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Warning signs of Primary Immunodeficiency for specialty care physicians

The clinical presentation of PID can be diverse. However, there are clinical findings at the level of different organs and systems requiring PID suspicion; these findings must be quickly recognized by specialty care physicians:

➢ ALLERGY:

Clinical manifestation	Suspicion of PID
Difficult-to-control asthma	• Selective IgA deficiency • Common variable immunodeficiency (CVID) • Specific antibody deficiency
Recurrent or complicated sinusitis	• Antibody deficiencies
Recurrent or complicated otitis	• Antibody deficiencies
Eczema	• Wiskott-Aldrich syndrome • Hyper-IgE syndrome • Omenn syndrome • IPEX ((immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) • Netherton syndrome (ichthyosiform erythroderma, ichthyosis linearis, bamboo hair)
Recurrent angioedema	• Hereditary angioedema (C1inh deficiency)
Severe food and/or drug allergies	• DOCK8 defect (hyper-IgE syndrome)

➢ CARDIOLOGY:

Clinical manifestation	Suspicion of PID
Congenital heart disease (interrupted aortic arch, pulmonary atresia, aberrant subclavian, tetralogy of Fallot)	• DiGeorge syndrome
Congenital heart defects	• CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)

➢ THORACIC SURGERY:

Clinical manifestation	Suspicion of PID
Thymoma and hypogammaglobulinemia	• Good syndrome
Congenital heart disease (interrupted aortic arch, pulmonary atresia, aberrant subclavian, tetralogy of Fallot)	• DiGeorge syndrome
Congenital heart defects	• CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)

➢ DERMATOLOGY:

Clinical manifestation	Suspicion of PID
Eczema or erythroderma	• Wiskott-Aldrich syndrome • Hyper-IgE syndrome • Omenn syndrome

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	• IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) • Netherton syndrome (ichthyosiform erythroderma, ichthyosis linearis, bamboo hair)
Partial albinism	• Immunodeficiencies with immune dysregulation and hypopigmentation (Griscelli syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome)
Warts (human papilloma virus recurrent infections)	• WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis) • Epidermodysplasia verruciformis • DOCK8 deficiency (hyper-IgE syndrome) • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • IRF8 deficiency • Combined immunodeficiencies
Molluscum contagiosum recurrent or generalized infections	• DOCK8 deficiency (hyper-IgE syndrome) • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • IRF8 deficiency • Wiskott-Aldrich syndrome • Combined immunodeficiencies • SPINK deficiency (Netherton syndrome)
Ectodermal dysplasia (scanty hair, thin skin, hypohidrosis, defective tooth formation, abnormal nails)	• NEMO deficiency (ectodermal dysplasia with immunodeficiency) • IκBa deficiency (ectodermal dysplasia with immunodeficiency)
Severe periodontal disease	• Neutropenia • Leukocyte adhesion defects (LAD) • Chronic granulomatous disease
Retained primary dentition	• STAT3 deficiency (hyper-IgE syndrome)
Sparse hair, short-limbed dwarfism, infections	• Cartilage-hair hypoplasia
Recurrent angioedema	• Hereditary angioedema (C1 inh deficiency)
Disseminated fusariosis	• STAT1 gain-of-function mutations
Chronic mucocutaneous candidiasis	• STAT1 gain-of-function mutations • CARD9 deficiency • IL-17F deficiency • IL17RA deficiency • APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) • Phagocyte defects
Café-au-lait spots	• PMS2 deficiency
Sun-sensitive telangiectatic erythema	• Bloom syndrome
Invasive dermatophytosis	• CARD9 deficiency
Ectodermal dystrophy	• APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy)
Lipodystrophy	• PSMB8 deficiency (autoinflammatory syndrome)
Ecthyma gangrenosum	• Agammaglobulinemia

➢ ENDOCRINOLOGY:

Clinical manifestation	Suspicion of PID
Neonatal diabetes	• IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-

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	linked syndrome)
Neonatal tetany or seizures	• DiGeorge syndrome • Calcium channels defects (ORAI1, STIM1)
Hypothyroidism, adrenal insufficiency, hypoparathyroidism	• APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy)
Short stature	• Cartilage-hair hypoplasia • STAT5b deficiency
Gonadal dysgenesis	• APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) • Ataxia telangiectasia

➢ GASTROENTEROLOGY:

Clinical manifestation	Suspicion of PID
Chronic diarrhea	• Antibody deficiencies • Combined immunodeficiencies • IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) • CD25 deficiency • CGD • IL10R deficiency • Trichohepatoenteric syndrome
Difficult-to-treat giardiasis	• Antibody deficiencies, including selective IgA deficiency, CVID, XLA
Autoimmune colitis	• IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) • CD25 deficiency • Omenn syndrome • XLP type 2 (XIAP deficiency) • IL-10R deficiency • NEMO
Esophageal candidiasis	• Combined immunodeficiencies • Phagocyte defects • Chronic mucocutaneous candidiasis (CMC) and associated defects (APECED, IL-17F, IL-17RA, CARD9, STAT1)
Hepatic abscess	• Chronic granulomatous disease
Recurrent abdominal pain attacks (simulates acute abdomen)	• Hereditary angioedema (C1 inh deficiency)
Celiac disease	• Selective IgA deficiency • Common variable immunodeficiency (CVID)
Inflammatory bowel disease	• Chronic granulomatous disease • IPEX • IL-10 deficiency • IL-10RA deficiency • IL-10RB deficiency • NEMO deficiency • CD25 (poor mitogens) • STAT5b (poor mitogens, GH insensitivity) • XIAP (can test NOD signaling with MDP or TriDAP) • Autoinflammatory disorders • XLA

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➢ GENETICS:

Clinical manifestation	Suspicion of PID
Cytogenetic abnormalities (e.g. multiradial chromosomes, breaks, deletions, isochromosomes)	• ICF (immunodeficiency, centromeric instability and facial anomalies • Ataxia-telangiectasia • DNA repair disorders

➢ HEMATOLOGY:

Clinical manifestation	Suspicion of PID
Thrombocytopenia with microplatelets	• Wiskott-Aldrich syndrome • X-linked thrombocytopenia
Autoimmune cytopenias	• Common variable immunodeficiency (CVID) • AID (activation-induced cytidine deaminase) deficiency • PNP deficiency • LRBA deficiency • IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) • CD25 deficiency • ALPS (autoinmune lymphoproliferative syndrome)
Aplastic anemia	• XLP type 1 (SAP deficiency) • Dyskeratosis congenita
Lymphadenopathy and hepatosplenomegaly	• XLP (X-linked lymphoproliferative syndrome) • ALPS (autoinmune lymphoproliferative syndrome) • AID (activation-induced cytidine deaminase) deficiency • UNG deficiency • Combined immunodeficiencies • Chronic granulomatous disease
Neutropenia	• Severe congenital neutropenia • Cyclic neutropenia • CD40L deficiency • XLA (X-linked agammaglobulinemia) • WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis) • Reticular dysgenesis (AK2 deficiency) • Ikaros deficiency • X-linked neutropenia (WASP gain-of-function mutation)
Haemolytic anemia	• PNP (purine nucleoside phosphorylase) deficiency • Wiskott-Aldrich syndrome • IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) • Common variable immunodeficiency (CVID)
Hemophagocytic lymphohistiocytosis, fulminant or chronic infection by Epstein-Barr virus	• Familial hemophagocytic lymphohistiocytosis (FHL) syndromes • XLP types 1 or 2 • Itk deficiency • CD27 deficiency • Magnesium channels defects
Marked leukocytosis	• Leukocyte adhesion defects (LAD) • ALPS
Thrombocytopenia in a male	• XLT (X-linked thrombocytopenia)

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SCID with megaloblastic anemia	• MTHFD1 deficiency (hyperhomocysteinemia)
Monocytosis	• NRAS/KRAS deficiency
Leukemia similarity	• NRAS/KRAS deficiency

➢ INFECTOLOGY:

Clinical manifestation	Suspicion of PID
Pneumonias, otitis and sinusitis by encapsulated bacteria	• Antibody deficiencies • Complement deficiencies
Lung abscess, pneumatoceles	• STAT3 associated Hyper-IgE syndrome
Pneumocystis jiroveci pneumonia	• Combined immunodeficiencies • CD4OL deficiency • Wiskott-Aldrich syndrome
Infections by atypical mycobacteria (including BCG), disseminated tuberculosis	• Combined immunodeficiencies • NEMO deficiency (ectodermal dysplasia with immunodeficiency) • Chronic granulomatous disease • Defect in the IFN-γ/IL-12 axis • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • STAT1 deficiency (AD) • IRF8 (interferon regulatory factor 8) deficiency
Hepatic abscess	• Chronic granulomatous disease
Infections by Burkholderia cepacia, Chromobacterium violaceum, Serratia marcescens	• Chronic granulomatous disease
Disseminated infection by Histoplasma sp or Paracoccidioides sp	• Defect in the IFN-γ/IL-12 axis • CD40L deficiency
Severe infection by Salmonella no typhi	• Defect in the IFN-γ/IL-12 axis
Fulminant or chronic infection by Epstein-Barr virus, hemophagocytic lymphohistiocytosis	• XLP types 1 or 2 • Itk deficiency • CD27 deficiency • Magnesium channels defects • Familial hemophagocytic lymphohistiocytosis (FHL) syndromes
Herpes simplex encephalitis	• Defect in TLR3 pathway
Trypanosomiasis	• APOL-I deficiency
Infections by Staphylococcus aureus	• Hyper-IgE syndrome • Chronic granulomatous disease • Antibody deficiencies • IRAK4/MyD88 deficiency
Infections by Streptococcus pneumoniae	• Antibody deficiencies • Complement deficencies • IRAK4/MyD88 deficiency
Infections by Cryptosporidium	• Combined immunodeficiencies • CD40L/CD40 deficiency • IL-21R deficiency
Meningoencephalitis by enteroviruses	• Agammaglobulinemia, X-linked
Mucocutaneous candidiasis	• Combined immunodeficiencies • Phagocyte defects

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	• Chronic mucocutaneous candidiasis (CMC) and associated defects (APECED, IL-17F, IL-17RA, CARD9, STAT1)
Severe infections by Neisseria sp	• Complement deficiencies (late C-components)
Warts (Human papilloma virus recurrent infections)	• WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis) • Epidermodysplasia verruciformis • DOCK8 deficiency (hyper-IgE syndrome) • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • IRF8 deficiency • Combined immunodeficiencies
Infections by molluscum contagiosum	• DOCK8 deficiency (hyper-IgE syndrome) • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • IRF8 deficiency • Combined immunodeficiencies • Wiskott-Aldrich syndrome
Pyoderma gangrenosum	• Agammaglobulinemias • PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, acne)
Severe infections by influenza virus	• IRF7 deficiency

➢ INTERNALMEDICINE:

Clinical manifestation	Suspicion of PID
Hemophagocytic lymphohistiocytosis	• Defects in PRF1, MUNC13-4, STXBP2
Thymoma and hypogammaglobulinemia	• Good syndrome
Recurrent respiratory infections, interstitial pneumonitis, granulomatosis, autoimmunity	• Common variable immunodeficiency (CVID)

➢ LABORATORY:

Clinical manifestation	Suspicion of PID
Elevated AFP and/or CEA	• Ataxia-telangiectasia
Elevated DN αβ-T cells (>5%)	• ALPS (frequently normal in KRAS/NRAS deficiency)
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➢ NEPHROLOGY:

Clinical manifestation	Suspicion of PID
Atypical hemolytic-uremic syndrome	• Complement deficiencies
Glomerulonephritis	• Complement deficiencies • IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)

➢ NEONATOLOGY:

Clinical manifestation	Suspicion of PID
Eczema or erythroderma	• Wiskott-Aldrich syndrome • Hyper-IgE syndrome • Omenn syndrome • IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-

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	linked syndrome) • Netherton syndrome
Thymus aplasia	• Severe combined immunodeficiency • Omenn syndrome • DiGeorge syndrome
Omphalitis, delayed umbilical cord separation, (later than 40 days of age)	• Leukocyte adhesion defects (LAD)
Typical facies	• DiGeorge syndrome • Deficiency of Cernunnos, ligase IV, etc. • STAT3 deficiency (hyper-IgE syndrome)
Neonatal diabetes	• IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)
Neonatal tetany or seizures	• DiGeorge syndrome • Calcium channels defects (ORAI1, STIM1)

➢ ORTHOPEDICS AND TRAUMATOLOGY:

Clinical manifestation	Suspicion of PID
Skeletal abnormalities	• STAT3 deficiency • Reticular dysgenesis (AK2 deficiency): squaring of the scapular tips; cupping and fraying of the rib costochondral junctions anteriorly • Schimke immuno-osseous dysplasia (spondyloepiphyseal dysplasia, dysplastic hips, small capital femoral epiphysis) • Cartilage-hair hypoplasia (chest deformities with flaring of ribs, fixed flexion deformity in elbow, long distal fibula, cone shaped epiphysis in the phalanges)
Septic arthritis	• Antibody deficiencies • IRAK4/MyD88/TIRAP deficiency
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➢ PNEUMONOLOGY:

Clinical manifestation	Suspicion of PID
Pneumonias, otitis and sinusitis by encapsulated bacteria	• Antibody deficiencies • Complement deficiencies
Lung abscess, pneumatoceles	• Hyper-IgE syndrome
Pneumocystis jiroveci pneumonia	• Combined immunodeficiencies • CD4OL deficiency • Wiskott-Aldrich syndrome
Infections by atypical mycobacteria (including BCG), disseminated tuberculosis	• Combined immunodeficiencies • NEMO deficiency (ectodermal dysplasia with immunodeficiency) • Chronic granulomatous disease • Defect in the IFN-γ/IL-12 axis • STAT1 deficiency (AD) • GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • IRF8 (interferon regulatory factor 8) deficiency • ISG15 deficiency
Pulmonary alveolar proteinosis	• GATA2 deficiency (Mono MAC syndrome, DCML deficiency) • CSF2RA deficiency
Interstitial pneumonitis	• Common variable immunodeficiency (CVID)

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	• STAT5b deficiency

➢ NEUROLOGY:

Clinical manifestation	Suspicion of PID
Ataxia	• Ataxia-telangiectasia • Ataxia-telangiectasia like disease (ATLD) • PNP deficiency
Microcephaly	• Cernunnos deficiency • Ligase IV deficiency • Ligase I deficiency • Nijmegen breakage syndrome • Dyskeratosis congenita
Deafness	• Reticular dysgenesis • ADA deficiency • CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)
Tetraphlegy	• PNP deficiency
Cerebellar hypoplasia	• Dyskeratosis congenita
Herpes simplex encephalitis	• Defect in TLR3 pathway
Meningoencephalitis by Neisseria sp	• Complement deficiencies (late components)

➢ DENTISTRY:

Clinical manifestation	Suspicion of PID
Ectodermal dysplasia (scanty hair, thin skin, hypohidrosis, defective tooth formation, conic teeth, abnormal nails)	• NEMO deficiency (ectodermal dysplasia with immunodeficiency) • IκBa deficiency (ectodermal dysplasia with immunodeficiency)
Severe periodontal disease	• Phagocyte defects (neutropenia, LAD, CGD)
Retained primary dentition	• STAT3 deficiency (hyper-IgE syndrome)

➢ ONCOLOGY:

Clinical manifestation	Suspicion of PID
EBV-related neoplasms (manly lymphomas)	• Ataxia telangiectasia • Wiskott-Aldrich Syndrome • XLP
HPV-related neoplasms	• Epidermodysplasia verruciformis • GATA2 deficiency • DOCK8 deficiency
Susceptibility to neoplasms	• Bloom syndrome
Colon and/or brain cancer (including hereditary nonpolyposis colon carcinoma)	• PMS2 deficiency

➢ OPHTALMOLOGY:

Clinical manifestation	Suspicion of PID
Coloboma	• CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness) • Cohen syndrome

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Aniridia	• Omenn syndrome
Conjunctival telangiectasia	• Ataxia-telangiectasia

➢ ORTHOPEDICS:

Clinical manifestation	Suspicion of PID
Septic arthritis	• Antibody deficiencies • Complement deficiencies (Neisseria sp infections) • IRAK4/MyD88 deficiencies
Metaphyseal dysostosis	• Cartilage-hair hypoplasia • ADA deficiency

➢ OTORHINOLARYNGOLOGY:

Clinical manifestation	Suspicion of PID
Atresia choanae, deafness	• CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)
Recurrent or complicated sinusitis	• Antibody deficiencies
Recurrent or complicated otitis	• Antibody deficiencies
Velopharyngeal insufficiency	• DiGeorge syndrome
Deafness	• Reticular dysgenesis • ADA deficiency • CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness)

➢ RADIOLOGY:

Clinical manifestation	Suspicion of PID
Thymic aplasia	• Severe combined immunodeficiency (SCID) • DiGeorge syndrome
Pneumatoceles	• STAT3 associated hyper-IgE syndrome
Granulomatous lesions	• Chronic granulomatous disease

➢ RHEUMATOLOGY:

Clinical manifestation	Suspicion of PID
Lupus-like syndrome	• Complement deficiencies (classical pathway) • PRKCD (PKCδ deficiency) • ALPS
Autoimmune cytopenias	• Common variable immunodeficiency (CVID) • AID (activation-induced cytidine deaminase) deficiency • PNP deficiency • LRBA deficiency • IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) • ALPS
Juvenile arthritis	• DiGeorge syndrome
Recurrent fever, serositis, arthritis	• Autoinflammatory disorders • Cyclic neutropenia
Septic arthritis	• Antibody deficiencies • Complement deficiencies (Neisseria sp infections) • IRAK4/MyD88 deficiencies

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Metaphyseal dysostosis	• Cartilage-hair hypoplasia • ADA deficiency