An Overview of Primary Immunodeficiencies

for Patients and Caregivers

Overview of Primary Immunodeficiencies

Primary immunodeficiencies (PIs) are a group of disorders characterized by a weakened or absent immune system. Unlike secondary immunodeficiencies, which are acquired later in life due to factors such as infections, medications, or other medical conditions, primary immunodeficiencies are usually present from birth and result from genetic mutations that affect the development or function of immune cells.

While individually rare, the aggregated number of individuals with PIs represents a significant health burden. Around the world, over 6 million people are affected by primary immunodeficiencies, with an estimated 70 to 90% of patients that are undiagnosed. More than 485 different primary immunodeficiencies or primary immunodeficiency diseases (PIs) have now been described, caused by inherited defects in one or more component of the immune system.

Primary Immunodeficiencies are genetically determined and they may occur alone or as part of a syndrome. In 2022, the International Union of Immunological Societies reported that 485 inborn errors of immunity (IEIs) have been linked to primary immunodeficiency disorders (1). Despite advances in genetics, only about 20 to 30% of current primary immunodeficiencies have a defined genetic mutation.

Primary immunodeficiencies typically manifest during infancy and childhood as abnormally frequent (recurrent) or unusual infections. About 70% of patients are less than 20 years of age at onset; because transmission is often X-linked, 60% are male. Overall incidence of symptomatic disease is estimated to be approximately 1 in 280 people.

The most common symptom of primary immunodeficiencies is recurrent infections. The age at which recurrent infections began can provide a clue as to which component of the immune system is affected. People living with Primary Immunodeficiency more prone to infections, but also to severe auto-inflammatiory disorders, allergies, and cancers.

Fast Facts: Primary Immunodeficiency (PI)

- There are more than 450 identified primary immunodeficiencies
- Many people have a primary immunodeficiency and have not yet been diagnosed
- The most common symptom of primary immunodeficiencies is recurrent infections
- A history of repeated sinus infections, bronchitis, and pneumonias can be a reason to get more tests
- The onset of disease for most people is under 20 years of age, but it can take many years to get an accurate diagnosis

Key Signs and Symptoms

The symptoms of primary immunodeficiencies can vary widely depending on the specific disorder and the severity of the immune dysfunction. However, some common symptoms include:

- Recurrent or severe infections, such as pneumonia, sinusitis, bronchitis, skin infections, or gastrointestinal infections
- Failure to thrive or poor growth in infants and young children
- Delayed or impaired wound healing
- Autoimmune disorders, such as rheumatoid arthritis, lupus, or autoimmune cytopenias
- Chronic diarrhea or gastrointestinal symptoms
- Recurrent abscesses or boils
- Persistent oral thrush or fungal infections
- Allergic reactions or atopic disorders

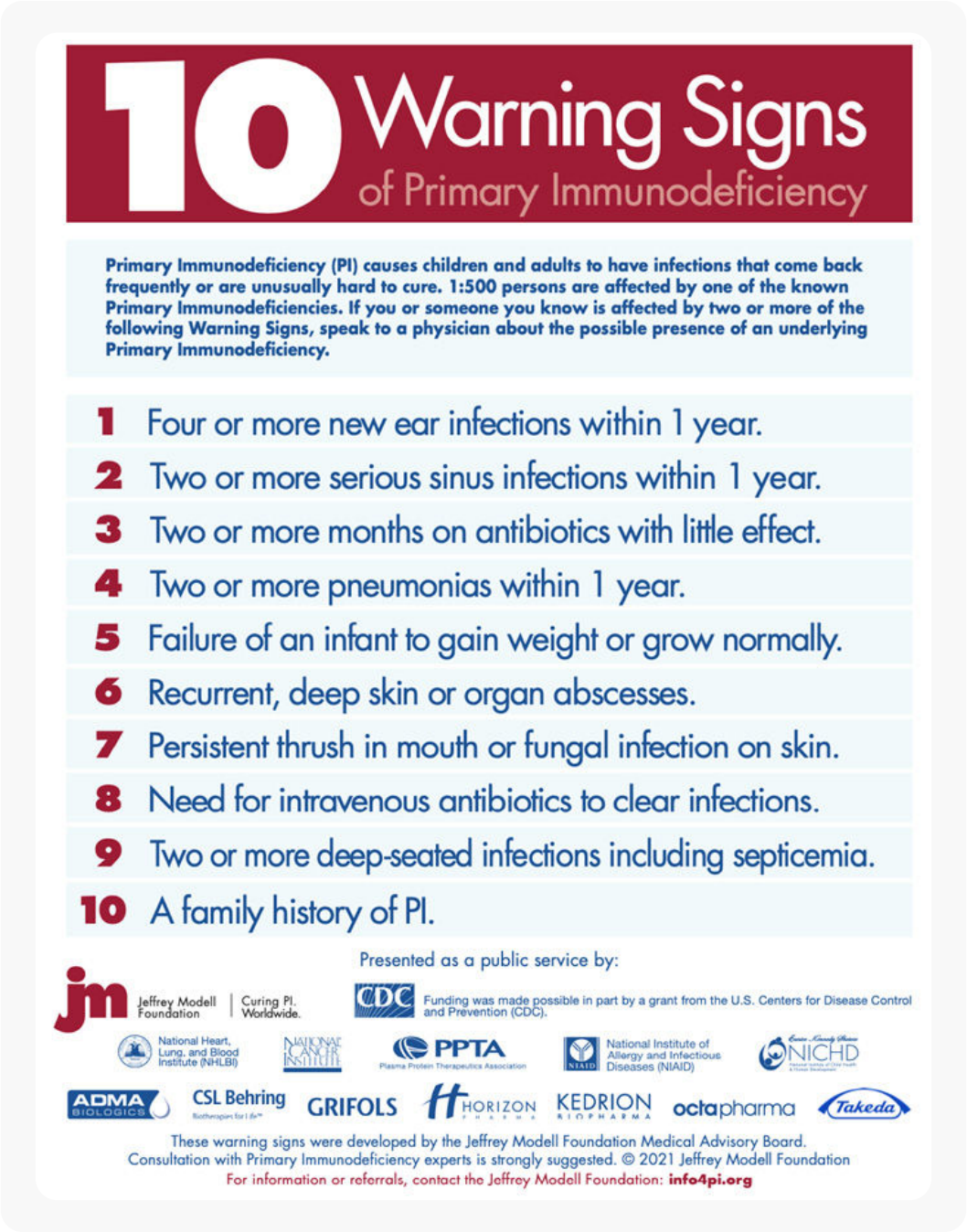
It is important to note that not all individuals with primary immunodeficiencies will experience the same symptoms, and some may remain asymptomatic for long periods, especially if their condition is mild or well-managed.

> My CVID wasn't diagnosed until I was in my 60s. A life-long history of sinus infections, bronchitis, pneumonias, and pleurisy, combined with decreasing antibiotic effectiveness, extended illnesses, and finding a good immunologist was my answer. A series of tests showed I wasn't making antibodies. I had an IgG, IgA, test as a base, then a pneumonia vaccine and tetanus shot and my levels went down.
>
> **-PI Patient**

JMF's 10 Warning Signs of Primary Immunodeficiency

The Jeffrey Modell Foundation (JMF) has created a network of specialized centers in primary immunodeficiencies, and developed 10 Warning Signs of PI (below).

These warning signs help guide patients and caregivers to have conversations with their physicians about primary immunodeficiencies.



Most Common and Well-Characterized Types of Primary Immunodeficiency

There are now over 485 known primary immunodeficiencies, each with its own specific genetic cause and set of symptoms. Some of the most common types include:

Selective Immunoglobulin A (IgA) Deficiency:

This condition is characterized by a deficiency of IgA, the most abundant antibody in mucosal secretions. While many individuals with selective IgA deficiency remain asymptomatic, some may experience recurrent infections, particularly in the respiratory and gastrointestinal tracts. IgA deficiency is the most common PI, with a prevalence up to 1 in 300 individuals, but it can be asymptomatic in approximately two-thirds of cases.

Common Variable Immunodeficiency (CVID):

CVID is the most common symptomatic immunodeficiency. CVID is a heterogeneous disorder characterized by low levels of serum immunoglobulins (antibodies) and recurrent infections, particularly of the respiratory and gastrointestinal tracts. Symptoms typically manifest in late childhood or early adulthood.

X-linked Agammaglobulinemia (XLA):

XLA is a primary immunodeficiency that primarily affects males and is characterized by the absence of mature B cells and low levels of immunoglobulins. Individuals with XLA are highly susceptible to bacterial infections, particularly in the respiratory tract.

Chronic Granulomatous Disease (CGD):

CGD is a rare primary immunodeficiency characterized by defects in the ability of phagocytes to generate reactive oxygen species, leading to recurrent bacterial and fungal infections and the formation of granulomas in various organs.

Severe Combined Immunodeficiency (SCID):

SCID is one of the most severe forms of primary immunodeficiency, characterized by a complete lack of functional T cells and often B cells. Individuals with SCID are highly susceptible to severe infections and typically require early intervention, such as bone marrow transplantation, to survive.

> It's kind of crazy, but Covid kind of helped us deal with my son's PI more easily. People became way more sensitive about masks, hand-washing and germs, and since so many people still wear masks, etc, we don't seem like such weirdos.
>
> **-Parent of a PI patient**

The Diagnostic Challenge

Many patients with PI are undiagnosed, under-diagnosed, or misdiagnosed.

A large proportion of patients do not receive an accurate and timely diagnosis, which is crucial for successful management and care of PI (2). Underdiagnosis can arise due to poor awareness, inadequate newborn screening, lack of family history or carrier testing, and asymptomatic PI (2,3,4).

It is estimated that between 70 and 90% of people living with a PI still remain undiagnosed worldwide (2). Although the diagnostic delay has largely improved over time, there are still many patients in the United States who are needlessly suffering, because they have not yet been accurately diagnosed.

Before a diagnosis is made, individuals suffering from recurrent bouts of infections, autoimmune disease, or inflammatory disease due to PI are often investigated by many different specialists, but without appropriate treatment or management. The end result is deterioration of the patient's condition, inappropriate use of health resources, and a feeling of helplessness (7).

As with many rare diseases, early testing and diagnosis are essential first steps in the care pathway toward timely and appropriate care and treatment, which are ultimately life changing and life enhancing for people living with PI. The negative consequences of diagnostic delay can include multiple hospital admissions, preventable infections, end-organ damage such as bronchiectasis or hearing loss, and sometimes neurologic problems (2).

Diagnosing a primary immunodeficiency typically involves a combination of medical history evaluation, physical examination, laboratory tests, and genetic testing. Recent advances in genetic technology have helped immensely in the diagnosis of PI.

Some common diagnostic tests may include:

- Complete blood count (CBC) to evaluate the levels of different blood cells
- Immunoglobulin levels to assess antibody production
- Flow cytometry to analyze immune cell populations
- Genetic testing to identify specific gene mutations associated with primary immunodeficiencies
- Functional assays to assess immune cell function, such as T cell proliferation or neutrophil oxidative burst tests

Early diagnosis is crucial for initiating appropriate treatment and preventing complications associated with primary immunodeficiencies.

> You can test your immunoglobulins and things like how well you respond to vaccines. It's fairly straight forward, but immunodeficiencies are just outliers, so doctors aren't looking for them.
>
> **-PI Patient**

Overall Management of Primary Immunodeficiencies

Managing a primary immunodeficiency requires a multidisciplinary approach involving healthcare providers, patients, and caregivers. Multiple medical specialists are usually required to help families manage the condition, including:

Immunologists/ Allergists

Pediatricians

Pulmonologists

Otolaryngologists (ENTs)

Infectious Disease Specialists

Hematologists

Rheumatologists

Some key strategies for managing primary immunodeficiencies include:

- Regular follow-up with a primary care physician or immunologist
- Adherence to prescribed treatment regimens, including immunoglobulin replacement therapy or prophylactic antibiotics
- Maintaining a healthy lifestyle, including proper nutrition, regular exercise, and adequate rest
- Avoiding exposure to known pathogens or infectious agents, such as practicing good hand hygiene and avoiding crowded or poorly ventilated environments
- Seeking prompt medical attention for any signs of infection or illness
- Connecting with support groups or patient advocacy organizations for information, resources, and emotional support

> The uncertainty of managing ongoing health flare-ups, infections, and IVIG infusions just wears me out. But the IVIG really works for me, so it's worth the hassle.
>
> **-PI Patient**

Treatment of Primary Immunodeficiencies

The treatment of primary immunodeficiencies aims to boost the immune system's function, prevent infections, and manage associated symptoms. Some common treatment options may include:

01

Immunoglobulin Replacement Therapy:

For individuals with antibody deficiencies, regular infusions of immunoglobulin (antibody) preparations can help provide passive immunity and reduce the risk of infections.

02

Antibiotic Prophylaxis:

Some individuals may benefit from long-term antibiotic therapy to prevent recurrent bacterial infections.

03

Antifungal and Antiviral Therapy:

In addition to antibiotics, antifungal and antiviral medications may be prescribed to prevent or treat fungal and viral infections.

04

Stem Cell Transplantation:

For severe primary immunodeficiencies, such as SCID or certain types of CGD, stem cell transplantation (bone marrow or hematopoietic stem cell transplantation) may be considered as a curative treatment option.

05

Supportive Care:

This may include measures to optimize nutrition, manage symptoms, and prevent complications associated with primary immunodeficiencies.

06

Gene Therapy:

Emerging treatments, such as gene therapy, hold promise for certain primary immunodeficiencies by correcting the underlying genetic defect.

New Information About Primary Immunodeficiencies

As scientists learn more about the immune system, more knowledge about primary immunodeficiencies has continued to accumulate. Now there are 485 defined types of primary immunodeficiency, and many more will be identified in the coming years. Increasing utilization of genetic testing and advances in the strategic evaluation of genetic variants has continued to drive the identification of new PIs. Defining and creating deeper understanding of each condition is the first step. Ongoing research has provided further insights into various aspects of PIs, including genetics, diagnosis, treatment, and management.

Identification of New Primary Immunodeficiencies:

The number of identified primary immunodeficiencies was approximately 200 in 2010; now it is 485. Several PIs have not only been defined, but also profiled genetically and can be found with genetic testing. For example, in 2013, scientists from NIAID and the National Human Genome Research Institute at the National Institutes of Health identified a novel, genetic human immunodeficiency called APDS (Activated phosphoinositide 3-kinase delta syndrome, formerly called PASLI disease). Ten years later, a new drug, designed specifically to treat APDS, was approved by the FDA.

Genetic Discoveries:

Advances in genetic sequencing technologies have facilitated the identification of novel gene mutations associated with PIs. Researchers continue to uncover new genetic variants contributing to different forms of PIs, expanding our understanding of the genetic basis of these disorders.

Precision Medicine Approaches:

With improved understanding of the genetic basis of PIs, there's a growing interest in personalized or precision medicine approaches. Tailoring treatment strategies based on an individual's specific genetic mutation or immune profile holds promise for optimizing therapeutic outcomes and minimizing adverse effects.

Gene Therapy and Gene Editing:

Gene therapy and gene editing technologies are being explored as potential treatment modalities for certain PIs. These approaches aim to correct underlying genetic defects in patients' immune cells, offering the possibility of long-term therapeutic benefits.

Novel Therapeutic Targets:

Research efforts are focused on identifying novel therapeutic targets for PIs. This includes exploring the role of various immune pathways and molecules in disease pathogenesis, with the goal of developing targeted therapies that can modulate immune function and mitigate disease manifestations.

Improved Diagnostic Tools:

Advances in diagnostic techniques, such as next-generation sequencing and functional assays, have enhanced the accuracy and efficiency of PI diagnosis. Early and precise diagnosis is crucial for initiating appropriate treatment and improving clinical outcomes in patients with PIs.

Immunomodulatory Therapies:

In addition to conventional treatments such as immunoglobulin replacement therapy and antibiotics, there's growing interest in exploring immunomodulatory therapies for PIs. These therapies aim to modulate the immune system's function, either by boosting immune responses or suppressing aberrant immune activation, to better control disease activity and prevent complications.

Patient Management and Care Guidelines:

There's an ongoing effort to develop comprehensive management and care guidelines for patients with PIs. These guidelines encompass various aspects of patient care, including diagnosis, treatment, monitoring, and supportive care measures, with the aim of improving clinical outcomes and quality of life for individuals with PIs.

Overall, ongoing research efforts continue to advance our understanding of PIs and contribute to the development of novel diagnostic and therapeutic strategies aimed at improving patient outcomes in this diverse group of immune disorders.

> My body doesn't produce antibodies on its own and that when I get sick, I get spectacularly sick. I have never had a cold that hasn't morphed into bronchitis or sinusitis. Or, if my lungs are feeling really lazy, a pneumonia.
>
> **-PI Patient**
> **The Mighty**

Patient and Caregiver Knowledge, Attitudes, and Experiences

Individuals with primary immunodeficiencies can be severely impacted by their disease and many experience chronic complications, treatment burden, and reduced quality of life.

Children

Living with PI is a challenge children and families. It is a time-consuming experience in all aspects of life (social, emotional,, and even financial aspects), and it has an enormous impact on children's future learning and health.

The impact of PIs on the quality of life of children can vary depending on several factors:

Frequency and Severity of Infections: Children with PIs often experience recurrent and severe infections, which can significantly impact their quality of life. Frequent hospitalizations, doctor visits, and missed school days can disrupt normal childhood activities and social interactions.

Chronic Health Issues: Some PIs can lead to chronic health problems beyond recurrent infections. These may include autoimmune disorders, inflammatory conditions, or organ damage, further affecting the child's well-being and daily life.

Physical Limitations: Children with PIs may experience physical limitations due to their health condition. Fatigue, weakness, or other symptoms associated with infections or underlying immune system dysfunction can restrict their ability to participate in physical activities or keep up with peers.

Emotional and Psychological Impact: Dealing with a chronic health condition can take a toll on a child's emotional and psychological well-being. They may experience anxiety, depression, or social isolation due to their health status or frequent absences from school and social events.

Treatment Burden: Managing PIs often requires regular medical interventions, including medications, immunoglobulin replacement therapy, and sometimes bone marrow transplantation. The burden of treatment can be significant, impacting the child's daily routine, school attendance, and overall quality of life.

Financial Strain: The cost of medical care for children with PIs can be substantial, especially if they require specialized treatments or frequent hospitalizations. This financial strain can further impact the family's quality of life and add stress to an already challenging situation.

Educational Challenges: Children with PIs may face educational challenges due to frequent absences, physical limitations, or cognitive impairments associated with their condition or its treatment. Access to appropriate educational support and accommodations is essential to mitigate these challenges and promote academic success.

Overall, primary immunodeficiencies can have a profound impact on the quality of life of affected children and their families. However, early diagnosis, comprehensive medical care, supportive services, and a nurturing environment can help mitigate some of these challenges and improve overall outcomes.

Adults

Adults tend to experience longer delays in diagnosis than pediatric populations. Although the median diagnostic delay has been reduced over recent decades, it is still quite long for some antibody deficiency variants, such as common variable immunodeficiency (CVID).

The largest impact on quality of life tends to be poorly controlled disease and persistent chronic conditions. Hospitalization, physician/emergency room visits, and bronchiectasis were the most expensive PI complications prior to diagnosis Adults with PI are at risk for depression and experience high levels of loneliness. Social maladjustment and loneliness contribute to anxiety and depression, and loneliness is correlated with impaired social functioning (5).

The impact of primary immunodeficiencies on the quality of life of adults shares some similarities with its impact on children but also presents unique challenges:

Chronic Health Issues: Adults with PIs may experience chronic health problems such as autoimmune disorders, inflammatory conditions, or organ damage. These conditions can significantly affect their daily life, work, and social activities.

Increased Susceptibility to Infections: Similar to children, adults with PIs are more susceptible to infections, which can be recurrent and severe. These infections can lead to frequent doctor visits, hospitalizations, and interruptions in daily routines.

Physical Limitations: PIs can cause physical limitations in adults, including fatigue, weakness, and decreased ability to engage in physical activities. These limitations can impact their ability to work, participate in hobbies, and maintain social relationships.

Emotional and Psychological Impact: Coping with a chronic health condition like PI can take a toll on an adult's emotional and psychological well-being. They may experience anxiety, depression, or feelings of isolation due to their health status and limitations.

Treatment Burden: Managing PIs often requires lifelong medical interventions, including medications, immunoglobulin replacement therapy, and sometimes invasive procedures like bone marrow transplantation. The burden of treatment can be significant and may interfere with daily life, work responsibilities, and social activities.

Financial Strain: The cost of medical care for adults with PIs can be substantial, especially if they require specialized treatments, frequent hospitalizations, or long-term medications. Managing these expenses can cause financial strain and impact overall quality of life.

Work and Career Challenges: Adults with PIs may face challenges in their careers due to frequent absences, physical limitations, or cognitive impairments associated with their condition or its treatment. Maintaining employment, advancing in their careers, or obtaining adequate insurance coverage can be difficult.

Social Isolation: Adults with PIs may feel socially isolated due to their health condition and its impact on their ability to participate in social activities, travel, or maintain relationships. This isolation can further exacerbate feelings of loneliness and depression.

Overall, primary immunodeficiencies can have a profound impact on the quality of life of affected adults, affecting various aspects of their physical, emotional, and social well-being. However, access to comprehensive medical care, support services, and a strong support network can help mitigate some of these challenges and improve overall outcomes.

Caregivers

The impact of primary immunodeficiencies extends beyond the individuals affected by the condition and also significantly affects their caregivers. Caregivers, often family members or close friends, shoulder a substantial burden in managing the care and supporting the well-being of individuals with PIs. Here are some of the key ways in which primary immunodeficiencies can impact caregivers:

Emotional and Psychological Strain: Caregivers may experience significant emotional stress and psychological strain in managing the challenges associated with PI. Witnessing their loved one's illness, coping with uncertainties about the future, and managing their own fears and anxieties can take a toll on caregivers' mental health.

Physical Demands: Caregiving for someone with PI may involve physically demanding tasks, such as administering medications, assisting with mobility, or providing personal care. The physical strain of caregiving can lead to fatigue, exhaustion, and increased susceptibility to health problems among caregivers.

Financial Burden: Managing the medical expenses associated with PI treatment can impose a substantial financial burden on caregivers. Costs may include medications, doctor visits, hospitalizations, specialized treatments, and supportive care services. Caregivers may need to navigate complex healthcare systems and insurance coverage to ensure their loved one receives the necessary care.

Impact on Employment and Career: Caregivers often face challenges balancing their caregiving responsibilities with work commitments. They may need to take time off work for medical appointments, hospitalizations, or caregiving duties, which can impact their career advancement, financial stability, and job security.

Social Isolation: Caregiving responsibilities can lead to social isolation as caregivers may have limited time and energy to engage in social activities or maintain relationships outside of their caregiving role. Feelings of loneliness and isolation can further exacerbate the emotional strain of caregiving.

Changes in Family Dynamics: The presence of PI within a family can alter family dynamics and relationships. Caregivers may need to assume additional responsibilities or roles within the family, leading to changes in roles, routines, and communication patterns.

Health Impact: The stress and demands of caregiving can have negative consequences on caregivers' physical health. Caregivers may neglect their own health needs, experience increased levels of stress-related health problems, and have higher rates of chronic illnesses compared to non-caregivers.

Limited Personal Time and Self-Care: Caregivers often have limited time for self-care and personal pursuits due to the demands of caregiving. Balancing caregiving responsibilities with personal needs and interests becomes challenging, leading to neglect of their own well-being.

Overall, caregiving for someone with PI can be emotionally, physically, and financially taxing. It is essential for caregivers to seek support, prioritize self-care, and access resources to help them navigate the challenges of caregiving effectively while maintaining their own well-being.

Primary Immunodeficiency (PI) Management: Tips from Caregivers

- You must be your child's (or other patient) advocate - no one else will do it for you
- The healthcare system is not set up for rare conditions like PI, so you may have to fight for more tests, and then more aggressive treatment
- Work on maintaining overall health - it may sound basic, but making sure that your child eats properly, exercises frequently, and sleeps well are keys to keeping the immune system functioning optimally
- Catch symptoms early - typically the earlier that you notice symptoms of a "flare", and the sooner the treatment, the less severe the flare tends to be
- Lean onto support networks (both in-person and online) - other caregivers have experiences and tips to share, and can help with emotional support

Patient Advocacy Groups

Immune Deficiency Foundation (IDF) - IDF is a national nonprofit organization dedicated to improving the diagnosis, treatment, and quality of life of individuals affected by primary immunodeficiency diseases through advocacy, education, and research.
https://primaryimmune.org

Jeffrey Modell Foundation (JMF) - JMF is a global nonprofit organization dedicated to early diagnosis, meaningful treatments, and ultimately cures for primary immunodeficiency diseases. The foundation provides support, education, and advocacy for patients and families affected by these conditions.
https://info4pi.org

Foundation for Primary Immunodeficiency Diseases (FPID) - Established in the United States to support the education, early diagnosis, genetic counseling, therapy, and research of PI in both India and the US.
https://fpid.org/wp

Advocacy & Awareness for Immune Disorders Association (AAIDA) - Dedicated to patients living with immune dysregulation and overlapping conditions with a focus on advocacy campaigns, educational initiatives, and research opportunities. AAIDA also provides patients and healthcare providers assistance with insurance denials and medication assistance programs available across the U.S.
https://www.godoaaida.org

American Partnership for Eosinophilic Disorders (APFED - While not exclusively focused on primary immunodeficiencies, APFED provides support, education, and advocacy for individuals with eosinophilic disorders, which can sometimes occur alongside primary immunodeficiency conditions.
https://apfed.org

Summary

Primary immunodeficiencies (PIs) are a group of disorders characterized by defects in the immune system, leading to increased susceptibility to infections and sometimes other complications. PIs are an important and rapidly advancing area of medicine. Recent advances in genetics, greater understanding and knowledge of the disease, and new therapies provide the promise of a better future for patients and their families. Despite the recent advances in diagnosis and management, PIs are still generally unknown by the general public and the majority of healthcare professionals.

Primary immunodeficiencies are complex disorders that require careful management and support. By understanding the condition, its symptoms, and available treatment options, patients and caregivers can work together with healthcare providers to optimize care and improve quality of life.

When to Talk to Your Physician About Immunodeficiencies

When you or someone that you care about has:

- Recurrent infections
- Delayed wound healing
- Chronic cough with mucus production
- Difficulty breathing
- Fungal infections/oral thrush
- Delayed growth (in young children)

> Make sure that when they are ordering blood tests they are checking for the immunoglobulin sub-classes, not just the overall numbers for the immunoglobulin types. For example, immunoglobulin G has four sub-classes. My overall IgG number is fine, but when further analysis is done, the specific deficiency becomes apparent.
>
> **-PI Patient**

Glossary

Primary Immunodeficiency (PI:
A group of disorders characterized by defects in the immune system present from birth, leading to increased susceptibility to infections.

Innate Immunity:
The first line of defense against pathogens, involving physical barriers (eg., skin), cellular responses (e.g., macrophages, neutrophils), and soluble factors (eg., complement proteins).

Adaptive Immunity:
The immune response mediated by lymphocytes (T and B cells) that specifically targets pathogens and develops memory for future encounters.

T-Cell Deficiency:
A primary immunodeficiency characterized by defects in T lymphocytes, leading to impaired cell-mediated immunity and increased susceptibility to viral, fungal, and certain bacterial infections.

B-Cell Deficiency:
A primary immunodeficiency characterized by defects in B lymphocytes, leading to impaired humoral immunity and increased susceptibility to bacterial infections, particularly encapsulated bacteria.

Combined Immunodeficiency:
A primary immunodeficiency characterized by defects affecting both T and B lymphocytes, leading to severe immunodeficiency and susceptibility to a wide range of infections.

Severe Combined Immunodeficiency (SCID):
A rare and severe form of combined immunodeficiency characterized by profound defects in both T and B lymphocytes, often resulting in life-threatening infections within the first few months of life.

Antibody Deficiency:
A primary immunodeficiency characterized by defects in antibody production, leading to impaired humoral immunity and increased susceptibility to bacterial infections, especially extracellular pathogens.

Common Variable Immunodeficiency (CVID):
A primary immunodeficiency characterized by low levels of serum immunoglobulins (particularly IgG and IgA), leading to recurrent bacterial infections, autoimmune disorders, and an increased risk of malignancy.

Complement Deficiency:
A primary immunodeficiency characterized by defects in components of the complement system, leading to impaired opsonization, chemotaxis, and lysis of pathogens, resulting in increased susceptibility to bacterial infections, particularly *Neisseria* species.

Phagocytic Defects:
A primary immunodeficiency characterized by defects in phagocytes (eg., neutrophils, macrophages), leading to impaired clearance of pathogens and increased susceptibility to bacterial and fungal infections.

Hyper IgM Syndrome:
A primary immunodeficiency characterized by defective class switching of immunoglobulins, resulting in low levels of IgG and IgA but normal or elevated levels of IgM, leading to increased susceptibility to bacterial infections.

X-linked Agammaglobulinemia (XLA):
A primary immunodeficiency caused by mutations in the gene encoding Bruton's tyrosine kinase (BTK), resulting in the absence of mature B cells and low levels of immunoglobulins, leading to recurrent bacterial infections.

Autoimmune Lymphoproliferative Syndrome (ALPS):
A primary immunodeficiency characterized by defective apoptosis of lymphocytes, leading to lymphoproliferation, autoimmune manifestations, and an increased risk of lymphoma.

Hematopoietic Stem Cell Transplantation (HSCT):
A procedure in which hematopoietic stem cells are infused into a patient to restore bone marrow function and immune system competence, often used as a treatment for severe primary immunodeficiencies.

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