

# Attending to Warning Signs of Primary Immunodeficiency Diseases Across the Range of Clinical Practice

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## Abstract

**Purpose** Patients with primary immunodeficiency diseases (PIDD) may present with recurrent infections affecting different organs, organ-specific inflammation/autoimmunity, and also increased cancer risk, particularly hematopoietic malignancies. The diversity of PIDD and the wide age range over which these clinical occurrences become apparent often make the identification of patients difficult for physicians other than immunologists. The aim of this report is to develop a tool for educative programs targeted to specialists and applied by clinical immunologists. **Methods** Considering the data from national surveys and clinical reports of experiences with specific PIDD patients, an evidence-based list of symptoms, signs, and corresponding

laboratory tests were elaborated to help physicians other than immunologists look for PIDD.

**Results** Tables including main clinical manifestations, restricted immunological evaluation, and possible related diagnosis were organized for general practitioners and 5 specialties. Tables include information on specific warning signs of PIDD for pulmonologists, gastroenterologists, dermatologists, hematologists, and infectious disease specialists.

**Conclusions** This report provides clinical immunologists with an instrument they can use to introduce specialists in other areas of medicine to the warning signs of PIDD and increase early diagnosis. Educational programs should be developed attending the needs of each specialty.

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**Keywords** Primary immunodeficiency · PIDD · recurrent infections · inflammation · autoimmunity · cancer · warning signs

### Abbreviations

ALPS	Autoimmune lymphoproliferative syndrome
ANA	Antinuclear antibodies
AP50	Alternative pathway of complement system
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
C1INH	C1 esterase inhibitor
CBC	Complete blood count
CD40L	CD40 ligand (L) deficiency
CGD	Chronic granulomatous disease
CSR	Class switch recombination
CVID	Common variable immunodeficiency
DHR	Dihydrorhodamine
EBNA	Epstein-Barr nuclear antigen
FHL	Familial hemophagocytic lymphohistiocytosis
HAE	Hereditary angioedema
HIES	Hyper-IgE syndrome
HLH	Hemophagocytic lymphohistiocytosis
IPEX	Immunodysregulation, polyendocrinopathy and enteropathy, X-linked
OPV	Oral poliovirus vaccine
RCP	Reactive C protein
SCID	Severe combined immunodeficiency
SLE	Systemic lupus erythematosus
TSH	Thyroid-stimulating hormone
WAS	Wiskott-Aldrich syndrome
WHIM	Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome
XLA	X-linked agammaglobulinemia
XLP	X-linked lymphoproliferative syndrome

### Introduction

Primary immunodeficiency diseases (PIDD) are a heterogeneous group of more than 150 disorders that result from many different congenital, or even acquired, genetic defects affecting the innate and adaptive immune systems [1, 2]. Despite major advances over the last 20 years in the clinical and molecular characterization of PIDD, many patients remain undiagnosed or have a substantially delayed diagnosis with adverse results on morbidity and mortality.

The diagnosis of PIDD is most often suggested by recurrent or unusual infections and inflammatory or autoimmune conditions. Several lists of warning signs for children or adults are based on these main clinical presentations and, in some cases, family history [3–6]. Arkwright and Genney

concluded that the 10 warning signs promoted by the Jeffrey Modell Foundation have a sensitivity of 56 % and a specificity of 16 % [7]. Subbarayan et al. evaluated 563 children and concluded that the strongest identifier of PIDD is family history. Of secondary relevance were the use of intravenous antibiotics for sepsis, and failure to thrive in children with T lymphocyte primary immunodeficiency disease [8]. Mehra et al. observed that 20 % of hospitalized patients with suspected immune defects would not be included for immunologic investigation according to the 10 warning signs [9].

All currently available lists of warning signs are based on family history and descriptions of infections suggestive of an immunodeficiency. These are general signs that should be known by all physicians. However, there are many specific warning signs that certain specialists need to be aware of. Because of the diversity of immune defects, their respective clinical presentations, and the difficulties in reaching many non-immunology subspecialists with these general warning signs, many signs that should raise suspicion of PIDD are missed by physicians and a large proportion of patients are not properly diagnosed [10–12].

Here, we provide lists of specific warning signs in tables that can be used to familiarize subspecialists with signs and symptoms of PIDD that they are likely to see in patients referred to their practices. The tables will provide quick summaries of the many warning signs and diagnoses encountered by different specialists, with suggestions for appropriate screenings, immunological evaluations, and proper referrals to clinical immunologists.

### Methods

The information offered in this article is based on a review of the pertinent literature and the clinical experience of all authors. Tables I and II list the tests that are recommended for screening of the main immunologic functions, along with histories and infections that all physicians and health care workers need to recognize as warning signs of a possible immunodeficiency. Subsequent tables list special clinical presentations that should alert specific groups of specialists. When presenting information about PIDD from this article, it is important to always include Tables I and II, and the pertinent tables prepared for various specialties.

#### General Screening and Evaluation

Table I lists the tests that should be performed according to the main clinical presentations specified in the subsequent tables. In some situations the relevant evaluation is not part of generally available screening tests, and it is preferable to refer the patient directly to an immunologist so that routine and specialized tests can be performed simultaneously. The tables for

specialists will provide data for further laboratory investigation.

#### Recurrent, Severe, or Unusual Infections

Our recommendations are similar to those in published lists of warning signs that consider the frequency of various types of infections. However, it is also important to consider the infection type, the circumstances under which infections occur, and which organs and tissues they affect. In our experience, this is a more effective way to identify PIDD than emphasizing exact numbers of different infections or special definitions of severity. When severity is considered, it is important to consider the pathogenicity of an infectious agent; infections with any pathogen of low pathogenicity, such as atypical mycobacteria or toxoplasma, are suggestive of an immune defect even if the infection is not severe. Epidemiological data about infectious agents should be considered as well. For example, paracoccidioidomycosis should be more commonly identified in tropical countries than in European or North American countries (Table II). A general condition that should make any infection suspicious is the concomitant presence of non-infectious complications commonly associated with PIDD, including severe allergy, autoimmunity, unregulated inflammation, or malignancies.

A positive family history definitely suggests a PIDD. However, it is also important to consider certain negative family histories—for example, a family in which only one of 4 siblings has recurrent infections. The fact that the other 3 siblings and parents are healthy rules out environmental factors as the factors predisposing an individual to recurrent infections; it also highlights the immunopathogenic effects of genetic alterations that may have occurred in a single family member.

Recurrent infections are often attributed to the presence of non-immune abnormalities, such as Down syndrome, muscular dystrophy, or various congenital heart defects. Such patients may also have an immunodeficiency, and appropriate recognition and treatment may significantly improve their quality of life.

#### Infectious Diseases

Many PIDDs have unique susceptibilities to some pathogens and/or sites of infections that are listed in Table III. Antibody-mediated immunity needs to be evaluated in all severe or unusual infections, in addition to other possible concurring immunological defects. A practical point is to screen for combined immunodeficiencies.

Infectious disease is the hallmark of PIDD, and infectious disease specialists are the physicians most likely to encounter patients with PIDD in their daily practice. The burden of infectious disease is immense even in children with healthy immune systems. Recurrent otitis media is considered to be

more than 4 episodes of acute otitis media during the past 12 months with complete resolution of the disease between episodes [13–15].

Any patient with severe or recurrent infections or infection by opportunistic or uncommon microorganisms must be investigated for PIDD after discarding the possibility of infection with human immunodeficiency virus (HIV).

Pyogenic encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*) are frequently associated with infections in patients with antibody or complement deficiencies. Patients with complement deficiencies may also present with meningitis and sepsis associated with pathogens such as *Neisseria* [16].

Agammaglobulinemic patients and, to a lesser extent, patients with common variable immunodeficiency (CVID) have an increased risk of developing bloodstream bacterial infections [17]. A study of 201 patients with X-linked agammaglobulinemia (XLA) indicated that 11 % had at least one episode of meningitis or encephalitis, 10 % had at least one episode of sepsis, and 8 % had at least one episode of septic arthritis [18]. Patients with XLA or CVID are at an increased risk for severe and often fatal infections with enteroviruses,

**Table I** Screening laboratory tests for the non-immunology specialist in order to detect patients with possible PIDD

Possible PIDD	Screening Tests
Antibody mediated immunity (AMI)	<ul style="list-style-type: none"> <li>• CBC and differential</li> <li>• Serum IgG, IgA, IgM</li> <li>• Antibody titers to protein and polysaccharide vaccines</li> </ul>
Cellular mediated immunity (CMI)	<ul style="list-style-type: none"> <li>• CBC and differential</li> <li>• Lymphocytes: CD3, CD4, and CD8; CD19; CD16/56</li> <li>• Chest x-ray</li> </ul>
Complement (C)	<ul style="list-style-type: none"> <li>• C4 (if angioedema without urticaria)</li> <li>• CH50</li> </ul>
Phagocytosis (P) Neutropenia Neutrophil function	<ul style="list-style-type: none"> <li>• Neutrophil counts</li> <li>• Oxidative burst by DHR test</li> </ul>
Autoimmunity	<ul style="list-style-type: none"> <li>• ANA, RCP</li> </ul>
Innate immunity (II)	<ul style="list-style-type: none"> <li>• Specialized tests (consult an immunologist)</li> </ul>

The screening lab tests should be part of any initial immune evaluation. Only the abbreviations in parentheses will be listed as suggested screening tests in all subsequent tables. HIV testing should be a routine test to exclude AIDS

*Abbreviations:* ANA antinuclear antibodies, CBC complete blood count, DHR dihydrochloramine, RCP reactive C protein

**Table II** Infections that are general warning signs of PIDD for all clinicians**Otitis media\***

- Early onset <3–4 months of age
- Recurrence after antibiotic treatment
- Complications: mastoiditis
- Association with invasive infections
- Recurrence after ear tubes
- Change to sinusitis after ear tubes
- Repeated ear tube placement

\* The number of otitis episodes that suggest PIDD varies with age:  
 ≥ 3 episodes/year under 5 years; ≥ 2 episodes/year ≥ 5 years

**Chronic recurrent rhinosinusitis**

- Association with persistent asthma
- Requirement for sinus surgery due to fungal infections

**Pneumonia**

Evaluate after a single pneumonia if the patient has:

- A personal history of recurrent upper respiratory infections (URI) including recurrent otitis media
- A personal history of other immune problems (autoimmunity, chronic diarrhea, periodic fevers, persistent skin rash, etc.)
- Pneumonia that requires hospitalization (any: ICU or regular service)
- Persistent pneumonia after adequate therapy with antibiotics
- Pneumonia requiring IV antibiotics
- Bilateral pneumonias
- Necrotizing pneumonia
- Interstitial pneumonitis

Evaluate patients with 2 or more pneumonias:

- All patients (preferred option)

Or evaluate only if:

- X-ray proven pneumonias in different lung sites
- Positive family history for early death or primary immunodeficiency (PIDD)
- Pneumonia that is complicated by pneumatocele or bronchiectasis

**Uncommon infections or uncommon presentations in HIV-negative patients\***

Atypical mycobacteriosis

Tuberculosis resistant infection

Histoplasmosis

Neurocryptococcosis

Aspergilosis

Leishmaniasis

Blastomycosis

\* More relevant signs in developed countries or non-endemic countries for these diseases

**Chronic diarrhea or colitis**

Evaluate if the patient has:

Rotavirus

Enteroviruses

**Table II** (continued)

*Campylobacter*

*Cryptosporidium*

Persistent *Salmonella*

*Clostridium difficile*

Recurrent giardiasis

**Chronic dermatitis**

Recurrent staphylococcal infections

Recurrent or persistent candidiasis or fungal infections

**Abscesses (liver, lungs, cutaneous)**

*Staphylococcus aureus*

**Infections of central nervous system (CNS)**

Meningococcal meningitis

Herpes encephalitis

Fungal infections

**Complications due to live attenuated vaccines**

Disseminated BCG (*Mycobacterium bovis* Bacillus Calmette-Guérin)

Poliomyelitis due to poliovirus vaccine

Diarrhea due to rotavirus vaccine

See text under “**Recurrent, Severe, or Unusual Infections**”

For all the common infections listed in this table, evaluation starts with a complete blood count to rule out neutropenia and assessment of antibody mediated immunity

including echoviruses, polioviruses, and coxsackie viruses [17]. The central nervous system is nearly always involved in these infections, and evidence of systemic involvement of muscle, liver, and/or joints is present in about 40 % of patients. These infections are associated with high mortality and morbidity [19].

Other organisms, including *Staphylococcus aureus*, *Pseudomonas* spp, *Mycoplasma* spp, Enterobacteriaceae, *Campylobacter* spp, *Giardia*, and enteroviruses, may be isolated from patients with specific types of PIDD [17]. Infections caused by *Serratia marcescens*, *Nocardia* spp, *Chromobacterium violaceum*, *Granulobacter bethesdensis*, *Burholderia cepacia*, and *gladioli* are strongly suggestive of chronic granulomatous disease (CGD). Evaluation of 259 patients with the X-linked recessive form of CGD indicated that 21 % had a history of either bacteremia or fungemia [20].

Infections caused by mycobacteria, *Salmonella*, *Leishmania*, and *Cryptococcus* suggest defects in the interferon- $\gamma$ /interleukin-12 axis included in innate immunity (Table III) [21]. As previously mentioned, the incidence of certain infectious agents must be considered according to their endemicity in particular geographical regions. Side effects of Bacillus Calmette-Guérin (BCG) occur in more than 50 % of the severe combined immunodeficiency (SCID) patients in Brazil and more than 17 % of CGD patients in Latin America; this is a relevant warning sign for PIDD [22]. Adverse reactions to other live attenuated viral vaccines such as poliovirus

**Table III** Warning signs of PIDD for infectious disease specialists

Clinical occurrences	PIDD	Lab screening tests
Infections from extracellular bacteria	Antibody deficiencies Complement deficiencies Neutropenias IRAK-4, MyD88	AMI C, ANA P II, RCP
Infections due to <i>Neisseria meningitidis</i>	Complement deficiency of terminal components (Membrane attack complex)	C + AP50
Infection from <i>S aureus</i> , and gram-negative bacterias: <i>Serratia marcescens</i> , <i>Burkholderia cepacia</i> and <i>gladioli</i> , <i>Nocardia spp</i> , <i>Chromobacterium violaceum</i> , <i>Granulobacter bethesdensis</i> .	Chronic granulomatous disease (CGD) Hyper IgE syndrome (HIES) Features: pneumonia from <i>S aureus</i> , eczema, fungal infection, joint hypermobility, coarse facial features	P Serum IgE, eosinophilia Specific Score <sup>a</sup>
Infection from fungi: <i>Pneumocystis jiroveci</i> ; <i>Aspergillus</i> and <i>Candida albicans</i> .	T cell defects CD40 ligand (L) deficiency HIES  CGD	CMI AMI Serum IgE, eosinophilia Specific Score <sup>a</sup> P
Infection from <i>Candida albicans</i>	Chronic mucocutaneous candidiasis	CMI + T lymphocyte proliferation induced by <i>Candida</i>
Infection by atypical <i>Mycobacteria/Salmonella</i> and/or <i>Bacillus Calmette-Guérin</i> side effects; <i>Paracoccidioides sp</i> , <i>Leishmania</i> , <i>Cryptococcus</i>	T cell deficiencies Severe combined immunodeficiency (SCID) Mendelian susceptibility to mycobacterial diseases	CMI AMI + CMI P and/or II
Infections from <i>Herpes</i>	T and NK cell deficiencies	CMI
Fulminant or chronic infection by Epstein-Barr virus	Familial hemophagocytic lymphohistiocytosis (FHL) syndrome X-linked lymphoproliferative (XLP) syndromes, types 1 or 2	CBC, triglycerides, ferritin, serology EBNA
Recurrent or persistent <i>Cryptosporidium</i> , <i>Isospora</i>	CD40L deficiency Common variable immunodeficiency (CVID)	AMI AMI
<i>Giardiasis</i>	Antibody deficiencies	AMI
Complications due to <i>BCG</i> , <i>rotavirus</i> or <i>Varicella</i> vaccines	SCID, CGD	CMI and/or II and/or P
Complications due to oral polio vaccine	Antibody deficiencies	AMI
Persistent fever of unknown origin	Autoinflammatory diseases	ANA, RCP, blood smear

*Abbreviations:* AMI antibody mediated immunity, ANA antinuclear antibodies, CBC complete blood count, CMI cellular mediated immunity, EBNA Epstein-Barr nuclear antigen, II innate immunity, P phagocytosis, RCP reactive C protein

<sup>a</sup> Score for classical hyper IgE diagnosis [26]

and rotavirus should be carefully observed as well [23]. Several developing countries maintain campaigns with Sabin immunization with the possibility to cause vaccine-derived disease [24].

Although the respiratory and gastrointestinal tracts are the most common systems for presenting illness, the authors observed lymphadenopathy as the most common manifestation in the group of combined T and B cell immunodeficiencies,



and superficial abscesses and lymphadenopathy in the group of congenital defects of phagocyte number and/or function [22, 25, 26] (Table III).

#### Otorhinolaryngology and Pulmonology

High percentages of pediatric and adult patients with PIDD have upper and/or lower respiratory tract bacterial infections; thus, they may be referred to otorhinolaryngologists or pulmonologists. Rezaei reported on 930 patients with PIDD, 353 cases of which were identified in the last 5 years. The most common presenting feature of PIDD was pneumonia, which was seen in 20.1 % of patients, followed by diarrhea (13.7 %), sinusitis (10.3 %), and otitis media (9.6 %) [27]. It is important to rule out the existence of cofactors that might be associated with upper respiratory infections (e.g., smoking, day care attendance, gastroesophageal reflux, allergy) before performing extensive immunological evaluation. The most common of these infections are recurrent otitis media, chronic sinusitis, and pneumonia. Recurrent sinus infections have been reported as a presenting occurrence in 19 % to 98 % of patients with PIDD (wide range reflects the variety of PIDD) [28, 29]. An assessment of 103 pediatric and adult patients with a history of recurrent or chronic ear, nose, or throat infections indicated that 16.5 % had defects in antibody-mediated immunity: CVID ( $n=2$ ), IgA deficiency ( $n=4$ ), IgG subclass deficiency ( $n=3$ ), and specific antibody deficiency against polysaccharide antigens ( $n=8$ ) [30]. Warning signs for patients with recurrent otitis include progressive infections leading to mastoiditis; associated abscesses or systemic infections; lack of responsiveness to adequate antibiotic treatment; or occurrence of unusual, severe, or frequently relapsing infections in other sites [31] (Table II).

Pneumonia is a common infectious manifestation of PIDD; one study of patients with CVID indicated that at least two-thirds had one or more pneumonia diagnoses prior to diagnosis of PIDD [32]. According to some registries [33, 34], approximately 50 % of patients with humoral immunodeficiency suffered from upper respiratory tract infections, and 40 % of XLA and CVID patients suffered from recurring pneumonia [27, 35]. Pathogens frequently associated with pneumonia in patients with antibody deficiencies include *S pneumoniae*, *H influenzae* type b, *Haemophilus parainfluenzae*, *Mycoplasma* spp, *Pseudomonas* spp, and *Staphylococcus* spp [17]. Patients with cellular deficiencies such as CD40 Ligand (CD40L) deficiency present with pneumonia that is a result of opportunistic pathogens such as *Pneumocystis*, fungal, or viral infections [36] (Table IV).

Several observational studies have indicated that complications and sequelae of infectious diseases such as bronchiectasis (76 %), recurrent chest infections (21 %), and granulomatous lung disease (5 %) should also raise suspicion of PIDD [37]. A systematic review of the literature conducted by Wood et al. included results from 7 surveys showing that respiratory/chest infections were presenting symptoms for 37 % to 90 % of patients with PIDD [29]. Touw et al. reviewed 26 studies that included 587 patients with CVID and found that up to 73 % developed chronic structural pulmonary complications—most often bronchiectasis and bronchial wall thickening [38]. In another study, pulmonary imaging by chest computed tomography in 30 patients with PIDD revealed abnormalities in 53 %; among these were bronchiectasis (75 %), peribronchial thickening (19 %), air trapping (31 %), lung volume reduction (25 %), atelectasis (12 %), follicular bronchiolitis (12 %), ground-glass abnormality (12 %), and parenchyma nodules (6 %). In this study, pulmonary function testing also indicated abnormalities in 18 patients; these included an obstructive (38.8 %), restrictive (44.4 %), or mixed (16.7 %) pattern of lung function abnormalities [39].

Results from other studies have indicated that *Staphylococcus*-associated pneumonia and bronchial aspergillosis [40] are seen in CGD; lung abscesses represent usual characteristics in hyper IgE syndrome (HIES); and interstitial pneumonia may be observed in patients with SCID [41] (Table IV).

#### Gastroenterology

Frequent gastrointestinal manifestations are malabsorption, diarrhea, hepatomegaly, and inflammatory bowel disease (IBD) and all of these are commonly associated with increased morbidity [42–44]. In a systematic review, Wood et al. indicated that GI infections were a presenting symptom in 6 % to 19 % of patients with PIDD [29]. Severe diarrhea can start early in life in patients with SCID or immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX); both of these PIDD are considered pediatric emergencies [45–47]. Rezei et al., in their study of 930 patients with PIDD, indicated that infectious diarrhea occurred in 40.4 % of patients [27]. Recurrent or chronic giardiasis is suggestive of an underlying antibody deficiency [17]. Other pathogens in patients with infectious colitis include rotavirus, *Campylobacter*, enteroviruses, *Cryptosporidium parvum*, *Salmonella* spp, and *Clostridium difficile* [18]. Liver abscesses caused mainly by *S aureus* may also be seen in patients with CGD and HIES (Table V).

Results from a study focusing mainly on pediatric patients with PIDD indicated clinical evidence of liver disease, including hepatomegaly, in 35.5 %; 8 patients (13 %) had clinical and/or laboratory evidence of chronic liver disease. Hepatobiliary infection, sclerosing cholangitis, nodular

**Table IV** Warning signs of PIDD for pulmonologists

Clinical occurrences	PIDD	Laboratory tests
Pneumonias due to extracellular bacteria + otitis and sinusitis	Antibody deficiencies Complement deficiencies	AMI C, ANA
Pulmonary abscess Pneumatocele	Hyper IgE syndrome (HIES) Features: pneumonia by <i>S aureus</i> , eczema, fungal infection, joint hypermobility, coarse facial features	Serum IgE, eosinophilia Specific Score <sup>a</sup>
Pneumonias due to <i>Staphylococcus</i> or fungi	Chronic granulomatous disease (CGD): susceptibility to infections by catalase positive microorganisms. Other infections: adenitis, liver abscess, osteomyelitis Glucose-6-phosphate dehydrogenase (G6PD) deficiency Myeloperoxidase deficiency (common in diabetes) HIES	P  G6PD activity Peroxidase level Serum IgE, eosinophilia Specific Score <sup>a</sup>
Pneumonia due to <i>P jiroveci</i>	T cell deficiencies/CD4 <sup>+</sup> lymphopenia  CD40 ligand (L) deficiency Wiskott-Aldrich syndrome (WAS), eczema + thrombocytopenia	CMI, AMI Lymphoproliferation assay AMI, CMI CBC including platelet number and size (small sized platelets); CMI, AMI
Pneumonia due to <i>Mycobacteria tuberculosis</i> or atypical mycobacteria	T cell deficiencies/CD40L deficiency Mendelian susceptibility to mycobacterial diseases	CMI, AMI II

*Abbreviations:* AMI antibody mediated immunity, ANA antinuclear antibodies, CBC complete blood count, CMI cellular mediated immunity, II innate immunity, P phagocytosis

<sup>a</sup> Score for classical Hyper IgE diagnosis [26]

regenerative hyperplasia, and portal hypertension are frequent conditions in CD40L deficiency [48, 49].

### Rheumatology

The risk for autoimmune diseases is elevated in patients with PIDD and is sometimes the only clinical manifestation of their causative condition. Results from a larger study of 248 patients with CVID indicated that 69 (27.8 %) had autoimmune disease. The most common conditions were thrombocytopenia in 18 patients, hemolytic anemia in 12, rheumatoid arthritis in 5, and juvenile rheumatoid arthritis in 4 [50, 51]. Results from another study of 189 patients with systemic lupus erythematosus (SLE) indicated that 6 % had IgA deficiency [52].

Other PIDD are the result of genetic defects that lead to immune dysregulation associated with autoimmune occurrences. Patients with autoimmune lymphoproliferative syndrome (ALPS) develop generalized lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, B cell lymphocytosis, and autoimmune manifestations that commonly include hemolytic anemia, glomerulonephritis, and idiopathic thrombocytopenic purpura [53]. Autoimmune polyendocrinopathy, candidiasis, and ectodermal

dystrophy (APECED) are also associated with symptoms of autoimmune disease [54]. Patients with IPEX have mutations in the FOXP3 gene in regulatory T cells, which leads to severe autoimmunity with a high mortality rate [55]. First components of complement deficiency have also been shown to be associated with conditions such as SLE and are likely to prompt referral to a rheumatologist [56]. An important “red flag” for SLE and complement defects is negative serology to double-stranded DNA [57].

Bone and joint abnormalities can occur in patients with PIDD. The most common of these is arthritis, which may be associated with antibody deficiencies, and, less often, with CGD and Wiskott-Aldrich syndrome (WAS) [58, 59]. Importantly, infections with *Ureaplasma urealyticum*, and *Mycoplasma ssp* may lead to erosive arthritis in patients with severe antibody deficiencies. These infections most often result in large-joint monoarthritis involving the knee, shoulder, elbow, or hip joints, and less often in symmetrical polyarthritis [17].

Patients with certain PIDD, such as autoinflammatory syndromes, will present with generalized serositis that might be confused with infectious arthritis. This is often accompanied by a myriad of symptoms, including elevation of acute phase

**Table V** Warning signs of PIDD for gastroenterologists

Clinical occurrences	PIDD	Laboratory tests
Chronic diarrhea	Antibody deficiencies	AMI
Inflammatory bowel disease	Combined immunodeficiencies (infants)	CMI, AMI
Chronic giardiasis		
Autoimmune enteropathy + severe intractable diarrhea. Other diagnoses associated: hypothyroidism, eczema, thrombocytopenia, autoimmune hemolytic anemia, neonatal diabetes	Immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX)	CMI, Coombs, glycemia, and TSH ANA
Persistent candidiasis	Combined immunodeficiencies	CMI
	Chronic mucocutaneous candidiasis	T cell Lymphoproliferative assay
	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)	Lymphoproliferation to <i>Candida</i> Candidin test ANA and endocrine evaluation
Severe abdominal pain emulating an acute abdomen	Hereditary angioedema	Dosage and/or functional activity assay of C1INH, C4, C1q
Liver abscess mainly due to <i>S aureus</i>	Chronic granulomatous disease (CGD)	P
	Hyper IgE syndrome (HIES)	Serum IgE, eosinophilia Specific Score <sup>a</sup>
Hepatobiliary infection due to <i>C parvum</i>	CD40 ligand (L) deficiency	AMI
Inflammatory bowel disease in infants	CGD	P
	Interleukin-10 (IL-10) or interleukin 10 receptor (IL-10R) deficiencies	II

*Abbreviations:* AMI antibody mediated immunity, ANA antinuclear antibodies, C1INH C1 esterase inhibitor, CMI cellular mediated immunity, CBC complete blood count, II innate immunity, P phagocytosis, TSH thyroid stimulating hormone

<sup>a</sup>Score for classical Hyper IgE diagnosis [26]

reactants, rash, deafness, joint deformity, and multifocal osteomyelitis [60].

#### Dermatology

Patients with PIDD may have skin conditions including fungal, bacterial, or viral infections; eczematous dermatitis; erythroderma; skin symptoms of autoimmune diseases such as SLE or scleroderma; vasculitis; granuloma formation; and/or problems characteristic of specific immunodeficiency syndromes (e.g., telangiectasia, gray hair, and depigmentation) [61]. An immunological assessment of 382,383 pediatric patients admitted to an outpatient dermatology group indicated that 130 had PIDD. Of these, 69 % had skin infections, 29 % had eczema-dermatitis, and 44 % had other associated cutaneous conditions. In 79 % of this cohort, cutaneous abnormalities preceded and were the basis for the clinical immunologic diagnosis [62], demonstrating the relevance and high frequency of dermatologic manifestations in PIDD patients.

Results from a cross-sectional study of 210 pediatric patients with PIDD (68 with antibody deficiencies, 22 with T cell and combined deficiencies, 57 with phagocytic defects, and 63 with other PIDD) indicated that 67 of the patients (31.9 %) had cutaneous abnormalities preceding the diagnosis of PIDD. Overall, 99 patients had infections and 27 had eczematous dermatitis [63].

*Candida* infections that may be among the first signs of PIDD include mucocutaneous candidiasis, *Candida paronychia*, granuloma formation, and erythroderma [64]. Patients with phagocytic, cellular, combined, and other PIDD exhibit immune deficits that confer increased susceptibility to fungal infections. Infections associated with *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Paecilomyces*, *Scedosporium*, *Trichosporon*, *Penicillium*, and other fungal organisms have been observed in patients with CGD, SCID, HIES, defects in the interferon- $\gamma$ /interleukin-12 axis, DiGeorge syndrome/22q deletion syndrome, CD40L deficiency, WAS, and CVID [64]. Patients with Chediak-Higashi or Griscelli syndromes present partial albinism



and gray hair; dermatologists are frequently the first consulted specialists [65]. Prompt diagnosis is established by demonstration of giant intracellular granules in eosinophils, basophils, and monocytes, and are pathognomonic of this disease [66].

Eczema and high serum IgE levels in the first months of life frequently lead to referral to allergists due to suspicion of cow milk protein allergy. However, these occurrences are also present in patients with hypomorphic SCID, IPEX, WAS, DOCK8, and HIES [67]; it has been shown that differential diagnosis is crucial for prognosis [68]. Zhang et al. described DOCK8 mutations in patients with a variant of combined immunodeficiency characterized by unusual susceptibility to cutaneous viral infections and cancers. In addition, DOCK8 deficiency was found in a subgroup of patients who were previously thought to have autosomal recessive HIES with severe allergic manifestations [69]. These syndromes exemplify the need for improved knowledge of PIDD for dermatologists (Table VI). In addition, angioedema without urticaria is often referred to both allergists and dermatologists. Family histories are helpful for such cases, and C4 levels could be a useful screening test [70].

## Hematology/Oncology

Autoimmune hemolytic anemia, thrombocytopenia, and/or neutropenia are also seen in patients with selective IgA deficiency, CVID, and class switch recombination (CSR) defects [50, 71]. In some patients, hematologic abnormalities reflect the underlying pathology responsible for the immunodeficiency. Wiskott-Aldrich syndrome is associated with defects in both B-lymphocyte and T-lymphocyte function, and these patients also have intrinsic platelet abnormalities and significant thrombocytopenia with small platelets [71]. In addition to congenital neutropenia, neutropenia is also associated with XLA, CD40L deficiency, CVID, SCID, and Shwachman-Diamond syndrome [72, 73]. Hemophagocytic lymphohistiocytosis (HLH) is characterized by multisystem inflammation, a reactive process resulting from hyperactivation of macrophages, histiocytes and CD8<sup>+</sup> T cells, and abnormalities in the function of natural killer cells (NK cells). The most frequent clinical and laboratorial findings include fever, splenomegaly, cytopenias, hypertriglyceridemia, and elevated ferritin [74]. Both Chediak-Higashi and Griscelli

**Table VI** Warning signs of PIDD for dermatologists

Clinical occurrences	PIDD	Laboratory test
Eczema	Wiskott-Aldrich syndrome (WAS)	CBC including platelet number and size (small sized platelets); CMI, AMI
	Hyper IgE syndrome (HIES)	Serum IgE, eosinophilia Specific Score <sup>a</sup>
	Immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX)	CMI, ANA, RCP Coombs, glycemia, and TSH
	Severe combined immunodeficiency (SCID), erythroderma	CMI
Cutaneous lesions by <i>Mycobacteria</i>	Combined immunodeficiencies	CMI
	Hyper-IgM syndromes	AMI
	Mendelian susceptibility to mycobacterial diseases	II
	Chronic granulomatous diseases (CGD)	P
Partial albinism, gray hair	Chediak-Higashi syndrome Griscelli syndrome	Enlarged cytoplasm granules in blood smear
Telangiectasias	Ataxia-telangiectasia	AMI; serum alfa-feto protein
Disseminated warts and molluscum Cutaneous herpes infections	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome Dedicator of cytokinesis 8 (DOCK8) deficiency Idiopathic CD4 lymphopenia	AMI, CMI lymphoproliferation assay
Fragile hair, conic teeth	Ectodermal dysplasia	II

*Abbreviations:* AMI antibody mediated immunity, ANA antinuclear antibodies, CBC complete blood count, CMI cellular mediated immunity, II innate immunity, P phagocytosis, RCP reactive C protein, TSH thyroid stimulating hormone

<sup>a</sup> Score for classical Hyper IgE diagnosis [26]

**Table VII** Warning signs of PIDD for hematologists

Clinical occurrences	PIDD	Laboratory tests
Thrombocytopenia with small-sized platelets	Wiskott-Aldrich syndrome (WAS) Other symptoms: eczema and recurrent infections X-linked thrombocytopenia	CBC including platelet number and size (small sized platelets); CMI, AMI
Autoimmune cytopenias (autoimmune anemia, thrombocytopenia and neutropenia)	Common variable immunodeficiency Other features: recurrent infections	AMI, ANA
Fever, splenomegaly without evidence of malignancy, cytopenias	Hemophagocytic lymphohistiocytosis (HLH)	CBC, triglycerides, ferritin, EBNA
Lymphadenopathy + Splenomegaly Excluding neoplasias and infections	Autoimmune lymphoproliferative disease Apoptosis defects	Increased number of alpha beta double-negative T cells (CD3 + CD4-CD8-), ANA, RCP
Quantitative and qualitative defects of neutrophils (neutropenia and neutrophilia)	Neutropenias Chronic granulomatous disease (CGD) Leukocyte adhesion deficiency Partial albinism, Chediak-Higashi or Griscelli syndrome	P  Leukocytosis, CD18 <sup>+</sup> cells Enlarged cytoplasm granules

*Abbreviations:* AMI antibody mediated immunity, ANA antinuclear antibodies, CBC complete blood count, CMI cellular mediated immunity, EBNA Epstein-Barr nuclear antigen, P phagocytosis, RCP reactive C protein

syndromes present as hemophagocytic, with an accelerated phase affecting all patients by late childhood. This accelerated phase is characterized by the infiltration of nonmalignant lymphoid and histiocytoid cells into the viscera, usually induced by Epstein-Barr virus. Clinical findings include hepatosplenomegaly, lymphadenopathy, and pancytopenia [75]. Impaired humoral and cellular immune responses, including disturbances in B, T, NK, and dendritic cells, along with chronic inflammatory autoimmune diseases, recurrent bacterial infections, and persistent antigenic stimulation, are speculated to favor carcinogenesis in CVID patients. Lymphoma and gastric cancer are the most frequent neoplasms related to this immunologic defect [76, 77]. The risk of cancer in PIDD patients mainly takes the form of T cell malignancies (70-fold and 250-fold increased risks of leukemia and lymphoma, respectively), and B cell malignancies are high when compared with the general population [78]. The Spanish registry identified that 1.3 % of the 1,069 patients developed cancer; however, the survey was developed within reference hospitals [34].

Non-Hodgkin lymphoma and Hodgkin lymphoma are 2 of the most common PIDD-associated malignancies [79]. A recent large-scale assessment of 1,132 patients in the PIDD registry of the Australasian Society of Clinical Immunology and Allergy indicated that this group had a 1.6-fold excess relative risk of cancer [80]. The relative risk was significantly increased for non-Hodgkin lymphoma, leukemia, and stomach cancer (Table VII).

## Conclusions

During recent years, new PIDD have been identified, including some with susceptibility to specific infectious agents and some diagnosed only in adulthood. Training specialists to recognize PIDD is important in order to identify the diverse PIDD phenotypes. The majority of patients initially present to hospital doctors; therefore, a focus on hospital specialists has been suggested.

Clinical immunologists have an important educational role. Introducing other specialists and health care workers to the relevant warning signs will facilitate the early diagnosis of PIDD in patients, leading to better treatments with less sequelae, or possible cures.

In this review we have addressed the presentations of PIDD that are seen by different medical subspecialists. These warning signs are further influenced by the socioeconomic, climate-related, and living conditions found in different regions of the world. A review of warning signs that are specific to different areas of the world should eventually be undertaken by a worldwide PIDD community of which LASID plays an important part.

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