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FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

PID **WARNING SIGNS ACROSS MEDICAL SPECIALTIES**

ABBREVIATIONS

ALPS	Autoimmune lymphoproliferative syndrome
APDS	Activated phosphoinositide 3-kinase delta syndrome
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
CAPS	Cryopyrin-associated periodic syndrome
CD40-L	Cluster of differentiation 40 ligand
CGD	Chronic granulomatous disease
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CMV	Cytomegalovirus
CRMO	Chronic recurrent multifocal osteomyelitis syndrome
CT	Computed tomography
CVID	Common variable immunodeficiency
DOCK8	Dedicator of cytokinesis 8
EBV	Epstein Barr virus
FCAS	Familial cold autoinflammatory syndrome
FMF	Familial Mediterranean fever
GLILD	Granulomatous-lymphocytic interstitial lung disease
GvHD	Graft versus host disease
HIDS	Hyperimmunoglobulinaemia D and periodic fever syndrome
HIES	Hyper IgE syndrome
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease

PID warning signs across medical specialties (1st edition)

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ABBREVIATIONS

IEI	Inborn errors of immunity
Ig	Immunoglobulin
ILD	Interstitial lung disease
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
IPOPI	International Patient Organisation for Primary Immunodeficiencies
ITP	Immune thrombocytopenia
MCV	Molluscum contagiosum virus
MHC	Major histocompatibility complex
MWS	Muckle-Wells syndrome
NHL	Non-Hodgkin's lymphoma
NOMID	Neonatal onset multi-system inflammatory disease
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome
PID	Primary immunodeficiency
PKCD	Protein kinase delta deficiency
RTI	Respiratory tract infection
SCID	Severe combined immunodeficiency
SLE	Systemic lupus erythematosus
STAT	Signal transducer and activator of transcription
TNF	Tumour necrosis factor
TRAPS	TNF receptor-associated periodic fever syndrome
WAS	Wiskott-Aldrich syndrome
WHIM	Warts, hypogammaglobulinemia, infections, and myelokathexis
XLA	X-linked agammaglobulinaemia
XLP	X-linked lymphoproliferative syndrome
XLT	X-linked thrombocytopenia

SUMMARY

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally. PID patients may present with recurrent infections that affect different organs, as well as allergies and organ-specific inflammation, autoimmunity, and/or granulomas. They also have an increased risk of developing cancer, particularly haematopoietic malignancies. The rarity and diversity of PIDs combined with the wide age range over which these clinical manifestations become apparent often make the identification of patients challenging for clinicians other than immunologists. This leaflet provides information on infectious and non-infectious warning signs of PIDs, together with specific warning signs of PIDs that might be observed in referrals to otorhinolaryngologists and pulmonologists, gastroenterologists, rheumatologists, dermatologists, and haematologists and oncologists. Patients with PIDs may require care from a range of specialties depending on their individual symptoms and the organ systems affected; thus, the multidisciplinary team plays a key role in the effective treatment and management of PIDs.

INTRODUCTION

This booklet outlines the warning signs of primary immunodeficiency (PID) from the perspectives of the different medical specialties that may encounter these patients.

Primary immunodeficiencies (PIDs), sometimes referred to as inborn errors of immunity (IEI), are rare diseases that occur when components of the immune system are either not present or are not functioning normally, rendering the patient susceptible to potentially life-threatening infections.

The presentation of a PID is often complex with clinical indicators being suggestive of multiple potential diagnoses. While many types of PID have been identified, the main types cause similar symptoms in those affected. Notably these symptoms are recurrent and/or unusual infections (including respiratory tract infections [RTIs]) that can be long-lasting and severe. However, it is now recognised that PIDs may present in other ways, including in people who may have non-infectious complications such as autoimmunity, inflammatory disorders with fevers, swollen joints, rashes and bowel problems, angioedema or sometimes even cancers, particularly lymphomas. Patients with non-infectious manifestations of PIDs may be first encountered by or referred to a variety of medical specialties with non-infectious symptoms. The following sections explain the warning signs of PIDs from the perspective of the different medical specialties that may encounter these patients.

INFECTIOUS AND NON-INFECTIOUS WARNING SIGNS OF PIDS

Over 485 different PIDs have been identified[1] ranging from the very rare (e.g. severe combined immunodeficiency [SCID]) to the relatively common (e.g. selective immunoglobulin A deficiency). While PIDs are often diagnosed early in life, they can be diagnosed throughout the lifespan of a person and 1 in 2,000–10,000 persons may be affected by a known PID.[2]

Key warning signs of a PID in children and adults are shown in Table 1.[3]

Infections are a common occurrence in persons with PIDs. Infectious warning signs of an underlying PID include recurrent infections, severe infections, infection by unusual pathogens and a restricted pathogen pattern, including opportunistic infections (see Table 1).

[1] Tangye SG, et al. J Clin Immunol 2022;42(7):1473–1507.

[2] Van Zelm MC, et al. Front Immunol 2020 Jan 22;10:3148.

[3] A Guide for General Practitioners. https://ipopi.org/wp-content/uploads/2017/07/WEB_IPOPI_GuideFOrGPs.pdf

TABLE 1. Warning signs of a PID[3]

CHILDREN	ADULTS
Known PID in the family	Known PID in the family
Failure to thrive	
Infections with an unusual course	Infections with an unusual course
Chronic candidiasis after the age of 3 months or cutaneous candidiasis	Persistent oral candidiasis or fungal skin-infections
One or more episode of pneumonia per year for multiple years / refractory pneumonia	One or more episode of pneumonia per year for multiple years
Invasive infections such as osteomyelitis, meningitis, sepsis or organ abscesses	Bronchiectasis, abscesses, recurrent sinusitis
Six or more sequences of middle-ear infections per year or otitis associated with mastoiditis or perforation of the tympanic membrane	Two or more middle ear infections within a year
Two or more sequences of sinusitis per year	Two or more episodes of sinusitis within a year (in the absence of allergy)
Chronic diarrhoea, weight loss and abdominal pain	Unusual infections or infections by unusual causes
Recurrent/Severe/Refractory/Unusual infection (any type of micro-organism)	Recurrent/Severe/Refractory/Unusual infection (any type of micro-organism)
Recurrent need for IV antibiotics to treat infections	Recurrent need for IV antibiotics to treat infections
Recurrent abscesses in the skin or in organs	Recurrent abscesses in the skin or in organs
Invasive infection with normally inoffensive mycobacteria	Invasive infection with normally inoffensive mycobacteria

Any patient with severe or recurrent infections or an infection by opportunistic or uncommon microorganisms must be investigated for a PID after ruling out the possibility of human immunodeficiency virus (HIV) infection or any other cause of secondary (e.g. acquired) immunodeficiency. Common infections that can occur include RTIs (including pneumonia and infections of the sinuses, ear passages and throat), skin infections (such as dermatitis and abscesses) and bowel infections (such as gastroenteritis and *Clostridium difficile* infection). Infections of the central nervous system (including the brain – such as meningitis and encephalitis) can also occur.

Pyogenic encapsulated bacteria (*Streptococcus pneumoniae*, some *Haemophilus influenzae*) are frequently associated with infections in patients with antibody or complement deficiencies. The latter may also present with meningitis and sepsis associated with pathogens such as meningococcus (*Neisseria sp.*).[4] Patients with agammaglobulinaemia and, to a lesser extent, those with common variable immunodeficiency (CVID) have an increased risk of developing septicaemia.[3] Nonetheless, the incidence of certain infectious agents must be considered alongside their endemicity in the specific geographical region of the person being evaluated.

WARNING SIGNS OF PID PER MEDICAL SPECIALTY

OTORHINOLARYNGOLOGISTS, PULMONOLOGISTS, ALLERGOLOGISTS

As a result of a high percentage of persons with a PID having upper and/or lower respiratory tract bacterial infections (the most common respiratory infections associated with a PID being bronchitis, pneumonia, acute and chronic sinusitis and recurrent otitis media[4]), they are often referred to otorhinolaryngologists or pulmonologists. Hence, before performing extensive immunological evaluation to determine if a person has a PID it is important to also rule out the existence of cofactors that might be associated with upper and/or lower RTIs, such as smoking, daycare attendance and gastroesophageal reflux (amongst others).

Certain PIDs cause imbalances in the immune system that can make patients susceptible to allergies, which are exaggerated reactions to specific triggers (or ‘allergens’). This susceptibility to allergies is called atopy and people who are atopic commonly have multiple allergic diseases, such as eczema (discussed later), rhinitis, asthma and food allergies. Atopy often first appears in infancy or early childhood. Clinicians need to consider the possibility of a PID in patients (especially infants or young children) with atopy that is severe or which does not respond to conventional treatment, or when the patient also shows a susceptibility to infections. Other lung complications caused by PIDs include interstitial lung disease (ILD) and some cancers.

[4] Costa-Carvalho BT, et al. J Clin Immunol 2014;34:10–22.

Non-infectious warning signs of PIDs that may be encountered in an otolaryngology/ pulmonology clinic include (amongst others):

- granulomatous disease that could manifest in the form of granulomatous-lymphocytic interstitial lung disease (GLILD)
- bronchiectasis
- bronchiolitis obliterans
- therapy-resistant asthma
- other respiratory allergies.

Table 2 provides an overview of warning signs of PIDs that may be encountered by otorhinolaryngologists, pulmonologists and allergologists.

TABLE 2. Warning signs of PIDs for otorhinolaryngologists, pulmonologists, allergologists (adapted from Costa-Carvalho et al 2014)[4]

CLINICAL OCCURRENCES (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Pneumonias due to extracellular bacteria + otitis and sinusitis	• Antibody deficiencies • Complement deficiencies • Combined immunodeficiencies
Eczema, recurrent severe skin infections by HSV, MCV, HPV, atopy, asthma	• Hyper-IgE syndrome (HIES) • Combined immunodeficiencies
Pulmonary abscess Pneumatocele	• HIES Features: pneumonia by *S aureus*, eczema, fungal infection, joint hypermobility, coarse facial features
Pneumonias due to *Staphylococcus* 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
Pneumonia due to *P. jiroveci*	• Combined immunodeficiencies (such as SCID, CD40/CD40 ligand (L) deficiencies) • Wiskott-Aldrich syndrome (WAS), eczema + thrombocytopenia
Pneumonia due to *Mycobacteria tuberculosis* or atypical mycobacteria	• Combined immunodeficiencies (such as CD40/CD40 ligand (L) deficiencies) • Mendelian susceptibility to mycobacterial diseases

HPV, human papilloma virus; HSV, herpex simplex virus; MCV, molluscum contagiosum virus.

GASTROENTEROLOGISTS

Gastrointestinal disorders, affecting the mouth, throat, stomach and intestines, are common in many patients with PIDs. The gastrointestinal system is constantly exposed to viruses, parasites and bacteria, all of which have the potential to cause irritation, inflammation and infection of the intestinal lining, particularly when the immune system is not functioning correctly. In addition, the gastrointestinal system contains the majority of the body's lymphocytes and produces immunoglobulins (Igs; also called 'antibodies') so it can be involved in a wide range of PIDs.

Usually, gastrointestinal non-infectious manifestations are not observed at the initial stage of a PID and patients with CVID or X-linked agammaglobulinaemia (XLA) often develop enteropathy or gastritis in the third or fourth decade of life and are susceptible to develop gastric and intestinal neoplasia. This said, some PIDs can present to a clinic with only gastrointestinal symptoms, with early-onset enteropathy and inflammatory bowel disease (IBD) being the most well-recognised gastrointestinal presentations of PIDs.[5]

Infants or children presenting with atypical gastrointestinal disease and/failure to respond to conventional therapies should raise suspicion of a PID. Warning signs of PIDs that may be encountered in a gastroenterology clinic include (also see Table 3):[6]

- Early-onset enteropathy (watery and bloody diarrhoea with malabsorption), presenting in the first months of life. It is one of the leading signs of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), often in the context of the classic triad with eczema and endocrinopathy.
- IBD, especially in patients with a family history of IBD and extraintestinal manifestations.

People with chronic granulomatous disease (CGD) might present with colitis and granulomas associated with CGD causing an IBD that is similar to Crohn's disease without the typical extraintestinal manifestations.
Recurrent or chronic giardiasis is suggestive of an underlying antibody deficiency. Other pathogens in PID patients with infectious colitis include rotavirus, *Campylobacter*, enteroviruses, norovirus, *Cryptosporidium parvum*, *Salmonella* spp, and *Clostridium difficile* (amongst others).

Hepatic involvement occurs with considerable frequency in PIDs, usually as the result of inflammatory or autoimmune hepatitis or regenerative nodular hepatic hyperplasia. It should be noted though that hepatic manifestations are rarely the only finding of a PID at disease onset. Liver abscesses caused mainly by S. aureus (amongst others) may also be seen in patients with CGD and Hyper IgE syndrome (HIES). Hepatobiliary involvement can be the result of parasitic infection caused by *Cryptosporidium*; especially in patients with a combined immunodeficiency (X-linked Hyper-IgM syndrome, CD40-L deficiency, DOCK8 deficiency, amongst others).

[5] Costagliola G, et al. Front Pediatr 2022;10:855445.
[6] PIDs and Gastrointestinal Disorders. https://ipopi.org/a-guide-for-gastroenterologists/
[7] Al-Muhsen SZ. Saudi J Gastroenterol 2010;16:66–74.

TABLE 3.Warning signs of PIDs for gastroenterologists[6] and hepatologists[7]

GASTROINTESTINAL/HEPATIC MANIFESTATIONS (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Hepatitis (CMV), colitis, candidiasis, chronic diarrhoea, materno-fetal GvHD [symptoms can be present from birth]	Severe combined immunodeficiency (SCID)
Hepatic veno-occlusive disease, hepatosplenomegaly	Veno-occlusive disease with SCID
Hepatosplenomegaly, diarrhoea, eosinophilic enteropathy, inflammatory skin disease	Omenn syndrome
Hepatitis (autoimmune, toxic, CMV), diarrhoea, colitis, candidiasis	Adenosine deaminase deficiency SCID
Progressive liver disease, sclerosing cholangitis, colitis and hepatitis (CMV), candidiasis, protracted diarrhoea (*Cryptosporidium*)	MHC-II deficiency (Bare lymphocyte syndrome)
Progressive liver disease, oral ulcers, diarrhoea (*Cryptosporidium*), sclerosing cholangitis, malabsorption	Hyper-IgM syndrome
Progressive liver disease, diarrhoea (Giardia lamblia), nodular lymphoid hyperplasia, villous blunting, IBD-like colitis, pernicious anaemia, nodular regenerative hyperplasia, hepatosplenomegaly	Common variable immunodeficiency (CVID)
Liver abscesses, periodontitis, eosinophilic enteropathy	Hyper-IgE syndrome (HIES)
Post-EBV fulminant hepatic failure, hepatosplenomegaly, lymphoma	X-linked lymphoproliferative syndrome (XLP)
Hepatitis, liver abscesses, oral ulcers, oesophageal dysmotility, gastric outlet obstruction, small bowel obstruction, colitis, perianal fistula and abscesses	Chronic granulomatous disease (CGD)
Severe enteropathy, severe chronic diarrhoea, malabsorption and failure to thrive	Immunodeficiency, polyendocrinopathy, enteropathy, X-linked (IPEX)

CMV, cytomegalovirus; EBV, Epstein Barr virus; GvHD, graft versus host disease; MHC, major histocompatibility complex; IBD, inflammatory bowel disease.

RHEUMATOLOGISTS

PIDs are frequently complicated by infections and/or autoimmune and autoinflammatory rheumatological component. The latter are often managed by clinicians specialising in rheumatology. Warning signs of PIDs that may be encountered in a rheumatology clinic include:

- Vasculitis.
- Bone and joint abnormalities. The most common of these is infectious arthritis, which may be associated with antibody deficiencies and, less often, with CGD and Wiskott-Aldrich syndrome (WAS). Infections with *Ureaplasma urealyticum*, and Mycoplasma spp (amongst others) may lead to erosive arthritis in patients with severe antibody deficiencies.
- Early-onset autoimmunity, particularly systemic lupus erythematosus (SLE), as SLE and other connective tissue diseases can develop in persons with PIDs.

It should be noted that persons with a positive family history, multiple autoimmune disorders, features of lymphoproliferation or hyperinflammation should be considered at high risk of an underlying PID.

Table 4 and 5 provide an overview of autoimmune respectively autoinflammatory warning signs of PIDs that may be encountered by rheumatologists.[8]

TABLE 4.Autoimmune warning signs of PIDs for rheumatologists[8]

AUTOIMMUNE MANIFESTATIONS (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Thrombocytopenia, Evans syndrome, autoimmune haemolytic anaemia, inflammatory bowel disease (IBD), neutropenia, rheumatoid arthritis, pernicious anaemia, systemic lupus erythematosus, psoriasis	Common variable immunodeficiency (CVID)
IBD	X-linked chronic granulomatous disease (CGD)
Juvenile rheumatoid arthritis, rheumatoid arthritis/dermatomyositis	X-linked (or Bruton's) agammaglobulinaemia (XLA)
Thrombocytopenia, haemolytic anaemia, dermatitis, IBD, vasculitis	Wiskott-Aldrich syndrome (WAS)
Autoimmune neutropenia, autoimmune haemolytic anaemia, IBD, rheumatoid arthritis, uveitis	Hyper IgM syndrome
Cytopenias (thrombocytopenia, anaemia, neutropenia), dermatitis, IBD, type 1 diabetes	Immune dysregulation, polyendocrinopathy and enteropathy X-linked (IPEX)
Several autoimmune endocrinopathies (adrenal insufficiency, dysthyroidism)	Autoimmune polyendocrinopathy candidiasis extodermal dystrophy (APECED)

TABLE 5.Autoinflammatory warning signs of PIDs for rheumatologists[8]

AUTOINFLAMMATORY MANIFESTATIONS (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Short duration of fever (24–48 hours), abdominal and chest pain, erysipelas (super infection of the skin)	Familial Mediterranean fever (FMF)
Recurring fevers, muscle, abdominal and chest pain, rash, nausea, vomiting, diarrhoea, sore eyes	Tumour necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS)
Recurring fevers, abdominal pain, vomiting, diarrhoea, joint pain, skin lesions, headache	Mevalonate kinase deficiency (Hyper IgD syndrome)
Headache, rash, joint and muscle pain, fever after cold exposure (seen in FCAS), kidney impairment (seen in MWS), hearing problems (seen in MWS), conjunctivitis (seen in MWS), organ damage (seen in NOMID)	Cryopyrin-associated periodic syndrome (CAPS) • Familial cold autoinflammatory syndrome (FCAS) • Muckle-Wells syndrome (MWS) • Neonatal onset multi-system inflammatory disease (NOMID)/ chronic infantile neurological cutaneous and articular syndrome (CINCA)
Rheumatoid arthritis, inflammation of the eye, skin rash and granuloma	Blau's syndrome
Pus-producing arthritis, skin ulcers, cystic acne	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)
Recurring fevers, bone pain and lesions	Chronic recurrent multifocal osteomyelitis syndrome (CRMO)
Recurring fevers, bone pain, skin inflammation	Majeed syndrome

[8] IPOPI Rheumatological Warning Signs leaflet. IPOPI-Rheumatological-Autoimmune-Autoinflammatory-Crossovers.pdf

DERMATOLOGISTS

Cutaneous manifestations are estimated to affect up to 70% of persons with a PID and their presence may be one of the first clinical indicators of the presence of an underlying PID.[3] Candida infections are often among the first signs of a PID and can include mucocutaneous candidiasis, *Candida paronychia*, granuloma formation, and erythroderma. Infections associated with *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Paecilomyces*, *Scedosporium*, *Trichosporon*, *Penicillium*, and other fungal organisms have been observed in patients with CGD, SCID, HIES, and CVID.

Eczema and high serum IgE levels in the first months of life frequently lead to referral to allergists because of suspicion of cow milk protein allergy but these occurrences are also present in patients with hypomorphic SCID, IPEX, WAS and HIES (amongst others). Other warning signs of PIDs that may be encountered in a dermatology clinic are documented in Table 6.

TABLE 6.Warning signs of PIDs for dermatologists (adapted from Sharma et al 2017)[9]

DERMATOLOGIC MANIFESTATIONS (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Early onset eczema, recurrent cold abscesses, coarse facies, skeletal defect, newborn rash	Classical Hyper-IgE syndrome (STAT3-loss of function mutations)
Eczema, recurrent severe skin infections by HSV, MCV, HPV, atopy, asthma	Hyper-IgE syndrome (Other gene defects)
Eczema, bleeding manifestations, recurrent infections, thrombocytopenia, small size platelets, autoimmune diseases	Wiskott-Aldrich syndrome (WAS) / X-linked thrombocytopenia (XLT)
Eczema, autoimmune enteropathy, endocrinopathy (hypo-/hyperthyroidism, Type I diabetes mellitus)	Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)

HPV, human papilloma virus; HSV, Herpes simplex virus; MCV, Molluscum contagiosum virus; STAT, signal transducer and activator of transcription.

[9] Sharma D,et al. Indian Dermatol Online J 2017;391–405.

HAEMATOLOGISTS/ONCOLOGISTS

Patients with a PID have a much higher risk of developing malignant and non-malignant haematological complications. The former may present as autoimmune cytopenia: anaemia and/or thrombopenia and/or leukopenia (or neutropenia) — all of them at the same time is called aplasia or pancytopenia.

Compared with individuals without a PID, patients with a PID are known to be at increased risk of developing certain types of cancer, including haematological conditions such as lymphoma and leukaemia, as well as solid organ malignancies like skin cancer, thyroid cancer, gastric cancer, liver cancer (linked to non-alcoholic cirrhosis), bladder and cervical epithelial cancer.[10,11] After infections, cancer is the leading cause of death among both children and adults with PIDs.

The observed malignancies in PIDs include a spectrum of tumour types. For instance, CVID is associated with a predominance of non-Hodgkin's lymphoma (NHL) and solid organ cancers such as stomach, breast, bladder, and cervical cancer. X-linked lymphoproliferative disease primarily presents with lymphomas (NHL and Hodgkin's lymphoma), while Wiskott-Aldrich syndrome is linked to diffuse large B-cell lymphoma, NHL, leukaemia, and Kaposi sarcoma. Ataxia-telangiectasia is associated with lymphoid leukaemias, T prolymphocytic lymphomas, and epithelial tumours.[12]

There is not yet enough published evidence to show that patients with a PID are at increased risk for the more common kinds of cancer such as lung, breast, ovary, prostate or large bowel cancer.

Non-malignant warning signs of a PID that may be encountered in a haematology or an oncology clinic include (also see Table 7):

- Autoimmune cytopenia: this could be the first manifestation of both systemic autoimmune diseases and PIDs. Currently, there are no specific diagnostic biomarkers to identify patients at risk of a PID among those presenting with autoimmune cytopenia, but unusual age at disease onset, chronic disease course, and refractory disease should be considered as suspect. Chronic immune thrombocytopenia (ITP) in a male patient should prompt for WAS diagnosis (especially with microthrombocytopenia). All patients with autoimmune haemolytic anaemia and/or ITP should have a PID workup (including looking for autoimmune lymphoproliferative syndrome [ALPS], activated PI3K delta syndrome [APDS] etc).
- Benign polyclonal lymphoproliferation: this is clinically expressed by lymphadenopathies and splenomegaly and is a relevant feature of PIDs such as APDS and ALPS, amongst others.

[10] Mayor PC, et al. J Allergy Clin Immunol 2018;141:1028–35.

[11] Jonkman-Berk BM, et al. Clin Immunol 2015;156:154–62.

[12] Shapiro RS. Am J Hematol 2011;86:48–55.

TABLE 7.Warning signs of PIDs for haematologists/oncologists

CLINICAL OCCURRENCE (NON-EXHAUSTIVE LIST)	POTENTIAL PID (NON-EXHAUSTIVE LIST)
Thrombocytopenia with small-sized platelets	• Wiskott-Aldrich syndrome (WAS)/ X-linked thrombocytopenia Other symptoms: eczema and recurrent infections
Autoimmune cytopenias (autoimmune anaemia, thrombocytopenia and neutropenia)	• Common variable immunodeficiency (CVID) Other features: recurrent infections • ALPS or APDS (organomegaly, non-malignant lymphadenopathy)
Lymphadenopathy + splenomegaly Excluding neoplasias and infections	• Autoimmune lymphoproliferative disease (Other apoptosis defects) • APDS
Quantitative and qualitative defects of neutrophils (neutropenia and neutrophilia) Neutropenia: autoimmune or caused by a myelodysplasia	• Congenital neutropenias (autoimmune or caused by a myelodysplasia) • Chronic granulomatous disease (CGD) • Leukocyte adhesion deficiency • Chediak-Higashi or Griscelli syndrome type 2 (Partial oculo-cutaneous albinism)

IMPORTANCE OF THE MULTIDISCIPLINARY TEAM

Patients with PIDs may require care from a range of specialties depending on their individual symptoms and the organ systems affected. Thus, referral to centres specialising in the management of PIDs may be appropriate where available.

During an initial diagnostic work-up, investigations should include complete blood count including leucocytes and differentiation, IgA, IgM, IgG and IgE. A computed tomography (CT) scan should be requested in cases of recurrent pulmonary infections to assess lung damage, and genetic or direct antigen testing may identify the specific genetic mutation and PID.

MANAGEMENT OF PIDs

Immunoglobulin replacement therapy combined with infection control and treatment remain the primary interventions for patients with PIDs. In addition, patients with PIDs should be offered dietary advice and support including dietary adjustment (for example, exclusion of gluten) and dietary considerations during prophylactic antibiotic treatment. Furthermore, patients with PIDs should be regularly screened for the emergence of malignancies.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

'Information presented within this leaflet is based on published literature at the time of production. The leaflet is intended to provide a broad overview rather than be a guide on clinical practice – for this, please consult the treatment guidelines in your country.'

GRIFOLS

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