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Management of humoral secondary immunodeficiency in hematological malignancies and following hematopoietic stem cell transplantation: Regional perspectives

Muhlis Cem Ar [a], Riad El Fakih [b], Saule Gabbassova [c,d], Ahmad Alhuraiji [e], Fady Nasr [f], Ahmad Alsaeed [g,h], Nilgun Sayinalp [i], Mahmoud Marashi [j,*]

[a] Division of Hematology, Department of Internal Medicine, Cerrahpaşa School of Medicine, Istanbul University, Cerrahpaşa, Istanbul, Turkey
[b] Oncology Center, Section of Stem Cell Transplant and Cellular Therapy, King Faisal Hospital and Research Center, Riyadh, Saudi Arabia
[c] Center for Hematology and Bone Marrow Transplantation, Kazakh Scientific Research Institute of Oncology and Radiology, Almaty, Kazakhstan
[d] Al-Farabi Kazakh National University, Almaty, Kazakhstan
[e] Department of Hematology, Kuwait Cancer Control Center, Kuwait City, Kuwait
[f] Department of Hemato-Oncology, Hôtel-Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University of Beirut, Beirut, Lebanon
[g] Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, Saudi Arabia
[h] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[i] Department of Hematology, Hacettepe University Medical School, Ankara, Turkey
[j] Department of Hematology, Mediclinic City Hospital, Dubai, United Arab Emirates

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ABSTRACT

Secondary immunodeficiency (SID) can occur as a result of multiple factors, including hematological malignancies, hematopoietic stem cell transplantation (HSCT), immunosuppressive treatment, biologics, and anti-inflammatory drugs. SID includes disorders resulting from impairment of both cellular and humoral immunity. This review focuses on the current risk factors, implications, and challenges in managing SID patients with impaired humoral immunity, which includes quantitative (hypogammaglobulinemia) and/or functional antibody and B-cell deficiencies specifically related to hematological malignancies and post-HSCT. Increased physician awareness is needed surrounding the disease presentation and early risk factors, as SID may be caused by several etiologies. Careful clinical assessment is then required to optimize management, which encompasses close monitoring of clinical parameters, vaccination, antibiotic prophylaxis, and immunoglobulin replacement therapy (IGRT). Novel methods of IGRT administration are associated with enhanced pharmacokinetics, IgG trough level stability, no need for venous access, as well as fewer systemic adverse events and better administration flexibility compared with traditional methods. Published international guidelines supported by observations from clinical data are broadly followed; however, best practices within each country have nuances that underline the need to tailor treatment plans to the individual patient.

1. Introduction

Secondary immunodeficiency (SID) diseases can be defined as transient or persistent impairment of the cellular or humoral components of the immune system, caused by extrinsic factors such as infectious agents, drugs, metabolic disorders, and environmental conditions that affect a host with an intrinsically normal immune system, leading to increased risk of infection [1–3]. One particular subset of SIDs encompasses a complex and heterogeneous group of conditions defined by compromised humoral immunity, secondary antibody dysfunction, and impaired immunoglobulin production leading to low levels of serum immunoglobulins (hypogammaglobulinemia). SID is frequently associated with hematological malignancies (eg chronic lymphocytic leukemia [CLL], multiple myeloma [MM], and lymphoma) or hematopoietic stem cell transplantation (HSCT); however, immunosuppressive treatment, biologics, and anti-inflammatory drugs can also further contribute to hypogammaglobulinemia, immune dysfunction, and increased risk of infections [1,2].

* Correspondence to: Department of Hematology, Dubai Hospital and Mediclinic City Hospital, Dubai Healthcare City, Umm Hurair, Dubai, United Arab Emirates.
E-mail address: mahmoud.marashi@mediclinic.ae (M. Marashi).

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Although there is no consensus on what the exact threshold of immunoglobulins should be as a clear cut definition of hypogammaglobulinemia, generally, immunoglobulin G (IgG) levels are used to grade the extent of the deficiency. In the authors' experience, serum IgG less than the lower limit of the local reference range on two separate occasions as well as a broader look at the individual patient's clinical presentation, such as presence of bacterial infection, may warrant the diagnosis of SID. However, assessment of IgG is commonly based on the need for immunoglobulin replacement therapy (IgRT) to avoid infectious complications, rather than to quantify the severity of the immunoglobulin deficiency [3,4].

Secondary antibody deficiency is estimated to be 30-fold more common than primary immunodeficiency (PID) and may be reversible if the underlying cause is identified, targeted, and managed correctly [3]. Clinical complications of SID can adversely impact the patient's quality of life and relay a substantial economic burden to the health system, as the duration and severity of SID directly correlate with the status of the underlying cause [2]. The spectrum of clinical impact as a result of immune dysfunction may range from moderate susceptibility to infections, to more significant burden characterized by recurrent, acute, or chronic severe infections resulting in frequent emergency department visits and hospitalizations [2].

While protection against infections remains the cornerstone of SID treatment, consensus opinion and guidelines addressing SID management with regards to infection prophylaxis and immunoglobulin replacement therapy (IgRT) are limited, meaning that physicians face hurdles when implementing standard of care [5,6]. Hence, the rationale for treatment is usually based on physicians' experience with SID or extrapolation of guidelines developed for PID [2,4,7]. However, the rise in prevalence of hematological malignancies, [8] combined with increased use of new therapies for autoimmune, inflammatory, and malignant diseases targeting the immune system, will likely result in increased rates of acquired deficiencies of humoral immunity and infections. This means that it is becoming increasingly important for physicians to understand the unmet needs of this at-risk patient population.

This review aims to provide an overview of the implications and management of immunodeficiency disorders secondary to compromised humoral immunity in the setting of hematological malignancies and post-HSCT. The review will also include insights and observations regarding SID management in the real-life setting to reflect standards of care and best practices in the authors' regions, including Turkey, the Middle East, and Asia.

2. Pathophysiology and risk factors revisited

2.1. Pathophysiology of SID in hematological malignancies

Infections are among the leading causes of morbidity and mortality among B-cell lineage lymphoproliferative malignancies such as CLL, MM, and lymphoma due to disease-intrinsic hypogammaglobulinemia, compounded by treatment secondary effects [1,9]. Incidence of hypogammaglobulinemia also increases with the stage and duration of disease [3,4,10]. Moreover, novel treatments are prolonging survival, transforming these malignancies into chronic conditions and resulting in an increased number of patients with advanced age and comorbidities. Also, the need for increased cumulative immunosuppression often leads to a higher risk of infections [9]. Respiratory tract infections, pneumonia, septicemia, meningitis, and urinary tract infections are among the most common manifestations in this patient population [3].

The mechanisms of hypogammaglobulinemia in patients diagnosed with CLL, MM, and lymphoma are thought to be multifactorial, caused by dysfunctional replication and abnormalities of B cells, T cells, dendritic cells, and natural killer (NK) cells [3,11]. In CLL, malignant B cells replace normal B cells, diluting and inhibiting their antibody-secreting function and subverting T-cell help. Malignant B cells also directly suppress IgG production in the bone marrow by CD95+ plasma cells via Fas-ligand/Fas interactions, which induce apoptosis. Decreased T-helper-cell activity for IgG synthesis and increased T-suppressor-cell activity are also postulated to contribute to hypogammaglobulinemia. [3,12]. Likewise, immune dysfunction in MM has been linked to suppression of CD19+ B cells, plasma-cell precursors, and abnormal expression of B-cell transcription factors. Increased catabolism of IgG, excessive production of transforming growth factor β (TGF-β), and T-helper-cell dysfunction caused by malignant MM cells are additional mechanisms that contribute to hypogammaglobulinemia [12].

Therapies used to treat CLL and MM may increase the likelihood of SID, depending on the drug, dose, duration of treatment, and stage of disease; iatrogenic causes are thought to account for 12.8–22.1% of all cases of secondary antibody deficiency worldwide [3]. Perhaps one of the most used treatment modalities known to induce hypogammaglobulinemia are the monoclonal antibodies directed against CD20 surface antigens, such as rituximab, which have potent B-cell-depleting effects that underpin their use to treat hematological malignancies and systemic autoimmune diseases. Removal of this cell population induces dysregulation of immune homeostasis, decreases IgG, and thus leads to increased risk of infection. Up to 38.5% of patients treated with rituximab experience transient hypogammaglobulinemia [13]. Female gender, combination therapy with fludarabine, and post-HSCT administration are common factors that exacerbate the risk of hypogammaglobulinemia in this setting [9]. Other agents suppress hyper-responsive immune functions and contribute to iatrogenic SID by targeting B-cell survival, B-cell activation, and T-cell/B-cell interaction [14]. Alkylating agents, corticosteroids, and purine analogs can also cause direct immunosuppression, decreased antibody production, neutropenia, and myelosuppression, with varying degrees of impact [1,3].

The dawn of novel immunotherapies, such as CD19-targeted chimeric antigen receptor (CAR) T-cell therapy, has also led to an increase in the potential for long-term dysfunction of the immune system. Despite advances made in bolstering the ability of the immune system to target and kill tumor cells, current therapeutic CAR-T agents have difficulty distinguishing between malignant B-lineage cells and normal CD19+ B cells through 'on-target, off-tumor' effects. This can result in persistent CD19+ B-cell aplasia with the possible risk of reduced humoral immunity, leading to increased risk of infection [15].

Determining the underlying cause of SID in hematological malignancies becomes particularly difficult following the administration of chemo- or immunotherapy and is more complex in heavily pre-treated patients and those who have received multiple lines of treatment over time [3]. Additionally, comorbidities that develop secondary to malignancy can increase the risk of infection, such as renal insufficiency, neutropenia, amyloidosis, and organ damage [1,3] The spectrum of infections often reflects the extent of the immune defect, predominantly caused by encapsulated bacteria such as certain strains of *Haemophilus influenzae*. However, other bacteria, including *Clostridium difficile*, *Escherichia coli*, *Staphylococcus aureus*, and fungal and viral infections such as Varicella zoster are also common in hematological malignancies [3,12].

2.2. Pathophysiology of SID post-HSCT

Advances in stem-cell transplantation techniques and improvements in supportive care have led to HSCT becoming a well-established therapy for malignant and non-malignant disease states. However, in the post-transplantation period, patients are at increased risk of developing severe infections and complications. Immunosuppressive and myelosuppressive conditioning regimens usually lead to cellular and humoral immune deficiencies, which result in an increased risk of infection and impair quality of life. Studies have shown that mortality 10 years after transplant is higher in HSCT patients compared with the general population [16]. Additionally, patients are at risk of developing graft-versus-host disease (GVHD), treatment of which further increases

infection risk [16,17].

The pathophysiology of post-HSCT hypogammaglobulinemia is thought to be twofold. On the one hand, delayed or dysfunctional reconstitution of immune-cell subsets after transplantation can cause decreased immunity. On the other, conditioning regimens given before allogeneic HSCT to eliminate the patient's own bone marrow and immune system in order to create space for the engraftment of donor stem cells, coupled with intensive immunosuppressive and biologic treatment to prevent stem-cell rejection and GVHD, impair both T- and B-cell function, contributing to aberrant SID [17].

Reconstitution of various immune-cell subsets after HSCT occurs in waves; patients undergo an engraftment phase characterized by cellular immunodeficiencies due to reduced numbers of NK cells in the innate and T cells in the adaptive immune system. Parts of the innate immune system, such as granulocytes, monocytes, T cells, and NK cells, show signs of recovery 2–6 months post-transplant [18]. The recovery of the T-cell compartment depends on the peripheral expansion of memory T cells, driven by cytokines and allogeneic antigens, followed by the production of naïve T cells. In certain patients, a lack of naïve T cells with a broad T-cell receptor repertoire can increase opportunistic infections, which is additionally aggravated by GVHD [18]. Similarly, reconstitution of the B-cell lineage can take up to 9 months to reach normal levels because of hindrances such as GVHD, age-related factors, and infections [19]. However, in some patients undergoing allogeneic HSCT, this process can take up to 5 years, [18] and patients who develop chronic GVHD may never acquire normal immune function [19].

In addition to its effect on the immune system, GVHD can also manifest and emerge in specific regions of the body, leading to particular subsets of complications and comorbidities that further complicate SID pathophysiology and management. For example, patients with GVHD in the lungs may go on to develop lower respiratory tract infections [20]. Immunoglobulin production is also usually impaired in the post-HSCT period, as is immunoglobulin class switching and development of complexity in immunoglobulin gene rearrangement patterns. IgG levels may take more than 12 months to recover, and in many instances, hypogammaglobulinemia can persist for more extended periods [19]. One study found low IgG levels (<400 mg/dL) in 24.1% and 27.1% of patients 1 and 3 years post-allogenic HSCT, respectively. Risk factors for hypogammaglobulinemia in this cohort included presence of lymphoid malignancies, history of previous HSCT, low pre-allogenic HSCT IgG levels, and acute GVHD [21]. As with hematological malignancies, infections associated with HSCT are commonly caused by encapsulated bacteria [19].

2.3. Epidemiology of SID associated with hematological malignancies and HSCT

The incidence and prevalence of SID associated with hematological malignancies and HSCT globally and in specific regions remain unclear and may indicate under-recognition and subsequent undertreatment. However, incidence of SID can be correlated with incidence of immunodeficiency in individual hematological malignancies, including CLL and MM. Up to 85% of CLL patients [12,22] and 45–83% of MM patients [3,10] have been reported to develop SID. Approximately 22% and 50% of deaths in MM and CLL patients, respectively, can be attributed to infections likely resulting from the underlying immunodeficiency, which reflects the magnitude of the disease [4,13].

HSCT has become the standard of care for many malignant and non-malignant disorders, resulting in a global incidence that is increasing by more than 7% per year [23]. Infections have been reported as the primary cause of mortality in 8% and 17–20% of autologous stem-cell transplant and allogenic HSCT patients, respectively [24] Immunosuppressive medications used for the prophylaxis or treatment of GVHD and patient-specific factors such as age and comorbidities have also been implicated in delayed immune reconstitution and resulting infection risk [25].

Although there is a lack of robust epidemiological data, several common observations were made based on the authors' regional experiences. In Turkey, the authors have seen an increasing number of fragile SID patients in daily practice, which may be a result of novel methods that require a greater extent of lymphosuppression, enabling complicated procedures such as haploidentical transplantations or reduced-intensity conditioning regimens expediting HSCT in patients of advanced age or with comorbidities. Additionally, higher numbers of patients with lymphoproliferative disorders are seen suffering from SID-associated infections, probably resulting from the use of newer immunotherapeutic agents, which cause impaired cellular and humoral immune responses. From the authors' perspective in Lebanon, many patients being monitored for SID have been diagnosed with CLL, and there has been an increase in utilization of IgG replacement therapy. Likewise, in Kazakhstan, the development of persistent cytopenia with symptoms of deep immunodeficiency is seen in patients who undergo treatment for CLL with subsequent rituximab maintenance therapy (sometimes followed by HSCT and GVHD), and about 70% of these patients are women. In Kuwait, the authors commonly see patients with hypogammaglobulinemia, especially in those treated with B-cell-targeted therapy such as rituximab, daratumumab, blinatumomab, and ibrutinib (usually for CLL) or as a result of the underlying disease. In contrast, in the United Arab Emirates (UAE), MM and CLL patients alike (especially males over 60 years old) are commonly seen presenting with SID. Patients are less frequently seen post-rituximab or on long-term steroid therapy as HSCT is not performed locally. The authors also note that the number of SID patients may be underestimated in certain countries, such as Saudi Arabia, which may lead to undertreatment of the condition.

3. Implications for the patient, physician, and healthcare system

The clinical, economic, and social burden of hypogammaglobulinemia leading to increased risk of infections in transplanted patients and those with hematological malignancies is considerably high, especially in resource-limited settings. Physicians recognize that patients with SID are prone to severe infections leading to hospitalization and expensive treatment costs, which insurance schemes or public funds do not always cover. In addition to the deleterious effects of infection on health, presence of comorbidities, worsened outcomes, and increased morbidity and mortality, patient burden is often augmented by suboptimal management [2].

However, substantial benefits are seen with patients who receive timely immunoglobulin replacement treatment to maintain adequate IgG levels, which can lead to significantly fewer infections and hospitalizations, reduced mortality, and a holistically increased quality of life. [2,3,26]. Increased infection risk also leads to cost implications such as frequent hospital admissions and visits to the emergency department, which create added burden for healthcare systems and payers; untreated SID patients with MM were found to have a total infection duration of 135 days per year and an average of 121 days of hospital stay per year, compared with 62 days and 8 days for patients treated with subcutaneous IgG replacement therapy, respectively [26]. A European study found that quality of life was significantly reduced for SID patients with hematologic malignancies across eight domains of physical function, emotional health, body pain, physical role functioning, emotional role functioning, social role functioning, energy, and perception of overall health compared with the general population [2,27]. This decrease in quality of life is reflected in clinical practice; for example, in Kazakhstan, the authors commonly see SID patients who present with severe somatic state anxiety accompanied by depression, panic, and deteriorating emotional health, and these factors are compounded by physical barriers and changes to daily routine, such as the inability to work.

Financial barriers can lead to poor outcomes concerning SID management; the cost of treatment can deter patients in countries such as the UAE, where replacement and prophylactic treatment are not always

covered by insurance or public funds. Long durations of hospitalization and stay in infusion wards can further compound the issue and limit optimal patient management. By contrast, in Turkey, prophylactic treatment and on-demand immunoglobulin replacement therapy in the setting of SID associated with CLL, MM, or HSCT are reimbursed by the national social security system, which gives full health insurance coverage for the majority of the Turkish population. Despite the cost, significant advantages associated with SID treatment are recognized in clinical practice; in the authors' experience in Lebanon, a lower infection rate is associated with the treated SID population, requiring less use of antibiotics and thus contributing to the fight against antibiotic resistance. Decreased hospitalization rates as a result of adequate SID

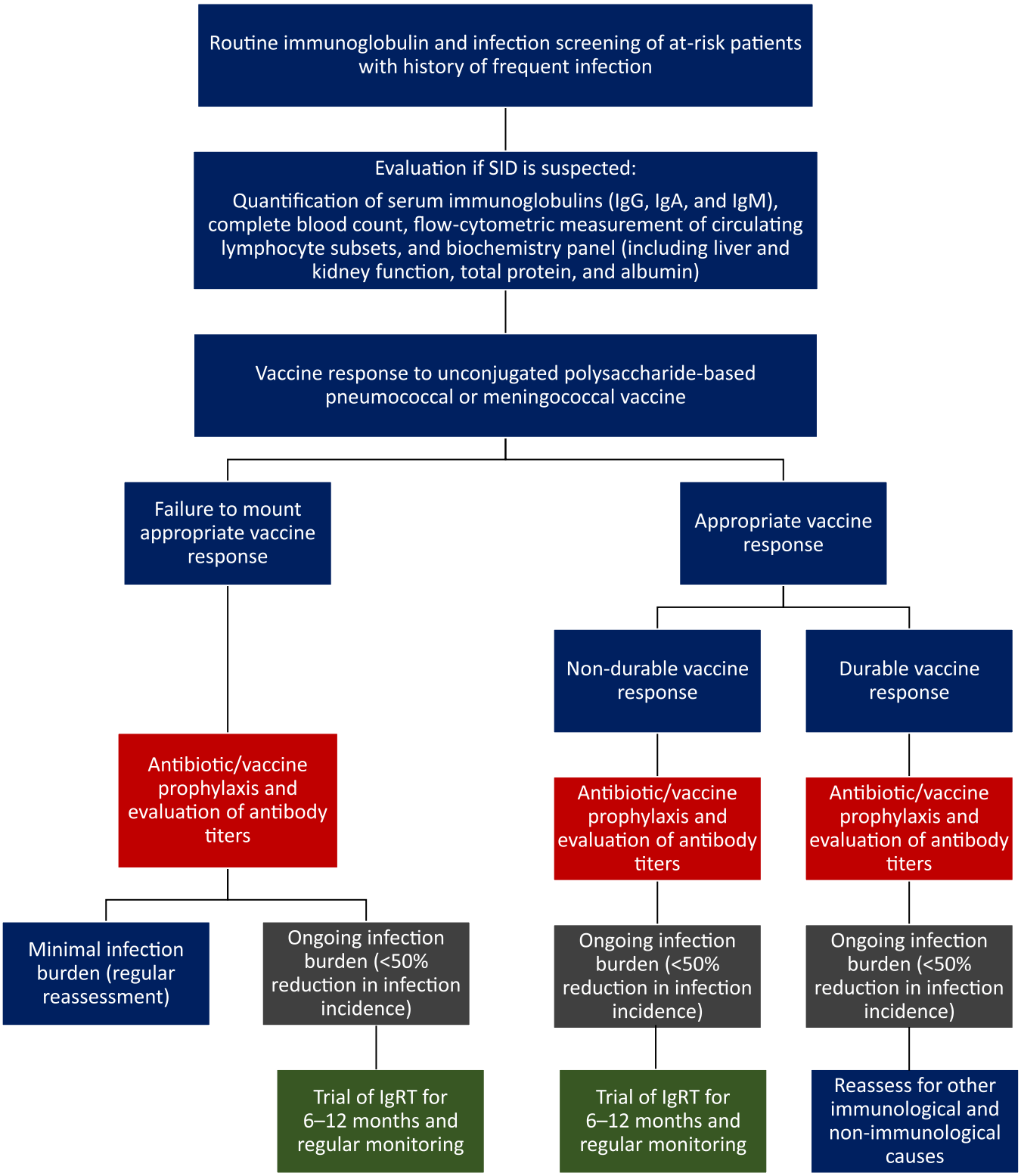

Fig. 1. SID assessment and management pathway for at-risk patients presenting with suspected hypogammaglobulinemia. Adapted from reference [3].

management may contribute to improved quality of life for Lebanese patients as well as a reduced economic burden on the healthcare system in this country.

As underdiagnosis, delayed diagnosis, and mismanagement can be detrimental to this patient population, increased awareness of SID disease burden is required for timely treatment via enhanced management guidelines and healthcare policies that optimize spending. Guidelines and recommendations based on expert opinion may help in the early identification and treatment of at-risk SID patient populations.

4. Management of SID in hematological malignancies and post-HSCT

Management of SID in the context of hematological malignancies and HSCT includes timely diagnosis, ongoing monitoring, prophylactic vaccines, antibiotics, and IgRT (Fig. 1). Antifungal and antiviral medications are also used in some cases [3].

4.1. Routine diagnostic tests and IgG monitoring

Patients with hypogammaglobulinemia secondary to hematological malignancies or HSCT can present with either clinical SID or a subtler state of antibody deficiency in which they appear asymptomatic. However, patients will still be at risk of severe infection, so prompt diagnosis and regular monitoring are crucial in reducing infection rates and disease burden; this relies heavily on physicians' awareness of the associated risk factors.

Standard evaluation for SID according to guidelines and published literature includes quantification of serum immunoglobulins (IgG, IgA, and IgM), a complete blood count (to identify neutropenia, lymphopenia, or lymphocytosis), flowcytometric measurement of circulating lymphocyte subsets (including CD4+ and CD8+ T cells, B cells, and NK cells), and a biochemistry panel (including basic liver and kidney function, total protein, and albumin) [1,4,14]. Based on the evidence obtained for PIDs, assessment of humoral immune function via test immunization response to diagnostic vaccines (specifically, unconjugated polysaccharide-based pneumococcal or meningococcal vaccine) can also be a useful tool; usually, the greater the reduction in IgG level, the greater the likelihood of impaired or non-durable vaccination response. Failure to mount a 'normal' locally defined post-immunization response or lack of a twofold rise in IgG antibody titers in vulnerable patients usually indicates the need for treatment initiation [4,14,28].

Thorough IgG evaluation is of particular importance as decreases in specific IgG subclasses can be correlated with increased susceptibility to infection, even if hypogammaglobulinemia is not apparent. In general, circulating IgG levels of <4–5 g/L are considered low in adults. [29]. Regular evaluation of immunological function in patients at high risk of developing SID may be warranted, including in patients with hematological malignancies, on cancer therapy, and post-HSCT, taking relevant regional endemic diseases into account. Routine assessment every 6–12 months and individual evaluation of suspected patients receiving immunosuppressive therapy or experiencing significant or frequent infections could assist in identifying high-risk cases before a severe infection develops [6,7].

Additional evaluations may be needed in specific patient populations. Low baseline IgG levels prior to treatment initiation are usually further suppressed with therapy modalities that target antibody formation, such as rituximab. This issue becomes of increased significance if the medication is to be used for long-term maintenance. Screening is also of use in patients with comorbidities (eg chronic heart disease, heart disease, or extra-articular rheumatoid arthritis) as the incidence of infection rises when IgG levels are low for more than 6 months [3].

In clinical practice throughout the authors' regions, SID evaluation is carried out following guidelines and the published literature; however, there are country-specific nuances to diagnostic testing that are important to note. In Turkey, all patients with lymphoproliferative disorders have their immunoglobulin levels checked at initial workup, and elderly patients at advanced stages of malignancy or with comorbidities are considered to be at higher risk of acquiring SID. However, test immunizations to identify at-risk patients are not commonly used in daily practice within Turkey; instead, physicians depend on immunoglobulin levels and history of frequent infections. In the UAE, flow cytometry is performed to measure lymphocyte subsets in those with lymphopenia, and bone marrow is examined in those with suspected bone marrow failure. In Kazakhstan, immunophenotyping of peripheral blood and bone marrow punctate with the determination of lymphocyte subpopulations is also performed. Patients are monitored on an ongoing basis, meaning that these indicators are determined before the start of therapy, during the treatment period, and after therapy discontinuation.

4.2. Infection prophylaxis

Protecting immunocompromised patients against infection by using a vaccine or antibiotic prophylaxis is a commonly missed opportunity because of the erroneous belief that treatment given to prevent disease would not work in a setting with inadequate humoral immune response. Although antibody response may not be optimal, vaccine or antibiotic prophylaxis does offer helpful antibody protection and T-cell-mediated immunity [3,29].

According to expert opinion, vaccinations should be maintained in patients before initiation of disease-specific treatment where possible and the response assessed [1,3]. Choice of vaccine prophylaxis should take individual patient considerations into account, including clinical presentation and likelihood of infection. Vaccination at an early stage, prior to chemotherapy or radiotherapy, may be helpful in generating immunological memory before more severe hypogammaglobulinemia occurs [3,12]. Although live vaccines are usually contraindicated (based on individual patient assessment), inactivated or conjugate polysaccharide vaccines prove highly immunogenic; hence, vaccinations against *Streptococcus pneumoniae* and *H. influenzae* are recommended [1,3]. Certain guidelines also recommend the routine use of inactivated vaccines in patients with MM unless they are actively receiving chemotherapy or monoclonal antibodies [30,31]. However, after vaccination, evaluation of antibody titers permits assessment of immunization efficacy while also allowing physicians to stratify patients into risk groups based on their immune response capacity. Expert recommendations state that blood should be tested 4 weeks post-vaccination; a typical response to pneumococcal capsular polysaccharide antigens has been defined as the induction of protective antibodies to 70% of the serotypes tested, with at least a twofold increase in titers [14].

The use of prophylactic antibiotics also represents a key opportunity to mitigate infection risk for SID patients with certain hematological malignancies or during immunosuppressive treatment (including chemotherapy) and neutropenia, according to experts [4]. Choice of antibiotic prophylaxis should be highly individualized to the patient, considering clinical presentation, allergies, tolerance, likelihood of infection, prevalent endemic infections, and local prescribing policy; however, indiscriminate use of antibiotics should be avoided to prevent the emergence of resistant strains [29]. Efficacy of prophylactic antibiotic therapy should be observed for 3 months initially, and ongoing monitoring may be needed for patients on long-term treatment [1]. In the event of breakthrough infections, a second course of antibiotics from a different class (eg macrolide vs penicillin or quinolone) or intravenous antibiotics may be considered, rather than increasing the dosage of the initial antibiotic [7,14,29].

Based on the authors' experience, many variances in determinants of prophylactic treatment initiation exist among countries; however, treatment goals remain similar. Current practice in Turkey permits starting antibiotic prophylaxis (usually different combinations of trimethoprim/sulfamethoxazole, quinolones, or fluconazole) according to the type of immunodeficiency, spectrum of infection risk, type of immunosuppressive treatment or chemotherapy, age, and comorbidities

of the patient. Patients who experience breakthrough infections of any origin despite effective antimicrobial prophylaxis (appropriate agent used for more than 3 months), enter an IgRT program to reduce infection-related complications. In Kuwait, use of prophylactic antimicrobial treatment is based on the underlying disease and the type of chemotherapy the patient is on, rather than infection rate or measured immunoglobulin levels. By contrast, in Lebanon, the primary determinant of prophylactic treatment is recurrent infection. After diagnostic confirmation of SID, prophylactic treatment is initiated based on local hospital microbial pathogen prevalence data, and failure of therapy is considered in cases of relapsing infection. Although there is no consensus regarding antimicrobial prophylaxis in Saudi Arabia, routine vaccinations are usually performed post-HSCT, and annual influenza vaccinations are recommended in line with local disease prevalence. In Kazakhstan, prophylactic prevention often encompasses bacterial, fungal, and viral infections. For example, patients diagnosed with CLL are given co-trimoxazole to prevent *Pneumocystis* pneumonia, and patients with MM receiving therapy with bortezomib take acyclovir for the prevention of Herpes zoster infection. Prophylactic treatments are usually taken during the main courses of chemotherapy, and peripheral blood analysis, C-reactive protein, procalcitonin, total protein and fractions, determination of immunoglobulin levels (IgG, IgA, and IgM), liver function tests, somatic status, and frequency of infection are all determined to ascertain the effectiveness of prophylactic therapy.

The authors note the need for prophylactic antibiotic and vaccine treatment in clinical practice is often justified as infection makes treatment compliance difficult, which may exacerbate the patient's somatic status and prognosis for the underlying disease. Moreover, the authors notice a lower infection rate in prophylactically treated populations, leading to lower hospitalization rates, which contribute to improved quality of life and reduced economic burden on the healthcare system. However, patients should be offered IgRT in cases of inadequate response to infection prophylaxis or treatment failure, especially when clinical signs indicate heightened susceptibility to infections [29].

4.3. Immunoglobulin replacement therapy

IgRT has become the mainstay of treatment in patients with hypogammaglobulinemia and persistent or recurrent infections despite prophylactic antibiotic therapy. IgRT is essentially a therapeutic concentrate of normal human polyclonal IgG prepared from pooled donated plasma of healthy donors. The large donor pool ensures diversity of immunoglobulin repertoire, meaning that IgRT contains an array of antibodies directed against pathogens and foreign antigens, the presence of which is crucial for the treatment of patients with humoral immune deficiencies [32].

4.3.1. Mechanism of action

IgRT has multiple modes of action thought to act synergistically in SID; it is believed to reduce the number and severity of infections via pathogen neutralization, toxin inactivation and opsonization, and complement-mediated bactericidal effects. Immunomodulatory effects induced by IgRT on cancerous B cells in hematological malignancies also have multiple mechanisms, including B-cell apoptosis, alteration of B-cell activation and proliferation, inhibition of B-cell antigen presentation, and in vitro differentiation of B cells to promote immunoglobulin secretion [7,33].

4.3.2. Route of administration

IgRT for SID patients with hematological malignancies or post-HSCT can be administered either intravenously (IVIG), subcutaneously (SCIG), or via facilitated SCIG (fSCIG) [2]. In the authors' experience, IVIG is the principal route of administration in countries such as Kazakhstan and Lebanon, where SCIG is not yet widely available. In Saudi Arabia, physicians give patients an initial dose of IVIG to assess response before considering SCIG treatment. IVIG remains a practical route of administration for treatments of short duration, often employed in hospital settings in response to severe infectious episodes or as part of the post-transplant management algorithm. However, IVIG requires trained personnel for administration, and the patient must visit the healthcare facility regularly [29].

By contrast, SCIG does not require venous access and allows for convenient self-administration at home [3,34]. Additionally, the pharmacokinetics (PK) of SCIG may be more favorable as it allows for lower IgG peak levels and higher IgG trough levels, providing patients with consistent protection against infections [9,34,35]. SCIG administration also imparts time and cost efficiencies to both patients and healthcare providers [3]. The more recent fSCIG method requires recombinant human hyaluronidase (rHuPH20) to be administered prior to IgRT preparation to permit higher IgG volumes to be infused into the subcutaneous tissue via one injection site. Patients are treated every 3–4 weeks because of increased bioavailability. [35] The efficacy of fSCIG has been studied in clinical trials in comparison with IVIG in PID, and bioavailability and infection rate reduction have been proven to be similar, with fewer systemic adverse drug reactions with fSCIG [36]. Likewise, a retrospective analysis examining fSCIG in SID with hypogammaglobulinemia had confirmatory findings [35].

In countries where SCIG has recently become available, such as Turkey, the authors are beginning to gain experience with these products and see that SCIG is a feasible route of administering IgRT. In the UAE, the authors see certain advantages in that SCIG injections bypass the difficulties with venous access for IVIG. Moreover, these formulations are administered by the patient or nurse in the home environment, which significantly relieves much-needed space in hospital infusion wards and day-care centers, especially during pandemic periods.

4.3.3. Clinical efficacy and safety data

Numerous studies conducted in the 1980–90s evaluated the efficacy and safety of IgRT prevention, specifically IVIG, against infections in CLL and MM patients. The beneficial effect of IVIG was initially demonstrated by a randomized, controlled, double-blind clinical trial conducted by the Cooperative Group for the Study of Immunoglobulin in CLL (N=81), which found that IVIG was associated with a lower incidence of bacterial infections compared with placebo, especially in patients who had completed a full year of treatment. Furthermore, the study found that IVIG treatment allowed for a longer infection-free duration than placebo [37].

Another randomized, double-blind, placebo-controlled trial (N=82) studying 400 mg/kg IVIG in plateau-phase MM patients for 12 months found a decrease in the number of severe and recurrent infections compared with placebo. Prior to treatment, patients were immunized with a pneumococcal polysaccharide vaccine, and specific IgG response was measured 4 weeks later; an inadequate response (less than twofold increase in antibodies) identified patients who were expected to gain maximum benefit from IVIG. Mild adverse reactions were noted [38]. A subsequent randomized, double-blind crossover study (N=34) comparing two doses of IVIG (250 vs 500 mg/kg) in CLL patients every 4 weeks for 12 months found decreased infection rates; however, there was no significant difference in incidence of bacterial infections between the two doses [39]. These preliminary findings indicated the efficacy of IVIG and formed the basis of guideline recommendations for IVIG prophylaxis in SID. From a cost-effectiveness standpoint, these results also revealed a need for appropriate patient selection and individualized dosing. Since then, this issue has been evaluated in observational studies and clinical trials with both IVIG and SCIG in CLL, MM, lymphoma and post-HSCT, however, heterogeneous definitions, infrequent reporting of statistical significance, and scarcity of data after the 1990s present a need for further investigation [2].

More recently, a body of evidence has been formed for fSCIG in the treatment of immunodeficiency. Initially studied in an open-label, multicenter, Phase III study in PID patients (N=89), [40] efficacy was then demonstrated in patients with immunodeficiency secondary to

hematological malignancies in a retrospective single-center analysis (N=33), which found low rates of infection and adverse drug reactions. The trial studied a dose of 0.4–0.8 mg/kg/month at 3- to 4-week intervals and concluded that fSCIG compared favorably with IVIG in the SID population [35]. A prospective, multicenter, observational study (FIGARO; N=156) aimed to provide insights on real-world utilization and tolerability of fSCIG in 3 groups of patients with PID and SID aged <18 years, 18–64 years and ≥65 years, respectively [41]. From the SID patients enrolled (n=31) and included in the analysis, indications for IgRT were CLL (n=20), indolent lymphoma (n=4), and SID due to other causes (n=7). The SID patients were distributed between treatment at home and at the hospital/doctor's office and between self-administration versus administration by a nurse/doctor. At 12 months, the proportion of the full PID and SID patient cohort infusing at home and self-administering were 85.8% and 88.2%, respectively, and regardless of age, most patients self-administered the full fSCIG dose at home every 3–4 weeks and required a single infusion site. Results demonstrated good infection control, with acute severe bacterial infections occurring in 0–9.1% of patients during follow-up visits up to 30 months; 22.9% of the PID cohort and 9.1% of the SID cohort experienced other bacterial infections at 36 months. The majority of SID patients did not report adverse drug reactions associated with fSCIG infusion; one reported infusion site inflammation, and one had severe headache at the inclusion visit. The study concluded by confirming the feasibility, tolerability, and infection control of fSCIG in PID and SID patients across the age spectrum while reinforcing the flexibility for administration in both the home-setting and medical facility [41].

Likewise, a long-term retrospective monocentric study assessed the efficacy of fSCIG in patients with PID (n=25) or SID due to hypogammaglobulinemia (n=5). The investigators concluded that self-administration of fSCIG resulted in a reduced rate of infectious events compared with the pre-treatment rate. Adverse events and local reactions were mild to moderate and did not lead to treatment discontinuation [42]. Retrospective data on the real-world use of fSCIG in elderly patients (mean age 69.9 years) with PID (n=10) or SID (n=6), who typically have a high number of comorbidities and physical challenges, found fSCIG to be a viable treatment option, whereby larger treatment volumes could be self-administered at home, similar to younger patients. Local adverse events such as redness, rash, pain at the infusion site, and bloating were reported by six patients, whereas systemic adverse events such as sleeplessness and malaise on the day of infusion were reported by two patients [43].

Reviews of overall published evidence show that IgRT is efficacious in decreasing rates of serious and recurrent infection and is generally well tolerated in hematological malignancies, with a low incidence of adverse events [2,44,45]. A recent systemic literature review found that IgRT has several beneficial effects on clinical outcomes, rate of infection, rate of hospitalization, and quality of life, ultimately decreasing the burden of SID in patients with hematological malignancies [2]. Furthermore, IgRT has proven to reduce infection rates and the risk of acute GVHD in the post-allogenic HSCT setting [46].

4.3.4. Guidelines and indications

Based on these data, current international guidelines in Western countries now indicate the use of IgRT in severe hypogammaglobulinemia (Table 1), as IVIG or SCIG may significantly decrease the number of infections and the use of antibiotics, which in turn reduces hospitalization need and disease burden. However, approved indications and implementation of recommendations are not always aligned and do vary by region. The authors note that the limited number of clinical studies, varying patient presentations, and various SID-associated infections can lead to decision-making difficulties.

The indications approved by the European Medicines Agency (EMA) for IVIG, SCIG and fSCIG in SID have widened to include patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment, and either proven specific antibody failure (failure to mount at least a twofold rise in IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of <4 g/L [47–49]. In the United States of America (USA), the American Academy of Allergy, Asthma, and Immunology recommends that patients with CLL or MM and recurrent serious bacterial infections who are hypogammaglobulinemic with subprotective antibody levels following immunization against diphtheria, tetanus, or pneumococcal infection should be considered eligible for immunoglobulin replacement therapy. [50]. Likewise, in Canada, IVIG is recommended as infection prophylaxis in adults with malignant hematological disorders associated with hypogammaglobulinemia and episodes of severe or recurrent infection

Table 1
Key features of international IgRT recommendations and indications for patients diagnosed with SID/secondary hypogammaglobulinemia.

Entity	IgRT recommendation/indication
European Medicines Agency [47–49]	IVIG, SCIG and fSCIG use permitted in: • SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment, and either proven specific antibody failure (failure to mount at least a twofold rise in IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of <4 g/L
American Academy of Allergy, Asthma, and Immunology [50]	Patients with CLL or MM and recurrent serious bacterial infections who are hypogammaglobulinemic with subprotective antibody levels following immunization against diphtheria, tetanus, or pneumococcal infection should be considered eligible for immunoglobulin replacement therapy
National Advisory Committee on Blood and Blood Products of Canada [51]	IVIG is recommended for infection prophylaxis in adults with malignant hematological disorders associated with hypogammaglobulinemia and either of the following: • A recent episode of a life-threatening infection that is reasonably thought to be caused by low levels of polyclonal immunoglobulins • Recurrent episodes of clinically significant infections (eg pneumonia) that are reasonably thought to be caused by low levels of polyclonal immunoglobulins
UK Department of Health [52,53]	Use permitted in hypogammaglobulinemia associated with non-Hodgkin lymphoma, CLL, MM, or other relevant B-cell malignancy confirmed by hematologist, AND: • Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months • IgG <5 g/L (excluding paraproteins) • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge
Australia National Blood Authority [54]	IgRT is indicated for the prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with hematological malignancies or post-HSCT, based on: • Significant hypogammaglobulinemia with serum IgG <4 g/L (excluding paraprotein) regardless of frequency and severity of infections; or • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range, with at least one life-threatening infection in the last 12 months; or • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range, with at least two serious infections in the last 6 months requiring more than standard courses of antibiotics (eg hospitalization, intravenous or prolonged antibiotic therapy)

[51]. In the United Kingdom (UK), the Department of Health recommends IgRT for hypogammaglobulinemia associated with HSCT, CLL, MM, non-Hodgkin lymphoma, or other relevant B-cell malignancies. Recommendations were recently updated to stipulate that this must be in combination with recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months, with IgG levels <4 g/L and documented failure of serum antibody response to vaccine challenge [52,53]. In Australia, IgRT is permitted for the prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with hematological malignancies or post-HSCT based on serum IgG level qualifying criteria [54].

Regional variations in SID management are also evident in the published literature and clinical practice. One study (N=230) assessing SID management in hematological malignancies among Western countries found that in Italy, Germany, Spain, and the USA, IgRT use was above average in patients with hypogammaglobulinemia. In contrast, considerably fewer patients received IgRT in the UK. Combined use of IgRT and antibiotics was more widespread in the USA than in Europe and rare in the UK. Out of the surveyed cohort, the use of SCIG was greatest in France and the USA and least in Spain and the UK. The survey also found discrepancies between clinical treatment and approved indications [34]. Variance in SID management among these regions reflects a lack of harmonized management guidelines and highlights the need for synchronization between physicians.

In the authors' experience, in Kazakhstan, physicians use a mixture of local disease-specific treatment protocols and international recommendations when making decisions and prescribing in lieu of one standard treatment algorithm for SID. In Turkey, Lebanon, and the UAE, no local guidelines regarding SID management are available; instead, various international guidelines are followed, depending on the choice or familiarity of the treating center. Available recommendations are heterogeneous and not evidence-based. Moreover, there are challenges in implementing international standards within certain countries given the different reimbursement policies and unavailability of IgRT formulations and diagnostic tests.

4.3.5. Initiation

Between the aforementioned international guidelines and indications, common criteria for initiation of IgRT include serious or recurrent bacterial infection with low serum IgG trough level in hematological malignancies and post-HSCT. The EMA, USA, and UK guidelines also usually require patients to have had failed antibiotic treatment or be unable to mount an antibody response after infection or vaccination. [5,47–49,52]. It is essential for physicians to consider which patient population is most likely to benefit from treatment, as initiation and dosing must be based on patient profile, depth of deficiency, and clinical phenotype. For example, some patients with severe deficiency but no history of infection may not require regular replacement. Thresholds for low immunoglobulin subclass levels indicating treatment initiation vary across the literature and regions; certain recommendations report that patients with low IgG levels (<4–5 g/L) should be considered as candidates for IgRT at the first sign of infection. However, the absolute threshold in the literature can vary, ranging from 5.4 to 6 g/L [2,6,29]. Some studies base treatment decisions on an 8 g/L cut-off for total combined immunoglobulin (IgG, IgA, and IgM), while others consider individual subset deficiency [2].

In the authors' clinical practice, recurrent or severe infections are the primary clinical endpoints that indicate the need for immunoglobulin testing and IgRT initiation among patients in Turkey, Saudi Arabia, Lebanon, Kuwait, and the UAE. However, the cost of treatment and insurance coverage seem to dictate this form of practice, and other endpoints are used if restrictions do not permit IgRT initiation at severe or recurrent infection. For example, IgRT is started at IgG <5 g/L in the UAE and <6 g/L in Kuwait. For countries such as Turkey, which implement health insurance coverage via national social security systems, the IgG threshold of <5 g/L for IgRT initiation in the setting of SID associated with CLL, MM, or HSCT might be extended to normal levels for patients with dysfunctional immunoglobulins via off-label application to the respective health authority. In contrast, the presence of various SID biomarkers denotes the initiation of IgRT in Kazakhstan in addition to ongoing prophylactic treatment. A holistic investigation is carried out, including a general analysis of peripheral blood, C-reactive protein, procalcitonin, total protein and fractions, determination of immunoglobulin levels (IgG, IgA, and IgM), liver function tests, somatic status, and frequency of infection.

Despite predefined IgG thresholds and biomarkers, physicians must also individualize and tailor SID management. Patients with more ambiguous profiles will need their complete clinical picture taken into consideration, including history, comorbidities, vascular risk factors, and neutrophil count [1]. Diminished severity and single episodes of specific infection may warrant early administration of IgRT before IgG levels become low [29]. For example, the authors note that in practice, some patients may have IgG levels <4 g/L with no history of recurrent infections, while others may have IgG levels >6 g/L with frequent infections; the former may not necessarily be treated with IgRT despite their low IgG levels, whereas the latter would require IgRT based on the increased infection rate. Additionally, challenges in accessibility to treatment (eg during a pandemic) mean that physicians treat patients with IgRT to maintain IgG levels >6 g/L in countries such as Kuwait, even in the absence of recurrent infection history.

IgRT has the potential to reduce the effectiveness of certain live vaccines (such as for measles or varicella) if administered shortly before or after the vaccine by inhibiting the immune response. Depending on the vaccine, it should either be administered at least 14 days prior to the IgRT, or delayed until the antibodies in the immunoglobulin concentrate or blood product have been cleared from the circulation, which could take up to 8 months depending on the content and dose of IgRT. If the interval between the administration of vaccine and subsequent IgRT is less than 14 days, or if vaccines are administered before the degradation of the replaced antibodies, it is recommended to repeat the vaccine dose after the clearance of immunoglobulins [55].

IgRT should be used with caution in high-risk patients due to potential adverse events which might result from particular components of the immunoglobulin product. Presence of anaphylactic or severe systemic allergic reactions to human immunoglobulins or other components of the individual products, IgA deficiency, or comorbidities including pre-existing cardiovascular disease, renal insufficiency, or hyperosmolarity may complicate the use of IgRT [56,57].

4.3.6. Dosing

The dose, route, and administration frequency of IgRT must be individualized to maintain IgG levels and prevent infection, and the use of clinical measures or trough IgG concentrations can guide adjustment. As a general guide according to the published literature, the IgRT dose for SID should be weight-based (with caveats for obese patients) at 0.2–0.4 g/kg over a 3- to 4-week period to maintain trough serum IgG levels within the normal range (6–8 g/L). The dosage interval when steady state has been reached should then typically be maintained at 3–4 weeks for IVIG and fSCIG, whereas SCIG is typically administered at more frequent dose intervals [47–49].

PK profile plays an essential role in optimizing therapy; clearance and trough IgG concentrations can be used to individualize dosing and frequency of IgRT. Baseline-corrected concentrations should be used to provide an accurate estimate of half-life and clearance; for example, baseline-corrected half-life is usually much shorter than uncorrected. SCIG dose should be adjusted based on the absolute bioavailability of the product determined against intravenous dosing [58]. Dosage and frequency should also be adjusted based on patient monitoring, depending on factors such as breakthrough infection, which may require an increased dose to aim for higher trough levels [47].

In the authors' clinical practice, patients are initially administered 0.4–0.5 g/kg IVIG every 3–4 weeks in Turkey. Dosing frequency is then

re-evaluated according to the number of breakthrough infections and trough IgG levels measured prior to the next IVIG infusion. In Saudi Arabia, patients receive 0.4 g/kg every 4 weeks. Trough levels are only measured if the patient shows no signs of improvement and infections persist; if trough levels prove to be low, the frequency of IgRT is increased to every 3 weeks. Similarly, in Kazakhstan, the initial dose of IgRT is 0.4–0.8 g/kg, and subsequent IgG infusions are usually then given at a reduced dose of 0.2 g/kg every 3–4 weeks for up to 6 months. In Kuwait, physicians administer 0.4–0.5 g/kg every 4–12 weeks while monitoring IgG levels and evaluating the patient's clinical status. In Lebanon, standard dosing recommendations are followed, and efficacy is assessed via measurement of IgG levels and clinical manifestations. In the UAE, MM and CLL patients with frequent infection receive 20 g IVIG every 4 weeks; however, shorter intervals are permissible in cases of breakthrough infection before the next scheduled dose, and trough levels are used to assess the reason for the breakthrough. Regarding dosing escalation, the authors often use clinical factors rather than specific biomarkers for IgRT decision making. Moreover, the authors are also beginning to gain dosing experience with SCIG in SID, given the recent availability of these products.

4.3.7. *Adverse event management*

Adverse events of IgRT can vary depending on the mode of administration and length of treatment. IVIG is commonly associated with a higher incidence of systemic adverse events in the published literature, including headaches, nausea, fever, and other symptoms that mimic hypersensitivity reactions [35]. On the other hand, reported adverse effects of SCIG are usually local, such as swelling, erythema, pain, and discomfort at infusion sites [13,35]. The use of prophylactic IgRT can lead to rare adverse events such as thromboembolism, veno-occlusive disease, and hemolysis [29,44]. Furthermore, stabilizers (ie sugars) added to IgRT products have also been implicated in the development of adverse renal events, including non-specific acute renal failure, renal dysfunction, and osmotic nephrosis [59,60].

However, the rate of systemic adverse events associated with IVIG may be mitigated by using low infusion rates to avoid delivering large osmolar loads over a short period of time. Patients must also be well hydrated prior to infusion and screened for risk factors such as renal failure, previous thromboembolic events, and hypertension [29]. Additional practical considerations specifically for patients at risk of renal failure include diluting the IgRT product to a concentration that will minimize the delivery rate to the kidney, as well as assessing renal function after each treatment [59,60]. The benefits of IgRT may outweigh the overall risk of adverse events in these cases; however, the recommended dose of IgRT must not be exceeded, and long-term surveillance is crucial [29].

The authors have identified nuances within certain countries regarding how patients are treated to pre-empt adverse events. In Saudi Arabia, IVIG is given over the course of 1 hour, and patients are premedicated with steroid and histamine (H1) blockers to reduce the risk of allergic reaction. Likewise, in Kazakhstan, physicians ensure that patients are sufficiently pre-hydrated and given low infusion rates, in accordance with local protocols and international recommendations. In Turkey, special preventative measures are taken in elderly or fragile patients with comorbidities such as renal dysfunction to reduce the risk of thrombosis and acute kidney injury. Similarly, in the UAE, reduced infusion concentrations at lower infusion rates are administered to patients with impaired renal function. Patients experiencing adverse reactions to IgRT in Lebanon are mainly given symptomatic and supportive treatment.

4.3.8. *Discontinuation*

In line with the published literature, clinical recommendations specify that patients complete a minimum of 12 months of IgRT, allowing for seasonal variation in infection frequency to gain maximum benefit and enable physicians to assess response to therapy [3,6]. This requires ongoing monitoring to review clinical changes in patient parameters and infection frequency [3]. Discontinuation of IgRT may be considered in stable patients who have achieved a clinically significant period without incidence of infection (usually 6 months), indicating that treatment has restored immunological function [6]. IgG levels and infection rates must be closely monitored during routine patient visits. If infections recur and hypogammaglobulinemia is present, IgRT may be restarted [6]. Treatment may also be discontinued in patients in whom infection is not effectively prevented after a suitable period. [3].

Within the authors' clinical practice in Turkey and the UAE, discontinuation or intermittent interruption of IgRT is usually permitted in stable patients once the underlying disorder is treated and immune status is improved. Physicians usually assess this after at least 6 months without infection and trough levels are confirmed to be >6 g/L. In Kazakhstan, 12-month IgRT courses are not always viable because of the high cost of treatment; instead, physicians usually trial patients on IgRT for 6 months. After treatment discontinuation, patients are monitored at follow-up appointments scheduled at least 2–3 times a year for 3–5 years, at which the status of the underlying disease is assessed via the evaluation of biomarkers to aid in correcting immunodeficiency states.

5. Conclusions

SID associated with hematological malignancy and post-HSCT is a complex condition with substantial prevalence and burden. With a rise in novel therapies being developed to treat these conditions, targeting the immune system and increasing life expectancy, physicians can expect to see a concomitant increase in fragile SID patients at an advanced age or with complex comorbidities in daily practice. Furthermore, greater numbers of patients with lymphoproliferative disorders suffering from SID-associated infections may occur, resulting from the use of newer immunotherapeutic agents, which can cause impaired cellular and humoral immune responses. If SID is not recognized early or adequately managed, the disease can give rise to severe and recurrent infections, which then contribute to substantial morbidity and mortality [2]. Moreover, the effects of SID can be highly detrimental to a patient's quality of life, and comorbidities can hinder daily activities.

Given the diverse etiology of the disease, physicians will need to proactively anticipate and recognize SID to ensure that missing of telltale infections, which commonly leads to delayed diagnosis and intervention, does not occur. Improved screening of at-risk patients, such as regular and ongoing monitoring of biomarkers that indicate infection risk, immunoglobulin quantification, complete blood count, and an extensive biochemistry panel, will be crucial in identifying and stratifying patients most likely to require or benefit from intervention.

IgRT (with or without prior infection prophylaxis) to maintain adequate IgG levels remains an effective method for at-risk patients diagnosed with SID to decrease infection risk, hospitalization, and mortality [2,3]. Moreover, novel routes of SCIG administration result in significant advantages with regards to PK and IgG control, venous access, and adverse events compared with traditional IVIG infusions [3,34,35].

However, discrepancies and gaps in the initiation, dosing, monitoring, and discontinuation of treatment are evident within the published literature, international guidelines, and regional practice, which ultimately limit the physician's ability to manage at-risk patients. Harmonization among countries in Turkey, the Middle East, Asia, and the West is urgently needed to optimize SID patient care and help clinicians make evidence-based decisions in their clinical practice to better utilize available therapies.

From an economic standpoint, the high cost of IgRT can act as a deterrent for patients and payers in the authors' regions; this is heightened for those uninsured or in countries where public funds are unavailable. High treatment costs mean that complete treatment protocols are not always viable, and treatment is often discontinued early,

leading to suboptimal outcomes. However, the authors believe that the benefits of IgRT outweigh the costs for this vulnerable patient population, and efforts must be made to improve access to treatment.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MCA has received honoraria from Takeda and CSL Behring. REF has received consultancy and speaker fees from Roche, Janssen, Novartis, Biologix, Newbridge, Gilead, BMS, MSD, Abbvie, Kyowa Kirin, Hikma, Pfizer, Sanofi, Servier, Amgen, Takeda, and AstraZeneca. MM has received honoraria and speaker fees from Amgen, Roche, Sanofi, Janssen, Takeda, AstraZeneca, Bristol-Myers-Squibb, Servier, Pfizer, Bayer, Sobi, Alexion, Novo, Novartis, Sandoz, Abbvie, and Astellas. SG, AA, FN, AA, and NS have no conflicts of interest to disclose.

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