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Review Article

National Consensus Guideline on Diagnosis and Management of Predominantly Antibody Deficiencies

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Abstract
At present, a national consensus or guideline for diagnosing and managing patients suspected of having predominantly antibody deficiencies (PADs) is lacking. This consensus is written based on a combination of scientific literature and comments from the expert panel of Iranian immunologists. A group of clinical immunologists reviewed the current consensus, presented their comments at a meeting titled 'First Meeting on the Diagnosis of Inborn Errors of Immunity (IEI) by IEI Experts,' and agreed on this consensus. This consensus guideline provides recommendations on the diagnosis, antimicrobial prophylaxis, management of clinical manifestations, and immunoglobulin replacement therapy (IgRT) for patients with PAD.

Keywords: Diagnosis; Inborn Errors of Immunity; Immunoglobulin Replacement Therapy; Management;National Consensus; Predominantly Antibody Deficiencies

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Introduction

Predominantly Antibody Deficiencies (PADs) are a group of diseases affecting humoral immunity, resulting in decreased antibody levels. Patients with PAD commonly exhibit normal T-cell immunity. Patients with PAD present various complications, including recurrent infections, pulmonary complications, autoimmunity, gastrointestinal problems, malignancy, and PAD-related lymphoproliferative diseases (1). Globally, patients with PAD are the most frequent type of inborn errors of immunity (IEI) (2). The International Union of Immunological Societies (IUIS) classification categorizes PADs into 4 major groups based on B cell numbers and immunoglobulin levels, including absence of B cells (agammaglobolinemia), hypogammaglobinemia (CVID), class switching defect (hyper IgM (HIGM)) and B cell normal but defective in isotype, light chain, or B cell functional (3).

In the last update of IUIS classification, 39 genes have been reported as causing PADs (3). The management approach for PADs is prevention through antimicrobial prophylaxis and treatment, including management of clinical manifestations and immunoglobulin replacement therapy [IgRT]). This national consensus recommends a guideline for diagnosing and managing PADs based on a combination of scientific literature and the comments of the expert panel of Iranian clinical immunologists.

Consensus on diagnosis of PADs

Diagnostic criteria for recognizing IEIs commonly rely on clinical phenotypes and laboratory findings. The most prominent diagnostic criteria include the European Society for Immunodeficiencies (ESID) (4), the Pan-American Group for Immunodeficiency (PAGID) (5), and IUIS (6). ESID and IUIS provide more comprehensive and frequently updated guidelines. ESID criteria consider clinical manifestations, laboratory data, and family history for diagnosing IEIs, with genetic testing utilized for a definitive diagnosis (4). This guideline is applicable even in regions where genetic testing is unavailable. On the other hand, IUIS focuses on genetic findings and clinical features for the diagnosis and classification of IEIs, suggesting a detailed diagnostic approach for research and clinical practice worldwide (6). IUIS categorized 4 major groups:

1) absent of B cells (agammaglobolinemia),
2) hypogammaglobinemia (CVID),
3) class switching defect (hyper IgM [HIGM])

4) normal B cells with isotype, light chain, or function defects.

The diagnostic approach for PADs is described based on 4 major groups of the IUIS classification in the following sections.

Agammaglobulinemia

Agammaglobulinemia patients with strongly decreased antibodies and absent B cells exhibit two types of inheritance, including X-linked agammaglobulinemia (XLA) and Autosomal Recessive Agammaglobulinemia (ARA). XLA is recognized by a mutation in the BTK gene. BTK gene is situated on the X chromosome, as males will be affected if the mother is a carrier, while females are typically carriers and asymptomatic. ARA have mutations in genes related to B cell development and function, including IGHM, IGLL1, CD79A, CD79B, BLNK, etc., which can affect both genders. Although XLA and ARA have different inheritance, they present similar clinical manifestations and laboratory findings. Both XLA and ARA present agammaglobulinemia phenotype with recurrent bacterial infections. Owing to the lack of B cells mediating the formation of lymphoid organs, these patients manifest significantly small or completely missing tonsils and lymph nodes.

According to ESID criteria, agammaglobulinemia patients are diagnosed by absent or severe reduction of total B cells (less than 2%), while the number and function of T cells remain normal. These patients demonstrate either a severely reduced IgG level or a normal IgG level accompanied by significantly decreased levels of IgA and IgM. A maternal family history confirming agammaglobulinemia or the occurrence of recurrent infections prior to the age of 5 is two key points in the diagnosis of these patients (4).

There is no diagnostic approach for distinguishing XLA and ARA, except through genetic analysis of known genes related to agammaglobulinemia (3).

CVID Phenotype

Patients with CVID phenotype exhibit defects in the molecules responsible for the activation and differentiation of B cells, thereby resulting in impaired antibody production (3). Patients with CVID are at risk for infections and may present non-infectious complications, including autoimmunity, lymphoproliferation, and malignancy (7). Owing to the wide variety of clinical features, these patients are classified into five different clinical phenotypes according to Chapel's criteria: infection only, enteropathy, autoimmune conditions, polyclonal lymphocytic infiltration, and lymphoid malignancy (8). Diagnosis of CVID is made after the age of 4 to exclude transient hypogammaglobinemia of infancy (9).

CVID patients experience a significant decrease in IgG levels, along with a severe decline in IgA levels, with or without decreased IgM levels. Response to specific antibodies is defective in CVID patients, resulting in inadequate secretion of specific antibodies against protein or polysaccharide antigens.

Patients commonly do not exhibit the presence of isohemagglutinins. Diagnosis of CVID is defined after excluding the secondary causes of hypogammaglobulinemia. For lymphocyte subsets, they typically have B cells of more than 2% and a low percentage of switched memory B cells-below 70% of the age-related normal value-but do not have severe T-cell deficiency. It has been reported that CVID patients with expanded CD21low B cell numbers in the peripheral blood are associated with autoimmunity and hepatosplenomegaly (10-12). If CD4+ T cell count is lowerin CVID patients compared to age-adjusted normal limits, or if the percentage of naive CD4+ T cells is decreased relative to age-adjusted normal limits, or if the T cell proliferation is notably low, they are considered to be combined immunodeficiency (9). Flow cytometric analysis forms a very useful approach for the diagnosis of CVID as it enables immunophenotyping of lymphocyte subsets and assessment of their functions (10).

CSR defects and HIGM syndrome

HIGM syndrome or CSR defects are defined by significantly decreased or undetectable serum levels of IgG, IgA and IgE, while IgM levels are usually within the normal range or increase (11). Defects in the molecules responsible for the CSR mechanism, somatic hypermutation, and DNA repair system contribute to the development of HIGM syndrome (3). HIGM syndrome is identified by a mutation in the AICDA (activation-induced cytidine deaminase), UNG (uracil-DNA

glycosylase), MSH6 (MutS Homolog 6), and INO80 (INO80 Complex ATPase Subunit) genes involving in class-switched mechanism (3). These genes are autosomal recessive. Although mutations in the CD40 ligand (CD40L) and CD40 genes are the most frequent genetic alterations in individuals with the HIGM phenotype, they are linked with T cell defects and are considered an entity of combined immunodeficiency.

Patients with HIGM syndrome typically manifest recurrent bacterial infections, due to the low level of switched immunoglobulin isotype. Some HIGM patients may also experience autoimmunity, lymphoproliferation, and malignancies (11). In the cases with associated T-cell defects (e.g., CD40L deficiency and CD40 deficiency), viral and opportunistic infections, such as Pneumocystis jirovecii pneumonia (PJP) and cryptosporidium diarrhea, can also be observed (12, 13). For diagnosing HIGM syndrome, it is crucial to exclude other causes of hypogammaglobulinemia, similar to those with CVID. According to ESID criteria (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria), these patients lack evidence of severe T cell deficiency, including low CD4 numbers/microliter (according to age-specific normal ranges), low naive CD4+ T cells (according to age-specific normal ranges) and impaired T cell proliferation (9).

Normal B cells with isotype, light chain, or function defects

Individuals with typically normal B cell counts who exhibit deficiencies in isotype, light chain, and functional aspects demonstrate a range of humoral immunodeficiency identified by specific defects in antibody production. These patients are not commonly associated with significant infections and may be asymptomatic. Except for patients with Kappa chain deficiency and CARD11 gain of function (GOF) mutations, other types did not demonstrate specific mutations associated with disease development.

Selective deficiency in each of the immunoglobulin isotypes, such as IgG, IgA, or IgM, determines selective isotype deficiency. These patients may manifest recurrent infections due to the inability to secret adequate antibodies against specific antigens. Assessment of the immunoglobulin isotypes and subclasses can identify these patients (14). Individuals with light chain deficiencies are characterized by insufficient production of one of the light chains of immunoglobulin, kappa or lambda chains, thus producing non-functional antibodies. Assessment of the amounts of free light chains in serum using electrophoresis or quantification of kappa-bearing lymphocytes by flow cytometry can be helpful (15).

Individuals with normal B cell and antibody levels who present recurrent respiratory bacterial infections should be considered for B cell function. Response to polysaccharide antigens after vaccination determines specific antibody deficiency (16). Individuals suspected of having transient hypogammaglobulinemia in infancy present a temporary decline in levels of IgG, which may coincide with decreased IgM and IgA levels. Transient hypogammaglobinemia of infancy (THI) typically resolves spontaneously by 3-4 years of age (17); therefore hypogammaglobinemia is defined after 4 years.

Overall, in addition to clinical features and family history, suspecting PADs requires a comprehensive evaluation of immunoglobulin levels and subclasses, as well as B-cell number and function. We present the laboratory findings for suspecting PADs in **Table 1**. However, for the precise diagnosis of PADs, genetic tests, including whole exome sequencing (WES) and whole genome sequencing (WGS), combined with flow cytometry, are essential.

Consensus recommendations and discussion on antimicrobial prophylaxis

The recurrent infections in PADs lead to the development of complications, therefore, treatments such as antibiotic prophylaxis and IgRT are essential. Although IgRT is a life-saving therapy, PAD patients still experience frequent infections despite receiving IgRT and achieving protective trough levels, although these are less severe (18-20). Hence, the administration of prophylactic antibiotics is a routine approach for PAD patients to complement other treatments, such as IgRT.

Recurrent infections (usually exceeding three per year), low immunoglobulin levels (particularly IgG or IgA), and chronic lung disease such as bronchiectasis require PAD patients to use antimicrobial prophylaxis (21). Although some stud-

Table 1. Summary of Clinical and Laboratory Findings for Suspecting PADs

	Agamma	CVID	HIGM	SAD	IgG SD	SIgAD	SIgAD with IgG SD	THI
Age		Age above 4 years				Age > 4 years		Age < 4 years
Clinic	the occurrence of recurrent infections prior to the age of 5	Recurrent infections (especially bacterial infections) and other complications, exclusion of other causes of antibody deficiencies	Recurrent sinopulmonary infections and additional complications, Exclusion of other causes of antibody deficiencies	Infections (recurrent or severe bacterial infections)	Infections (recurrent or severe bacterial infections)	Recurrent infections and other complications, or asymptomatic	Infections (recurrent or severe bacterial)	Ruling out other causes of antibody deficiencies and spontaneous resolution around the age of 4
Serology	Absence or severe reduction in all isotype Ig OR normal IgG alongside reduced IgA and IgM levels	Reduction in IgG and IgA levels (with or without IgM)	Low IgG with either high or normal IgM levels.	Normal total and subclass Ig levels	Normal serum/plasma levels of IgG, IgA, and IgM AND Reduced levels in one or more IgG subclasses	Absent of serum IgA (< 0.07 g/L) while serum IgG and IgM levels are normal	Absent of serum/plasma IgA level (with normal/slightly low IgG and IgM levels) AND Reduced levels in one or more IgG subclass	Low IgG in the first three years of life
Vaccine response		Inadequate antibody response to vaccines (and/or lack of iso hemagglutinins);		No response to polysaccharide vaccines, response to protein vaccines is normal	Adequate IgG antibody response to specific vaccinations	Adequate IgG antibody response to all vaccinations	Adequate IgG antibody response to all vaccinations	Adequate IgG antibody response to all vaccinations
Flow cytometry	< 2% circulating B cells Normal T cell	> 2% circulating B cells low-switched memory B cells Elevated $CD21^{low}$ B cells No profound T cell deficiency	Normal or low circulating B cells No profound T cell deficiency	Normal B and T cell number	Normal B and T cell number	Normal B and T cell number	Normal B and T cell number	Normal B and T cell number

ies have investigated the efficacy of antimicrobial prophylaxis on PAD patients, its impact on these patients has not been thoroughly addressed. The effectiveness of prophylactic cotrimoxazole or amoxicillin was evaluated on a group of PAD patients, comprising 19 individuals diagnosed with XLA and 20 diagnosed with CVID, who experienced infections more than once each month even while receiving IgRT (22). They have revealed that XLA patients receiving prophylaxis experienced lower infections, while no reduction in infection frequency was found in the CVID group. Furthermore, no significant differences were observed between the different regimens, and infections caused by resistant organisms did not occur (22). Another study investigated the impact of prophylactic antibiotics on respiratory infections over a period of more than three months in 18 patients with CVID and 8 patients with XLA (23). A few patients (3 patients) manifested a strong decrease in their annual infection score, while others continued to experience severe infections (22). However, antibiotic prophylaxis alone is effective in PAD patients with milder phenotypes, including THI, selective IgA deficiency (SIgAD), or IgG subclass deficiency (IgG SD), who manifest recurrent upper respiratory infections (24, 25). PAD patients with mild phenotype commonly need antibiotic prophylaxis during the winter months for several years (26).

Evidence-based guidance and consensus on the administration of antibiotic prophylaxis in PAD patients are absent. In agammaglobulinemia patients receiving IgRT, an effective response was observed in some individuals when sulfamethoxazole-trimethoprim (SMX-TMP) was used as adjunctive antibiotic prophylaxis (25). In case of chronic lung illnesses like chronic cough or bronchiectasis, patients are often administered either SMX-TMP or macrolides for their anti-inflammatory properties (27). Azithromycin, cotrimoxazole, amoxicillin and ciprofloxacin have also been shown to have positive effects when administered as prophylactic regimens in patients with

PAD (28, 29). Other factors such as microbiology findings, sputum tests, and the assessment of the sensitivity of the cultured organisms to antibiotics, also assist in determining the antibacterial prophylaxis in PAD patients (30). PAD patients with mild phenotypes who suffer recurrent infections may gain advantages from prophylactic antibiotic management on a continuous or seasonal intermittent schedule (24, 26). Some prophylactic antibiotic regimens with optimal doses for PAD diseases are suggested in **Figure 1**.

Consensus recommendations and discussion on the management of clinical manifestations in PADs

PAD patients experience various clinical complications in various stages of life, from infancy to late adulthood. The management of major complications is briefly discussed in the following sections.

Infectious complications

PAD patients are prone to infectious complications, particularly the respiratory tract and gastrointestinal infections. Streptococcus pneumonia and Haemophilus influenza are the most typical pathogens in the development of respiratory tract infections in PAD patients. Sinusitis, otitis media, pneumonia, and chronic enteroviral are the major respiratory tract infections in patients with PAD (31, 32). Giardia lamblia, Cryptosporidium, and Campylobacter jejuni are the most common pathogens associated with infectious gastrointestinal complications (33).

In patients with PAD, respiratory tract infections are the leading cause of mortality, therefore, managing infection in those is vital (34). IgRT, in the form of intravenous or subcutaneous administration, is the key treatment for preventing recurring infections in PAD patients (35). As described above, antibiotic prophylaxis is useful for the prevention of infection in PAD patients. Even though culture findings can guide antibiotic choices, starting treatment shouldn't be delayed while waiting for them. Regarding gastrointestinal infections, which are the second most prevalent type of infection in PADs, treatment often initiates with antibiotics, along with restoring nutrients and fluids, based on culture and biopsy results (36). Routine examinations every 3-6 months are recommended for identifying infections in PAD patients who need prompt treatment.

Pulmonary complications

Pulmonary complications may develop at any age in PAD patients. Monitoring lung function and promptly diagnosing new complications represent the cornerstone of treatment in PAD, since pulmonary complications remarkably play a role in the morbidity and mortality rate in patients with IEI, especially in those with PAD (34). Respiratory infections can result in the onset of bronchiectasis in most forms of PAD, but especially in agammaglobulinaemia and CVID patients (34). It is, therefore, recommended that HRCT be carried out every 3-5 years to monitor for pulmonary complications; this should, however be more frequent, i.e., every 2 years for those patients with established chronic lung disease (37). PAD patients should perform pulmonary function tests (PFT) annually to monitor interstitial lung disease development (38). The best available treatment thus far to defer the progression of pulmonary complications is to administer very high doses of immunoglobulin, 600 mg/kg/month, along with regular suppressive anti-microbial therapy (39). Macrolides are commonly used drugs in the management of chronic lung diseases, especially for their anti-infective and anti-inflammatory properties (40). In such patients with PAD, follow-up on lung function by spirometry and sputum and clinical response should be done after the institution of therapy for follow-up of the patient's respiratory status.

Autoimmune complications

The causes of autoimmunity in IEIs are still not fully understood. CVID patients experience more autoimmune complications compared to those with SIgAD and HIGM (41).

Among autoimmune complications in PAD patients, ITP and AIHA are relatively more common (7, 42, 43). The treatment approach for autoimmunity in PAD patients is typically similar to those used in immunocompetent patients. This includes administrating increased-dose IgRT and immunosuppressive medications, such as corticosteroids, methotrexate, and azathioprine along

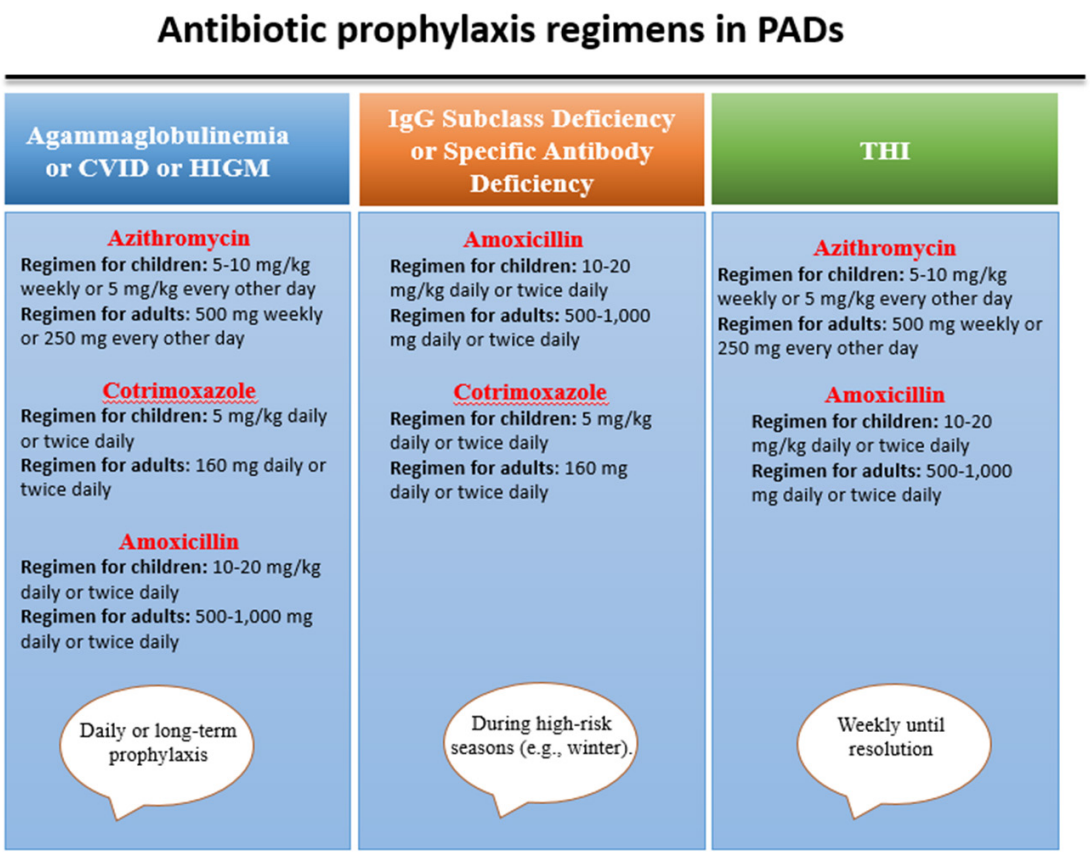

Figure 1. Prophylactic antibiotic regimens with optimal doses for PADs. Abbreviations: CVID, common variable immunodeficiency; HIGM, hyper IgM; mg/kg, milligram/kilogram; THI, Transient hypogammaglobulinemia of infancy. References: (14, 25, 67, 68).

with eliminating the autoantibodies by plasmapheresis; although this treatment increases the risk of infections. IgRT and rituximab have a beneficial impact on decreasing the occurrence of autoimmune manifestations, especially in cases of ITP and AIHA (36, 44). Of note, the administration of monthly IgRT can affect other immunologic tests, hence, it is recommended to maintain the serum samples after IgRT is started. Delay diagnosis and treatment in autoimmunity contribute to poor quality of life, increased medical needs, and higher mortality rates in PAD patients (34, 45, 46). Monitoring autoimmunity in PAD patients at intervals of 3 to 6 months is recommended for assessing hematologic autoimmunity.

Gastrointestinal complications

Gastrointestinal complications are common among patients with PAD. Most CVID patients present chronic diarrhea and malabsorption, while XLA patients experience Crohn's disease and ulcerative colitis (7). Gastrointestinal tumors are observed in HIGM patients accompanied by CID like CD40L deficiency, while HIGM patients experience commonly gastrointestinal infections (11), indicating that patients with HIGM associated with CID experience more severe forms of gastrointestinal problems than those with HIGM. Patients with SIgAD may exhibit gastrointestinal complications such as celiac disease, inflammatory bowel disease (IBD), nodular lymphoid hyperplasia (NLH), and food allergy (47). First-line treatment for managing gastrointestinal compilations is serving corticosteroids and/or mesalazine. However, some patients may need additional immunosuppressive medications, such as azathioprine and cyclosporine.

In PAD patients receiving IgRT, an increased dose provides sufficient serum IgG levels leading to ameliorating gastrointestinal problems (48). Although biological treatment, including TNFα inhibitors (adalimumab, infliximab) and vedolizumab or ustekinumab, has been used in PAD patients, their efficacy was low. Therapeutic strategies for gastrointestinal complications depend on the severity of manifestations, as low-dose im-

munomodulators such as azathioprine or 6-mercaptopurine, in conjunction with TNF-α inhibitors like infliximab or etanercept are appropriate for managing severe inflammatory enteropathy (49, 50). Meanwhile, patients with mild IBD are managed similarly to those immunocompetent individuals (51). The occurrence of gastrointestinal complications should be monitored during the progression of the disease in PAD patients. This monitoring can vary from comprehensive questioning to surveillance colonoscopy or other imaging procedures.

Lymphoproliferative diseases and malignancy

Overall, the etiology of most PAD-related lymphoproliferative diseases is still unclear, though some immunological abnormalities, such as reduced switched memory B cells and CD4+ naive T cells, may be associated with lymphoproliferative and granulomatous diseases in patients with PAD (52). Among PAD diseases, PAD-related lymphoproliferative diseases are more prevalent in patients with CVID and HIGM (7, 11). Lymphoproliferative diseases complicate and delay the diagnostic process in patients with PAD. IgRT does not prevent lymphoproliferative diseases in PAD patients (53), and management of lymphoproliferation is based on the cause of the condition. Administration of glucocorticoids (first dose, 30-60 mg daily for a median of 18 months) is recommended for granulomatous infiltration (54), although they are not always useful. Abatacept, which inhibits T cell activity, has been also suggested for the treatment of granulomatous infiltration such as interstitial lung disease (ILD) (55).

Granulomatous and lymphocytic interstitial lung disease (GLILD) is the leading cause of diffuse parenchymal lung disease in CVID patients and typically does not improve with IgRT alone, hence further treatment is recommended for patients experiencing worsening respiratory symptoms, declining lung function (such as a ≥10 percent decrease in forced vital capacity [FVC] or diffusing capacity for carbon monoxide [DLCO]), or progression on HRCT even when IgG levels are normal. The most effective first treatment for GLILG can be a combination of rituximab and an antimetabolite drug (56). PAD-related lymphoproliferative diseases increase the risk of developing malignancies (57, 58). Among PAD diseases, CVID with cancer has the highest number of reported cases (59). Digestive/gastrointestinal cancer is the most frequent cancer in patients with XLA and SIgAD, while hematologic/blood cancer, including both NHL and Hodgkin lymphomas, is more prevalent in patients with CVID and HIGM (59). The therapeutic approach to cancer in PADs is almost similar to that for patients without PAD. Although patients with PAD may experience extensive cancer requiring more intensive cytotoxic treatment (60). Standard rituximab protocols and surgical modalities are lifesaving for cancers diagnosed at an early stage (36). Allogeneic stem cell transplantation (ASCT) can be considered for managing CVID patients with non-Hodgkin lymphoma, as ASCT can address the complications associated with CVID (61).

Consensus recommendations and discussion on immunoglobulin replacement therapy (IgRT) for patients with PAD

IgRT is utilized for managing patients with antibody deficiencies. IgRT must be given under medical supervision in a hospital. Among PAD patients, those who experience a lack of B cells, those with low protective immunoglobulin levels along with defective specific antibody secretion, or those with normal immunoglobulin but defective specific antibody secretion may require IgRT. The following PAD diseases require IgRT:

1. CVID with recurrent infections
2. CVID without recurrent infections but with significant autoimmunity or inflammatory disease (eg GLILD)
3. Agammaglobulinemia (XLA/ARA)
4. HIGM
5. Patients with low IgG levels or specific antibody responses, experiencing very frequent and/or severe infections.

The use of IgRT requires careful consideration in the steps of starting, monitoring, and stopping (62), which are discussed in detail in the following sections.

1. Starting immunoglobulin replacement therapy

Recommendation 1: PAD patients who expe-

rience their first treatment with IgRT should be checked for infections such as hepatitis C and B, renal function, as well as complete blood count (CBC), liver function test, and urinalysis.

Recommendation 2: PAD patients with severe active infection can receive IgRT as long as they are receiving appropriate antibiotic treatment.

Recommendation 3: Anti-IgA levels are not usually indicated before IgRT unless there is a previous history of allergic reactions.

Recommendation 4: IgG level and severity of infection determine the necessity for starting IgRT **(Table 2)**.

Recommendation 5: A preliminary dosage of 400-600mg/kg every 3 to 4 weeks should be considered for PAD patients. Notably, clinical effects and body weight can adjust the starting dose of IgRT, but less than 400mg/kg and greater than 800mg/kg should not be recommended.

Recommendation 6: A starting dose of 100–200 mg/kg followed by 160 mg/kg, should be considered weekly if the administration is subcutaneous.

Recommendation 7: IgG levels should be monitored every 3 months during the first year of treatment. For stable patients, IgG monitoring should be done at least twice a year.

2. Monitoring immunoglobulin replacement therapy

Recommendation 9: Previous studies demonstrated that IgG trough levels between 500 to 800 mg/dl have a protective effect against acute infections (63-65). IgG trough levels ≥ 800 mg/dl avoid recurrent infection, particularly in patients with no endogenous immunoglobulin production. In some PAD patients, including XLA with end-organ damage/persistent infections, it is recommended to sustain IgG levels ≥ 1000 mg/dl.

Recommendation 10: Immunoglobulin doses can be increased based on the rate of infections and progression of organ disease. If the patient presents mild infection or is free of infection, immunoglobulin doses should be decreased. Increased doses should be considered for patients who experience two or more severe infections yearly.

Recommendation 11: IgRT-treated patients with normal IgG trough levels who present a high infection burden should receive additional medications, including antibiotic prophylaxis and physical therapy before the elevation of immunoglobulin doses. Increased immunoglobulin dose can be maintained for 6 to 12 months.

Recommendation 12: PAD patients receiving IgRT should be monitored every six months regarding their immunoglobulin levels, blood count cells, liver function, and urine tests.

Recommendation 13: Patients receiving IgRT with signs suggestive of bacterial infections, IgRT should be administrated promptly alongside antibiotic therapy.

Recommendation 14: Batch numbers for every immunoglobulin infusion should be recorded and stored at the center.

Recommendation 15: Immunoglobulin products should not be switched for patients receiving IgRT except for clinical necessity or availability constraints. Blood samples should be collected for storage if a switching product is required.

Recommendation 16: In patients who do not manifest with hypersensitivity reaction within the first 30 minutes of infusion, Flow rates may be elevated stepwise based on manufacturer instructions.

Recommendation 17: To avoid adverse reactions after IgRT, the following precautions should be implemented (66):

- Knowing the history of adverse reactions after the previous infusion can prevent complications for the next infusion.
- For patients who had adverse reactions after IgRT, it is recommended to use anti-inflammatory drugs, including corticosteroids, acetaminophen, antihistamines, and others, before the infusion.
- Rapid infusions should not be given. To avoid adverse reactions, initial infusions should be administered at a slow rate, 0.01 mL/kg/min by an infusion pump. The infusion rate can be increased by 0.02 mL/kg every 30 minutes, up to a maximum of 0.08 mL/kg.
- The patient should be followed for over 20 minutes after the infusion
- Avoid utilizing preparations having a sugar stabilizer in patients with diabetes.
- Carefully measure the risk factors associated with renal failure, cardiovascular impairment, thromboembolic risk, and sepsis.
- It is desirable that patients keep themselves hydrated; hence, water should be available and readily accessible.

3. Stopping immunoglobulin replacement therapy

Recommendation 18: Except for patients with significantly reduced immunoglobulin, including those with agammaglobulinemia, CVID, and HIGM, patients presenting no signs of increased frequency and severity of infection compared with the general population should be considered for IgRT discontinuation.

Recommendation 19: Patients discontinuing their IgRT should be closely monitored, have a self-medication plan, and be provided with access to the specialist immunology service.

Recommendation 20: IgG level should be monitored no less than every 12 weeks in patients with discontinued IgRT until the patient is stable.

Recommendation 21: If a patient experiences a decreased IgG level than the normal population after discontinuing IgRT, prophylactic antibiotics should be administrated for the patient.

Table 2. IgG Level Cut-offs for Recommending IgRT

IgG level	IgRT is not routinely recommended	IgRT is routinely recommended
IgG level of ≥ 400 mg/dl	Low incidence of infection and low or normal vaccine responses	Recurrent and/or severe infection
IgG level of < 400 mg/dl	Normal vaccine responses	Poor vaccine responses (unless the patient has a low-frequency or severe infection)
IgG level of < 200 mg/dl		Increased burden of infection (IgRT may be started without a trial of prophylactic antibiotics)

Conclusions

We provide the first national consensus guideline on the diagnosis and management of patients with PAD in IRAN in light of scientific literature and comments from the expert panel of Iranian clinical immunologists. We hope this national consensus guideline can raise the awareness of clinicians and improve the diagnosis and management of patients with PAD.

Conflict of interest

The authors have no conflicts of interest.

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