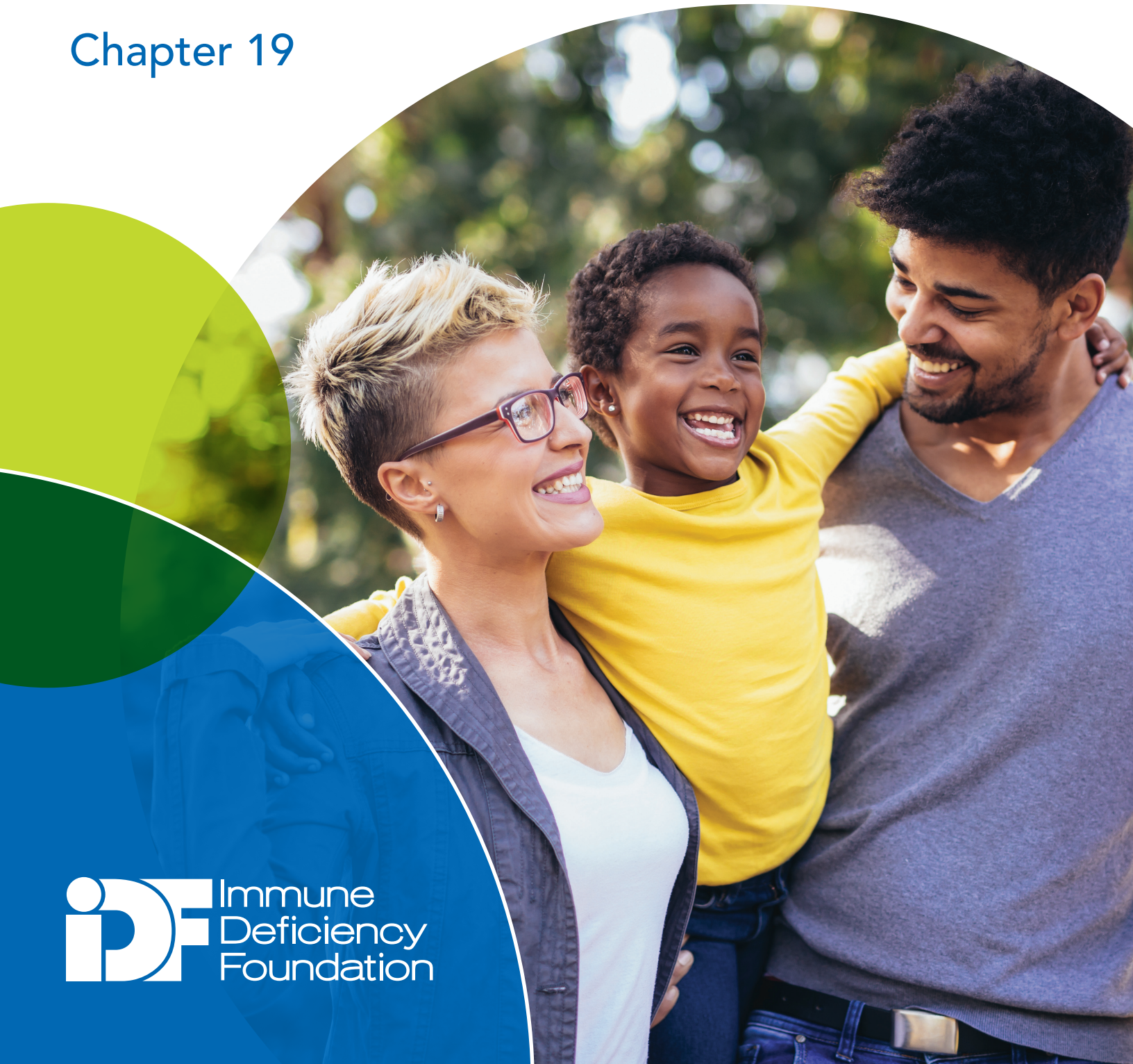
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 19



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6th Edition

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Chapter 19

Immune Dysregulation, Enteropathy, and Colitis

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Primary immune regulatory disorders (PIRD) are characterized by a disturbance of immune tolerance (See Autoimmunity Chapter) and excessive inflammation. Inflammation in the gastrointestinal (GI) tract presenting as colitis (inflammation and ulcers of the bowel wall of the colon) and enteropathy (inflammation of the bowel especially the small bowel) is a common presentation of PIRD that can significantly affect the quality of life in individuals with PIRD. Colitis can be the presenting manifestation of an underlying broader immune dysregulation (abnormality or impairment in the regulation of some part of the immune system), or it could develop later in the disease course. Other types of broader immune dysregulation include multi-system autoimmune conditions, such as low blood cell counts, thyroid failure, pancreatic failure, and arthritis. Lymphoproliferation (excessive lymphocyte production) and susceptibility to infections can co-exist or develop later in the disease course. It is important to identify individuals who have colitis or enteropathy as the presenting manifestation of PIRD as it can help in both early identification and initiation of treatment. This approach can result in better control of disease. Very early onset inflammatory bowel disease (VEO-IBD) is common in this population, but the age of onset should not be the only reason for initiation of immune and genetic evaluation to identify underlying PIRD in individuals with inflammatory bowel disease.

Immunobiology

A healthy gastrointestinal tract needs robust interaction between the gut, skin barrier function, the immune system, and the microscopic living organisms of the gut. Dysregulation or deficiency in any compartment of the immune system, such as neutrophils, T and B cells, and macrophages, can cause colitis and enteropathy in children. While colitis is associated with inflammation in the GI tract and is associated with painful often bloody bowel movements, enteropathy is associated with an autoimmune response that leads to large volume watery bowel movements. Both can be associated with poor weight gain and failure to thrive.

Depending on what causes the underlying immune dysregulation and inflammation, GI tract colitis in PIRD can be classified as:

- **Colitis due to defects in neutrophil function:** Chronic Granulomatous Disease (CGD), which is a form of primary immunodeficiency disease characterized by defect in neutrophil function, is a prototype of this group. (See Chronic Granulomatous Disease Chapter.) Individuals with CGD can present with varying severity of colitis and perianal disease.

- **Autoimmune enteropathy due to defects in T cell immune tolerance:** This group has a genetic defect that results in either decreased T regulatory cell numbers or function; T regulatory cells are a subpopulation of T cells that can control the immune system by maintaining tolerance to self-tissues and prevent autoimmune disease. IPEX syndrome due to FOXP3 mutation is the prototype of this group. IPEX is a syndrome of immune dysregulation, endocrine failure and enteropathy in an X-linked inheritance pattern. (See IPEX Chapter.) Several other immunodeficiencies (IPEX-like) with functional T regulatory cell defects are also associated with autoimmune enteropathy. In all these conditions, the functional deficiency of T regulatory cells leads to unchecked T cell activation. This results in autoimmune disease against cells in the intestines as well as other parts of the body.
- **Colitis due to defects in IL-10 and IL-10R signaling:** GI inflammation due to excess pro-inflammatory signals from the macrophages has been proposed to be the primary driver of inflammatory bowel disease (IBD) in infants and children with genetic defects in IL-10 and IL-10R.
- **Colitis due to hyper-inflammatory disorders:** Excess inflammation due to defects in critical proteins involved in the inflammatory cascade can also lead to GI inflammation and colitis.
- **Colitis due to isolated or combined T and B cell defects:** Varying degree of T and B cell immune defects can present with colitis. Classical examples are Wiskott-Aldrich Syndrome (See Wiskott-Aldrich Syndrome Chapter), Common Variable Immune Deficiency (CVID), and genetic defects that present with CVID-like illness. A significant percentage of these individuals have associated colitis (See Common Variable Immune Deficiency Chapter.)

Clinical Presentation

Colitis as a presentation of underlying immune dysregulation can have a varied presentation with regard to age of onset, severity, and pathology findings. Though several of them present at a younger age with infantile onset (less than two years) or VEO-IBD (less than six years), a significant proportion of them will present with colitis after age 6. Colitis in these individuals can have a slow, gradual onset with frequent small volume bloody and mucousy diarrhea. Due to the slow onset, it is common for these infants to have been evaluated for allergic colitis and to have had multiple formula changes for presumed allergic colitis. GI inflammation resulting in perianal fistula can be seen in individuals with IL-10 and IL-10R signaling defects, XIAP deficiency (X-linked inhibitor of apoptosis protein), and CGD.

On the contrary, clinical presentation of severe enterocolitis in infants is usually much more dramatic. There is typically explosive large volume watery diarrhea. This presentation is common in infants with IPEX and IPEX-like disorders. Biopsy findings include villous atrophy and apoptotic enterocolitis.

In addition to colitis, other autoimmune symptoms of PIRD include autoimmune endocrinopathy (such as type 1 diabetes), autoimmune cytopenia (such as immune thrombocytopenia), and lymphoproliferation (generally manifests as enlarged lymph nodes, liver or spleen). Furthermore, the presence of unusual or difficult to treat infections can be another associated symptom of PIRD. Evaluation of underlying PIRD should be considered if colitis or enteropathy is associated with early onset colitis or enteropathy, especially associated with autoimmune disease or lymphoproliferative disorders, fistula formation, non-responsiveness to first and second line IBD therapy, recurrent fevers, or difficult to treat eczema.

Diagnosis

To diagnose underlying PIRD with colitis, a combination of immune and genetic testing is warranted in most individuals. Immune studies to look at the number, proportion, activation status, and functional status of the different immune cells might be done. Immune studies could give a clue to the nature of immune dysregulation and in some cases clues to possible underlying genetic defects. Increasingly, genetic studies are being done upfront for most individuals. Instead of testing one gene at a time most physicians now rely on gene panels (usually ten to several hundred genes) that include the genes that are likely to result in immune dysregulation. If the gene panel is negative, several clinical centers will proceed to whole exome sequencing, wherein all the genes that are known to cause disease in humans are looked at. When whole exome sequencing is done, samples from the parents are often requested to improve the diagnostic accuracy.

Inheritance

The genetics and mode of inheritance of PIRD presenting with colitis is varied, and summarized in the table below (Table 19:1). It is important to realize, especially with autosomal dominant inheritance that more than one family member might be affected with the same genetic defect. Severity and the age of onset is variable with family members with the same genetic defect. De-novo mutations (neither of the parents are carriers of the defective genes) are known to be the cause of genetic defect in some PIRD.

Known Causes of Genetic Defect in Some PIRD

Table 19:1

Mode of Inheritance	Gene Mutation
Autosomal recessive (both copies of gene affected)	LRBA
Autosomal dominant (only one affected copy needed to cause disease by several mechanisms)	One defective copy/one normal copy (CTLA4, NFKB1, NFKB2) Gain of function (GOF)-defective copy is over active: STAT1 GOF, STAT3 GOF
X linked (males are affected, females can be carriers)	FOXP3, IKBKG, WAS

Treatment

It is important to understand there is not a defined protocol for management of colitis in individuals with broader immune dysregulation. The underlying genetics and immune defect will often guide the immunologist in the selection of medicines that are likely to be most effective for the management of colitis as well as the other manifestations of immune dysregulation. Individuals with underlying broader immune dysregulation and colitis may not respond adequately to medications, such as anti-TNF agents including infliximab or adalimumab.

Treatment with other biologic drugs, such as vedolizumab or ustekinumab, may be considered early in the management. Also, non-conventional targeted treatments might be tried; these agents might include immune suppression with tacrolimus, cyclosporine, sirolimus, abatacept, ruxolitinib or anakinra. However, in some of these individuals, multiple trials of different medications are needed to find the best combination.

Allogeneic hematopoietic stem cell transplantation (HSCT) is being increasingly considered in the management of genetically defined immune dysregulation disorders with colitis. Though the disease might be well controlled medically, long-term quality of life may not be good with medical management alone. Disease flares, loss of response to therapy, and other autoimmune manifestations, infections or lymphoproliferative complications are common findings in these individuals. If matched sibling or matched unrelated donor options are available the role of HSCT should be discussed. Usually, HSCT in these disorders is not an emergency; efforts are made to control colitis and other autoimmune complications, and to nutritionally rehabilitate as aggressively as possible before HSCT. The outcome is improved if the overall immune dysregulation and colitis are better controlled before HSCT. HSCT gives a possible definitive treatment option of the immune system defect. However, careful consideration regarding the long-term risks from chemotherapy before HSCT, the risk of graft vs. host disease after transplant, the risk of infection, and the small but significant risk of graft failure need to be considered (See Hematopoietic Stem Cell Transplantation Chapter).

Expectations

The process of diagnostic immune and genetic evaluation is time-consuming. In some individuals, there is development of more autoimmune or infectious symptoms over months to years. Colitis can be an early presenting symptom of underlying immune dysregulation or a late presentation that follows other autoimmune complications. Despite extensive immune and genetic evaluation, a significant majority of individuals with immune dysregulation might not have a genetic diagnosis. However, every year new genes are being identified that cause immune dysregulation; in the future we expect a higher percentage might have a recognized genetic basis.

Additionally, since the GI inflammation in these individuals might be different, they may not have a positive response to traditional first and second line IBD therapy (anti-TNF agents). In some non-classical IBD, treatment addressing broader immune dysregulation might be a better approach. If the immune and genetic basis is identified and medical management alone results in a poor response or if the treatment has significant side effects limiting the long-term options, HSCT to correct the underlying immune defect might be an option.

If an underlying genetic defect is identified, genetic counseling to identify other family members with carrier or disease state might be recommended. Additionally, for parents who are carriers of genetic defects, genetic counseling and techniques such as in-vitro fertilization and pre-implantation genetics could give an option of having a healthy child.

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