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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON AND C KUO, SECTION EDITORS)

Inflammatory Bowel Disease in Primary Immunodeficiencies

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Abstract
Purpose of Review Inflammatory bowel disease is most often a polygenic disorder with contributions from the intestinal microbiome, defects in barrier function, and dysregulated host responses to microbial stimulation. There is, however, increasing recognition of single gene defects that underlie a subset of patients with inflammatory bowel disease, particularly those with early-onset disease, and this review focuses on the primary immunodeficiencies associated with early-onset inflammatory bowel disease.
Recent Findings The advent of next-generation sequencing has led to an improved recognition of single gene defects underlying some cases of inflammatory bowel disease. Among single gene defects, immune response genes are the most frequent category identified. This is also true of common genetic variants associated with inflammatory bowel disease, supporting a pivotal role for host responses in the pathogenesis.
Summary This review focuses on practical aspects related to diagnosis and management of children with inflammatory bowel disease who have underlying primary immunodeficiencies.

Keywords Crohn's colitis · Ulcerative colitis · Early-onset IBD · Monogenic IBD

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Introduction

Inflammatory bowel disease (IBD) includes ulcerative colitis, Crohn's disease, and indeterminate colitis. It is a heterogeneous disorder with contributions from genetic background, microbiota, and other environmental factors. There has been a dramatic increase in the incidence of IBD over the past 50 years accompanied by a gradually decreasing median age of onset. At one time, the suspicion of primary immune deficiency disorder (PIDD) as a cause for IBD was low and restricted to patients with pediatric-onset and severe disease. With the changing epidemiology of IBD, it has become more difficult to define the population that would benefit from an evaluation for PIDD. This review will discuss the key clinical features of ulcerative colitis and Crohn's disease, the occurrence of PIDD in early-onset IBD, and the potential approaches for the diagnosis and management of such patients.

The Changing Epidemiology

Several large European cohorts have demonstrated a dramatic increase in incidence in IBD, but the findings are particularly notable for pediatric-onset Crohn's disease. In Scotland, there has been a 500% rise in pediatric Crohn's disease over the last 40 years with the most rapid rate of increase in just this past decade [1]. In Canada, one of the areas with the highest incidence of pediatric IBD, the most pronounced increase was seen in the very young children diagnosed less than five years of age, known as very early-onset IBD (VEO-IBD) [2]. There is a recognized North–South gradient with a higher incidence of IBD in the northern latitudes [3]. This North–South gradient is being altered, because developing countries have among the greatest increase in the rates of pediatric-onset IBD [4]. Other recognized epidemiologic features of IBD are familial

occurrences. Fifteen to 20% of the patients with IBD will have a similarly affected family member, and for those patients with a pediatric presentation, 30% have a positive family history [5]. The risk of developing Crohn's disease in monozygotic twins is as high as 30–50% whereas the rate for dizygotic twins is only 2–4% [6, 7]. The most commonly identified genetic variants in genome-wide association studies for Crohn's disease are variants in the NOD2 (CARD15) gene [8•, 9]. This is in fact a mild immune deficiency with altered responses to muramyl dipeptide, a bacterial cell wall product [10]. Other common genetic variants that contribute to IBD include variants in genes related to autophagy, immune responses, and responses to the microbiome [11]. The major histocompatibility complex has also been frequently identified in genome-wide association studies, as is true for most autoimmune diseases. Genetic contributions to the etiology of IBD therefore are well established. Non-genetic contributors to the susceptibility to IBD are believed to include Western diet, obesity, dysbiosis of the gastrointestinal tract, sunlight exposure, and antibiotic use. The interplay between all of these identified epidemiologic associations is not well understood, and their specific contributions to the rising incidence of pediatric-onset IBD are not understood at all.

Clinical Features of IBD

Ulcerative colitis typically begins in the rectum and proceeds proximately, involving the mucosa in a symmetric uninterrupted pattern. The most common presenting symptoms are rectal bleeding, diarrhea, and abdominal pain. Pediatric cohort studies performed in the late 1990s demonstrated that 43% of the patients had mild disease at presentation, while 57% of the children had severe disease [12]. Patients with mild disease have limited systemic signs and negligible effects on nutrition. These patients typically respond well to therapy. Those who have moderate disease may have bloody diarrhea and abdominal tenderness. Weight loss, fever, anemia, and frequent cramps are common in this group. Severe colitis is seen in approximately 10% of the pediatric patients in which abdominal tenderness, fever, elevated inflammatory markers, and frequent bloody diarrhea are seen. These patients may have serious complications including hemorrhage, toxic megacolon, or perforation. Severity at presentation somewhat predicts the course. At 1 year following diagnosis, 1% of those with initial mild disease and 8% with moderate/severe required colectomy, and at 5 years, the risk of colectomy was 9 and 26% in the two groups, respectively [12]. A report of a regional incident cohort from Northern France in 2009 that included 113 pediatric patients showed progression from initial extensive disease in 37% at diagnosis to 60% by last follow-up and a cumulative colectomy rate of 20% by 5 years [13]. These studies demonstrate that while the presentation is modestly predictive of the ultimate course of disease, that overall morbidity is very high in early-onset IBD. A small fraction of patients will present with extra-intestinal manifestations, and those are described in Table 1. Having one extra-intestinal manifestation is a risk for additional extra-intestinal manifestations.

Crohn's disease can involve any portion of the gastrointestinal tract. The symptoms relate to the site of involvement, and small bowel involvement is often heralded by poor growth, weight loss, abdominal pain, and nutritional deficiencies [15]. Disease location and behavior are highly variable at diagnosis and are not fixed over time. Data from a large multicenter European registry found the initial disease location of 582 children with Crohn's disease to be widely distributed, and over time, disease extension was noted in 39% of the patients [16, 17]. Additionally, disease can present as an inflammatory phenotype and can progress to stricturing or penetrating disease over time [18]. The majority of children have involvement of the terminal ileum, and colonic involvement is most often in the ascending portion. Exclusive colonic disease is seen in 10–20% of the children, and this can cause confusion with the diagnosis of ulcerative colitis. Crohn's disease has a more variable presentation than ulcerative colitis, and it is not unusual for growth failure to precede the onset of frank gastrointestinal symptomatology by several years. Table 1 details common extra-intestinal manifestations of Crohn's disease. In some cases, these manifestations are synchronized with disease activity, whereas in others, they arise independently of gastrointestinal inflammation. In the case of Crohn's disease, key extra-intestinal features are skin tags, genital lymphedema, orofacial granulomatosis, or oral ulcers. Extra-intestinal manifestations were present in 20% of the children with IBD in a large European cohort [16].

Indeterminate colitis refers to IBD in which the patient cannot be clearly assigned to either Crohn's disease or ulcerative colitis. This diagnostic category is more often seen in children than in adults, and over time, many patients will evolve more clearly into one or the other of the classical diagnoses [19•].

PIDD Associated with IBD

There are now over 50 single gene or monogenic defects and a common polygenic PIDD associated with IBD [20, 21••]. The genes known to be associated with early-onset IBD are listed in Table 2. Inclusion in this table requires more than a single case report of IBD in association with that specific immune deficiency. In the table, disorders in which IBD is likely to be a presenting manifestation are distinguished from those where IBD is more likely to arise later in the course. This distinction is useful, because it also defines a set of patients where infantile onset is seen versus those more likely to appear in later in

Table 1 Extra-intestinal manifestations in IBD

	Crohn's disease	Associated with active Cohn's disease	Ulcerative colitis	Associated with active ulcerative colitis
Erythema nodosum	6%	X	3%	X
Pyogenic granuloma	2%	+/−	2%	X
Skin tag	37%		Low	
Oral ulcers	10%	X	4%	?
Orofacial granulomatosis	?		Low	
Asymmetric large joint arthritis	10–20%	X	5–10%	X
Seronegative spondyloarthropathy	6%		2%	
Uveitis	6%	X	4%	X
Sclerosing cholangitis	<1%		3%	
Nephrolithiasis	5%		5%	

Data have been taken from the Swiss adult IBD cohort [14•]

childhood and adulthood. In large studies, the rate of monogenic disorders ranges from 10 to 20%. XIAP deficiency and IL-10 pathway defects have been most commonly reported [22]. Thus, they represent a minority of the cases; however, their distinct therapeutic requirements mandate that they be identified and managed according to the gene defect. As may be seen, a very broad range of types of immune deficiency can be associated with IBD. In certain cases, the pathophysiology is well understood whereas in others, there is limited understanding of the mechanism linking the immune deficiency with IBD. In general, susceptibility to IBD is thought to revolve around dysbiosis of the intestinal microbiota, breach of the intestinal epithelial layer, and aberrant regulation of host responses to bacteria. Encompassing these three broad tenets, a variety of patterns emerge. Dyskeratosis congenita, TTC7A mutations, trichohepatoenteric syndrome, and the ectodermal dysplasias may be seen as specific defects that impact the epithelial barrier function. Maintenance of the epithelial barrier requires contributions from innate lymphoid cells, and it may be that some immune deficiencies contribute to the pathogenesis of IBD through their effects on the innate lymphoid cell populations [23]. It is thought that many of the immune deficiencies impact the microbiota both by failing to tune the colonizing populations through immune responses and also due to frequent antibiotic use. Aberrant host responses to bacteria are a theme that links the IL-10 pathway and many of the antibody deficiencies. Nevertheless, these primary immune deficiencies probably have complex contributions to the susceptibility of IBD and therefore this reflects as incomplete penetrance of the IBD [24]. Only a very small number demonstrate rates of IBD in over half of the patients. This would include the IL-10 pathway defects, early-onset dyskeratosis congenita, the ectodermal dysplasias, and chronic granulomatous disease (in adults). Only the IL-10 pathway defects, trichohepatoenteric syndrome defects, and early-onset dyskeratosis congenita are likely to present with IBD.

Monogenic defects account for a minority of early-onset IBD. There may be clinical clues to help focus the work-up to identify those patients. Sequencing panels and whole exome sequencing represent the mainstays of the diagnostic approach; however, certain red flags in the history or pathology may allow the clinician to focus on higher risk cases. Infantile onset and association with other autoimmune disease represent historical features that may identify patients at high risk for monogenic diseases. Pathologic features that seem to associate with monogenic defects are high rates of apoptosis (seen in the dyskeratosis congenita defects and certain other PIDD), villous atrophy and increased intraepithelial lymphocytes (classically seen in immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) and a subset of patients with common variable immunodeficiency), and a lymphocytic colitis (seen in some T cell defects). Pathologic features associated with chronic granulomatous disease are not consistent, but the Hermansky–Pudlak group of disorders has an association with pigmented macrophages [25•, 26–29].

There are a number of monogenic defects that present classically with a malabsorptive picture. Congenital tufting enteropathy is an example. These disorders have a high rate of concomitant IBD, presumably on the basis of impaired barrier function. These conditions present nearly always in infancy with sever watery diarrhea, unresponsive to intake restrictions. Biopsies are most often characterized by a bland cellularity and pronounced villous atrophy. Diagnosis can be by characteristic pathology, special stains, or through genetic testing. A diagnostic approach to these children has been published [30].

Table 2 PIDD associated with IBD (alphabetized according to gene)

Condition	Gene	Inheritance	Type of PIDD	Likely to present as IBD
ADA deficiency	ADA	AR	T cell	
Inflammatory skin and bowel disease-1	ADAM17	AR	Innate	
AID deficiency	AICDA	AR	B cell	
X-linked agammaglobulinemia	BTK	XL	B cell	
CD3γ deficiency	CD3G	AR	T cell	
CD40 ligand deficiency	CD40LG	XL	T cell	
Dystrophic bullosa	COL7A1	AR	Epithelial	
Chronic granulomatous disease	CYBA	AR	Innate	
Chronic granulomatous disease	CYBB	XL	Innate	
Artemis deficiency	DCLRE1C	AR	T cell	
Dyskeratosis congenita (severe form)	DKC1	XL	Epithelial	X
DOCK8 deficiency	DOCK8	AR	T cell	
Tufting enteropathy	EPCAM	AR	Epithelial	
Kindler syndrome	FERMT1	AR	Innate	
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome	FOXP3	XL	T cell	
Severe congenital neutropenia type 4	G6PC3	AR	Innate	
Glycogen storage disease type 1b	G6PT1	AR	Innate	
Familial diarrhea	GUCY2C	AD	Epithelial	
Hermansky–Pudlak syndrome	HPS1	AR	Most cells	
Hermansky–Pudlak syndrome	HPS4	AR	Most cells	
Common variable immunodeficiency	ICOS	AR	B cell	
EDA-ID	IKBA	AD	Most cells	
XL-EDA-ID	IKBKG	XL	Most cells	
IL-10 deficiency	IL10	AR	Innate	X
IL-10Rα deficiency	IL10RA	AR	Innate	X
IL-10Rβ deficiency	IL10RB	AR	Innate	X
IL-21 deficiency	IL21	AR	T and B cell	X
CD25 deficiency	IL2RA	AR	T cell	
γc deficiency	IL2RG	XL	T cell	
Leukocyte adhesion deficiency type 1	INTGB2	AR	Innate	
DNA ligase IV deficiency	LIG4	AR	T cell	
LRBA deficiency	LRBA	AR	T cell	
MASP2 deficiency	MASP2	AR	Innate	
Familial Mediterranean fever	MEFV	AR	Innate	
MVK deficiency	MVK	AR	Innate	
Chronic granulomatous disease	NCF1	AR	Innate	
Chronic granulomatous disease	NCF2	AR	Innate	
Chronic granulomatous disease	NCF4	AR	Innate	
NFAT5 haploinsufficiency	NFAT5	AD	Many cells	
Phosphatidylinositol 3-kinase deficiency	PIK3R1	AR	T and B cells	
Phospholipase C-γ2 deficiency	PLCG2	AD	T and B cells	
RAG1 deficiency	RAG1	AR	T cell	
RAG2 deficiency	RAG2	AR	T cell	
Hirschsprung's disease	RET	AD	Unknown	
Hoyeraal–Hreidarsson syndrome	RTEL1	AR	Epithelial cells	X

Table 2 (continued)

Condition	Gene	Inheritance	Type of PIDD	Likely to present as IBD
Trichohepatoenteric syndrome	SKIV2L	AR	Epithelial cells	X
STAT1 deficiency	STAT1	AD	T cell	
Familial hemophagocytic lymphohistiocytosis type 5	STXBP2	AR	T cell	
Immunodeficiency with multiple intestinal atresia	TCC7A	AR	Epithelial cells	X
Trichohepatoenteric syndrome	TTC37	AR	Epithelial cells	X
Wiskott–Aldrich syndrome	WAS	XL	Hematopoietic cells	
X-linked lymphoproliferative syndrome type 2	XIAP	XL	Unknown	
ZAP70 deficiency	ZAP70	AR	T cell	
Common variable immunodeficiency	Polygenic	Polygenic	B cell	

Diagnosis of IBD

Diarrhea is a common symptom in patients with primary immune deficiency, and the natural inclination is to assume that the cause is infectious. Culture for *Salmonella*, S*higella*, *Campylobacter*, and testing for *Clostridium difficile* toxin production is a common starting point. Parasitic infections should be sought specifically looking for Giardia, cryptosporidium, and Entamoeba. Other parasites and bacteria should be sought depending on their prevalence in the specific geographic area. Many immune deficient patients are also susceptible to viral infections, and for this reason, Epstein–Barr virus and CMV infections should be evaluated. In some settings, serologic testing for responses to *Saccharomyces* has been advocated. The serologic tests are thought to have limited sensitivity and specificity in patients with immune deficiency [31]. Initial blood tests should include a CBC and differential, serum albumin; C-reactive protein; and erythrocyte sedimentation rate. However, it is important to note that 21% of the children with mild Crohn's disease have normal results on all of these tests. The preferred test to screen for intestinal inflammation is a fecal calprotectin level [32]. Magnetic resonance enterography is the imaging modality of choice for the detection of small intestine involvement [33•]. Wireless capsule endoscopy is a useful alternative; however, it cannot be used in the setting of small bowel narrowing. Additionally, some children cannot swallow the capsule, therefore it must be placed endoscopically [34]. Abdominal ultrasound may reveal large inflammatory masses, and some institutions utilize dedicated small bowel ultrasound to screen for small bowel disease. While used often in Europe, this use of ultrasound is limited to a few centers in the USA. The gold standard for the diagnosis of IBD is endoscopic visualization of the gastrointestinal tract and multiple biopsies, including intubation of the terminal ileum [33•]. Diagnostic biopsies must demonstrate evidence of chronic active changes in the small bowel and or colon (Fig. 1).

Therapy of IBD in Patients with Primary Immune Deficiency

In general, therapy for IBD in patients with PIDD is not well established. The general goal for management should be to achieve clinical and laboratory control of the disease, optimization of growth and development, normalization of daily functioning, while minimizing side effects. Therapy often utilizes a rapid step-up approach, although the optimal strategy for patients with PIDD is not known.

For mild ulcerative colitis and colonic Crohn's disease, mesalamine given as an oral drug, an enema, or a suppository can achieve adequate results. Steroid enemas are also frequently used in the setting of left-sided colonic disease. For patients with moderate ulcerative colitis, the strategies include antibiotics, mesalamine, and, in some cases, an induction regimen with oral steroids and then tapering once disease is in control. Patients who require steroids, however, are then likely to be initiated on immunomodulator therapy and or biologic therapy. Patients with mild–moderate Crohn's disease can be treated with nutritional therapy, which is probably underutilized but does have a very high response rate. As we understand more about how diet plays a role in the composition and function of the gut microbiota, and may be involved in the pathogenesis of the disease, it has become an obvious therapeutic target. Nutritional therapy can include total parenteral nutrition (TPN) and complete bowel rest (which is seldom used today) or enteral nutrition with a defined formula. TPN can achieve a response rates as high as 90% whereas enteral nutrition has remission rates between 50 and 80% after

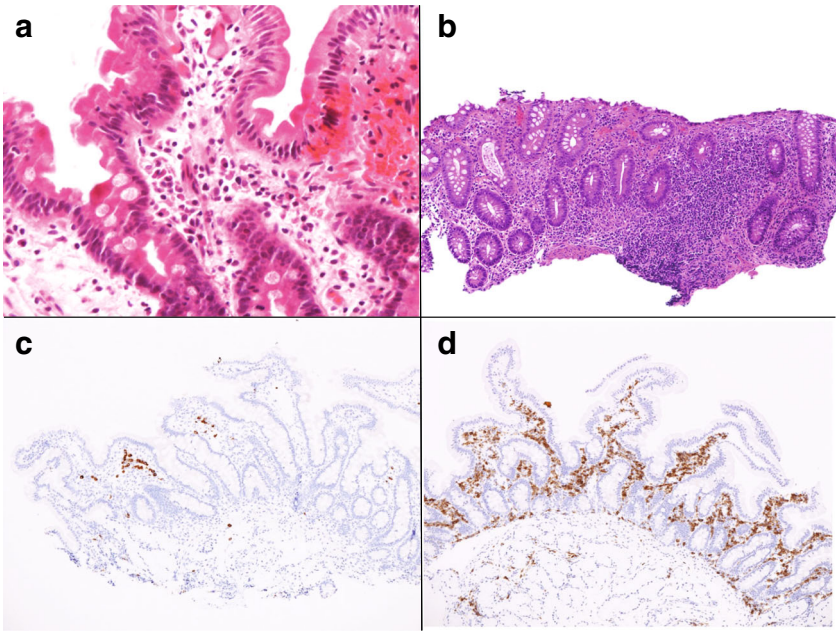

Fig. 1 Duodenal biopsy of a 5-year-old male with confirmed ZBTB24 mutation. Mutations in ZBTB24 are associated with immunodeficiency–centromeric instability–facial anomalies syndrome. The rate of diarrhea in this syndrome is high, but the prevalence of IBD is not known. These biopsies show several atypical features for IBD. (**a**) The lamina propria is relatively hypocellular with few plasma cells in loose aggregates (hematoxylin–eosin). (**b**) The small bowel demonstrates villous blunting (hematoxylin–eosin). (**c**) The plasma cells have been stained with CD79a to demonstrate their paucity in the small bowel, compared to (**d**) a normal control stained for CD79a

4 weeks [35–37]. A number of defined diets have been used for the treatment of IBD. Exclusive enteral nutrition (EEN) has been extensively studied in pediatric IBD and has been shown to be effective in inducing and maintaining remission [38, 39]. Formula is the sole source of nutrition in this approach. There is no difference in efficacy between polymeric, semi-elemental, or elemental formulas. Partial EN has been shown to be effective as well, in which children receive 50–80% of the caloric requirements via formula and remaining of calories comes from food [40]. Other diets are utilized as therapy as well, including the specific carbohydrate free diet and the anti-inflammatory diet [41]. While nutritional therapy is more effective for Crohn's disease than ulcerative colitis, it can be an effective intervention for ulcerative colitis particularly in children who have poor nutrition.

For those patients who have disease refractory to the previous interventions or who cannot be tapered from oral steroids, remission can be induced with immunomodulatory therapy (6-mercaptopurine, azathioprine, or methotrexate) or anti-TNF therapy. Safety remains a concern, and growing evidence has demonstrated an increased risk of malignancy with 6-mercaptopurine and azathioprine, particularly lymphomas [42–44]. Today, severe disease is most often treated with TNF inhibitors as a first choice, and in some centers, TNF inhibitors are used for moderate disease as well. Other therapeutic options now include anti-integrin (vedolizumab) and IL-12/IL-23 blockade with ustekinumab.

Therapy for patients with PIDD does have some recognized differences from therapy for IBD in the general population. A key consideration is that TNF inhibitors are associated with an unacceptable risk of serious fungal infections in patients with chronic granulomatous disease. Therefore, testing for chronic granulomatous disease should be performed before the initiation of TNF inhibitor use. It may be imagined that this high risk is also seen in the ectodermal dysplasias, but data are lacking. Some of the monogenic forms of humoral immunodeficiency can be treated with rapamycin, and LRBA deficiency may be treated with hydroxychloroquine. CTLA4 deficiency has been treated successfully with abatacept. One approach for therapy in patients with PIDD is to assess the character of the inflammatory infiltrate. When lymphocytic infiltrates are noted, particularly in the small bowel with villous atrophy, rapamycin is a more reasonable choice than a TNF inhibitor. T cell processes may also be treated with vedolizumab. Conversely when the inflammatory infiltrate is neutrophilic and limited to the colon, then a TNF inhibitor approach may be more likely to be beneficial.

The outcome for certain PIDD associated with IBD is poor, and therefore, bone marrow transplantation should be considered as a therapy. Although there are no hard and fast rules and donor availability represents a major contributor to the decision to proceed to transplant, chronic granulomatous disease, IPEX, IL-10 pathway defects, and all of the severe T cell deficiencies should have a consideration for bone marrow transplantation. Settings where transplantation does not seem to be warranted include those defects that are primarily driving epithelial defects such as trichohepatoenteric syndrome, Hirschsprung's disease, and severe dyskeratosis congenita.

Conclusions

Today, with a rapidly rising incidence of IBD, it is more difficult than ever to identify patients who have monogenic

PIDD. Patients who have infantile onset, atypical inflammatory infiltrates, and association with other autoimmune disease may have a PIDD. Management of patients can be exceedingly complex, and balancing the immune suppression with the underlying susceptibility to infection is often a challenge. Certain number of the monogenic defects can be approached with bone marrow transplantation, and this can be curative in those cases.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Henderson P, Hansen R, Cameron FL, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. Inflamm Bowel Dis. 2012;18:999–1005.
2. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. Am. J. Gastroenterol. 2017.
3. Armitage EL, Aldhous MC, Anderson N, et al. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. Gastroenterology. 2004;127:1051–7.
4. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504–17.
5. Russell RK, Satsangi J. IBD: a family affair. Best Pract Res Clin Gastroenterol. 2004;18:525–39.
6. Halfvarson J. Genetics in twins with Crohn's disease: less pronounced than previously believed? Inflamm Bowel Dis. 2011;17:6–12.
7. Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut. 1988;29:990–6.
8. • Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001;411:599–603. **This study provided the first recognized genetic cause for IBD and described a potential mechanism**
9. Hampe J, Cuthbert A, Croucher PJ, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet. 2001;357:1925–8.
10. Mo J, Boyle JP, Howard CB, Monie TP, Davis BK, Duncan JA. Pathogen sensing by nucleotide-binding oligomerization domain-containing protein 2 (NOD2) is mediated by direct binding to muramyl dipeptide and ATP. J Biol Chem. 2012;287:23057–67.
11. Van Limbergen J, Radford-Smith G, Satsangi J. Advances in IBD genetics. Nat Rev Gastroenterol Hepatol. 2014;11:372–85.
12. Hyams JS, Davis P, Grancher K, Lerer T, Justinich CJ, Markowitz J. Clinical outcome of ulcerative colitis in children. J Pediatr. 1996;129:81–8.
13. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104:2080–8.
14. • Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106:110–9. **This large data set contributes to our understanding of extraintestinal manifestations and their co-occurrence**
15. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17:1314–21.
16. de Bie CI, Paerregaard A, Kolacek S, et al. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS registry. Inflamm Bowel Dis. 2013;19:378–85.
17. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114–22.
18. Abraham BP, Sellin JH. Disability in inflammatory bowel disease. Gastroenterol Clin N Am. 2012;41:429–41.
19. • Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis. 2008;14(Suppl 2):S9–11. **This paper emphasizes that the IBD seen in children is not simply an early version of adult IBD but has a distinctive natural history**
20. Uhlig HH, Schwerd T. From genes to mechanisms: the expanding spectrum of monogenic disorders associated with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:202–12.
21. •• Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut. 2013;62:1795–805. **This paper is the most up to date compendium of monogenic causes of IBD in children. The layout and explanations are particularly accessible**
22. Kelsen J, Dawany N, Martinez A, et al. A de novo whole gene deletion of XIAP detected by exome sequencing analysis in very early onset inflammatory bowel disease: a case report. BMC gastroeneterology. 2015.
23. Simoni Y, Fehlings M, Kloverpris HN, et al. Human innate lymphoid cell subsets possess tissue-type based heterogeneity in phenotype and frequency. Immunity. 2017;46:148–61.
24. Kelsen JR, Dawany N, Moran CJ, et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. Gastroenterology. 2015.
25. • Hussain N, Quezado M, Huizing M, et al. Intestinal disease in Hermansky-Pudlak syndrome: occurrence of colitis and relation to genotype. Clin Gastroenterol Hepatol. 2006;4:73–80. **This manuscript is an excellent overview of the complex subject of Hermansky–Pudlak's association with IBD**
26. Liu S, Russo PA, Baldassano RN, Sullivan KE. CD68 expression is markedly different in Crohn's disease and the colitis associated with chronic granulomatous disease. Inflamm Bowel Dis. 2009;15:1213–7.
27. Broides A, Sagi O, Pinsk V, Levy J, Yerushalmi B. Subclinical intestinal inflammation in chronic granulomatous disease patients. Immunol Res. 2016;64:155–9.
28. Alimchandani M, Lai JP, Aung PP, et al. Gastrointestinal histopathology in chronic granulomatous disease: a study of 87 patients. Am J Surg Pathol. 2013;37:1365–72.
29. Khangura SK, Kamal N, Ho N, et al. Gastrointestinal features of chronic granulomatous disease found during endoscopy. Clin Gastroenterol Hepatol. 2016;14:395–402. **e395**

30. Terrin G, Tomaiuolo R, Passariello A, et al. Congenital diarrheal disorders: an updated diagnostic approach. Int J Mol Sci. 2012;13:4168–85.
31. Yu JE, De Ravin SS, Uzel G, et al. High levels of Crohn's disease-associated anti-microbial antibodies are present and independent of colitis in chronic granulomatous disease. Clin Immunol. 2011;138:14–22.
32. Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. Am J Gastroenterol. 2012;107:941–9.
33.• Turner D, Travis SP, Griffiths AM, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. Am J Gastroenterol. 2011;106:574–88. **This paper represents the most current consensus guidelines for management**
34. Cohen SA, Ephrath H, Lewis JD, et al. Pediatric capsule endoscopy: review of the small bowel and patency capsules. J Pediatr Gastroenterol Nutr. 2012;54:409–13.
35. Triantafillidis JK, Vagianos C, Papalois AE. The role of enteral nutrition in patients with inflammatory bowel disease: current aspects. Biomed Res Int. 2015;2015:197167.
36. Day AS, Lopez RN. Exclusive enteral nutrition in children with Crohn's disease. World J Gastroenterol. 2015;21:6809–16.
37. Durchschein F, Petritsch W, Hammer HF. Diet therapy for inflammatory bowel diseases: the established and the new. World J Gastroenterol. 2016;22:2179–94.
38. Grover Z, Biron R, Carman N, Lewindon P. Predictors of response to Infliximab in children with luminal Crohn's disease. J Crohns Colitis. 2014;8:739–46.
39. Ruemmele FM, Pigneur B, Garnier-Lengline H. Enteral nutrition as treatment option for Crohn's disease: in kids only? Nestle Nutr Inst Workshop Ser. 2014;79:115–23.
40. Gupta K, Noble A, Kachelries KE, et al. A novel enteral nutrition protocol for the treatment of pediatric Crohn's disease. Inflamm Bowel Dis. 2013;19:1374–8.
41. Olendzki BC, Silverstein TD, Persuitte GM, Ma Y, Baldwin KR, Cave D. An anti-inflammatory diet as treatment for inflammatory bowel disease: a case series report. Nutr J. 2014;13:5.
42. Kopylov U, Vutcovici M, Kezouh A, Seidman E, Bitton A, Afif W. Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec claims database study. Inflamm Bowel Dis. 2015;21:1847–53.
43. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54:1121–5.
44. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009;7:874–81.