pruritus, jaundice, fatigue and anorexia, although they can be asymptomatic. Pancreatitis can also be an EIM, but it is more commonly due to duodenal CD, PSC, or is secondary to medications [27].

Thrombosis has been reported in 1.8% of patients with UC and 3.1% of patients with CD, but is less frequently reported in pediatric patients. Reports in adults suggest that IBD patients have a threefold greater risk compared with subjects without IBD for developing deep venous thrombosis and pulmonary embolism [28]. The mechanism for a hypercoagulable state in IBD is unknown at this time, but some of them are found to have high antiphospholipid antibodies. The IBD patients have several risk factors that put them at risk, including inflammation, fluid depletion, immobilization, surgery, steroids, central venous lines, thrombocytosis, and an increase in acute-phase reactants during active inflammation. If a child has not been previously diagnosed with IBD but has a thromboembolism and the hematologic work-up is negative, they should be evaluated for IBD.

Diagnosis

Differential diagnosis

Diagnosis of IBD is based on clinical presentation and subsequent imaging, laboratory, and endoscopic assessments. In a child with bloody diarrhea, bacterial infectious etiologies need to be ruled out first. The differential diagnosis also includes vasculitides (Henoch–Schonlein purpura), ischemic bowel, radiation colitis, and hemolytic–uremic syndrome. Rectal bleeding without diarrhea can be due to fissure, polyp, rectal ulcer syndrome, or Meckel diverticulum. Perirectal disease, while very suspicious for CD, can be the result of fissure or streptococcal infection. Etiologies that can mimic CD pain include appendicitis, although this would have an acute presentation, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst, or lymphoma. In addition, some infections such as *Yersinia* infection and gastrointestinal tuberculosis can cause similar radiographic and endoscopic findings to small-bowel CD. However, localized pain, especially to the right lower quadrant, is a red flag. Celiac disease can have some of the same clinical symptoms as CD, including weight loss, diarrhea, growth retardation, anorexia, and protein-losing enteropathy. Arthritis can be due to rheumatological or collagen vascular disease or infection.

Laboratory

Laboratory studies can be helpful in a child suspected of having IBD if they are abnormal. Tests should include complete blood count with white blood cell differential, sedimentation rate, total protein/albumin, aminotransferases, alkaline phosphatase, bilirubin, and C-reactive protein. Serologic markers have recently been introduced as a possible tool to help diagnose IBD and also differentiate between UC and CD. These markers are indirect and detect antibodies in the serum that have been found in patients with IBD. One of the commonly ordered panels includes the following antibodies: atypical perinuclear anticytoplasmic antibodies (pANCA), antibodies to *Saccharomyces cerevisiae* (ASCA), anti-*E. coli* outer-membrane porin C antibodies (anti-OmpC), and antibodies to bacterial flagellin (anti-CBir1). Antibodies to a bacterial sequence from *Pseudomonas fluorescens* (anti-I2) and antiglycan antibodies are also being investigated for their possible use as serologic markers [29]. These tests have many limitations, especially in children. Seroconversion may depend on exposure, and children may not have sufficiently mature immune systems to produce these antibodies. Also, the tests have higher specificity than sensitivity and should not be used as a general screening tool [30]. In addition, a positive antibody screen alone is not sufficient to make a

diagnosis of IBD, and gastrointestinal work-up (including endoscopy) is still needed.

Radiology

The diagnosis of inflammatory bowel disease is dependent on the endoscopic, histologic, and radiologic findings. Radiography is necessary at diagnosis to determine extent, location, and severity of disease. In the past, upper gastrointestinal series (UGI) with small bowel follow-through was the "gold standard." However, technology has made great strides in the last decade, and other modalities like magnetic resonance imaging (MRI), computed tomography scans (CT), and ultrasound (US) have been used with success [31]. A 2008 meta-analysis comparing US, MRI, CT and scintigraphy (white blood cell scan) found that there was no significant difference in the yield among the imaging techniques [32]. Plain abdominal X-rays can be abnormal in up to 60% patients with IBD. However, the findings are very nonspecific and can include colonic dilatation, small bowel distention, and "thumbprinting." In the acute abdomen, when toxic megacolon or obstruction is suspected, plain films should be ordered before any contrast study. In toxic megacolon, abdominal X-rays will show marked colonic dilation and can be followed to monitor for possible bowel perforation. Contrast enema can be used to evaluate the extent of colonic disease if needed.

The UGI series with small bowel follow-through has been considered the "gold standard" imaging technique in IBD, and is widely used to determine mucosal irregularities, indicating the presence of small-bowel CD, strictures and fistulas. It becomes even more sensitive if done by enteroclysis. This technique increases radiation and can be uncomfortable for the patient, and so is rarely used in pediatrics.

Abdominal/pelvic CT scans have proven to be helpful in the evaluation of stricture in known disease, and especially to rule out an abscess or fistula that cannot be seen on UGI. Intravenous and oral contrast, and in some instances rectal contrast, should be used. The major disadvantage of CT scan is the large radiation exposure.

CT may be superior for large bowel imaging, but MRI can be superior to CT scan in evaluating small-bowel disease. MRI is advantageous in patients with equivocal studies and is a crucial tool in distinguishing inflammation from fibrosis in patients with obstructive symptoms. MRI has become the imaging modality of choice for perianal disease. Most children with IBD receive multiple radiological exams throughout their life, increasing their lifetime radiation exposure, making MRI especially promising in the pediatric population because of the lack of ionizing radiation [31]. Abdominal US has shown to be sensitive and specific in the detection of CD; Doppler is particularly popular. However, this is highly dependent on the experience of the technician and the reading radiologist. It is recommended only in centers that have experience with this technique [31].

White blood cell scan (scintigraphy) can be indicative of IBD in the pediatric population. WBC scan can also help distinguish between CD and UC. In UC, the scan would not have uptake in the small bowel and uptake should be continuous, starting in the rectum. Any uptake in the small bowel would indicate CD, and there could be discontinuous uptake throughout the large and small bowel [33]. Positron emission tomography (PET) scan has been shown to be as accurate as WBC scan for detecting an inflamed GI tract in children. However, the data is limited and PET scans are not widely available, so they currently play a minimal role in evaluating IBD in children [33].

Video capsule endoscopy

One of the most promising additions in imaging has been video wireless capsule endoscopy (WCE). WCE allows small-bowel visualization with no radiation. It has been shown to be well tolerated in the pediatric population. The capsule is the size of a large multivitamin (1.1 cm $\times$ 2.6 cm or 1 in. $\times$ 0.5 in.), and contains a videochip, radio transmitter, and battery; video images are transmitted to a portable device via an abdominal antenna array, and later downloaded to a computer and read by a gastroenterologist. Small-bowel transit time is approximately 4 h, and the single-use capsule is passed in the stool in 24–48 h. The risk with this procedure is retention of the capsule. Capsule retention requiring intervention has been reported in $<1\%$ of subjects. Nevertheless, its use is contraindicated in patients with known or suspected stricture. WCE does have limitations. It can detect nonspecific lesions (that may or may not be IBD), lesions cannot be biopsied, and it cannot detect extraluminal abnormalities. However, this technology has made evaluation of the small bowel more sensitive [34].

Endoscopy

The diagnosis of IBD is virtually impossible without endoscopic evaluation. Endoscopy with biopsy is the most sensitive and specific evaluation of colon/ileum. During initial work-up, endoscopy aids in diagnosing IBD, differentiating between UC and CD, and assessing extent and severity of disease. Macroscopic findings, depending on the disease, can include patchy or continuous inflammation, ulcerations, nodularity, and strictures. After diagnosis, it is used to monitor response to therapy, for cancer surveillance, and to perform procedures, such as stricture dilatation. Endoscopic work-up of IBD differs in adults and

pediatrics. For example, pediatric gastroenterologists consider an exam without ileal intubation to be incomplete, and random biopsies (from the upper and lower GI tract) are taken even in the absence of macroscopic disease. In addition, after several studies showed that performing an esophagogastroduodenoscopy (EGD or upper endoscopy) during the work-up for pediatric IBD resulted in higher rates of diagnosis confirmation, it has become standard practice to perform upper endoscopy at diagnosis; either during the initial endoscopy or soon after [35].

Histology

Biopsies are usually taken from all areas, even in the absence of obvious lesions, because histological abnormalities (even granulomas) can be present in biopsies of "normal"-appearing tissue. Noncaseating granulomas are pathognomonic for CD; however, 60% of biopsies will not show granulomas, and the diagnosis must be made from other radiological, histological, or endoscopic findings [36].

Treatment and management

Induction of remission and maintenance of remission are the main goals of treatment in IBD. Optimal treatment consists of a multidisciplinary approach, including medications, nutrition, psychiatric assessment, and enrollment of general practitioners, as well as—if necessary—other specialists to help with complications and EIM. Long-term goals should include preventing relapses (which includes encouraging compliance), optimizing growth and development, improving quality of life, and limiting disease complications.

Medications

Medical therapy has evolved significantly over the last 15 years. Today there are many options for treating IBD, and it is even possible to "spare the corticosteroids" in some cases. Classes of drugs include aminosalicylates, immunomodulators, and biologics. As knowledge of the genetics of IBD and the pathways involved in the development of IBD increases, it is anticipated that drugs that can specifically target those pathways will be developed, resulting in improved outcomes.

Steroids

Corticosteroids are still used as the main treatment for inducing remission in moderate to severe CD and UC. They are typically used in conjunction with a maintenance therapy to induce remission; the slower-acting drug takes effect as the steroids are slowly weaned. Intravenous solumedrol can be used in severe UC and CD to induce remission. Oral prednisone dosing is 1 mg/kg/day with a max of 40 mg/day, since doses greater than this have not shown increased efficacy [37]. Budesonide, an oral steroid preparation that is released in the distal ileum and proximal colon, can be considered in patients with limited disease of the distal ileum and proximal colon. It has less systemic side effects than prednisone but is not completely without them, and quick withdrawal can lead to adrenal insufficiency. Rectal steroid enemas are available and can be used for proctitis and sigmoid disease without the systemic side effects.

Steroids have multiple side effects. Reversible short-term side effects include moon facies, acne, weight gain, hirsutism, mood swings and psychoses. Long-term side effects are the result of cumulative doses of steroids. They include growth retardation, osteopenia, permanent skin striae, and cataract. For these reasons, in addition to the lack of efficacy in maintenance and healing of IBD and the introduction of newer medications, they should only be only as a short-term treatment, ideally for <3 months.

Aminosalicylates

Aminosalicylates (5-ASA), used as a first-line therapy, have proven their efficacy in the induction and maintenance of remission in mild to moderate UC [38, 39]. They also have some benefit in the maintenance of remission in mild CD [40]. 5-ASAs have various delivery systems that target specific parts of the bowel, so when choosing which 5-ASA to use, knowledge of the disease distribution for that patient is extremely important. In general, these drugs are well tolerated. Main side effects include headache and rash; rare but more serious side effects include hepatitis, pancreatitis, colitis, and decreased sperm count in males.

6-Mercaptopurine and azathioprine

Azathioprine and its metabolite 6-mercaptopurine (6-MP) belong to the class of thiopurine immunomodulators. They have been used for steroid-refractory CD for decades, and are also used in the maintenance of remission in moderate to severe UC and CD [41–43]. These drugs have a very slow onset of action and may take 3–6 months to reach maximal effect. However, they are often started in conjunction with steroids in moderate to severe disease and can decrease the duration of steroid use. These drugs have both idiosyncratic and dose-dependent side effects. Idiosyncratic side effects include pancreatitis, fevers, and myalgias. Dose-dependent side effects include myelosuppression, infections, and elevated liver enzymes. Patients

have different genotypes for thiopurine methyl transferase activity (TPMT), the enzyme that metabolizes the drugs. Lab tests to determine genotypes or to measure TPMT activity directly are available commercially and can be done before starting therapy to help guide dosing [44]. Slow metabolizers are at a higher risk for myelosuppression and require reduced doses of the medication. Although rare, there are patients who have no or very low TPMT activity. Using thiopurines for them is dangerous and is clearly contraindicated. 6-Thioguanine nucleotide levels can be monitored to optimize the dose or check compliance.

Methotrexate

Methotrexate is an immunomodulator that has been proven to be efficacious in inducing and maintaining remission in adult CD patients [45]. To date there have been no controlled trials of its use in pediatric CD, but reports from retrospective reviews and uncontrolled trials have shown good remission rates in patients that fail 6-MP or are intolerant to thiopurines [46, 47]. Methotrexate is a teratogen and a powerful abortifacient, so pregnancy counseling should be given to all females of child-bearing age who are started on this treatment.

Biologic therapies

Biologic therapies have dramatically changed the treatment and management of IBD over the last few years. Tumor necrosis factor alpha is a cytokine involved in systemic inflammation that can stimulate the acute phase reaction. Infliximab, the first in this class to be approved in pediatric IBD, is a chimeric monoclonal IgG1 antibody (part mouse and part human) that is given intravenously. It blocks the action of TNFα by preventing it from binding to its receptor in the cell. This biologic is approved for adult patients with moderate to severe UC and CD [48, 49], and for pediatric patients with moderate to severe and CD [50]. Infliximab is also efficacious in fistulizing and perianal CD [51].

The most common side effects for infliximab include infusion reactions, infections, and abnormal ALT elevations. Infusion reactions are usually mild and respond to antihistamine therapy. This is not a contraindication for further infusions, but patients do need to be premedicated with diphenhydramine. The most commonly reported infections are upper respiratory tract infection and pharyngitis. Infliximab can reactivate latent *Mycobacterium tuberculosis*, and all patients should have a documented negative PPD before starting treatment.

Although an overall slightly increased risk of lymphoma has been reported in patients with IBD who have been exposed to biologic or immunomodulator therapy, a rare fatal form of lymphoma, "hepatosplenic T cell lymphoma," has been observed only in children and young adults with IBD exposed to immunomodulators while taking biologics. Infliximab has a black box warning regarding this rare lymphoma. There have been approximately 18 cases of HTLC with individuals on both 6MP/AZA and infliximab so far. These cases reveal a preponderance for young male patients, although the mechanism of this preponderance is unknown. For this reason, most pediatric patients do not receive concomitant therapy with these two classes of medications (there are some exceptions in severe children).

Other anti-TNF agents have been approved for the treatment of IBD in adults, and are undergoing trials in pediatrics [52, 53]. Adalimumab is a recombinant human IgG1 monoclonal antibody. Being primarily human, it is seldom the target of antibody formation. An additional advantage of adalimumab is that it is given as a subcutaneous injection instead of an intravenous infusion like infliximab [54]. Most recently, a PEGylated, humanized anti-TNF-α antibody fragment, certolizumab pegol, has been introduced for the treatment of adult IBD [55, 56]. It is different from the other two anti-TNF drugs in that it does not induce apoptosis of T cells or monocytes or fix complement, but whether this has clinical significance is still under investigation. It is also given as a subcutaneous injection and is not approved in pediatrics to date.

Other biologics

Natalizumab, a humanized antibody against α4-integrin, is the first drug developed from the class of selective adhesion molecule inhibitors. α4-Integrin is required for white blood cells to move into organs from blood vessels. Natalizumab's mechanism of action is believed to involve the inhibition of neutrophils from crossing blood vessel walls to reach affected organs like the gastrointestinal tract. It is FDA-approved for both induction of remission and maintenance of remission for moderate to severe CD [57, 58]. The drug was originally approved for the treatment of multiple sclerosis, but was temporarily pulled from the market after progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the Creutzfeldt–Jakob virus that typically occurs in patients who are immunocompromised, developed in seven patients. It has been brought back, but has a black box warning stating that the drug has only been linked to PML when combined with other immune-modulating drugs. Therefore, natalizumab is contraindicated for use with other immunomodulators. In addition, the prescribing information from the package insert recommends that people taking corticosteroids for the treatment of CD should have their

doses reduced before starting natalizumab treatment to reduce immunosuppressive effects. The risk of developing PML was later estimated to be 1 in 1,000 (0.1%) over 18 months, though the longer-term risks of PML are unknown. Due to the uncertain risk of PML, natalizumab is only available through a restricted distribution program, and patients must enter a registry for monitoring.

Other classes of biologics are under investigation. This is an exciting area of research and discovery, but still leaves many questions unanswered. This is especially important for the pediatric population, as long-term side effects and complications of new drugs are unknown. The FDA now requires post-marketing studies to be incorporated into drug trials.

Other treatment modalities

Antibiotics are used widely in the treatment of IBD, with metronidazole and ciprofloxacin being at the top of the list. However, their efficacy in treating intestinal inflammation has not been proven [59]. In cases of perianal abscess or fistulae they may have some benefit [60]. Cyclosporine is indicated only in severe refractory UC as a rescue therapy. It has not been shown to be efficacious in CD [61, 62]. The risks and benefits must be weighed and other options exhausted. Thalidomide is given in severe refractory CD, but no standardized controlled trials have been done to accurately measure its efficacy or outweigh the risks and benefits [63]. Given the well-known risk of severe birth defects and other side effects, the use of thalidomide is only given in severe cases of refractory disease.

Tacrolimus is used in patients with treatment-resistant UC, and can help in reducing symptoms. Tacrolimus is a potent immunosuppressant, so risks and benefits need to be weighed up before a patient is started on this medication. Probiotics have not been shown to add any benefit to conventional therapy in maintaining remission of UC or CD. However, many patients and parents may add this to conventional therapy, and at this time there are no contraindications to this [64, 65].

Nutrition

Nutritional therapy consists of using formula (both elemental and nonelemental) as primary therapy to induce and maintain remission in CD, as a supplement to improve growth, or to replenish micronutrient deficiency. The evidence to support the use of enteral nutrition as primary therapy is controversial, and it is not widely practiced in the United States due to societal expectations. It is more widely used in the Europe and Canada, with remission rates in CD reported as 50–80% [66]. Studies in pediatric patients have produced varying results. *Supplemental* nutritional therapy, on the other hand, is used for patients who cannot maintain weight on "normal' caloric intake and cannot consume the required 100–150% of the recommended daily allowance through a regular diet. Other nutritional modifications, such as low residue, specific carbohydrate, lactose-free or other elimination diets have not been sufficiently studied, and to date there is no evidence to suggest that they should be recommended in the general IBD population [67]. However, a low-fiber diet is recommended in patients who have active colitis or a narrowing/stricture of the small bowel.

Surgical management

Medical management remains the first-line treatment in IBD. Indications for surgery are relatively similar between UC and CD, but the approach and the outcomes differ. Indications for surgery include fulminant colitis, massive hemorrhage, perforation, stricture, abscess, fistula (in CD), toxic megacolon, failure of medical therapy, steroid dependency, and dysplasia. Pediatric patients also have other indications, including growth failure and pubertal delay. It has been shown that children will have catch-up growth after surgery [68, 69].

In UC, total colectomy and ileoanal pull-through with anal anastomosis (IPAA) is the current standard surgical procedure for UC [69]. This removes the colon and rectal mucosa and eventually a distal ileal reservoir or "pouch" is created. This technique avoids permanent ileostomy and preserves anorectal function. The surgery can vary between 1 and 3 surgeries with months in-between (with a temporary ileostomy), depending on the patient, the disease, and the surgeon. Laparoscopic surgery is also becoming an option for some patients. Complications include pouchitis (inflammation of the pouch), small bowel obstruction, anastomotic leak, fecal incontinence, strictures, fistula, and dysplasia of the anal transition zone [70].

Many patients with CD will require surgery during their lifetimes, although the number is decreasing due to improved medical therapy. The aim of surgery in CD is to resect as little bowel as possible, since CD will recur in most patients within 5 years of surgery. This is also why CD is a relative contraindication to IPAA.

Inflammatory bowel disease is a relapsing disease that has high morbidity but low mortality. Most children with IBD lead active, normal lives, with no limitations except during flares. However, patients with IBD are at increased risk for some malignancies. In UC, the greatest risk is colonic dysplasia/cancer. The risk has been estimated to be up to 25% after 30 years of disease [71]. Risk factors for development of colorectal cancer in UC patients are long

duration of disease, early onset, chronic inflammation, family history of colorectal cancer, and PSC. Patients with colonic CD share the same risk factors as UC patients. CD patients are known to have a slightly increased risk of lymphoma over their lifetimes.

The diagnosis and management of IBD in children has changed dramatically over the last decade, due mainly to increased awareness, availability of newer diagnostic modalities such as MRI and video capsule endoscopy, and newer and powerful treatments such as biologics. It is hoped that a combination of innovative research and advances in drug discoveries will change the natural history of IBD and make a huge difference in children who are suffering from this unfortunate chronic inflammatory bowel disorder.

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