

# Executive Summary of the Consensus Document on the Diagnosis and Management of Patients with Primary Immunodeficiencies



Elisa Cordero, MD, PhD<sup>a,b</sup>, Walter Goycochea-Valdivia, MD, MSc<sup>c</sup>, Ana Mendez-Echevarria, MD, PhD<sup>d</sup>, Luis M. Allende, PhD<sup>e</sup>, Laia Alsina, MD, PhD<sup>f</sup>, Maria Bravo García-Morato, PhD<sup>g</sup>, Juana Gil-Herrera, MD, PhD<sup>h</sup>, Carlota Gudiol, MD, PhD<sup>i</sup>, Oscar Len-Abad, MD, PhD<sup>j</sup>, Francisco López-Medrano, MD, PhD, MSc<sup>k</sup>, David Moreno-Pérez, MD, PhD<sup>l</sup>, Patricia Muñoz, MD, PhD<sup>m</sup>, Peter Olbrich, MD, PhD<sup>c</sup>, Silvia Sánchez-Ramón, MD, PhD<sup>n</sup>, Pere Soler-Palacín, MD, PhD, MSc<sup>o</sup>, Clara Aguilera Cros, MD<sup>p</sup>, Juan Ignacio Arostegui, MD, PhD<sup>q</sup>, Isabel Badell Serra, MD, PhD<sup>r</sup>, Javier Carbone, MD, PhD<sup>s</sup>, Jesús Fortún, MD, PhD<sup>t</sup>, Luis I. Gonzalez-Granado, MD<sup>u</sup>, Eduardo López-Granados, MD, PhD<sup>v</sup>, José Manuel Lucena, PhD<sup>x</sup>, Rocío Parody, MD, PhD<sup>y</sup>, Jan Ramakers, MD, PhD<sup>z</sup>, José R. Regueiro, PhD<sup>aa</sup>, Jacques G. Rivière, MD<sup>o</sup>, Cristina Roca-Oporto, MD<sup>a</sup>, Rebeca Rodríguez Pena, MD, PhD<sup>v</sup>, Juan Luis Santos-Pérez, MD, PhD<sup>bb</sup>, Carlos Rodríguez-Gallego, PhD<sup>cc,dd</sup>, and Olaf Neth, MD, PhD<sup>c</sup> *Seville, Madrid, Barcelona, Málaga, Palma de Mallorca, Granada, and Las Palmas de Gran Canaria, Spain*

Consensus Document of the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Immunology (SEI), the Spanish Society for Paediatric Infectious Disease-Spanish Paediatric Association (SEIP-AEP), and the Spanish Society for Clinical Immunology, Allergology, and the Paediatric Asthma-Spanish Paediatric Association (SEICAP-AEP).

**ABSTRACT:** Primary immunodeficiencies (PIDs) are rare, undiagnosed and potentially fatal diseases.

Clinical manifestations of PID can be fatal or leave sequelae that worsen the quality of life of patients. Traditionally, the treatment of PIDs has been largely supportive, with the exception of bone marrow transplantation and, more recently, gene therapy. The discovering of new affected pathways, the development of new molecules and biologics, and the increasing understanding of the molecular basis of these disorders have created opportunities in PIDs therapy. This document aims to review current knowledge and to provide recommendations about the diagnosis and clinical management of adults and

children with PIDs based on the available scientific evidence taking in to account current practice and future challenges. A systematic review was conducted, and evidence levels based on the available literature are given for each recommendation where available. © 2020 American Academy of Allergy, Asthma & Immunology; Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [Published by Elsevier Inc./Elsevier Espana]. All rights reserved. (*J Allergy Clin Immunol Pract* 2020;8:3342-7)

**Keywords:** Primary immunodeficiencies; Vaccination; Treatment; Haematopoietic progenitors transplantation; Antibiotics

<sup>a</sup>Clinical Unit of Infectious Diseases University Hospital Virgen del Rocío, Institute of Biomedicine, CSIC, University of Seville, Seville, Spain

<sup>b</sup>Department of Medicine, University of Seville, Seville, Spain

<sup>c</sup>Paediatric Infectious Diseases, Rheumatology and Immunology Unit, University Hospital Virgen del Rocío, Institute of Biomedicine, Seville, Spain

<sup>d</sup>Servicio de Pediatría y Enfermedades Infecciosas, Hospital Universitario La Paz, Madrid, Spain

<sup>e</sup>Servicio de Inmunología, Hospital Universitario 12 de Octubre, Instituto de Investigación i+12, Universidad Complutense de Madrid, Madrid, Spain

<sup>f</sup>Clinical Immunology and Primary Immunodeficiencies Unit, Pediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Institut de Recerca Sant Joan de Déu, Clinical Immunology Unit Hospital Sant Joan de Déu-Hospital Clínic Barcelona, Barcelona, Spain

<sup>g</sup>Servicio de Inmunología, Hospital Universitario La Paz, Instituto de Investigación Biomédica del Hospital La Paz (IdiPAZ), Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain

<sup>h</sup>Department of Immunology, Hospital General Universitario and Health Research Institute Gregorio Marañón, School of Medicine, Universidad Complutense, Madrid, Spain

<sup>i</sup>Infectious Diseases Department, Hospital Universitari de Bellvitge and Institut Català d'Oncologia (ICO), Hospital Duran i Reynals, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>j</sup>Infectious Diseases Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>k</sup>Infectious Diseases University Unit, Hospital 12 de Octubre, Instituto de Investigación Biomédica i+12, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

<sup>l</sup>Pediatric Infectology and Immunodeficiencies Unit, Department of Pediatrics, Hospital Regional Universitario de Málaga, IBIMA, RECLIP, University of Málaga, Málaga, Spain

<sup>m</sup>Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

<sup>n</sup>Department of Immunology, IML and IdSSC, Hospital Clínico San Carlos, Madrid, Spain

<sup>o</sup>Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona (UAB), Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Spain

<sup>p</sup>Department of Rheumatology, University Hospital Virgen del Rocío, Sevilla, Spain

<sup>q</sup>Department of Immunology, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, School of Medicine, Universitat de Barcelona, Barcelona, Spain

<sup>r</sup>Unidad de Hematología, Oncología y Trasplante Hematopoyético, Servicio de Pediatría, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

## INTRODUCTION

### Justification

The field of Primary Immunodeficiencies (PID) has experienced an enormous increase in the last years. The first PID were identified in the 1950s, and in 1970 16 distinct disorders were included in the first World Health Organization report. PIDs were then defined as fulling penetrant mendelian traits predisposing to multiple, recurrent, and opportunistic infections. Since the mid 1990s, several PIDs predisposing to life-threatening infections in otherwise healthy, even adult, individuals were reported. Some of these PIDs predispose to a narrow range of microorganisms, and frequently, these monogenic diseases do not display a full penetrance. Currently, over 400 PID have been identified, more than 350 out of them with a recognized gene defect.<sup>1</sup> A growing group of PIDs are now known to associate with immune dysregulation often leading to autoimmunity, lymphoproliferation and malignancy, which may be the predominant, and even the only, clinical phenotype.<sup>2</sup> The descriptor Inborn Errors of Immunity (IEI) is gaining acceptance to encompass dysregulation and autoinflammatory disorders and PID, as the latter was traditionally used to define inborn errors of immunity to infection.<sup>1</sup>

Clinical manifestations of PID can be fatal or leave sequelae that worsen the quality of life (QoL) of patients. Traditionally, the treatment of PIDs has been largely supportive, with the exception of bone marrow transplantation and, more recently, gene therapy.<sup>3-8</sup> The twenty-first century has witnessed exciting advances in immunoglobulin replacement therapy, hematopoietic stem cell transplantation, and gene therapy.<sup>6-8</sup> Nevertheless, the discovering of new affected pathways, the development of new molecules and biologics, and the increasing understanding of the molecular basis of these disorders, have created opportunities and paved the way for the implementation of precision medicine as a therapy of PIDs.<sup>9</sup>

It is assumed that PIDs may be greatly underdiagnosed, and their diagnosis and management usually require a multidisciplinary approach. The objective of this consensus document is to provide a practical clinical guide for the suspicion, diagnosis and management of PID patients. Experienced researchers and clinicians, with expertise in pediatric and adult PIDs and infectious

diseases, have developed this consensus document, which was endorsed by four Spanish scientific societies.

### Target populations and objectives of the document

The target populations of this document are children and adults with PID, healthcare and PID relatives. The classification of PIDs was based on the 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity.<sup>1</sup> Patients with autoinflammatory disorders were not included in this document, due to the high variability in symptoms and recommended treatments, which often differ from those used for other PID.

The intended guideline audience includes physicians involved in the care of PID patients (including primary care physicians), and other healthcare workers attending PID patients. Here we report a consensus from a public health policy perspective with the objective of assessing the available overall evidences and to propose recommendations on the following key questions:

1. When should a primary immunodeficiency (PID) be suspected in a child and in an adult? (provided that acquired immunodeficiencies were ruled out)
2. What immunological tests should be performed if a PID is suspected?
3. What other clinical studies and measures should be performed in children and adults with PIDs at diagnosis? And during follow-up?
4. How should PID be screened in neonates?
5. When and what type of antimicrobial prophylaxis should be offered to a child and an adult with PID?
6. What type of vaccines can be offered to children and adults with PID?
7. When can immunoglobulin replacement therapy (IGRT) can be advised? Which route is advisable? How should IGRT be monitored during follow-up?
8. When is a hematopoietic stem cell transplantation (HSCT) considered in a child with PID?
9. When is a HSCT considered in an adult with PID?
10. Which other immunomodulatory, supportive and curative therapies can be used?
11. When is genetic counselling needed?

<sup>\*</sup>Servicio de Inmunología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

<sup>†</sup>Servicio de Enfermedades Infecciosas, Hospital Universitario Ramón y Cajal, Madrid, Spain

<sup>‡</sup>Primary Immunodeficiencies Unit, Pediatrics, Hospital 12 de Octubre, Research Institute Hospital 12 octubre (i+12), School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

<sup>§</sup>Servicio de Inmunología, Instituto de Investigación Biomédica del Hospital La Paz (IdIPAZ), Hospital Universitario La Paz, Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain

<sup>||</sup>Immunology Unit, University Hospital Virgen del Rocío, Sevilla, Spain

<sup>¶</sup>Servicio de Hematología Clínica, Institut Català d'Oncologia H. Duran i Reynalds, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>‡‡</sup>Department of Pediatrics, Pediatric Rheumatology and Immunology, Son Espases University Hospital, Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain

<sup>‡‡‡</sup>Department of Immunology, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

<sup>‡‡‡‡</sup>Infectious Diseases and Immunodeficiencies Unit, Service of Pediatrics, University Hospital Virgen de las Nieves, Granada, Spain

<sup>‡‡‡‡‡</sup>Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

<sup>‡‡‡‡‡‡</sup>University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain

No funding was received for this work.

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

This article has been copublished with permission in The Journal of Allergy and Clinical Immunology: In Practice and Enfermedades Infecciosas y Microbiología Clínica. The complete consensus document is available as [Appendix A](#) in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).

Received for publication May 4, 2020; accepted for publication May 6, 2020.

Corresponding authors: Elisa Cordero, Clinical Unit of Infectious Diseases, Instituto de Biomedicina, University Hospital Virgen del Rocío, Sevilla, Spain; CSIC, University of Sevilla, Sevilla, Spain; Department of Medicine, University of Sevilla, Sevilla, Spain. E-mail: [elisacorderom@gmail.com](mailto:elisacorderom@gmail.com). Or: Carlos Rodríguez-Gallego, Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Barranco de la Ballena, s/n. 35010, Las Palmas de Gran Canaria, Spain; University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. E-mail: [jroddgal@gobiernodecanarias.org](mailto:jroddgal@gobiernodecanarias.org).

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology; Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [Published by Elsevier Inc./Elsevier Espana]. All rights reserved.

<https://doi.org/10.1016/j.jaip.2020.05.008>

## Abbreviations

ADA- Adenosine deaminase  
 AGREE- Appraisal of Guidelines Research & Evaluation  
 ALPS- Autoimmune lymphoproliferative syndrome  
 ANA- Antinuclear antibodies  
 AT- Ataxia-telangiectasia syndrome  
 ATG- Anti-thymocyte globulin  
 AUC- Area under the curve  
 BCG- Bacille Calmette-Guérin  
 BM- Bone marrow  
 CBC- Complete blood count  
 CGD- Chronic granulomatous disease  
 CHH- Cartilage-hair hypoplasia  
 CSF- Cerebrospinal fluid  
 CHARGE- Coloboma heart defects, atresia choanae, growth retardation  
 CID- Combined immunodeficiencies  
 CLOVES- Congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies, and/or scoliosis  
 CMC- Chronic mucocutaneous candidiasis  
 CNS- Central nervous system  
 CVID- Common variable immunodeficiency  
 CyA- Cyclosporine  
 DCLO- Diffusing capacity of the lung for carbon monoxide  
 EFS- Event-free-survival  
 EBV- Epstein-Barr virus  
 EBV-PTLD- Epstein-Barr virus post-transplant lymphoproliferative disorder  
 EDA-ID- Ectodermal dysplasia-associated immunodeficiency  
 ERT- Enzyme replacement therapy  
 ESR- Erythrocyte sedimentation rate  
 GVHD- Graft-versus-host disease  
 GOF- Gain-of-function  
 Hib- Haemophilus influenzae type b  
 HIES- Hyper-IgE  
 HLH- Hemophagocytic lymphohistiocytosis  
 HRCT- High resolution computed tomography  
 HSCT- Hematopoietic stem cell transplantation  
 IDSA- Infectious Diseases Society of America  
 IFN $\gamma$ - Interferon gamma  
 IGRT- Immunoglobulin replacement therapy  
 IV- Intravenous  
 KREC- K-deleting recombination excision circles  
 LAIV- Live-attenuated influenza vaccine  
 LDH- lactate dehydrogenase  
 MFD- Matched-family donor  
 MMF- Mycophenolate mofetil  
 MMR- Measles, mumps, rubella  
 MMRV- Measles, mumps, rubella, varicella  
 MRI- Magnetic resonance imaging  
 MSD- Matched-sibling donor  
 MTX- Methotrexate  
 NBS- Newborn screening  
 NADPH- Nicotinamide adenine dinucleotide phosphate  
 NEMO- Nuclear factor-kappa B essential modulator  
 NGS- Next generation sequencing  
 OPV- Oral polio virus vaccine  
 PAD- Predominantly antibody deficiencies  
 PBSCs- Peripheral blood stem cells  
 PCV13- 13-valent pneumococcal conjugate vaccine  
 PFT- Pulmonary functional test  
 PID(s)- Primary immunodeficiency(ies)  
 PJP- Pneumocystis jirovecii pneumonia  
 PPSV23- 23-valent polysaccharide vaccine  
 QoL- Quality of life

RIC- Reduced-intensity conditioning  
 R-ADA- Recombinant adenosine deaminase  
 SC- Subcutaneous  
 SCID- Severe combined immunodeficiencies  
 SCN- Severe congenital neutropenia  
 STAT- Signal transducer and activator of transcription  
 TAR- Thrombocytopenia and absent radius  
 TCL- T-cell lymphopenia  
 SCID- Severe combined immunodeficiency  
 SEIMC- Sociedad Española de Infectología y Microbiología Clínica  
 SPURR- Severe, persistent, unusual, recurrent infections with a history of PID running in the family  
 TREC- T-cell receptor excision circles  
 TSH- Thyroid stimulating hormone  
 Ty21a- Oral live Salmonella typhi vaccine  
 UD- Unmatched donor  
 US- Ultrasound  
 USA- United States of America  
 VEO-IBD- Very early onset inflammatory bowel disease  
 WAS- Wiskott-Aldrich syndrome  
 WES- Whole exome sequencing  
 WHIM- Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis  
 WGS- Whole exome/genome sequencing  
 XLA- X-linked agammaglobulinemia

## General methodology of the document

To develop the recommendations included in the consensus document, the expert panel conducted a systematic review of the literature in PubMed, and established the quality of the evidence using the Infectious Diseases Society of America (IDSA) grading system for ranking recommendations.<sup>10</sup>

The contents of the document and the conclusions have been agreed by all the authors and the coordinators of the Statement. Before publication, the manuscript was presented to and approved by the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Immunology (SEI), the Spanish Society for Paediatric Infectious Disease-Spanish Paediatric Association (SEIP-AEP) and the Spanish Society for Clinical Immunology, Allergology and Paediatric Asthma-Spanish Paediatric Association (SEICAP-AEP).

1. When should a PID be suspected in a child and in an adult? (provided that acquired immunodeficiencies were ruled out)

## Recommendations

- It is critical to maintain a high index of suspicion for PID in patients presenting with recurrent infections, autoimmune disease, malignancy, and combinations of these conditions (AII).
- It is mandatory to obtain a focused family history when the differential diagnosis includes a PID (AII).
- PID must be screened in patients with recurrent infection and at least one of the following ones: family history, failure to thrive, autoimmunity, lymphoproliferative disease, malignancy or requirement of intravenous (IV) antibiotics for treating and clearing infections that usually do not require it (AII).
- PID must be screened in patients with one or more infections caused by opportunistic organisms that are rarely pathogenic for immunocompetent subjects (AII).
- PID must be screened in patients with one or more severe infections caused by low virulence pathogens (AII).

- PID screening may be considered in children with a sole severe infection, and in patients with recurrent infections depending on the clinical context and the level of suspicion of the physician (BII).
2. What immunological tests should be performed if a PID is suspected?

*Recommendations*

- Diagnostic process of PID must be done attending clinical phenotype, physical exam and family history (AIII).
  - A stepwise approach is recommended as the most likely cost-effective strategy for diagnosis of PID (AIII).
  - Complete blood count (CBC) and immunoglobulins levels should be performed as first line tests for diagnosis of PID (AIII).
  - Second line (non-disease specific or disease specific) tests include functional, molecular and genetic tests, which must be tailored by experts in PID (AIII).
  - We recommend targeted sequencing of candidate genes if a disease is highly suspected (based on clinical and laboratory findings), a semi-targeted approach in overlapping clinical presentations (PID genetic panels), and whole exome/genome sequencing (WES/WGS) when the previous fail or an unbiased approach to PID genetic testing is advantageous (AIII).
3. What other clinical studies and measures should be performed in children and adults with PIDs at diagnosis? And during follow-up?

*Recommendations*

- A multidisciplinary approach coordinated by an expert in PID is recommended in these patients (AIII).
- At diagnosis the following tests should be performed:
  - Blood analysis: CBC, liver and renal function, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR); in PID related to autoimmunity, include antinuclear antibodies (ANA), thyroid stimulating hormone (TSH) and celiac markers; in T cell defects, include screening for viruses including cytomegalovirus (AIII).
  - In PID with potential lung involvement, pulmonary functional test (PFT), including diffusing capacity of the lung for carbon monoxide (DLCO), and lung high resolution computed tomography (HRCT), is recommended (AIII).
  - Chest X-ray and an abdominal ultrasound should be performed in all PID patients. (AIII).
- During follow-up, the following tests should be performed:
  - Yearly blood analysis (CBC, liver and renal function, glucose; include uric acid, LDH, ESR and beta-2-microglobulin in PID at risk of lymphoma and/or with chronic lymphadenopathy; include ANA, TSH and celiac markers in PID related to autoimmunity; besides immunological parameters depending on the PID (AIII).
  - Yearly PFT, including DLCO, in PID with potential lung involvement (AIII).
  - Yearly abdominal ultrasound (BIII).
  - In PID with lung involvement, HRCT should be repeated every 5 years when baseline is normal (AIII), or every 1–2

years in case of active bronchiectasis or interstitial lung disease (BIII).

- Dental evaluation and QoL scale should be performed at diagnosis and yearly (AIII).
- The high variability of PID and their clinical presentations makes it difficult to establish common recommendations. Other tests will be performed depending on the clinical context (AIII).
- In patients with bronchiectasis, physiotherapy and respiratory rehabilitation are key in the treatment (AIII).
- When there is suspicion of infection in patients with bronchiectasis, it is recommended to optimize general, microbiological and imaging methods (AIII).

4. How should PID be screened in neonates?

*Recommendations*

- In severe combined immunodeficiency (SCID) individuals, haematopoietic stem cell transplantation (HSCT) performed in the first 3–4 months of life and while the newborn is asymptomatic, improves the prognosis of patients resulting in a survival rate of >90% (AII).
  - Newborn screening (NBS) for T cell deficiencies has shown to reliably identify patients with SCID in the asymptomatic phase (AII).
  - T-cell receptor excision circles (TREC) is currently the most appropriate biomarker for the early identification of neonates with SCID through systemic NBS programs (AII).
  - TREC based SCID NBS programs are cost effective (AII).
  - TREC and K-deleting recombination excision circles (KREC) assays allows detection of congenital B cell defects and some additional combined immunodeficiencies may be missed when using TREC alone (AII).
5. When and what type of antimicrobial prophylaxis should be offered to a child and an adult with PID?

*Recommendations*

- Infants older than 4 weeks of age with SCID must receive prophylaxis for *Pneumocystis jirovecii* as soon as they are diagnosed (AII).
- *Pneumocystis jirovecii* prophylaxis is indicated for other specific T cell deficiencies with a high susceptibility to this microorganism infection (AIII).
- All patients with CGD should receive prophylactic cotrimoxazole (AII) and itraconazole (AI).
- Adult patients with humoral immunodeficiency could benefit from prophylaxis with azithromycin when respiratory infections persist despite IGRT (AI). There are no published controlled studies of the benefits of this prophylaxis in children with humoral immunodeficiency, although the same benefit is expected (AIII).
- Antibiotic prophylaxis with penicillin V or amoxicillin is recommended for patients with complement component deficiencies and congenital asplenia (AII).
- Other specific antibiotic prophylaxis can be prescribed, chronically or intermittently, according to the type of the primary immunodeficiency.

6. What type of vaccines can be offered to children and adults with PID?

*Recommendations*

- Live attenuated vaccines, including BCG, are contraindicated in patients with complete T-cell defects because of known or theoretical risks of disseminated infection resulting from viable vaccine organisms (DIII).
- PID patients can be safely vaccinated with inactivated vaccines, however, vaccine immune response can be suboptimal (AIII).
- Live-attenuated influenza vaccine is contraindicated in immunocompromised patients, and it is not recommended to the household contacts, except in case of minor antibody deficiencies (DIII).
- Annual vaccination with influenza inactivated vaccines are recommended in all PID patients and their household contacts, including those with CVID receiving IGRT (AII).
- Vaccination in patients receiving IGRT with inactivated antigens could be considered, although efficacy or effectiveness of the intervention has not been yet determined (CIII).
- MMR and varicella are not required in PID patients receiving IGRT, however these vaccines may be considered according to their risk of exposure and immune status (CIII).
- In children with PID, unless contraindicated, systematic immunization schedule with inactivated vaccines should be completed (AIII).
- Pneumococcal vaccination is recommended in PID patients, unvaccinated >60-month-old patients should receive one dose of the 13-valent pneumococcal conjugate vaccine (PCV13) (BIII). For those receiving IGRT, pneumococcal vaccination may be considered (safe intervention) although cost-effectiveness remains to be elucidated (CIII).
- The 23-valent polysaccharide vaccine (PPSV23) is recommended for PID patients  $\geq 2$  years of age with 2-dose scheme five years apart (BII). No additional doses of PPSV23 are recommended (DIII).
- Vaccination against *H. influenzae* type b is recommended in PID patients, unimmunized patients  $\geq 5$  years of age and adults at high risk (complement deficiency, asplenia) (AII).
- Wide protection against serogroups B and ACWY is recommended for patients with PID, especially in those with complement defects or congenital asplenia/hyposplenism (AII).

7. When can immunoglobulin replacement therapy (IGRT) be advised? Which route is advisable? How should IGRT be monitored during follow-up?

*Recommendations*

- IGRT is indicated in cases of agammaglobulinemia due to absence of B cells and hypogammaglobulinemia with low antibody production function (AII).
- The use of IGRT should be individually assessed in patients with normal Ig and deficiency of antibody production, hypogammaglobulinemia with normal antibody function, isolated deficiency of an IgG subclass with recurrent infections, and recurrent infections due to a complex immune mechanism related to a genetically defined PID disease (CIII).
- Intravenous and subcutaneous route for IGRT are equivalent in terms of efficacy (AI).

- The route of administration should be selected individually in every patient (AI).
- Patients' preferences should be considered when choosing the route of administration (BIII).
- In patients with humoral immune defects on IGRT, trough serum IgG levels above 500 mg/dL are effective in prophylaxis against bacterial infections, particularly against pneumonia (AI).
- Patients on IGRT should be periodically monitored for trough IgG levels: first control after 3 months except for the loading dose. Then every 3–6 months in children, and at least once a year in adults afterwards to ensure they are kept above the recommended levels (600–800 mg/dl), depending on the underlying PID and the presence of lung disease (AIII). More frequent studies should be performed in presence of complications such as cancer, chronic lung disease or malabsorptive syndrome) (AIII).
- It is recommended to stratify patients with antibody production deficits according to lung damage, and to maintain trough IgG levels consequently: above 600 mg/dL for patients without pulmonary abnormalities and above 800 mg/dL for those with chronic lung damage (AIII).
- The presence of low trough IgG levels despite adequate IGRT must prompt the search of protein loss (urinary and gastrointestinal) or consumption due to pneumopathy, complications to be considered in the follow-up (BII).
- Dose IGRT adjustments are required in special situations, such as acute illnesses, before or after surgery, chronic diarrhoea or weight changes, and during pregnancy (BIII).
- It is advisable to maintain serum bank during IGRT (BIII).

8. When is a HSCT considered in a child with PID?

*Recommendations*

- Allogeneic (allo-) HSCT in children is recommended as potentially curative procedure for SCID and CGD (AII).
- In patients with CID, allo-HSCT is recommended in the following conditions: CD40L, WAS, CHH, ZAP70, MHC-class II deficiency and NEMO (AII).
- Allo-HSCT is recommended in severe congenital neutropenia if treatment with colony stimulating factor lacks efficacy, or when the disease progresses to myelodysplastic syndrome or acute myeloid leukaemia (BII).
- Allo-HSCT should be performed in all patients with primary HLH (AII). Remission of the disease is recommended to avoid relapses (A-II). In CVID with immune dysregulation (CTLA4, LRBA, PI3K $\delta$ /R1, STAT3 gain-of function mutations), HSCT should be considered after failing first-line therapies with abatacept, PIK3 or JAK inhibitors, or in cases of incomplete response (CIII).
- Allo-HSCT is recommended in: patients with complete IFN $\gamma$ -receptor defects and complete STAT-1 deficiency, complete LAD 1, and DOCK8 deficiencies and severe forms of IPEX non-responsive to other treatments, (BII), patients with IL-10 receptor-deficiency and selected patients with ADA2 deficiency (CECR1), STAT-1 GOF and STAT-3 GOF. (BIII).
- Indication of allo-HSCT in SCID, CID and CGD is preferred during childhood, the earlier the better but not sooner than 2 months of age, provided that there's a suitable donor and the patient is at the best expected condition (AII).

- Whenever possible, a matched sibling donor should be used (AII). Otherwise, a fully matched unrelated donor is the recommended alternative (AII).
- If only haploidentical or mismatched unrelated donors are available, T-cell depletion techniques (TCRab and CD19 + depletion) ensure the lowest risk of acute graft-versus-host-disease, along with serotherapy (antithymocyte globulin or alemtuzumab) (BII).

9. When is a HSCT considered in an adult with PID?

*Recommendations*

- Chronic granulomatous disease and CVID are the most common indications of allo-HSCT in adolescents and young adults with PID, mainly in patients presenting with a complicated disease course (BII).
- Allo-HSCT is also recommended in other PID, such as T-lymphocyte immunodeficiencies, WAS, phagocyte disorders, hemophagocytic syndromes, and a growing number of other immunodeficiencies (BII).
- An adapted strategy with a reduced-intensity conditioning regimen based on the combination of fludarabine and melphalan or busulfan, with *in vivo*-T cell depletion (with antithymocyte globulin or alemtuzumab), minimizes the risk of graft-versus-host disease and transplant related mortality (CIII).

10. What other immunomodulatory and curative therapies can be used?

*Recommendations*

- The identification of underlying disease-causing or -modifying pathways is encouraged as this might direct immune suppression treatment strategies (BII).
- Immune suppression in PID should be considered in order to treat autoimmune, autoinflammatory, lymphoproliferation or granulomatous disease manifestations (AII).
- Infectious prevention with Interferon gamma should be considered for CGD patients (BI).
- ADA enzyme-replacement therapy should be given to all patients with a new diagnosis of ADA deficiency or ADA-SCID (AI).
- Gene therapy should be pursued for all ADA-SCID patients with no matched-sibling or matched family donor (AII)
- Gene therapy should be considered and might be indicated as a suitable alternative to HSCT even for those ADA-SCID patients with matched-sibling donor (MSD) or matched-family donor (MFD) (CIII).
- Gene therapy should be considered in patients with CGD or WAS if HSCT cannot be performed (AIII)
- Treatment with granulocyte colony-stimulating factor is recommended as first-line treatment for patients with congenital neutropenia (AI).

11. When is genetic counselling needed?

*Recommendations*

- Genetic counselling must be always ensured when a genetic study with medical purposes is conducted (AIII).
- Genetic counselling for PIDs must be conducted by a professional with deep knowledge in these diseases (BII).
- New therapeutic approaches are improving the prognosis of PID patients and must be considered during the genetic counselling process (AII).
- Prenatal and preimplantation diagnosis are ways to ensure healthy offspring and must be explained to mutation carriers during the genetic counselling act (AIII).
- Voluntary interruption of pregnancy may be a possibility when a PID is detected in the foetus and must be considered in the context of the current law (BIII).

**APPENDIX A. SUPPLEMENTARY DATA**

The complete consensus document is available as Appendix A in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).

**REFERENCES**

1. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. *J Clin Immunol* 2018;38:96-128.
2. Delmonte OM, Castagnoli R, Calzoni E, Notarangelo LD. Inborn errors of immunity with immune dysregulation: from bench to bedside. *Front Pediatr* 2019;7:353.
3. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* 2015;136:1186-1205.e78.
4. Milito C, Pulvirenti F, Cinetto F, Lougaris V, Soresina A, Pecoraro A, et al. Double-blind, placebo-controlled, randomized trial on low-dose azithromycin prophylaxis in patients with primary antibody deficiencies. *J Allergy Clin Immunol* 2019;144:584-593.e7.
5. Bonilla FA. Update: Vaccines in primary immunodeficiency. *J Allergy Clin Immunol* 2018;141:474-81.
6. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol* 2017;139:S1-46.
7. European Society, for Immunodeficiencies (ESID). Inborn Errors Working Party (IEWP) Updated! EBMT/ESID Guidelines for haematopoietic stem cell transplantation for PI. 2017. Available from: <https://esid.org/Working-Parties/Inborn-Errors-Working-Party-IEWP/Resources/UPDATED!-EBMT-ESID-GUIDELINES-FOR-HAEMATOPHOIETIC-STEM-CELL-TRANSPLANTATION-FOR-PI>. Accessed June 23, 2019.
8. Booth C, Romano R, Roncarolo MG, Thrasher AJ. Gene therapy for primary immunodeficiency. *Hum Mol Genet* 2019;28(R1):R15-23.
9. Leiding JW, Forbes LR. Mechanism-based precision therapy for the treatment of primary immunodeficiency and primary immunodysregulatory diseases. *J Allergy Clin Immunol Pract* 2019;7:761-73.
10. Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis* 1994;18:421.