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Research Article

Evolving a Single Institution's Approach to Very Early Onset Inflammatory Bowel Disease (VEO-IBD) through Literature Review and Collaborative Efforts

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Abstract

Objective: Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is defined as a diagnosis of IBD before 6 years of age. VEO-IBD often follows a more recalcitrant disease course and can be associated with underlying Inborn Errors of Immunity (IEI). **Methods:** We describe our single institution experience in caring for patients with VEO-IBD as a tertiary referral center for pediatric IBD, how we utilized this most recent literature review to provide self-assessment in workup, and how we transformed our approach to VEO-IBD care through collaboration, using a stepwise laboratory and clinical paradigm for this vulnerable cohort of IBD patients. **Results:** A retrospective review of 34 patients was performed with description of clinical phenotypes, tissue pathology, clinical management and outcomes. The majority of our VEO-IBD patients presented with colonic Crohn's disease. A high percentage of patients were refractory to anti-Tumor Necrosis Factor (TNF) therapy. Only 26/34 (76%) of our VEO-IBD patients had any immunological testing done and genetic testing was performed on only 5/34 patients (15%). **Discussions:** Our review process identified a need for expedited standardized immune workup for this population at our institution. Based upon this introspective work, an algorithm for immunological and genetic evaluation at time of diagnosis was developed, aimed at creating a multi-disciplinary approach for the comprehensive evaluation of this at-risk patient population.

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Keywords: Very Early Onset Inflammatory Bowel Disease (VEO-IBD); Inborn Errors of Immunity (IEI); Crohn's Disease; Ulcerative Colitis; Genetics; Immune Testing

Introduction

Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is defined as a diagnosis of IBD before 6 years of age. Patients diagnosed before 2 years of age are subcategorized into infantile-onset IBD [1]. The incidence of pediatric IBD and VEO-IBD has continued to rise with VEO-IBD being the fastest growing age group of IBD in certain parts of the world [2-4]. The cause of this increased incidence is unknown. In contrast to older IBD patients, VEO-IBD is more often associated with monogenic mutations in Inborn Errors of Immunity (IEI) [1,5,6]. Currently over 70 genes have been causatively associated with VEO-IBD and additional genetic candidates are being discovered as sequencing technology improve [1]. VEO-IBD associated monogenic variants are classified into 5 distinct groups: 1) Epithelial barrier defects; 2) Phagocytic defects; 3) T and B cell defects; 4) T regulatory cells and signaling defects; and 5) Hyper- and auto-inflammatory conditions [1,5-7] (Figure 1). Identifying a monogenic etiology of VEO-IBD can have significant impact on treatment regimens, as specific immunological mechanisms can be targeted [1,6,8-10].

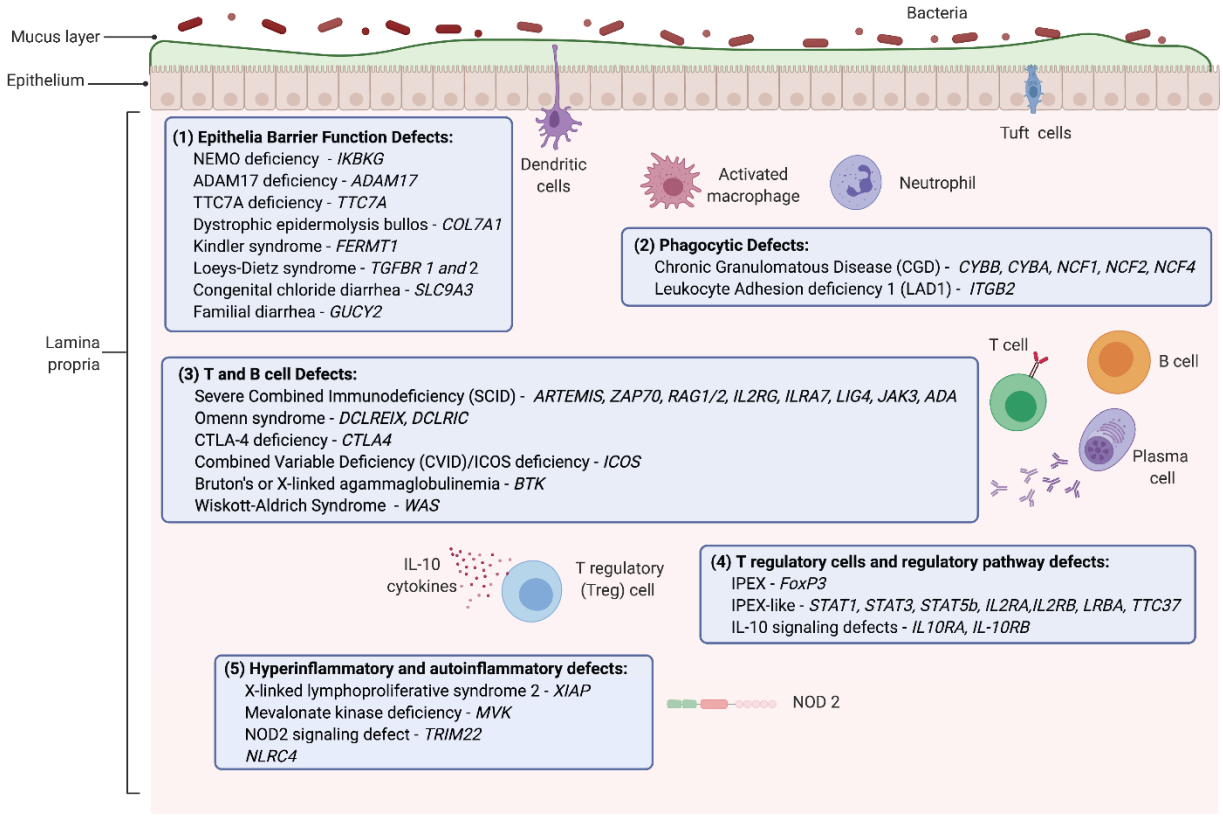


Figure 1: Monogenic variants of VEO-IBD. Created in Biorender.com.

Based on a 2020 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) position paper on VEO-IBD, recommendations of clinical approach and diagnostic strategies have shifted in the past year [9]. In response to rapidly evolving clinical paradigms, in this paper, we aim to understand our own experience with VEO-IBD patients presenting to a tertiary pediatric IBD center in the Pacific Northwest. Based on this evaluation, we present the outcome of the collaborative work from Division of

Gastroenterology and Division of Immunology which culminated in a diagnostic algorithm targeting the timely diagnosis and identification of monogenic defects and IEI in VEO-IBD patients. These efforts were aimed to improve our institutional approach to treating VEO-IBD patients by standardizing evaluation.

Materials and Methods

A retrospective chart review of pediatric patients diagnosed with VEO-IBD from March 2010 to September 2021 at Seattle Children's Hospital was conducted in accordance with institutional review board approved protocol (STUDY00002723). Pediatric patients diagnosed with VEO-IBD through endoscopy with biopsies were included for review. Patients were subcategorized into infantile IBD for patients diagnosed at less than 2 years of age, and as an older cohort diagnosed between 2 years and 6 years of age. 34 patients with VEO-IBD were identified, 12 of whom were diagnosed before the age of 2 years (infantile cohort) and 22 diagnosed between the ages of 2 and 6 years of age (older cohort).

Patient clinical courses were captured at the time of presentation and at 12 months of follow-up. Clinical characteristics were recorded, including disease type, age of onset, race, sex, disease location/behavior/perineal disease, weight z-score, height z-score, BMI z-score, and clinical disease severity using the abbreviated Pediatric Crohn's Disease Activity Index (aPCDAI), with a score above 26 indicating moderate to severe disease, and Pediatric Ulcerative Colitis Activity Index (PUCAI), with a score above 35 indicating moderate to severe disease [11,12]. Relevant past medical history was obtained, such as hospitalizations, infections, antibiotic use, surgical intervention, and family history of autoimmunity and immunodeficiencies. Laboratory studies, including C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), albumin, Complete Blood Count (CBC) with differential, and fecal calprotectin, were recorded at time of diagnosis and at 12 months post diagnosis. Immune workup, if obtained with laboratory evaluation, included lymphocyte subsets, immunoglobulin levels, mitogen stimulation test, vaccine titers, neutrophil oxidative burst, B-cell phenotyping, XIAP protein levels, FOXP3 flow assays, and other genetic tests such as IL-10 (as deemed necessary at the discretion of immunology). Clinic notes, procedure notes, and pathology notes were reviewed via the electronic medical records. Medical management as dictated by clinicians and medication use was recorded up to 12 months post diagnosis. Targeted Gene Panels (TGP) were evaluated, including the University of Washington Immunoplex™ panel [13] and Invitae Monogenic IBD panel, to detect mutations that are known to be linked to IEI [14].

Categorical data is listed as number of patients or percentages of the whole. Continuous data (age at diagnosis, height z-score, weight z-score, weight-for-height z-score, CRP, ESR, albumin, calprotectin, and CBC with differential) is listed as medians with ranges. The younger cohort was compared to the older group to determine if a statistically significant difference was present between the two groups with regards to laboratory evaluation. Statistical analysis was done using Mann-Whitney U test to detect differences between the two age cohorts with significance indicated by p value <0.05. Graphpad prism was used for statistical calculations and figure generation. Biorender was used for Figure 1 generation.

Based upon the retrospective chart review, members of the Division of Gastroenterology's Inflammatory Bowel Disease Center and the Division of Immunology at Seattle Children's Hospital devised an algorithm to expedite and simplify the multidisciplinary evaluation of our VEO-IBD patients. We facilitated and streamlined electronic order sets, genetic panel testing, and drafted letters for rapid insurance appeals for a comprehensive immunological evaluation of these patients. In addition, we recommended early consultation with multiple other services including nutrition, social work, psychologists, and other subspecialties as clinically needed i.e. dermatology and rheumatology.

Results

Data at Diagnosis

Of the patients diagnosed before 2 years of age, males and females were evenly distributed, whereas the older cohort had more females (59%). Median age of onset was 4 years of age for females and 2 years of age for males. Demographic data reflects the general population breakdown of the Pacific northwest with 17% Asian, 8% Pacific Islander, 50% Caucasian, 17% Hispanic, and 8% unknown in the infantile IBD group, and 14% Asian, 9% Black or African American, 68% Caucasian, and 9% Hispanic in the older IBD cohort.

Of the infantile group, 1 (8%) was diagnosed with ulcerative colitis (UC) and 11 with Crohn's disease (CD) (92%), as compared to 6 (27%) with UC and 16 (73%) with CD in the older cohort. Of the UC phenotype, 4/7 (57%) presented with moderate to severe colitis with PUCAI >35. With CD presentation, 14/27 (52%) presented with moderate to severe Crohn's with aPCDAI >26.

Endoscopic findings with esophagogastroduodenoscopy and ileocolonoscopy with biopsies at time of diagnosis showed upper tract disease in 9/12 (75%) for infantile IBD cohort and 15/22 (68%) of older cohort. Within the infantile IBD cohort, isolated colonic disease was found in 8/12 (67%), whereas 4/12 (33%) presented with ileocolonic disease. In contrast, 8/22 (36%) in the older cohort presented with isolated colonic disease, 12/22 (54%)

presented with ileocolonic disease, and 2/22 (9%) presented with only ileal involvement. Perianal disease was present in 1/12 (8%) in the infantile IBD cohort and 1/22 (4%) in patients in the older cohort. No patients had structuring or penetrating phenotypes. Histopathologic evaluation revealed apoptosis in biopsies in 1/12 (8%) of patients diagnosed before 2 years of age. Granulomas were detected in 5/12 (42%) of biopsies in the infantile cohort and 11/22 (50%) of patients in the older cohort.

Past medical history revealed, 5/12 (42%) of infantile IBD patients had a history of prior hospitalization as compared to 8/22 (36%) in the older cohort. Most admissions in the infantile cohort were for respiratory support for presumed viral infections or reactive airway. Admissions in the older cohort were for respiratory support and Intravenous (IV) antibiotics use (4/8). History of diagnosed infection at initial presentation including viral and bacterial etiologies was 4/12 (33%) and of those infections, 3/4 required oral outpatient antibiotic use and 1/4 required inpatient IV antibiotic use in the infantile IBD patients. In the older cohort, 19/22 (86%) had a history of infection of viral and bacterial etiologies and 14/19 required antibiotics (4/14 required IV antibiotic use inpatient and 10/14 were managed with outpatient oral antibiotics) (Table 1).

	Age at Diagnosis		**Total**
	<2 years (n=12)	**2 years <6 years (n=22)**	**Median Age at Diagnosis (years)**
Demographics			
Female sex	6 (50%)	13 (59%)	4
Male sex	6 (50%)	9 (41%)	2
Asian	2 (16%)	3 (13%)	4
Black or African American	0	2 (9%)	3
Native Hawaiian or Other Pacific Islander	1 (8%)	0	1
Non-Hispanic White or Caucasian	6 (50%)	15 (68%)	3
Hispanic	2 (16%)	2 (9%)	3
Unknown	1 (8%)	0	1
Type of IBD			
Crohn's Disease	11 (92%)	16 (73%)	27 (79%)
Ulcerative Colitis	1 (8%)	6 (26%)	7 (21%)
Disease Activity at Diagnosis PUCAI score, n			
<10 (remission)	0	0	
10-34 (mild)	0	3 (13%)	
≥35 (moderate and severe)	1 (8%)	3 (13%)	
aPCDAI, *n*			
<10 (remission)	0	0	
10-25 (mild)	5 (42%)	8 (36%)	
≥26 (moderate and severe)	6 (50%)	8 (36%)	
Height Z-score, median (range)		-0.43 (-3.12 – 1.39)	
Weight Z-score, median (range)		-0.47 (-3.09 – 1.42)	

Weight for Height Z-score, median (range)		-0.03 (-2.65 – 1.27)	
Laboratory Markers			
CRP, median (range)	2.6 (<0.8 – 7)	<0.8 (<0.8 – 7.4)	
ESR, median (range)	24 (8 – 78)	8 (<1 – >129)	
Albumin, median (range)	3.2 (2 – 4.3)	3.6 (2 – 4.9)	
Calprotectin, median (range)	686 (529 – 731)	1180 (432 – >3000)	
White Blood Cell Count, median (range)	12.2 (4.8 – 14.5)	11.1 (3.5 – 35.4)	
Hemoglobin, median (range)	10.2 (6.5 – 14)	11 (4.7 – 13.8)	
Platelet Count, median (range)	423 (278 – 732)	410 (197 – 1,186)	
Lymphocyte Count %, median (range)	39.2 (21.2 – 72)	37.2 (8 – 67.8)	
Lymphocyte Absolute, median (range)	3,770 (1,018 – 9,072)	3.306 (1,160 – 9,240)	
Absolute Neutrophil Count, median (range)	5,612 (2,168 – 9,280)	4,867 (1,072 – 21,948)	
Eosinophil Count %, median (range)	1.7 (0 – 6)	1.7 (0 – 11)	
Eosinophils Absolute, median (range)	126 (0 – 612)	118 (0 – 3,894)	
Initial Treatment at Diagnosis			
Adalimumab	0	2 (9%)	
Infliximab	1 (8%)	1 (4%)	
Ustekinumab	0	0	
Vedolizumab	0	0	
Mesalamine	1 (8%)	7 (32%)	
Methotrexate	0	3 (13%)	
Tacrolimus	0	1 (4%)	
Azathioprine	2 (16%)	2 (9%)	
Sulfasalazine	3 (35%)	5 (23%)	
EEN	6 (50%)	2 (9%)	
SCD	2 (16%)	2 (9%)	
Corticosteroids			
Systemic	6 (50%)	14 (63%)	
Topical (steroid enemas)	0	1 (4%)	

Endoscopic disease location at diagnosis			
Presence of Upper track disease	9 (75%)	15 (68%)	
Ileum with or without caecum involvement	4 (33%)	14 (63%)	
Isolated colonic	8 (67%)	8 (36%)	
Ileo-colonic	4 (33%)	12 (54%)	
Penetrating (intra-abdominal)	0	0	
Perianal			
Fistualizing	1 (8%)	0	
Skin tags	1 (8%)	1 (4%)	
Structuring	0	0	
Histologic findings location at diagnosis			
Presence of apoptosis	1 (8%)	0	
Presence of granuloma	5 (42%)	11 (50%)	
Medical History			
Hospitalization	5 (42%)	8 (36%)	
Infection	4 (33%)	19 (86%)	
Surgical	1 (8%)	4 (18%)	
Family history of immunodeficiency or autoimmunity	1 (8%)	4 (18%)	
Antibiotic history	3 (25%)	14 (63%)	
Consanguinity	0	0	

Table 1: Initial Demographics and VEO-IBD Characteristics.

Labs at diagnosis revealed a median CRP of 2.6 mg/dL in the infantile IBD cohort and <0.8 mg/dL in the 2 to < 6 year old cohort. Median ESR was 24 mm/hr as compared to 8 mm/hr and albumin was 3.2 g/dL compared to 3.6 g/dL within the infantile IBD versus older cohort. Median fecal calprotectin was 686 ug/g in the younger cohort as compared to 1180 ug/g in the older cohort. The normal fecal calprotectin range for our laboratory is <50 ug/g, with a value >150 ug/g indicating an abnormally high result. CBC with differential was also evaluated in 32/34 (94%) of the VEO-IBD patients (Figure 2A). No statistical significance using Mann-Whitney U-test was found in any of the laboratory studies, although there was a trend towards lower fecal calprotectin the infantile cohort (Figure 2A).

Immunologic workup (Table 2) was performed on 26/34 (76%) of our VEO-IBD patients, with genetic testing performed on only 5/34 patients (15%): 1/5 (20%) University of Washington (UW) Immunoplex™, 1/5 (20%) Invitae, and 3/5 (60%) other genetic testing which includes next generation sequencing of bone marrow aspirate (MarrowSeqPanel™) [15,16], targeted next generation sequencing of peripheral blood for autism (Autism/ID Xpanded Panel) [17], and standard karyotype and chromosomal microarray of peripheral blood. All 5 patients that had genetic testing done, had mutations or genetic anomalies identified: one patient was diagnosed with Diamond-Blackfan anemia using MarrowSeqPanel™ [15,16] with a heterozygous deletion in RPS10 (RPS10pR113x) leading to the truncation and disruption of RPS10, one was diagnosed with a NONO (c.1028+1G>A) gene mutation using commercially available Autism/ID Xpanded Panel [17], one was diagnosed with MYO5B (heterozygous MN.0001080467.2:c.1966C>T) and MPO (heterozygous NM.000250.1:c.2031-2A>C) mutations using UW Immunoplex™ [13], one was diagnosed with an unbalanced chromosomal

translocation resulting in the loss of 18p and gain of 20p (18p11.32p11.21x1, 20p13p11.1x3) using standard karyotype and chromosomal microarray, and one was found to have Variants of Unknown Significance (VUS) in FANCI [heterozygous c.467G>A (p.Cys156Tyr)], COL7A1 [heterozygous c.6497A>G (p.Lys2166Arg)], and FAT4 [heterozygous c.14831T>G (p.Val4944Ala)] using Invitae [14]. Of the genetic abnormalities diagnosed, 3 patients with the mutations (NONO, MYO5B and MPO, unbalanced chromosomal translocation with loss of 18p and gain of 20p) were diagnosed before the onset of IBD symptoms and 2 patients diagnosed after the diagnosis of IBD (RSP10 and 3 VUS).

	Age at Diagnosis		**Total**
	<2 years (n= 12)	**2 years <6 years (n= 22)**	**<6 years (n= 34)**
Immunologic or Genetic Workup	10	16	26 (76%)
Lymphocyte Subset Analysis	9	13	22 (65%)
Immunoglobulin	12	15	27 (79%)
Neutrophil Oxidative Burst	7	14	21 (62%)
Titers to vaccines			
Tetanus toxoid IgG antibody	6	9	15 (44%)
Streptococcus pneumoniae IgG	4	10	14 (41%)
Mitogen Stimulation Test	5	8	13 (38%)
B Cell Phenotype	1	0	1 (3%)
XIAP Protein Expression	3	1	4 (12%)
FoxP3 Protein Expression	3	1	4 (12%)
IL-10 Receptor Function	2	1	3 (9%)
Genetic Testing			
UW Immunoplex™ panel	0	1	1 (3%)
Invitae panel	1	0	1 (3%)
Other	1	2	3 (9%)
Mutation	2 (One with COL7A1, FANCI, and one with FAT4, RPS10)	3 (One with NONO gene mutation, one with MYO5B and MPO mutations, and one with chromosomal translocation)	5 (15%)

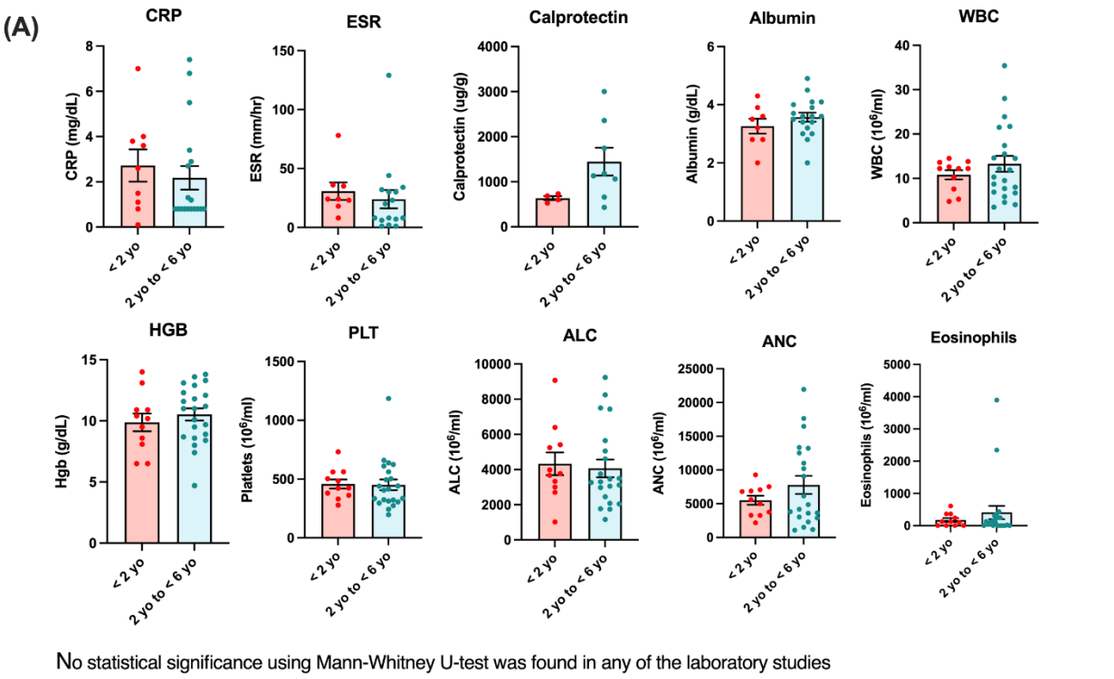
Table 2: Immunological and Genetic workup.

22/34 (65%) of patients had lymphocytes subsets performed, 27/34 (79%) had immunoglobulin levels, and 21/34 (62%) had neutrophil oxidative tests (Table 2). Only 13/34 (38%) had mitogen stimulation test done, 15/34 (44%) had vaccine titers to Tetanus toxoid, 14/34 (41%) had vaccine titers to *Streptococcus pneumoniae*, 1/34 (3%) had B-cell phenotyping done, 4/34 (12%) had XIAP and FoxP3 protein levels, and 3/34 (9%) had IL-10 receptor function assessed. Of the immunological testing that was done, two had abnormal findings: one in the younger cohort with a lower XIAP level that turned out to have Diamond-Blackfan syndrome later on and one in the younger cohort with lower percentage of FOXP3+ cells of CD4+ T cell population (2.8% versus normal percentage at 4.1%). The latter patient did not have further genetic testing done and was lost to follow-up.

Clinical Course

During 12 months of follow-up of the patients with infantile IBD, 4/12 patients (33%) were started on anti-TNF antibody therapy (2 adalimumab and 2 infliximab). (Table 3) In the older cohort, 15/22 patients (68%) were started on anti-TNF therapy (6 adalimumab and 9 infliximab). Of the patients who received anti-TNF therapy, therapy was discontinued in 11/19 (58%) at 12 months of follow-up with discontinuation rates of 75% (3/4) in the infantile group and 53% (8/15) in the older cohort (Table 3, Figure 2B). Vedolizumab was used in 3/34 patients (1 in the infantile group and 2 in the older cohort) and discontinued in 1/1 patients (100%) in the infantile IBD cohort and 1/2 (50%) in the older cohort. Mesalamine/sulfasalazine was used in 22/34 patients (65%) and discontinued at 1 year follow up in 2/7 (29%) in the infantile group and 9/15 (60%) in the older cohort. Immunomodulators were used in 13/34 (38%) of patients. In the infantile cohort, immunomodulators were discontinued in 1/5 (20%) patients (azathioprine). In the older cohort, 3/8 patients (38%) had immunomodulators discontinued (2 methotrexate and 1 azathioprine). One patient (8%) in the infantile cohort was maintained on cyclosporine. Tacrolimus was started and discontinued in 1 (4%) patient in the older cohort (Table 3, Figure 2B). All medication discontinuation was secondary refractory clinical symptoms and lack of biochemical laboratory improvement.

Figure 2. (A) Clinical lab parameters from blood work and fecal calprotectin from stool in the Very Early Onset Inflammatory Bowel Disease (VEO-IBD) cohort. **(B)** Percentage of patients refractory to medications at 1 year followup.



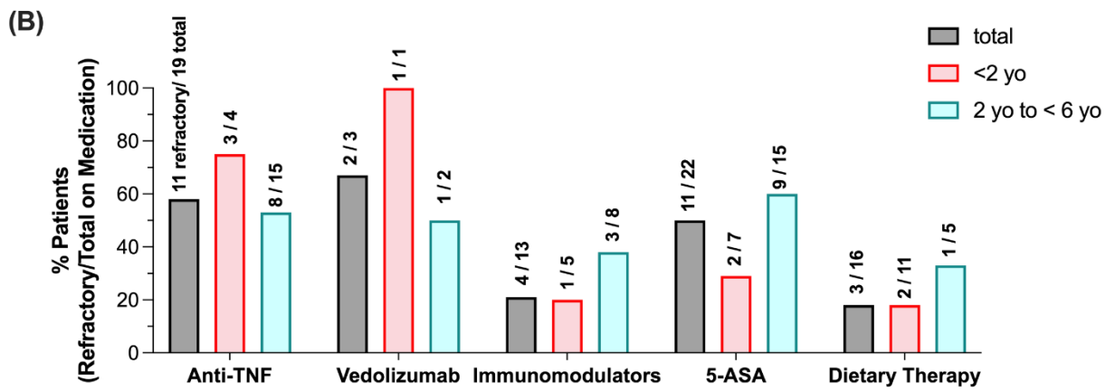


Figure 2: Laboratory parameters at diagnosis and medication use at followup.

Nutritional therapy, Exclusive Enteral Nutrition (EEN) and the Specific Carbohydrate Diet (SCD), was used in 16/34 patients (47%). Nutritional therapy was discontinued at 1 year follow up in 2/11 patients in the infantile cohort with 1 patient stopping EEN and 1 patient stopping SCD. In the older cohort, nutritional therapy was discontinued at 1 year in 1/5 for EEN (Table 3, Figure 2B).

	Trialed and Failed		**Total**	**Trialed and Maintained**		**Total**
	<2 years (n=12)	**2 years <6 years (n=22)**	**<6 years (n=34)**	**<2 years (n=12)**	**2 years <6 years (n=22)**	**<6 years (n=34)**
Anti-TNF antibodies Totals	3	8	11 (58%)	1	7	8 (42%)
Adalimumab	1	2	3 (38%)	1	4	5 (62%)
Infliximab	2	6	8 (73%)	0	3	3 (27%)
Vedolizumab	1	1	2 (67%)	0	1	1 (33%)
Immunomodulators	1	3	4 (21%)	4	5	9 (69%)
Methotrexate	0	2	2 (40%)	1	2	3 (60%)
Azathioprine	1	1	2 (25%)	3	3	6 (75%)
Cyclosporine	0	0	0	1	0	1 (100%)
Tacrolimus	0	1	1 (100%)	0	0	0
5-ASA	2	9	11 (50%)	5	6	11 (50%)
Sulfasalazine	1	4	5 (50%)	3	2	5 (50%)
Mesalamine	1	5	6 (50%)	2	4	6 (50%)
Dietary Therapy	2	1	3 (18%)	9	4	13 (82%)
EEN	1	1	2 (25%)	5	1	6 (75%)
SCD	1	0	1 (13%)	4	3	7 (87%)
Ustekinumab	0	0	0	0	0	0

Table 3: 1 year Follow-up Medication Data.

At the end of 1 year of follow-up, sustained clinical remission was achieved in 8/12 (67%) of the infantile IBD cohort. In the older cohort, 17/22 (77%) patients achieved sustained clinical remission using clinical scores (aPCDAI and PUCAI). Within the infantile IBD cohort, 2/12 patients required repeat hospitalizations, 1/12 required a total abdominal colectomy, and no infections were documented. Of the older cohort patients, 7/22 were re-hospitalized, 1/22 required a total abdominal colectomy, and 4/22 had infections (Table 4).

	Age at Diagnosis		**Total**
	<2 years (n=12)	**2 years <6 years (n=22)**	**<6 years (n=34)**
Remission			
Clinical Remission (n=25)	8 (n=12 flaring at diagnosis) (67%)	17 (n=22 flaring at diagnosis) (77%)	25 (74%)
Normalization of CRP (n=9)	2 (n=4 abnormal at diagnosis) (50%)	7 (n=9 abnormal at diagnosis) (78%)	9 (69%)
Hospitalization			
Number (n=9)	2 (17%)	7 (32%)	9 (26%)
Surgical intervention (n=2)	1 (total abdominal colectomy) (8%)	1 (total abdominal colectomy) (5%)	2 (6%)
Infection (n=4)	0	4 (18%)	4 (12%)

Table 4: 1 year Follow-up Clinical Data.

Discussion

Over the last half century, VEO-IBD has increased in incidence worldwide, though the characteristics of the disease appear to be similar across time and institutions without obvious regional differences within the United States. Similar to other reports in the medical literature, our patient cohorts were more often diagnosed with CD-phenotype, with the majority having isolated colonic disease [6,18].

Although the diagnostic gold standard for VEO-IBD diagnosis is through endoscopy and histopathological review, fecal calprotectin was obtained for patients in both cohorts. Traditionally fecal calprotectin in infants tend to be more elevated as compared to older children [19], our VEO-IBD population shows a higher level in the older cohort, perhaps reflecting a higher disease burden at presentation however the role of fecal calprotectin and correlation to disease location and activity in VEO-IBD is not fully elucidated.

The rate of infections in VEO-IBD has not been described in detail. Our VEO-IBD population appears to have a higher incidence of infections especially severe infections requiring antibiotic use more so than the general pediatric population [20-22]. The effects of antibiotic use and infection in the role of developing IBD in general deserves further evaluation especially in the younger cohorts. The rate of inpatient admission in both cohorts are increased for respiratory and IV antibiotic support. The presence of IEI underlying the VEO-IBD population and increased infection risk also warrants further evaluation.

From a treatment perspective, VEO-IBD represents a population of IBD patients that is often refractory to medical therapies. 58% of our population of VEO-IBD patients who trialed an anti-TNF therapy were refractory to therapy within 12 months of clinical follow-up (Table 3, Figure 2B). Although the number of patients started on vedolizumab was quite small, 67% were refractory to vedolizumab (Table 3, Figure 2B). The large percentage of patients who trialed nutritional therapy in the form of EEN and SCD and sustained this therapy reflects our institution's experience with nutritional therapy in IBD and integration of nutrition in IBD care. This also highlights the potential role of nutrition in IBD and shows that nutritional therapy can be safely used in VEO-IBD [23].

The disease course of our VEO-IBD population is similar to that of populations found at other large institutions in the United States. A 2019 retrospective single-center review from Children's Hospital of Philadelphia (CHOP) also found the majority of their VEO-IBD patients presented with colonic Crohn's disease and had a more severe disease course as compared to patients who were diagnosed after 6 years of age. Patients with VEO-IBD at CHOP were more likely to be refractory to anti-TNF therapy than older pediatric IBD patients (62.4% vs. 14.6%) and failed immunomodulatory therapy more frequently as well (69.1% vs 19.5%) when assessed 1 year after initiation of therapy. 88% of CHOP VEO-IBD patients with identified monogenic defects failed medical treatment, 50% required surgical intervention, and 100% presented with stunted growth and required hospitalization. This indicates the same importance for early identification of monogenic variants that we are highlighting at our center, given the widespread impact on disease severity [6]. Through the literature review and shared clinical experiences, we inspire to improve our overall diagnostic approach through algorithm development and automated electronic medical orders.

Our study has several limitations. This is a retrospective cohort study and a single center review, thus confining data collection to what already exists within our center's electronic medical records system. Our analysis was based on ICD-9 and 10 codes, which might not have been assigned to all possible VEO-IBD patients at our center. Our patient demographics reflect the population of the Pacific Northwest, and in combination with our small overall cohort, are not identically reflective of the greater VEO-IBD patient population. In our population, it was difficult to link phenotypic IBD features and clinical outcome of medication response to the genetic mutations detected in the 5 patients with genetic mutations found though that is an area of study for future directions.

Proposed Multidisciplinary Approach

The most notable finding from our study is the inconsistency in approach to workup and genetic testing in this population. Of the abnormal immunological studies done, only one had follow-up genetic testing and overall, very few patients had follow-up genetic testing done in general. Thus, we designed and implemented a tiered approach to establish an immunological diagnosis and screen for IEI with tier 1 and 2 VEO-IBD order sets, with the understanding that the required blood volumes can be a challenge in young pediatric patients (Figure 3). This systematic tiered approach for the immunologic evaluation of VEO-IBD patients was based on the approaches previously outlined by Uhlig, et al. [1], Ouahed, et al. [5], and new 2020 NASPGHAN guidelines [9]. Baseline evaluation involves basic laboratory studies including Complete Blood Count (CBC) with differential, inflammatory markers (CRP, ESR), comprehensive metabolic panel, and stool studies, often obtained before endoscopy. "Tier 1" evaluation includes functional immunological screening, including T-, B-, and NK-cell population subsets by flow cytometry, along with immunoglobulin levels to evaluate for adaptive immunological defects and humoral immunity. Additionally, neutrophil oxidative burst assay is obtained to screen for chronic granulomatous disease. Male patients additionally are evaluated for XIAP and FOXP3

expression recent literature describes older male patients have later diagnosis of XIAP and IPEX [24,25]. Il-10 receptor evaluation will be done per Immunology recommendation depending on age of diagnosis and clinical phenotypic presentation of severe fistulizing perianal disease. Tier 2 evaluation involves a more granular evaluation of the adaptive immune system, including memory subsets of T and B cells, B cell phenotype via flow cytometry, mitogen stimulation tests, and vaccine titers to assess T cell and B cell memory and subset switching.

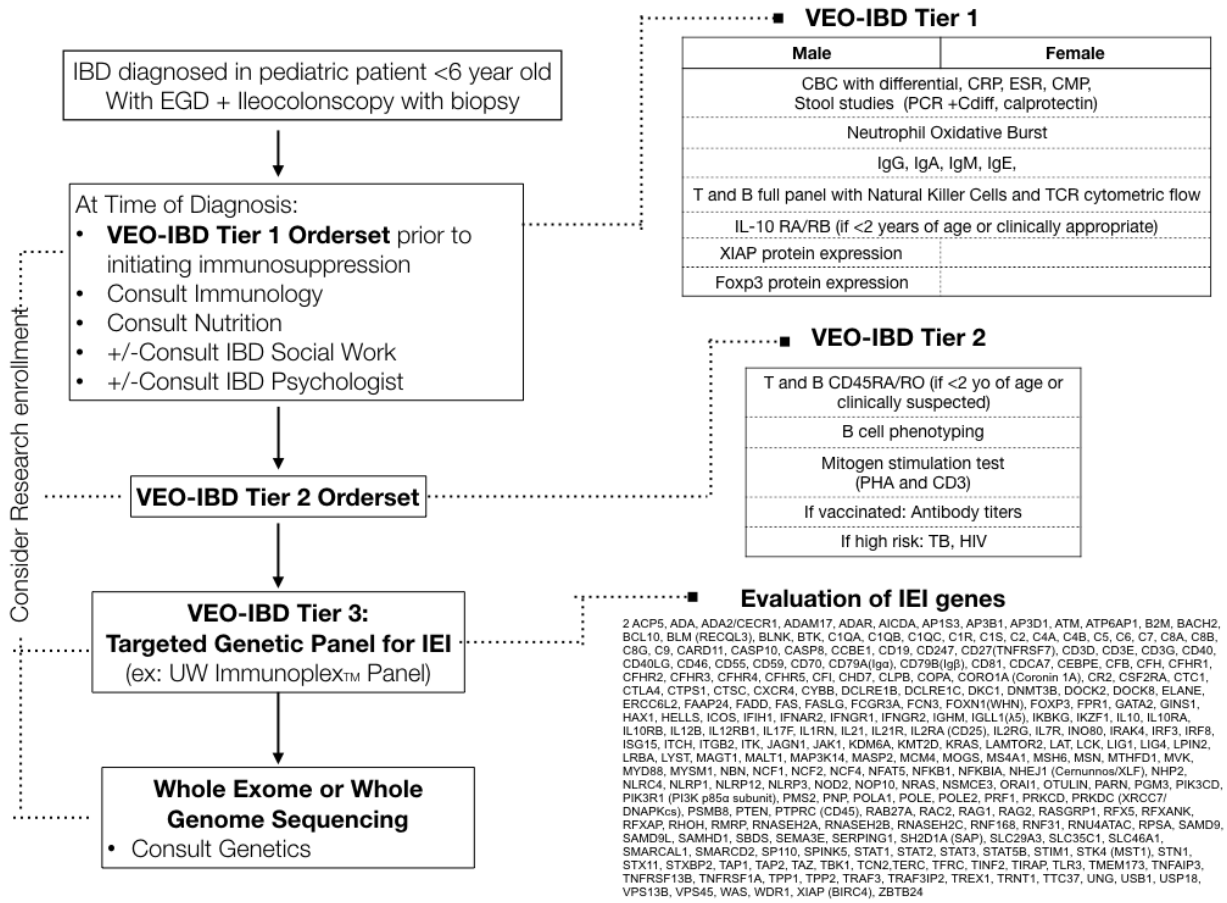


Figure 3: Proposed Algorithm for Expedited Immunological Workup for VEO-IBD.

Definitive monogenic diagnosis of an IEI as the cause of VEO-IBD is ultimately performed with genetic testing. While it has been previously reported that up to 20% of VEO-IBD patients have monogenic etiologies, identifying IEI remains limited by our knowledge of known monogenic etiologies of IEI [5]. The known number of IEI is increasing with significant improvements in next generation genetic sequencing. Notably, the number of single-gene IEI has increased from 65 to 485 in the 2022 update of the International Union of Immunological Societies (IUIS) Phenotypical Classification [26]. As such, Targeted Gene Panels (TGP) have been utilized to capture the most likely genetic culprits of monogenic IEI in VEO-IBD with high diagnostic accuracy. Ultimately, TGP testing is a necessary step in the complete evaluation of VEO-IBD patients.

Based on the IUIS classification, our institution has created the University of Washington (UW) ImmunoplexTM Panel uses next-generation sequencing to detect mutations in 249 genes known to cause IEI, completely sequencing all exons of these genes and detects large deletions, duplications, and mosaicism [13]. The Invitae Monogenic IBD panel evaluates 67 genes that are known to be associated with IEI that lead to VEO-IBD utilizing full-gene sequencing and deletion/duplication analysis using next-generation sequencing [14]. In our experience, in order to facilitate access to data and ability to evaluate more genes associated with IEI, we decided to rely more

heavily on the UW ImmunoplexTM to evaluate our institutions VEO-IBD patients.

For clinicians who are considering using genetic testing, it is important to note that Invitae is a private TGP though available to clinicians and UW ImmunoplexTM Panel is only available at University for Washington. We recognize that not all clinicians have access to these specialized institutional TGP though will want to focus on the specific IEI genes working alongside an expert Immunologist. In our experience, in order to facilitate access to data and ability to evaluate more genes associated with IEI, we decided to rely more heavily on the UW ImmunoplexTM to evaluate our institutions VEO-IBD patients.

With more direct access to patient genetic data, next generation sequencing can be repeated as new IEI are described, particularly if no genetic defect is found on initial evaluation. Also if TGP is negative, procession to whole genome or exome sequencing through collaboration with the Genetics team is recommended. As further blood draws and volume can become an issue, we would consider DNA sample collection through other sources such as saliva or buccal swabs. These evaluations are essential to improving outcomes of VEO-IBD given focused therapeutic treatments dependent on the monogenic cause of VEO-IBD.

Conclusion

Here, we strive to improve our understanding of the clinical course and management of VEO-IBD and apply most recent literature reviews to our own institutional approach in order to improve outcomes for this vulnerable patient population. With increasing therapeutic modalities for patients with VEO-IBD and medicine's improved ability to identify monogenic causes of VEO-IBD, the clinical course and outcomes for these patients can be significantly impacted. For our institution, evolving our practices through most up-to-date literature has allowed us to standardize practice for VEO-IBD diagnosis in hopes to improve outcomes for this vulnerable population.

References

1. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, et al. (2014) The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 147: 990-1007 e3.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, et al. (2011) Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 17: 423-439.
3. Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, et al. (2017) Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol 112: 1120-1134.
4. Bequet E, Sarter H, Fumery M, Vasseur F, Armengol-Debeir L, et al. (2017) Incidence and Phenotype at Diagnosis of Very-early-onset Compared with Later-onset Paediatric Inflammatory Bowel Disease: A Population-based Study [1988-2011]. J Crohns Colitis 11: 519-526.
5. Ouahed J, Spencer E, Kotlarz D, Shouval DS, Kowalik M, et al. (2020) Very Early Onset Inflammatory Bowel Disease: A Clinical Approach With a Focus on the Role of Genetics and Underlying Immune Deficiencies. Inflamm Bowel Dis 26: 820-842.
6. Kelsen JR, Conrad MA, Dawany N, Patel T, Shraim R, et al. (2020) The Unique Disease Course of Children with Very Early onset-Inflammatory Bowel Disease. Inflamm Bowel Dis 26: 909-918.
7. Zheng HB, de la Morena MT, Suskind DL (2021) The Growing Need to Understand Very Early Onset Inflammatory Bowel Disease. Front Immunol 12: 675186.
8. Sullivan KE, Conrad M, Kelsen JR (2018) Very early-onset inflammatory bowel disease: an integrated approach. Curr Opin Allergy Clin Immunol 18: 459-469.
9. Kelsen JR, Sullivan KE, Rabizadeh S, Singh N, Snapper S, et al. (2020) 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. J Pediatr Gastroenterol Nutr 70: 389-403.
10. Levine AE, Zheng HB, Suskind DL (2022) Linking Genetic Diagnosis to Therapeutic Approach in Very Early Onset Inflammatory Bowel Disease: Pharmacologic Considerations. Paediatr Drugs 24: 207-216.
11. Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, et al. (2010) Appraisal of the pediatric Crohn's disease activity index on four prospectively collected datasets: recommended cutoff values and clinimetric properties. Am J Gastroenterol 105: 2085-2092.
12. Hoekman DR, Diederen K, Koot BG, Tabbers MM, Kindermann A, et al. (2016) Relationship of clinical symptoms with biomarkers of inflammation in pediatric inflammatory bowel disease. Eur J Pediatr 175: 1335-1342.
13. https://testguide.labmed.uw.edu/public/view/IMD
14. https://www.invitae.com/en/physician/tests/08122/#info-panel-assay_information
15. Nord AS, Lee M, King MC, Walsh T (2011) Accurate and exact CNV identification from targeted high-throughput sequence data. BMC Genomics 12: 184.
16. https://testguide.labmed.uw.edu/public/view/MRW
17. https://www.genedx.com/tests/detail/autism-id-xpanded-panel-849
18. Conrad MA, Carreon CK, Dawany N, Russo P, Kelsen JR (2019) Distinct Histopathological Features at Diagnosis of Very Early Onset Inflammatory Bowel Disease. J Crohns Colitis 13: 615-625.
19. Li F, Ma J, Geng S, Wang J, Liu J, et al. (2015) Fecal calprotectin concentrations in healthy children aged 1-18 months. PLoS One 10: e0119574.
20. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE (2012) Antibiotic exposure and IBD development among children: a population-based cohort study. Pediatrics 130: e794-e803.
21. Weintraub B (2015) Upper Respiratory Tract Infections. Pediatr Rev 36: 554-556.

22. Van den Bruel A, Bartholomeeusen S, Aertgeerts B, Truyers C, Buntinx F (2006) Serious infections in children: an incidence study in family practice. BMC Fam Pract 7: 23.

23. Miller TL, Lee D, Giefer M, Wahbeh G, Suskind DL (2017) Nutritional Therapy in Very Early-Onset Inflammatory Bowel Disease: A Case Report. Dig Dis Sci 62: 2196-2200.

24. Chang I, Park S, Lee HJ, Kim I, Park S, et al. (2021) Interpretation of XIAP Variants of Uncertain Significance in Paediatric Patients with Refractory Crohn's Disease. J Crohns Colitis 15: 1291-1304.

25. Zama D, Cocchi I, Masetti R, Specchia F, Alvisi P, et al. (2014) Late-onset of immunodysregulation, polyendocrinopathy, enteropathy, x-linked syndrome (IPEX) with intractable diarrhea. Ital J Pediatr 40: 68.

26. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, et al. (2022) Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 42: 1473-1507.