

Spanish Consensus on the Diagnosis and Management of Patients With Activated PI3K Delta Syndrome (APDS)

Neth O¹, Alsina L^{2,3}, Rivière JG^{4,5,6}, López-Granados E^{7,8,9}, Seoane-Reula ME^{10,11}, González Granado LI^{12,13}, Sánchez-Ramón S¹⁴, Rodríguez-Gallego C^{15,16,17,18}, and the Spanish APDS Study Group#

¹Paediatric Infectious Diseases, Rheumatology and Immunology Unit, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, IBiS /Universidad de Sevilla/CSIC, Red de Investigación Translacional en Infectología Pediátrica (RITIP) Seville, Spain

²Clinical Immunology and Primary Immunodeficiencies Unit, Pediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

³Study Group for Immune Dysfunction Diseases in Children, Institut de Recerca Sant Joan de Déu, Barcelona, Spain

⁴Infection and Immunity in Pediatric Patients Research Group, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain

⁵Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Infantil i de la Dona Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

⁶Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Spain

⁷Center for Biomedical Network Research on Rare Diseases (CIBERER U767), ISCIII, Madrid, Spain

⁸Lymphocyte Pathophysiology in Immunodeficiencies Group, La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

⁹Clinical Immunology Department, La Paz University Hospital, Madrid, Spain

¹⁰Primary Immunodeficiencies Unit, Pediatric Allergy and Immunology Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

¹¹Laboratory of Immune-Regulation, Gregorio Marañón Health Research Institute (IISGM), Madrid, Spain

¹²Primary Immunodeficiencies Unit, Pediatrics, Hospital 12 de Octubre, Research Institute Hospital 12 octubre (i+12), Madrid, Spain

¹³School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

¹⁴Department of Immunology, IML and IdSSC, Hospital Clínico San Carlos, Madrid, Spain, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

¹⁵Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

¹⁶Department of Medical and Surgical Sciences, School of Medicine, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

¹⁷Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain

¹⁸CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

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■ Abstract

Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is an ultrarare genetic disorder characterized by overlapping immunodeficiency and immune dysregulation. Its diagnosis poses challenges owing to its clinical similarities with other inborn errors of immunity (IEIs), compounded by the absence of targeted treatments in today's medical landscape. The standard approach involves symptom management, reducing infection through immunoglobulin replacement therapy and prophylactic antimicrobials, and treating immune dysregulation with immunomodulators. This approach considerably hampers effective management of APDS, as the diverse nature of the disease necessitates a personalized strategy, in which the advantages and risks of immunosuppression are weighed against the potential for recurrent infections and lymphoproliferative complications. To address these challenges, a group of Spanish experts in the management of IEIs, including APDS, collaborated to develop Delphi-based consensus recommendations. The primary goal of the initiative was to offer guidance on various aspects of this complex disease, marking a pioneering effort in Europe. The consensus aims to facilitate early diagnosis and provide clues for individual patient-based decisions that could favor balanced risk-benefit estimations for treatment.

Key words: APDS. Recommendations. PI3k. IEI. Personalized medicine.

■ Resumen

El síndrome de fosfoinositida 3-quinasa (PI3K) delta (APDS) es un trastorno genético ultra raro caracterizado por el solapamiento de inmunodeficiencia y una desregulación inmunitaria. Su diagnóstico plantea desafíos debido a sus similitudes clínicas con otros errores innatos de inmunidad (EII), agravado por la ausencia de terapias dirigidas en el arsenal terapéutico actual. En la actualidad, el enfoque clásico implica el tratamiento sintomático, centrado en la reducción de las infecciones a través del tratamiento con inmunoglobulinas y profilaxis antimicrobiana, así como el abordaje de la desregulación inmunitaria a través de inmunomoduladores. Esto crea dificultades sustanciales para los clínicos para el manejo del APDS, ya que la naturaleza heterogénea de la enfermedad requiere una estrategia personalizada, valorando las ventajas y los riesgos de la inmunosupresión frente a las posibles infecciones recurrentes y complicaciones linfoproliferativas.

Para abordar estos retos, un grupo de expertos españoles en la gestión de IEI, entre los que se incluye el APDS, desarrollaron una serie de recomendaciones a través de una metodología Delphi. El objetivo principal de esta iniciativa es ofrecer orientación sobre diversos aspectos de este trastorno complejo a través de un trabajo pionero en Europa. El consenso señala que mejorar en el diagnóstico temprano y proporcionar un enfoque personalizado para el tratamiento de los pacientes con APDS contribuirá a reducir la carga de morbilidad de esta enfermedad.

Palabras clave: APDS. Recomendaciones. PI3k. EII. Medicina personalizada.

1. Introduction

Activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) is an ultrarare genetic disease involving both immunodeficiency and immune dysregulation. It is caused by autosomal dominant pathogenic variants in *PIK3CD* (APDS1, OMIM #615513) or *PIK3R1* (APDS2, OMIM #616005) that increase the activity of the PI3K δ pathway [1,2].

The definitive diagnosis is made through genetic testing for mutations if the variants meet the criteria of the American College of Medical Genetics and Genomics [3] for pathogenicity, as APDS overlaps clinically with other inborn errors of immunity (IEIs) [4]. Functional assessment, such as measuring hyperactivation of the PI3K δ pathway, may complement genetic findings and provide insight into the disease mechanism [5]. Diagnosis is clinically challenging owing to the overlap with other IEIs, and management strategies are limited due to the lack of pathway-specific treatments in our setting. Treatment is usually symptomatic, aiming to reduce the burden of infection with immunoglobulin replacement therapy (IgRT) and prophylactic antimicrobials and to manage dysregulatory manifestations with immunomodulators. Accordingly, clinicians face significant hurdles in managing APDS. The heterogeneity of the disease requires a personalized approach that balances the benefits and risks of immunosuppression against the possibility of recurrent infections and lymphoproliferative complications. For medical professionals acquainted with IEIs, APDS exemplifies the complex interplay between genetic diagnosis, functional understanding, and clinical care, underscoring the need for continuous research and targeted therapies [6,7].

Given the important unmet needs and the lack of published evidence in most areas, a Delphi methodology was used to generate consensus [6,8]. With the objective of gathering the most robust evidence complemented by clinical expertise, a selected group of Spanish physicians, all directly involved in the care of patients with APDS, were invited to participate in the Delphi process. This multidisciplinary team of experts in the management of IEIs, including APDS, formulated Delphi-based consensus recommendations. The initiative, the first of its kind in Europe, aims to provide guidance on various aspects of this complex disease. The prevalence of APDS in Spain was estimated. The consensus recommendations and a treatment algorithm were specifically designed to enhance the early diagnosis and personalized management of APDS patients and thus reduce disease burden.

2. Methods

This study was conducted following the Delphi consensus methodology developed by RAND/University of California, Los Angeles (RAND/UCLA) [9]. The recommendation preparation group (RPG) comprised 8 experts in IEIs with clinical, diagnostic, and research laboratory experience in APDS from 5 reference centers in Spain. At the first meeting, held in March 2023, the concepts on which the consensus was to be developed were defined. The consensus processes are applicable to situations in which evidence is limited or lacking, yet there are still opportunities to reduce uncertainty and improve quality of care [10].

2.1. Literature Search and Review

Based on the initial design, an exhaustive nonsystematic, targeted literature review of articles published between 2016 and July 2023 was conducted primarily in the PubMed database following the search strategy outlined by Moriya et al [11]. Briefly, the search was based on all reports in English or Spanish containing “Activated PI3K-delta syndrome”, acronyms and synonyms (APDS, PIK3CD, PIK3R1), and the appropriate Medical Subject Headings term, and the literature retrieved was manually checked and classified according to the topic. Additional searches for gray literature were performed. The RPG revised the literature retrieved and included additional relevant literature where applicable. Topics were assigned to the RPG members (Supplementary Table 1), who performed a critical reading of the publications related to the topic assigned, provided an evidence synthesis, and proposed statements to be revised by the entire RPG in successive on-line meetings and written rounds performed on June 22, 2023; July 04, 2023; and July 12, 2023. The final list of statements was agreed upon in a final meeting where the RPG discussed and finalized the definitive wording.

2.2. Panelists, Epidemiological Data, and Voting Process

The panelists were selected considering their professional profile (pediatricians, immunologists, hematologists, pulmonologists, and internists/infectious disease specialists with extensive experience in IEIs) and to ensure a broad geographical distribution across Spain (Supplementary Table 2). The first step involved phone calls and e-mails to immunologists and pediatricians treating IEIs in Spain, as

well as to Spanish companies involved in the genetics of IEs. Those involved in the management of APDS patients were selected as panelists. Epidemiological data were subsequently collected using a questionnaire, which was completed by the panelists between September 4, 2023 and October 1, 2023 via an online platform. In this questionnaire, the panelists were asked about the number of patients with APDS/IEs regularly followed at their clinic. Considering that cases can be declared more than once by different specialties, particularly by pediatric and adult specialties, the panelists were asked to provide information about possible duplications. To estimate the prevalence, the data obtained were extrapolated to the data for the current Spanish population [12]. In any case, we cannot rule out the possibility that some patients may have been missed, with the result that prevalence might be underestimated.

For the voting process, panelists were invited via electronic mail and given access to a Delphi-dedicated on-line platform containing the proposed statements. Those professionals who agreed to participate were granted access (Supplementary Figure 1). Thirty-four statements were evaluated in a 2-round Delphi-type iterative process using a Likert scale ranging from 1 to 9 (1, strongly disagree; 9, strongly agree) in an on-line questionnaire.

2.3. Statistical Analysis

The RAND/UCLA methodology was used for consensus analysis in Delphi panels, where appropriateness and the level of agreement were analyzed based on the median and distribution of the responses, respectively [9]. Each item in the questionnaire was classified according to the level of agreement and the panel's median score as "appropriate" (median in the 7-9 range), "uncertain" (median in the 4-6 range or any median with disagreement), or "inappropriate" (median in the 1-3 range). Consensus was reached if at least two-thirds of the sample responded within the same score range as the median. Disagreement was considered to occur if the median score was at either of the 2 extremes and more than one-third of the sample responded in the opposite extreme range, or if the median was in the central range and at least one-third of the panelists responded in 1 of the other 2 ranges. If the assessment of the statement did not meet any of the previous criteria, it was considered neutral.

3. Epidemiology and Pathogenesis

Of the 42 invited panelists with recognized expertise in APDS and/or in clinically related IEs, 33 completed the questionnaire (78% response rate). The level of expertise of the panelists was corroborated through a series of questions regarding their experience. Since all statements were approved after the first Delphi round (100% approval rate), further rounds were not needed. The analyses were performed using the statistical package R version 4.4.0 for Windows [13]. The results were discussed, and the treatment algorithm and figures were agreed on by the RPG in a final consensus meeting held on November 2, 2023.

3.1. Estimated Prevalence of APDS in Spain

Data collected from the survey suggested an estimated prevalence of APDS in Spain of 0.722 cases/million population. This value was calculated based on the 35 patients obtained from the survey, 29 of whom were ≥ 12 years old, and the current Spanish population as of November 9, 2023 (48 446 594 inhabitants) [12]. Given that cases could be declared more than once by different specialties, the highest number of cases reported by each hospital was considered. Additionally, keeping in mind that cases could be reported by pediatric and adult specialties, the case count was based on the declaration by specialists in the pediatric area. In cases where pediatric specialists did not respond, the count declared by adult specialists was used.

3.2. Molecular Pathogenesis of APDS

PI3Ks are a family of kinases that participate in key signal transduction pathways in various cell types. They are heterodimers formed by a catalytic and a regulatory subunit. The many types of class I PI3Ks in humans present various combinations of catalytic and regulatory subunits and cellular expression patterns [14]. In lymphocytes, the main PI3K is the heterodimer formed by the regulatory p85 α subunit and the catalytic p110 δ subunit, which phosphorylates membrane phosphatidylinositol-4,5-bisphosphate and generates a second messenger, phosphatidylinositol-3,4,5-trisphosphate [1,15]. PI3K δ signals downstream from a variety of receptors, such as the B-cell receptor and T-cell receptor, and interaction with other receptors, such as the Toll-like receptors, has also been described [16,17]. APDS can be caused by gain-of-function (GOF) variants in the gene that encodes for the PI3K 110 δ catalytic subunit (*PI3KCD gene*: APDS1) [1,2] or loss-of-function (LOF) variants in the gene that encodes for the PI3K p85 α regulatory subunit of PI3K δ (*PI3KR1 gene*: APDS2) [18,19] (Figure 1).

Engagement of the B-cell receptor upon antigen encounter activates an intracellular activation signal that is amplified through several pathways, which are largely dependent on phosphorylation events, ultimately modulating gene expression [15,20]. Activation of the B-cell receptor requires PI3K signaling, which is essential for B-cell proliferation, survival, Ca²⁺ flux mobilization, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B). PI3K activation also promotes protein kinase B (Akt) signaling, which has several key targets, such as the ribosomal S6 kinase protein (S6), the regulator of the mammalian target of rapamycin (mTOR) complex, and the transcription factor FOXO. Activation of Akt and S6 is mediated by phosphorylation. The PI3K-Akt pathway is fundamental for lymphocyte homeostasis [21-23]. Statements regarding the molecular pathogenesis of APDS were included in the Delphi process (Statements 1-2, Table 1).

4. APDS: Diagnosis and Management

Patients with APDS exhibit diverse clinical and immunological abnormalities. Up to 50% of APDS patients present marked CD4⁺ T-cell lymphopenia due to a reduction

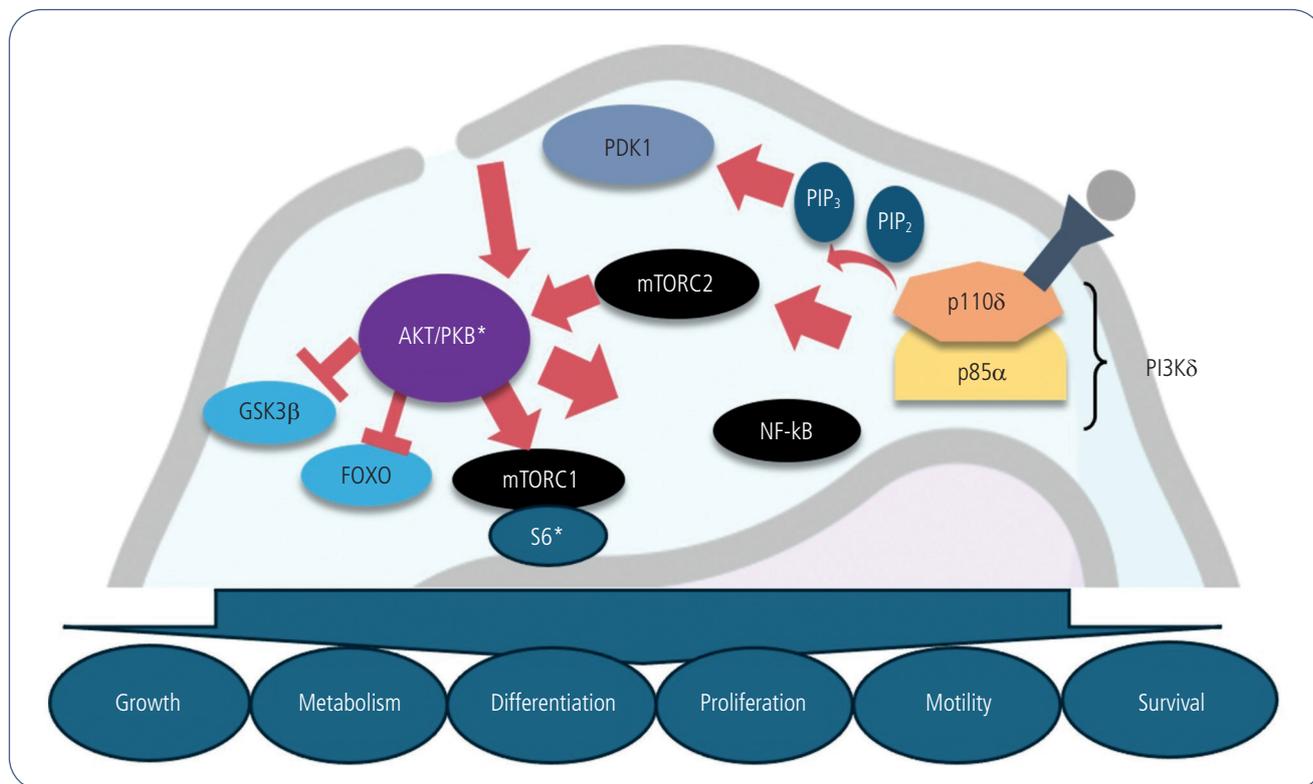


Figure 1. PI3K delta-mediated activation and signaling showing the major molecules downstream of the p110δ/p85α PI3K complex (adapted from [2,87]). The phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PI3Kδ) is found primarily, but not exclusively, in leukocytes. Upon signaling through a cellular receptor, such as the B- and T-cell receptors, the PI3Kδ enzyme complex is recruited to the cellular membrane, where, upon relief of inhibitory binding by p85, p110 converts phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 recruits and activates downstream messengers, such as phosphatidylinositol 3-dependent kinase 1 (PDK1) and protein kinase B (Akt). Akt has many downstream effects, including the GSK3 (glycogen synthase kinase-3), FOXO (forkhead box O), mTOR and ribosomal S6 kinase protein (S6). Activation of Akt and S6 is mediated by phosphorylation. The PI3K-Akt pathway is fundamental for lymphocyte homeostasis. Activated phosphoinositide 3-kinase delta syndrome (APDS) can be caused by pathogenic gain-of-function variants in the gene that encodes for the PI3K 110δ catalytic subunit (*PI3KCD gene*: APDS1) or loss-of-function variants in the gene that encodes for the PI3K p85α regulatory subunit (*PI3KR1 gene*: APDS2). Both APDS1 and 2 result in hyperactivation of the PI3K-Akt pathway that ultimately leads to many of the cellular alterations observed in patients with APDS, significantly disrupting the development, differentiation, and/or effector function of major lymphocyte subpopulations.

Table 1. Molecular Pathogenesis of APDS: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
1. APDS is an ultrarare genetic disease involving immunodeficiency and immune dysregulation, together with an increased risk of lymphoma, overlapping clinically with other inborn errors of immunity.	9	Appropriate	Agreement
2. A better understanding of the myriad of lymphocyte alterations imposed by enhanced PI3Kδ function has strengthened the rationale for pharmacologically targeted downmodulation, aiming to restore a balanced PI3K pathway.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3Kδ syndrome.

in the number of naïve CD4⁺ T cells [24]. Within the memory CD4⁺ T-cell compartment, disruptions in circulating T follicular helper cells lead to a skewed distribution towards an effector type 1 helper T cells (T_H1), which is less efficient in promoting B-cell activation, likely contributing to impaired terminal B-cell differentiation and antibody production. Enhanced production of IL-4, IL-5, and IL-13 might explain the presence of T_H2-related pathologies observed in some APDS patients [24].

Cytotoxic T-cell responses are also affected, leading to poor control of latent viral infections such as Epstein-Barr virus and cytomegalovirus. Indeed, CD8⁺ B cells specific for Epstein-Barr virus are normally generated or expanded, although they exhibit phenotypic features compatible with senescence and exhaustion, leading to poor cytotoxicity against autologous B cells. Natural killer lymphocytes and their subtypes are also produced under normal conditions but present decreased

cytotoxic capacity [24]. In addition, T regulatory (Treg) cells are affected (low circulating FoxP3⁺ Treg and altered suppressive capacity) [25].

Enhanced PI3K δ activity compromises peripheral naïve B-cell survival, increasing the transitional B-cell compartment and leading to progressive peripheral B-cell lymphopenia. Naïve B cells present intrinsic defects, such as increased activation-induced cell death, defective Ig class switch recombination, and somatic hypermutation, all of which contribute to poor specific antibody responses to infections and vaccines but enhance production of IgM plasma and memory CD27⁺IgM⁺ B cells, with increased IgM production. Paradoxically, naïve B cells show increased activation, promoting the appearance of exhausted CD27⁻IgD⁻ double-negative B cells [26]. A combination of defective cytotoxic responses with poorer control of latent viral infections in addition to disruption of the B-cell compartment might account for the increased risk of lymphoma in APDS patients [4].

Lymphoproliferative complications arise in up to 90% of APDS patients [4,19,27,28]. Benign lymphoproliferation is the second most frequent clinical sign of APDS following repeated infections and may manifest as lymphadenopathy, splenomegaly, and/or hepatomegaly. Lymphadenopathy and splenomegaly in APDS patients can be massive and mimic malignant lymphoma [5]. Increased risk of lymphoma is the most severe complication in APDS.

The relative frequency of clinical and immunological manifestations in APDS can be estimated based on recent publications that have collectively compiled data from 250 patients with genetically confirmed APDS1 or APDS2

from Europe, the USA, Iran, and Japan (mean age 15 years, range 1-65 years) [4,28-30]. The most common clinical features of APDS are shown in Table 2. To some extent, sequential appearance of clinical manifestations can be inferred from published studies [27-29]. In Figure 2, we attempted to graphically represent what could be considered sequential symptom onset during the course of APDS. It is crucial to emphasize that progression varies between individuals, and not everyone affected will experience all clinical stages of APDS following sequential onset of symptoms. As mentioned, APDS is characterized by low genetic heterogeneity, early onset, and high penetrance, and many symptoms develop by age 15 years. Of note, the mortality rate for APDS patients is 8% at a median

Table 2. Frequency of Clinical Features of APDS1 and APDS2 [4,30,84].

Clinical feature	APDS1	APDS2	Ref.
Chronic/recurrent respiratory tract infections	95%	85%	[30]
Bronchiectasis	60%	26%	[30]
Chronic herpes infection	46%	22%	[84]
Benign lymphoproliferation	86%	86%	[30]
Autoimmunity	56%	13%	[4]
Enteropathy	30%	45%	[30]
Lymphoma	8%	23%	[30]
Neurological abnormalities	17%	17%	[4]

Abbreviations: APDS, activated PI3K δ syndrome; Ref. reference.

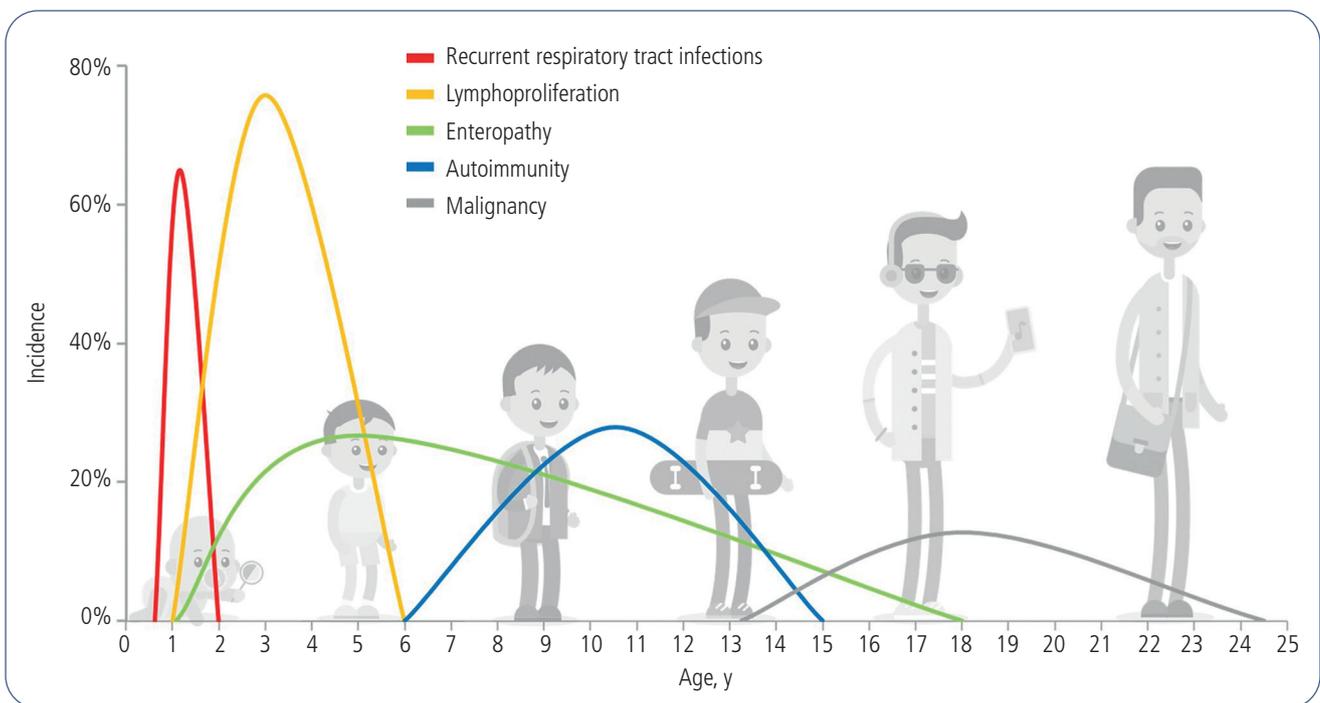


Figure 2. Sequential symptom onset in activated phosphoinositide 3-kinase delta syndrome (APDS) (data from [4]). The apex of the curves represents the median age at onset and the width of the curve the interquartile range of onset in years. This process describes the natural progression of APDS-related manifestations over time, usually starting in childhood. In this context, children may initially develop recurrent respiratory tract infections in their early years, followed by benign lymphoproliferation, enteropathy, and enteropathy later in childhood, ultimately progressing to autoimmunity and malignancy in adolescents and young adults.

Table 3. Clinical and Immunological Features of APDS: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
3. APDS is associated with increased susceptibility to recurrent sinopulmonary infections in children; lymphadenopathies, autoimmune cytopenia and enteropathy are common clinical manifestations in APDS.	9	Appropriate	Agreement
4. Evaluation of T-cell subpopulations and lymphoproliferative responses, as well as B-cell populations, is recommended in patients with APDS.	9	Appropriate	Agreement
5. Evaluation of antibody responses, Ig levels (IgG, IgA, and IgM), and specific antibody response based on antibody titers after vaccination is recommended in all patients with APDS.	9	Appropriate	Agreement
6. In APDS, elevated serum IgM, low frequency of naïve CD4 T cells, and aberrant B-cell phenotype with decreased switched memory B cells and increased transitional B cells may be present.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K δ syndrome.

age of 18.5 years [30]. Growth impairment (over 50%) is mostly observed in APDS2 [27-29]. Dysgammaglobulinemia is common in APDS, typically with elevated IgM levels and low IgG, IgG2, and IgA levels. In addition, phenotypic lymphocyte alterations, such as decreased CD4⁺ T cells, decreased naïve CD45RA⁺ T cells, increased T follicular helper cells, decreased Treg and memory B cells, and increased transitional B cells are observed in peripheral blood [2,21,22,27]. The clinical and immunological features of APDS are addressed in Table 3 (statements 3-6).

4.1. Keys to Diagnosis of APDS

High suspicion leading to early diagnosis of APDS is crucial for initiating prompt treatment, which has prognostic implications and underscores the need for a multidisciplinary team and reference center. As mentioned above, patients with APDS present immune system defects in the form of infections and other alterations associated with defective regulation of the immune response, such as autoimmunity, inflammation, and lymphoproliferation (Table 4).

Table 4. Clues for Diagnosis of APDS: Common Clinical Manifestations and Immunological Features [1,2,7,11,29,85,86].

	Clinical manifestation	Immunological feature
Nonspecific	Recurrent severe persistent infections: <ul style="list-style-type: none"> – Recurrent sinusitis and upper respiratory infections in early childhood – Pneumonia – Herpes virus infections – Chronic EBV and CMV viremia – Bronchiectasis – Skin and oral abscesses 	Immunoglobulin levels: <ul style="list-style-type: none"> – Low to normal serum IgA/IgG levels – Normal to high serum IgM – Low serum IgG2 – Suboptimal specific antibody responses Immune phenotype: <ul style="list-style-type: none"> – Low circulating T and B cells – Increased transitional and CD21^{low} CD38^{low} B cells, low memory (CD27⁺) B cells, and low class-switched memory B cells. – Low naïve CD4⁺ T cells and increased effector memory T cells expressing markers of senescence/terminal differentiation (CD57⁺)
	Lymphoproliferation: <ul style="list-style-type: none"> – Lymphadenopathy – Splenomegaly/hepatomegaly – Nodular lymphoid hyperplasia – EBV-related lymphoma 	Functional studies: <ul style="list-style-type: none"> – Increased activation-induced cell death of T cells. – Low in vitro T- and B-cell proliferation – Low CD8⁺ T- and NK-cell cytotoxicity – Expansion of γ/δ T cells – Increased phosphorylation levels of AKT and S6 proteins
	Enteropathy <ul style="list-style-type: none"> – Chronic diarrhea with malabsorption or colitis 	
	Autoimmune/autoinflammatory diseases: <ul style="list-style-type: none"> – Autoimmune cytopenia – Primary sclerosing cholangitis 	
Specific	Syndrome phenotype: growth impairment and facial dysmorphism (APDS2)	Genetic study: <ul style="list-style-type: none"> – APDS1: gene <i>PIK3CD</i> (GOF) – APDS2: gene <i>PIK3R1</i> (LOF) – APDS-L: gene <i>PTEN</i> (LOF)

Abbreviation: Ab, antibody; APDS, activated PI3K δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GOF, gain of function; LOF, loss of function.

When a patient presents clinical signs suggestive of APDS (see above), a thorough immunological assessment should be undertaken. This evaluation should include the measurement of serum immunoglobulins, as well as a detailed immunophenotypic analysis [2,11,21,22,27].

A substantial number of cases clinically diagnosed as hyper IgM syndrome, common variable immunodeficiency, or lymphoma have been retrospectively identified as APDS [4]. Therefore, when the underlying causative gene has not been identified in patients presenting with clinical characteristics of the aforementioned conditions [4], the possibility of APDS should be considered. Table 5 shows statements and recommendations (7-11) related to the diagnosis of APDS.

Upon strong clinical suspicion, patients should be referred to a specialized reference center for a comprehensive diagnostic evaluation. This must include a genetic assessment, although pathological and immunological work-ups are also recommended [31]. As in other IELs, a careful review should be performed, and the role of genetic variants in pathogenesis, including familial segregation, should be assessed.

Functional analysis is also valuable when attempting to confirm the diagnosis, especially in cases of variants of uncertain significance. This test usually consists of confirming increased activation of the PI3K-AKT-mTOR pathway by demonstrating increased phosphorylation levels of AKT and S6 proteins in resting and/or activated T or B lymphocytes in suspected APDS (Figure 1) [5]. However, functional assays of the PI3K-AKT-mTOR pathway are not yet available in many centers owing to the difficulties in establishing a widely standardized approach.

4.2. Clinical Management of APDS

4.2.1. Nonpharmacological treatments

4.2.1.1. Health education and pulmonary rehabilitation

Chronic and recurrent respiratory symptoms are characteristic of APDS. As with other IELs, patients with APDS require comprehensive care involving health education and pulmonary rehabilitation [32-35], which has proven vital for managing the condition and can preserve and improve lung function.

Health education plays a crucial role in APDS care, providing patients with information about the disease, its genetic origins, symptoms, and self-care strategies [36]. Recognizing and managing respiratory symptoms associated with APDS, as well as educating patients about potential complications and available treatments, are essential components of care. Adopting a healthy lifestyle (vaccination with inactivated vaccines, such as tetanus toxoid, conjugated or polysaccharide pneumococcal vaccine, anti-SARS-CoV-2 vaccine, and inactivated influenza vaccine) and strategies to prevent respiratory infections are highly important [36-39]. Table 6 provides specific statements and recommendations (12-13) related to nonpharmacological treatment of APDS.

4.2.2. Pharmacological treatments

4.2.2.1. Treatment and prevention of complications

– *Immunoglobulin replacement therapy.* IgRT is the mainstay of long-term therapy in patients with APDS [40]. Most patients with APDS reported in the literature have received IgRT since early childhood to

Table 5. Diagnosis: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
7. The definitive diagnosis of APDS is based on genetic studies, and in case of the presence of a new variant, evaluation of its functional impact is recommended in both APDS types (PIK3CD and PIK3R1).	9	Appropriate	Agreement
8. APDS should be considered in the presence of infections, immune dysregulation, and/or lymphoproliferative complications.	9	Appropriate	Agreement
9. Early onset of clinical manifestations of lymphoproliferation and infections in APDS suggests a poorer prognosis.	9	Appropriate	Agreement
10. Chronic viral infections are a prognostic factor for lymphoma.	9	Appropriate	Agreement
11. Early diagnosis of APDS is crucial, enabling appropriate interventions to mitigate disease progression.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K δ syndrome.

Table 6. Nonpharmacological Treatments: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
12. A broad, patient-focused health education program is recommended for all families and patients with APDS.	9	Appropriate	Agreement
13. Pulmonary rehabilitation is recommended for patients with APDS, especially those with bronchiectasis or chronic productive cough.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K δ syndrome.

reduce the incidence of infections [11]. This therapy can help prevent infections and protect individuals from additional infections that may lead to organ damage.

The recommended starting dosage is 0.4 g/kg/mo administered either subcutaneously or intravenously in order to maintain IgG trough levels >600 mg/dL and >800 mg/dL in the case of lung disease [41]. Table 7 shows a relevant statement/recommendation (14) related to IgRT.

- *Antibiotic prophylaxis.* In addition to IgRT, patients with APDS may require antibiotic prophylaxis in selected cases to prevent respiratory infections, as described in common variable immunodeficiency and an evidence-based consensus publication [42]. In the event of splenectomy, long-term penicillin prophylaxis is required for 1-3 years after the procedure; it is also required in children aged <5 years owing to the risk of postsplenectomy sepsis [43]. Since APDS affects T- and B-lymphocyte compartments, prophylaxis with sulfamethoxazole-trimethoprim 1-3 days a week is indicated if CD4⁺ lymphopenia is <200 cells/ μ L and/or <15% of total lymphocytes or there is a significant alteration in T-lymphocyte proliferation [44,45]. See Table 7 for statements and recommendations (15-17) related to antibiotic and antiviral prophylaxis.
- *Vaccination.* Patients with APDS can receive all inactivated vaccines [42,46,47]. No specific statement has been drafted regarding vaccination, as the decision should be on a case-by-case basis. The achievement of protective antibody titers following vaccination will

depend on the residual production of IgG: if IgG is <100-200 mg/dL prior to IgRT, vaccination is likely to be ineffective [48,49]. However, T-cell priming still justifies routine immunizations with inactivated vaccines [50]. Attenuated vaccine administration should be guided by the total CD4⁺ count and severity of the humoral defect. Oral polio and BCG vaccines are contraindicated. Live vaccines are contraindicated if CD4⁺ lymphopenia is <200 cells/ μ L or if there is an alteration in proliferation or a moderate-to-severe antibody defect [42,46,47].

In selected cases, varicella vaccine (potentially followed by acyclovir if necessary) may be administered prior to vaccination against measles, mumps, and rubella. This prevents complications derived from vaccine virus infection in the absence of antiviral treatment. In any case, prior to the initiation of IgRT, the presence of IgG against varicella-zoster, rubella, measles, and mumps should be checked. Novel vaccines such as the inactivated varicella-zoster vaccine, which are currently being evaluated in clinical trials in the setting of organ transplantation [51], may alter current recommendations for patients with IEs in the future.

4.2.2.2. Immunomodulatory treatments

No treatments for APDS have been approved in Europe to date, with management restricted to the aforementioned symptomatic treatments, as well as off-label immunosuppressants and immunomodulators, including corticosteroids, mTOR inhibitors, and rituximab. None of these immunomodulators can effectively resolve all symptoms and are associated with adverse events, which may be severe.

Table 7. Pharmacological Treatments: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
14. Immunoglobulin replacement therapy should be considered in patients with APDS and hypogammaglobulinemia, recurrent infections, and/or bronchiectasis.	9	Appropriate	Agreement
15. Patients with APDS may require antibiotic prophylaxis in selected cases to prevent sinopulmonary infections.	9	Appropriate	Agreement
16. Long-term antiviral therapy is not recommended for chronic EBV or CMV infection in APDS.	8	Appropriate	Agreement
17. <i>Pneumocystis jirovecii</i> prophylaxis may be considered in selected APDS patients with severe T-cell defects.	9	Appropriate	Agreement
18. Corticosteroid use should be limited to short courses and "add on" therapy in case of clinical relapse or in the initial phase of immunomodulatory treatment during diagnostic evaluation.	9	Appropriate	Agreement
19. Caution should be exercised when considering off-label rituximab in APDS owing to the risk of sustained B-cell lymphopenia associated with the need for immunoglobulin replacement.	9	Appropriate	Agreement
20. Off-label rituximab may be used as treatment for autoimmune cytopenia and nonneoplastic lymphoproliferation, such as lymphadenopathy and hepatosplenomegaly, when rapamycin is ineffective or not tolerated.	9	Appropriate	Agreement
21. Off-label rapamycin in APDS patients appears to improve lymphoproliferative manifestations, such as lymphadenopathy and hepatosplenomegaly, although it is less effective in cytopenia, prevention of infections, and gastrointestinal manifestations.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

In addition, efficacy data are limited and based on clinical experience, case series, cohort studies, and systematic reviews, as detailed below.

– *Corticosteroids*. The European Society for Immunodeficiencies (ESID) registry reports that 31 out of 77 (42%) patients with APDS1/2 enrolled in the APDS registry up to December 2017 had received corticosteroids, with 27 (87%) showing at least a partial and short-term clinical benefit. More than half had received corticosteroids by the age of 20 [28]. In a series of patients from China, lymphoproliferation (93%), enteropathy (50%), and cytopenia (70%) improved at least partially [52]. Nevertheless, major adverse effects have been described, including long-term toxicity, osteoporosis, hypertension, diabetes, and increased susceptibility to infections [53].

See Table 7 for statements and recommendations (18) related to the use of corticosteroids in APDS.

– *Anti-CD20 antibodies*. The anti-CD20 monoclonal antibody rituximab has been reported to reduce the frequency and relieve the symptoms of autoimmune cytopenia and decrease overall nonneoplastic lymphoproliferation, including lymphadenopathy and hepatosplenomegaly. However, its clinical benefit in reducing the frequency and relieving the symptoms of enteropathy and colitis remains limited [27-29]. Rituximab results in sustained, potentially permanent, B-cell lymphopenia [29], which can increase susceptibility to infections [54], especially to novel or emergent infections, for which vaccination strategies are less effective [55]. Furthermore, its use does not resolve the underlying immunodeficiency [56] and may induce secondary hypogammaglobulinemia, thus necessitating long-term IgRT [57].

See Table 7 for statements and recommendations (19-20) related to anti-CD20 therapy in APDS.

– *mTOR inhibitors*. Whilst rapamycin is the main mTOR inhibitor used for treating APDS, its derivative everolimus has been used in a limited number of patients [58]. Up to 40% of patients have received mTOR inhibitor treatment [28,36,59]. In a series of 26 patients treated with rapamycin, the best response was observed for lymphoproliferation (present in 25 patients) based on the physician visual analog scale (8 complete, 11 partial, 5 no remission, 1 worsening/new manifestation), while the response to bowel inflammation (3 complete, 3 partial, 9 no remission) and cytopenia (3 complete, 2 partial, 9 no remission) was less pronounced [28].

Other authors have also reported mTOR inhibitors to be very efficacious in both lymphoproliferation and cytopenia [52]. In a group of 8 patients taking corticosteroids at initiation of treatment with rapamycin, 7 were able to discontinue corticosteroids and 1 was able to reduce the rapamycin dose [28]. mTOR inhibition therapy was found to restore T-cell phenotypes [2,59,60] and increase serum IgG levels [61] in some cases, although no significant effects were found in a series of patients from China [52].

The adverse events leading to complete discontinuation of rapamycin in APDS patients include severe headaches, anorexia, and renal toxicity. Adverse events requiring treatment to be interrupted temporarily include aphthous ulcers, stomatitis, and liver and renal toxicity (proteinuria) [27-29,61-64].

Relapse of cutaneous T-cell lymphoma has been reported in a patient receiving rapamycin [28], and deterioration of the clinical course of the disease requiring hematopoietic stem cell transplantation (HSCT) has also been documented [65]. See Table 7 for a relevant statement and recommendation (21) related to this subject.

4.2.2.3. Personalized Medicine

– *PI3K δ inhibitors*. Several selective PI3K δ inhibitors have been developed for the treatment of APDS, although clinical trial results have been mixed. A 12-week dose-finding trial of oral leniolisib in 6 APDS patients demonstrated good tolerance, partially reconstituted lymphocyte subsets, and decreased lymphoproliferation [66].

In a subsequent 12-week phase 3 study involving 31 genetically confirmed APDS patients, outcomes were positive for leniolisib, with 26% achieving complete absence of index lymphadenopathy and 74% achieving a partial response. Leniolisib also normalized immune cell subsets and improved cytopenia, with fewer treatment-related adverse events than placebo [67].

An open-label extension study with 37 patients revealed a 62.7% reduction in mean index lymph node size and a 37.6% reduction in mean spleen volume. After a median exposure of 102 weeks, 37% of patients decreased or stopped IgRT, with reduced infection rates. Limited data on gastrointestinal manifestations indicate a probable reduction with leniolisib [68-70].

Furthermore, no progression was observed in 3 of 6 patients with established bronchiectasis prior to the trials [68]. Leniolisib maintained durable responses after up to 5 years of exposure in 37 APDS patients [71] and in 6 APDS patients from a 12-week dose trial after 6 years of follow-up [68]. An interim analysis in March 2023 confirmed these results [72]. Leniolisib was approved by the United States Food and Drug Administration in March 2023 for APDS patients aged 12 and older [73]. As of the time of writing, the drug is under regulatory review by the European Medicines Agency.

Other PI3K δ inhibitors explored in APDS include inhaled nemiralisib, which showed acceptable safety and tolerability in a completed phase 2 trial but was not pursued further since appropriate treatment concentrations were not achieved [74]. Seletalisib, an oral inhibitor, demonstrated improvements in clinical and immunological parameters in a phase 1b trial, although serious adverse events occurred in 3 of 7 patients. A phase 3 trial faced enrollment challenges and was terminated prematurely in 2020 (European Clinical Trials Database 2015-005541) [75].

See Table 8 for statements and recommendations (22-23) related to PI3K δ inhibitor therapy.

Table 8. Personalized Medicine: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
22. The current understanding of the etiology and pathogenesis of APDS supports the potential use of targeted therapy in the form of selective PI3K δ inhibitors.	9	Appropriate	Agreement
23. The selective PI3K δ inhibitor leniolisib improves manifestations of lymphoproliferation, including splenomegaly, infections, and cytopenia. It also normalizes T- and B-cell subsets and is well tolerated.	9	Appropriate	Agreement
24. HSCT as potential curative therapy for APDS may be an option for selected patients, although it is associated with risk of graft failure, graft-versus-host disease, and infections.	9	Appropriate	Agreement
25. It remains to be established when and how HSCT should be performed and which patients with APDS are suitable candidates.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K δ syndrome; HSCT, hematopoietic stem cell transplant.

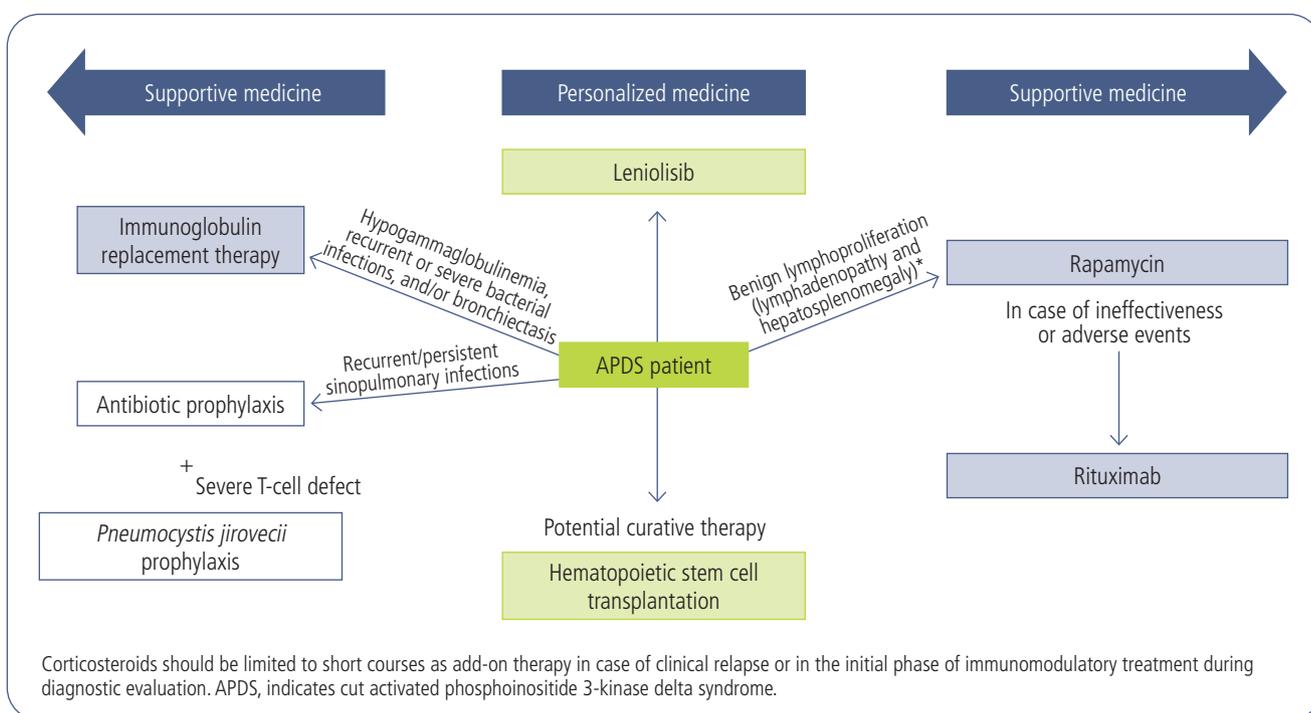


Figure 3. Overview of therapeutic approaches for management of activated phosphoinositide 3-kinase delta syndrome (APDS). The figure outlines the various treatment strategies for APDS, highlighting both conventional and emerging therapeutic options. Leniolisib is not currently approved in Spain, although it is available through early access programs.

– *Hematopoietic stem cell transplantation.* HSCT for APDS is the only potentially curative therapy today and should be an option for selected patients, especially those who were unable to achieve remission or who experienced disease progression despite having received different immunomodulatory therapies.

In a retrospective study of 57 patients who underwent HSCT, 49% had prior mTOR inhibitor therapy, and 26% had been treated with rituximab [65]. The authors reported 2-year overall and graft failure-free survival rates of 86% and 68%, respectively, with no significant differences observed between APDS1 and APDS2, donor type, or conditioning intensity. However, HSCT-

associated complications were notable, including acute and chronic graft-versus-host disease in 39% and 16% of patients, respectively. Graft failure required donor cell infusions in 39% of patients, and 9 of the 57 patients required retransplantation [65,76].

The role of HSCT in APDS remains to be established, and several areas remain open to debate, namely, optimal patient selection, timing, conditioning regimens, and immunomodulatory management before, during, and after transplantation. Additionally, long-term post-HSCT follow-up data are lacking, thus making it difficult to provide definitive recommendations on prognosis and optimal treatment.

See Table 8 for statements and recommendations (24-25) related to HSCT.

An algorithm summarizing current treatment options can be found in Figure 3.

4.2.3. Integrated care and follow-up

4.2.3.1. Patient journey

Considering the wide range of symptoms and complications of APDS, follow-up should involve multidisciplinary teams, including specialists from various fields [5]. Additionally, the chronic and potentially serious nature of the syndrome makes psychological support fundamental for both patients and their families [31].

4.2.3.2. Tests, clinical markers, and biomarkers

Longitudinal follow-up in the same health care centers facilitates consistent imaging, pathology evaluations, and monitoring of immunological and pulmonary status. This approach permits early detection of complications and deterioration of affected organs, thus facilitating reassessment of therapeutic options [42].

For patients receiving pharmacological PI3K inhibition activity, improvement in lymphoproliferative complications and even phenotypic and functional immunological abnormalities could be identified through imaging modalities such as ultrasound, computed tomography, and magnetic resonance imaging to better define personalized clinical outcomes. Promising diagnostic, prognostic, and therapeutic biomarkers are under investigation [42,67].

Periodic monitoring of functional assays to assess PI3K-AKT-mTOR pathway activity could complement clinical evidence of pharmacological response in the long term. Standardized protocols for periodic testing in primary immunodeficiency can be applied to the follow-up of APDS patients [42].

See Table 9 for relevant statements and recommendations (26-30) related to tests, clinical markers, and biomarkers.

4.2.3.3. Genetic counseling

Upon diagnosis, the patient must receive support in understanding the implications and challenges of carrying a genetic abnormality. Carriers will therefore require assistance and guidance in managing and planning future pregnancies to minimize the risks of having an affected child and to adapt to the psychosocial aspects involved [77,78]. As in other, similar IEIs, all APDS patients and their relatives should be offered genetic counseling [79].

Key aspects of genetic counseling for APDS include the following:

- Mode of inheritance and recurrence risk. APDS follows an autosomal dominant inheritance pattern with high penetrance.
- Management and treatment options. Current and future treatment options should be discussed, especially in cases of prenatal diagnosis.
- Reproductive considerations. Available options should be explored to prevent transmission to offspring in patients of reproductive age or before starting treatment that may affect fertility.

Table 9. Integrated Care and Follow-up: Statements and Recommendations Validated by the Panelists During the Consensus Process.

Statement/recommendation	Median	Appropriateness	Level of agreement
26. A full immunological evaluation, including T- and B-cell phenotyping, viral load, and basic complete blood count and biochemistry should be performed every 6-12 months.	9	Appropriate	Agreement
27. A yearly pulmonary function test, including DLCO, is recommended in patients with lung involvement.	9	Appropriate	Agreement
28. Ultrasound imaging of the abdomen and areas of clinical adenopathy should be performed annually.	9	Appropriate	Agreement
29. A CT-scan should be repeated every 5 years when baseline is normal or every 1-2 years in the case of active bronchiectasis or interstitial lung disease.	9	Appropriate	Agreement
30. When there is suspicion of infection in patients with bronchiectasis, it is recommended to optimize general, microbiological, and imaging methods.	9	Appropriate	Agreement
31. Genetic counseling should be offered to all APDS patients and relatives owing to its autosomal dominant pattern of inheritance and high clinical penetrance compared to other IEIs.	9	Appropriate	Agreement
32. Close relatives (parents and siblings) of newly diagnosed patients should be evaluated for testing according to regulations, even if asymptomatic.	9	Appropriate	Agreement
33. Emotional and psychological support is recommended for APDS patients and relatives.	9	Appropriate	Agreement
34. There should be fluid interaction and clear channels for referral between the IEI national reference center and other centers to ensure prompt diagnosis and advice on proper clinical management and regular follow-up of APDS.	9	Appropriate	Agreement

Abbreviation: APDS, activated PI3K syndrome; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; IEI, inborn error of immunity.

See Table 9 for relevant statements and recommendations (31-32).

4.2.3.4. Emotional monitoring and psychological support

APDS is a chronic and potentially serious disease, making emotional and psychological support essential for both patients and their families [77,78]. The main aspects to consider are the following:

- Communication of the diagnosis. Prompt diagnosis and reliable results are crucial. The diagnostic process should be conducted by trained personnel in a face-to-face setting to ensure clear communication and emotional support [77].
- Support groups and additional resources. Offer access to support groups and patient organizations where patients and their families can obtain additional information, share experiences, and receive support from individuals facing similar challenges [77].

Table 9 presents statements and recommendations (33-34) related to emotional monitoring and psychological support in APDS.

5. Discussion

The current challenges and treatment landscape for APDS involve the identification and early diagnosis of patients and the limitations of current therapeutic options; hence the importance of developing consensus protocols [80]. In addition, effective follow-up of APDS patients requires multidisciplinary teams capable of addressing their diverse medical and psychosocial needs, preferably in an experienced reference center [78]. A high degree of coordination between services is critical to prevent delays and duplications that could affect the prognosis of APDS patients.

Activities that increase awareness and education among health care professionals and enable them to recognize IEs and to know when to refer patients for diagnostic studies are particularly relevant. The lack of disease-specific protocols and consensus statements hampers management of APDS by the professionals who see affected patients, potentially resulting in inequities that should be addressed [42].

Also challenging is the treatment of APDS. Current therapies, such as mTOR inhibitors and IgRT, have demonstrated efficacy in improving symptoms and stabilizing serum immunoglobulin levels [28,30]. However, they do not address the underlying cause of the disease and are associated with adverse events that add complexity to patient management and negatively affect the patient's experience. Additionally, there is limited guidance on when treatment needs to be initiated and for how long it should continue.

To date, HSCT remains the only curative approach. Emerging clinical data suggest that HSCT can be considered at any stage following the diagnosis of APDS; however, frequent and severe associated complications require candidates to be selected carefully based on a multidimensional analysis of each case. Moreover, HSCT might not address all the manifestations of hyperactive PI3K outside the immune system, especially in APDS2 [76].

The emergence of novel, targeted therapies for APDS may change the natural history of the disease. Leniolisib,

a highly selective oral PI3K δ inhibitor, restores immune function and treats the underlying pathology of APDS [66]. During its clinical development, leniolisib demonstrated efficacy in reducing infections and improving immune-related symptoms while maintaining a favorable safety and tolerability profile [67].

Although leniolisib is not yet approved for APDS in Europe, except in the United Kingdom [81], its targeted action against PI3K δ pathway hyperactivation suggests long-term benefits. It may be considered a disease-modifying therapy owing to its ability to improve the pathognomonic features of APDS [67].

However, the role of immunomodulatory therapy such as sirolimus or leniolisib in combination with HSCT remains unclear. A multicenter retrospective observational study led by the Inborn Errors Working Party of the European Society of Immunodeficiencies is planned to address this issue [82].

We recognize that achieving consensus in this area presents several challenges. A median score of 9 across most statements, with low dispersion, as seen in Supplementary Table 3, is surprising, given the heterogeneity of the clinical experience, variations in diagnostic criteria, and variations in patient management practices between centers in Spain. This could be attributed to the lack of well-established evidence on the manifestations and natural course of APDS, as well as the potential bias introduced by the limited number of participating reference centers and their unequal geographical distribution.

Most statements were based on the most reliable evidence available. Therefore, after reviewing the selected literature, the panelists agreed with most statements, reflecting a shared understanding of APDS management despite differences in clinical practice. Recently, APDS management has been reviewed and discussed in articles including the Japanese guidelines [11] and the multicriteria decision analysis by Abad et al [8], which highlight the unmet needs and scarce available evidence.

The collaborative effort involved in drafting this consensus has enhanced the breadth and scope of the recommendations, ensuring they are representative of the varying clinical practices and management strategies applied across Spain. Although discrepancies in practice were noted, this consensus constitutes a capacity-building exercise that could set the grounds for a more comprehensive, systematic, and harmonized multidisciplinary approach across various levels of care that enables us to bridge gaps in the management of APDS and improve patient management. Future compilation of real data could therefore be enhanced, thus facilitating the identification of gaps in the diagnosis and treatment of APDS.

We also estimated the prevalence of APDS in our setting, keeping in mind several limitations. Patients seen in the reference hospitals could have been treated in other centers, and, thus, counted twice, although this was not verified owing to limitations in the duplication-checking process.

Responses were received from only 8 of Spain's 17 Autonomous Regions, with overrepresentation of the Community of Madrid (13 individuals), Catalonia (9 individuals), and Andalucía (5 individuals), likely because Madrid, Barcelona, and Sevilla serve as national referral centers for IEs, with the result that most patients were

reported from said centers. In addition, limitations may arise in capturing single APDS cases during follow-up, as cases can be reported by more than 1 specialist.

Although the exact number of people with this condition at the population level is unknown, the figures we obtained appear to be consistent with the literature [6]. Our survey reports 35 patients with genetically confirmed APDS, 75.7% of whom were over 12 years old. We must also consider the previously described memory bias, inherent to surveys where professionals rely on the simple recall of cases [83].

In conclusion, this consensus document was developed with the objective of providing practical orientation based on present knowledge of and experience in the treatment of APDS, an ultrarare IEI that poses important challenges owing to its complex pathophysiology and variable manifestations.

Although many aspects are the object of ongoing research, discussion, and debate, clinical and scientific knowledge of APDS will continue to grow as experience with novel therapies expands.

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Spanish APDS Study Group

Mejía MA¹, Belendez Bieler C¹, Cardozo C², Colino Gil E³, Del Rosal T⁴, Deyà Martínez A⁵, Diab L⁶, Domínguez-Pinilla N⁶, García-Soidán A⁷, Gimeno Díaz de Atauri A⁶, Martín Nalda A⁸, Montes-Ares O⁹, Moral Moral P¹⁰, Murciano Carrillo T¹¹, Nuñez-Beltrán M¹⁰, Ocejo-Vinyals G¹², Olbrich P¹³, García AP⁵, Ramakers J¹⁴, Rodríguez Pena R⁴, Sabado C⁸, Solanich X¹⁵, Soler Palacín P⁸

¹Hospital General Universitario Gregorio Marañón, Madrid, Spain

²Hospital Clinic, Barcelona

³Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas, Spain

⁴Hospital la Paz, Madrid, Spain

⁵Hospital San Joan Déu, Barcelona, Spain

⁶Hospital Doce de Octubre, Madrid, Spain

⁷Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas, Spain

⁸Hospital Universitario Vall d'Hebron, Barcelona, Spain

⁹Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

¹⁰Hospital Universitario y Politécnico La Fe, Valencia, Spain

¹¹Pediatric Hematology and Oncology Department, Hospital Universitario Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

¹²Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain

¹³Hospital Universitario Virgen del Rocío, Sevilla, Spain

¹⁴Department of Pediatrics, Hospital Universitari Son Espases.

Multidisciplinary Group for Research in Pediatrics, Hospital Universitari Son Espases; Balearic Islands Health Research Institute (IdISBa), Palma, Spain

¹⁵Hospital Universitario Bellvitge, L'Hospitalet del Llobregat, Spain

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References

- Angulo I, Vadas O, Garçon F, Banham-Hall E, Plagnol V, Leahy TR, et al. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. *Science*. 2013;342(6160):866-71.
- Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. *Nat Immunol*. 2014;15(1):88-97.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-24.
- Jamee M, Moniri S, Zaki-Dizaji M, Olbrich P, Yazdani R, Jadidi-Niaragh F, et al. Clinical, Immunological, and Genetic Features in Patients with Activated PI3Kdelta Syndrome (APDS): a Systematic Review. *Clin Rev Allergy Immunol*. 2020;59(3):323-33.
- Vanselow S, Wahn V, Schuetz C. Activated PI3Kdelta syndrome - reviewing challenges in diagnosis and treatment. *Front Immunol*. 2023;14:1208567.
- Vanselow S, Hanitsch L, Hauck F, Korholz J, Maccari ME, Meinhardt A, et al. Future Directions in the Diagnosis and Treatment of APDS and IEI: a Survey of German IEI Centers. *Front Immunol*. 2023;14:1279652.
- Michalovich D, Nejentsev S. Activated PI3 Kinase Delta Syndrome: From Genetics to Therapy. *Front Immunol*. 2018;9:369.
- Abad MR, Alerany C, Alsina L, Granados EL, Neth O, Poveda JL, et al. Determining value in the treatment of activated PI3Kdelta syndrome in Spain: a multicriteria decision analysis from the perspective of key stakeholders. *Glob Reg Health Technol Assess*. 2024;11:124-30.
- Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. RAND/UCLA appropriateness method user's manual: RAND corporation Santa Monica, CA; 2000.
- European U, on European Reference N. Handbook #5: Methodology for the Development of Clinical Consensus Statements for Rare or Low-Prevalence and Complex Diseases 2020. Available from: <https://health.ec.europa.eu/document/>

- download/92d12de1-aae6-4dd5-b9d9-9afce9042ba3_en?filename=ern_cpg-cdst_hb5_en.pdf.
11. Moriya K, Mitsui-Sekinaka K, Sekinaka Y, Endo A, Kanegane H, Morio T, et al. Clinical practice guideline for activated phosphatidyl inositol 3-kinase-delta syndrome in Japan. *Immunol Med*. 2023;46(4):153-7.
 12. INEbase / Demografía y población / Cifras de población y Censos demográficos / Estadística continua de población / Últimos datos 2023 [cited 2024 Jan]. Available from: https://www.ine.es/dyns/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736177095&menu=ultiDatos&dp=1254735572981.
 13. Download R-4.4.2 for Windows. The R-project for statistical computing 2024. Available from: <https://cran.r-project.org/bin/windows/base/>.
 14. Lucas CL, Chandra A, Nejentsev S, Condliffe AM, Okkenhaug K. PI3Kdelta and primary immunodeficiencies. *Nat Rev Immunol*. 2016;16(11):702-14.
 15. Jastrzebski K, Hannan KM, Tchoubrieva EB, Hannan RD, Pearson RB. Coordinate regulation of ribosome biogenesis and function by the ribosomal protein S6 kinase, a key mediator of mTOR function. *Growth Factors*. 2007;25(4):209-26.
 16. Pourrajab F, Yazdi MB, Zarch MB, Zarch MB, Hekmatimoghaddam S. Cross talk of the first-line defense TLRs with PI3K/Akt pathway, in preconditioning therapeutic approach. *Mol Cell Ther*. 2015;3:4.
 17. Okkenhaug K. Signaling by the phosphoinositide 3-kinase family in immune cells. *Annu Rev Immunol*. 2013;31:675-704.
 18. Deau MC, Heurtier L, Frange P, Suarez F, Bole-Feysot C, Nitschke P, et al. A human immunodeficiency caused by mutations in the PIK3R1 gene. *J Clin Invest*. 2014;124(9):3923-8.
 19. Lucas CL, Zhang Y, Venida A, Wang Y, Hughes J, McElwee J, et al. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. *J Exp Med*. 2014;211(13):2537-47.
 20. Limon JJ, Fruman DA. Akt and mTOR in B Cell Activation and Differentiation. *Front Immunol*. 2012;3:228.
 21. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. *Cell*. 2017;170(4):605-35.
 22. Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. *Nat Rev Immunol*. 2003;3(4):317-30.
 23. Tsujita Y, Mitsui-Sekinaka K, Imai K, Yeh TW, Mitsuiki N, Asano T, et al. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase delta syndrome-like immunodeficiency. *J Allergy Clin Immunol*. 2016;138(6):1672-80 e10.
 24. Tangye SG, Bier J, Lau A, Nguyen T, Uzel G, Deenick EK. Immune Dysregulation and Disease Pathogenesis due to Activating Mutations in PIK3CD-the Goldilocks' Effect. *J Clin Immunol*. 2019;39(2):148-58.
 25. Kennedy-Batalla R, Acevedo D, Luo Y, Esteve-Sole A, Vlasea A, Correa-Rocha R, et al. Treg in inborn errors of immunity: gaps, knowns and future perspectives. *Front Immunol*. 2023;14:1278759.
 26. Wang W, Min Q, Lai N, Csomos K, Wang Y, Liu L, et al. Cellular Mechanisms Underlying B Cell Abnormalities in Patients With Gain-of-Function Mutations in the PIK3CD Gene. *Front Immunol*. 2022;13:890073.
 27. Elkaim E, Neven B, Bruneau J, Mitsui-Sekinaka K, Stanislas A, Heurtier L, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase delta syndrome 2: A cohort study. *J Allergy Clin Immunol*. 2016;138(1):210-8 e9.
 28. Maccari ME, Abolhassani H, Aghamohammadi A, Aiuti A, Aleinikova O, Bangs C, et al. Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase delta Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase delta Syndrome Registry. *Front Immunol*. 2018;9:543.
 29. Coulter TI, Chandra A, Bacon CM, Babar J, Curtis J, Screaton N, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase delta syndrome: A large patient cohort study. *J Allergy Clin Immunol*. 2017;139(2):597-606 e4.
 30. Maccari ME, Wolkewitz M, Schwab C, Lorenzini T, Leiding JW, Aladjdi N, et al. Activated phosphoinositide 3-kinase delta syndrome: Update from the ESID Registry and comparison with other autoimmune-lymphoproliferative inborn errors of immunity. *J Allergy Clin Immunol*. 2023;152(4):984-96 e10.
 31. Alvaro-Sanchez S, Abreu-Rodriguez I, Abuli A, Serra-Juhe C, Garrido-Navas MDC. Current Status of Genetic Counselling for Rare Diseases in Spain. *Diagnostics (Basel)*. 2021;11(12):2320.
 32. Zanini A, Aiello M, Adamo D, Cherubino F, Zampogna E, Sotgiu G, et al. Effects of Pulmonary Rehabilitation in Patients with Non-Cystic Fibrosis Bronchiectasis: A Retrospective Analysis of Clinical and Functional Predictors of Efficacy. *Respiration*. 2015;89(6):525-33.
 33. Condliffe AM, Chandra A. Respiratory Manifestations of the Activated Phosphoinositide 3-Kinase Delta Syndrome. *Front Immunol*. 2018;9:338.
 34. Lee AL, Hill CJ, McDonald CF, Holland AE. Pulmonary Rehabilitation in Individuals With Non-Cystic Fibrosis Bronchiectasis: A Systematic Review. *Arch Phys Med Rehabil*. 2017;98(4):774-82 e1.
 35. Tarzi MD, Grigoriadou S, Carr SB, Kuitert LM, Longhurst HJ. Clinical immunology review series: An approach to the management of pulmonary disease in primary antibody deficiency. *Clin Exp Immunol*. 2009;155(2):147-55.
 36. Coulter TI, Cant AJ. The Treatment of Activated PI3Kdelta Syndrome. *Front Immunol*. 2018;9:2043.
 37. Chapel H, Prevot J, Gaspar HB, Espanol T, Bonilla FA, Solis L, et al. Primary immune deficiencies - principles of care. *Front Immunol*. 2014;5:627.
 38. Peshko D, Kulbachinskaya E, Korsunskiy I, Kondrikova E, Pulvirenti F, Quinti I, et al. Health-Related Quality of Life in Children and Adults with Primary Immunodeficiencies: A Systematic Review and Meta-Analysis. *J Allergy Clin Immunol Pract*. 2019;7(6):1929-57 e5.
 39. Andersen JB, Middtun K, Feragen KJB. Measuring quality of life of primary antibody deficiency patients using a disease-specific health-related quality of life questionnaire for common variable immunodeficiency (CVID_QoL). *J Patient Rep Outcomes*. 2019;3(1):15.
 40. Ewertowska M, Grzesk E, Urbanczyk A, Dabrowska A, Babol-Pokora K, Lecka M, et al. Activated phosphoinositide 3-kinase delta syndrome 1 and 2 (APDS 1 and APDS 2): similarities and differences based on clinical presentation in two boys. *Allergy Asthma Clin Immunol*. 2020;16:22.

41. Routes J, Abinun M, Al-Herz W, Bustamante J, Condino-Neto A, De La Morena MT, et al. ICON: the early diagnosis of congenital immunodeficiencies. *J Clin Immunol*. 2014;34(4):398-424.
42. Cordero E, Goycochea-Valdivia W, Mendez-Echevarria A, Allende LM, Alsina L, Bravo Garcia-Morato M, et al. Executive Summary of the Consensus Document on the Diagnosis and Management of Patients with Primary Immunodeficiencies. *J Allergy Clin Immunol Pract*. 2020;8(10):3342-7.
43. Lee GM. Preventing infections in children and adults with asplenia. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):328-35.
44. Freeman AF, Holland SM. Antimicrobial prophylaxis for primary immunodeficiencies. *Curr Opin Allergy Clin Immunol*. 2009;9(6):525-30.
45. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for *Pneumocystis pneumonia* (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev*. 2014;2014(10):CD005590.
46. Bemben NM, Berg ML. Efficacy of inactivated vaccines in patients treated with immunosuppressive drug therapy. *Pharmacotherapy*. 2022;42(4):334-42.
47. Poyhonen L, Bustamante J, Casanova JL, Jouanguy E, Zhang Q. Life-Threatening Infections Due to Live-Attenuated Vaccines: Early Manifestations of Inborn Errors of Immunity. *J Clin Immunol*. 2019;39(4):376-90.
48. Bloomfield M, Klocperk A, Zachova R, Milota T, Kanderova V, Sediva A. Natural Course of Activated Phosphoinositide 3-Kinase Delta Syndrome in Childhood and Adolescence. *Front Pediatr*. 2021;9:697706.
49. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract*. 2016;4(1):38-59.
50. Hanitsch LG, Lobel M, Mieves JF, Bauer S, Babel N, Schweiger B, et al. Cellular and humoral influenza-specific immune response upon vaccination in patients with common variable immunodeficiency and unclassified antibody deficiency. *Vaccine*. 2016;34(21):2417-23.
51. Boeckh MJ, Arvin AM, Mullane KM, Camacho LH, Winston DJ, Morrison VA, et al. Immunogenicity of Inactivated Varicella Zoster Vaccine in Autologous Hematopoietic Stem Cell Transplant Recipients and Patients With Solid or Hematologic Cancer. *Open Forum Infect Dis*. 2020;7(7):ofaa172.
52. Qiu L, Wang Y, Tang W, Yang Q, Zeng T, Chen J, et al. Activated Phosphoinositide 3-Kinase delta Syndrome: a Large Pediatric Cohort from a Single Center in China. *J Clin Immunol*. 2022;42(4):837-50.
53. Yasir M GA, Sonthalia S. Corticosteroid Adverse Effects. [Updated 2022 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK531462/>.
54. Varley CD, Winthrop KL. Long-Term Safety of Rituximab (Risks of Viral and Opportunistic Infections). *Curr Rheumatol Rep*. 2021;23(9):74.
55. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. *Int J Infect Dis*. 2011;15(1):e2-16.
56. Gobert D, Bussel JB, Cunningham-Rundles C, Galicier L, Dechartres A, Berezne A, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. *Br J Haematol*. 2011;155(4):498-508.
57. Labrosse R, Barmettler S, Derfalvi B, Blincoe A, Cros G, Lacombe-Barrios J, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. *J Allergy Clin Immunol*. 2021;148(2):523-32 e8.
58. Oh J, Garabedian E, Fuleihan R, Cunningham-Rundles C. Clinical Manifestations and Outcomes of Activated Phosphoinositide 3-Kinase delta Syndrome from the USIDNET Cohort. *J Allergy Clin Immunol Pract*. 2021;9(11):4095-102.
59. Wang Y, Wang W, Liu L, Hou J, Ying W, Hui X, et al. Report of a Chinese Cohort with Activated Phosphoinositide 3-Kinase delta Syndrome. *J Clin Immunol*. 2018;38(8):854-63.
60. Elgizouli M, Lowe DM, Speckmann C, Schubert D, Hulsdunker J, Eskandarian Z, et al. Activating PI3Kdelta mutations in a cohort of 669 patients with primary immunodeficiency. *Clin Exp Immunol*. 2016;183(2):221-9.
61. Kang JM, Kim SK, Kim D, Choi SR, Lim YJ, Kim SK, et al. Successful Sirolimus Treatment for Korean Patients with Activated Phosphoinositide 3-kinase delta Syndrome 1: the First Case Series in Korea. *Yonsei Med J*. 2020;61(6):542-6.
62. Olbrich P, Lorenz M, Cura Daball P, Lucena JM, Rensing-Ehl A, Sanchez B, et al. Activated PI3Kdelta syndrome type 2: Two patients, a novel mutation, and review of the literature. *Pediatr Allergy Immunol*. 2016;27(6):640-4.
63. Scott JR, Courter JD, Saldana SN, Widemann BC, Fisher M, Weiss B, et al. Population pharmacokinetics of sirolimus in pediatric patients with neurofibromatosis type 1. *Ther Drug Monit*. 2013;35(3):332-7.
64. Schubert M, Venkataramanan R, Holt DW, Shaw LM, McGhee W, Reyes J, et al. Pharmacokinetics of sirolimus and tacrolimus in pediatric transplant patients. *Am J Transplant*. 2004;4(5):767-73.
65. Dimitrova D, Nademi Z, Maccari ME, Ehl S, Uzel G, Tomoda T, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. *J Allergy Clin Immunol*. 2022;149(1):410-21 e7.
66. Rao VK, Webster S, Dalm V, Sediva A, van Hagen PM, Holland S, et al. Effective "activated PI3Kdelta syndrome"-targeted therapy with the PI3Kdelta inhibitor leniolisib. *Blood*. 2017;130(21):2307-16.
67. Rao VK, Webster S, Sediva A, Plebani A, Schuetz C, Shcherbina A, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kdelta inhibitor leniolisib for activated PI3Kdelta syndrome. *Blood*. 2023;141(9):971-83.
68. Rao VK, Kulm E, Grossman J, Buchbinder D, Chong H, Bradt J, et al. Long-term treatment with selective PI3Kdelta inhibitor leniolisib in adults with activated PI3Kdelta syndrome. *Blood Adv*. 2024;8(12):3092-108.
69. Semeraro M, Chentout L, Moshous D, Morelle G, Suarez F, Broissand C, et al. Sustained Clinical improvement in three patients by Activated PI3K δ Syndrome (APDS) Treated With Leniolisib. INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS 2022.
70. Rao VK, Kulm E, Kleiner GI, Boggs NA, Khan YW, Orpia A, et al. editors. Gastrointestinal Manifestations in Patients With Activated PI3K δ Syndrome (APDS) Treated With

- Leniolisib. INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS; 2023; ROTTERDAM, THE NETHERLANDS.
71. Rao VK, Kulm E, Sediva A, Plebani A, Schuetz C, Shcherbina A, et al. Interim analysis: Open-label extension study of leniolisib for patients with APDS. *J Allergy Clin Immunol*. 2024;153(1):265-74 e9.
 72. Rao VK, Šedivá A, Dalm VASH, Plebani A, Schuetz C, Shcherbina A, et al. Results of a Second Interim Analysis of an Ongoing Single-Arm Open-Label Extension Study of Leniolisib in Activated PI3K δ Syndrome: Long-Term Efficacy and Safety Through to March 2023. INTERNATIONAL PRIMARY IMMUNODEFICIENCIES CONGRESS; ROTTERDAM, THE NETHERLANDS 2023.
 73. FDA. FDA approves first treatment for activated phosphoinositide 3-kinase delta syndrome | FDA 2023 [cited 2023 June]. Available from: <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-activated-phosphoinositide-3-kinase-delta-syndrome>.
 74. Begg M, Amour A, Jarvis E, Tang T, Franco SS, Want A, et al. An open label trial of nemoralisib, an inhaled PI3 kinase delta inhibitor for the treatment of Activated PI3 kinase Delta Syndrome. *Pulm Pharmacol Ther*. 2023;79:102201.
 75. Diaz N, Juarez M, Cancrini C, Heeg M, Soler-Palacín P, Payne A, et al. Seletalisib for Activated PI3K δ Syndromes: Open-Label Phase 1b and Extension Studies. *J Immunol*. 2020;205(11):2979-87.
 76. Nademi Z, Slatter MA, Dvorak CC, Neven B, Fischer A, Suarez F, et al. Hematopoietic stem cell transplant in patients with activated PI3K delta syndrome. *J Allergy Clin Immunol*. 2017;139(3):1046-9.
 77. Merker VL, Plotkin SR, Charns MP, Meterko M, Jordan JT, Elwy AR. Effective provider-patient communication of a rare disease diagnosis: A qualitative study of people diagnosed with schwannomatosis. *Patient Educ Couns*. 2021;104(4):808-14.
 78. Ormondroyd E, Mackley MP, Blair E, Craft J, Knight JC, Taylor J, et al. Insights from early experience of a Rare Disease Genomic Medicine Multidisciplinary Team: a qualitative study. *Eur J Hum Genet*. 2017;25(6):680-6.
 79. Ameratunga R, Lehnert K, Woon ST. All Patients With Common Variable Immunodeficiency Disorders (CVID) Should Be Routinely Offered Diagnostic Genetic Testing. *Front Immunol*. 2019;10:2678.
 80. Nunes-Santos CJ, Uzel G, Rosenzweig SD. PI3K pathway defects leading to immunodeficiency and immune dysregulation. *J Allergy Clin Immunol*. 2019;143(5):1676-87.
 81. MHRA approves first medicine for rare immune disease APDS 2024. Available from: <https://www.gov.uk/government/news/mhra-approves-first-medicine-for-rare-immune-disease-apds>.
 82. ESID. Inborn Errors Working Party (IEWP) 2024 [cited 2024 oct]. Available from: <https://esid.org/working-parties/inborn-errors-working-party-iewp/>.
 83. Rivas-Ruiz F, Perez-Vicente S, Gonzalez-Ramirez AR. Bias in clinical epidemiological study designs. *Allergol Immunopathol (Madr)*. 2013;41(1):54-9.
 84. Cohen JI. Herpesviruses in the Activated Phosphatidylinositol-3-Kinase-delta Syndrome. *Front Immunol*. 2018;9:237.
 85. Crank MC, Grossman JK, Moir S, Pittaluga S, Buckner CM, Kardava L, et al. Mutations in PIK3CD can cause hyper IgM syndrome (HIGM) associated with increased cancer susceptibility. *J Clin Immunol*. 2014;34(3):272-6.
 86. Ruiz-Garcia R, Vargas-Hernandez A, Chinn IK, Angelo LS, Cao TN, Coban-Akdemir Z, et al. Mutations in PI3K110delta cause impaired natural killer cell function partially rescued by rapamycin treatment. *J Allergy Clin Immunol*. 2018;142(2):605-17 e7.
 87. Cant AJ, Chandra A, Munro E, Rao VK, Lucas CL. PI3Kdelta Pathway Dysregulation and Unique Features of Its Inhibition by Leniolisib in Activated PI3Kdelta Syndrome and Beyond. *J Allergy Clin Immunol Pract*. 2024;12(1):69-78.

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■ **Olaf Neth**

Hospital Infantil Universitario Virgen del Rocío
 Instituto de Biomedicina de Sevilla (IBiS)
 Alteraciones congénitas de Inmunidad (Lab 205)
 Av Manuel Siurot, s/n
 41013 Sevilla, Spain
 E-mail: oneth-ibis@us.es