Immunology and Genetics Journal

Reveiw Article

Received: 19 January 2019
Accepted: 24 February 2019
Published online: 22 March 2019
Doi: 10.22034/igj.2019.172502.1009

National Consensus on Diagnosis and Management Guidelines for Primary Immunodeficiency

Hassan Abolhassani[1,2,3], Marzieh Tavakol[4], Zahra Chavoshzadeh[5], Seyed Alireza Mahdaviani[6], Tooba Momen[7], RezaYazdani[1,3], Gholamreza Azizi[8], Masoud Movahedi[9], Amir Ali Hamidieh[10], Nasrin Behniafard[11,30], Mohammamd Nabavi[12], Saba Arshi[12], Mohammad Hassan Bemanian[12], Morteza Fallahpour[12], Sima Shokri[12], Rasol Molatefi[13], Roya Sherkat[14], Afshin Shirkani[16], Reza Amin[17],Soheila Aleyasin[17], Reza Faridhosseini[18], Farahzad Jabbari-Azad[18], Iraj Mohammadzadeh[19], Javad Ghaffari[20], Alireza Shafiei[21], Arash Kalantari[22], Mahboubeh Mansouri[15], Mehrnaz Mesdaghi[15], Delara Babaie[5], Hamid Ahanchian[18], Maryam Khoshkhui[18], Habib Soheili[23], Mohammad Hossein Eslamian[24] , Taher Cheraghi[25], Abbas Dabbaghzadeh[19], Mahmoud Tavassoli[26], Rasoul Nasiri Kalmarzi[27], Seyed Hamidreza Mortazavi[28], Sara Kashef[17], Hossein Esmaeilzadeh[17], Javad Tafaroji[29], Abbas Khalili[30], Fariborz Zandieh[21], Mahnaz Sadeghi-Shabestari[31], Sepideh Darougar[44], Fatemeh Behmanesh[17], Hedayat Akbari[17], Mohammadreza Zandkarimi[18], Farhad Abolnezhadian[32], Abbas Fayezi[32], Mojgan Moghtaderi[17], Akefeh Ahmadiafshar[33], Behzad Shakerian[26], Vahid Sajedi[34], Behrang Taghvaei[35], Mojgan Safari[24], Marzieh Heidarzadeh[36], Babak Ghalehbaghi[25], Seyed Mohammad Fathi[37], Behzad Darabi[38], Saeed Bazregari[16], Nasrin Bazargan[39], Morteza Fallahpour[12], Alireza Khayatzadeh[1], Naser Javahertrash[12], Bahram Bashardoust[6], Mohammadali Zamani[40], Azam Mohsenzadeh[41], Sarehsadat Ebrahimi[9], Samin Sharafian[16], Ahmad Vosughimotlagh[9], Mitra Tafakoridelbari[9], Maziar Rahimi[9], Parisa Ashournia[9], Anahita Razaghian[9], Fatemeh Aghaeimeybodi[43], Setareh Mamishi[42], Nima Parvaneh[1,3], Nima Rezaei[1,3], Asghar Aghamohammadi[1,3]

[1]. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, and the University of Medical Science, Tehran, Iran
[2]. Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden
[3]. Iranian Primary Immunodeficiencies Network (IPIN), Tehran University of Medical Science, Tehran, Iran
[4]. Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[5]. Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]. Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]. Department of Allergy and Clinical Immunology, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[8]. Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[9]. Division of Allergy and Clinical Immunology, Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center, Tehran, University of Medical Sciences, Tehran, Iran
[10]. Hematology, Oncology and Stem Cell Transplantation Research Centre, Tehran University of Medical Sciences, Tehran, Iran
[11]. Department of Allergy and Clinical Immunology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[12]. Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
[13]. Department of Pediatrics, Bo-Ali children's Hospital of Ardabil University of Medical Sciences, Ardabil, Iran
[14]. Acquired Immunodeficiency Research Center, lsfahan University of Medical Sciences, Isfahan, lran
[15]. Immunology and Allergy Department, Mofid Children's Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran
[16]. Allergy and Clinical Immunology Department, Bushehr University of Medical Science, School of Medicine, Bushehr, Iran
[17]. Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[18]. Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[19]. Noncommunicable Pediatric Diseases Research Center, Amirkola Hospital, Babol University of Medical Sciences, Babol, Iran
[20]. Department of Pediatrics, Mazandaran University of Medical Sciences, Sari, Iran
[21]. Department of Immunology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran
[22]. Department of Immunology and Allergy, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[23]. Department of Pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[24]. Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran
[25]. Department of Pediatrics, 17th Shahrivar Children's Hospital, Guilan University of Medical Sciences, Rasht, Iran
[26]. Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[27]. Cellular & Molecular Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
[28]. Department of Pediatrics, Kermanshah University of Medical Sciences, Kermanshah, Iran
[29]. Department of Pediatrics, Qom University of Medical Sciences, Qom, Iran
[30]. Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[31]. Department of Immunology and Allergy, Tabriz University of Medical Sciences, Tabriz, Iran
[32]. Department of Immunology and Allergy, Ahvaz University of Medical Sciences, Ahvaz, Iran
[33]. Mousavi Hospital, Zanjan University of Meical Sciences, Zanjan, Iran
[34]. Department of Immunology and Allergy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[35]. Department of Immunology and Allergy, Semnan University of Medical Sciences, Semnan, Iran
[36]. Department of Immunology and Allergy, Kashan University of Medical Sciences, Kashan, Iran
[37]. Department of Immunology and Allergy, Qazvin University of Medical Sciences, Qazvin, Iran
[38]. Department of Immunology and Allergy, Ilam University of Medical Sciences, Ilam, Iran
[39]. Department of Immunology and Allergy, Kerman University of Medical Sciences, Kerman, Iran
[40]. Department of Immunology and Allergy, Shahrekord University of Medical Sciences, Shahrekord , Iran
[41]. Department of Pediatrics, Lorestan University of Medical Sciences, Khorramabad, Iran
[42]. Pediatric Infectious Diseases Research Center, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

Abstract

Primary immunodeficiency (PID) is a group of more than 400 distinct genetic disorders affecting both children and adults. As signs and symptoms of PID are usually heterogeneous and unspecific, diagnosis and follow-up of these patients can be challenging based on the available human resources and laboratory facilities.

In order to reach a distinct national protocol and due to little evidence to guide appropriate or universal guidelines to improve the current status of management of the disease, the Iranian PID network designed a consensus appropriate for regional resources. This review summarizes this PID guideline based on the importance of different clinical complications and the level of medical authority visiting those at the first line. Moreover, for each complication, appropriate interventions for improving approach are mentioned.

Keywords Primary immunodeficiency, Symptoms, Management, Consensus, Guideline.

*** Corresponding author:** Asghar Aghamohammadi
E-mail: aghamohammadi@tums.ac.ir

1. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, and the University of Medical Science, Tehran, Iran

2. Iranian Primary Immunodeficiencies Network (IPIN), Tehran University of Medical Science, Tehran, Iran

Introduction

Primary immunodeficiency (PID), as a heterogeneous group of inherited disorders, is characterized by higher incidence of frequent infections, immune dysregulations and cancers, as well as non-immune complications in syndromic forms of PID. The prevalence of these disorders should not be thought of as being rare (1:600), where the onset (early or late) and clinical manifestations (distinct phenotypes) of the disease have heterogeneous presentations. This variability in clinical phenotype and immunologic profile of disease may lead to delayed PID diagnosis.

Heterogeneity in PID refers to variability in genetic defects underlying the diverse clinical symptoms described in this group of patients. However, dealing with these patients should not be delayed until molecular diagnosis and different medical authorities from family physicians, to general practitioners (first line referrals), and specialists (second line referrals mainly pediatricians and infectious disease specialists) and clinical immunologists (third line referrals). In the third level of approach regarding clinical diagnosis, since 2011 onwards, European Society for Immunodeficiencies has updated the clinical diagnostic criteria regarding PID (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria). Further, for molecular diagnosis and definite classification of PIDs, International Union of Immunological Societies (IUIS) has categorized these diseases since 1999 (1).

However, the task of family physicians, as well as first and second line physicians toward diagnosis of PID and completing the cycle is rather elementary. Here, the expert panel of clinical immunologists in Iranian national PID network review the recent advances in stepwise diagnosis and management of PID, specifically the clinical features on the focus in on the correct approach to different signs and symptoms associated with PID.

Consensus on diagnosis and approach to PID

In 1970, Professor Farhoudi established the Division of Clinical Immunology and Allergy as well as the Immunology Laboratory in the Children's Medical Center affiliated with Tehran University of Medical Sciences (TUMS) which revolutionized the PID care in the country (2, 3). Since that time and with training of more clinical immunologists covering different regions of the country, the PID networks was formed in 2016 (2, 3).

Although it is generally accepted that diagnostic evaluation of PID requires various components which should be included in the diagnostic work-up of a patient starting from clinical evaluation, immunological work-up, selection of genetic testing, analysis of results, routine follow-up visits, and updating diagnosis and clinical management, there is no clear written guideline within PID network in this regard. To make a timely diagnosis of PID, it is essential to assign clinical experts capable of analyzing and interpreting clinical signs and symptoms, and then integrate molecular and genetic data with clinical findings (4).

Concerning the current condition in the region, the basic and clinical experts in this network realized that it is the time to focus on understanding whether approach to PID could be categorized across different medical authorities to facilitate diagnosis and referral to third line physicians for molecular diagnosis and targeted treatment. Table 1 summarizes the suggested national guidelines to approach to different signs and symptoms associated with PID including immune and non-immune related complications.

Discussion

By unifying the diagnostic approaches at different medical authority levels, the next step will be improvement of the clinical therapy and follow-up visit schedules in all patients with different types of PID. Although for some rare genetic diseases, it is more difficult to find a consensual guideline on the precise modalities as many of them need further patients' cohort with long term prognostic analysis. However, in regard to frequent clinically diagnosed PIDs including antibody deficiencies and combined immunodeficiencies, the therapeutic protocols should be determined and provided accessible nationally (**Table 2**).

Despite efforts on national activity to distribute comprehensively therapeutic and prophylactic antibiotics for infections, the most common treatment options for PID patients are immunoglobulin replacement therapy which still encounters difficulties in sustainability within some regions of the country. Further, different immunoglobulin products, particularly subcutaneous route should be developed soon to improve therapeutic options in patients with lack of antibody production. We have also designed a national protocol regarding immunoglobulin replacement therapy where 1282 (17.09% of estimated number of patients) patients were diagnosed and underwent appropriate treatments (replacement dose of 400–600 mg/kg/ 3-4 weeks) (5, 6).

We have also evidence on impact of the national guideline for immunoglobulin replacement therapy in reducing the burden of many aspects of PIDs, including patient's quality of life and mortalities from life-threatening invasive infections (7, 8).

In the national protocol for immunoglobulin replacement therapy, we have considered the risk of adverse reactions during infusion, and have mentioned the required supervision of trained physicians and nurses who are aware of these complications (9-12). Nowadays, with this platform, all established immunoglobulin units in the peripheral centers perform regular monitoring on patients who receive the replacement therapy. Further, the efficacy as well as the adverse reactions of this treatment is continuously recorded.

Table 1. Abstracted guideline for the approach to complications associated with primary immunodeficiency (PID)

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
Recurrent, multiple, severe infections with usual pathogens			
In pediatrics 4 or more ear infections in one year 2 or more severe sinus infections in one year Insufficient weight gain or growth delay Persistent thrush in mouth or fungal Infection on skin Family history of a PID 2 or more months of treatment with antibiotics with little effect Need for intravenous antibiotics to clear infections Exclusion of passive smokers, daily care infections, anatomical abnormalities, secondary immunodeficiency Pathogen detection (Absence of tonsils?) (Hearing loss and perforation or scarring of tympanic membrane?) (Impaired pulmonary function tests?)	In pediatrics 2 or more pneumonias per year Recurrent deep skin or organ abscesses (e.g. liver, lungs) 2 or more deep seated infections (e.g. septicemia, meningitis) Exclusion of atopic disorders and functional abnormalities Advanced microbiological assays CBC with differential Quantitative serum immunoglobulins—IgG, IgA, IgM , IgE Lymphocyte subset analysis by flow cytometry for B and T cells (CD3,4,8, 16, 56 and 19) Specific antibody production to vaccine (Tetanus/diphtheria, Pneumococcal and meningococcal, Haemophilus influenzae B) Isohemagglutinins (IgM antibodies to A and B blood group antigens) Imaging appropriate for the site of infection Puncture appropriate for the site of infection Evaluation of Dihydrorhodamine (DHR) or NBT for screening CGD Evaluation of CH50 and AP50 for screening complement deficiency Sweat test to exclude cystic fibrosis Nasal mucosa biopsy to rule out immotile cilia syndrome	Evaluation of HLA-DR for screening of MHC class II deficiency IgG subclasses (IgG1, IgG2, IgG3 and IgG4) In vitro IgG synthesis by stimulation of PBL or purified B cells cultured (in the presence of anti-CD40 and IL-4, lymphokines) Biopsies from rectal mucosa and lymph nodes In vitro proliferation of T-lymphocytes to mitogens (PHA, ConA), allogeneic cells (MLC), and specific antigens (candida, tetanus toxoid) Delayed-type hypersensitivity skin tests (Mumps, Candida, Tetanus and fungal antigens only in older children and adults) Production of cytokines by activated T-lymphocytes Expression of activation markers (e.g., CD40L, CD69) and lymphokine receptors (e.g., IL-2Rγc, IFN-γR) after mitogenic stimulation Enumeration of MHCI and MHCII expressing lymphocytes Enzyme assays (ADA, PNP, MPO, G6PD, Glutathione peroxidase, NADPH oxidase) Biopsies from skin, lymph node, thymus, bone marrow Lymphocyte-mediated cytotoxicity—NK and ADCC activity Signal transduction studies Chromosome analysis (probe for 22q11) Molecular and mutation analysis	B cell defects T cell defects Phagocytosis defects Innate immune defects Complement defects
In adults 2 or more ear infections in one year 2 or more sinus infections in one year in the absence of allergies Chronic diarrhea with weight loss Repeated viral infections (colds, herpes, warts, condyloma) Persistent thrush or fungal infection on skin or elsewhere Family history of a PID 1 pneumonia per year for more than one year Recurrent need for intravenous antibiotics to clear infections Infection with normally harmless tuberculosis-like bacteria Pathogen detection	In adults Recurrent, deep abscesses of the skin or internal organs (e.g. liver, lungs) Microbiological assays Advanced microbiological assays CBC with differential Quantitative serum immunoglobulins—IgG, IgA, IgM, IgE Lymphocyte subset analysis by flow cytometry for B and T cells (CD3,4,8 and 19) Specific antibody production to vaccine (Tetanus/diphtheria, Pneumococcal and meningococcal, Haemophilus influenzae B) Isohemagglutinins (IgM antibodies to A and B blood group antigens) Imaging appropriate for the site of infection Puncture appropriate for the site of infection Evaluation of Dihydrorhodamine for screening CGD Evaluation of CH50 and AP50 for screening complement deficiency	Absolute neutrophil count (serially to rule out cyclic neutropenia) WBC turnover Anti-neutrophil antibody Assessment of chemotaxis, adhesion in vivo and in vitro CD11/CD18 assessment by flow cytometry NBT slide test; metabolic burst by flow cytometry Chemiluminescence Analysis of quantity and function of C components Chemotactic activity of complement split products (C3a, C5a)	B cell defects Atypical T cell defects Complement defects
Infections with unusual/ opportunistic pathogens and attenuated vaccines			
NU	Burkholderia cepacia confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease
NU	Mycoplasma/Ureaplasma confirmed by infectious specialists	Approach to B cell defects Confirmation of clinical ESID Diagnostic Criteria	Antibody deficiencies
NU	Neisseria meningitides confirmed by infectious specialists	Approach to Complement defects Confirmation of clinical ESID Diagnostic Criteria	Deficiencies of alternative or terminal complement pathways components C5, C6, C7, C8a–g, C8b, C9, factor D, properdin, factor I, factor H deficiencies
NU	Nocardia spp. confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease
NU	Pseudomonas aeruginosa (severe) confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Neutropenia

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
NU	Salmonella spp. (severe) onfirmed by infectious specialists	Approach to Phagocytosis defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease Macrophage activation disorders
NU	Serratia marcesens confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease
NU	Staphylococcus aureus (severe) confirmed by infectious specialists	Approach to Phagocytosis defects and T cell defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease Hyper IgE syndrome
NU	Streptococcal sepsis (severe) confirmed by infectious specialists	Approach to Innate immune defects , T cell defects, Complement defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	IRAK4 deficiency NEMO deficiency MyD88 deficiency Asplenia Complement deficiencies Antibody deficiencies
NU	Atypical mycobacteria confirmed by infectious specialists	Approach to Phagocytosis defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Macrophage activation disorders Chronic granulomatous disease
NU	Cytomegalovirus(CMV)/Epstein-Barr virus (EBV) (severe) confirmed by infectious specialists	Approach to T cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	X-lined lymphoproliferative disease Familial hemophagocytic lymphohistiocytosis Serious T cell deficiencies
NU	Herpes simplex virus (HSV) confirmed by infectious specialists	Approach to T cell defects and Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	UNC-93B and TLR3 deficiencies (STAT1, Caspase 8, and NEMO deficiencies)
NU	Influenza (severe) confirmed by infectious specialists	Approach to T cell defects and Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	TLR3 deficiency
NU	JC virus confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Ig CSR deficiencies Hyper IgE syndrome
NU	HHV8 confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Severe T cell deficiencies Wiskott–Aldrich syndrome
NU	Varicella (severe) confirmed by infectious specialists	Approach to T cell defects and Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	Most significant T and NK cell deficiencies
NU	Papilloma virus (severe) confirmed by infectious specialists	Approach to T cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Warts, hypogammaglobulinemia infections, myelokathexis syndrome Epidermodysplasia verruciformis
NU	Aspergillus confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease
NU	Candida (severe) confirmed by infectious specialists	Approach to Phagocytosis defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy
NU	Histoplasmosis confirmed by infectious specialists	Approach to T cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Macrophage activation deficiencies
NU	Low pathogenicity fungi confirmed by infectious specialists	Approach to Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Chronic granulomatous disease
NU	Cryptosporidia confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Ig CSR deficiencies
NU	Giardia (severe) confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Antibody deficiencies
NU	Pneumocystis jiroveci confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Severe T cell deficiencies NEMO deficiency

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
NU	Toxoplasmosis confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	Severe T cell deficiencies Ig CSR deficiencies
BCGitis-BCGosis, and chicken pox after varicella vaccination Refer to infectious specialists	Bacillus Calmette–Guérin confirmed by infectious specialists	Approach to T cell defects , B cell defects, Phagocytosis defects and Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	MSMD, SCID, combined immunodeficiency, CGD, NEMO deficiency
Paralysis or diarrhea after taking poliovirus vaccine Prolonged viral shedding in stool examination	Immunodeficiency-related vaccine-derived poliovirus (iVDPV) mainly serotype 2 confirmed by infectious specialists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	SCID, XLA, CVID
Disseminated vaccine-strain measles after MMR Refer to infectious specialists	Measles, Mumps, and Rubella confirmed by infectious specialists	Approach to T cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	STAT2 deficiency
Autoimmunity, lymphoproliferation and immune dysregulation			
Pale skin color Anemia Exclusion as whether the patient has an isolated anemia or if other cell lines (ie, white blood cells and platelets)	In pancytopenia exclusion of leukemia, infection, myelosuppressive medications, aplastic anemia, and hypersplenism. In anemia with thrombocytopenia exclusion of hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and Evans syndrome In anemia with thrombocytosis exclusion of Iron deficiency anemia, post-splenectomy anemia and infection or inflammation. In anemia with leukocytosis, exclusion of leukemia and infection. In microcytic anemia, exclusion of iron deficiency and thalassemia. In normocytic anemia, exclusion of hemolytic anemias, blood loss, infection, medication, and anemia of chronic disease. In macrocytosis anemia, exclusion of exposure to certain medications (e.g., anticonvulsants, zidovudine, and immunosuppressive agents), vitamin B12 or folate deficiency, liver disease, hypothyroidism, and aplastic anemia. In high reticulocyte count anemia, exclusion of hemorrhage; autoimmune hemolytic anemia; membranopathies (e.g., hereditary spherocytosis); enzymopathies (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency); hemoglobinopathies (e.g., sickle cell disease); and microangiopathic hemolytic anemia (e.g., hemolytic uremic syndrome). In low or normal reticulocyte count, exclusion of inadequate marrow response including infections, lead poisoning, hypoplastic anemias, transient erythroblastopenia of childhood (TEC), Diamond-Blackfan anemia (which typically presents with macrocytic anemia), drugs (most drugs that decrease erythropoiesis affect other cell lines as well; cisplatin is an example of a medication that can cause isolated suppression of erythropoiesis), and kidney disease.	Approach to T cell defects, B cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Diamond-Blackfan anemia, CVID, IgAD, CTLA4 deficiency, LRBA deficiency, IPEX, APECED, CD40L deficiency, Transcobalamin 2 deficiency, SLC46A1 deficiency, Methylene-tetrahydrofolate dehydrogenase 1 deficiency, Spondyloenchondro-dysplasia with immune dysregulation, Majeed syndrome, CD59 deficiency, Large granular lymphocytosis, PNP deficiency, TRNT1 deficiency, SH2D1A deficiency, CD27 deficiency, LPIN2 deficiency
Bleeding tendency/ petechiae and purpura Thrombocytopenia Exclusion whether the patient has an isolated thrombocytopenia or if other cell lines (i.e. white blood cells and Hemoglobin)	In immune thrombocytopenia, exclusion of antiphospholipid antibody syndrome, systemic lupus erythematosus, Crohn's disease, autoimmune hepatitis, autoimmune thyroid disease and drug-induced including valproic acid, quinine, quinidine, trimethoprim-sulfamethoxazole and vancomycin. In platelet activation and consumption, exclusion of disseminated intravascular coagulation and the thrombotic microangiopathies hemolytic uremic syndrome (HUS), microangiopathic disorders, Upshaw-Shulman syndrome, major surgery or trauma, hemangioendotheliomas, and tufted hemangiomas. In mechanical destruction, exclusion of extracorporeal therapies, such as extracorporeal membrane oxygenation, cardiopulmonary bypass, hemodialysis, and apheresis, associated with mechanical destruction of platelets. In sequestration and trapping, exclusion of hypersplenia and rare forms of von Willebrand disease (VWD). In impaired platelet production, exclusion of bone marrow infiltration, suppression or failure, or a defect in megakaryocyte development and differentiation due to infection, disseminated intravascular coagulation, Epstein-Barr virus, cytomegalovirus, parvovirus, varicella, and rickettsia, HIV, bacterial sepsis, nutritional deficiencies of folate and vitamin B12 and Iron , bone marrow dysfunction (due to infection, aplastic anemia, chemotherapeutic agents, or radiation) or infiltrative disease (leukemia, lymphoma, fibrosis, hemophagocytic lymphohistiocytosis)	Approach to T cell defects, B cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALSP, IPEX, CVID, CTLA4 deficiency, LRBA deficiency, DiGeorge syndrome, WAS, WIP deficiency, ARPC1B deficiency, GATA1 deficiency, ACP5 deficiency, CD40L deficiency, TFRC deficiency, Hepatic veno-occlusive disease, TWEAK deficiency, MKL1 deficiency, Fanconi anemia, Dyskeratosis congenital, Shwachman-Diamond syndrome.
Neutropenia Exclusion as whether the patient has an isolated thrombocytopenia or if other cell lines (i.e. platelets and Hemoglobin)	In acquired neutropenias, exclusion of post-infectious neutropenia (e.g. Hepatitis B virus, Epstein-Barr virus, and human immunodeficiency virus), drug-induced neutropenia and agranulocytosis (e.g. clozapine, the thionamides (antithyroid drugs), and sulfasalazine), Nutritional neutropenia (e.g. severe vitamin B12 deficiency, folate deficiency, and copper deficiency), hypersplenism, bone marrow disorders (e.g. aplastic anemia, the leukemias, myelodysplasia, and postchemotherapy, neutropenia). In immune-mediated neutropenias, exclusion of T-gamma lymphocytosis (large granular lymphocyte syndrome) and Felty's syndrome. In the former disorder, there is infiltration of the bone marrow with large granular lymphocytes (LGL), most often due to a clonal expansion of cytotoxic T-cells and often associated with rheumatoid arthritis and complement activation.	Approach to Phagocytosis defects, T cell defects, and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Congenital neutropenias Myeloperoxidase deficiency Isoimmune neonatal neutropenia Chronic autoimmune neutropenia Chronic idiopathic neutropenia Pure white cell aplasia CD40L/CD40 deficiency, MST1 deficiency, Moesin deficiency, WAS, GINS1 deficiency, MTHFD1 deficiency, TWEAK deficiency, CHS, Griscelli syndrome, Hermansky-Pudlak Syndrome, WHIM,

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
Lymphopenia Exclusion as whether the patient has an isolated thrombocytopenia or if other cell lines (i.e. platelets and Hemoglobin)	In infection induced lymphopenia exclusion of bacterial (e.g., tuberculosis, typhoid fever, brucellosis), viral (e.g., HIV, severe acute respiratory syndrome [SARS], measles, hepatitis), Fungal (e.g., histoplasmosis), and Parasitic (e.g., malaria). In iatrogenic lymphopenia, exclusion of immunosuppressive agents (e.g., glucocorticoids, antilymphocyte globulin, alemtuzumab, rituximab) chemotherapy (e.g., fludarabine, cladribine), hematopoietic cell transplantation and radiation therapy (e.g., total body irradiation, radiation injury) and postoperative state. In systemic disease lymphopenia, exclusion of autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome) lymphoma, other malignancies, sarcoidosis, renal failure, aplastic anemia, Cushing's syndrome, allergic disease (e.g., atopic dermatitis, food allergy, allergic rhinosinusitis, asthma). Exclusion of zinc deficiency, malnutrition, stress, exercise, trauma, thoracic duct leak, rupture, diversion, protein-losing enteropathy.	Approach to T cell defects, B cell defects and innate immune deficiency Confirmation of clinical ESID Diagnostic Criteria	SCID, CID, B cell deficiency, NK cell deficiency, innate immune deficiency.
Pale skin color / bleeding tendency/ petechiae and purpura Pancytopenia	Exclusion of coagulopathy, malignant disorders, hypoproliferative conditions, splenomegaly and/or liver disease, lymphadenopathy, autoimmune conditions, constitutional symptoms, metabolic abnormalities, suspected medications and multifactorial causes (e.g. alcohol use, folate deficiency, cirrhosis, splenomegaly, HIV infection, multiple medications, AIDS-associated lymphoma, autoimmune disorder, splenomegaly, multiple medications, and lymphoma with autoimmune cytopenias, cytotoxic medications).	Approach to T cell defects, B cell defects, immune dysregulation and innate immune deficiency Confirmation of clinical ESID Diagnostic Criteria	ALPS, RAS-associated autoimmune leukoproliferative disease, Good syndrome, MST1 deficiency, Dyskeratosis congenital, STN1 deficiency, SAMD9/L deficiency, Transcobalamin 2 deficiency, CVID, IgAD, CTLA4 deficiency, LRBA deficiency, NFKB1/2 deficiency, Familial hemophagocytic lymphohistiocytosis, Tripeptidyl-peptidase II deficiency, Shwachman-Diamond syndrome, GATA2 deficiency, STAT1 GOF,
Family history of other autoimmune disorders Signs/symptoms of autoimmune endocrine disorders	Evaluation by endocrinologists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALPS, IPEX, CVID, CID, CTLA4 deficiency, LRBA deficiency, CD25 deficiency, APECED, Calcium channel defects, STAT3 GOF, ITCH deficiency, STAT1 GOF
Failure to thrive Anal fissures or perianal abscesses Family history of other autoimmune disorders Signs/symptoms of inflammatory bowel disease and autoimmune enteropathy	Evaluation by GI specialists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALPS, IPEX, CVID, CID, CTLA4 deficiency, LRBA deficiency, CD25 deficiency, APECED, C1s,r,q deficiency, STAT3 GOF, ITCH deficiency, STAT1 GOF
Family history of other autoimmune disorders Signs/symptoms of autoimmune arthropathy and rheumatologic disorders	Evaluation by rheumatologists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALPS, CVID, CID, CTLA4 deficiency, LRBA deficiency, CD25 deficiency, APECED, STAT3 GOF, ITCH deficiency, STAT1 GOF, NLRP1 deficiency, COPA defect, MASP2 deficiency
Family history of other autoimmune disorders Signs/symptoms of alopecia, vitiligo, and dermatologic autoimmunity	Evaluation by dermatologists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALPS, CVID, CID, CTLA4 deficiency, LRBA deficiency, CD25 deficiency, APECED, Calcium channel defects, ITCH deficiency, STAT1 GOF
Family history of other autoimmune disorders Signs/symptoms of autoimmune vasculitis	Evaluation by dermatologists Evaluation by cardiologists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	WAS, CVID, CID,
Family history of other autoimmune disorders Signs/symptoms of autoimmune uveitis	Evaluation by ophthalmologists	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	ALPS, CVID, CID
Family history of other autoimmune disorders Signs/symptoms of autoimmune glomerulonephritis	Evaluation by nephrologists	Approach to T cell defects, B cell defects, complement defects Confirmation of clinical ESID Diagnostic Criteria	Complement component 3
Family history of other lymphoproliferative disorders Signs/symptoms of adenopathies, lymphadenopathy, splenomegaly, hepatomegaly, granulomatous disease, and hyperinflammation	Evaluation by hematologists/oncologists Evaluation by Pulmonologists for GLILD, pulmonary fibrosis and interstitial lung disorders	Approach to T cell defects, B cell defects, immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	MST1 deficiency, CVID, PTEN Deficiency, PI3K deficiency, Familial hemophagocytic lymphohistiocytosis, CTLA4 deficiency, LRBA deficiency, CD25 deficiency, IPEX, STAT3 GOF, CD27/70 deficiency, ALPS, SH2D1A deficiency, XIAP deficiency, CTPS1 deficiency, ITK deficiency, MAGT1 deficiency, PRKCD deficiency
Family history of other atopic disorders Signs/symptoms of severe allergic reaction, asthma, eczema, urticaria and atopy Impaired pulmonary function tests	Evaluation by dermatologists Evaluation by pulmonologists	Approach to T cell defects, B cell defects, immune dysregulation and innate immune defects Confirmation of clinical ESID Diagnostic Criteria	DOCK8 deficiency, WAS, PGM3 deficiency, RLTPR (CARMIL2) deficiency, Muckle-Wells syndrome, NLRP3/12 deficiency, PLCG2 deficiency, CANDLE syndrome, OTULIN deficiency, STAT5b GOF,

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
Other signs and symptoms			
NU	Intrauterine polyhydramnios confirmed by neonatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Immunodeficiency with multiple intestinal atresias
NU	Intrauterine growth retardation confirmed by neonatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	X-linked DKC, Schimke syndrome
Poor wound healing	Evaluation by infectious specialists confirmed by dermatologists	Approach to Phagocytosis defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	LADs, RAC2 deficiency
Delay in shedding of primary teeth	Evaluation by dentists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
Delayed separation umbilical cord	Evaluation by a neonatologist	Approach to Phagocytosis defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	LADs, RAC2 deficiency
Skeletal abnormality Short stature, skeletal dysplasia, and limb dwarfism	Evaluation by a neonatologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	RNF168, MCM4, b-Actin, STAT5B, FILS deficiencies, SPENCD, Schimke, Bloom syndromes, Cartilage hair hypoplasia
Mental retardation	Evaluation by a nutrition and growth experts Evaluation by a neurologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	b-Actin deficiency, ICF syndrome
Microcephaly	Evaluation by a neonatologist Evaluation by a neurologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Nijmegen breakage syndrome, X-linked DKC, DNA ligase IV, Cernunnos, RAD50, RNF168, DNAPKcs deficiencies
Facial abnormality	Evaluation by a neonatologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	DiGeorge, ICF, FILS, Bloom, Nijmegen breakage, 3MC, Cohen syndromes, ITCH, STAT5B, RNF168 deficiencies
Developmental delay	Evaluation by a neonatologist Evaluation by a neurologist	Approach to T cell defects, Phagocytosis defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	3MC, Cohen-Barth, LAD type 2 syndromes, ITCH, ADAR1, P14 deficiencies
Cognitive defects	Evaluation by a neonatologist Evaluation by a neurologist	Approach to T cell defects, Phagocytosis defects Confirmation of clinical ESID Diagnostic Criteria	Kostmann disease, AT
Ataxia	Evaluation by a neurologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	AT, AT –like disease, RNF168, purine nucleoside phosphorylase deficiencies
Signs of maternal GVHD	Evaluation by a dermatologist Evaluation by a hematologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	SCID
Telangiectasia	Evaluation by an ophthalmologist Evaluation by a dermatologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	AT, autosomal recessive DKC
Bamboo hair	Evaluation by dermatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Comel–Netherton syndrome
Sparse scalp hair and eyelashes	Evaluation by dermatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	NEMO, Winged helix deficiency, autosomal recessive DKC
Skin lived	Evaluation by dermatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	FILS syndrome
Hypo pigmentation	Evaluation by dermatologists	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	CHS, Hermansky Pudlak syndrome type2, Griscelli syndrome type 2, P14 deficiency
Anhidrotic ectodermal dysplasia	Evaluation by dermatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	NEMO, STIM1, ORAI1 deficiencies
Hypoplastic nails	Evaluation by dermatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	RTLE1, NOP10, NOLA2, Winged helix, X-linked DKC deficiencies
Cafe.au.lait spots	Evaluation by dermatologists Evaluation by neurologists	Approach to T cell defects and B cell defects Confirmation of clinical ESID Diagnostic Criteria	WAS, Nijmegen breakage, ICF syndromes, PMS2, MSH2 deficiencies
Disseminated cutaneous viral infection	Evaluation by infectious specialists Evaluation by dermatologists	Approach to T cell defects and Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	DOCK8, STAT2 deficiencies
Venous angeictasis	Evaluation by dermatologists Evaluation by hematologists	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	G6PC3 deficiency

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
Neonatal onset of rash	Evaluation by dermatologists	Approach to T cell defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Muckle–Wells, Omenn, WAS, IPEX and Comel–Netherton syndromes
Inner ear deafness	Evaluation by ENT specialists	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	G6PC3 deficiency
Coloboma	Evaluation by ophthalmologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	CHARGE syndrome
Dental enamel hypoplasia	Evaluation by dentists	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	APECED syndrome
Conotruncal malformation	Evaluation by cardiologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	DiGeorge syndrome
Congenital heart disorder	Evaluation by cardiologists	Approach to Phagocytosis defect and T cell defects Confirmation of clinical ESID Diagnostic Criteria	G6PC3, MST1 deficiencies, CHARGE syndrome
Vesico-renal- genital anomaly	Evaluation by urologists	Approach to Phagocytosis defect and T cell defects Confirmation of clinical ESID Diagnostic Criteria	3MC, Charge syndrome, G6PC3 deficiency
Hyper extensive joint	Evaluation by rheumatologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
Dystrophy	Evaluation by rheumatologists Evaluation by neurologists	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	CANDLE syndrome
Chondrodysplasia	Evaluation by rheumatologists	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	Shwachman–Diamond syndrome
NU	Hemophagocytic lymphohistiocytosis giant lysosome	Approach to Phagocytosis defect and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	CHS
NU	Hypocalcemic seizure	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	DiGeorge syndrome
Reduced level of PTH	Evaluation by endocrinologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	DiGeorge syndrome
NU	Exocrine pancreatic insufficiency	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	Shwachman–Diamond syndrome
Absent or hypoplastic thymus	Evaluation by hematologists Evaluation by radiologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	SCID, DiGeorge syndrome, Winged helix deficiency
Congenital asplenia	Evaluation by hematologists Evaluation by radiologists	Approach to Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	Isolated congenital asplenia
Abnormal thymic epithelium	Evaluation by hematologists Evaluation by radiologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Winged helix deficiency
Viral encephalitis	Evaluation by neurologists Evaluation by infectious specialists	Approach to Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	TLR3, UNC93B1, TRAF3, TRIF, TBK1deficiencies
NU	Hepatic veno-occlusive disease	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	VODI syndrome
NU	Intracranial calcification as confirmed by radiologists/ Neurologists	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Aicardi–Goutieres, SPENCD syndromes
NU	Aneurysm as confirmed by cardiologists/ neurologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
NU	Choanal atresia as confirmed by cardiologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	CHARGE syndrome
Early onset enteric fistula	Evaluation by GI subspecialists Evaluation by surgeons	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	IL10, IL10RA, IL10 RB deficiencies
Neonatal sterile multifocal osteomyelitis	Evaluation by rheumatologists Evaluation by orthopedic surgeons	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	DIRA syndrome
NU	Palmoplantar keratoderma as confirmed by a dermatologist	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	Papillon–Lefevre syndrome
NU	Multiple intestinal atresia as confirmed by GI specialists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Immunodeficiency with multiple intestinal atresias

Signs by patients/ symptoms identified by first line approach/ General practitioner	Second line approach/ Specialists and non-immunology subspecialist	Third line approach/ Clinical immunologists*	Differential diagnosis as primary immunodeficiency
NU	Pulmonary alveolar proteinosis as confirmed by pneumologists	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	Mono MAC, Pulmonary alveolar proteinosis syndromes
NU	Amilopectinosis as confirmed by pathologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	HOIL1 deficiency
NU	Premalignant leukokeratosis of mouth mucosa as confirmed by pathologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal recessive DKC
NU	Neuronal dysplasia of intestine as confirmed by pathologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Cartilage hair hypoplasia
NU	IgA nephropathy as confirmed by pathologists/nephrologists	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	WAS
NU	Extramedullary hematopoiesis as confirmed by hematologist	Approach to Phagocytosis defect Confirmation of clinical ESID Diagnostic Criteria	Severe congenital neutropenia type 5
Family history of other malignancies	Lymphoid cancers as confirmed by hematologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	AT, MRE11, RAD50 and NBS, DNA ligase IV, XLF, Artemis deficiencies
Angioedema	Evaluation by cardiologists Evaluation by dermatologist	Approach to Complement defects and immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	C1 inhibitor, factor XII deficiencies
Hypertension	Atypical hemolytic uremic syndrome and preeclampsia as confirmed by hematologist	Approach to Complement defects Confirmation of clinical ESID Diagnostic Criteria	CD46, factor B, factor I, factor H, factor H-related protein and thrombomodulin deficiencies
Infertility	Impaired spermatogenesis as confirmed by urologist/gynecologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Cartilage hair hypoplasia
Coarse facies	Evaluation by dermatologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
NU	Bone degeneration as confirmed by a hematologist	Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	Cherubism
Scoliosis	Evaluation by rheumatologists Evaluation by orthopedic surgeons	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
Osteoporosis	Evaluation by rheumatologists Evaluation by orthopedic surgeons	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Autosomal dominant HIES
Chronic cough Pleurisy	Bronchiectasis confirmed by a pneumologist/radiologist	Approach to B cell defects Confirmation of clinical ESID Diagnostic Criteria	CVID, IgA deficiency, XLA
Costochondral junction flaring	Evaluation by rheumatologists Evaluation by orthopedic surgeons	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Adenosine deaminase deficiency
Family history of other malignancies Early screnning tests	Solid tumors as confirmed by a hematologist/oncologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	Nijmegen breakage syndrome
Family history of other malignancies Early screnning tests	Gastric cancers as confirmed by a hematologist/oncologist	Approach to B cell defects Confirmation of clinical ESID Diagnostic Criteria	CVID
Family history of other malignancies Early screnning tests	HPV-related papilloma cancer as confirmed by a hematologist/oncologist	Approach to Innate immune defects Confirmation of clinical ESID Diagnostic Criteria	EVER1, EVER2, MST1, RhoH, MAGT1, ITK deficiencies, WHIM
Family history of other malignancies Early screnning tests	EBV-related lymphoma as confirmed by a hematologist/oncologist	Approach to immune dysregulation and Approach to immune dysregulation Confirmation of clinical ESID Diagnostic Criteria	CD27, ITK, XIAP, SH2D1A, PRKC gamma, MST1, coronin A deficiencies, ICL syndrome
Family history of other malignancies Early screnning tests	Colorectal carcinoma as confirmed by a hematologist/oncologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	PMS2 deficiency
Family history of other malignancies Early screnning tests	HHV8-related Kaposi sarcoma as confirmed by a hematologist/oncologist	Approach to T cell defects Confirmation of clinical ESID Diagnostic Criteria	OX40 deficiency
Family history of other malignancies Early screnning tests	Thymoma as confirmed by a hematologist/oncologist	Approach to B cell defects Confirmation of clinical ESID Diagnostic Criteria	Good syndrome

* Molecular diagnosis using TGS or WES are conducting in Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, and the University of Medical Science, Tehran, Iran

Table 2. Abstracted national guideline for approach to treatment of primary immunodeficiency (PID)

Disease	Ig replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Severe combined immunodeficiency	Yes	Yes	Avoid live vaccines	Gene therapy for IL2RG * Blood products irradiated CMV- PCP prophylaxis Antimicrobial treatment and prophylaxis
Combined immunodeficiency	Yes	Yes	Avoid live vaccines	Gene therapy for ADA* PEG-ADA* G-CSF for CD40/CD40L Blood products irradiated CMV- PCP prophylaxis Antimicrobial treatment and prophylaxis
Wiskott–Aldrich syndrome	Yes	Yes	Avoid live vaccines	Multidisciplinary care Splenectomy Immunomodulation as needed
Ataxia telangiectasia	Some	No	Avoid live vaccines	Multidisciplinary care Chemotherapy as needed Antimicrobial treatment and prophylaxis
DiGeorge syndrome	Some	No	Avoid live vaccines	Thymus transplantation* Supplementation with vitamin D or calcium and with parathyroid hormone Surgical repair for cleft palate and heart defects Antimicrobial treatment and prophylaxis
Hyper IgE syndrome	Some	Rare	Avoid live bacterial vaccines	Antimicrobial treatment Immunomodulation as needed Multidisciplinary care
Other syndromes	Some	Some	Some avoid live vaccines	Multidisciplinary care Immunomodulation as needed Antimicrobial treatment and prophylaxis
Agammaglobulinemia	Yes	No	Avoid live vaccines	Antimicrobial treatment and prophylaxis
Common variable immunodeficiency	Yes	Rare	Avoid live vaccines	Antimicrobial treatment and prophylaxis Immunomodulation as needed Splenectomy as needed Chemotherapy as needed
Other antibody deficiencies	Some	No	Pneumococcal vaccine	Antimicrobial treatment
Familial hemophagocytic lymphohistiocytosis	No	Yes	Routine vaccination	Antimicrobial as needed Chemotherapy as needed Immunomodulation as needed
Autoimmune lymphoproliferative syndrome	No	Yes	Routine vaccination	Antimicrobial as needed Chemotherapy as needed Immunomodulation as needed
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome	No	Yes	Routine vaccination	Antimicrobial as needed Chemotherapy as needed Immunomodulation as needed
Autoimmune polyendocrine syndrome	No	No	Routine vaccination	Antimicrobial as needed Chemotherapy as needed Immunomodulation as needed

Disease	Ig replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Other immune dysregulations	Some	Some	Routine vaccination	Antimicrobial as needed Chemotherapy as needed Immunomodulation as needed
Neutropenia	No	Yes	Avoid live bacterial vaccines	Antimicrobial treatment and prophylaxis G-CSF treatment
Chronic granulomatous disease	No	Yes	Avoid live bacterial vaccines	Antimicrobial treatment and prophylaxis Gene therapy* IFN-gamma treatment Surgical or dental debridement Granulocyte transfusion
Leukocyte adhesions deficiency	No	Yes	Avoid live bacterial vaccines	Antimicrobial treatment and prophylaxis Surgical or dental debridement Granulocyte transfusion Fucose in type II
NEMO deficiency	Yes	Yes	Avoid live vaccines	PCP prophylaxis Antimicrobial treatment and prophylaxis
Mendelian susceptibility to mycobacterial diseases	No	Some	Avoid live bacterial vaccines	Surgical or debridement Antimicrobial treatment
Chronic mucocutaneous candidiasis	No	No	Avoid live vaccines	Antimicrobial treatment and prophylaxis
Warts, Hypogammaglobulinemia, Infections, and Myelokathexis	Yes	Some	Avoid live vaccines	Antimicrobial treatment and prophylaxis G-CSF treatment
Autoinflammatory disorders	No	No	Routine vaccination	Cytokine (IL-1, TNF, IL-6) inhibitor Immunomodulation as needed Retinoids for DIRTA Colchicine for TRAPS and FMF
Complement deficiency	No	No	Pneumococcal vaccine for C1- C4 Meningococcal vaccine for C5-C9	Antimicrobial treatment Immunomodulation as needed for C1, C2, C4, factor H and I Danazol and C1q inhibitor for hereditary angioedema

* Not yet available nationally

Granulocyte colony stimulating factor (G-CSF) and interferon gamma (IFN-γ) therapy injection are two other major medical agents which should become uniquely available in all peripheral secondary and tertiary centers. G-CSF is regularly administered to all patients suffering immunodeficiency associated with neutropenia. Important PIDs treated by G-CSF therapy include congenital and severe congenital neutropenia, cyclic neutropenia, and Kostmann syndrome. Many patients undergoing chemotherapy and hematopoietic stem cell transplantation (HSCT) or those affected by secondary neutropenia require G-CSF therapy as well. For most patients, G-CSF is administered on a daily dosage of 5-20 μg/kg of body weight by subcutaneous injection, but for others the dosage might vary considerably. This therapy is effective for increasing blood neutrophil levels, but has several side effects including skin reactions, osteoporosis, arthralgia, and alopecia. Currently, almost a quarter of estimated neutropenic patients are under the treatment with G-CSF. IFN-γ is the treatment of choice in many primary phagocytic killing disorders, the most common of which in Iran is chronic granulomatous disease (CGD). IFN-γ acts on macrophages and other cells and activates them in response to infection, causing an increase in the macrophage killing and antigen presenting abilities. As a potent macrophage activator, this drug has side effects such as fever, weight loss, fatigue, and gastrointestinal complications. The average required dose is 50 μg per m^2 of body surface for those with a body surface of greater than 0.5 m^2 and 1.5 μg per m^2 of body surface area for those with a lower body surface area. The drug is usually administrated by subcutaneous injection 3 times a week. Of the estimated 400 patients in Iran, the coverage of these patients is 42.5%.

However, the most problematic at in the national level which should be resolved rapidly is HSCT mainly required for combined immunodeficiency and phagocytosis disorders as well as some syndromic PIDs. On many instances, HSCT increases PID patients' quality and quantity of life by dramatically decreasing their various complications and sometimes (typically in younger patients) nearly reconstructing their defective immune system. Considering the costs of the procedure and the essential advanced HLA blood bank for donors, we still face obstacles and only less than 5% of diagnosed cases have gone under therapy or been awaiting it (13, 14).

To improve the current therapeutic quality of PID in Iran and make it a unique and comprehensive guideline nationally, we need to focus on several issues in upcoming years. We should continuously work on reducing the unawareness on PIDs amongst general population and health staff providers and physicians and improve the training program in basic and clinical immunology for targeting remaining issues in the field of PID (15). Changing policies to direct efforts toward neonatal screening, providing agonist and antagonist monoclonal antibody agents, revising the vaccination routine, propagation of genetic test nationwide, and prenatal diagnostic assays for affected families and carriers would be important challenges for the PID network (16). In order to achieve these goals, we also need a well-developed functional referral system to utilize the abovementioned guideline regarding diagnosis of PID.

Conclusion

Our ultimate goal will be to implicate recent developments in the field of clinical and molecular immunology to determine underlying genetic etiologies and environmental modifiers of PIDs and perform a personalized medical intervention with a unique standardized method available for everyone.

Conflicts of interest The authors declare that they have no conflicts of interest.

References

1. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. Interna-

tional Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018;38(1):96-128.
2. Aghamohammadi A, Moin M, Rezaei N. History of primary immunodeficiency diseases in iran. Iranian. J Pediatr. 2010;20(1):16-34.
3. Abolhassani H, Rezaei N, Aghamohammadi A. Recent Advances and Current Status of Primary Immunodeficiency Disease in Iran. Immunol Genet J. 2018;1(1):1-33.
4. Richardson AM, Moyer AM, Hasadsri L, Abraham RS. Diagnostic Tools for Inborn Errors of Human Immunity (Primary Immunodeficiencies and Immune Dysregulatory Diseases). Curr Allergy Asthma Rep. 2018 22;18(3):19.
5. Aghamohammadi A, Moin M, Farhoudi A, Rezaei N, Pourpak Z, Movahedi M, et al. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. FEMS Immunol Med Microbiol. 2004;40(2):113-8.
6. Rezaei N, Abolhassani H, Aghamohammadi A, Ochs HD. Indications and safety of intravenous and subcutaneous immunoglobulin therapy. Exp Rev Clin Immunol. 2011;7(3):301-16.
7. Mozaffari H, Pourpak Z, Pourseyed S, Moin M, Farhoodi A, Aghamohammadi A, et al. Health-related quality of life in primary immune deficient patients. Iran J Allergy Asthma Immunol. 2006;5(1):23-7.
8. Aghamohammadi A, Pouladi N, Parvaneh N, Yeganeh M, Movahedi M, Gharagolou M, et al. Mortality and morbidity in common variable immunodeficiency. J Trop Pediatr. 2007;53(1):32-8.
9. Aghamohammadi A, Farhoudi A, Moin M, Pourpak Z, Rezaei N, Nikzad M, et al. Adverse effects of intravenous immunoglobulin therapy in patients with antibody deficiency. Iran J Allergy Asthma Immunol. 2003;2(3):121-6.
10. Dashti-Khavidaki S, Aghamohammadi A, Farshadi F, Movahedi M, Parvaneh N, Pouladi N, et al. Adverse reactions of prophylactic intravenous immunoglobulin; a 13-year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases. J Invest Allergol Clin Immunol. 2009;19(2):139-45.
11. Aghamohammadi A, Farhoudi A, Nikzad M, Moin M, Pourpak Z, Rezaei N, et al. Adverse reactions of prophylactic intravenous immunoglobulin infusions in Iranian patients with primary immunodeficiency. Ann Allergy Asthma Immunol. 2004;92(1):60-4.
12. Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. J Clin Immunol. 2012;32(6):1180-92.
13. Ghavamzadeh A, Alimoghaddam K, Ghaffari F, Derakhshandeh R, Jalali A, Jahani M. Twenty years of experience on stem cell transplantation in iran. Iran Red Crescent Med J. 2013 ;15(2):93-100.
14. Hamidieh A, Pourpak Z, Jalili M, Fazlollahi M, Behfar M, Movahedi M, et al. Haematopoietic stem cell transplantation in primary immunodeficiency diseases: the Iranian experience. 2012.
15. Nourijelyani K, Aghamohammadi A, Salehi Sadaghiani M, Behniafard N, Abolhassani H, Pourjabar S, et al. Physicians awareness on primary immunodeficiency disorders in Iran. Iranian journal of allergy, asthma, and immunology. 2012 Mar;11(1):57-64. PubMed PMID: 22427477.
16. Isaian A, Moin M, Pourpak Z, Rezaei N, Aghamohammadi A, Movahedi M, et al. DNA banking of primary immunodeficiency disorders in iran. Iran J Allergy Asthma Immunol. 2006;5(4):201-2.