Very Early Onset Inflammatory Bowel Disease Work Up

Introduction

Very early onset inflammatory bowel disease (VEO-IBD) is defined as IBD that presents in infants and children less than 6 years of age. Patients presenting less than 2 years of age are further sub-categorized as having infantile-onset IBD and those presenting at less than 27 days of age can be classified as neonatal-onset IBD (Kelsen et al., 2020; Ouahed et al., 2019). Often, these patients have a more severe and difficult to manage disease course than older patients. The incidence of IBD among this population is increasing; therefore, it is important to be familiar with additional considerations when evaluating these patients.

Between 6-15% of pediatric IBD patients develop symptoms under 6 years of age. Of these patients, 15-20% have a monogenic defect (one gene is involved in causing the IBD phenotype). This is in contrast to older patients who are more likely to have polygenic inheritance defects (multiple genes are involved in the IBD phenotype (Kelsen et al., 2020). It is important to emphasize, especially when counseling families of patients who have VEO-IBD, that a majority (about 80%) will likely not have a monogenic defect identified given the currently available testing (Ouahed et al., 2019). The process for further evaluation and treatment should be based on the clinician's experience and expert opinion.

Many of the monogenic defects that have been identified in patients with VEO-IBD are also found in primary immune deficiency syndromes which often present with GI symptoms. These defects can affect the following processes: IL-10 signaling defects, immune dysregulation, T and B cell dysfunction, phagocytic defects, hyperinflammatory and autoinflammatory dysfunction, and epithelial barrier dysfunction.

Examples for currently known genetic causes of VEO-IBD:

- IL-10 signaling defects
- Immune dysregulation
    - Immunodysregulation Polyendocrinopathy X linked Syndrome (IPEX)
- T and B cell defects
    - Wiscott Aldrich Syndrome
    - Severe Combined Immunodeficiency (SCID)
    - Common Variable Immune Deficiency (CVID)
- Phagocytic defects

    - Chronic Granulomatous Disease (CGD)
- Hyperinflammatory and autoinflammatory disorders
    - X-linked lymphoproliferative syndrome 2 (XIAP)
    - Hermansky-Pudlak Syndrome
- Epithelial barrier dysfunction
    - Nuclear factor-kappa B Essential Modulator Deficiency Syndrome (NEMO)

Goals of Diagnostic Evaluation for VEO-IBD is to identify patients (Kelsen et al., 2020):

1. With an underlying genetic cause of their VEO-IBD.
2. With an underlying primary immune deficiency.
3. Who could benefit from non-standard IBD therapies.
   For example:
   - In those with IL-10 defects, hematopoietic stem cell transplantation has been shown to be potentially lifesaving.
4. Who are at increased risk for other non-GI complications so that they can be appropriately monitored.
   For example:
   - Anti-TNF therapy is contraindicated in patients with Chronic Granulomatous Disease (CGD), a more common monogenic cause of VEO-IBD, due to increased infection risk.
   - Patients with IL-10 defects are at increased risk for certain types of lymphomas.

The identification of several monogenic defects has led to effective targeted therapies (Kelsen et al., 2020).

Index of Suspicion for VEO-IBD

Clinical Presentation

Presenting symptoms of VEO-IBD are nonspecific, variable, and can include:

- Age less than 6 years old
- Bloody and/or mucus containing diarrhea
- Frequent emesis
- Growth failure
- Perianal skin tags/fistulas
- Intermittent fevers
- Arthritis
- Arthralgias
- Folliculitis
- Uveitis

With this variable clinical presentation, it is important to rule out more common causes of symptoms such as cow's milk protein intolerance, infection, celiac disease, nutritional and/or caloric deficits, and food allergies while including VEO-IBD in the differential. In patients less than 12 months of age, a 2-week trial of an elemental formula to rule out cow's milk protein intolerance and allergic colitis should be considered unless not indicated clinically due to severity of presentation (Ouahed et al., 2019). Additionally, other hereditary and primary immunodeficiencies should be considered (Ouahed et al., 2019).

It is important to review in any patients' past medical or relevant family history (particularly inquiring about consanguinity, miscarriages) for other factors which may increase suspicion for the diagnosis of VEO-IBD. Findings on physical examination are often the key for consideration for further work up. The HPI, family history and physical exam may provide signs for a monogenic disease (See Table 1).

Table 1

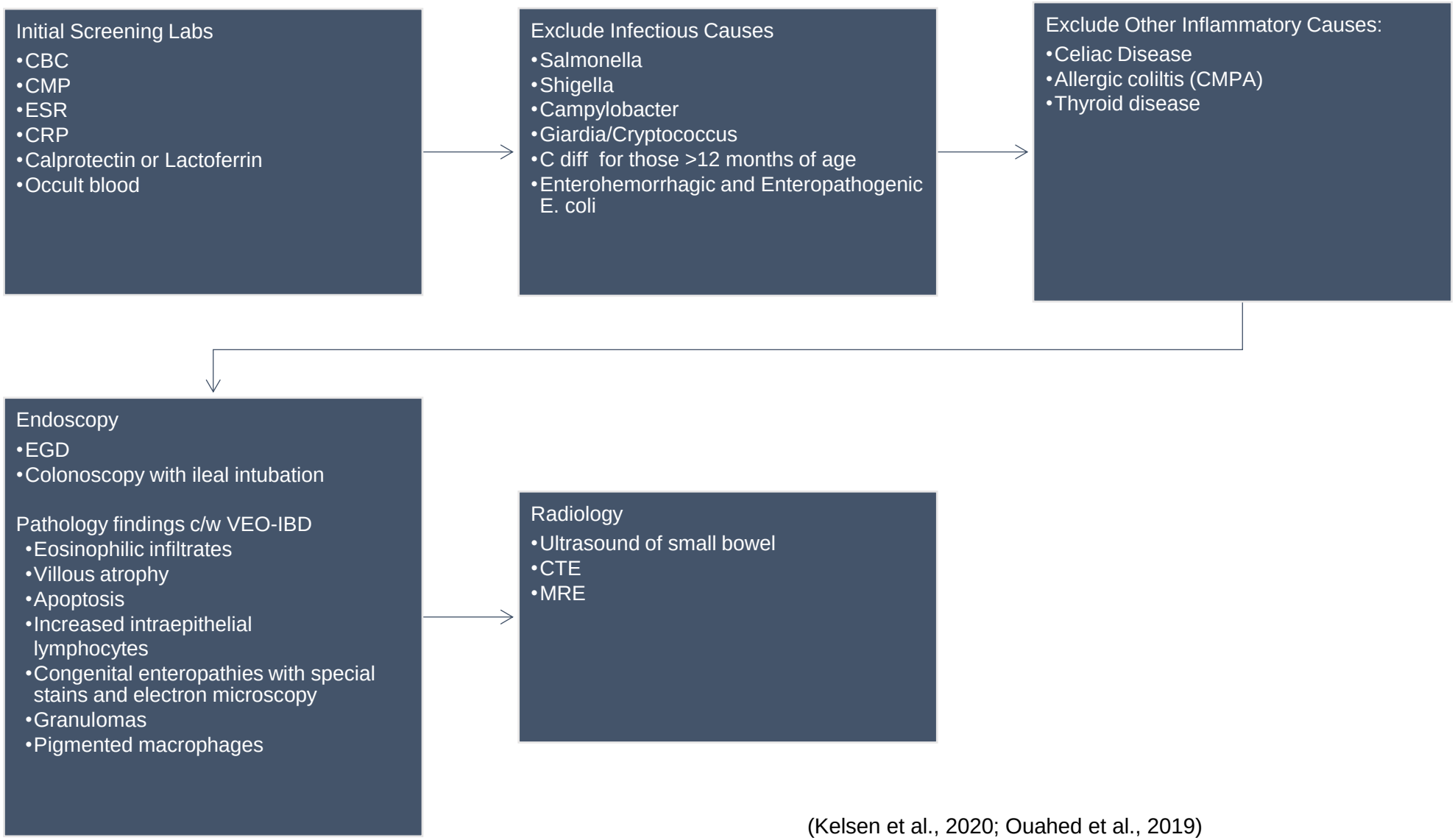
History of Presenting Illness	Family History	Physical Exam
•Age of onset •GI History of: •Abnormal stooling •Diarrhea • Blood in stool • Mucous in stool •Frequent emesis •Intermittent fevers •Perianal disease •Skin tags •Fistula • Deep fissures • Excoriation •Non GI history of: •Skin findings •Folliculitis •Dermatitis •Pyoderma gangrenosum •Erythema nodosum •Significant or recurring infections •Associated autoimmunity	•Consanguinity •Autoimmune or inflammatory disease •Hemophagocytic Lymphohistiocytosis (HLH) •Arthritis •Susceptibility of severe infections •Malignancy •Skin diseases •Atopy •X linked diseases	•Signs of disease acuity •Pallor •Abdominal tenderness •Abdominal distention, etc •Perianal disease •Skin tags •Fistula •Deep fissures •Excoriation •Oral lesions •Skin findings •Folliculitis •Dermatitis •Pyoderma gangrenosum •Erythema nodosum •Arthritis •Growth delay •Failure to thrive •Splenomegaly •Adenopathy

(Kelsen et al., 2020; Ouahed et al., 2019).

Initial Workup

Initial work up to rule out more common causes of the presenting symptoms include (see Table 2):

Table 2



(Kelsen et al., 2020; Ouahed et al., 2019)

If initial screening studies (laboratory, endoscopic and/or radiographic studies) to rule out other causes of presenting symptoms raise concern for VEO-IBD, then additional second-tier testing should be considered (see Table 3).

Table 3

Second Tier Testing

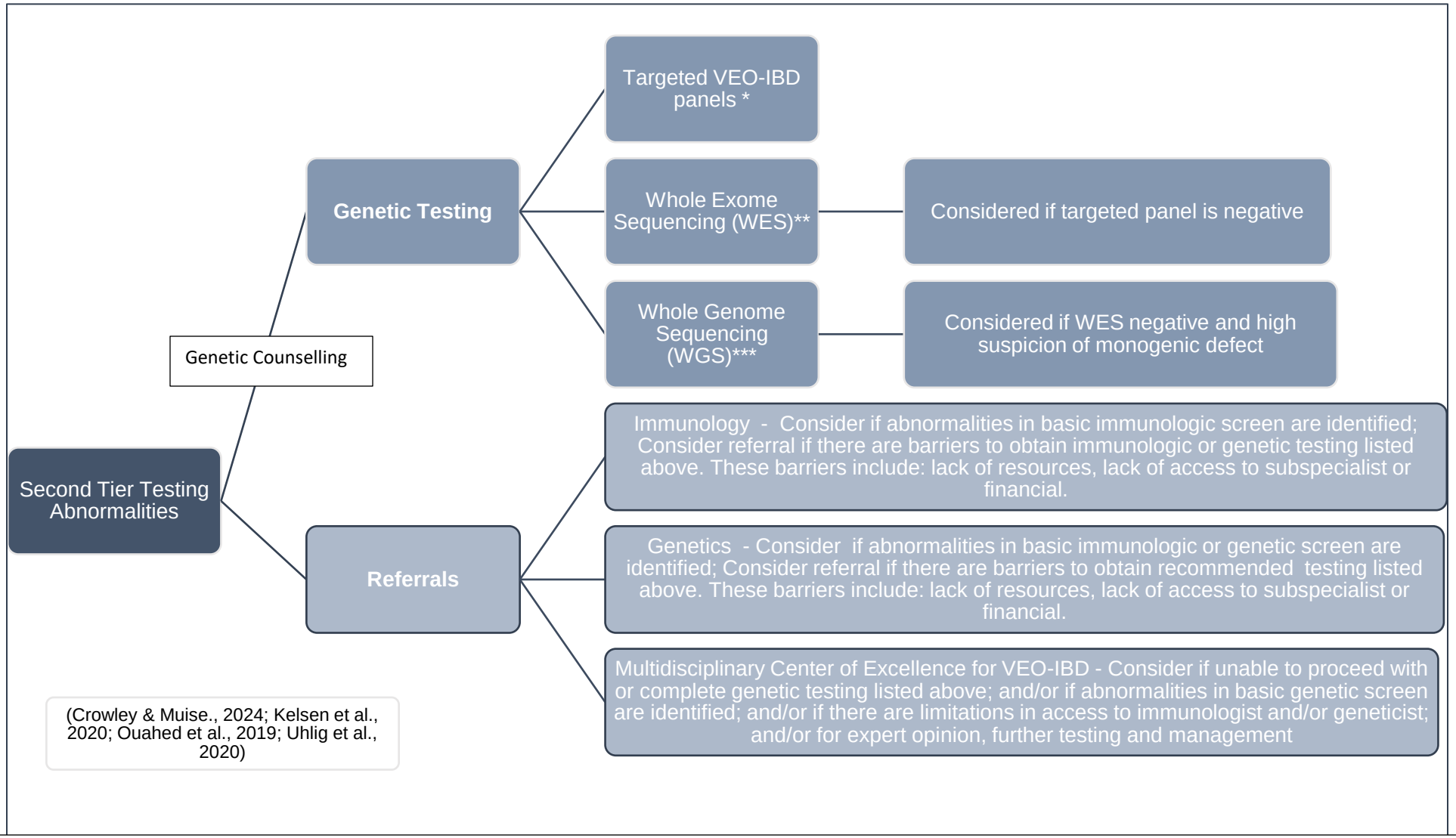
- Immunoglobulins (IgA, IgM, IgG, IgE)
- Vaccine Titers (Obtain vaccine history)
- Lymphocyte subsets
- Neutrophil oxidative burst assay
- HIV
- TB testing (PPD, Quantiferon TB Gold, T spot)

(Kelsen et al., 2020; Ouahed et al., 2019)

Based on second-tier testing results, additional genetic testing may be indicated.

Current recommendations are that genetic testing should be guided by the clinical presentation, index of clinical suspicion, availability of resources, institutional policies, and costs (Uhlig et al., 2020). Every patient with suspected VEO-IBD does NOT require genetic sequencing (Uhlig et al., 2020). According to recent ESPGHAN guidelines (Uhlig et al., 2020), genetic sequencing is recommended for those with infantile IBD (presentation less than 2 years of age) and should be considered in those <6 years of age especially when there is high concern for monogenic cause (Uhlig et al., 2020). The decision to proceed with genetic testing is best done in coordination with a multidisciplinary team approach which includes the availability and support of genetic counselling. This may be available at your institution or could require referral for additional work up. (see Table 4):

Table 4



* **Target Sequencing Panels** for VEO-IBD have been developed. Unfortunately, the sensitivity of these panels has not yet been vigorously tested (Kelsen et al., 2020). According to NASPGHAN guidelines, 'targeted panels should first be performed in: Cases of Infantile VEOIBD; when the phenotype is consistent with a known defect; history of consanguinity; and abnormal immunology studies ` (Kelsen et al., 2020). See Clinical Pearls

****Whole Exome Sequencing** (WES) - Clinical judgement should guide who undergoes WES. This often requires input from Genetics, Immunology or VEO-IBD Center of Excellence. It requires genetic testing of the patient and parents. Should include both pre and post testing counseling (Crowley & Muise, 2014). Often done for further evaluation after negative Target Sequencing Panel results or instead of Targeting Sequencing Panel in some cases. Often done under research protocols. (Kelson et all, 2020). See Clinical Pearls

*****Whole Genome Sequencing** (WGS)- Recommendations for referral to center of excellence for genetic testing and work with multidisciplinary team which includes gastroenterology, bioinformatics, genetics and immunology (Kelson et al., 2020; Crowley & Muise, 2014). Reserved for high index of suspicion but negative WES and Targeted Sequencing Panel. (Kelsen et al., 2020). See Clinical Pearls

Clinical pearls:

- Pancolitis is noted at initial presentation in about 40% of patients with VEO-IBD. However, disease phenotype can change over time to include features that are suggestive of Crohn's disease (Kelsen et al., 2020)
- Consider IL-10 deficiency or defects if the patient presents with infantile or neonatal VEO-IBD with severe enterocolitis, folliculitis, perianal disease, arthritis (Kelsen et al., 2020)
- Villous atrophy in the small bowel may indicate a regulatory T cell defect such as IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). Type 1 diabetes is also a key feature of IPEX. (Kelsen et al., 2020)
- Thin hair and decreased number of teeth should raise suspicion for NEMO (Kelsen et al., 2020)
- Wiscott-Aldrich Syndrome should be considered with low platelets and eczema (Kelsen et al., 2020)
- Consider XIAP (X-linked inhibitor of apoptosis protein) deficiency in patients with severe colonic and fistulizing perianal involvement. In these patients, there is risk of fatal HLH with infections, most commonly EBV (Kelsen et al., 2020).
- Cost of genetic testing may or may not be covered by insurance companies. These tests can cost thousands of dollars. It is important to let parents/patients know this up front. Recommend that they check with their insurance company for coverage **before** the tests are done. For those in whom the cost is prohibitive, consider enrollment in a clinical research program which could potentially defer testing costs (Kelsen et al., 2020).

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