

## **Very Early Onset Inflammatory Bowel Disease: A clinical approach with a focus on the role of genetics and underlying immune deficiencies**

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Word summary:

Very Early Onset inflammatory bowel disease (VEOIBD) reflects IBD presenting prior to six years of age. We provide an approach to diagnosis and management of patients with VEOIBD, based on expert opinion from members of the VEOIBD Consortium ([www.veoibd.org](http://www.veoibd.org)).

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**Abstract:**

Very Early Onset inflammatory bowel disease (VEOIBD) is defined as IBD presenting prior to six years of age. When compared to IBD diagnosed in older children, VEOIBD has some distinct characteristics including a higher likelihood of an underlying monogenic etiology or primary immune deficiency. In addition, patients with VEOIBD have a higher incidence of inflammatory bowel disease unclassified (IBD-U) as compared to older-onset IBD. In some populations, VEOIBD represents the age group with the fastest growing incidence of IBD. There are contradicting reports on whether VEOIBD is more resistant to conventional medical interventions. There is a strong need for ongoing research in the field of VEOIBD in order to provide optimized management of these complex patients. Here we provide an approach to diagnosis and management of patients with VEOIBD. These recommendations are based on expert opinion from members of the VEOIBD Consortium ([www.veoibd.org](http://www.veoibd.org)). We highlight the importance of monogenic etiologies, underlying immune deficiencies and provide a comprehensive description of monogenic etiologies identified to date that are responsible for VEOIBD.

# **Very Early Onset Inflammatory Bowel Disease: A clinical approach with a focus on the role of genetics and underlying immune deficiencies**

## ***Introduction***

Inflammatory bowel disease (IBD) is comprised of a manifold of diverse diseases that are multifactorial in origin and usually are categorized clinically into Crohn's disease (CD), Ulcerative colitis (UC), and IBD-unspecified (IBD-U) based on phenotypic characteristics. These disorders of chronic intestinal inflammation are thought to develop primarily in genetically susceptible subjects in association with a dysregulated immune response, microbial dysbiosis, and environmental triggers. Very Early Onset IBD (VEOIBD) is defined as clinical manifestations and/or receiving the diagnosis at less than six years of age<sup>1,2</sup>. While genetics play a role in IBD at any age, monogenic etiologies are more highly represented in patients presenting with VEOIBD as compared to IBD diagnosed at an older age. Indeed, a growing number of *causative* monogenic variants have been and are continuing to be identified among patients with VEOIBD, especially within the *infantile-onset IBD* (<2 years old)<sup>1,3-7</sup>. Uhlig et al reported that, while the majority of monogenic IBD cases occur under 6 years, this is a spectrum with a predominance of cases occurring before the age of two<sup>1</sup>. A large proportion of monogenic etiologies reflect underlying primary immune deficiencies (PID), highlighting the importance of a dysregulated immune system in VEOIBD<sup>1,8,9</sup>. The monogenic etiologies of VEOIBD identified to date can be divided into six main (and sometimes overlapping) categories: (1) General immune dysregulation; (2) T and B cell defects; (3) Phagocytic defects; (4) Hyper- and auto-inflammatory conditions; (5) Epithelial barrier dysfunction; and (6) other conditions<sup>1,8,9</sup>. It is important to emphasize that while some patients with VEOIBD have underlying monogenic etiologies, often reflecting PID, the majority (>70-80%) of VEOIBD patients will not have a specific identified causal genetic etiology and are simply a variant of IBD presenting in very young patients<sup>10</sup> (and unpublished results, VEOIBD Consortium, [www.veoibd.org](http://www.veoibd.org)). Unlike older-onset IBD, patients with VEOIBD have a higher rate of inflammatory bowel disease – Unclassified (IBDU) (18-33%) as compared to adult patients (6%)<sup>11,12</sup>. Additionally, a positive family history is also more likely within this group (19–41% compared to 5-10% in adults), supporting an increased genetic contribution<sup>13,14</sup>. Finally, some, but not all, studies have suggested that the VEOIBD group is often resistant to conventional therapy for IBD<sup>15,16</sup>. It is hard to categorize VEOIBD based on standard clinical and histological features of classic polygenic IBD. Multi-disciplinary approaches, including a comprehensive immune evaluation, are important in directing the management of VEOIBD<sup>1,2,17</sup>. In this review, we will summarize the background, clinical characteristics and treatment strategies of VEOIBD, while highlighting the importance of identifying underlying PID.

## ***Definition***

The age cut-off of VEOIBD is currently defined as clinical manifestations and/or being diagnosed prior to 6 years of age. This has its origins in the fact that there is an increase in monogenic etiologies of VEOIBD prior to 6 years old as compared to that diagnosed in older ages<sup>1,2,12,18-20</sup>, though this definition continues to evolve with

increasing knowledge. A sub-category of VEOIBD is *infantile-onset IBD*, reflecting patients diagnosed <2 years old. Some further sub-categorize *neonatal-onset IBD* as that presenting within the first 27 days of life<sup>1,16</sup>.

### ***Epidemiology:***

Epidemiologic data indicates that the incidence of IBD is rising, especially in the pediatric population<sup>21-27</sup>. Currently, it is estimated that 3 million Americans have IBD<sup>28</sup>, and approximately 25% of those patients will develop the disease during childhood or adolescence<sup>29</sup>. A retrospective review of the Canadian population identified that the incidence of childhood-onset IBD is 9.68 in 100,000 children with a prevalence increasing significantly over recent years to 38.25 per 100,000 children<sup>27</sup>. VEOIBD makes up 3-15% of all pediatric IBD<sup>12</sup>. Although relatively rare, it appears, at least in Canada, to be the fastest growing subset of all IBD patients. Among children aged 0-5 years old, the incidence increased most notably (+7.2% per year)<sup>27</sup>. [Ong et al recently published increases in pediatric IBD in Singapore with roughly 20% of their cohort being under 6 years of age at diagnosis \(a higher proportion that referenced in other populations\)](#)<sup>30</sup>. A French study reported that VEOIBD represented 3% of their pediatric population with no increase in VEOIBD over time<sup>31</sup>. While genetics play an important role in this age group, environmental triggers are likely also contributory.

### ***Clinical approach to patients with VEOIBD:***

#### **Multidisciplinary team approach:**

The diagnostic approach and management of infants and young children with VEOIBD is challenging, especially when manifesting a concurrent underlying PID. However, while there is an increase likelihood of monogenic etiologies and underlying PIDs in patients with VEOIBD than in those with older-onset disease, most children with VEOIBD do not have an underlying PID. Given the rarity of IBD in this age group and the challenges in making a diagnosis, pediatric gastroenterologists often feel hesitant to label a young infant/toddler with a chronic inflammatory disease necessitating medical interventions with significant risk profiles. Understandable concerns exist regarding the use of conventional immunosuppressive IBD therapies, especially given potential underlying immune deficiency. There is additional responsibility to assure appropriate vaccination schedule, growth, nutrition and overall health. Care of a patient with VEOIBD should be a coordinated effort of a team of specialists, including, not only gastroenterologists, but also immunologists, geneticists, bone marrow transplant experts, nutritionists, and surgeons, and other specialties depending on the extra-intestinal manifestations. Referral to centers with expertise in this field is often pursued. The following approach and guidelines are based on expert opinion of the tertiary referral centers among our VEOIBD Consortium ([www.veoibd.org](http://www.veoibd.org)).

#### **Distinguishing VEOIBD from more common presentations:**

Patients with VEOIBD can present with a wide variety of symptoms both gastrointestinal and extra-intestinal. Gastrointestinal symptoms include bloody and/or mucus-containing

diarrhea, frequent emesis, failure to thrive, perianal skin tags or fistulas. Systemic symptoms and/or extra-intestinal symptoms include: intermittent fevers, arthritis, arthralgias, folliculitis, uveitis and dermatologic manifestations. Often the initial set of diagnoses considered by the practicing pediatrician or general gastroenterologist are *not* chronic inflammatory bowel diseases, since more common etiologies with similar symptoms are usually considered first, including cow's milk protein intolerance or other food allergies, infections, celiac disease, and inadequate caloric consumption. While it may initially be challenging to distinguish these more common causes of gastrointestinal symptoms from VEOIBD, it is important to keep VEOIBD on the list of differential diagnoses<sup>21,32</sup>, so as not to delay treatment

In patients with chronic diarrhea, infection should be ruled out regardless of age. These include: *Shigella*, *Salmonella*, *Yersinia*, *E. coli*, *Campylobacter*, *Cryptosporidium*, *Giardia*, and, depending on patient's geographic location and risk factors, TB and HIV. For patients >12 months of age, one should also consider testing for *C. difficile*. In patients presenting between 12 months to 6 years of age, stool lactoferrin/calprotectin can be elevated in either infection, chronic inflammation or allergic gastrointestinal disorders. Stool lactoferrin and calprotectin have not been well validated in very young children and can be elevated above the adult range in infants. Intestinal TB is challenging to diagnose, as it can easily be misdiagnosed as Crohn's disease<sup>33</sup>.

For infants under 12 months of age presenting with bloody stools, cow's milk protein intolerance or allergic colitis and infection are often the initial considerations. Distinguishing features that should raise suspicion for VEOIBD include: failure to thrive, weight loss, frequent infections, arthritis, folliculitis, intermittent fevers and severe perianal disease (skin tags, abscesses, fistulae). Additionally, a refractory course with persistent symptoms despite an appropriate 2-week trial of an exclusive amino acid-based diet should prompt consideration for further investigation for VEOIBD. It is important to mention that patients with IBD as well as those with cow's milk protein intolerance can both improve significantly within 2 weeks of providing exclusive elemental amino-based formula feeds. This can make the distinction between VEOIBD and cow's milk protein intolerance challenging if there is a positive response. If patients are not thriving despite these dietary changes for 2 weeks or have other concerning features for VEOIBD, more extensive workup for VEOIBD should be pursued.

Celiac disease is another disease often considered before VEOIBD in patients presenting with non-bloody diarrhea, malabsorption, anemia, weight loss, and failure to thrive. Serologies for celiac disease can be helpful in distinguishing the two, but there can be concurrent IBD and celiac disease, especially in light of the increased risk of underlying autoimmunity. In addition, certain primary immunodeficiencies can be nearly indistinguishable from celiac disease (e.g. CTLA4 deficiency)<sup>34</sup>. It is important to remember in young children, particularly those <2 years old, that deamidated gliadin peptide IgG may be more helpful than tissue transglutaminase IgA in screening for celiac disease, especially in patients with IgA deficiency<sup>35,36</sup>.

#### **Other non-inflammatory diagnoses:**

While the focus of this manuscript is VEOIBD, it is important to keep in mind that there are numerous additional non-inflammatory etiologies for diarrhea. These include a variety of congenital intestinal transport defects such as specific carbohydrate malabsorption (e.g. Glucose-galactose malabsorption), disorders of amino acid and peptide assimilation (e.g. Enterokinase synthesis deficiency), disorders of fat assimilation (e.g. Abetalipoproteinemia), and disorders of mineral and electrolyte absorption and secretion (e.g. Congenital chloride diarrhea and Congenital sodium diarrhea)<sup>37</sup>. In contrast, VEOIBD more commonly presents as bloody diarrhea, while these disorders usually do not. Additionally, inflammatory markers in the blood and stool can help distinguish VEOIBD from non-inflammatory etiologies.

### **Appreciation for underlying PID increases suspicion for VEOIBD:**

Many of the currently identified monogenic etiologies of VEOIBD are associated with PID. It follows that PID should be considered in any patient with VEOIBD and a thorough immune workup be completed in patients with VEOIBD to identify possible underlying immunodeficiency. PID should be strongly considered and evaluated in patients with  $\geq 4$  new ear infections per year;  $\geq 2$  severe sinus infections in a year;  $\geq 2$  months of antibiotic treatment with little effect;  $\geq 2$  pneumonias per year; insufficient weight gain or growth delay; recurrent deep skin or organ abscesses; persistent thrush in mouth or fungal infection of the skin; need for intravenous antibiotics to clear infections;  $\geq 2$  deep seated infections, or a family history of PID<sup>38</sup>. History of infection with an unusual microbe (e.g., *Serratia*) should raise suspicion for this as well. Nevertheless, in some cases, IBD is the initial manifestation of a PID and the infectious problems will develop later. Therefore, a detailed immune work-up in patients with VEOIBD is required, even in the absence of chronic, recurrent or atypical infections.

### ***Clinical Assessment:***

A high index of suspicion is needed to guide the history and physical exam in order to diagnose VEOIBD. Distinguishing which patients with VEOIBD also have an underlying PID is a challenge, but there are certain manifestations that support the diagnosis of an underlying immune disorder. For instance, thrombocytopenia and eczema are common in patients with Wiskott-Aldrich syndrome. Glycogen storage disease type 1b typically presents with hypoglycemia and hepatomegaly. Recurrent infections are commonly identified in patients with chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID) or common variable immune deficiency (CVID). An extensive list of monogenic etiologies of VEOIBD and their associated distinguishing clinical and laboratory features are presented in **Table 1**, which has been expanded from that of Uhlig et al<sup>1</sup>. Equipped with this understanding and a systematic approach of a targeted history, physical exam, blood work, and stool studies, it should become apparent which subset of patients merits further investigation.

**Comprehensive history:** A detailed history should identify the onset of symptoms, with careful attention to stooling pattern, frequency, consistency, evidence of macroscopic or

microscopic blood or mucus, the progression over time, and the response to dietary or other interventions. It is imperative to inquire about energy, appetite, tolerance of feeds, vomiting, and irritability. Careful review of the patient's growth parameters as well as history of frequent or recurrent fever and infections, especially opportunistic or refractory infections, rashes, arthritis or arthralgias, and perianal disease are instrumental. Family history of consanguinity or relatives with immune deficiency, recurrent infections, IBD, autoimmunity (such as Type 1 diabetes, autoimmune thyroiditis, autoimmune liver disease) and atopy might point to a possible monogenic disease.

Physical exam: General clinical features that can be seen in IBD at any age include clubbing, rashes (e.g. erythema nodosum and pyoderma gangrenosum), and perianal disease (e.g. fistulas, skin tags and perianal abscesses). In Crohn's disease, the oral exam may be notable for classic features of aphthae and orofacial granulomatosis. Manifestations of nutritional deficiencies might also be noted such as peripheral edema from hypoalbuminemia, angular cheilitis from iron/vitamin deficiencies, as well as perianal and perioral rash reminiscent of acrodermatitis enteropathica. In VEOIBD there are unique physical exam findings that may increase suspicion for a monogenic etiology. These include dysmorphic features, hepatomegaly, splenomegaly, atopic dermatitis, hyperkeratosis, albinism, and epidermyolysis bullosa. To give some specific examples, a constellation of severe perianal disease, folliculitis and arthritis in young patients presenting within the first few months of life is suggestive of IL10 signaling defects<sup>3</sup>. Oral leukoplakia is suggestive of underlying dyskeratosis congenita<sup>39</sup>. Features of common variable immunodeficiency such as LRBA or CTLA4 deficiency include recurrent infections, various autoimmune and endocrine features and organomegaly<sup>40,41</sup>. Similarly, patients with IPEX syndrome not only manifest enteropathy, but commonly have type 1 diabetes mellitus, eczema, food allergies, and a variety of other autoimmune manifestations<sup>6,42</sup>. Patients with NEMO mutations often have ectodermal dysplasia as an easily recognizable feature on physical examination<sup>43</sup>. Lastly, abnormalities in the hair and/or nails are found in Hoyerall Hreidarsson syndrome, trichohepatoenteric syndrome and ADAM17 deficiency. The physical exam remains a useful tool that may help distinguish monogenic causes of VEOIBD.

### ***Basic workup, initial investigations and early interventions:***

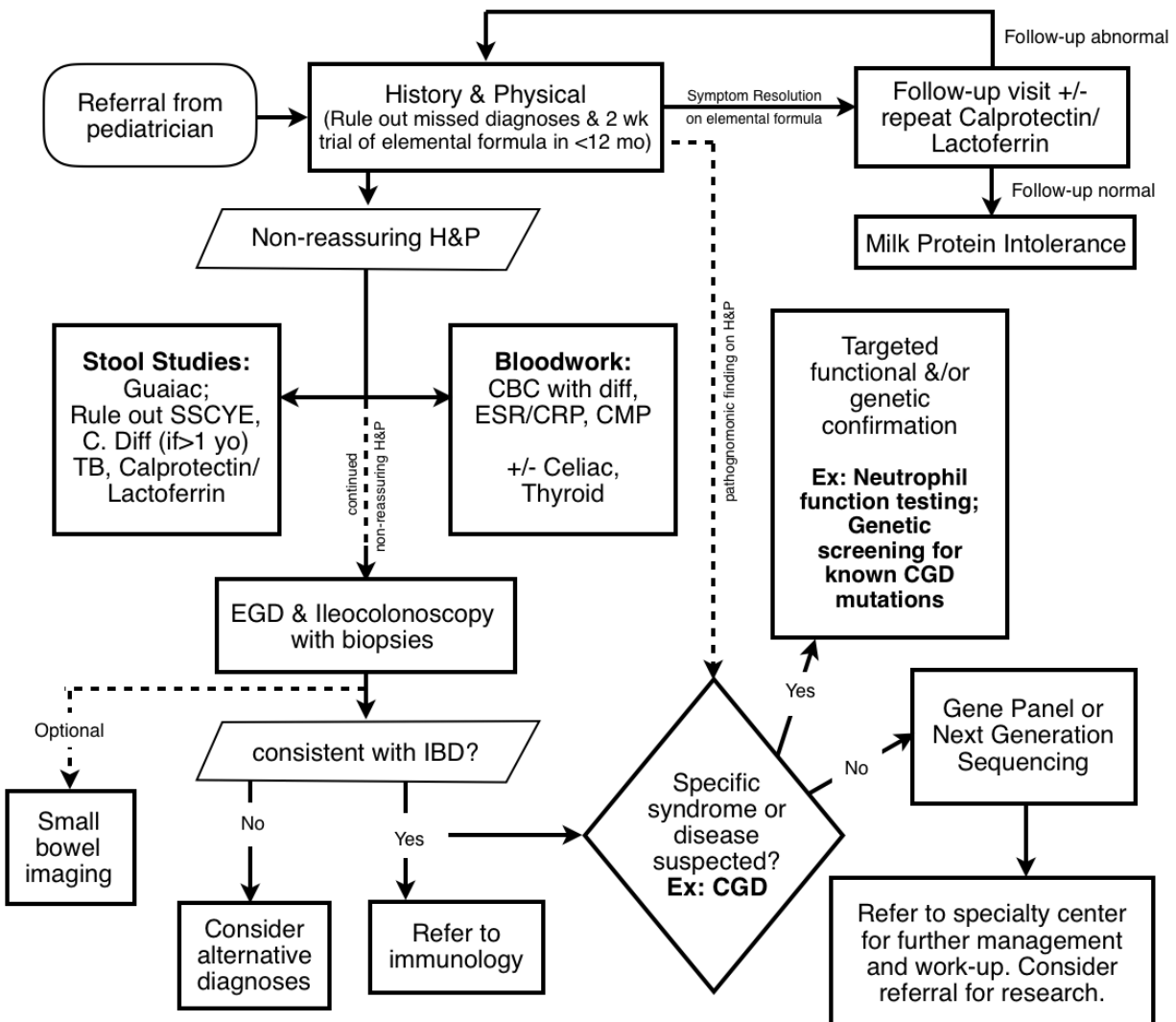
Upon referral from the general pediatrician, it is vital to confirm that more common causes of colitis have been ruled out (e.g., infection, Figure 1). Stool studies and lab tests can be sent to rule out other causes on the differential (Table 2). Of note, serologic markers commonly obtained due to their association with IBD, such as antibodies to microbial antigens (e.g., ASCA, CBir1) and autoantibodies (e.g., pANCA), have been noted to be different within younger age groups, and they likely have a limited role for VEOIBD<sup>44,45</sup>. Patients less than 12 months of age suspected to have VEOIBD should receive an exclusive, elemental formula for at least two weeks unless the severity of the patient's symptoms prompts an expedited work-up.

If the initial labs, symptoms, or physical exam findings discussed above are concerning or refractory to a two week trial of an elemental diet in infants less than 12 months old, it



is recommended to proceed with expedited upper endoscopy and ileocolonoscopy. Endoscopy is technically feasible in the youngest patients (<1 month old), but requires the expertise of an experienced pediatric gastroenterologist. Endoscopy will help to determine if the pattern of disease is more consistent with an allergic, inflammatory, or infectious process. A detailed gross assessment with multiple biopsies is critical to aid in diagnosis. Features consistent with VEOIBD include evidence of chronic inflammation (architectural changes, crypt branching, increase in chronic inflammatory cells in the lamina propria, and non-caseating granulomas in CD). While we typically find evidence of chronic inflammation, in some rare cases, early evolving VEOIBD without the typical features of VEOIBD may be captured on initial scope, so it is important to not definitively [rule out VEOIBD based alone on the lack of chronic features where clinical suspicion for VEOIBD is high](#). One feature suggestive of an underlying monogenic etiology of VEOIBD is the presence of epithelial cell apoptosis. This finding is identified in several monogenic etiologies of epithelial barrier function (such as dystrophic bullosa, Kindler syndrome, X-linked ectodermal immunodeficiency, TTC7A deficiency and ADAM17 deficiency) as well as in IPEX syndrome. Abnormalities in the hair and/or nails are found in telomerase disorders (e.g. Hoyerall Hreidarsson syndrome), trichohepatoenteric syndrome and ADAM17 deficiency. Many monogenic etiologies have a variety of extra-intestinal autoimmune features. Some are associated with either hemophagocytic lymphohistiocytosis (HLH) or macrophage activating syndromes and some have increased predilection for development of neoplasias (such as diffuse large B cell lymphoma in IL10 signaling defects).

**Figure 1: Algorithm for VEO-IBD Work-up**



**Figure 1:** Algorithm for work up of VEOIBD: Abs- Antibodies; CBC with diff- complete blood count with differential; CGD- chronic granulomatous disease; CMP- comprehensive metabolic panel; CRP- C reactive Protein; EGD- esophogastroduodenoscopy; ESR- erythrocyte sedimentation rate; H&P- History and physical; mo- month; NOBA- neutrophil oxidative burst assay; TB – tuberculosis, SSCYE – Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica, and E coli; C. Diff- C. Difficile; Wk- week;

Despite the predominance of colonic inflammation in VEOIBD, imaging of the small intestine is helpful in determining the extent of intestinal disease. This is more complicated in very small children. A wireless capsule endoscopy (WCE), which has been used in a child as small as 7.9 kg<sup>46</sup>, requires sedation to place the capsule itself,

and consideration of preliminary placement of a patency capsule. A magnetic resonance enterography (MRE) requires a significant amount of contrast and expertise of the radiologist. There are also safety concerns regarding sedating patients for lengthy MREs after providing oral contrast. Because of these concerns, feasible options to image the small intestine in this age group are typically a small intestine abdominal ultrasound by a skilled radiologist or more specifically a small intestinal contrast ultrasound (SICUS), a minimized-radiation CT scan, if available, or, a small bowel follow through<sup>47</sup>.

Consultation with an expert immunologist for the consideration of an underlying immunodeficiency is warranted in all patients with VEOIBD. Examples of underlying PIDs can be found in Table 1. The immunologist will typically send a basic immune workup (listed as 2<sup>nd</sup> tier in Table 2, in addition to potentially additional investigations such as soluble IL2 receptor, IL-18, FOXP3, and XIAP by FACS analysis among others). These initial studies will help direct further specialized work-up for specific syndromes or diseases. These tests are best performed before therapy is initiated, as many treatments can obscure the results.

<b>Table 2: Initial bloodwork and stool studies</b>		
	1 <sup>st</sup> tier tests	2 <sup>nd</sup> tier considerations
Bloodwork	CBC and differential Comprehensive Metabolic Panel (CMP) ESR CRP <i>Consider celiac screen and thyroid function tests depending on presentation</i>	Immunoglobulin classes (IgA, IgG, IgM, IgE) – <i>Must use age-specific norms, especially in infants</i> Lymphocyte subsets by flow cytometry Antibody to vaccines – <i>Vaccination history must be obtained to evaluate this</i> Allergen testing for older children DHR testing TREC/TCR repertoire TB testing HIV serology
Stool studies	Occult blood <i>Shigella</i> <i>Salmonella</i> <i>Yersinia</i> <i>Enterohemorrhagic and Enteropathogenic E. coli</i> <i>Campylobacter</i> <i>C. difficile</i> (if >12 months) Calprotectin or	<i>Giardia</i> <i>Cryptococcus</i>

	quantitative lactoferrin	
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NOBA- Neutrophil Oxidative Burst Assay, also known as DHR- dihydrohodamine 123

### ***Genetic sequencing: Targeted gene panels and next generation sequencing***

If there is no clear clinical suspicion for an underlying monogenic etiology, or if specialized directed testing is unrevealing, then a more expansive evaluation using either targeted gene panels for VEOIBD or next generation sequencing is warranted. In many instances this is performed in research settings<sup>48</sup>. Physicians and patient families must understand that despite such efforts, the underlying etiology of the disease will remain unknown in most cases. Successful identification of known causal variants typically range between 5-20%. Some studies have reported a higher identification rate, up to 31%, but these were conducted in tertiary care referral medical centers<sup>49</sup>. Clinical judgment is required to assess the necessity of genetic testing in those with a relatively benign course without any red flag features who do not fall in the Infantile IBD cohort as the incidence of monogenic mutations does decrease successively with age; however, given the ready availability of genetic panels and even NGS, genetic testing should still be considered. While only a minority will be identified as having a known monogenic etiology, this holds significant clinical and therapeutic implications when variants are identified. For instance, in VEOIBD patients with IL10 receptor signaling deficits, identification enables the possibility for a *curative* bone marrow transplantation<sup>3</sup>. As research continues and we understand more about the underlying monogenic etiologies of VEOIBD, we anticipate an improved detection rate of causative variants over time. It is important to appreciate that the turnaround time for these tests, both CLIA-approved and research-based, can be very lengthy (i.e., weeks to many months).

Available CLIA-certified genetic panels for VEOIBD exist. They allow the investigation of a large number of genes known to be causative for infantile/VEOIBD in a CLIA-approved fashion (e.g.: Invitae). However, these gene panels often contain only a subset of known genetic etiologies of VEOIBD, often missing critical candidate genes and lacking interpretation of variants of unknown significance. It is important that if performed and unrevealing, this should not reassure the physician or family that a genetic etiology is not at play, as the list of genes tested is incomplete and should reflex to Next Generation Sequencing (WES or WGS).

An alternative is to send Next Generation Sequencing (WES or WGS) straight away. If performed as part of a research endeavor, any pertinent findings would need to be CLIA-confirmed before being communicated back to the family. Appropriate patient/parent and physician expectations need to be set as genetic testing can take months. Additionally, a genetic counselor should be made available to discuss any CLIA-confirmed findings.

Finally, within classically polygenic diseases, genetic risk scores are gaining popularity<sup>50</sup> having been shown in some chronic disease, including IBD, to perform as well in disease prediction as monogenic mutations. Prior to the inception of current day polygenic risk scores, using a genetic risk score incorporating 163 risk alleles, a trend

was shown in CD towards higher genetic risk scores in those with a lower age of diagnosis ( $P_{\text{trend}} = 0.008$ )<sup>51</sup>. Use of the polygenic risk score has not been studied within the VEOIBD population specifically as the focus remains on identifying actionable monogenic variants.

All in all, while there is great promise in these approaches, because of the time lag, often clinical management must be initiated prior to receipt of results.

### ***Functional testing:***

While the list of monogenic disorders linked to IBD has rapidly increased in the last decade, the number of functional tests that can be applied is very limited. Depending on the clinical features, if there is strong suspicion for a particular underlying genetic etiology, specific functional tests can be valuable. Functional testing will often provide results faster than genetic sequencing. However, it is important to note that any positive functional test should be confirmed by targeted genetic sequencing. Below are a few illustrative examples.

Patients presenting with VEOIBD and either recurrent infections or numerous granulomas warrant assessment of their neutrophil oxidative burst capacity (NOBA). Dihydrohodamine 123 (DHR) testing is a NOBA that can be helpful in two regards. In one respect, classic chronic granulomatous disease (CGD) can present as VEOIBD associated with an abnormal NOBA. On the other hand, some patients with VEOIBD without infections may have low-normal NOBA, which has been associated with mutations in various members the NADPH-oxidase complex<sup>52,53</sup>.

Patients presenting with classic manifestations of IL10 signaling defects such as severe colitis, perianal disease, arthritis, and folliculitis, within the first months of life warrant functional testing of the IL10 signaling pathway (either for defects in IL10 or the IL10 receptor). Functional assays are available in both research-based non-CLIA approved labs (inquiries can be sent to [info@veoibd.org](mailto:info@veoibd.org) to learn about the types of functional assays offered by the VEOIBD Consortium; VEOIBD.org) and CLIA-approved labs.

Patients with XIAP may present with severe Crohn's like colitis, perianal fistula, hemophagocytic lymphohistiocytosis (HLH), splenomegaly, cholangitis, skin abscesses and or fulminant infection to Epstein-Barr virus (EBV) and/or hypogammaglobulinemia. Functional studies have been employed to diagnose XIAP by use of a flow-based assay measuring TNF expression in response to muramyl dipeptide (MDP)<sup>54,55</sup>.

### ***Clinical and Treatment patterns:***

The severity of the clinical course and response to therapy of VEOIBD patients compared to IBD patients presenting at an older age is inconclusive. Some studies report that there is an increased risk of earlier colectomy and increased risk for earlier biologic use in patients with IBD in infants less than one year of age<sup>16</sup>, while other data suggest that patients with VEOIBD have lower rates of hospitalization, emergency

department utilization and surgical resection<sup>15,21</sup>. A prospective observational review by Oliva-Hemker *et al* of VEOIBD patients diagnosed between 1-5 years old showed that most presented with moderate-to-severe disease activity<sup>15</sup>. Among those with CD, there was no significant difference in terms of exposure to infliximab, enteral nutrition or hospitalization. However, these patients were more often exposed to steroids and methotrexate as compared to patients of older ages<sup>15</sup>. With respect to patients with UC, there was no significant difference in use of antibiotics, 5-ASAs, steroids or thiopurines. Conversely, five years after diagnosis, a larger proportion of the youngest patients were on mesalamine and thiopurine as compared to older age groups. Once again, exposure to infliximab and hospitalizations were not significantly different between age groups. It is important to keep in mind that this review did not capture patients diagnosed prior to 1 year of age, so it may not be capturing those with underlying PID or monogenic etiology.

### ***Therapeutic approaches:***

While some studies include patients with VEOIBD, there are no randomized controlled studies focused on this age group to inform on the therapeutics of choice in patients specifically with VEOIBD, which can largely be attributed to their rarity. Prioritized medication choices reflect data from older children and adult-onset IBD. We discuss below various therapeutic approaches for VEOIBD including medications, surgery, allogeneic hematopoietic stem cell transplantation (HSCT), nutrition, and complementary medicine.

### **Medical Therapies:**

Some but not all studies suggest that VEOIBD patients may be more refractory to standard therapeutic choices especially in patients less than one year of age. These include 5-ASA, immunomodulators (6MP, Azathioprine, methotrexate), and anti-TNF antibodies. It is not surprising that there are also no comprehensive studies using vedolizumab, ustekinumab, tofacitinib, tacrolimus or thalidomide in this age group<sup>56-60</sup>. Antibiotics have been tried in small cohorts of VEOIBD with UC. Turner *et al* report some promising results including some very early onset UC patients receiving either Metronidazole, Amoxicillin, Doxycycline +/- Vancomycin<sup>61,62</sup> and also on use of oral Gentamycin and/or Vancomycin for treating VEOIBD<sup>63</sup>.

When there is a monogenic cause, identifying the underlying genetic etiology can enable more targeted and successful therapeutic interventions and/or help avoid ones that would be especially harmful to a patient. For example, abatacept, a CTLA4-IgG1 fusion drug and hydroxychloroquine can be given to patients with CTLA4 and LRBA deficiency as LRBA deficiency also results in a loss of CTLA4<sup>64</sup>. For patients with CGD, some centers avoid use of anti-TNF therapy for fear of perpetuating disseminated severe infection<sup>65</sup>, and clinicians rely instead on antibiotic therapies, thalidomide, or off-label vedolizumab/ustekinumab. One can also consider anakinra, an IL1 receptor antagonist, in patients with IL10 signaling defects who are too ill to undergo transplant or while searching for a suitable donor, as this has led to marked clinical, endoscopic and histologic improvement in some patients<sup>66</sup>. Blocking IL1 has also been shown to be

effective in patients with Mevalonate Kinase Deficiency (MVK)<sup>67</sup>. As we learn more about these diseases, it is anticipated that our repertoire of therapeutic alternatives will grow.

**Surgery:**

Reports on the need for surgical intervention in patients with VEOIBD is inconclusive. While Benchimol et al reported less need for surgical intervention among a Canadian cohort of VEOIBD as compared to that of older onset<sup>21</sup>, and Al-Hussaini et al reported no significant difference in surgical interventions in a Saudi Arabian VEOIBD cohort<sup>68</sup>. In contrast, Kammermeier et al report an increase need for surgical intervention in infantile Crohn’s-like disease diagnosed prior to two years of age at their European center<sup>49</sup>. A recent single center studying surgical interventions in patients with monogenic etiologies of IBD from China report that surgical interventions should be performed earlier because of risk of perforations in monogenic IBD<sup>69</sup>. These discrepant reports may be due to the fact that surgery may hinge more on the underlying immunodeficiency or monogenic etiology than age of onset of disease.

**Hematopoietic stem cell transplantation (HSCT):**

HSCT may be curative for several monogenic causes of VEOIBD, including CGD, IPEX syndrome and IL10 receptor signaling defects<sup>3,70,71 72-74</sup>. Umbilical cord transplantation may also correct IL10RA-associated disease<sup>75</sup>. Consideration for HSCT should be discussed with experienced physicians who have expertise in transplantation for PID. The risks of HSCT include life-threatening infection, failure of engraftment, graft versus host disease, and acute and long-term toxicity from medications used for conditioning, including infertility and secondary malignancy. Risks and benefits must be carefully weighed. For instance, VEOIBD is life-threatening in patients with IL10 signaling defects, and HSCT can be life-saving. However, VEOIBD in CGD is more indolent, and the decision to perform HSCT is more nuanced. Thus, even though the procedure is potentially curative, the not insignificant risk of mortality and morbidity must be evaluated carefully. In some diseases, such as WAS, genotype-phenotype correlation can predict whether an individual patient is likely to have a severe course without HSCT<sup>76</sup>. For others, the variability of penetrance and symptoms among family members with the same mutation make the decision of whether to proceed to HSCT much more challenging. Finally, the timing can also be important, such as in IPEX syndrome, where the pretreatment organ involvement score at time of transplant is associated with improved survival<sup>77</sup>. It is important to remember that some monogenic causes of IBD have both immune and epithelial defects: accordingly, HSCT may not ameliorate all symptomatology. **Table 3** reviews some genetic etiologies of IBD and highlights when HSCT for the purpose of correction of IBD should be strongly considered, discouraged, or where we currently have insufficient evidence to provide strong recommendations.

Table 3: Efficacy of healing intestinal disease with stem cell transplantation in some cases of VEOIBD:

Condition	HSCT may be	HSCT not
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	<b>efficacious for intestinal disease</b>	<b>efficacious for intestinal disease</b>
	IL10RA, IL10RB, IL10 deficiency	TTC7A
	IPEX	STXBP2
	WAS	IKBKG (NEMO)
	Many forms of SCID	
	CD40L	
	XIAP	
	CGD	
	LRBA	
	CTLA4	
	DOCK8	

### **Nutritional approaches:**

There are no quality studies assessing the use of nutritional approaches in VEOIBD. Again, we extrapolate our therapeutic approach from older onset pediatric IBD. For CD, especially that affecting infants with small intestinal disease, use of exclusive enteral nutrition is a consideration for induction therapy. This can be given orally, or via nasogastric or gastric tube. At present, no data supports the use of nutritional therapy in UC. The Specific Carbohydrate Diet (SCD), Mediterranean diet, and newer anti-inflammatory diets are being actively investigated for management of patients with IBD. We currently do not have sufficient data to routinely recommend these to VEOIBD patients as primary modes of therapy.

### **Complementary medicine:**

Many caretakers are fearful of the risks associated with medications available for patients with VEOIBD. Families often inquire about nutritional, homeopathic or complementary approaches and seek out naturopaths and homeopaths for guidance. Physicians should encourage families to discuss the use of alternative therapies. It is important to ascertain whether alternative or complementary agents interact with prescribed therapy or cause harm (e.g. CYP450 interactions, drug-induced liver injury, etc). While we currently do not have enough information to routinely support such interventions as primary therapeutic interventions, some have more scientific validity than others. Use of curcumin has been shown to be helpful in adults with mild-to-moderate ulcerative colitis<sup>78</sup>. While no studies have been performed in IBD, let alone VEOIBD, cinnamon has been recognized as a potent anti-inflammatory agent<sup>79</sup>. Some studies have looked at the potential positive effects of fish oil in IBD as well<sup>80,81</sup>.

### **Experimental Fecal Microbiota Transplantation (FMT):**



While fecal microbiota transplant (FMT) is being actively studied in children with IBD, its efficacy is unclear. Only a few non-randomized control studies have been performed in older children (youngest child 7 years old with divergent results)<sup>82</sup>. This is continuing to be investigated, though at this time, we do not currently have evidence of consistent benefit in VEOIBD<sup>83</sup>. Furthermore, long-term effects of manipulating the developing microbiome are unknown.

### ***Health Maintenance:***

Children with VEOIBD have unique health supervision considerations, similar to all pediatric IBD patients. Several aspects are described below including: immunizations, bone health, skin care, and visual health.<sup>84</sup>

Immunizations: Prior to starting an infant/toddler on immunomodulators or biologics, it is recommended to assure completion of their vaccination status if time permits. While evaluating infants for VEOIBD who have not yet received their full set of immunizations, offering a trial of an exclusive elemental diet can optimize nutrition, help their inflammatory disease, and provide time to expedite catch up immunization prior to initiating immunosuppression. Annual influenza vaccine and confirmation of immunization against Hepatitis B are imperative. If the child did not respond to Hepatitis B immunization, it is recommended they repeat the full immunization course. Titers for Hepatitis B surface antibody should be rechecked within 4-8 weeks following the repeat immunization course. Pneumococcal 23 vaccine should be provided to children over two years of age as long as they complete the Prevnar 13 series. Once on an immunomodulator or biologic, children should not receive live vaccines.

Bone health: Assuring appropriate Vitamin D and Calcium and regular weight bearing exercise is important for bone health in IBD, especially in patients with poor nutrition and frequent steroid use<sup>85</sup>. As no norms for DEXA scans exist prior to 3 years of age, a DEXA scan should be started at 3 years of age to assess and monitor bone density. Minimizing exposure to frequent steroid use is imperative.

Skin care: Infants six months and older should use regular sunblock, we recommend at least SPF 50, especially when concurrently using immunomodulators or biologics given the slightly increased risk of skin cancer<sup>86,87</sup>. Barrier protection of skin is recommended for infants under six months old.

Visual health: Children should be assessed yearly by an ophthalmologist for possible ocular manifestations of VEOIBD, such as uveitis and episcleritis, as well as possible cataract formation from regular steroid use.

### **Ongoing research:**

VEOIBD presents unique challenges in comparison to later-onset IBD such as the increased risk of a monogenic disorder, anticipation of a long disease time course, and lack of clinical and scientific research in this young age group. VEOIBD is increasing in

frequency paralleled by an increasing awareness of the need to better understand these diseases and their management. At present, there is little data to guide optimal management of VEOIBD. Large international efforts are in place to better understand the progression of disease over time and to ascertain the ideal therapeutic interventions. Knowledge continues to evolve on the genetics and immunologic status of patients presenting with IBD at such a young age. VEOIBD may represent a greater contribution of genetics, epigenetics, and early life events than later-onset IBD, as the time for environmental influences is less. Next generation sequencing has already identified a variety of novel monogenic etiologies underlying these diseases and has shed light on alternate and targeted therapies. Patients, families and physicians are encouraged to partake in ongoing research studies. Much work is being performed on murine models of colitis, patient-derived intestinal organoids, assessment of patient microbiome, use of various diets and antibiotics, among other promising avenues of interest. With advances in next generation sequencing, more tailored approaches can be developed to help unravel the functional genomic relevance of new variants identified. With a better understanding of the underlying genetics and pathophysiology of disease in patients with VEOIBD, one strives to target the underlying defect directly in a personalized fashion. The Very Early Onset IBD Consortium ([www.veoibd.org](http://www.veoibd.org)) is a helpful resource for patients, parents, and physicians, representing a large international team devoted to advancing this field.

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