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North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Evaluation and Management for Patients With Very Early-onset Inflammatory Bowel Disease

*Judith R. Kelsen, †Kathleen E. Sullivan, ‡Shervin Rabizadeh, §Namita Singh, ||¶Scott Snapper, #Abdul Elkadri, and *Andrew B. Grossman

ABSTRACT

The rate of pediatric inflammatory bowel disease (IBD) has been increasing over the last decade and this increase has occurred most rapidly in the youngest children diagnosed <6 years, known as very early-onset inflammatory bowel disease (VEO-IBD). These children can present with more extensive and severe disease than older children and adults. The contribution of host genetics in this population is underscored by the young age of onset and the distinct, aggressive phenotype. In fact, monogenic defects, often involving primary immunodeficiency genes, have been identified in children with VEO-IBD and have led to targeted and life-saving therapy. This position paper will discuss the phenotype of VEO-IBD and outline the approach and evaluation for these children and what factors should trigger concern for an underlying immunodeficiency. We will then review the immunological assays and genetic studies that can facilitate the identification of the underlying diagnosis in patients with VEO-IBD and how this evaluation may lead to directed therapies. The position paper will also aid the pediatric gastroenterologist in recognizing when a patient should be referred to a center specializing in the care of these patients. These guidelines are intended for pediatricians, allied health professionals caring for children, pediatric gastroenterologists, pediatric pathologists, and immunologists.

Key Words: Crohn disease, ulcerative colitis, very early-onset inflammatory bowel disease

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Inflammatory bowel disease (IBD) that presents in children <6 years of age is known as very early-onset IBD (VEO-IBD). The disease course in this population can be more severe and refractory than older children and adults. Additionally, these children can present with a distinct phenotype (1). The aggressive disease and young age of onset points to a more significant genomic contribution to the disease compared with the polygenic inheritance seen in the older populations. Indeed, monogenic defects, including genes involved in primary immunodeficiency and intestinal barrier processes, have been identified in children with VEO-IBD (2–7). Importantly, these findings have led to effective targeted therapies (2–4,8). Of concern, this disease is rapidly increasing in incidence and thus, improved recognition of this disease is critical (7,9–11). This position paper will discuss the phenotype of VEO-IBD and outline the laboratory, endoscopic, and histologic evaluation and what factors should trigger concern for an underlying immunodeficiency. We will then review the immunological assays and genetic studies that can facilitate the identification of the underlying diagnosis in patients with VEO-IBD and how this evaluation may lead to directed therapies. The position paper will also aid the pediatric gastroenterologist in recognizing when a patient should be referred to a center specializing in the care of these patients. These guidelines are intended for pediatricians, allied

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From the *Division of Gastroenterology, Hepatology, and Nutrition, the †Division of Immunology and Allergy, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, the ‡Division of Gastroenterology, Hepatology, and Nutrition, Cedar-Sinai Medical Center, Los Angeles, CA, the §Division of Gastroenterology, Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA, the ||Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, the ¶Division of Gastroenterology, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, and the #Division of Gastroenterology, Hepatology, and Nutrition, Medical College of Wisconsin, Milwaukee, WI.

Address correspondence and reprint requests to Judith R. Kelsen, MD, Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (e-mail: kelsen@email.chop.edu).

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EPIDEMIOLOGY

Approximately 6 to 15% of the pediatric IBD population presents at <6 years of age, including, although rare, children diagnosed in the first year of life (9). The phenotype of VEO-IBD is heterogeneous and while some children have mild disease, others can present with more extensive and severe disease than older onset pediatric and adult IBD (12–15). Due to the more aggressive phenotype, early age of onset, and strong family history, a subset of VEO-IBD is now considered to be a monogenic disease, often involving genes associated with primary immunodeficiencies (16–18). Other factors, however, contribute to the development of VEO-IBD (and IBD in general) as well, including environmental exposures. Supportive of this notion is the rise in incidence of VEO-IBD from 1.3 to 2.1 per 100,000 children from 1994 to 2009, with a mean annual incidence of 7.2% (9). Prominent among the environmental exposures is the gut microbiome, which develops between birth and 3 years of age, coincident with the onset of disease in many cases of VEO-IBD (19). Exposures, such as route of delivery, gestational age, maternal diet, and infant feeding practices shape the colonization of infants' microbiome and can impact health and disease. The immune system also develops during these first 3 years of life, and is similarly influenced by the infant's exposures and by the gut microbiome. In fact, the immune system and the gut microbiome educate and regulate one another as they mature (20). This interaction is well balanced in healthy children; however, disruptions in development of either structure may lead to disease. Thus, in addition to the genetic investigations being performed in this population, there are several ongoing studies examining the association between the intestinal microbiome and VEO-IBD.

DISEASE CLASSIFICATION

Children who are diagnosed with IBD in the first 2 years of life are often referred to as infantile onset IBD, and those diagnosed between 2 and 6 years of age are classified as VEO-IBD. Approximately 40% of children with infantile and VEO-IBD have extensive colonic disease (pancolitis) at presentation (7,13); however, the extent and location of disease can change and progress, making it difficult to differentiate ulcerative colitis (UC) from Crohn disease (CD). For example, initial isolated colonic disease can extend overtime to include the small bowel (21). Furthermore, while the endoscopic findings often show a colonic distribution of disease, over time, the histology in some of these children can change and demonstrate features consistent with CD, such as granulomas or duodenal villous blunting. These findings can have important implications when determining the appropriate surgical approach in patients with severe colitis. Therefore, IBD-unclassified (IBD-U) is diagnosed more often in patients with VEO-IBD (11%–22%) as compared with older onset IBD (4%–10%) (14,15,22,23).

UNIQUE GENOMICS OF VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE

Although the rate of genetic discoveries is increasing, monogenic defects have been detected in only approximately 15% to 20%, of patients with VEO-IBD (24–26). Additionally, many of the defects have been identified in the youngest patients, neonates, and infants with IBD, although this is not a universal finding. As we improve our ability to identify these genetic drivers, the number of genes that contribute to disease will likely increase. Thus far, these findings include >50 genes, many of which involve primary immunodeficiency genes. When a genetic etiology is clinically suspected, every effort to detect these defects must be made, as the finding may radically affect therapy. Next generation sequencing technology, such as whole exome sequencing (WES) and targeted sequencing panels are a key component of the diagnostic approach, and 0in combination with the clinical history, can be powerful tools to identify monogenic disease. As discussed below, clinical clues including a history of infantile-onset disease, perianal disease, infection history, and association with other autoimmune diseases should trigger concern for genetic defects. Additionally, certain histopathologic features may point the clinician to focus on specific affected pathways, and this will be reviewed below.

IDENTIFICATION OF MONOGENIC DISEASE

A very broad range of immunodeficiencies and epithelial cell defects can be associated with VEO-IBD. The different functional immune pathways and underlying immunodeficiencies or genetic disorders that have been identified in VEO-IBD include intestinal epithelial barrier function, phagocyte bacterial killing, hyper- or autoimmune inflammatory pathways, and development and function of the adaptive immune system (3,13,18,27–29).

Genetic Variants Influencing the Integrity of Intestinal Barrier

The epithelial surface is the first line of host defense. The intestinal barrier is necessary to maintain a physical separation between commensal bacteria and the host immune system, and any break in this defense can lead to chronic intestinal inflammation (29,30). Increased translocation of bacteria or translocation of inappropriate bacteria, as is the case in dysbiosis, drives an inflammatory loop.

Some epithelial barrier defects resulting in neonatal inflammatory skin and bowel lesions include loss-of-function mutations in *ADAM17* resulting in ADAM17 deficiency (31,32), *IKBKG* (encoding NEMO) resulting in X-linked ectodermal dysplasia and immunodeficiency (33), *COL7A1* resulting in dystrophic epidermolysis bullosa (34), *FERMT1* resulting in Kindley syndrome (35–37), and TTC7A (5) resulting in multiple intestinal atresias as well as severe combined immunodeficiency syndrome. Other defects include gain-of-function mutations in *GUCY2* resulting in familial diarrhea (27,38), *EGFR* leading to neonatal skin and inflammatory bowel disease, and *TGFBR1* and *2*, which are also linked to Loeys-Dietz syndrome, type 1 and 2, connective tissue disorders, respectively (39).

Genetic Variants Influencing Bacterial Recognition and Clearance

Chronic granulomatous disease (CGD) is a result of defective intestinal phagocytes, specifically the granulocytes, responsible for bacterial killing and clearance (40). The NADPH oxidase complex is responsible for killing of ingested microbes through its production of superoxide, the precursor to reactive oxygen species (ROS) that are critical for both immunoregulatory and antimicrobial function (41). Superoxide (O_2) is converted to hydrogen peroxide (H_2O_2) and other ROS; together these lead to the killing of phagocytized microorganisms (42). Mutations in any part of the complex molecules (*CYBB, CYBA, NCF1, NCF2, NCF4*) can result in loss of superoxide production and CGD, with subsequent intestinal inflammation as well as autoimmune disease (43,44). Intestinal inflammation can be observed in as high as 40% of patients with CGD (45–48). Other genes involved in bacterial recognition and clearance include those related to defects in motility. Some

examples are *ITGB2*, leukocyte adhesion deficiency type 1 (LAD1), *SLC35C1* (LAD2), and *RAC2* (RAC 2 deficiency) (49).

Genetic Variants in the IL-10-IL-10R Pathway and Related Cytokine Family Members

IL-10 is an anti-inflammatory cytokine secreted by a variety of cells, including dendritic cells, natural killer (NK) cells, eosinophils, mast cells, macrophages, B cells, and $CD4^+$ T-cell subsets (including Th1, Th2, Th17 cells, and Tregs) (50,51). IL-10 maintains homeostasis through suppression of an excessive pro-inflammatory response and exerts its effect through binding to the IL-10 receptor, IL-10R, which is a tetrameric complex (52). It is composed of 2 distinct chains, 2 molecules of IL-10R1 (α chain) and 2 molecules of IL-10R2 (β chain) (53). IL-10 binding to IL-10R activates the JAK1/STAT3 cascade, which subsequently limits pro-inflammatory gene expression (53). Homozygous loss-of-function mutations in *IL10* ligand and receptors *IL10RA* and *IL10RB* were the first genes to be identified as causative for VEO-IBD (2). They are associated with severe intestinal inflammation, particularly in neonatal or infantile VEO-IBD, with a phenotype of severe enterocolitis, folliculitis, and perianal disease (2,54). In addition, compound heterozygote loss-of-function mutations of *IL10RA* have been reported with neonatal Crohn disease and enterocolitis (55). IL-10 defects are not only associated with intestinal inflammation but also arthritis as well as folliculitis and predispose to lymphoma, particularly large B-cell lymphoma (55,56). Hematopoietic stem cell transplantation (HSCT) has proven to be a successful, potentially life-saving treatment for these patients (57,58).

Genetic Variants Impairing Regulatory T Cells

Defects in regulatory T cells can have a variety of intestinal manifestations including enteropathy and severe colitis. The prominence of villous atrophy in the small bowel is a clue to these disorders. Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) is most often secondary to mutations of forkhead box protein 3 (*FOXP3*) gene, a transcription factor that is essential for the development and immunosuppressive activity of CD4 $Foxp3^+$ regulatory T cells (59–62). Other notable genetic defects have been found to cause IPEX-like disease, including loss-of-function mutations impacting IL2-IL2R interactions, *STAT5b,* and *ITCH*, or gain-of-function mutations in *STAT1* (63), all of which critically influence the development and function of regulatory T cells (59). Further, a novel loss-of-function mutation has been identified in *CTLA4* (cytotoxic T lymphocyte-associated antigen-4), a surface molecule of regulatory T cells that directly suppresses effector T cell populations, in VEO-IBD (64), and is discussed more below.

Genetic Variants Impairing Development of the Adaptive Immune System

Several genetic variants can alter the development and function of adaptive immune cells in a cell-intrinsic or -extrinsic manner. Multiple gene defects that impact the development or function of the adaptive immune system have been associated with severe combined immunodeficiency (SCID) (29,65,66). Defects that affect development or function of B cells and T cells by blocking either early lymphocyte survival or recombination of the B-cell receptor (BCR) or T-cell receptor (TCR) (67–69) can occur with loss-of-function mutations in recombination activating genes (*RAG1* or *RAG2*) or *IL-7R* causing Omenn syndrome and the *PTEN* gene causing PTEN hamartoma syndrome (70). Omenn syndrome, a recessive form of SCID also associated with defects in *DCLRE1C,* which encodes the protein Artemis, can manifest with intestinal disease as well as severe eczematous rash (59,66). Laboratory studies can show increased oligoclonal T cells and reduced B cells, and histology can reveal an intestinal graft versus host appearance, including crypt apoptosis (71,72).

Defects in B-cell development lead to an absence of circulating mature B cells and antibody production, which have been linked to an IBD phenotype (65). Examples include agammaglobulinemia, X-linked agammaglobulinemia (XLA) (73), common variable immune deficiency (CVID), and IgA deficiency, a complex and heterogeneous disease, with the responsible mutations known for only a minority of cases (74). The relationship between B-cell defects and intestinal disease may reflect changes to the microbiome because of the lack of selective pressure (75), altered immune tolerance, increased microbial translocation, compromised signaling within the gastrointestinal tract, or stimulation of an aberrant response because of active infection (76–79). Other gene defects that can lead to lymphocyte dysfunction, CVID, and IBD phenotypes include *CTLA4* and *LRBA* (lipopolysaccharide [LPS]-responsive and beige-like anchor protein) (80). *CTLA4* deficiency, while phenotypically very heterogeneous, can present with lymphadenopathy, splenomegaly, and lymphocytic infiltrate of the gut (as well as the brain and lungs) (81,82). Both heterozygous mutations (dominantly inherited) and autosomal recessive inheritance have been identified in patients with intestinal disease and immune dysregulation (83,84). CTLA4 is a negative regulator of T-cell-mediated immune responses, and essential for the function of regulatory T cells (Tregs). It plays a critical role in immune homeostasis (84). LRBA controls the intracellular trafficking and degradation of CTLA4 as well as other immune effector molecules. Loss of function of *LRBA* results in multiple defects in immune cell populations leading to a VEO-IBD phenotype (80).

Wiskott-Aldrich syndrome (WAS) results from a loss-of-function mutation in Wiskott-Aldrich syndrome protein (*WASP*), and is characterized by abnormal lymphocyte function leading to systemic autoimmunity and recurrent infections (85). Both B- and T-cell responses are ineffective and patients can exhibit thrombocytopenia, eczema, immune deficiencies, and intestinal inflammation (86). The intestinal phenotype in patients with VEO-IBD with WAS is often exclusive colonic disease. In addition to thrombocytopenia, these children can have other associated systemic autoimmunity.

Genetic Variation Resulting in Autoinflammatory Disorders

Several autoinflammatory conditions can lead to an inflammatory bowel disease phenotype that most frequently presents at a very young age. These include mevalonate-kinase deficiency (Hyper IgD) (87), mutations in *NLRC4*, (8,88) familial Mediterranean fever (FMF) with MEFV mutations (89,90), Hermansky-Pudlak syndrome (91), Hyper IgE syndromes (92) and X-linked lymphoproliferative syndrome (types 1 and 2) (3,4,93,94). Approximately 20% of patients with X-linked lymphoproliferative syndrome, with loss-of-function defects in the gene X-linked inhibitor of apoptosis protein (*XIAP*), present with IBD, particularly VEO-IBD (95). *XIAP* is involved in NOD2-mediated NFκB signaling, and therefore, these patients may have an impaired ability to sense bacteria (96). In addition, as an inhibitor of apoptosis, *XIAP* prevents apoptosis of activated T cells, thus allowing for expansion and survival of T cells in response to pathogens (96,97). In XIAP deficiency, however, the inability to clear pathogens leads to a hyperinflammatory state, with increased production of cytokines

and ultimately an IBD phenotype (95,96). Children with these mutations can present with severe colonic and perianal fistulizing disease (3,98) and, of great concern, would be prone to fatal hemophagocytic lymphohistiocytosis in the setting of infection, most typically EBV (98).

TRIM22 has recently been identified as a causal single gene defect in VEO-IBD patients, with mutations resulting in impaired NOD2 binding and signaling, and leading to a phenotype of severe perianal disease and granulomatous colitis (99). TRIM proteins are important components of both the innate and adaptive immune system, including cell proliferation, apoptosis, and autoimmunity. Defects in these proteins are involved in malignancies, autoimmune disease, FMF, and Opitz syndrome type 1. Monogenic defects in *TRIM22* can result in VEO-IBD and can play a role in older onset disease as well (99).

EVALUATION

The goal of a diagnostic evaluation in VEO-IBD is to identify children who will benefit from nonstandard therapies or who are at risk of non-GI complications that need to be monitored. The evaluation, therefore, constitutes multiple facets and a thorough history, including family history, physical examination, endoscopic evaluation, and pathologic review are essential. At the dawn of the era of precision medicine, we can expect that in the near future, there will be clear biomarkers to guide treatment. At this time, the early evaluation is focused on identifying and defining children with a genetic basis of their VEO-IBD because for that subset of children, therapy can be directly targeted to the dysfunctional pathway. As mentioned above, in the small number of cohorts where the frequency of single gene defects causing VEO-IBD has been performed, the frequency appears to be 15% to 20% (24–26). Therefore, the current strategies are focused on identifying this subset, which we will refer to as children with monogenic VEO-IBD. This Position Paper provides recommendations regarding, which tests may be appropriate for the gastroenterologists to perform and which require more extensive immunological and genetic training.

Aspects of the history, which can be particularly useful in the setting of VEO-IBD include age of onset, with the earliest ages of onset being more strongly associated with monogenic causes. A history of folliculitis, dermatitis, significant infections, and associated autoimmunity are critical in defining a differential diagnosis. A history of neonatal onset perianal disease, fistulas, and diarrhea should prompt an evaluation for an IL-10R defect. A history of early-onset infection with or without perianal disease, and intestinal symptoms should lead to investigation of CGD and XIAP deficiency. CGD is one of the more common monogenic forms of VEO-IBD, and can manifest with discoid lupus in the mothers who are X-linked carriers and an infectious susceptibility for the child (100). The testing for these immune deficiencies is relatively straightforward and because of the consequences of these findings, should be performed on all neonatal onset and early-onset disease. As treatment of patients with CGD with anti-tumor necrosis factor (TNF) alpha antibodies is contraindicated (101), it is necessary to obtain the test for this immune deficiency early on. XIAP can lead to the sequale of hemophagocytic lymphohistiocytosis (HLH), and therefore should also be identified. Other monogenic disease can present in infancy with HLH, or develop HLH later in childhood after the diagnosis of VEO-IBD is made (102,103). This one diagnosis of HLH conveys the importance of collecting information broadly when the child presents and continues to collect important historical updates on the child and the family over time, such as infection history, if there is no clear etiology initially. Although the family history is often more extensive in early-onset IBD overall, a clear family history suggesting an autosomal recessive inheritance pattern, an X-linked pattern or even autosomal dominant inheritance is always a red flag for a monogenic form of VEO-IBD. In considering the family history, it is important to recognize that family members with HLH, arthritis, susceptibility to infections, and malignancy should be noted. Some immune dysregulation conditions do not have the same phenotype in every affected family member, but instead display pleomorphic autoimmunity with or without susceptibility to infection.

A physical examination is central to every pediatric visit. In the setting of VEO-IBD, the physical examination should focus on signs of acuity of the disease, such as pallor and tender abdomen. It is also critical to specifically evaluate for perianal disease, folliculitis, arthritis, and growth. Certain monogenic forms of VEO-IBD can be associated with splenomegaly or adenopathy (8,105). Therefore, a focused physical examination can be highly revealing in this setting.

A standard comprehensive laboratory evaluation should be performed by the pediatric gastroenterologist, including complete blood count, comprehensive metabolic profile, and inflammatory markers. A CBC can be very informative beyond the usual findings expected in IBD and can point to monogenic defects. Defects involving neutrophils can be associated with VEO-IBD, and neutropenia as well as leukocytosis (seen in leukocyte adhesion deficiency) can be seen in some cases. Markedly elevated inflammatory markers can be seen in hyperinflammatory defects, such as XIAP and NLRC4, as well as others. Additional testing that is critical in the very young child includes a comprehensive immunologic evaluation. A basic screen should be performed by the pediatric gastroenterologist who is performing the initial evaluation; however, abnormalities should prompt a full evaluation by an immunologist. Due to the potential complexity of infantile onset disease and the need for more in depth immunology expertise in the interpretation of studies performed in this age group, these infant cases should be cared for by a team including a pediatric gastroenterologist and pediatric immunologist.

The initial immunological studies that should be performed on all patients with VEO-IBD includes evaluation of humoral immunity and antibody deficiency. These studies can detect selective antibody deficiencies, such as IgA deficiency, or agammaglobulinemia leading to lack of mature B cells and absent IgM, IgG, and IgA, or the combined T-cell and B-cell defects described above. Therefore, a patient with VEO-IBD should have immunoglobulins (IgG, IgA, IgM, IgE) and vaccine titers (if the child is old enough to have been immunized), which will look for defects in memory, performed. The initial immunological screen should also include a neutrophil respiratory burst assay to evaluate for CGD. The test that is most widely available is the dihydrorhodamine (DHR) test, which is a flow-based assay with a very rapid turnaround time. It does rely on living neutrophils to be accurate, and therefore, it cannot be run when there is significant neutropenia. It is also important to account for the short half-life of neutrophils, that is, 18 hours, and the impact of extreme temperatures and shipping time on neutrophil survival. Other screening tests include evaluation for XIAP, a flow cytometry-based assay, which should generally always be performed in infantile onset disease, particularly male patients. There are a small number of patients with XIAP deficiency who may have normal production of protein but absent function; therefore, if the suspicion is high, targeted gene sequencing is always recommended.

The following studies should be performed in collaboration with pediatric immunology: Lymphocyte subset analyses can be very informative and collaboration with an immunologist with experience in VEO-IBD can help guide the extent of lymphocyte subset profiling that is appropriate in the individual child. This is particularly critical, because while the majority of the known

monogenic defects have an immunologic phenotype that is demonstrable, the key findings in each disease are highly diverse. These studies can detect T-cell defects by assessing T-cell subset frequencies, B-cell maturation by assessing the presence and frequency of switched memory B cells and combined defects. Furthermore, defects in cytolytic killing (including HLH genes) can be detected as well. This approach will unquestionably identify some proportion of patients with monogenic etiologies of their VEO-IBD.

Phenotype-specific Studies

Further gene-specific studies also should be performed and interpreted in collaboration with a pediatric immunologist, and will be directed by the patient's phenotype. For example, patients who present in the neonatal period with severe intestinal and perianal disease should undergo evaluation for IL-10/IL-10R defects. The assay for IL-10R defects. which detect lack of IL-10 inhibition to lipopolysaccharide, will confirm receptor mutations (but will not validate IL-10 ligand defects). In some patients, the presentation of systemic inflammation, high inflammatory markers, and in some cases, a sepsis-like picture, may suggest a defect in the cytotoxic T cells, similar to what is seen in HLH, and measuring CD107a externalization is a widely available screen for this category of disorders.

Genetic Evaluation

Although the above evaluation is vital to determine the extent of disease and determine the immunophenotype, genetic sequencing is often necessary to identify the specific monogenic forms of VEO-IBD, or to confirm a suspected defect. Targeted sequencing panels have been developed, but the sensitivity of these panels has not been rigorously tested. Nevertheless, they represent a reasonable approach to test for the more common monogenic forms of VEO-IBD. Targeted panels should be performed first in cases of infantile onset IBD, when the phenotype is consistent with a known defect, history of consanguinity, and abnormal immunology studies. The current commercially available VEO-IBD-targeted panels have some differences in their analytical pipeline and in the number of genes that are sequenced. Some centers have developed panels that will reflex to WES if the targeted panel is negative.

As both the technology and bioinformatics analyses have improved, WES has already played an important diagnostic role in VEO-IBD. Currently, WES is most often performed in the setting of a negative targeted panel, however, there are select cases in which WES may be indicated instead of a targeted panel, such as those patients who present with a phenotype that is not previously described. In addition, WES has been performed under research protocols in cases when a targeted panel is not able to be obtained or covered by insurance; however, any finding made in the research setting must be then validated in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Whole genome sequencing (WGS) will likely play an increasing central role in the identification of congenital conditions in general, including VEO-IBD, as advances improve, similar to WES, and as it becomes more cost-effective. At this time, WGS should be reserved for cases in which WES is negative, yet there remains a high suspicion of a monogenic defect given the young age of onset, disease severity, family history, and complex phenotype including associated autoimmunity. Given the large amount of data generated and complexity of the data, interpretation of WES, and certainly WGS, typically requires a team that includes bioinformaticians, geneticists, immunologists, and often experts in VEO-IBD. Very frequently, partially because of the rapid pace of insight into the disease and identified defects, a previously reported *VEO-IBD* gene is not detected on the initial genetic study. Rather, a variant that has not been previously validated as causal for VEO-IBD (known as variant of unknown significance: VOUS) may be detected on WES or WGS and further investigation is necessary. As part of the investigation, mode of inheritance is critical, thus trio analysis, including both parents whenever possible, will provide the most valuable information. Additionally, the potential pathogenicity and frequency of the variant in the healthy population (a common variant is unlikely to be causative of your patient's phenotype) must be considered when determining the relevance of a candidate variant.

Table 1 lists a number of common causes of VEO-IBD and some of the clinical and laboratory features that are seen. The disorders are categorized in 3 tiers according to the frequency of IBD within that condition. Within each tier, the genes are listed alphabetically. For some of these conditions, the immunologic phenotype evolves over time and may not be obvious early in the course of disease. In general, the gene defects that have been detected with the highest frequency in patients with VEO-IBD can prompt specific targeted therapies that include: defects that lead to CGD (NADPH complex defects), *IL-10R* and *XIAP*. All of these defects should prompt a HSCT evaluation.

Endoscopic and Histologic Evaluation

As with all patients who present with signs and symptoms consistent with IBD, endoscopy and colonoscopy remain the gold standard for diagnosis of VEO-IBD. Even in the young child, a full colonoscopy with ileal intubation should be performed. Video capsule endoscopy may be helpful, as in older onset IBD; however, the size of the patient in VEO-IBD often limits use of the study.

The setting of VEO-IBD is one of the circumstances in which a true partnership with the pathologist is required. Beyond the description of chronic inflammation and changes associated with IBD, it is critical to identify (if present) specific features that can be clues to a monogenic form of VEO-IBD. Pathologic features that seem to be associated with monogenic defects include eosinophilic infiltrates, villous atrophy, apoptosis, and increased intraepithelial lymphocytes. Apoptosis can be a clue that there may an underlying genetic defect and can look similar to graft-versus-host disease (GVHD). Apoptosis is markedly increased in the defects of telomere maintenance (dyskeratosis cogenita) (159), TTC7A, SCID, and certain other primary immunodeficiencies. Another important pathologic feature is villous blunting or villous atrophy with a lymphocytic infiltrate. This is typically considered to be a manifestation of celiac disease; however, gluten nonresponsive villous blunting is a strong indication of some of the T-cell dysregulation disorders. This combination of villous blunting/atrophy with a lymphocytic infiltrate is classically seen in immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, or IPEX, and a subset of patients with common variable immunodeficiency, and lymphocytic colitis (seen in some T-cell defects) (160). In the setting of villous blunting and certainly when there is evidence of secretory diarrhea, it is important for the pathologist to evaluate for some of the congenital enteropathies that may or may not include an element of inflammation. Congenital chloride diarrhea, associated with mutations in SLC26A3, is an example of this (110). These congenital enteropathies can be diagnosed using special stains and electron microscopy. Pathologic features associated with CGD can include granulomas, pigmented macrophages and increased eosinophils. Hermansky Pudlak syndrome and related disorders of organelle formation can also demonstrate granulomas and pigmented macrophages (161–165). Overall, granulomas are not seen more frequently in VEO-IBD as compared with older-onset IBD (166).

TABLE 1. Key evaluation features of the more common monogenic forms

Gene	Disease	Pathogenic inheritance	Phenotype	Immunologic features
Defects in epithelial barrier function				
ADAM17 (32,105,106)		AR	Staphylococcal infections Psoriasiform erythroderma, pustules, broken hair, abnormal nails, diarrhea	Slightly low TNF response to LPS, in PBMCs, and T cells
IKBKG (92,107)	NEMO	XL	Infections Hypodontia, poor sweat, thin hair, frontal bossing, poor growth, and diarrhea	Poor titers, low NK function, abnormal TLR responses, low memory B cells
GUCY2C (38)	Familial diarrhea	AD GOF	Ileal obstruction, adhesions, esophagitis, electrolyte abnormalities Dilation of small intestine	Unknown
TTC7A (5,108–110)	Hereditary multiple intestinal atresia	AR	Intestinal atresia Dermatitis, alopecia	Low T cells, absent low TRECs
SLC26A3 (110–112)	Congenital chloride diarrhea	AR	Onset of secretory diarrhea at birth, inflammation occurs later in life	
COL7A1 (113)	Epidermolysis bullosa	AR	Recurrent blistering or erosions, esophageal stricture, anal fissures and stenosis, enteropathy, hair and nail abnormalities	
FERMT1 (35)	Klinder syndrome	AR	Recurrent skin blisters, esophageal strictures, colonic involvement	
Defects in adaptive immunity				
IL10 (54,114)	IL-10 deficiency	AR	IBD onset near birth, folliculitis, perianal disease, arthritis, increased risk of lymphoma, particularly large B-cell lymphoma	Defective IL10 signaling, dysfunctional Tregs
IL10RA, IL10RB (2,115) (2,55,115)	IL-10RA/RB deficiency	AR	IBD, onset near birth Folliculitis, perianal disease, arthritis, increased risk of lymphoma, particularly large B-cell lymphoma	Dysfunctional Tregs, reduced frequency of $T_{FH,}$ lack of IL-10 suppression of LPS response
BTK (115)	X-linked agammaglobulinemia, Bruton's agammaglobulinemia	XL	Infections, small tonsils, diarrhea	Very low B cells and immunoglobulins
DKC1 (116)	Dyskeratosis congentia	XL	Microcephalic, cerebellar hypoplasia, IUGR, small, nail dystrophy, aplastic anemia, and bone marrow failure	Progressive decrease in B and T cells, low NK cells
DOCK8 (117,118)	Hyper-IgE syndrome	AR	Presents in infancy, cutaneous viral, fungus, staphylococcus infections, eosinophilia, eczema, poor growth, diarrhea with or without blood	Low T cells and poor proliferation, poorly function Tregs, very low memory B cells, poor peripheral B-cell tolerance, low NK cells
ICOS (119)	Common variable immunodeficiency	AR	Infectious enteritis, founder effect along the Danube river, small bowel disease prominent and nodular lymphoid hyperplasia of GI tract Splenomegaly	Absent class switched memory B cells, low TFH, poor germinal centers in lymph nodes, low IgG
ITGB2 (120)	Leukocyte adhesion deficiency	AR	Severe infections, delayed separation of umbilical cord gingivitis, scarring (poor wound healing), poor growth, diarrhea	High WBC/ANC, low CD18 expression, reduction of factor XIIIa+ DC in lymph node
ZBTB24 (6)	Immunodeficiency with centromeric instability and facial anomalies, ICF2	AR	Diarrhea, facial dysmorphic features, developmental delay, bacterial/opportunistic infections, cytopenias, malignancies, multiradial configurations of chromosomes 1, 9, 16	Decreased B cells, T cells can be decreased or normal
*PIK3CD*P100 (121)		AD GOF	Infections, PSC, herpes, lymphoma Bronchiectasis, adenopathy, HSM, nodular lymphoid hyperplasia, EBV viremia	High IgM, low IgG, low CD4/CD45RA, EBV, viremia
PIK3R1 P85 (122)		AD LOF	Severe bacterial infections, insulin resistance, short stature, nodular lymphoid hyperplasia	High IgM, low IgG, low CD4/CD45RA,

TABLE 1. (*Continued*).

Gene	Disease	Pathogenic inheritance	Phenotype	Immunologic features
PTEN (123)		AD	Autoimmunity: thyroiditis, autoimmune hemolytic anemia; hamartomas, lymphoproliferation, adenopathy, large tonsils, macrocephaly, developmental	low IgG
ITCH (124)		AR	Autoimmune inflammatory cell infiltration of lungs, liver, gut, growth failure, diarrhea, hepatosplenomegaly, enteropathy, dysmorphic facial features	T-cell abnormalities, increased Th2, decreased switched memory B cells
RAG1 RAG2 (67,68,125)	Omenn syndrome/SCID	AR	Recurrent severe infections, chronic diarrhea, failure to thrive, variable intestinal involvement	Very low T and B cells
ZAP70 (126)	Omenn syndrome/SCID	AR	Recurrent severe infections, chronic diarrhea, failure to thrive, variable intestinal involvement	Low CD8+ T cells, normal CD4, but poor function
IL7R (71,125)	Omenn syndrome/SCID	AR	Skin inflammation, variable intestinal involvement	Very low T cells
WASP (85,127)	Wiskott-Aldrich syndrome	XL AR LOF	Thrombocytopenia with small platelets, recurrent bacterial and viral infections, eczema, bloody diarrhea, lymphoma, autoimmune disease	Poor T/B/NK function,progressively lower number T cells
ARPC1B (128)		AR LOF	Thrombocytopenia with normal size platelets, recurrent invasive infections, eczema, bloody diarrhea, eosinophilia	Poor T/B/NK function
TGFBR1 (129)		AD	Aneurysms, also affects epithelial barrier Cleft palate/uvula, hypertelorism, arachnodactyly, pectus, joint laxity	Eosinophilic colitis, high IgE, high eosinophils
TGFBR2 (129)		AD	Aneurysms, also affects epithelial barrier Cleft palate/uvula, hypertelorism, arachnodactyly, pectus, joint laxity	Eosinophilic colitis, high IgE, high eosinophils
Impaired regulatory T cells				
FOXP3 (130–133)	Immunodysregulation polyendocrinopathy x linked (IPEX)	XL	Onset near birth diarrhea, with or without blood, autoimmunity: psoriaform dermatitis, alopecia, endocrinopathies: type 1 diabetes	Low regulatory T cells, elevated IgE, IgA
CTLA4 (81–84)		AD	Autoimmunity, autoimmune cytopenias, recurrent infections, interstitial pneumonitis, lymphocytic infiltration	Low immunoglobulins, low switched memory B cells, low CD4 T cells
LRBA (82,84)	LRBA deficiency	AR	Infections, interstitial pneumonitis, autoimmunity (idiopathic thrombocytopenia, autoimmune hemolytic anemia, type 1 diabetes, etc) and IBD	Low immunoglobulins, low switched memory B cells, low CD4 T cells
STAT1 (134)	STAT1 deficiency	AD GOF	Pleomorphic autoimmunity, candida, other infections Poor growth	Low NK cells, low IgA
STAT3 (135–137)		AD GOF	Lymphoproliferation, recurrent infections, pleomorphic autoimmunity: diabetes, thyroid, poor growth, eczema	Decreased B and T cells, low regulatory T cells, low IgG
STAT5b (138)		AR	Growth failure, IGF-I deficiency, chronic pulmonary disease, dysmorphic features, autoimmunity	Modestly decreased T cells
IL-2RB (139)		XL	Enteropathy, eczema, autoinflammatory disease, lymphoproliferation	Normal to decreased T cells, impaired T-cell profileration
IL21R (140,141)		AR	Recurrent infection, *Pneumocystitis jiroveci*, Cryptosporidia, cholangitis	Low cytokine production, low switched memory B cells
IL21 (140,141)		AR	Severe early-onset colonic disease, recurrent sinopulmonary infections	T cells poor function, low B cells, low switched memory B cells, low IgG
Autoinflammatory and Hyperinflammatory defects				
SKIV2L (142,143)		AR	IUGR, FTT, trichorrhexis nodosa, frontal bossing, villous atrophy	Low immunoglobulins, low T cells
TTC37 (144)		AR	IUGR, FTT, trichorrhexis nodosa, frontal bossing, villous atrophy	Low immunoglobulins, low T cells
RTEL (145)	Regulator of telomere elongation (RTEL1) deficiency	AR or AD	IUGR, FTT, microcephaly, fine hair, hyperpigmentation of skin, palmar hyperkeratosis, premalignant oral leukoplakia, pancytopenia, myelodysplasia, +/-, apoptosis in biopsy	Low NK cells
STXBP2 (146)		AR	Fever, hepatosplenomegaly, cytopenias, HLH	Poor NK function, low IgG

TABLE 1. (*Continued*).

Gene	Disease	Pathogenic inheritance	Phenotype	Immunologic features
XIAP (3,4,104,147)	XIAP deficiency (XLP2)	XL	Infantile onset IBD, EBV infection, hepatitis, HLH, splenomegaly	Normal or increased activated T cells, low/normal iNK T cells, normal or reduced memory B cells, hypogammaglobulimemia
NLRC4 (8,88)	NLRC4-MAS (macrophage-activating syndrome) or familial cold autoinflammatory syndrome 4	AD	Severe early onset IBD, macrophage activation syndrome, episodic inflammation	-
MEFV (89,90)	Familial Mediterranean fever	AR	Periodic fever, founder effect in Mediterranean Oral ulcers, arthritis, serositis, rash, enteropathy	
MVK (148,149)	Mevalonate kinase deficiency (hyper IgD syndrome)	AR	Nausea, fever episodically, abdominal pain Adenopathy, oral ulcers, arthritis, splenomegaly, enteropathy, perianal disease	Elevated IgD, increased urine mevalonic acid
HPS1 (150–152)	Hermansky-Pudlak syndrome type 1	AR	Bleeding disorder, recurrent infections, oculocutaneous albinism, pulmonary fibrosis, colitis, can develop HLH	
HPS4 (153)	Hermansky-Pudlak syndrome type 4	AR	Bleeding disorder, recurrent infections, oculocutaneous albinism, pulmonary fibrosis, colitis, can develop HLH	
TRIM22 (99)		AR	Granulomatous colitis, severe perianal disease	
CASP8 (154)		AR	Recurrent bacterial and viral infections, especially sinopulmonary infections, hypogammaglobuilnemia, enteropathy Lymphadenopathy, splenomegaly	Slightly increased T cells
PLCG2 (155,156)	PLAID, PLAID (PLCg2-associated antibody deficiency and immune dysregulation) or familial cold autoinflammatory syndrome 3 or APLAID (c2120A>C)	AD	Pleomorphic inflammation, cold urticaria, dermatitis	Low immunoglobulins, low switched memory B cells
Phagocytic and NADPH oxidase complex defects				
CYBA P22phox (46,100)	Chronic granulomatous disease	AR	Infections, autoinflammatory phenotype	Low DHR, reduced switched memory B cells, low T cells
CYBB Gp91phox (46,100)	Chronic granulomatous disease	XL	Infections, autoimmunity, maternal discoid lupus	Low DHR, reduced switched memory B cells, low T cells
NCF1 P47phox (45,46)	Chronic granulomatous disease	AR	Infections, autoinflammatory phenotype	Low DHR, reduced switched memory B cells, low T cells
NCF2 (45,46) P67phox (157)	Chronic granulomatous disease	AR	Infections, autoinflammatory phenotype	Low DHR, reduced switched memory B cells, low T cells
NCF4 P40phox (42)	Chronic granulomatous disease	AR	Infections, autoinflammatory phenotype	DHR slightly low only
G6PC3 (29)	Congenital neutropenia	AR	Cardiac anomalies, urogenital defects, IUGR Superficial vessels enlarged	Neutropenia, intermittent thrombocytopenia, lymphopenia in severe forms
SLC37A4 (158)		AR	Hypoglycemic episodes Hepatomegaly	Neutropenia

ANC = absolute neutrophil count; DC = dendritic cells; DHR = dihydrorhodamine; EBV = Epstein-Barr virus; FTT = failure to thrive; GI = gadtrointestinal; GOF = gain-of-function mutation; HLH = hemophagocytic lymphohistiocytosis; IBD = inflammatory bowel disease; Inheritance is given as AD = autosomal dominant, AR = autosomal recessive; IUGR = intrauterine growth retardation; LPS = lipopolysaccharide; y natural killer; PBMCs = peripheral blood mononuclear cells; PSC = primary sclerosing cholangitis; SCD = severe combined immunodeficiency; TFH = T follicular helper cells; TLR = toll-like receptor; TNF = tumor necrosis factor; Trecs = T cell receptor excision circles; WBC = white blood cells; XL = X-linked.

When detected, however, in the very young child, an underlying immune-mediated process should be considered.

Radiology Studies

Radiologic imaging is a critical component of the evaluation for patients with IBD. The optimal modality to diagnose and monitor disease in the young child depends on the specific center's resources and experience. With advances in sequencing technology, upper gastrointestinal series with small bowel follow-through study are being used less frequently in pediatric IBD. Ultrasound, MRE, and CT are now part of the management at most centers. In the young child, however, MRE can be difficult, therefore, ultrasound of the small bowel by an experienced radiologist can be used to delineate the extent of disease.

THERAPEUTIC STRATEGIES FOR CHILDREN WITH VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE

VEO-IBD has become a model for the change in the treatment paradigm across all IBD to a more personalized precision medicine approach. Though there is a paucity of data and large clinical trials, the higher rate of monogenic defects makes this population ideal for individualized treatment. Currently, although much of the data on therapy comes in the way of case reports or small case series, it has become clear that the therapeutic approach for children with VEO-IBD should focus on the individual patient's history and diagnostic evaluation. Treatments targeted to one of the identified causative pathways may require use of agents not part of the standard IBD arsenal used for older children and adults. It is, therefore, extremely useful to collaborate with an immunology team with experience in treating VEO-IBD or a center with the resources and experience in caring for these children. In cases in which there are no genetic or immunologic defects identified, therapy is often similar to older patients. The approach discussed below is by no means an exhaustive description of therapies for children with VEO-IBD, but rather illustrates the different modes of treatment utilized and provides a framework to assist in the care of VEO-IBD and guidelines of when to refer to a treatment center.

GENERAL THERAPEUTIC APPROACH FOR VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE

Though genetic testing is important, many patients remain without an identified causal variant. Often, working with a multidisciplinary team and an evaluation at a center with experience will allow for an effective therapeutic plan. Although some children may have a mild disease course and respond to minimal therapy, a substantial subset of children with VEO-IBD will have a less robust response to conventional therapies and may require escalated dosing strategies or a different approach altogether. A more severe or refractory course may be indicative of underlying disease severity or different drivers of disease, such as a monogenic etiology that has not yet been detected.

PRECISION THERAPY TO SPECIFIC GENETIC DEFECTS

As noted previously, genetic testing through WES or a targeted gene panel in order to identify a causal defect is highly recommended in most cases of VEO-IBD. Detection of the disease-causing variant may allow for the appropriate therapy to be chosen. The landmark discovery of loss-of-function mutations in IL-10 and IL-10 receptor (IL-10R) in a cohort of patients with infantile onset IBD led to the use of allogeneic HSCT for induction of remission; this can be life-saving (2). These children typically presented with disease within the first 3 months life. Five of the 16 patients in this cohort received HSCT with successful achievement of clinical remission in 4 patients at 2 years posttreatment and improvement in the fifth patient (2). Without HSCT, these patients are at risk of developing large B-cell lymphoma (56), therefore, it is critical to identify these mutations and proceed to transplant.

Similar to the treatment of IL-10 deficiency, HSCT has been proven to curative, and in some cases, life-saving, for children with VEO-IBD with other identified gene defects. Some of these mutations, including *XIAP* and *STXBP2,* are associated with the risk of developing hemophagocytic histocytosis (HLH) (95,96,167). T-cell and T-regulatory cell defects, B-cell defects, and combined defects have also been successfully treated with HSCT. A few examples include FOXP3 deficiency (168), IL2RB defects (147), DOCK8 immunodeficiency (169), RAG1 and RAG2 defects (125), STAT1 (170), PIK3CD (171), and SCID (172), and CVID (173) pathways.

Targeted medical therapies can be used in a variety of identified gene defects. These therapies are used as maintenance therapy, and in some cases, as a bridge to HSCT. Some examples of monogenic defects with identified therapeutic targets include *CTLA4* or *LRBA* defects. Therapies that can inhibit the hyperactive T-cell signaling in these defects through inhibition of CD28 pathways (which competes with CTLA4) or replaces CTLA4 by CTLA-4-Fc have proven to be successful. Abatacept, a *CTLA4* agonist, has been used to treat patients with these defects (84). Rapamycin has also been used successfully in these patients. Both drugs have been used in other defects that involve loss of Tregs or unchecked T-cell activation, such as *FOXP3* and *PIK3CD* mutations as a maintenance as a bridge to HSCT (168). They have also been used in other cases of VEO-IBD that are driven by a lymphocytic process. Anti-IL18, in combination with IL-1 blockade, is an effective approach for patients with mutations in *NLRC4* (7), and has potential benefits in other hyperinflammatory disease that lead to inflammasome activation with overproduction of IL-18, such as *XIAP*.

Identification of the causative gene defect is also critical in avoiding therapy that is potentially harmful. For example, in CGD, HSCT is now considered curative, but more optimized use of steroids to treat inflammatory complications and the use of antibiotics to treat infections while awaiting transplant is common (40). Conversely, because of further immunosuppression risks, anti-TNFα therapy is contraindicated and has been associated with adverse outcomes, including death (101). Interferon gamma (IFN-gamma) has been used to treat CGD long-term, with the thought that it improves the oxidative capacity of neutrophils, increases the production intracellular of nitrous oxide, and induces autophagy (174). Anti-IL1 therapy, anakinra or canakinumab has also been used as bridge therapy for patients awaiting transplant (175). These drugs have also been used for hyperinflammatory defects with overproduction of IL-1, or in neutrophilic predominant disease.

MEDICAL THERAPY

As in older children, medical and surgical treatments remain the mainstay of VEO-IBD management. Due to the relatively recent awareness of VEO-IBD, there are limited studies on therapeutics in this population. This Position Paper will include those therapies that have been published in the IBD or immunology literature and will review treatment options and challenges for this population. A further consideration is that as these children are often started on therapy at a very young age, immunization schedules may need to

be altered. See below for recommendations on vaccinations with immune suppression.

Immunomodulatory Therapy

Immunomodulatory therapy, such as methotrexate and thiopurines, can be used as monotherapy in some patients with VEO-IBD, or as dual therapy when used in conjunction with a biologic therapy (176). Azathioprine/6-mercaptopurine (AZA/6-MP) has been utilized less since the identification of its link to hepatosplenic T-cell lymphoma (HSTC). Further, a recent large multicenter center study that looked at long-term outcomes of pediatric patients from 2007 to 2016 found that thiopurine exposure was an important risk factor for the development of malignancy or HLH in pediatric patients with IBD (177). When thiopurines are used as therapy in patients with VEO-IBD, higher dosing is often required to obtain therapeutic levels. A retrospective review of 30 patients with VEO-IBD demonstrated that patients who received a standard dose of 2 to 3 mg/kg/day of azathioprine or equivalent doses had a median 6-thioguanine level of 154, with no patients being in therapeutic range (178). Only 5 patients actually achieved therapeutic ranges of 6-TGN levels, all with doses of AZA/6MP in the >3 mg/kg/day AZA equivalent range, and some reaching 5.1 mg/kg/day. This finding may be because of age-related pharmacokinetics or decreased bioavailability. Another possibility may be because of the ability of azathioprine to suspend within the solution, and hence parents should be advised to mix the suspension well or encourage their children to attempt to swallow the pill. For these reasons, if this therapy is chosen, it is advisable to closely monitor thiopurine metabolites, especially when children grow older and when changing to the pill form of drug. Although there are no studies looking at safety and efficacy of methotrexate specifically in VEO-IBD, this drug is also used in this population. Dosing is based upon body surface area, and therefore, optimization of therapeutic levels may be less of an issue as compared with the thiopurines.

Biologic Therapies

Biological medications have become one of the most important components of adult and pediatric IBD therapy. A less robust response to these therapies, however, has been observed in patients with VEO-IBD. A review of 33 children with VEO-IBD showed maintenance of infliximab (IFX) therapy at 1, 2 and 3 years of 36%, 18%, and 12%, respectively. Nine percentage of patients demonstrated response and were steroid free at 1 year (179). This is well below the levels of infliximab therapy maintenance seen in the REACH trial of 93%, 78%, and 67% at 1, 2, and 3 years (180). Similar findings of a less robust response to IFX in children with VEO-IBD compared with older children was seen in a recent study of 42 patients with VEO-IBD compared with 130 children with older onset IBD. In this study, 42.9% children with VEO-IBD discontinued IFX before week 14, compared with 7.7% of older onset IBD ($P < 0.01$). These findings are reflective of the poorer response to IFX in the very young children as compared with older patients with IBD. The difference in response may be secondary to immune-mediated pathways involved in disease, or because of differences in pharmacokinetics with body surface area and distribution differences in the VEO-IBD age group. Alternative dosing strategies, such as starting with infliximab 10 mg/kg, more frequent infusions, and optimization of the regimen based on drug levels may improve long-term durability of the treatment regimen, although this requires further investigation. Similar strategies can be used with other forms of anti-TNF therapies, particularly with adalimumab where therapeutic drug monitoring can also be performed.

There is no published data regarding the use of anti-integrin antibody therapies, including vedolizumab and natalizumab, in the VEO-IBD population. The risk of JC virus and progressive multifocal leukoenceophalopathy have limited the use of natalizumab. Anecdotal reports have shown response to vedolizumab in children with VEO-IBD who have lymphocytic predominant disease (similar to rapamycin); this agent has also successfully been used in CTLA4-associated enteropathy (181). Similarly, there are no published data on the efficacy of ustekinumab in patients with VEO-IBD, although it has been used in few cases with varying degrees of success.

Other therapies, biologic, small molecules, and immunomodulators, are being studied in this population, and over time, we anticipate a therapeutic approach that is different than that employed for pediatric, adolescent, and adult IBD.

SURGICAL INTERVENTION

Due to the often refractory nature of the disease, surgical intervention can be a necessary component of the treatment course in VEO-IBD patients. A large retrospective study showed that VEO-IBD patients were more likely to require surgery (diverting ostomy and colectomy) (15). Surgical rates have been reported higher in other smaller series with one noting surgical rates of 50% for patients with onset before 1 year of age and 29% for those with onset after 1 year of age (15,21).

As there is a predominately colonic distribution of disease in this population, colectomy or ileal diversion are the most common surgeries performed. Although colectomy followed by ileal pouch-anal anastomosis is often curative in patients with severe UC, there is a high risk of complications, such as pouchitis, stricture formation, and fistula in patients with CD. As discussed above, the predominantly colonic presentation in VEO-IBD prevents the ability to definitively characterize the disease as CD or UC, particularly as the disease can extend and progress. Therefore, one should exercise great caution before proceeding with colectomy in these patients; colonic fecal diversion by creation of a temporary ileostomy can be an effective alternative management strategy (182). The mechanisms through which ileal diversion promotes colonic healing have not been fully elucidated, but possible factors include elimination of pro-inflammatory elements found in the fecal stream and the benefit of colonocyte ''rest'' (182).

IMMUNIZATION STRATEGY IN VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE

Due to the age of onset of the disease, it is necessary to consider the timing of vaccination during the evaluation and initiation of therapy for children with VEO-IBD. Regardless of choice of immune suppression, avoidance of live vaccines is required. Measles, Mumps and Rubella (MMR), rotavirus, varicella, intranasal influenza, BCG vaccine, oral typhoid, and yellow fever vaccines are all live attenuated vaccines and should be avoided while on immune suppressive medications. The recommendations, after weighing risks and benefits of the current clinical picture, is to avoid immune suppression for at least 1 month for corticosteroid administration and 3 months for azathioprine/6-MP and biological medication (183,184). The timing between immunization and initiative of immunosuppressive therapy should be made in collaboration with an immunology colleague.

CONCLUSIONS

This position paper, while not exhaustive in description of genetic and immune defects and treatments, highlights the complex drivers of disease and necessity to utilize a multidisciplinary team

approach when caring for these children. An individualized and targeted evaluation combining an immunological assessment, the standard IBD evaluation, and genetic studies can lead to life saving therapies for these children. Utilizing WES or targeted panels can improve detection of variants and diagnosis of disease. Treatments guided towards the specific defect, such as HSCT, IL-1 antagonists, and IL-18 blockade can be used if the defect is determined. Additionally, monitoring for potential complications associated with a genetic defect is essential, such as in XIAP, IL-10 gene variants, and CGD. In addition to these monogenic diseases, VEO-IBD has been shown to have a high degree of genetic heterogeneity and the treatment algorithm is based on the individual patient's complete evaluation. Utilizing a collaborative team approach in caring for these patients is essential, and consideration of a referral to a center that has an expertise in this population can be beneficial. Going forward, translational studies looking at the function of newly identified genes and pathways will allow for better mechanistic insight into the role of immune dysregulation in intestinal inflammation and provide an opportunity to expand our ability to deliver true precision medicine to children with VEO-IBD.

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