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Recommendations for Management of Secondary Antibody Deficiency in Multiple Myeloma

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Abstract

Secondary antibody deficiency (SAD) is a subtype of secondary immunodeficiency characterized by low serum antibody concentrations (hypogammaglobulinemia) or poor antibody function. SAD is common in patients with multiple myeloma (MM) due to underlying disease pathophysiology and treatment-related immune system effects. Patients with SAD are more susceptible to infections and infection-related morbidity and mortality. With therapeutic advancements improving MM disease control and survival, it is increasingly important to recognize and treat the often-overlooked concurrent immunodeficiency present in patients with MM. The aims of this review are to define SAD and its consequences in MM, increase SAD awareness, and provide recommendations for SAD management. Based on expert panel discussions at a standalone meeting and supportive literature, several recommendations were made. Firstly, all patients with MM should be suspected to have SAD regardless of serum antibody concentrations. Patients should be evaluated for immunodeficiency at MM diagnosis and stratified into management categories based on their individualized risk of SAD and infection. Infection-prevention strategy education, early infection reporting, and anti-infective prophylaxis are key. We recommend prophylactic antibiotics or immunoglobulin replacement therapy (IgRT) should be considered in patients with severe hypogammaglobulinemia associated with a recurrent or persistent infection. To ensure an individualized and efficient treatment approach is utilized, patient's immunoglobin G concentration and infection burden should be closely monitored throughout treatment. Patient choice regarding route and IgRT treatment is also key in reducing treatment burden. Together, these recommendations and proposed management algorithms can be used to aid physician decision-making to improve patient outcomes.

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Background

Secondary immunodeficiency (SID) is a broad term used to describe a diverse group of acquired conditions that affect normal functioning of the immune system.[1] SID can arise from a wide range of noninherited factors including malnutrition, infections (eg, human immunodeficiency virus), metabolic disorders, malignancies such as hematological malignancies (HMs), and therapies (including various cancer treatments).[1,2] A common subtype of SID is secondary antibody deficiency (SAD).[1] SAD is characterized by low serum antibody (immunoglobulin [Ig]) concentrations due to decreased antibody production and/or impaired levels of functional antibodies, predisposing individuals to serious and life threatening infections (bacterial, viral, or fungal), eg, sinopulmonary infections predominantly caused by bacteria.[3-5] Five classes of Ig are produced by plasma cells, typified by their heavy chains; namely IgD, IgG, IgA, IgM, and IgE, with IgG having the highest serum concentration.[6,7]

SAD can be caused by low concentrations of IgG, IgA, and/or IgM (hypogammaglobulinemia) or decreased functionality of Ig (dysgammaglobulinemia or specific/functional antibody deficiency) or a combination of both; both may be caused by various disease- and/or treatment-related mechanisms.[1,3,8] Disease-related SAD is common but likely underestimated in patients with HMs.[1,8] It can arise due to the multiple impacts of the presence of malignant B cells on normal B cells, T cells, antigen-presenting cells, and other immune defense pathways.[1,8] Treatments which are commonly used in B cell HMs, such as monoclonal antibodies against CD38 and B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell (CAR T) therapy, can result in treatment-related SAD as a consequence of their impact on B- and T-cell targets.[1,4,8-10]

Patients with SAD are more susceptible to recurrent, persistent, and/or severe infections, increasing the risk of infection-related morbidity and mortality than those without SAD.[1,4,11] To better understand the infection risk in patients with SAD, early assessment of IgG concentrations at SAD diagnosis and continued monitoring throughout the disease course is key to ensure suitable treatment and infection prevention strategies are established and adapted as needed. Infection-prevention strategies include hand washing, safe food preparation, avoiding close contact with people who are sick, wearing masks to prevent the spread of respiratory infections (eg, influenza, coronavirus disease 2019 [COVID-19]), and reporting early signs of infection to healthcare practitioners (HCPs). Although SAD and infection risk are increasingly recognized and acknowledged by HCPs, a need for greater awareness and structured collaboration persists across specialties, including hematologists/oncologists. Consequently, SAD management in HMs, including chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM), is often overlooked and remains an area of unmet need. Recently, a SAD treatment and management European expert consensus was published to provide recommendations and management algorithms for physicians, focusing on early monitoring, risk stratification, and treatment with anti-infective agents or, in selected cases, Ig replacement therapy (IgRT), in patients with HMs.[12]

Here, we focus on SAD management in patients with MM, in whom SAD and/or functional antibody deficiency is common.[1] Indeed, immunoparesis (reduction in Ig concentrations not associated with the patient's specific myeloma variant [uninvolved Ig]) is observed in patients with MM and patients with precursor plasma cell disorders such as monoclonal gammopathy of undetermined significance (MGUS). Immunoparesis has been found to occur in 24% to 40% of MGUS cases,[13,14] 53% of smoldering multiple myeloma (SMM) cases,[14] over 90% of newly diagnosed MM cases,[15] and in 75% of plateau phase myeloma cases.[16,17] Although the incidence of immunoparesis is fewer in patients with MGUS than patients with SMM or MM, some studies have suggested that MGUS patients are at an increased risk of bacterial infections, which may potentially be related to underlying SAD.[18] Therefore, patients with MGUS may represent a larger population who could benefit from SAD assessment and management, more than previously thought. Furthermore, the evolution of novel treatment strategies to prevent progression of high-risk SMM to MM may increase treatment-related SAD in these patients with SMM.[19,20] Consequently, all patients across the disease spectrum of MM should be considered at risk of SAD, and therefore potentially at increased risk of infections.

Infections continue to be a major cause of morbidity and mortality in patients with MM and plasma cell disorders,[21] with one study finding that approximately 45% of all early deaths in patients with MM were attributable to infection.[22] Consequently, standardized strategies need to be developed for early detection, prevention, and management of infections. Strategies to reduce infection-related mortality are multimodal and IgRT is only one of many modalities. Due to their parallels in disease pathophysiology, and diagnostic and treatment approaches, specific recommendations for management of CLL and NHL are addressed together in a separate publication.[23] However, as MM has unique physiology, diagnostics, and management strategies, this review will provide distinct recommendations for management and treatment of SAD in patients with MM.

Purpose of This Review

This review aims to provide international expert opinion and practical recommendations for patients with MM and SAD, including SAD diagnosis and treatment to aid physician decision making to improve patient outcomes.

Methodology and Approach

This review builds upon the recently published 2021 European expert consensus by Jolles et al.[12] which used a Delphi exercise and extensive published literature. In addition, this review incorporates additional disease-specific perspectives from a meeting of a multidisciplinary international panel of experts in immunology, hematological oncology, and infectious diseases.

During this meeting, the expert author panel assessed and refined each statement, extending the expert opinion statements, using a stepwise approach until a consensus was reached. A minimum consensus of >70% was used. Together, these published and novel statements were used to develop SAD management algorithms that can be used as a tool in clinical practice. Unless noted by reference

to a published study, guideline, or expert opinion article, the recommendations reflect those of the expert author panel.

Multiple Myeloma

MM is the second most common HM, with an estimated incidence of 7.1 and 4.5 to 6.0 cases per 100,000 people per year in the United States and Europe, respectively.[24,25] In general, MM is marginally more common in men than in women and is most frequently diagnosed in patients aged between 65 and 74 years (median age 65-69 years). As MM is considered a disease of older age, patients often have multiple comorbidities, including diabetes mellitus, cardiovascular disease, renal impairment, or pulmonary disease, which are associated with increased risk of mortality. Common symptoms of MM include bone pain, pathologic fractures, anemia, hypercalcemia, renal failure, and infections.

MM is a clonal disorder characterized by the accumulation of malignant mature plasma cells in the bone marrow (and sometimes also with extramedullary involvement) and the production of an abnormal monoclonal paraprotein, named the M protein.[26] Subtypes of MM can be determined by their cytogenetic abnormality; with high-risk MM defined by the presence of t(4;14), t(14;16), t(14;20), deletion 17p, gain 1q or p53 mutation.[27] Consequently, the clinical presentation of MM is highly heterogenous, with a patient's clinical course and prognosis highly influenced by their MM subtype.

Evolution of Plasma Cell Disorders to Multiple Myeloma

MM is consistently preceded by the asymptomatic premalignant plasma cell disorder MGUS and each year approximately 1% of all patients progress from MGUS to MM. This suggests that many MGUS cases can go undiagnosed or do not evolve to a symptomatic malignancy.[28,29] MGUS incidence increases with advancing age and is characterized by serum M-protein levels (IgG or IgA) <30 g/L, clonal bone marrow plasma cells <10%, and absence of end-organ damage.[30,31] A study conducted in France deduced that the world standardized incidence rate for MGUS was 3.76 ± 0.26 per 100,000 and that incidence also increased with age.[32] Currently, in the United States the estimated incidence of patients with MGUS by age 50 years is 120 per 100,000 for men and 60 per 100,000 for women; increasing to 278 per 100,000 for men and 188 per 100,000 for women by age 70 years (Table 1).[33]

SMM is a more advanced disease stage than MGUS and is considered an intermediary stage that can progress to active MM. SMM is an asymptomatic stage characterized by serum M-protein levels (IgG or IgA) ≥30 g/L, urinary monoclonal protein ≥500 mg over 24 hours, clonal bone marrow plasma cells between 10% and 60%, or no myeloma-defining events ie, the so-called CRAB criteria (CRAB: C-hyperCalcemia, R-Renal impairment, A-Anemia, B-Bone lesions related to MM).[20,30] The current estimated incidence of SMM in the United States is 0.4 to 0.9 per 100,000, although this may be an underestimation due to the asymptomatic nature of the disease. Over the first 5 years, SMM progresses to MM at a rate of 10% per year, before typically declining to 3% per year for the following 5 years.[34] This rate of progression to MM is influenced by cytogenetic factors; patients with t(4;14) translocation, del(17p), and gain(1q) are at a high risk of progression from MGUS or SMM to MM.[44,45] Furthermore, a recent literature review highlighted that gut microbiota can modulate cancer immunity and may have an impact on the progression of asymptomatic MGUS and SMM to symptomatic MM disease.[46] However, currently there are no risk stratification models available to accurately predict the risk of progression to MM.[19]

Treatment of Multiple Myeloma

The treatment landscape for MM has changed dramatically over the last 10 years. The advent of new, highly-effective therapies, such as proteasome inhibitors (eg, bortezomib, carfilzomib, ixazomib); immunomodulatory drugs (eg, lenalidomide, pomalidomide); monoclonal antibodies (eg, daratumumab, elotuzumab, and isatuximab); and BCMA-targeted therapeutics, including antibody-drug conjugates, CAR T therapies (eg, lisocabtagene maraleucel and ciltacabtagene autoleucel), and bispecific T-cell engagers (eg, teclistamab); have improved survival and response rates in patients with MM.[47–51] These new therapies have a variety of mechanisms of actions to target MM, for example, proteasome inhibitors block proteasomes from clearing damaged or unwanted proteins from cells, a process that myeloma cells are more dependent on compared with normal cells; the build-up of unwanted proteins consequently results in cell death.[52] The mechanism of action of immunomodulatory drugs can involve the inhibition of proliferation and promotion of apoptosis directly within the cancer cell, and immunomodulatory regulation of stimulation of CD4+ and CD8+ T-cells.[53] Monoclonal antibodies, such as anti-CD38 agents, have several mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct cellular apoptosis.[54,55] As CD38 is expressed in many immune cell types, including monocytes, bone marrow progenitors, natural killer cells, and activated T- and

Table 1 Incidence and Prevalence Rates of MGUS, SMM, and MM and the Estimated Frequency of Hypogammaglobulinemia Within These Populations[20,24,31,33–36].

Disease	Median age at Diagnosis	Incidence Rates (per 100,000)	Prevalence (%)	Hypogammaglobulinemia Frequency (%)
MGUS	70[37]	60-120 at 50 years[33] 188-278 at 80 years[33]	1.7 at 50-59 years[35] 6.6 at >80 years[35]	25-29[35,36,38]
SMM	62-67[39,40]	0.4-0.9[39]	NR	45-83[34,41,42]
MM	69[24]	7.1[24]	0.8[24]	Up to 90[15,43]

Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; NR = not reported; SMM = smoldering multiple myeloma.

B- lymphocytes, off-target effects are common.[55,56] BCMA is restrictively expressed on normal and malignant plasma cells, which makes it an attractive target antigen for novel MM therapies.[57] Bispecific T-cell engagers are molecules with dual binders, one targeting part of a cancer cell and the other binding to CD3 on the surface of T cells to enable immune activity against the cancer, for example, teclistamab binds to both BCMA and CD3.[58] Many novel agents target aspects of the immune system and as a result, increased risk of infections is a concern with many treatment options for MM,[9] for example, BCMA-CD3 directed bispecific antibodies, such as the recently approved teclistamab, have a high incidence of serious infections; the incidence of these infections are expected to increase as BCMA-targeted therapies move to earlier lines of therapy.[59]

Currently, MM is associated with a 5-year relative survival of 55.6%. Overall survival for both younger patients with MM (between the ages of 60-70 years)[60] and patients over 65 years[61] has improved significantly over the past few decades, attributable to both the use of one or more new agents in initial therapy and improvements in supportive care measures.[60,61] A recent analysis from Sweden looked at survival in a 4-year period (between year 1 after MM diagnosis and year 5) and found that the relative 1- and 5-year survival increased constantly, with the main survival gain being apparent in the first year after diagnosis.[62]

Treatments are often given as doublet, triplet or in some cases quadruplet regimens, with treatment choice depending on a patient's age, individualized risk (standard or high risk), disease stage, comorbidities, treatment history, and eligibility for stem-cell transplantation.[26,47,48] Eligibility for autologous hematopoietic cell transplantation (auto-HCT) varies across centers but typically depends on patients' age, presence of comorbidities, and performance status.[25,26,63] In addition, the availability of drugs, based on regulatory body approvals and reimbursements in different countries, can greatly influence which treatment is given to patients with MM.[26,47] The current standards of care in MM and effective treatments for patients with MM are summarized in Table 2 and Table 3. Time will tell if the newer available treatments, such as BMCA, will become standard of care treatments and if the risk of infection is considered just an acceptable adverse event in comparison with their anti-cancer efficacy.

Despite recent advances in the treatment of MM, patients may relapse or become refractory to treatment. For patients with relapsed/refractory MM, the treatment options depend on many factors, including the number of prior lines of therapy, previous response to therapy, therapy-related toxicity, and aggressiveness of the relapse. A full description of available treatments for patients with relapsed/refractory disease are outlined in the National Comprehensive Cancer Network® guidelines.[80]

Secondary Antibody Deficiency in Multiple Myeloma
Incidence and Causes of Secondary Antibody Deficiency in Multiple Myeloma and its Precursors

Across the disease spectrum of MM, certain patients may be at greater risk of experiencing immunodeficiency. Indeed, studies have shown that hypogammaglobulinemia is observed in up to 29% of all MGUS cases[35,36] and in 45% to 83% SMM cases (Table 1).[34,41] Consequently, patients with MGUS or SMM may have an increased susceptibility to infection. A population-based study demonstrated that patients with MGUS have a significantly increased risk of bacterial (eg, pneumonia, endocarditis, meningitis), and viral (influenza and herpes zoster) infections compared with controls ($p < .05$); with the highest risk of infections observed in patients who had M-protein concentrations over 25 g/L at diagnosis.[81]

In MM, hypogammaglobulinemia may occur in up to 90% of patients depending on MM subtype (Table 1).[15,34,35,43,82] Data from a UK randomized trial investigating antibiotic prophylaxis demonstrated that, at diagnosis, polyclonal IgG, IgA, and IgM concentrations were lower than the normal reference range reported by the Protein Reference Units, in 71%, 83%, and 90% of patients with MM, respectively.[83] The increase of monoclonal paraproteins and proliferation of tumor cells in the bone marrow, which inhibit B-lymphocyte function and prevent normal hematopoiesis, can lead to disease-mediated SAD.[8] The clonal expansion of plasma cells can also inhibit immune function and prevent cytokine regulation of immune cells such as neutrophils, dendritic cells, and follicular T-helper cells (CD4-positive T cells found in B-cell follicles of secondary lymphoid organs), impairing immune responses and increasing infection risk.[8] SAD can also arise in patients with MM due to altered activity of immune checkpoints and T-cell exhaustion, resulting in a reduction in proliferation and functionality of T cells that provide help to B cells.[8]

Although the advent of novel, effective therapies has improved survival for patients with MM, many of these treatments, given their immunosuppressive nature, can also affect normal immune function, leading to hypogammaglobulinemia/dysgammaglobulinemia.[3,84,85] Furthermore, treatment related SAD may occur in patients with high-risk MM who are treated early to prevent disease progression to MM.[19,20] The wide range of treatments for MM that can induce SAD and associated typical infections are shown in Table 3.

A Lack of Routine Secondary Antibody Deficiency Diagnostic Assessment in Multiple Myeloma

The diagnostic criteria for MM are outlined by the International Myeloma Working Group.[30] It is noteworthy that none of the criteria for MM, SMM, or MGUS diagnoses or staging currently include routine diagnostic assessment of SAD.

A Management Algorithm for Secondary Antibody Deficiency
Early Monitoring of Secondary Antibody Deficiency and Infections

Patients with MM often experience a significant burden of recurrent, persistent, and/or severe infections, definitions that have been previously delineated and published by Jolles et al.[12] in a recent European expert consensus focusing on SAD in HMs. Briefly, a "severe infection" is defined as one that requires immediate or prolonged hospitalization, or emergency or intensive care treatment. A "persistent infection" is defined as one that is caused by the same microbe, and which does not improve despite appropriate selection and duration of the anti-infective treatment. "Recurrent infections"

Table 2   **Current Standard of Care and New Approved First-Line Regimens in Different MM Types[28,47].**

Myeloma type	Current Standard of Care First-Line Regimens	Recently Approved First-Line Regimens
Low-risk SMM	Observed without therapy every 3-4 months[64]	
High-risk SMM	Lenalidomide with/without dexamethasone for 2 years[64]	
Newly diagnosed standard risk MM in patients eligible for HCT	Triplet regimen: VRd followed by auto-HCT and lenalidomide maintenance[65] Triplet regimen: VRd followed by delayed auto-HCT, therefore additional VRd, lenalidomide plus dexamethasone until progression[65] Triplet regimen: bortezomib/cyclophosphamide/dexamethasone	Doublet regimen: lenalidomide/dexamethasone[66] Triplet regimen: bortezomib/doxorubicin/dexamethasone[66] Triplet regimen: bortezomib/thalidomide/dexamethasone[66] Quadruplet regimen: dara-VTD[66]
Newly diagnosed high-risk MM in patients eligible for HCT	Triplet regimen: CRd Triplet regimen: IRd Triplet regimen: VRd followed by auto-HCT[65] Quadruplet regimen: daratumumab plus VRd, followed by auto-HCT then bortezomib-based maintenance[47]	Triplet regimen: CyBorD[66]
Newly diagnosed standard risk MM in patients ineligible for HCT	Lenalidomide[65] VRd followed by lenalidomide maintenance Doublet regimen: lenalidomide plus dexamethasone[65] Triplet regimen: VRd[65] Triplet regimen: DRd[65]	Triplet regimen: VMP[66] Triplet regimen: MPT[66] Triplet regimen: MPR[66] Quadruplet regimen: dara-VMP[66]
Newly diagnosed high-risk MM in patients ineligible for HCT	VRd is recommended followed by bortezomib-based maintenance Triplet regimen: VRd followed by proteasome inhibitor Doublet regimen: lenalidomide/low-dose dexamethasone Doublet regimen: bortezomib/dexamethasone Triplet regimens: bortezomib/cyclophosphamide/dexamethasone; VMP; D-VMP	Triplet regimen: CyBorD[66]
Regimens after first-line		
Patients with one prior therapy	Lenalidomide/dexamethasone-based regimen Pomalidomide/dexamethasone-based regimen Venetoclax with bortezomib/dexamethasone[a]	
Patients with two or more prior lines of therapy	Venetoclax with bortezomib/dexamethasone[a]	
Patients with three or more prior lines of therapy	Selinexor/dexamethasone	
Patients with RRMM, with four or more prior lines of therapy	BCMA-directed (or other MM antigens) autologous CAR T therapy	

[a] To be considered in MM patients with translocation of chromosomes 11 and 14 only. Abbreviations: BCMA = B-cell maturation antigen; CAR T = chimeric antigen receptor T-cell; CRd = carfilzomib/lenalidomide/dexamethasone; CyBorD, bortezomib/cyclophosphamide/dexamethasone; dara-VMP = daratumumab/bortezomib/melphalan/prednisone; dara-VTD, daratumumab/bortezomib/thalidomide/dexamethasone; DRd = daratumumab/lenalidomide/dexamethasone; D-VMP = daratumumab plus bortezomib, melphalan and prednisone; HCT = hematopoietic cell transplantation; IRd = ixazomib/lenalidomide/dexamethasone; MM = multiple myeloma; MPR = melphalan/prednisone/thalidomide; MPT, melphalan/lenalidomide/dexamethasone; RRMM = relapsed/refractory multiple myeloma; SMM = smoldering multiple myeloma; VMP = bortezomib, melphalan and prednisone; VRd = bortezomib/lenalidomide/dexamethasone.

are defined as clinically documented infections (such as sinusitis, pneumonia, or cellulitis) occurring after the resolution of the prior infection with appropriate anti-infective treatment.[12,23]

In patients with newly diagnosed MM, infections are common, with one study observing infections in 78.3% of patients during their first hospitalization with newly diagnosed MM.[86] A study by Blimark et al.[85] demonstrated that patients with MM have a 7-fold higher risk of infections overall compared with matched controls, with 7- and 10-fold higher risk of bacterial and viral infections, respectively. In the first year after MM diagnosis, the risk of infections is much greater, with bacterial infections 11-fold higher than matched controls and viral infections 18-fold higher compared with controls.[85] Usually, bacterial infections are more responsive to treatment compared with viral infections (except for herpes simplex

viruses and varicella-zoster virus). A study conducted in the United States using the National Inpatient Sample database, which tracks 20% of national admissions and gives weighted estimates on total number of hospitalizations, demonstrated that 47.8% of patients hospitalized with MM died with infections (n = 41,063 infections; n = 85,816 hospitalizations). Additional data from a UK retrospective 6-month landmark analysis demonstrated that overall survival was significantly shorter in patients with infection compared with those without infection, both in the case of any-grade infection (23.0 vs 44.7 months, respectively [$P = .0838$]) and >grade 3 infections (17.7 vs 43.8 months, respectively [$P = .0176$]).[87] This study further confirms that infections are a major cause of death in patients with MM and therefore warrants efforts to improve early detection of potential immunodeficiency.[22,88]

Table 3   **MM Treatments, the Associated Impact on Immune System, and the Ensuing Infection Risk.**

Class	Examples	Reported immune effects
Anti—plasma-cell monoclonal antibodies	Anti-CD38 (eg, Daratumumab, Isatuximab) Elotuzumab (anti-SLAMF7)	• Decreased plasma cells can lead to increased infection incidence[67] • Hypogammaglobulinemia[67,68] • Increased risk of neutropenia and lymphocytopenia[69]
Alkylating agents	Cyclophosphamide Melphalan Bendamustine	• Immunosuppression may lead to hypogammaglobulinemia which is associated with increased infection risk[70]
BCMA-targeted therapeutics	Idecabtagene vicleucel (Ide-cel) Ciltacabtagene autoleucel (Cilta-cel) Teclistamab Talquetamab	• Hypogammaglobulinemia[71] • High incidence of serious infections[59]
HCT	Allo- and auto-HCT	• Hypogammaglobulinemia; particularly associated with GVHD[72] • Lymphopenia during recovery and engraftment
Immunomodulatory drugs	Lenalidomide Thalidomide Pomalidomide	• Increased infection incidence (mechanism remains unclear)[73–75]
Proteasome inhibitors	Bortezomib Carfilzomib Ixazomib	• Decreased plasma cells and decreased cytotoxic T-cell and natural killer cell proliferation can lead increased incidence of grade 3 adverse events and herpes zoster infections[76] • Suppression of polyclonal Ig's, leading to an increased relative risk of serious infections up to 40%[77] • Maintenance therapy is associated with higher incidences of grade 3-4 infections[78]
Steroids	Dexamethasone	• High dose associated with an increased infection risk; Increased infection incidence when used within triplet regimens[79]

Abbreviations: BCMA = B-cell maturation antigen; CAR T = chimeric antigen receptor T-cell; GVHD = Graft-vs-host disease; HCT = hematopoietic cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; SLAMF7 = signaling lymphocytic activation molecule family member 7.

In patients with MM, infection risk peaks in a bimodal distribution throughout the MM disease course with peaks generally linked to treatment types known to be risk factors (Figure 1). This was demonstrated in a longitudinal cohort study which found that, following diagnosis, the incidence of bacterial infections in patients with MM peaked at around 4 to 6 months and 70 to 72 months, and viral infections peaked at around 7 to 9 months and 52 to 54 months. In the same study, increased risk of infection was observed in patients treated with certain chemotherapy regimens (melphalan and cyclophosphamide), in patients treated with intensive combination systemic chemotherapy, and in patients with higher cumulative doses of corticosteroids.[84] In patients with progressive end-stage disease, infection risk is greater and reflects immunosuppression following multiple lines of therapy and intensive salvage therapy.[84] This further highlights the importance of assessing infection risk in newly diagnosed cases of MM, as well as in later stage disease or in patients with relapsed or refractory MM when certain treatment regimens are utilized.

Recommendation: Improving awareness around the significant infection burden in patients with MM is critical to promote a more proactive approach in terms of intervention by HCPs. In patients with MM, we recommend that a SAD management plan should be part of a patient's overarching treatment regimen. As treatment regimens are often complex and there are currently no unified guidelines for treating patients with SAD and MM, a collaborative and individualized approach supported by a multidisciplinary team is preferred; the different treatment options must be discussed with

the patients, taking their preferences into account.[3] Furthermore, patients should be educated on their increased infection risk and encouraged by HCPs to adopt measures and changes in behavioral patterns to mitigate those risks. These may include simple measures such as attention to hygiene (eg, frequent hand washing), reducing exposure to sick people and large crowds where possible, use of masks, and being up to date with both seasonal vaccinations (eg, influenza) and vaccinations for pneumococcus, diphtheria/tetanus/pertussis, and COVID-19. In addition, if a patient has any signs or symptoms of infection such as temperatures above 37.8 degrees centigrade/Celsius (100.0 Fahrenheit) or patients experience chills, they should contact their clinical team. The clinical team should carefully monitor the patients' symptoms, and attempt to identify and treat the source of the symptoms, as well as assess their response to treatments.

Infection Risk Factors

Several assessments and patient measures are available to evaluate a patient's risk of infection. Methods to stratify patients into low-, medium-, or high-risk categories may be based on a framework of known risk factors, laboratory results, infection history, disease characteristics, patient demographics, and treatment effects. A recent study demonstrated that a number of factors pre-SID diagnosis (12-month baseline timeframe) were predictive of severe infections post-SID diagnosis, including the number of hospitalizations, antibiotic use, and ≥3 prior infections. Key risk factors for infection are highlighted in Table 4.

Figure 1 Infection risk throughout the patient journey from diagnosis through multiple lines of therapy[84,79,89].
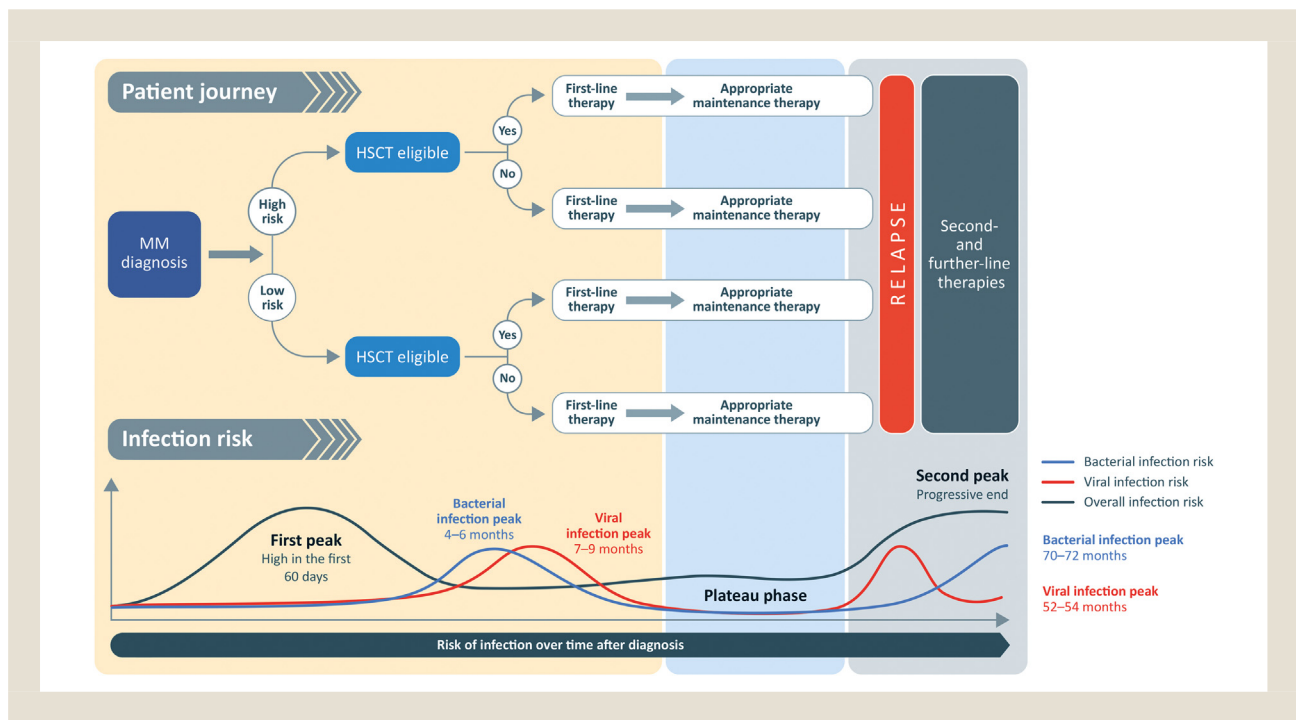
Abbreviations: HCT = hematopoietic cell transplantation; MM = multiple myeloma.

Table 4 List of Potential Infection Risk Factors in MM.

SAD Risk Factors in MM

- Increasing age
- Disease stage (ISS stage [higher risk with later stages of disease])
- Disease status (relapsed/refractory higher risk than newly diagnosed)
- Number of prior treatment lines (1, 2, >3)
- Comorbidities (frailty, performance status, nutrition, diabetes mellitus, smoking, renal impairment, COPD)
- Use of B-cell targeting therapies
- CAR T therapy
- Severity of hypogammaglobulinemia (<4 g/L)
- Degree of antibody deficiency (hypogammaglobulinemia [only IgG decreased] vs panhypogammaglobulinemia [IgG, IgA, and IgM decreased])
- Prior infections and infection-related hospitalizations
- Poor response to vaccines

Abbreviations: CAR T = chimeric antigen receptor T-cell; COPD = chronic obstructive pulmonary disease; Ig = immunoglobulin; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; ISS = international staging system; MM = multiple myeloma; SAD = secondary antibody deficiency.

Additional known risk factors for infection in patients with MM include disease stage and time from diagnosis (ie, higher in the first year and during end-stage disease), type of treatments (ie, transplant-eligible patients are at a high risk of infection immediately after HCT), and the number of prior lines of therapy (ie, patients treated with multiple lines of therapy are at the greatest risk of infection)[47] (Figure 1; Table 4). For example, patients with newly diagnosed MM who are eligible for HCT are at significant risk of infection during their initial therapy.[22] Data from a Danish nationwide population-based myeloma database showed that in the first 180 days after diagnosis, 22% of patients (n = 330) died, with 50.9% (n = 212) of these deaths attributable to infection.[90] The study concluded that high-tumor burden combined with severe infections and impaired renal or liver function can lead to early death.[90] Additional data from UK Medical Research Council Trials between 1980 and 2002 showed that early mortality (≤60 days post-diagnosis) occurred in 10% of all patients with newly diagnosed MM; of which 45% were attributable to infection.[22] However, in both these studies, immunologic evaluations for SAD were not performed.

Recommendation: To prevent early death from infections in newly diagnosed patients with MM, assessing for SAD and starting appropriate anti–infective therapies early, such as prophylactic antibiotics, would be beneficial although additional clinical evidence is needed. In addition, the use of antiviral prophylaxis, eg, for herpes virus infections, is recommended particularly when T cell immunity is

impaired and such infections are encountered; meanwhile, both impaired T cells and neutrophils may also increase the risk of fungal infection. The degree of these impairments will vary due to numerous risk factors, therefore individualization is recommended (Figure 1).

Patient-specific factors are also known to increase the risk of infection and include characteristics such as older age, gender, advanced disease, and certain comorbidities.[11,84] Infection risk is also associated with exposure to bacterial or viral pathogens, which can be more common in multigenerational households and those with young children.[91]

All therapies, including both old and new drug regimens for patients with MM, are also known risk factors for SAD and hypogammaglobulinemia. For example, in patients treated with B-cell targeting or BCMA-targeted CAR T therapies, hypogammaglobulinemia and increased infection incidence are common (Table 4).[10] This was demonstrated in a single-center retrospective analysis of infection outcomes by Kambhampati et al.[71] in which 55 patients were treated with BCMA-targeted CAR T therapies (JCARH125, 31%; BB2121, 42%; BB21217, 13%; JNJ-4528, 15%). Results from this analysis demonstrated that 76% of patients had severe hypogammaglobulinemia at 1-year post infusion, with 53% (n = 29) of patients experiencing infections (40% bacterial, 53% viral, and 6% fungal). Approximately half (53%) of these infections occurred within 100 days post-CAR T therapy.[71] In an additional study assessing the effects of BCMA-targeting CAR T therapy (CD28- or 4-1BB-costimulated) in 40 patients who had responded to treatment, a decrease in serum IgG, IgM, and IgA was observed in all patients.[92] Recovery of serum IgG, IgM, and IgA to normal concentrations (often different thresholds are used across different institutions) was observed in 53.3%, 73.1%, and 23.8% respectively, at year 1; IgG took 386 days to recover and IgM took 54 days to recover.[92] IgA concentrations did not recover in these patients during the 1-year follow-up.[92] These observations demonstrate that patients may experience sustained humoral deficiency following treatment.

Risk Stratification. For patients with MM, attempts to stratify by infection risk have been performed. One study has assessed a numerical Multiple Myeloma Index for Risk of Infection (MMIRI) to predict infection and identify patients who may benefit from prophylactic antibiotics. In this study, points were assigned to factors that could influence the incidence of infections based on their strength of association, including gender, disease stage via the international staging system (ISS), disease duration, and therapy type. Using this scoring system, an optimal cut-off score of six or above was indicative of "significant risk for infection" with a sensitivity of 93.2% and specificity of 80.2%.[93]

Recommendation: We propose that the utilization of standardized, validated risk stratification such as the MMIRI for patients with MM is highly warranted to allow HCPs to adopt a SAD management plan early, based on an individualized risk of SAD and infection. However, at present, the data available for risk stratification and novel infection risk indexes remain limited and as such, this represents a significant unmet need.

Immunologic Assessment and Diagnosis of Secondary Antibody Deficiency

To ensure patients with MM and SAD are given appropriate treatment, early diagnosis is key.

Recommendation: We recommend evaluating for SAD across the MM disease spectrum (from patients with MGUS, SMM and at initial MM diagnosis) and throughout the disease course by performing a full immunologic evaluation (Figure 2). For this evaluation, we recommend performing CD19+ or CD20+ lymphocyte counts, quantifying IgG, IgA, and IgM concentrations, and assessing production of specific antibody titers in response to vaccinations when initial levels are low.[94] Although different thresholds are used across different institutions, approximate normal ranges based upon literature and the authors' clinical experience are as follows: CD19+ or CD20+ lymphocyte counts 50–500 × 10^6/L; IgG 0.7–1.6 g/L; IgA 0.07-0.4 g/L; IgM 0.04–0.23 g/L.[95,96] We also suggest T-cell immunophenotyping (CD3, CD4, CD8), where available.

Hypogammaglobulinemia. Hypogammaglobulinemia was defined in the European expert consensus by Jolles et al.[12] as "serum IgG levels of <4 g/L." To assess for hypogammaglobulinemia, the total concentrations of IgG, IgA, and IgM should be measured.[4] Circulating B-cell (CD19+ or CD20+) count may be useful to assess humoral immune function indirectly, if applicable, although this is not current standard practice (Figure 2). By assessing serum IgG concentrations and other Ig's early, disease-related SAD can be diagnosed prior to the initiation of therapies. However, IgG paraproteins and therapeutic monoclonal antibodies can interfere with accurate measurement of IgG concentrations. There are immunoglobulin calculation methods that can be used to detect and exclude paraproteins and the monoclonal peak (produced by monoclonal antibody therapy) from Ig counts, helping to determine residual polyclonal IgG concentrations.[99] However, these methods are not validated and are not routinely used owing to potential concerns over accuracy.

Moreover, assessing antibody function via test immunizations to diagnose SAD is important in patients who have received B-cell targeting therapies, particularly in patients with a mild or moderate reduction of IgG concentrations (>4 g/L) as these therapies are known to diminish immune response to vaccinations.[12]

Recommendation: We recommend that a serum IgG concentration <4 g/L should be defined as "severe hypogammaglobulinemia," and that serum IgG concentrations between 4 and 6 g/L should be defined as "mild hypogammaglobulinemia."

Test Immunization and Poor Vaccine Response. Test immunization and vaccine response are useful tools to help probe a patient's humoral immunity and characterize their risk of infection and is particularly important in patients with only a mild reduction in IgG.[4] Serum specific antibody concentrations are measured before and after vaccination with polysaccharide and polypeptide pneumococcal vaccines such as the polysaccharide-based *pneumococcal* vaccine (PPV23; Pneumovax®), *Haemophilus influenzae* type B (HiB) or tetanus vaccines to assess immune/antibody responses.[4,12] Following vaccination, antibody concentrations that remain lower than protective cut-off concentrations suggest functional

Figure 2   Algorithm for SAD diagnosis in patients with MM.
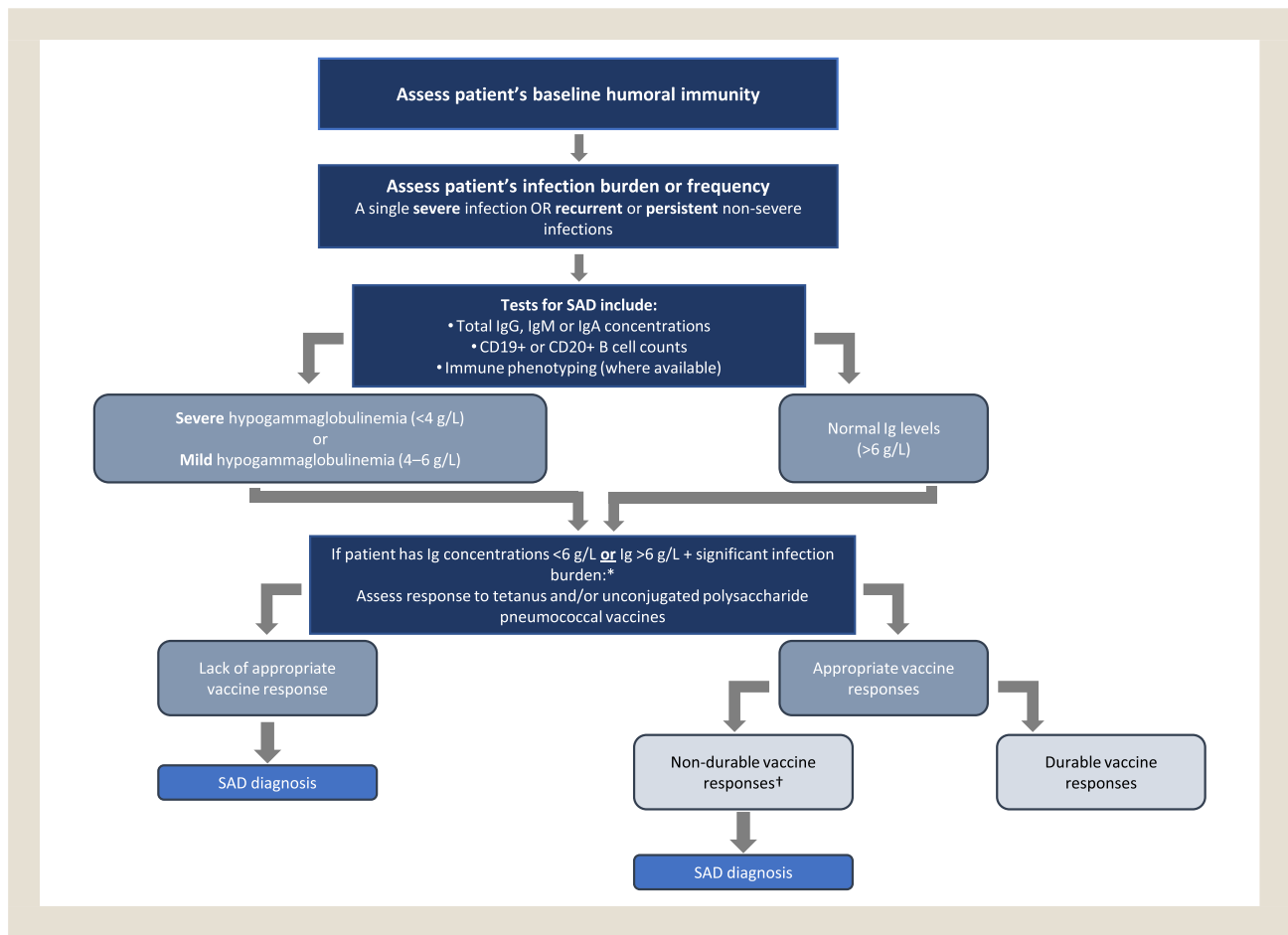
* A minimal infection burden was previously defined as viral infections not requiring antibiotics and two or less 1-week courses of oral antibiotics in 12 months.[4]
† A nondurable vaccine response is usually defined as concentrations below the protective level within 6 months of the initial response to vaccination.[97,98]
Abbreviations: Ig = immunoglobulin; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MM = multiple myeloma; SAD = secondary antibody deficiency.

impairment of antibody production. Protective cut-off values for different antibodies may vary between institutions and physicians should refer to their institute-level laboratory for specific postimmunization response levels.[4]

Recommemdation: Typically, a failure to mount a 2-fold rise in antibody titer can be considered as a cut-off for a poor vaccine response and antibody failure (Figure 2).[12]

There may also be limitations in the utility of test immunizations in relation to the lack of protocol standardization, vaccine types available, differences in protective cut-off values used, and access to diagnostic testing with ongoing challenges in interpretation and harmonization of diagnostic vaccinations.[12]

In the recently published European expert consensus by Jolles et al.,[12] it was recommended that test immunizations can be used to help determine whether IgRT should be initiated, particularly in patients who have serum IgG concentrations between 4 and 6 g/L with an infection burden. A previous study has reported that patients who showed a poor response to unconjugated pneumococcal polysaccharide vaccines benefited from IgRT.[3,100] However,

additional trials are required to assess when IgRT may provide benefit.[3]

Management of Secondary Antibody Deficiency

Antibiotic Prophylaxis. In patients with newly diagnosed MM, antibiotic prophylaxis may be given. However, there remains conflicting data surrounding the use of prophylactic antibiotics.

Recently, several studies and guidelines were published that demonstrated the beneficial use of prophylactic antibiotics within the first 2 to 3 months after myeloma-treatment initiation.[21,101,102] A UK-based, prospective, multicenter, double-blind, placebo-controlled randomized trial (TEAMM, Tackling EArly Morbidity and Mortality in Myeloma) demonstrated that overall survival was increased ($P = 0.0081$) in newly diagnosed patients with myeloma receiving prophylactic levofloxacin alongside their active myeloma treatment compared with patients receiving placebo during the first 12 weeks of therapy.[101] In addition, a retrospective data study using the MMIRI scoring system was able to predict the occurrence of infections in patients with MM and determine which patients may

benefit from prophylactic antibiotic treatment, helping to individualize care and prevent the unnecessary prescription of antibiotics.

Although data from the TEAMM showed levofloxacin prophylaxis could reduce deaths in the first 12 weeks, the study also showed no survival difference at 1 year in the levofloxacin group compared with the placebo group.[101] In addition, a recent systematic review and meta-analysis assessing the use of prophylactic antibiotics for patients with newly diagnosed MM demonstrated that while prophylactic antibiotic treatment could reduce the incidence of infection within the first 12 weeks following diagnosis, this did not translate to reduced mortality in those first 12 weeks.[102]

Additionally, emergence of antibiotic-resistant pathogens, development of *Clostridium difficile*-associated colitis, and possible interactions with MM therapies need to be considered. Consequently, we recommend that potential risks and benefits of prophylactic antibiotics should be assessed on an individual basis.[21]

Use of Immunoglobulin Replacement Therapy. Patient-specific clinical information and laboratory assessments should be used to guide treatment decision-making with IgRT at an individual level. Such information includes a patient's serum IgG, IgA, and IgM concentrations; vaccine responses; infection onset, frequency, duration, site, pathogen, and severity; as well as prior hospitalizations. Infection treatment type, frequency, duration, route of administration, and failure are also useful factors to consider. For example, in patients with SAD where prophylactic antibiotics have failed, IgRT may be the next appropriate approach.[4] It is recommended that patients with a prior history of severe or life-threatening infections with IgG <4 g/L and/or functional antibody deficiency should be considered for either antibiotics or IgRT.[12] An inadequate humoral response to vaccination (protein, unconjugated, and conjugated polysaccharide mRNA/DNA), particularly in patients with non-severe hypogammaglobulinemia, is another assessment that can be used to help determine functional humoral immunity and whether a patient should receive IgRT for infection prevention (please see test immunization and poor vaccine response section).

Recommendation: We recommend that IgRT should be considered for infection prevention in any patient who experiences severe hypogammaglobulinemia and who has previously experienced a severe bacterial infection at any time in the past that could be considered related to MM diagnosis or treatment. In addition, we recommend IgRT for infection prevention in patients with hypogammaglobulinemia who experience ≥3 recurrent or persistent infections over a 12-month period, despite appropriate anti-infective treatment. In patients who have serum IgG concentrations >6 g/L, experience recurrent infections, and have a poor vaccine response, IgRT should be considered for infection prevention. Where possible and reliable, assessments to calculate the true IgG level should be performed by subtracting the monoclonal component IgG from the total IgG as a pragmatic approach to determine the underlying non−paraprotein IgG level.
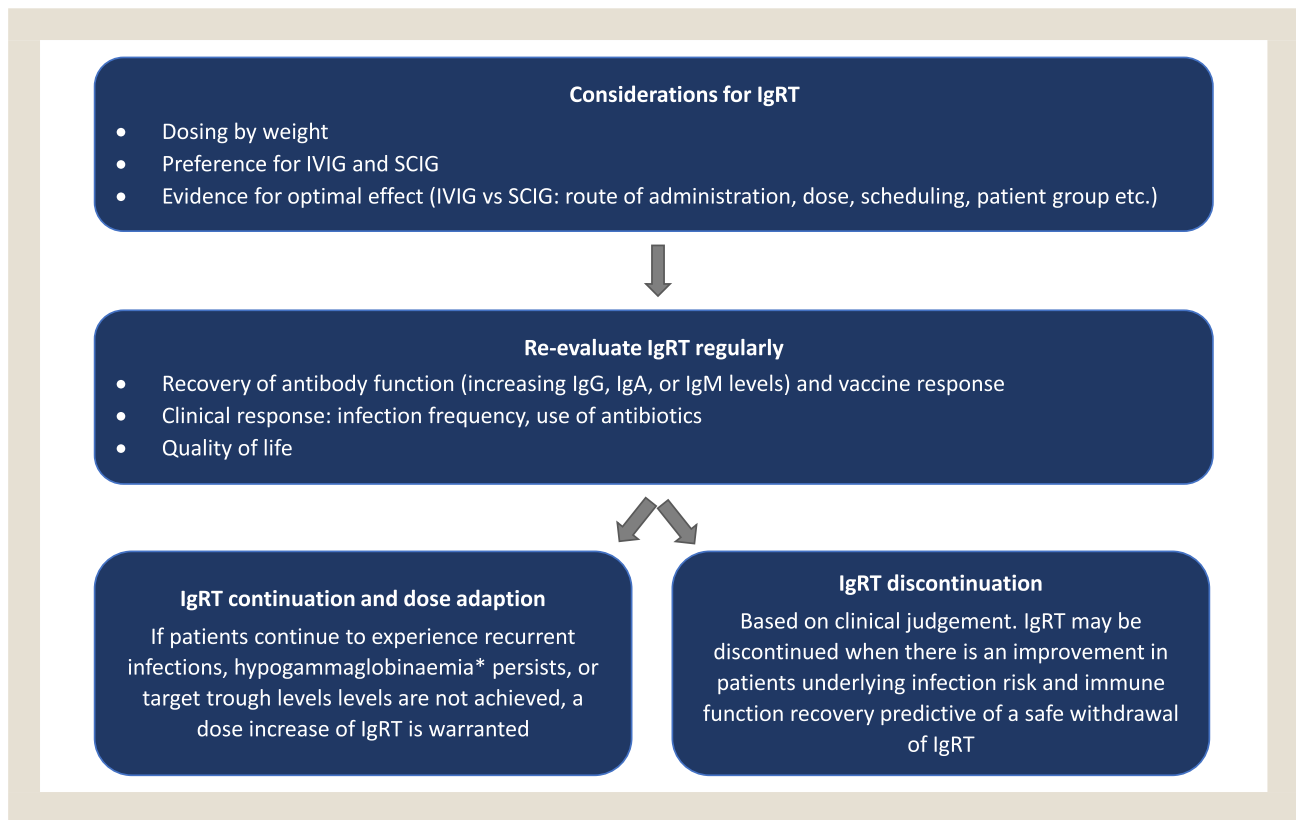
Recommendation: We recommend that IgRT should be considered in patients with a significant infection burden alongside hypogammaglobulinemia as a result of BCMA-targeted therapeutics.[3,103,104] As BCMA-targeted therapy use evolves from resistant disease to early disease, it will be important to monitor both infection burden

and antibody deficiency. To risk stratify the need for prophylactic IgRT after stopping treatment with BCMA-targeted therapeutics, we recommend immune monitoring of IgG levels and lymphocyte subsets every 1 to 2 months until 6 months post-infusion and then twice a year subsequently.[3]

Shared decision making should be utilized in terms of the route, site, and cycle duration of IgRT, taking into account both scientific evidence and patient preference to find a suitable strategy to minimize treatment burden. To determine if intravenous Ig (IVIG) or subcutaneous Ig (SCIG) is more suitable, shared decision making should consider the relative advantages and disadvantages of IVIG and SCIG treatments, including frequency of dosing, venous access, differences in adverse event profile, training and self-administration, and convenience of administration (hospital setting vs home).[105,106] These advantages and disadvantages are summarized in more detail in Jolles et al.[23] Although shared decision making and patient preference is key to determining the therapeutic approach for SAD, other factors can also impact the choice. Two additional important factors are reimbursement and access to IgRT, which differs across countries, influenced by drug availability, regionally approved indications, and differences in local guidelines regarding starting and/or maintenance doses.[105,107] Lack of physician experience and confidence in using the subcutaneous route may also limit patient choice.[105]

The European Medicines Agency recommends both forms of IgRT (IVIG or SCIG) for patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of <4 g/L.[108,109] When calculating dosing regimens, both should be based on the patient's actual body weight, but may need to be individualized dependent on their clinical response, serum IgG levels, and if the patient is underweight/overweight. The recommended dose of IVIG is 0.2 to 0.4 g/kg actual body weight, administered every 3 to 4 weeks. The recommended SCIG regimen should aim to achieve a trough level of IgG level of at least 6 g/L within the normal reference range for the population age.[108] A loading SCIG dose of at least 0.2 to 0.5 g/kg actual body weight may be required which may need to be divided over several days.[108] After steady state IgG levels have been attained, maintenance SCIG doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4 to 0.8 g/kg actual body weight.[108]

Immunoglobulin Replacement Therapy Monitoring and Discontinuation. In general, patients on IgRT require ongoing monitoring from efficacy, adverse events, dosing, and hemovigilance perspectives, and although there is no formal recommendation or discontinuation algorithm for SAD, an assessment frequency of every 4-6 months is suggested. Assessments should include a detailed infection history and serum IgG concentrations (noting the interpretational challenges posed by the paraprotein).[107,110] In certain circumstances, and if available, measuring response to certain vaccines may allow assessment of functional antibody responses even while a patient is on IgRT, alongside any change in infection status. Here, vaccine response producing antibodies which are not significantly present in Ig preparations (eg, *Typhim Vi*® indicated for tetanus) can be measured to gauge antibody dysfunction and if Ig continu-

Figure 3 | Algorithm for IgRT initiation and discontinuation in patients with MM.

Considerations for IgRT
- Dosing by weight
- Preference for IVIG and SCIG
- Evidence for optimal effect (IVIG vs SCIG: route of administration, dose, scheduling, patient group etc.)

Re-evaluate IgRT regularly
- Recovery of antibody function (increasing IgG, IgA, or IgM levels) and vaccine response
- Clinical response: infection frequency, use of antibiotics
- Quality of life

IgRT continuation and dose adaption
If patients continue to experience recurrent infections, hypogammaglobinaemia* persists, or target trough levels levels are not achieved, a dose increase of IgRT is warranted

IgRT discontinuation
Based on clinical judgement. IgRT may be discontinued when there is an improvement in patients underlying infection risk and immune function recovery predictive of a safe withdrawal of IgRT

* A serum IgG concentration <4 g/L should be defined as "severe hypogammaglobulinemia" and "mild hypogammaglobulinemia" may be defined as 4 to 6 g/L. Abbreviations: IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MM = multiple myeloma; IgRT = immunoglobulin replacement therapy; IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

ance is needed. Where available, such approaches may be utilized when considering IgRT discontinuation or if vaccine responses had not been assessed before commencement of IgRT (Figure 3).[12]

The exact time frame for any immune recovery is dependent on the underlying disease and medications used, which can further exacerbate SAD. An international survey identified that patients with MM (who do not undergo HCT) are usually treated with IgRT for 6 to 12 months; however, monitoring and discontinuation parameters varied across countries and were dependent on a stable infection burden and adequate antibody response.[107] Consequently, IgRT discontinuation should be determined on a per-patient basis.[12,110] It was recommended in the European expert consensus by Jolles et al.[12] that IgRT should be discontinued in patients with HMs when infections are controlled for ≥6 months and show signs of immunological recovery, such as recovery of non-paraprotein IgG, IgA, or IgM concentrations (eg, IgG concentrations >7-8 g/L) or improved responses to vaccines.[12,110] In previous studies, immunoparesis recovery following auto-HCT is associated with greater overall and progression free survival in patients with MM compared with patients with no Ig recovery.[111,112] Consequently, assessing the efficacy of IgRT on immunoparesis and polyclonal Ig recovery may be a useful tool to aid decisions on IgRT discontinuation. Following IgRT discontinuation, patients should be closely monitored for any signs of new infections, and it is recom-

mended that IgG concentrations should be evaluated during routine check-ups in this wash-out period.[12,110] During this Ig wash-out period patients should have access to emergency antibiotics and medical advice, should infections reoccur. If infections recur and SAD persists, IgRT should be re-initiated.[12]

Recommendation: We recommend that IgRT should be evaluated regularly by assessing the patient's antibody recovery (increasing Ig concentrations and response to vaccines) as well as their clinical response. Here, the impact of IgRT on paraprotein levels and subsequent effects on immunoparesis and polyclonal Ig recovery, infection frequency, antibiotic use, and quality of life should be considered. In patients in whom infections are not optimally controlled, we recommend that IgRT should be continued with consideration of an increased Ig dose. In patients with reduced infection frequency and any evidence of immune function recovery, we recommend that IgRT be discontinued when parameters are predictive of a safe withdrawal, this being based on clinical judgment and supportive laboratory parameters.

Conclusions

This review provides recommendations for treatment and management of patients with MM, and aims to raise the awareness of SAD in MM, SMM, and MGUS. The algorithms presented in this review serve as a practical tool to guide physicians on aspects

of diagnosis, monitoring, and treatment. This algorithm integrates recommendations on serum IgG concentrations, risk stratification, and when to initiate and discontinue IgRT. We believe that increasing awareness and refining management of SAD in patients with MM can improve patient outcomes by reducing the number of infections and infection-related mortality and create the motivation for initiating prospective trials.

Author Contributions

All authors contributed equally to the review approach/design, meetings, recommendations, interpretation of literature, writing, and critical review of this article. All authors reviewed the final manuscript and agreed on the decision to submit it for publication.

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