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Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees

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Secondary hypogammaglobulinemia (SHG) is characterized by reduced immunoglobulin levels due to acquired causes of decreased antibody production or increased antibody loss. Clarification regarding whether the hypogammaglobulinemia is

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secondary or primary is important because this has implications for evaluation and management. Prior receipt of immunosuppressive medications and/or presence of conditions associated with SHG development, including protein loss syndromes, are histories that raise suspicion for SHG. In patients with these histories, a thorough investigation of potential etiologies of SHG reviewed in this report is needed to devise an effective treatment plan focused on removal of iatrogenic causes (eg, discontinuation of an offending drug) or treatment of the underlying condition (eg, management of nephrotic syndrome). When iatrogenic causes cannot be removed or underlying conditions cannot be reversed, therapeutic options are not clearly delineated but include heightened monitoring for clinical infections, supportive antimicrobials, and in some cases, immunoglobulin replacement therapy. This report serves to summarize the existing literature regarding immunosuppressive medications and populations (autoimmune, neurologic, hematologic/oncologic, pulmonary, posttransplant, protein-losing) associated with SHG and highlights key areas for future investigation. (J Allergy Clin Immunol 2022;149:1525-60.)

Key words: *Secondary hypogammaglobulinemia, immunosuppression, immunosuppressive medication, B-cell–targeted therapy, rituximab, ocrelizumab, autoimmunity, solid organ transplant, CD19 CAR-T-cell therapy, protein-losing enteropathy, protein loss*

Abbreviations used

ANCA:	Antineutrophil cytoplasmic antibody
BCTT:	B-cell–targeted therapy
CDC:	Centers for Disease Control and Prevention
CF:	Cystic fibrosis
CLL:	Chronic lymphocytic leukemia
COPD:	Chronic obstructive pulmonary disease
COVID-19:	Coronavirus disease 2019
FcRn:	Neonatal Fc receptor
HG:	Hypogammaglobulinemia
HSCT:	Hematopoietic stem cell transplant
HT:	Heart transplant
IEI:	Inborn error of immunity
IgG-RT:	IgG replacement therapy
IVIG:	Intravenous immunoglobulin
KT:	Kidney transplant
LT:	Lung transplant
MM:	Multiple myeloma
MS:	Multiple sclerosis
NMOSD:	Neuromyelitis optica spectrum disorder
OLT:	Liver transplant
PCV13:	Pneumococcal 13-valent conjugate vaccine
PI:	Primary immunodeficiency
PLE:	Protein-losing enteropathy
PPSV23:	Pneumococcal polysaccharide vaccine
RA:	Rheumatoid arthritis
RCT:	Randomized clinical trial
RTX:	Rituximab
SCIG:	Subcutaneous immunoglobulin
SHG:	Secondary hypogammaglobulinemia
SLE:	Systemic lupus erythematosus
SOT:	Solid organ transplant
TPE:	Therapeutic plasma exchange
VEO-IBD:	Very early onset inflammatory bowel disease

Secondary hypogammaglobulinemia (SHG) is characterized by reduced immunoglobulin levels due to a medication or a disease process, leading to decreased antibody production or increased antibody loss. SHG is distinct from primary hypogammaglobulinemia (HG) due to underlying inborn errors of immunity (IEI), or primary immunodeficiencies (PIs), which comprise more than 400 inherited disorders of immunity resulting in a departure from normal immune development and function.[1] Of note, the distinction between primary HG and SHG can be challenging to make, and we recommend thorough consideration of both primary and secondary causes when evaluating HG.

A large proportion of SHG is due to the increasing use of immunosuppressive treatments, most notably B-cell–targeted therapy (BCTT), in autoimmune rheumatologic and neurologic conditions as well as hematologic/oncologic conditions. Corticosteroids are another common cause of iatrogenic SHG, although it does not appear to be associated with significant increases in frequency or severity of infectious complications. This is discussed further in the Medications section.

Studies have shown that antibody defects are also observed in autoimmune and hematologic/oncologic conditions before initiation of immunosuppressive treatment.[2-11] Adding complexity, there is an increasingly recognized category of IEI/PI called primary immune regulatory disorders that presents primarily with autoimmunity and lymphoproliferation rather than the classic PI presentation of severe, recurrent, and/or unusual infections.[12] This is discussed further in the Rheumatology, Neurology, and Hematology/Oncology sections.

Conversely, SHG observed in pulmonary conditions appears largely driven by immunosuppression rather than immune aberrations due to the underlying disease, although there may be subsets of chronic obstructive pulmonary disease (COPD) with frequent acute exacerbations[13-17] and cystic fibrosis (CF)[18-22] that present with antibody deficiency before immunosuppression. SHG observed after solid organ transplant (SOT) for lung, heart, and kidney transplant (KT) also appears largely iatrogenic in nature due to immunosuppression, with additional contribution of protein losses coming into play particularly for KT patients with nephrotic syndrome.[23-25] This is discussed further in the Pulmonary and Solid Organ Transplant sections.

Protein loss syndromes that can cause SHG, including nephrotic syndrome, are covered in the Protein-Losing Conditions section. Although there are a number of acquired causes for protein-losing enteropathy (PLE) (Table I) and intestinal lymphangiectasia (most commonly structural heart disease and its surgical repair), there is interplay between certain protein loss syndromes and IEI as there is with autoimmune conditions. Primary causes including monogenic causes of very early onset inflammatory bowel disease (VEO-IBD) such as FOXP3, IL10RA, and XIAP,[26,27] and loss-of-function mutations in SLCO2A1, CD55, and DGAT1, also exist, and more may be uncovered.

This report reviews published literature regarding SHG seen in the above-mentioned clinical settings to provide a basis for the development of clinical guidance regarding diagnosis and management, and to guide future research efforts in advancing the field (Tables II and III). This report focuses on IgG HG because data regarding isolated low IgA, low IgM, and IgG subclass levels are limited and mostly reported in the context of IgG HG. Given the lack of rigorous studies and clinical trials in SHG, this report is

TABLE I. Causes of PLE[317,328]

Inflammatory exudative processes
Inflammatory bowel disease
Gastrointestinal malignancy
Clostridium difficile colitis
Erosive gastritis
Gastric ulcers
Nonsteroidal anti-inflammatory drug enteropathy
Chemotherapy-induced
Graft versus host disease
Increased mucosal permeability
Celiac disease
Amyloidosis
Lymphocytic gastritis
Infections (bacterial overgrowth, viral, parasite, Whipple disease)
Rheumatologic diseases (eg, SLE)
Allergic gastroenteropathy
Eosinophilic gastroenteritis
Congenital disorders of glycosylation
Intestinal loss of lymphatic fluid
Primary lymphangiectasia
Secondary lymphangiectasia
Congenital heart disease

not meant to serve as a formal guideline but a summary of what has been reported to date and a call for future studies. Unless a specific national society guideline (Tables IV and Table V) or published expert opinion article is referenced, the recommendations reflect expert opinion of the authors.

DEFINITIONS

Throughout the report, we use the term HG to mean a low IgG level as defined in the articles reviewed. We have used the term SHG to mean HG due to a medication or non-PI pathophysiology that causes low IgG production or increased IgG loss, distinct from primary HG due to an underlying IEI or PI. We use the term intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) when specifically discussing one of the forms and IgG replacement therapy (IgG-RT) when discussing IgG replacement, which could be either IVIG or SCIG.

IgG level cutoffs used to define HG vary in the literature. Although this report is a summary and not reanalysis of what has been previously published, to aid in standardizing future studies, we propose the definition of HG in adult patients to be a serum IgG level below 700 mg/dL, with further stratification into brackets of 400 to 699 mg/dL, 200 to 399 mg/dL, and 0 to 199 mg/dL. Age-appropriate reference ranges for pediatric patients and variability between laboratories in the reference ranges of immunoglobulins should be considered. To better clinically phenotype transient versus persistent SHG, we propose stratification of SHG duration into SHG lasting 3 to 6 months, 6 to 12 months, 12 to 24 months, and more than 24 months.

Consensus definitions of what is considered "clinically significant" SHG is complicated and hindered by a lack of consensus regarding what infection severity constitutes "severe" and what frequency constitutes "recurrent." However, these definitions are integral in both SHG evaluation and management. Given that definitions are variable and subject to interpretation in context of the whole clinical picture, clinicians are often left to referencing the PI literature in the absence of SHG-specific studies. To standardize research efforts toward defining clinically significant in SHG, we propose defining severe as an infection requiring emergency department visit or hospitalization, requiring intravenous antibiotics, or requiring antibiotic/antiviral/antifungal therapy specifically for the purposes of treatment (vs prophylaxis). We propose following Jeffrey Modell Foundation criteria (4 or more new ear infections, 2 or more serious sinus infections, 2 or more pneumonias, and 2 or more deep-seated infections including septicemia) to define recurrent infections.[28]

GENERAL CONSIDERATIONS FOR EVALUATION AND MANAGEMENT

Published guidelines and recommendations for SHG vary in their approach to diagnosis and management. This is likely a reflection of (1) the heterogeneity of the patient populations and non-PI conditions associated with SHG, (2) differences in treatment protocols and supportive care, and (3) lack of a unified consensus about what defines clinically meaningful SHG. Given these challenges, it is important for clinical immunologists to be involved in care teams so that each patient's clinical presentation and immunologic testing can be considered for individualized evaluation and management. In situations where recommendations specific to SHG do not exist, clinicians are left to rely on the PI literature. General considerations for screening, monitoring, evaluation, and management are outlined in Figs 1 and 2.

When HG is discovered, it is important to clarify, if possible, whether the HG is primary or secondary, because this distinction has implications for evaluation and management. A history of having received immunosuppressive medications and/or presence of conditions associated with SHG development raise suspicion for SHG. Use of therapeutic plasma exchange (TPE) can complicate interpretation of IgG levels as TPE with non-plasma replacement fluid depletes immunoglobulins, with studies showing an approximately 63% decline in IgG levels after one exchange.[40] Whether decreases in IgG level due to TPE are associated with an increased susceptibility to infections remain inconclusive.[171,219] Reviewing the history for prior use of TPE is important when evaluating SHG as common indications for TPE span a broad range of conditions, including neurologic (acute inflammatory demyelinating polyradiculoneuropathy, acute short-term treatment of myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy), hematologic (thrombotic thrombocytopenic purpura, symptomatic hyperviscosity in hypergammaglobulinemia), and renal (microscopic polyangiitis/granulomatous polyangiitis, anti-glomerular basement membrane disease, focal segmental glomerulosclerosis).[350] Often, it is not possible to definitively determine whether the HG is due to PI or condition/medication-associated SHG because baseline immune laboratories are not available. This highlights the importance of screening for HG before immunosuppressive treatments are initiated or when conditions known to cause SHG are diagnosed.

Society guidelines for screening and monitoring of immunoglobulin levels exist for systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibodies (ANCAs)-associated vasculitis, rheumatoid arthritis (RA), chronic lymphocytic leukemia (CLL), and SOT and are presented in Table IV. In line with these guidelines, general recommendations for screening would be to obtain baseline immunoglobulin levels at the time of diagnosis of conditions associated with SHG, and before the initiation of immunosuppressive medications, especially those targeting B

TABLE II. Immunosuppressive medications and reported immune effects*

Medication	Mechanism	Reported immune effects	Discussed further in
Anti-CD20 therapy (BCTT)[56,76,348,349,351,352]	Antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and direct effects on B cells	B-cell depletion HG Rituximab: late-onset neutropenia	BCTT Rheumatology Hematology/oncology Nephrotic syndrome
Anti-CD22 therapy[353-355]	Downregulation of BCR signaling leading to diminished B-cell activation	No change in serum IgG, IgA, or IgM levels reported in both NHL and autoimmune disease studies Cytokine release syndrome Neurotoxicity	CLL
Anti-CD38 therapy[356-361]	Induces apoptosis directly through Fc-mediated cross linking, and immune-mediated tumor cell lysis through complement- dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis	Decreased plasma cells Lymphopenia HG	
CD19 CAR-T-cell therapy[29,229,232,362,363]	Targeted elimination of $CD19^+$ B cells using single-chain variable fragment of mAb linked to T-cell signaling domains	Immune-related adverse effects: cytokine release syndrome, neurotoxicity B-cell aplasia HG	CD19 CAR-T-cell therapy
BTK inhibitors (ibrutinib)[190,364]	Inhibition of BCR signaling by irreversible binding to active site of BTK	↓ IgG levels starting at 12 mo, but increases in IgA, with increase in IgA ≥50% from baseline associated with significantly less infections	CLL
Bortezomib[365,366]	Proteasome inhibition leading to apoptosis of plasma cells	HG (IgG < 500 mg/dL) in 42% (5 of 12) with lupus nephritis; no opportunistic infections observed	
Corticosteroids[133-137,143]	Broad effects on gene transcription, including inhibition of inflammatory cytokines such as NF-kB	HG in 12%-56% on prolonged or high-dose corticosteroids IgG more affected than IgA or IgM Specific antibody responses typically preserved CD4 lymphopenia	Corticosteroids Pulmonary SOT Rheumatology Protein-losing conditions
FcRn antagonists[378]	Bind to FcRn with higher affinity than endogenous IgG, interfering with FcRn-mediated recycling of IgG and leading to reduction in serum IgG levels	↓ IgG, transient and reversible after drug discontinuation IgA, IgM, B cells are not affected	Neurology
Methotrexate[99,367-376]	Interference with folate metabolism due to inhibition of dihydrofolate reductase	HG ↓ IgG, IgA, IgM ↓ antibody responses to nonlive vaccines (influenza, pneumococcal)	
Mycophenolate[24,65,72,73,148,149,252,270,377]	Decreased lymphocyte proliferation due to inhibition of inosine monophosphate dehydrogenase required for purine synthesis	May increase risk of RTX-induced SHG Associated with mild/moderate HG in settings of LT, KT, and SLE	SOT Rheumatology Nephrotic syndrome
Sulfasalazine[380-383]	Decreased lymphocyte proliferation and antibody production; inhibition of DNA synthesis, cell cycle progression, and IL-2 production *in vitro*	Rare HG	
Cyclophosphamide[148,149,165,384]	Alkylating agent that causes crosslinking of DNA, RNA, and proteins, leading to cell death	HG in MS and SLE ↑ post-RTX SHG in GPA	Rheumatology Hematology/oncology Nephrotic syndrome
Purine analogs (azathioprine, cladribine, fludarabine)[385,368]	Inhibition of purine synthesis leading to lymphocyte apoptosis	10%-25% decrease in IgG, IgA, IgM with azathioprine ↓ IgG and IgM production with azathioprine	SOT Rheumatology Hematology/Oncology
Clozapine[386-389]	Blockade of $D_{1\text{-}5}$ dopamine receptors (especially D_4) and 5-HT_{2A} serotonin receptor, muscarinic receptors, and histamine receptors; 5-HT_{1A} partial agonis	Antipsychotic most often associated with immunosuppression and need for IgG-RT in 1 cohort ↓ IgG, IgA, and IgM ↓ class-switched memory B cells and plasmablasts Longer duration associated with ↓ IgG and ↓ class-switched memory B cells ↑ pneumonia ↑ antibiotic use	

(Continued)

TABLE II. *(Continued)*

Medication	Mechanism	Reported immune effects	Discussed further in
Chlorpromazine[390]	Blockade of D2 dopamine receptors	HG	
Antiepileptic medications (phenytoin, carbamazepine, valproate)[386,392-410]	Sodium channel blockers (phenytoin, carbamazepine, valproate, lamotrigine); calcium channel blockers (valproate, lamotrigine); inhibition of GABA metabolism and reuptake (valproate)	Phenytoin: HG, B-cell and T-cell lymphopenia Carbamazepine: HG, B-cell lymphopenia, transient monoclonal gammopathy, recurrent HSV encephalitis, interstitial pneumonitis Valproate: HG Lamotrigine: IgA deficiency	

BCR, B-cell receptor; *GABA*, Gamma-aminobutyric acid: *GPA*, granulomatosis with polyangiitis; *HSV*, herpes simplex virus.
*Mechanism of action and reported immune effects of immunosuppressive medications are presented. The areas in which each immunosuppressive medication is discussed further are also mentioned.

TABLE III. Conditions associated with development of SHG*

Specialty	Conditions
Rheumatology	ANCA-associated vasculitis Eosinophilic granulomatosis with polyangiitis Granulomatosis with polyangiitis Juvenile idiopathic arthritis RA SLE
Neurology	MS NMOSD
Hematology/oncology	CLL Lymphoma MM
Pulmonary	COPD CF
Protein-losing conditions	Nephrotic syndrome PLE

*Conditions that have been associated with development of SHG are mentioned. Notably, almost all of these conditions are treated with immunosuppression or treatment that can lower immunoglobulin levels. Studies are needed to determine the relative contributions of the underlying condition and the immunosuppression to the development of SHG.

cells. Including B-cell enumeration and peripheral B-cell flow cytometry in screening could improve longitudinal monitoring by enabling comparisons over time, particularly in patients receiving BCTT. Additional studies are needed to clearly define which patient populations benefit from screening and monitoring and whether additional laboratories should be included. In particular, there is a case to be made for and against assessing specific antibody titers as part of routine screening. On one hand, the clinical significance of detecting isolated specific antibody deficiency before immunosuppression is unclear. Interpretation of vaccine responses is complicated and best undertaken by clinical immunologists. On the other hand, because immunosuppression is known to decrease vaccine responses, it may be prudent to maximize patients' vaccination status before immunosuppression.

In addition to society guideline recommendations presented in Table IV, there are expert recommendations for specific disease states. For example, in CLL, experts have recommended monitoring immunoglobulins and specific antibody responses every 6 months or as needed on the basis of patient's infection history.[11] Experts have also recommended that baseline immunoglobulin levels, specific antibody titers, and lymphocyte subsets be obtained before initiation of CD19 CAR-T-cell therapy, and immune monitoring be performed with immunoglobulins and specific antibody titers or lymphocyte subsets either 3 months after initiation of CD19 CAR-T-cell therapy or monthly until the sixth month after infusion and then twice a year after that.[29,30] For patient populations discussed in this report for whom there are no existing guidelines or recommendations, we recommend periodic laboratory and clinical monitoring every 6 to 12 months and whenever there are significant or recurrent infections to identify patients with persistent immune dysfunction who may benefit from IgG-RT. Additional studies are needed to clearly define the optimal frequency for monitoring and the laboratories that should be included in different patient populations.

HG by itself is a laboratory definition (with a cutoff that varies with age and between different laboratories) and does not necessarily indicate a clinically symptomatic syndrome. IgG levels alone do not measure B-cell function, and antibody function and vaccine responses need to be evaluated and taken into consideration.[31] If SHG is uncovered, referral to a clinical immunologist can be considered to aid in these evaluations (Fig 2).

Treatment of SHG includes removal of iatrogenic causes (eg, discontinuation of an offending drug) or treatment of the underlying condition (eg, management of nephrotic syndrome). If iatrogenic causes cannot be removed or underlying conditions cannot be treated, management options include heightened monitoring for clinical infections, antimicrobials, and in some cases, IgG-RT.

HG is often accompanied by suppression of vaccine responses, and we have reviewed existing recommendations regarding the timing of vaccine administration in relation to the timing of immunosuppression in relevant sections. Of note, guidance for coronavirus disease 2019 (COVID-19) vaccination in immunocompromised patients continues to be updated. Most recently, the Centers for Disease Control and Prevention (CDC) has recommended that moderately to severely immunocompromised people receive an additional dose, followed by a booster dose 6 months later. Most patients with SHG fall into the CDC-defined category of moderate to severe immunocompromise (eg, received organ transplant, received stem cell transplant within last 2 years, receiving active cancer treatment, and taking medication to suppress immune system).[32]

Initiating IgG-RT is a complex decision without unified guidelines, and shared decision making with the patient and multidisciplinary clinical team is often needed. Guidance for initiating IgG-RT on the basis of existing SHG-specific society guideline recommendations (Table V) and PI literature is shown

TABLE IV. Summary of guidelines regarding screening and monitoring of immunoglobulin levels*

Patient group	Year	Society	Recommendation
CLL	2012	BCSH	Measure serum immunoglobulins as part of the workup of asymptomatic stage A CLL at time of diagnosis[176]
CLL	2015	ESMO	Measure baseline serum immunoglobulins as part of the diagnostic and staging workup for CLL before initiating any treatment[175]
SOT	2017	AAAAI	Monitor for HG after transplantation[35]
ANCA vasculitis	2014	BSR BHPR	Measure serum immunoglobulin before each cycle of RTX[69]
ANCA vasculitis	2016	EULAR ERA EUVAS	Measure serum immunoglobulin levels before each course of RTX and in patients with recurrent infection[150]
SLE	2018	BSR	Measure immunoglobulins at time of diagnosis and before starting drugs with the most risk of inducing HG that might increase infection risk (eg, MMF, cyclophosphamide, and RTX). Repeat serum immunoglobulins about 3-6 mo later and then annually[151]
RA	2011	RCEC	Measure baseline IgG levels before the first dose and before each subsequent cycle of RTX. Close monitoring of IgG levels and infections for patients at risk for HG (eg, reduced IgG levels at baseline) or high-risk groups (eg, elderly)[68]
RA	2011	BSR BHPR	Measure immunoglobulin levels before initiating RTX as well as 4-6 mo after infusions and before any re-treatment[70]

AAAAI, American Academy of Allergy, Asthma & Immunology; *BCSH*, British Committee for Standards in Haematology; *BSR*, British Society for Rheumatology; *BHPR*, British Health Professionals in Rheumatology; *ERA*, European Renal Association; *ESMO*, European Society for Medical Oncology; *EULAR*, European League Against Rheumatism; *EUVAS*, European Vasculitis Society; *MMF*, mycophenolate; *RCEC*, Rituximab Consensus Expert Committee.

*Previously published recommendations regarding screening and monitoring of immunoglobulin levels are presented. Of note, IgG levels alone do not indicate normal B-cell function in the way that the ability to make specific antibodies in response to vaccination does. In addition, these guidelines do not comment specifically on whether IgG should be checked with IgA or IgM or IgG subclasses or on assessment of specific antibody responses, highlighting the need for inclusion of clinical immunologists in the development of SHG guidelines. The functional assessment of antibodies is paramount, and thus additional testing regarding specific antibody responses should be considered.

in Fig 2. Of note, the IgG level below which IgG-RT should be started prophylactically in the absence of other laboratory abnormalities is unclear and needs to be studied in SHG. In the absence of data, an IgG level below 150 mg/dL should certainly warrant initiating IgG-RT without the need for additional functional testing based on what is widely accepted in the PI literature, and an IgG level cutoff of 400 mg/dL has been referenced in SOT and hematologic malignancy literature. In addition, SHG may be transient, and studies are needed to determine the duration of time a low IgG level should be monitored before additional evaluation and possible treatment are considered. A scoring system previously investigated for PI may prove helpful in guiding decisions for SHG, and studying its use in patients with SHG could prove useful.[33] In clinical practice, decisions to start IgG-RT as a replacement product are often complicated by the fact that IVIG is used for its immunomodulatory effects in the practice of rheumatology, neurology, hematology/oncology, and SOT.

If the decision to initiate IgG-RT is made, dosing and adjustment are based on the PI literature in the absence of SHG-specific recommendations. A starting dose of 400 to 600 mg/kg every 4 weeks using actual body weight is accepted practice. Although there is 1 study in hematologic malignancies showing that precision or ideal body weight was equally effective at preventing infections,[34] there otherwise does not appear to be a role for using ideal body weight in dosing for SHG. The optimal trough level is unclear and varies on the basis of the underlying disease state. Target trough IgG levels of 800 mg/dL with subsequent adjustment to the "biological trough level" that keeps a patient infection-free is recommended in PI guidelines and is a reasonable starting point when IgG-RT has been started for SHG *with* infections.[35,36] However, target levels of 400 mg/dL or 500 mg/dL (cutoffs often referenced in SOT and hematologic malignancy), 700 mg/dL (the lower limit of normal for IgG levels in healthy adults), or 1000 mg/dL in patients with associated bronchiectasis or chronic pulmonary disease are all potentially reasonable alternatives that need to be studied.[8,23,24,29,30,37-39] Dose adjustments can be guided by increasing the IVIG dose by 100 mg/kg/mo to increase the trough IgG by 121 mg/dL[36] and increasing the SCIG dose by 100 mg/kg/mo to increase the serum IgG by 84.4 mg/dL.[41]

Studies of IgG-RT in SHG have been mostly performed with IVIG (Table VI). There are potential benefits to SCIG including better tolerance of infusions and reduced protein loss, and reports of SCIG used for SHG associated with hematologic malignancy,[42,43] SOT,[44,45] and protein-losing conditions[46-49] suggest that it is well tolerated and effective at increasing IgG levels in these cases. In the absence of additional data, the decision to initiate IVIG or SCIG needs to involve shared decision making with the patient. Studies investigating the use of SCIG in SHG are needed.

After initiation of IgG-RT, periodic assessments to evaluate response are needed.[25] In patients who have paused or discontinued immunosuppression or whose SHG-associated condition has been successfully treated, assessments may include pausing IgG-RT to determine ongoing need. Although there are no formal recommendations for timing of reevaluation of immune function after pausing IgG-RT, a period of 3 to 4 months is reasonable based on the fact that the half-life of IVIG is approximately 21 days, and it takes 4 to 5 half-lives to clear exogenous IgG from the system.[50-53]

MEDICATIONS

Many immunosuppressive medications have been associated with SHG, which can but does not always lead to secondary recurrent infections (Table II). Studies of clinical outcomes with SHG from medications, aside from BCTT and corticosteroids, are limited mostly to case reports, expert opinion, or reviews.[6,7,54] Interpretation of these reports is complicated by the fact that many of these medications are prescribed in combination with

TABLE V. Summary of guidelines regarding IgG replacement therapy in SHG*

Patient group	Society	Year	IgG-RT recommendations
SHG	EMA	2018	IVIG as replacement therapy for secondary immunodeficiencies (IgG < 400 mg/dL or specific antibody failure defined as <2-fold increase in antibody titers to pneumococcal polysaccharide and polypeptide antigen vaccines) with severe or recurrent infections and ineffective antimicrobial treatment[347]
SOT, BCTT, or other causes excluding hematological malignancy and HSCT	ANBA	2020	Emerging but insufficient data for IVIG and SCIG as replacement therapy for[411]: ● IgG < 400 mg/dL regardless of infection frequency/severity ● IgG > 400 mg/dL with at least 1 life-threatening infection in the last 12 mo or at least 2 serious infections in the last 6 mo requiring more than standard outpatient antibiotic therapy
SOT	AAAAI	2017	IVIG or SCIG replacement is recommended for HG[35]
ANCA vasculitis	ACR	2021	Immunoglobulin supplementation is conditionally recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis receiving remission maintenance therapy with RTX who have IgG <300 mg/dL and recurrent severe infections, or without recurrent infections but with impaired vaccine responses, in collaboration with an allergist/immunologist[132]
Hematological malignancies or HSCT	ANBA	2020	Evidence of probable benefit with more research needed for IVIG and SCIG as replacement therapy for[412]: ● IgG < 400 mg/dL regardless of infection frequency/severity ● IgG > 400 mg/dL with at least 1 life-threatening infection in the last 12 mo or at least 2 serious infections in the last 6 mo requiring more than standard outpatient antibiotic therapy
HSCT	Joint†	2009	IVIG should not be routinely administered but may be considered for patients with IgG <400 mg/dL[178]
Myeloma	NICE	2016	Consider IVIG for patients with HG and recurrent infections (low-quality evidence suggesting IVIG is effective in preventing major and clinically documented infections)[413]
CLL	BCSH	2012	IVIG or SCIG as replacement therapy for IgG <500 mg/dL and recurrent or severe infection with encapsulated bacteria despite oral antibiotic prophylaxis[176]
CLL	ESMO	2015	IgG-RT recommended only for severe HG and repeated infections[175]
B-cell CLL	AAAAI	2017	IgG-RT should be considered for HG and recurring bacterial infections and inadequate antibody levels in response to diphtheria, tetanus, or pneumococcal vaccinations[35]
CLL	NCCN	2019	Physician guidelines indicate IVIG or SCIG as supportive treatment for IgG <500 mg/dL, with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization[414]
B-cell CLL	FDA		IVIG is FDA-approved for prevention of bacterial infections in HG and/or recurrent bacterial infections[35]

ANBA, Australian National Blood Authority; *BCSH*, British Committee for Standards in Haematology; *EMA*, European Medicines Agency; *ESMO*, European Society for Medical Oncology; *NCCN*, National Comprehensive Cancer Network; *NICE*, National Institute for Health and Care Excellence.
*Recommendations regarding whether/when IgG-RT can be considered for SHG and conditions associated with SHG.
†Report cosponsored by the Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, European Blood and Marrow Transplant Group, American Society for Blood and Marrow Transplant, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Association of Medical Microbiology and Infectious Diseases, the CDC, and the Health Resources and Services Administration.

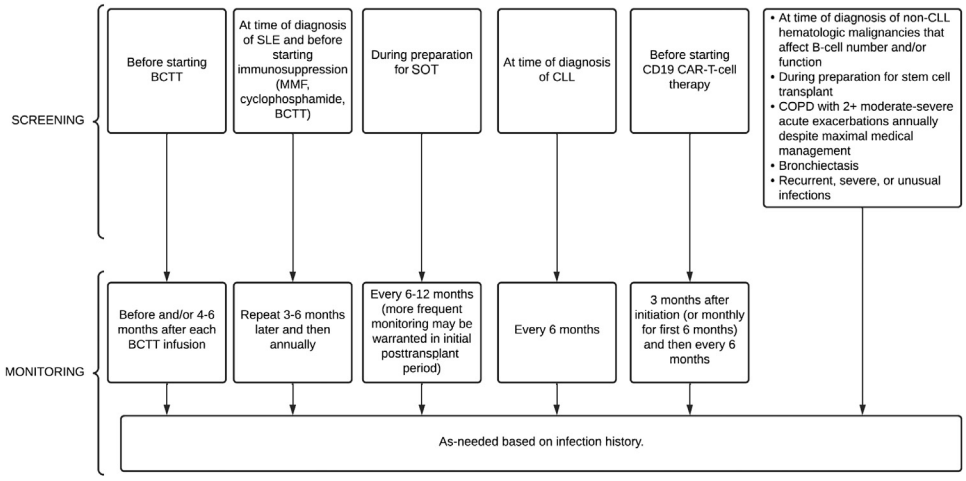

FIG 1. General considerations for screening and monitoring. At a minimum, screening and monitoring should include an IgG level. Non-IgG immunoglobulins and specific antibody responses have also been recommended because IgG levels alone do not indicate normal B-cell function. Lymphocyte subsets for B-cell enumeration and peripheral B-cell flow cytometry for phenotyping can be considered, particularly in patients about to receive or receiving immunosuppression. Additional studies are needed to clearly define which patient populations benefit from screening and monitoring as well as the timing of and the laboratories to include in screening and monitoring. *MMF*, Mycophenolate. See also Table IV.

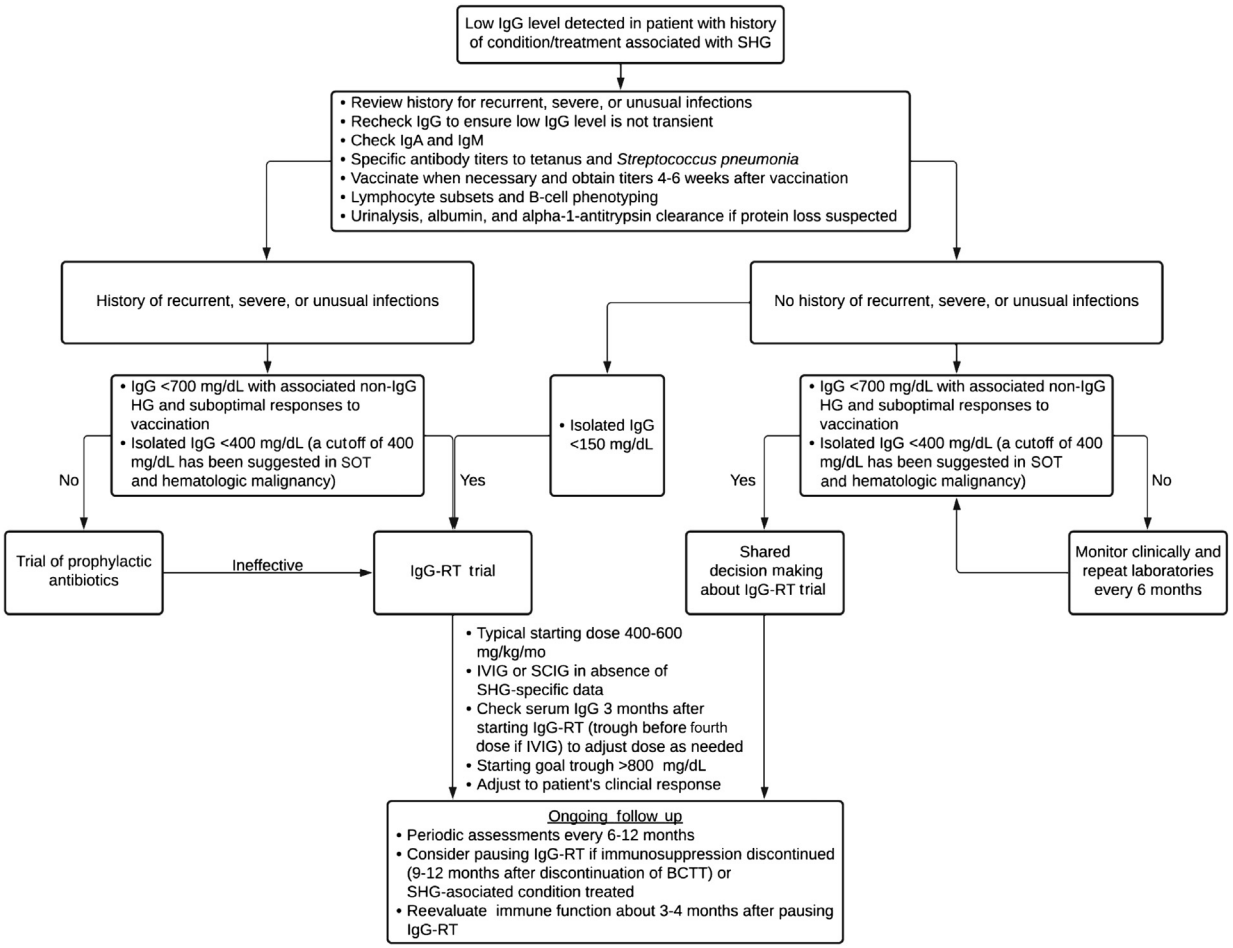

FIG 2. General considerations for evaluation and management. If SHG is uncovered, it is important to assess additional measures of immune function. Infection history is an important piece of determining next steps for management. Given the paucity of SHG-specific data, many recommendations are based on PI literature and shared decision making plays a large role in treatment planning. SHG-specific studies are needed to clearly determine if and when to start IgG-RT and SHG-specific considerations for dosing and adjustment. If IgG-RT is initiated, continued assessments are needed to evaluate the ongoing need for IgG-RT.

biologic agents, corticosteroids, BCTT, and/or chemotherapy, making it difficult to determine the contribution of individual agents. Table II includes a summary of the mechanism of action and reported immune effects of immunosuppressive medications including anti-CD22 therapy, anti-CD38 therapy, and bortezomib.

BCTT in adults

SHG occurs commonly after BCTT, which is used for a wide array of conditions including B-cell malignancies and autoimmune conditions. The incidence of BCTT-associated SHG is affected by the underlying condition and other immunosuppressive or immune-ablative treatments used. This is discussed further in the Rheumatology, Neurology, and Hematology/Oncology sections.

Most of the literature regarding BCTT-associated SHG and its infectious complications exists for rituximab (RTX), a chimeric anti-CD20 mAb. RTX targets CD20-expressing B cells in the pre- to pre-plasma cell stages and does not target plasma cells, which produce most antigen-specific IgG.[55] However, its use has still been associated with development of SHG, which can be persistent and lead to serious and recurrent infections in a subset of patients.[56,57]

Several second-generation anti-CD20 mAbs have been designed to be more effective and better tolerated, with lower immunogenicity than RTX. These include the humanized mAbs ocrelizumab, obinutuzumab, and veltuzumab, as well as the fully human mAb ofatumumab. There have been reports of patients developing SHG after receipt of these medications including ocrelizumab[58,59] and obinutuzumab.[60-62] Belimumab, a human mAb inhibiting B-cell activating factor, is not associated with high rates of SHG.[63,64]

Several potential risk factors have been associated with the development of SHG after RTX. Malignant diseases appear to be associated with higher rates of post-RTX SHG than nonmalignant (including autoimmune) disease, with rates ranging from 14% to 50% for lymphoma compared with 3.5% in RA or 4.2% in ANCA-associated vasculitis.[65] Lower pretreatment IgG levels have consistently been identified as a risk factor for developing post-RTX SHG.[55,65-67] Increased RTX exposure has been

TABLE VI. IgG replacement studies in SHG*

Group	Year	Design	*N* (patients unless specified)	IgG-RT type, dose, frequency	Results
SOT	2014[415]	Retrospective	37 with IgG <400 mg/dL (liver, small bowel, kidney, pancreas, heart, lung)	IVIG, median 2 doses (range, 0-38)	Survival, rejection rate, and graft loss rates did not differ between patients with IgG ≥400 mg/dL at last follow-up (n = 23) and IgG <400 mg/dL at last follow-up (n = 14) Variability in timing of last follow-up, organs transplanted, 2 patients had PI
SOT	2019[278]	Meta-analysis	16 studies 887 transplant recipients (heart, lung, liver, multiple organs)	IVIG	LT: IgG-RT improved mortality in patients with HG to level comparable to those without HG HT: IgG-RT significantly reduced mortality in patients with HG IT: No survival benefit with IgG-RT
LT	2015[279]	Cohort	● No HG (n = 60) ● HG treated with IVIG (n = 59)	IVIG, median 5 doses with goal trough 700 mg/dL	5-y survival and 5-y CLAD-free survival comparable between LT recipients with HG receiving IVIG and LT recipients without HG
LT	2014[282]	Randomized, double-blind, placebo-controlled 2-period crossover	● IVIG first (n = 5) ● Placebo first (n = 6)	IVIG 400 mg/kg or placebo monthly for 3 doses followed by 3-mo washout followed by IVIG or placebo monthly for 3 doses	No difference in number of bacterial infections during IVIG or placebo phases. IgG trough levels of mean 765 (720-811) achieved during the IVIG phase compared with 486 (441-532) during the placebo phase
LT	2018[39]	Retrospective	● No HG (n = 76) ● Untreated HG (n = 192) ● HG treated with IVIG (n = 216)	IVIG, median 2 doses	On-demand therapy with IVIG did not mitigate increased CLAD and mortality associated with HG
LT	2018[24]	Prospective observational	133 (78 received median 1 dose)	IVIG, median 1 dose	No differences in incidence or number of days of pneumonia between patients who had or had not received IVIG Study also showed that severe HG associated with 2 or more pneumonias but not with incidence or number of days of pneumonia in first year after transplant
LT	2013[44]	Case series	10	SCIG	SCIG well tolerated and increased IgG levels
HT	2001[259]	Retrospective	● No IVIG (n = 11) ● CMV-Ig (n = 9)	CMV-Ig, mean 1.3 doses	Significantly fewer opportunistic infections (CMV, Nocardia, Aspergillosis, Candida) and rejection in patients with IgG <350 mg/dL who received CMV-Ig
HT	2005[416]	Randomized placebo-controlled	● Placebo (n = 10) ● CMV-Ig (n = 13)	CMV-Ig, mean 1.4 doses	Significantly fewer CMV infections in patients with IgG 350-500 mg/dL who received CMV-Ig

(Continued)

TABLE VI. *(Continued)*

Group	Year	Design	*N* (patients unless specified)	IgG-RT type, dose, frequency	Results
HT	2007[417]	Retrospective	235	IVIG 400 mg/kg every 3 wk for goal IgG trough >700 mg/dL	Incidence of *Clostridium difficile*– associated diarrhea significantly decreased after routine IgG screening and replacement was initiated for patients with IgG <700 mg/dL and severe infections or IgG <400 mg/dL
HT	2007[280]	Retrospective	● No IVIG (n = 94) ● IVIG (n = 29)	IVIG 400 mg/kg every 3 wk for goal IgG trough >700 mg/dL	IgG-RT associated with decreased risk of death and significantly lower infections in patients with IgG <600 mg/dL and infections requiring IV anti-infective therapy
HT	2016[281]	Open-label	● No HG (n = 11) ● HG, IVIG (n = 12) ● HG, no IVIG (n = 13)	IVIG 200 mg/kg 2 wk apart followed by 5 doses of 300 mg/kg every 30 d if IgG remained <750 mg/dL	Significantly lower incidence of severe infections in HG treated with IVIG group compared with no IVIG group
KT	2019[283]	Meta-analysis	18 studies (8 RCCT)	IVIG	IVIG might possibly reduce incidence of rejection and graft loss but did not affect mortality or CMV infection Data limited and inconclusive
IT	2016[284]	Retrospective	23 (liver-small bowel, liver-small bowel-kidney, small bowel)	IVIG, median 3 doses (range, 1-11) 12 patients also received CMV-Ig	Increasing IgG levels to ≥400 mg/dL not associated with improvement in survival, rejection rate, or graft loss CMV-Ig had subtle but not significant impact on survival
CLL	1988[418]	Multicenter, double-blind, randomized, placebo-controlled	81 patients with IgG level ≤50% LLN and serious infections requiring systemic antibiotics	IVIG 400 mg/kg every 3 wk for 1 y vs placebo (saline)	IVIG decreased number and severity of bacterial infections Longer time to first serious bacterial infection on IVIG No difference in nonbacterial infections or all-cause mortality at 1 y No serious adverse reactions
CLL/NHL	1989[419]	Double-blind, randomized, crossover	CLL (n = 8) and NHL (n = 4) patients with IgG <350 mg/dL and recurrent infections	IVIG 400 mg/kg every 3 wk for 1 y vs placebo (saline) then switched over for 1 y	Fewer serious bacterial infections on IVIG No serious adverse reactions
CLL	1994[187]	Double-blind, randomized	34 patients with IgG level below LLN and 1 or more serious infection	IVIG 500 mg/kg every 4 wk for 1 y vs 250 mg/kg	No difference in infection frequency or all-cause mortality No serious adverse reactions
CLL	1994[420]	Open-label	15 patients with IgG level below LLN and recurrent infections	IVIG 10 g every 3 wk for a mean of 15 doses	Fewer hospital admissions and febrile episodes on IVIG No difference in antibiotic prescriptions or severe infections IgG levels stabilized after 11 doses

(Continued)

TABLE VI. *(Continued)*

Group	Year	Design	*N* (patients unless specified)	IgG-RT type, dose, frequency	Results
CLL	1995[421]	Double-blind, randomized	42 patients with IgG <550 mg/dL and 2 or more infections	IVIG 18 g every 3 wk for 1 y (increased to 24 g if breakthrough infections) vs placebo (albumin)	Fewer bacterial infections 50% of patients required dose increase to become infection-free
CLL/MM	1993[422]	Multicenter, randomized, parallel dosing study to determine the dose causing increase in 12 pneumococcal antibody types	● CLL (n = 31) ● MM (n = 31)	IVIG 100 mg/kg vs 400 mg/kg vs 800 mg/kg every 3 wk	Recommended dose for CLL: 400 mg/kg every 3 wk until week 12 when steady state reached Recommended dose for MM: 800 mg/kg loading dose followed by 400 mg/kg every week
CLL/MM	2009[180]	Meta-analysis	9 trials of patients with CLL and/or MM	IVIG	No survival benefit Significant decrease in frequency of major infections and clinically documented infections
CLL	1996[423]	Randomized, crossover	42 patients with IgG <600 mg/dL and at least 1 episode of severe infection during previous 6 mo	300 mg/kg IVIG every 4 wk for 6 mo vs no treatment followed by switch to other arm for 12 mo followed by switch back to initial arm for 6 mo	Significantly fewer bacterial infections on IVIG
CLL	1988[424]	Descriptive	2	IVIG	Home self-administration feasible and safe without serious adverse reactions and improved patient compliance
CLL/NHL	2013[9]	Retrospective	● Diffuse large B-cell lymphoma (n = 65) ● FL (n = 42) ● CLL- SLL (n = 38) ● MZL (n = 30) ● MCL (n = 19) ● Other (n = 17)	IVIG	Significantly decreased frequency of recurrent nonneutropenic infections in the 6 mo after initiation of IVIG compared with the 6 mo before

CLAD, Chronic lung allograft dysfunction; *CMV*, cytomegalovirus; *FL*, follicular lymphoma; *IV*, intravenous; *IT*, intestinal transplant; *LLN*, lower limit of normal; *MCL*, mantle cell lymphoma; *MZL*, marginal zone lymphoma; *NHL*, non-Hodgkin lymphoma; *RCCT*, randomized controlled clinical trial; *SLL*, small lymphocytic lymphoma.
*Results of studies investigating potential utility of IgG-RT in SHG are summarized.

identified as a risk factor for developing post-RTX SHG, but this finding has not been observed consistently across all studies.[55,65,66] Mycophenolate and cyclophosphamide exposure has been associated with increased risk for post-RTX HG,[55,65] whereas methotrexate has not.[67] Clinically, post-RTX SHG has been associated with increased numbers of infections.[56]

Guidelines recommend routine pre-RTX screening to identify patients with underlying immune dysfunction, because they may be at a higher risk of developing infectious complications.[68-70] Furthermore, immune evaluation may reveal the underlying PI.[71] Low baseline CD4 lymphocyte counts, post-RTX SHG persisting for more than 6 months, and comorbidities (chronic lung disease, cardiac insufficiency, extra-articular involvement in patients with RA, diabetes, and neutropenia requiring granulocyte colony-stimulating factor) are risk factors for developing infections post-RTX.[65,72] Older age has also been found to be predictive of sustained SHG and increased infections in multiple studies.[56,66,67,73]

Use of corticosteroids and other immunosuppressants affects the risk for post-RTX SHG, although study results are mixed, likely due to the heterogeneity of the patient populations studied and differences in dosing and length of treatment. It is important to note that corticosteroid-associated SHG does not result in increased frequency or severity of infectious complications and that corticosteroids do not appear to affect specific antibody responses to tetanus, pneumococcal, and influenza vaccines.[74] Mycophenolate and corticosteroid use may contribute to post-RTX SHG, and corticosteroid use has been identified as a risk factor for developing infections post-RTX.[65,72,73]

B-cell reconstitution occurs approximately 6 to 9 months after RTX monotherapy, and after 18 to 24 months in patients receiving a combination of chemotherapy and RTX.[75,76] Differential recovery is seen between conditions, with B-cell depletion lasting a median of 8 months in connective tissue disease, 9 months in RA, 21 months in eosinophilic granulomatosis with polyangiitis, and 26 months in granulomatosis with polyangiitis/microscopic polyangiitis.[77] There have been reported cases of B-cell depletion persisting up to 12 years after RTX treatment.[78] The recovery of the $CD27^+$ memory B-cell pool is delayed beyond the recovery of B cells.[79,80] Immune reconstitution post-RTX is likely influenced by several factors including underlying immune disease, age-related immune maturation,[65] and concomitant treatments.

B-cell recovery after non-RTX BCTT has been shown to take a median of 72 weeks after ocrelizumab treatment.[81] Higher doses of ofatumumab have been associated with lower rates of and/or longer time to B-cell repletion.[82]

Bacterial sinopulmonary infections are the most common infectious complications in patients with post-RTX SHG.[9] However, as with many other forms of SHG, post-RTX SHG has also been associated with nonbacterial infections, including latent hepatitis B reactivation and progressive multifocal leukoencephalopathy.[83] RTX and ofatumumab both have a black box warning regarding the increased risk of hepatitis B virus reactivation in patients positive for hepatitis B virus surface antigen or core antibody.[84,85] Progressive multifocal leukoencephalopathy has been reported in patients after treatment with RTX for lymphoproliferative disease, SLE, RA, idiopathic autoimmune cytopenia, and immune thrombocytopenia, with a case-fatality rate of 90%.[86,87] Progressive multifocal leukoencephalopathy has also been reported in patients treated with other BCTTs including obinutuzumab and ofatumumab.[88] Several other viral infections have also been described in association with RTX, including enteroviral meningoencephalitis,[57,89] cytomegalovirus infections,[90-92] and parvovirus B19 infections.[93-96] As such, patients on BCTT should be carefully monitored for early signs and symptoms of viral infections in addition to bacterial infections.

Evaluation. Rheumatology guidelines have screening and monitoring recommendations for patients with ANCA-associated vasculitis, RA, and SLE treated with BCTT (Table IV). Screening and monitoring serum IgG levels and clinical monitoring for infections may help mitigate morbidity and mortality by allowing timely identification of patients with clinically significant SHG who may benefit from IgG-RT. Peripheral B-cell flow cytometry before and after initiating BCTT to quantitate B cells could improve longitudinal monitoring by enabling comparisons over time (Fig 1).

Management. Vaccinations are an important part of infection prophylaxis in patients treated with RTX. Because B-cell depletion occurs with BCTT, there is concern for blunted immunization responses. Multiple studies have found that RTX treatment decreases immune responses to recall antigens tetanus toxoid and poliomyelitis vaccine[97] as well as polysaccharide and conjugated vaccines.[98-100] Live vaccines are not recommended during treatment with BCTT until B-cell repletion occurs.[101-103]

The most rigorous studies include 2 randomized clinical trials (RCTs) in adult patients with RA. An RCT of 103 patients with RA found that RTX-treated patients had decreased responses to pneumococcal polysaccharide vaccine (PPSV23) but preserved responses to tetanus toxoid vaccine compared with controls, and the authors concluded that polysaccharide and primary immunizations should be administered before RTX infusions to maximize responses.[104] Another RCT comparing untreated healthy patients, methotrexate-treated patients with RA, and RTX-treated patients with RA found that anti-influenza antibodies increased after vaccination in untreated healthy controls, methotrexate-treated patients with RA, and a subgroup of RTX-treated patients with RA who received the influenza vaccine 6 to 10 months post-RTX but not in the other RTX-treated patients with RA.[105] The authors concluded that RTX reduces humoral vaccine responses in patients with RA, with modest restoration 6 to 10 months after RTX administration.[105]

Given these findings, multiple groups including the European League Against Rheumatism have recommended that vaccines be given before (ideally 4 weeks before) administration of RTX. For patients who have already received RTX, vaccines are recommended 5 to 6 to 12 months after the last course of BCTT and 4 weeks before the next if possible.[68,106-109] The European League Against Rheumatism and Infectious Diseases Society of America consider RTX high-level immunosuppression and recommend avoidance of live vaccines for patients on RTX.[108,110]

The COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force recommends initiating the COVID-19 vaccine series approximately 4 weeks before the next scheduled RTX cycle and administering the next RTX infusion 2 to 4 weeks after the full vaccine series, in patients whose COVID-19 risk is low or mitigated by preventive health measure and when disease activity allows.[111] Following recommendations for other vaccines, in addition to initiating the COVID-19 vaccine series 4 weeks before the next scheduled RTX cycle, initiating the COVID-19 vaccine series 5 to 6 to 12 months after the last RTX cycle could allow for better recovery of immune responses. Given the nuances in balancing disease management with infection prevention, decisions about vaccine timing should be made primarily by the treating physician with input by clinical immunology if needed.

Data regarding vaccine efficacy in non-RTX BCTT are limited. The VELOCE study investigated vaccine responses to tetanus toxoid vaccine, PPSV23 alone, PPSV23 followed 4 weeks after by pneumococcal 13-valent conjugate vaccine (PCV13), influenza vaccine, and neoantigen keyhole limpet hemocyanin in patients treated with ocrelizumab.[112] This study was interesting in that investigators attempted to home in on the specific effect of 1 cycle (2 doses) of ocrelizumab by excluding patients who had preexisting HG, had prior treatment with BCTT, or had received non-BCTT immunosuppressive treatment (lymphocyte-trafficking blockers, alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate, cyclosporine, methotrexate, total body irradiation, bone marrow transplant). Patients were also excluded if they had received tetanus toxoid vaccines in the 2 years before screening or PPSV23 in the 5 years before screening.

The VELOCE study found that antibody responses were present but attenuated to tetanus toxoid vaccines, all 23 serotypes in PPSV23, and the influenza vaccine, with pneumococcal responses being the most affected of the 3. Additional vaccination with PCV13 4 weeks after PPSV23 did not lead to significant increases in the antibody responses to the serotypes included in PCV13. Another key finding from the study was that responses to keyhole limpet hemocyanin requiring recognition by naive B cells were the most significantly attenuated of all. This suggests that plasma cells less affected by BCTT can retain and exert some memory function from pre-BCTT exposures through routine vaccination and natural infection, and highlights the importance of ensuring that appropriate vaccinations are completed before initiation of BCTT.[113]

Appropriate vaccinations may be adequate to prevent infections in patients on limited immunosuppression and/or with shorter-term exposure to BCTT.[56,57] Patients with persistent SHG and serious and/or recurrent infections who do not improve with vaccination may benefit from consideration of antibiotic prophylaxis and/or IgG-RT to reduce the risk of infections.[56,57] However,

TABLE VII. SOT HG and associated clinical outcomes*

Patient group	Immune changes posttransplant	Clinical outcomes
LT HG IgG <600 or <700	HG (adult): ● 89% during first 72 h[24] ● 56%-73% during first year[24,247,252,253,255,256] Associated immune changes (adult): ● Low IgA in 26%-27%,[247,254] with lower post-LT IgA levels associated with pretransplant bronchiolitis obliterans and COPD[253,254] ● Low IgM in 9%[247,254] ● 30%, 15%, and 19% of patients with HG lacked protective responses to pneumococcus, diphtheria, and tetanus, respectively[247] Immune recovery: HG rate down to 44% 2.5 y after transplant[254] Pediatric: ● HG in 49% during first year post-LT[248] ● Low IgA in 12% post-LT[248] ● Low IgM in 17% post-LT[248]	● IgG levels inversely correlate with bacterial infections, hospital days, bronchiolitis obliterans-free survival, invasive fungal infections[248,254] ● 7 d post-LT: ■ IgG <600 mg/dL associated with ↑ risk of CMV infection and serious fungal infections (systemic aspergillosis, systemic candidiasis)[255] ■ IgG decrease of ≥700 mg/dL compared with baseline was risk factor for serious bacterial infection[255] ● 3 mo post-LT: ■ Lower IgG levels predictive of ↑ 1-y mortality[24] ■ Lower ALC associated with developing 2 or more pneumonias[24] ● Lower IgA and IgM levels associated with invasive aspergillosis, ↑ community-acquired respiratory viral infections, ↑ bacterial infections, ↑ hospital days[248]
LT severe HG IgG <400	Severe HG in 6%-37%[24,247,252,255,256] Immune recovery: Severe HG improves with time[24,255] ● 32% in the first 72 h post-LT ● 21% at 7-30 d post-LT ● 6%-9% at 3, 6, 9, 12 mo post-LT	Severe HG associated with: ● Worse survival and ↑ odds of 1-y all-cause mortality (21.91 times higher for patients with severe HG) ● ↑ overall infections, bacterial infections, fungal infections, respiratory infections and pneumonias, bacteremia, CMV infections and invasive CMV, Aspergillus infections, and invasive aspergillosis ● ↑ antibiotic courses ● ↑ median hospital days per posttransplant year ● Not associated with rejection[23,24,247,253,256]
HT HG IgG <600	HG in 54%-70% post-HT[417,425]	● ↓ pretransplant and posttransplant IgG and pretransplant IgG_1 associated with ↑ infection[425,426] ● HG 7-d post-HT risk factor for any infection, bacterial infection, and CMV infection in analysis of 170 adult HT recipients at 8 centers in Spain[427]
HT Severe HG IgG <350	Severe HG in 10% during first year post-HT[259]	
KT HG IgG <650-<700	HG in 40% post-KT[23] Immune recovery: HG improves with time[262-264] ● 56% of patients 15 d post-KT ● 52% at 1 mo ● 45% at 3 mo ● 31%-37% at 6 mo ● 30% at 12 mo	● ↓ IgG levels associated with significant infection, sepsis, respiratory tract infections, severe bacterial infections, severe bacterial infection-free survival, *C difficile* infections, and CMV infections refractory to antiviral therapy[261,264-269] ● ↓ IgG level at time of transplant associated with ↑ infections in the first 3 mo post-KT[262] ● ↓ levels of any immunoglobulin class 1-mo post-KT associated with ↑ overall infection, bacteremia, and acute pyelonephritis in the 6 mo post-KT[263] ● ↓ levels of any immunoglobulin class 6 mo post-KT associated with ↑ overall infection and bacterial infection 6-12 mo after transplant[263]

ALC, Absolute lymphocyte count; *CMV*, cytomegalovirus.
*Reported observations regarding immune changes and associated clinical outcomes observed in SOT are shown.

it is important to note that SHG due to BCTT is currently not a Food and Drug Administration (FDA)-approved indication for IgG-RT (IVIG or SCIG).

Given the existing guidelines and literature regarding BCTT-associated SHG, screening and monitoring of immunoglobulins as well as careful consideration of heightened clinical monitoring, vaccinations, antibiotic prophylaxis, and/or IgG-RT when appropriate may improve clinical outcomes by decreasing infections. Facilitating adoption across the many specialties in which BCTT is used may be helpful.

BCTTs (pediatric considerations)

There are increasing reports of pediatric patients developing SHG on RTX, with some receiving IgG-RT (IVIG or not specified in report if IVIG or SCIG).[114-125] The kinetics of humoral immune depletion/recovery post-RTX in pediatric patients are similar to those in adults, with B-cell numbers starting to recover at approximately 6 months and recovering by approximately 12 months post-RTX treatment.[123,126] The timing of immune reconstitution is influenced by the underlying condition, concomitant treatments, and age-related immune maturation.[126,127]

Persistent SHG has been observed 6 to 12 months after the last dose of RTX in 32% to 44% of children with autoimmune cytopenia, SLE, central nervous system disease, and ANCA-associated vasculitis.[120,121] In a case series of 12 pediatric patients on RTX and 16 patients on oral immunosuppression (mycophenolate or cyclosporine), SHG was observed in 67% (8 of 12) on RTX compared with 31% (5 of 16) on oral immunosuppression.[125]

There are reports of patients with HG who were ultimately diagnosed with PI both before and after RTX initiation.[122,124,128] In a study of 53 patients with autoimmune cytopenia treated with RTX, 17% (9 of 53) were later diagnosed with PI, and PI was more prevalent in the group with persistent HG (53%; 9 of 17).[121] This highlights a recurring theme throughout this work group report—the importance of involving clinical immunologists in the evaluation of HG given the possibility of underlying PI.

Reported risk factors for persistent SHG in the pediatric population include younger age, diagnosis of autoimmune hemolytic anemia or Evans syndrome versus immune thrombocytopenia, autoimmune manifestations other than autoimmune cytopenia, lower pre-RTX IgA and IgM levels, and impaired post-RTX recovery of IgA and IgM levels and B-cell numbers.[121] Low IgG pre-RTX has also been associated with an increased risk of persistent HG post-RTX.[124] Interestingly, low lymphocyte counts have not been associated with SHG post-RTX as it has been in adult populations.[121] In a study of 136 patients with lymphoma treated with combination chemotherapy and 8 or more RTX doses, low IgG levels at time of lymphoma diagnosis and particularly combination fludarabine/RTX therapy were associated with SHG lasting longer than 6 months.[129]

Low IgG at any time post-RTX has been associated with a higher risk of serious infections.[124] In addition, 1 study found that 12% of patients with persistent SHG 12 months post-RTX developed infections requiring hospitalization and 15% developed recurrent respiratory infections.[121] The study of 136 patients with lymphoma found that SHG after combination fludarabine/RTX therapy was associated with severe infections and infection-related mortality.[129] However, not all cases of pediatric SHG post-RTX are associated with infections.

Summary of previously published literature: BCTT

SHG with the potential risk for infections occurs commonly after BCTTs.

- *Evaluation:* Serum IgG levels and peripheral B-cell flow cytometry before and after initiating BCTT help identify HG that exists before starting BCTT and allow timely identification of SHG that occurs after starting BCTT (Society Guideline, Table IV) (Fig 1).
- *Vaccination:* Vaccinations are an important part of infection prophylaxis in patients treated with RTX, but immunization responses can be blunted. A previous review has recommended administering vaccines at least 6 months after the last course of RTX and 4 weeks before the next if disease activity allows, and the American College of Rheumatology published similar recommendations regarding timing of COVID-19 vaccination.[111,130] Passive immunization with tetanus immunoglobulin has been recommended for patients at high risk for tetanus who have been treated with RTX in the last 24 weeks.[130] Live vaccines are not recommended until B-cell repletion occurs. Vaccine recommendations in pediatric patients on RTX are similar to those in adults, with establishment of adequate antibody titers before RTX initiation considered the best preventative measure.[131] Given the nuances in balancing disease management with infection prevention, decisions about vaccine timing should be made primarily by the treating physician with input by clinical immunology if needed.
- *Management:* Per the American College of Rheumatology, IgG-RT can be considered in collaboration with a clinical immunologist for patients with granulomatosis with polyangiitis or microscopic polyangiitis receiving remission maintenance therapy with RTX who have IgG levels less than 300 mg/dL and recurrent severe infections, or without recurrent infections but with impaired vaccine responses (Table V).[132] Based on the PI literature, IgG-RT could be considered even in the absence of infections if IgG levels are persistently low (Fig 2). Given what is known about the kinetics of B-cell and IgG recovery following RTX,[76-78] reevaluation of immune function could be considered in patients who are clinically stable and infection-free 9 to 12 months after RTX discontinuation. Based on previous observation and the clinical experience of the authors, IgA and IgM levels as well as B-cell counts could be followed to assess recovery in patients still on IgG-RT.[78] Assessment of specific antibody response to immunization with neoantigens for patients still on IgG-RT could theoretically be helpful but logistically challenging.[31]
- *Areas of uncertainty:* Clinical studies are needed to validate these recommendations, including studies to further establish the benefit of IgG-RT in adult patients with SHG and recurrent sinopulmonary infections from BCTT. There are no studies investigating IgG-RT as infection prophylaxis in pediatric post-RTX SHG without infections, and most studies in the pediatric population are needed. RCTs comparing IgG-RT with vaccination/antibiotic prophylaxis are needed to identify the optimal treatment strategies that would improve clinical outcomes. RCTs are needed to demonstrate the equivalency of SCIG to IVIG.

Corticosteroids

CD4 T-cell lymphopenia is the immune defect most commonly associated with chronic systemic corticosteroid use.[133] SHG has been described in 12% to 58% of patients on chronic or high-dose corticosteroid therapy in adult patients.[134-136] IgA and IgM levels are less affected than IgG levels by corticosteroids.[137]

Short courses of oral corticosteroids have been associated with a transient drop in serum IgG, which can last for several weeks beyond the cessation of the corticosteroid burst.[138,139] Long-term oral corticosteroid therapy has been associated with more significantly decreased IgG levels.[135,136] High-dose inhaled corticosteroids have not had a demonstrable effect on serum IgG levels.[135]

Proposed mechanisms for corticosteroid-associated SHG include elevated immunoglobulin catabolism, decreased immunoglobulin synthesis due to increased apoptosis of B-cell subsets and/or plasma cells, or downregulation of genes involved in immunoglobulin synthesis.[136,140-142]

Unlike other types of SHG discussed in this report, corticosteroid-associated SHG does not appear to be associated with an increased frequency or severity of infectious complications. Studies have demonstrated normal specific antibody

responses in patients with corticosteroid-associated SHG. Specific antibody responses to tetanus, pneumococcal, and influenza vaccines were not shown to differ between patients on chronic oral corticosteroids with and without SHG, and patients not on oral corticosteroids.[74] Normal antibody responses to protein, polysaccharide, and bacteriophage antigens were found in 9 pediatric patients on chronic oral corticosteroids with SHG.[143] In a case series, impaired pneumococcal response in 3 adults on chronic oral corticosteroids with IgG levels less than 400 mg/dL and normal tetanus protein antibody responses did not correlate with sinusitis or pneumonia frequency.[134]

Of note, high-dose corticosteroid use is associated with increased susceptibility to infections, particularly opportunistic infections, but largely in part due to corticosteroid-associated lymphopenia rather than SHG.[144-146] Pneumocystis pneumonia prophylaxis is recommended for patients with underlying immunocompromising conditions (eg, posttransplant, malignancy, and additional immunosuppression) on high doses of corticosteroids (prednisone ≥20 mg daily or equivalent dosing for ≥1 month) and for 1 month after discontinuation.[144,147]

Summary of previously published literature: Corticosteroids

Although infection is a well-documented risk of corticosteroid use, corticosteroid-associated SHG itself does not seem to result in increased frequency or severity of infectious complications.

- *Evaluation:* Because corticosteroid-associated SHG is not typically associated with increased infection risk, screening and monitoring of IgG levels is not routinely recommended.
- *Vaccination:* Vaccine responses may be preserved in patients on chronic oral corticosteroids, but further study is needed in this area.
- *Management:* In the absence of severe or recurrent sinopulmonary bacterial infections, use of IgG-RT is not routinely recommended for corticosteroid-associated SHG.
- *Area of uncertainty:* Additional studies are needed to clarify the effect of corticosteroid-associated SHG on vaccination responses and infection outcomes.

RHEUMATOLOGY

SHG has been observed in 8.4% to 15.7% of adult patients with SLE previously on immunosuppressive therapy (including corticosteroids, azathioprine, mycophenolate, low-dose cyclophosphamide).[148,149] Selective IgA deficiency has been observed in 2.4%, and decreased IgM in 17%.[148] Duration of renal disease, nephrotic range proteinuria, and degree of immunosuppression have been associated with increased rates of SHG.[148,149]

Evaluation

Multiple rheumatology society guidelines recommend baseline screening and monitoring of immunoglobulin levels for patients with RA and ANCA-associated vasculitis who will receive BCTT.[68-70,150] Baseline screening and monitoring of immunoglobulin levels are also recommended for patients with SLE before starting immunosuppressive agents such as mycophenolate, cyclophosphamide, and RTX, which place patients at risk for SHG.[151] This allows heightened monitoring for infections and timely initiation of IgG-RT and/or antibiotic prophylaxis when appropriate.[2,4,152]

Furthermore, in pediatric patients with autoimmune manifestations, baseline screening of humoral immunity could identify undiscovered PI.[2,4,5] In a study of 86 pediatric patients with SLE, HG was identified in 7% (6 of 86) a median of 27 months after SLE diagnosis.[3] Three patients were started on IVIG due to increased infections, and 1 patient started IVIG as infection prophylaxis for an IgG level of 65 mg/dL.[3] In this study, HG development was associated with white race, male sex, and presence of lupus nephritis but not with use of immunosuppressive therapy.[3]

Management

Currently, studies specifically investigating the use of IgG-RT for SHG in rheumatologic disease are lacking, and decision making is primarily guided by the PI literature. The persistence of HG, coexisting specific antibody defects, infection history, and the immunosuppressive therapy in use or being considered are important considerations for deciding whether IgG-RT is indicated for HG treatment in rheumatologic disease.[4,148,152] In 1 study, higher cumulative doses of IgG-RT (not specified if IVIG or SCIG) for post-RTX SHG were associated with reduced risk of serious infectious complications.[56] IgG-RT treatment decisions are further complicated by the fact that IVIG is often used as an immunomodulatory, not replacement, therapy for autoimmune conditions including Kawasaki disease, chronic inflammatory demyelinating polyneuropathy, acute inflammatory demyelinating polyradiculoneuropathy, inflammatory myopathies, SLE,[151] and ANCA-associated vasculitis.[35,153]

In addition to the vaccination recommendations for patients receiving BCTT reviewed in the BCTT section, there is a recommendation to hold methotrexate for 2 weeks before influenza vaccination.[154,155]

Summary of previously published literature: Rheumatology

Multiple societies recommend baseline screening and monitoring of immunoglobulin levels for patients with SLE, RA, and ANCA-associated vasculitis who receive BCTT and/or other immunosuppressive agents that place patients at risk for SHG. In RA, IgG level screening is recommended before starting RTX. Subsequent monitoring is recommended 4 to 6 months after RTX infusions and before re-treatment, particularly in patients with low baseline IgG levels and other groups at high risk for infections.[68,70] In ANCA-associated vasculitis, IgG level screening is recommended before starting RTX and in patients with recurrent infection.[69,150] In SLE, IgG level screening is recommended at time of diagnosis and before starting immunosuppressive agents that place patients at most risk for SHG (mycophenolate, cyclophosphamide, RTX). After initiation of immunosuppression, repeat immunoglobulin levels are recommended 3 to 6 months later and then annually[151] (Table IV).

- *Evaluation:* Evaluation of humoral immunity at time of autoimmune diagnosis can uncover PI, with implications for subsequent workup and management. Including peripheral B-cell flow cytometry in screening and monitoring can possibly aid in identifying high-risk patients and assessing immune reconstitution after BCTT. In patients with a history of infections, we recommend screening for PI at time of autoimmune

diagnosis if not already performed. In addition to infections, a history of autoimmune cytopenia, splenomegaly, lymphoma, interstitial/inflammatory lung disease with benign lymphoproliferative pathology on lung biopsy, atrophic gastritis, chronic enteropathy, and autoimmune liver disease should prompt a PI consultation and evaluation by a clinical immunologist, and consideration of genetic testing may be helpful in patients who have already received immunosuppressive therapy for whom baseline evaluations cannot be performed[156,157] (Fig 1).

- *Vaccination:* Given the number of immunosuppressive agents administered for rheumatologic conditions, completing vaccination series before initiation of said immunosuppressive agents is recommended.[130] In particular, influenza and pneumococcal vaccinations have been recommended.[130] Additional recommendations specific to BCTT are included in the previous BCTT section. COVID-19–specific recommendations have been published by the American College of Rheumatology.[111]
- *Management:* Per the American College of Rheumatology, IgG-RT can be considered in collaboration with a clinical immunologist for patients with granulomatosis with polyangiitis or microscopic polyangiitis receiving remission maintenance therapy with RTX who have IgG levels less than 300 mg/dL and recurrent severe infections, or without recurrent infections but with impaired vaccine responses (Table V).[132] Based on the PI literature, IgG-RT could be considered even in the absence of infections if IgG levels are persistently low (Fig 2). Decisions regarding initiation of IgG-RT are heavily based on the PI literature and complicated by the fact that IVIG is used in autoimmune purposes as an immunomodulatory therapy distinctly separate from replacement therapy.
- *Areas of uncertainty:* Studies are needed to identify features that differentiate PI with autoimmune manifestations from autoimmune conditions with SHG. In addition, as with other patient populations, investigation into optimal criteria for initiating antibiotic prophylaxis and/or IgG-RT is needed. RCTs are needed to demonstrate the equivalency of SCIG to IVIG.

NEUROLOGY

SHG has been identified in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) in large part due to the increasing use of BCTT.[158,159] Risk factors for SHG include low IgG levels before BCTT, duration of BCTT, and use of other immunosuppression (including cyclophosphamide and corticosteroids) before or in conjunction with BCTT.[158]

In MS, the underlying disease process and use of immunosuppression may contribute to SHG development. In a recent study comparing patients with and without MS, a trend toward lower IgG levels was observed in patients with MS, and lower IgG levels were observed in secondary progressive MS compared with relapsing- remitting and primary progressive MS.[160] In addition, use of disease-modifying therapies was associated with a higher prevalence of IgG levels less than 700 mg/dL (26.4% [34 of 129] vs 8.1% [16 of 198]), and treatment with RTX, intravenous corticosteroids, natalizumab, and fingolimod was significantly associated with lower IgG levels (no patients in this study were treated with ocrelizumab).[160] In another cohort of patients with MS, SHG was mostly associated with prior receipt of BCTT (RTX, ocrelizumab, or both), but was also observed in patients who received only non-BCTT immunomodulatory agents.[161]

In NMOSD, HG has been observed in patients both before and after RTX initiation. Infectious complications have been reported in up to 17% to 45% of patients with SHG.[161-164]

Common variable immunodeficiency has been diagnosed in patients with MS and NMOSD found to have HG, highlighting the importance of involving clinical immunologists in the evaluation of these patients.[160,161]

Non-BCTTs used to treat MS and NMOSD have also been associated with SHG and other iatrogenic immunodeficiencies. Natalizumab and cyclophosphamide have been associated with SHG,[165,166] and dimethyl fumarate and fingolimod with lymphopenia.[159] Studies are needed to elucidate the baseline incidence of HG in these patient populations before BCTT and the contribution of other immunosuppressive agents used to treat these conditions.

FcRn antagonists are being evaluated as a treatment approach for myasthenia gravis, pemphigus and other conditions.[378,379,428] Efgartigimod is the first of this new class of medication to receive FDA approval in December 2021 for the treatment of myasthenia gravis.[429,430] Neonatal Fc receptor (FcRn) antagonists bind to FcRn with increased affinity compared to endogenous IgG; this interferes with the FcRn-mediated recycling of the IgG molecule, leading to reduction in serum IgG levels.[378] Although pathogenic IgG autoantibodies and total IgG are reduced, other serum immunoglobulins, plasma cells, and B cells are not affected.[378] Functional antibody responses during/after FcRn inhibition have not been fully evaluated but are expected to remain unaffected as FcRn inhibition does not alter B cell numbers or function.[378]

Evaluation

Neurology publications have recommended monitoring immunoglobulins and regular screening for infections during BCTT treatment, similar to the recommendations made in rheumatology guidelines.[158,163] Of note, autoimmune neurologic conditions can be a manifestation of common variable immunodeficiency, and attention is needed to the possibility that PI could be the cause of pretreatment HG.[167] Lymphocyte counts, typically monitored to adjust dosing schedules on the basis of timing of B-cell repletion, can also help identify patients with prolonged B-cell depletion or low memory B-cell counts.[158]

Management

Vaccination is arguably one of the most effective methods for infection prophylaxis in MS.[168] However, patients with MS and NMOSD frequently receive BCTT and are therefore subject to potentially attenuated vaccine responses.[113] Vaccination strategies are largely extrapolated from the RTX literature discussed in the BCTT section. Studies investigating the effects of BCTT specifically in patients with MS and NMOSD remain limited, but include the VELOCE study discussed in the BCTT section and another study that found attenuated antibody responses to influenza vaccination in RTX-treated patients with NMOSD compared with azathioprine- or IFN-β–treated patients with NMOSD and healthy controls.[100,112] Administering vaccines (particularly pneumococcal, influenza, and recombinant adjuvanted zoster vaccine) before the initiation of BCTT has been recommended.[113]

Although the reduction of IgG was transient and reversed following discontinuation of efgartigimod in clinical trials, the FDA package insert recommends against vaccination with live-attenuated or live vaccines during treatment with efgartigimod due to these transient decreases in IgG levels.[428,430]

In addition, antibiotic prophylaxis in patients with NMOSD with SHG experiencing recurrent infections or with bronchiectasis has been reported as a strategy for infection prophylaxis.[162] Adjustment of RTX doses or treatment schedules for patients with infections, SHG, and persistent leukopenia has also been reported.[164]

Reports of IgG-RT use in patients with NMOSD with SHG and infections are limited to case reports, and decisions to initiate IgG-RT (IVIG or not specified if IVIG or SCIG) in patients with neurologic conditions are heavily based on PI guidelines.[59,161-163,169]

Summary of previously published literature: Neurology

Recommendations for SHG evaluation and management in neurologic conditions are heavily based on Rheumatology/BCTT and PI guidelines (Tables IV and V) given the paucity of literature investigating SHG in this specific patient population.

- *Evaluation:* Screening at time of diagnosis and before initiation of BCTT with at least a serum IgG level is recommended. Monitoring serum IgG levels and examining peripheral B-cell flow cytometry before and after initiating therapy allow timely identification of SHG and heightened clinical monitoring for infections as appropriate (Fig 1).
- *Vaccination:* Vaccinations are an important part of infection prophylaxis. When possible, vaccinations should be administered before initiation of immunosuppressive agents other than IFN-β (generally considered to exert less negative effect on immunization responses).[101,170] BCTT-specific recommendations are outlined in the BCTT section. In addition, in this specific patient population, influenza, pneumococcal, and recombinant adjuvanted zoster vaccine have been recommended before initiation of BCTT if applicable.[113]
- *Management:* In addition to vaccination, antibiotic prophylaxis, BCTT dose/frequency adjustment or discontinuation, and IgG-RT have been reported as strategies for infection prevention. Clinical immunologists can aid in SHG management by creating a plan for infection prevention with vaccination, antibiotic prophylaxis, and possibly IgG-RT while allowing BCTT to be continued without adjustment/discontinuation. If IgG-RT is initiated and there are no plans for BCTT readministration, it may be reasonable to pause IgG-RT after 9 to 12 months depending on the clinical situation to allow for reevaluation of immune function in patients who are clinically stable and infection-free (Fig 2).
- *Areas of uncertainty:* Clinical studies are needed to validate these recommendations, including studies to investigate optimal screening protocols and refine criteria for whether and when to initiate IgG-RT. RCTs comparing IgG-RT with vaccination/antibiotic prophylaxis are needed to identify the optimal treatment strategies that would improve clinical outcomes. RCTs are needed to demonstrate the equivalency of SCIG to IVIG.

HEMATOLOGY/ONCOLOGY

Evaluation

Immune evaluation in cases of suspected SHG in hematologic/oncologic conditions is based on PI evaluation[7,172-174] and currently include quantitative immunoglobulins, specific antibody titers, and T/B/natural- killer-cell immunophenotyping.[7] BCTT and other immunosuppressive or immune-ablative therapies commonly used to treat hematologic/oncologic conditions as well the underlying pathophysiology of B-cell malignancies contribute to SHG development.[7,172-174]

Screening humoral immune function before initiation of treatment should be considered when there is a high risk for developing SHG. Currently, it is recommended at time of CLL diagnosis and before initiation of CD19 CAR-T-cell therapy, which can cause SHG by depleting $CD19^+$ B cells.[11,29,174-176]

Management

Treatment guidance for IgG-RT in SHG due to hematologic malignancies has not been standardized, and clinical practice varies despite treatment guidelines.[174,177] Prophylactic IgG-RT (IVIG or SCIG) in the absence of infections has only been recommended for IgG levels less than 400 mg/dL during the first 3 months after initiation of CD19 CAR-T-cell therapy.[29] There is agreement that IgG-RT should be considered in patients with SHG associated with hematologic/oncologic conditions and severe and/or recurrent infections, particularly if infections are sinopulmonary or secondary to encapsulated bacteria.[7,42,173,174,178] Consultation with a clinical immunologist is recommended for cases in which IgG-RT use has not been clearly defined.[174]

When IgG-RT is clinically indicated, a dosing range of IVIG 0.4 to 0.8 mg/kg of absolute body weight every 28 days is recommended.[7,42,172-174,178-180] Alternatively, using precision body weight (ideal or adjusted body weight) instead of the actual body weight to dose IVIG was shown to be equally effective at preventing infections in patients with hematologic malignancies with cost saving.[34] In addition, SCIG appears to be a reasonable alternative to IVIG for SHG in hematologic/oncologic conditions, with a recent study finding that SCIG was well tolerated, decreased infections, improved quality of life, and was fairly cost-effective.[42,43] However, SCIG is not currently approved by the FDA for SHG in hematologic/oncologic conditions in the United States.

Chronic lymphocytic leukemia

SHG in CLL can be seen frequently both as a consequence of the underlying disease process affecting immunoglobulin production and the BCTT and immunosuppressive agents used for treatment.[6-8,176,181] SHG incidence increases with longer disease duration and immunosuppressive therapy.[181,182]

Immune changes in CLL that lead to SHG include defective B-cell maturation due to decreased T_H-cell or increased suppressor T-cell activity,[183] poorly functioning nonclonal CD5-negative B cells,[184] and direct CD95L/CD95 suppression of $CD95^+$ bone marrow plasma cells.[185] CLL-B cells can replace normal B cells[183,186] and directly suppress IgG production by plasma cells in the bone marrow.[181]

The clinical spectrum of SHG in CLL ranges from asymptomatic laboratory abnormality to increased infectious burden with frequent/chronic or severe sinopulmonary and/or opportunistic

infections.[6-8] Independent of B cells, dysfunctional dendritic cells or natural killer cells and neutropenia also modulate the risk and spectrum of infections.[8,187] Renal and gastrointestinal losses can further exacerbate SHG, infection burden, and mortality risk.[11,188]

Evaluation of immunosuppression is further complicated in CLL given the number of immunosuppressive agents that are used for treatment. Patients on epratuzumab, an anti-CD22 therapy that targets plasma cells and diminishes IgG and IgM, are at increased risk for varicella-zoster virus infection and may benefit from prophylactic or prompt access to antiviral medication.[189]

Inhibitors of Bruton tyrosine kinase and PIK3 have the potential to mimic PIs that are caused by mutations in the genes encoding these proteins.[190,191] In 1 study, treatment with Bruton tyrosine kinase inhibitor (ibrutinib) was associated with decreases in IgG levels starting at 12 months.[190] However, in the same study, there were increases in IgA (with increases in IgA levels ≥50% from baseline to 12 months associated with significantly less infections), nonclonal free light chains, and the percentage of normal B cells on ibrutinib compared with pretreatment, highlighting the complexity of immune evaluations in CLL in which immunosuppressive therapies can also lead to immune recovery.[190] HG with recurrent infections responding to SCIG has been reported in a patient with CLL on ibrutinib.[192]

The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency recommends that patients receiving idelalisib, a PIK3 inhibitor, be informed about the risk of serious and/or fatal infections, given Pneumocystis pneumonia prophylaxis, and closely monitored for signs and symptoms of infection throughout treatment.[6,7]

Obtaining baseline IgG levels at time of CLL diagnosis[175,176] and monitoring immunoglobulins and specific antibody responses every 6 months or as needed on the basis of patient's infection history has been recommended.[11] Of note, evaluation of vaccine response in CLL is complicated because responses to protein-conjugated vaccines are weak to moderate in up to 50% of patients and responses to polysaccharide vaccines are essentially absent.[181,191]

Although the protective effect of vaccines is questionable, vaccination against influenza, *S pneumoniae*, and *H influenzae* is still recommended in CLL.[175,193] In patients with low IgG and specific antibody levels who received unconjugated pneumococcal or other polysaccharide vaccine challenge many years ago, it has been suggested that revaccination be considered before making the decision to prescribe IgG-RT.[176]

IVIG, specifically Gammagard S/D, FDA-approved for SHG in patients with B-cell CLL to prevent bacterial infections (Table V).[35,391] Studies including a meta-analysis of randomized trials in patients with CLL and lymphoma have found that although IVIG does not appear to provide a survival benefit, it does appear to significantly decrease infections (Table VI). Society guidelines have recommended IgG-RT (both IVIG and SCIG, although only IVIG is FDA-approved) for SHG in CLL with varying criteria for initiation (Table V). Although a decision-analysis model did not find IVIG to be cost-effective in patients with CLL with IgG levels less than or equal to 400 mg/dL,[194] this finding was called into question because the model did not select patients with associated infections who would be most likely to benefit from IgG-RT.[195] Most recently, the AAAAI 2017 Work Group Report recommended that IgG-RT be considered for patients with CLL with SHG and recurring bacterial infections and inadequate antibody levels in response to diphtheria, tetanus, or pneumococcal vaccinations.[35] Specific cutoffs for the number of infections, degree of SHG, or level of antibody titers at which to start IgG-RT were not specified.[35] Thus, our practice is to follow PI guidelines to interpret vaccine response.[31]

In patients with B-cell monocytosis who do not meet criteria for CLL, there is a paucity of data. In the absence of data, we recommend similar assessment of IgG levels and specific antibody titers to assess antibody function.

After starting IVIG, hematology/oncology publications have suggested IgG trough levels greater than or equal to 500 mg/dL or higher to achieve complete infection rate reduction, considering cessation/reevaluation 1 year after starting IgG-RT, and continuing longitudinal follow-up every 12 months to review ongoing need for and response to IgG-RT.[8,37]

Summary of previously published literature: CLL

CLL is associated with a high risk for developing SHG and infections, both due to the underlying nature of the condition and due to the high number of immunosuppressive treatment options.

- *Evaluation:* Guidelines (Table IV) have recommended obtaining serum immunoglobulins at time of diagnosis.[175,176] Published expert opinion has also recommended monitoring every 6 months[11] (Fig 1).
- *Vaccination:* Vaccines are recommended per CDC and Infectious Diseases Society of America guidance for immunocompromised patients.
- *Management:* Multiple guidelines (Table V) indicate that IgG-RT is a treatment option for SHG associated with recurrent or severe infections, with some guidelines recommending additional initiation criteria of prophylactic oral antibiotic therapy failure[176] or inadequate specific antibody responses to diphtheria, tetanus, or pneumococcal vaccines[35] (Fig 2). Currently, SHG associated with B-cell CLL is the only SHG type for which the FDA has approved IVIG (Table V).
- *Areas of uncertainty:* Optimal initiation criteria for IgG-RT and the optimal strategy to identify immune recovery remain to be determined. RCTs are needed to demonstrate the equivalency of SCIG to IVIG.

Lymphoma

SHG occurs in B-cell lymphoma at a lower frequency than in multiple myeloma (MM) and CLL, with reported rates between 7% and 15% before treatment.[9,10] Median time to diagnosis of SHG was 29.5 months (range, 4.6-164 months) in a large retrospective analysis.[10] Decreased vaccination responses such as attenuated responses to influenza vaccine have been observed.[196-198]

SHG incidence increases in lymphoma after treatment with RTX. After RTX treatment, *de novo* SHG was observed in up to 38.5%, with 14.5% of those with *de novo* SHG developing symptomatic SHG (defined as ≥2 nonneutropenic infections within a 6-month period post-RTX and treatment with IVIG).[9] SHG also occurs in lymphoma after hematopoietic stem cell transplant (HSCT), and this is discussed further in the HSCT section.

There are limitations to interpreting the clinical relevance of these studies. SHG definitions are not always reported. When reported, cutoffs differ between studies, with some using a cutoff

between 600 and 700 mg/dL, which could be considered normal in a PI evaluation depending on the clinical situation. These studies span a period when immunosuppressive therapies were introduced, and there is a lack of clarity regarding the degree to which different therapies contribute to SHG development. It is also notable that decisions to initiate IgG-RT are often extrapolated from CLL guidance, because there have not been studies enrolling only patients with lymphoma.

Summary of previously published literature: Lymphoma

Data regarding evaluation and management of lymphoma-associated SHG are limited, and decisions are often extrapolated from CLL guidance.

- *Evaluation:* Following CLL guidance, it may be beneficial to obtain serum immunoglobulins at time of diagnosis to establish a baseline[175,176] (Fig 1).
- *Vaccination:* Vaccines are recommended per CDC and Infectious Diseases Society of America guidance for immunocompromised patients.
- *Management:* Following CLL guidance, IgG-RT may be a treatment option for SHG associated with recurrent or severe infections (Fig 2).
- *Areas of uncertainty:* Studies specifically investigating whether IgG-RT could provide clinical benefit in SHG associated with lymphoma are needed.

Multiple myeloma

HG in MM is thought to be due to clonal expansion of paraprotein-producing plasma cells leading to suppression of normal $CD19^+$ B- and plasma-cell precursors.[11,173] Immunoparesis is common in MM: 25% to 40% in monoclonal gammopathy of undetermined significance, 52% in smoldering MM, more than 90% in newly diagnosed MM, and 75% in remission MM.[11]

The significant humoral immune defects that exist could explain the finding that infections in MM are predominantly due to encapsulated bacteria.[7,11,172-174] It is important to further evaluate how and when SHG contributes to the infections that account for an estimated 22% to 30% of all deaths in MM and up to 45% of deaths within the first 6 months,[7,11,172] so that strategies to ameliorate the negative effects of SHG can be developed.

Currently, it remains unclear whether and when IgG-RT should be initiated in SHG due to MM. One initial study demonstrated that 12 months of IVIG decreased infections in patients with stable MM on mild immunosuppression who were not rigorously vaccinated or treated with antibiotic prophylaxis before IVIG initiation.[172] This study also suggested that patients with poor responses to PPSV23 benefited the most from IgG-RT.[172] A 2-year crossover study also found that prophylactic IVIG decreased infections in patients with MM undergoing chemotherapy.[199] However, more contemporary studies did not demonstrate the same positive effect of IVIG on the rate, severity, or duration of infections.[173,179] There have also not been studies investigating the use of IgG-RT specifically in newly diagnosed or untreated MM. The more recent results and the fact that initial positive studies were done in an era before the use of HSCT and novel treatments weaken the recommendation for routine IgG-RT use in MM-associated SHG.[174,180]

Summary of previously published literature: MM

SHG and infections with encapsulated bacteria are common in MM, but there is insufficient evidence to recommend the routine use of IgG-RT.

- *Evaluation:* Immune evaluation is recommended in the setting of severe or recurrent infections.
- *Vaccination:* Vaccines are recommended per CDC and Infectious Diseases Society of America guidance for immunocompromised patients.
- *Management:* IgG-RT may provide benefit for those patients who have decreased IgG levels and evidence of attenuated antibody responses. However, decisions regarding IgG-RT should be made in light of the treatments being used, because previous studies have shown variable results in IgG-RT efficacy between patients receiving different treatments.
- *Areas of uncertainty:* RCTs are needed to determine whether and when IgG-RT may provide benefit.

Hematopoietic stem cell transplant

HSCT is the transplant of healthy hematopoietic stem cells into patients with dysfunctional or depleted bone marrow and is an important therapeutic option for malignant and nonmalignant hematologic conditions as well as PI.[178] Immune reconstitution/competence can take months to years to attain and is marked by the ability of the HSCT recipient to produce protective antigen-specific antibodies to live vaccine.[178] In a pediatric study of 185 patients undergoing HSCT, 77% of the patients developed SHG a median of 56 days (range, 15-339) post-HSCT.[200]

Post-HSCT, lymphocytes typically take the longest time to recover, with NK cells recovering first, followed by $CD8^+$ T cells 2 to 8 months post-HSCT, followed by B cells and then $CD4^+$ T cells.[178] B-cell recovery typically occurs 3 to 6 months post-HSCT.[201-203] Because humoral immunocompetence depends on the recovery of memory B cells in addition to naive B cells, full humoral immune recovery does not occur even after normalization of total B-cell numbers within the first 6 months posttransplant.[201-203]

Fludarabine and maintenance RTX after HSCT have been implicated as risk factors for increased SHG incidence, severity, and duration.[10,204-207] It is unclear whether SHG seen with post-HSCT maintenance RTX is associated with increased infections, because 1 study showed an association with increased infections and another did not.[205,207]

B-cell recovery after autologous stem cell transplant is faster than after allogeneic transplant. After autologous transplant, B cells began to reappear after 20 days, and can recover to normal by 3 to 4 months. However, RTX treatment before autologous stem cell transplant can render B-cell counts undetectable or extremely low even 6 to 12 months after the transplant.[202,208] After allogeneic transplant, B-cell recovery began after 6 months initially with naive B cells, and it takes about 2 years for IgM-positive memory B cells to recover. This process can be further delayed by the presence of graft versus host diseases, different types of donor cells, and pretransplant conditioning regimens.[208-212]

Serum IgG and total B-cell numbers are not adequate markers of humoral immune reconstitution because long-lived plasma cells can survive and produce IgG without providing specific antibody responses.[213] True recovery of B-cell function starts in a

specialized marrow microenvironment that is susceptible to damage by ablative regimens and requires help from $CD4^+$ T cells, which take the longest time to recover.[214] Until HSCT recipients regain the ability to produce antigen-specific neutralizing antibodies, they remain predisposed to infections from encapsulated bacteria and viruses.[178] Indeed, studies have demonstrated that earlier $CD4^+$ T-cell recovery is associated with decreased infections and improved survival.[215-217]

In patients with recurrent severe infections but normal serum IgG level, low $CD4^+$ T-cell counts by flow cytometry and less than 50% response rates to 23-valent pneumococcal vaccination indicate a persistent immunodeficient state. Low $CD4^+$ counts have been associated with less robust response to revaccination,[218] and $CD4^+$ counts less than 200 cells/μL at 3 months post-transplant have been associated with decreased overall survival, increased infection, and nonrelapse mortality.[216] However, predictive cutoff values of $CD4^+$ counts after transplant have not been studied as extensively as they have been for HIV. Full immunization is typically repeated 2 years post-HSCT, when the patient is off all immunosuppression and $CD4^+$ T-cell count is above 200, using the principle of infection prevention developed by the Infectious Diseases Society of America and the US Public Health Service for prevention of opportunistic infections among HIV-infected patients.[178,220]

Routine use of IgG-RT for infection prophylaxis is not recommended, although it may be considered for severe SHG (IgG < 400 mg/dL) particularly with bacteremia or recurrent sinopulmonary infections despite adequate personal hygiene and antimicrobial prophylaxis.[178] Factors associated with post-HSCT SHG requiring 3 or more months of IgG-RT (both IVIG and SCIG) in children were younger age (<5 years), higher incidence of acute graft versus host disease, better overall survival, and significantly higher pre-HSCT IL-6 and IL-7 and post-HSCT BAFF and APRIL levels.[221]

Summary of previously published literature: HSCT

Immune reconstitution can take months to years after HSCT and as such SHG is commonly seen post-HSCT.

- *Evaluation:* Immune evaluation post-HSCT is unique in that $CD4^+$ T-cell enumeration has been identified as an indicator of a patient's immune status.
- *Vaccinations:* Immune reconstitution is marked by recovery of the ability to produce antigen-specific antibody to live vaccines. Normal $CD4^+$ T-cell counts and adequate antibody responses to pneumococcal polysaccharide antigens could indicate immune recovery and the ability to receive live vaccines. Full immunization is typically repeated 2 years post-HSCT when patients are off all immunosuppression and the $CD4^+$ T-cell count is above 200.
- *Management:* IVIG has been used in patients post-HSCT with severe SHG and severe infections, but there is insufficient evidence to recommend routine use outside of this. Of note, the American Society for Blood and Marrow Transplantation and Canadian Blood and Marrow Transplant Choosing Wisely recommend against routine IVIG after HSCT.[222]
- *Areas of uncertainty:* Further identification of additional predictors of immune recovery is needed. Studies are needed to identify the optimal initiation criteria for IgG-RT in patients with infections as well as whether there is utility for IgG-RT in the absence of infections for a specific immune phenotype (eg, below a certain IgG level). RCTs are needed to determine the equivalency of SCIG to IVIG.

CD19 CAR-T-cell therapy

CD19 CAR-T-cell therapy is a relatively novel treatment option for acute lymphoblastic leukemia and adult B-cell lymphoma and is a cause of SHG due to its $CD19^+$ B-cell–depleting effect.[7,29,223] Currently, there are 2 anti-CD19 CAR-T-cell drugs, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), which differ in the costimulatory domain engineered for cell activation. CD19 CAR-T-cell therapy has significant immune adverse effects including B-cell aplasia and SHG.[29] Because CAR-T cells can survive for years after infusion, there is the potential for prolonged B-cell aplasia. Indeed, prolonged $CD19^+$ B-cell aplasia has been reported in a number of patients.[38,224] However, $CD19^+$ B cells can start to recover in some patients by 3 months after infusion.[225-227] One study observed that time to $CD19^+$ B-cell recovery was a median of 6.7 months (0.3-12 months).[228] Therapeutic efficacy of CD19 CAR-T-cell therapy does not appear to be affected by the timing of $CD19^+$ B-cell recovery.[29]

SHG has been reported as the most common on-target, off-tumor toxicity of CD19 CAR-T-cell therapy.[7,29,223,229] The reported incidence and severity of SHG varies widely between studies. For example, SHG has been reported in 14% to 15% of adult patients with lymphoma,[29] as a late adverse effect in 44% to 74% of patients with lymphoma,[229] and in 43% of pediatric patients with acute lymphoblastic leukemia.[29] Variable definitions of HG, variable IgG replacement protocols, and lack of clarity regarding baseline rates of HG could contribute to discrepancies in reported rates.[29,30] Preexisting HG has been identified as a risk factor for SHG on CD19 CAR-T-cell therapy in a multicenter trial for tisa-cel, where 74% of patients had low IgG, 63% low IgM, and 49% low IgA levels.[29]

Bacterial, viral, and fungal infections have been reported in patients after receiving CD19 CAR-T-cell therapy, with the highest infection frequencies observed in the first 28 days after CAR-T-cell infusion.[225,230] Interestingly, some patients in CD19 CAR-T-cell therapy trials received IgG-RT (not specified if IVIG or SCIG), and it is not clear to what degree this may have prevented infectious complications.[38,226,228,231,232] In 1 study in which all 30 patients received IgG-RT (not specified if IVIG or SCIG) to maintain IgG levels above 500 mg/dL, no infections were reported in a 12-month follow-up period.[183] In other trials where IVIG was initiated in only a subset of patients per local guidance, for low (undefined) IgG level with systemic infection, or to maintain IgG levels above 400 mg/dL especially in the setting of infection, infections were reported.[226,228,232]

Baseline immunoglobulin levels, specific antibody titers, and lymphocyte subsets before initiation of CD19 CAR-T-cell therapy have been recommended.[29,30] Immune monitoring has also been recommended, with 1 publication recommending immunoglobulins and specific antibody titers 3 months after initiation of CD19 CAR-T-cell therapy to risk stratify the need for prophylactic IgG-RT.[29] A position paper from Spain recommended immunoglobulin levels and lymphocyte subsets monthly until the sixth month after infusion and then twice a year after that.[30]

CD19 expression decreases as B cells differentiate into plasma cells,[233] and memory B-cell responses may persist even after

CD19 CAR-T-cell therapy. Similar to how specific antibody titers attained before initiation of anti-CD20 therapy could be maintained despite attenuation of responses to vaccines administered after initiation of anti-CD20 therapy,[234] there could be some maintenance of humoral immunity following CD19 CAR-T-cell therapy due to the survival of CD19-negative plasma cells. Patients receiving CD19 CAR-T-cell therapy may also have undergone HSCT, and vaccination strategies are modeled after HSCT vaccination schedules.[30]

In the absence of data regarding the efficacy of prophylactic IgG-RT after CD19 CAR-T-cell therapy, expert opinion has recommended prophylactic IgG-RT (IVIG or SCIG) for IgG levels less than 400 mg/dL during the first 3 months after initiation of CD19 CAR-T-cell therapy.[29] After the first 3 months, the same expert opinion has recommended consideration of IgG-RT for patients with IgG levels less than or equal to 400 mg/dL and serious, persistent, or recurrent bacterial (particularly sinopulmonary) infections, based on data from PI, SOT, HSCT, and B-cell malignancies.[29]

A position paper from Spain has proposed an IgG trough level above 400 mg/dL with consideration of increasing the dose in patients with persistent sinopulmonary infections despite replacement, as well as IgG-RT (IVIG or SCIG) in all pediatric patients approximately 1 month after initiation of CD19 CAR-T-cell therapy.[30] It is important to note that this recommendation is based on the authors' clinical experience with other B-cell malignancies such as CLL and MM rather than CD19 CAR-T-cell therapy literature. The same position paper from Spain recommended antiviral prophylaxis for herpes simplex virus–seropositive patients, fluconazole for patients with 2 or more risk factors for invasive fungal infections, and Pneumocystis pneumonia prophylaxis for all patients.[30]

Summary of previously published literature: CD19 CAR-T-cell therapy

SHG was the most common on-target, off-tumor toxicity reported during the use of CAR-T cells.

- *Evaluation:* Published expert opinion has recommended screening quantitative immunoglobulins and specific antibody titers in response to vaccines before and 3 months after initiation of CD19 CAR-T-cell therapy to risk stratify the need for prophylactic IgG-RT[29] (Fig 1).
- *Vaccination:* Vaccination strategies are modeled after HSCT vaccination schedules.
- *Management:* Hematology/oncology published expert opinion has proposed prophylactic IgG-RT for IgG levels less than 400 mg/dL during the first 3 months after initiation of CD19 CAR-T-cell therapy and consideration of IgG-RT after the first 3 months for patients with IgG levels less than or equal to 400 mg/dL and serious, persistent, or recurrent bacterial (particularly sinopulmonary) infections[29] (Fig 2). Of note, this preliminary guidance was made in the absence of specific data regarding the efficacy of prophylactic IgG-RT after CD19 CAR-T-cell therapy and is based on PI, SOT, HSCT, and B-cell malignancy literature. IgG level cutoffs for IgG-RT initiation need to be interpreted in the context of other indicators of immune function such as IgA and IgM levels, specific antibody responses, lymphocyte counts, and infections.
- *Areas of uncertainty:* Studies are needed to investigate the effect of HG on clinical outcomes in patients who have received CD19 CAR-T-cell therapy and to identify whether IgG-RT is effective at mitigating any of these effects. Preliminary recommendations regarding whether and when to initiate IgG-RT need to be confirmed or refined, with studies identifying the optimal initiation criteria for IgG-RT and the optimal strategy to identify immune recovery. RCTs are needed to determine the equivalency of SCIG to IVIG.

PULMONARY

Chronic obstructive pulmonary disease

Studies have suggested a possible association between antibody deficiency and frequent acute exacerbations of COPD.[13] Higher incidence of COPD hospitalizations has been observed with low IgG levels compared with normal IgG levels.[14] In a cohort of 1497 individuals with or at risk for COPD, higher serum IgG level was associated with a lower risk of acute exacerbations.[16] In a case series of 42 patients with 2 or more acute exacerbations per year despite maximal medical therapy, 29 were found to have antibody deficiency syndrome.[17] It is unclear whether findings of antibody deficiency in these patients represent underdiagnosis of PI or true SHG due to immunosuppression.[15]

IgG-RT use is not routinely recommended but has been described in patients with defined antibody deficiency syndromes and COPD exacerbations.[17] Significantly reduced rates of acute exacerbations have been observed in 14 patients with COPD who received IgG-RT (IVIG and SCIG) for different conditions.[13] Although only PPSV23 is recommended by the CDC for children and adults aged 6 to 64 years with chronic lung disease,[235] patients with moderate to severe COPD have a deficient response to PPSV23, and vaccination with the conjugated pneumococcal vaccine may provide benefit to these patients at risk for pneumococcal disease.[236]

Summary of previously published literature: COPD

Although a possible association between frequent acute exacerbations of COPD and antibody deficiency has been observed, it is unclear whether this represents underdiagnosis of PI or true SHG due to immunosuppression.[15]

- *Evaluation:* Screening for antibody deficiency in select patients with COPD who continue to have 2 or more moderate to severe acute exacerbations per year despite maximal medical management may identify antibody deficiency in certain patients.
- *Vaccination:* In addition to routine vaccine recommendations per CDC guidance, patients with moderate to severe COPD who demonstrate a deficient response to PPSV23 may benefit from consideration of conjugated pneumococcal vaccination at least 1 year after the last dose of PPSV23.
- *Management:* Data are limited regarding the role for IgG-RT in patients with frequent COPD exacerbations and well-defined antibody deficiency. Until additional studies are conducted in patients with COPD, decisions to initiate IgG-RT remain heavily based in the PI literature.
- *Areas of uncertainty:* Additional studies are needed to clarify whether there is a true association between frequent acute COPD exacerbations and antibody deficiency and whether there is a role for IgG-RT in the management of these patients.

Asthma

Although SHG has been observed among severe corticosteroid-dependent asthma in 2 studies, it did not appear to be associated with worse clinical outcomes because patients had either preserved specific antibody responses or no change in the number of sinopulmonary infections.[134,143] This would be consistent with what was discussed in the Corticosteroid section about the effect of corticosteroids on quantitative antibody levels and antigen-specific titers. Of note, because asthma can be misdiagnosed or overdiagnosed,[237] the diagnosis of asthma should be established and a detailed infection history should be elicited before definitively diagnosing a patient with "asthma and corticosteroid-dependent SHG."

Existing literature does not support routine use of IgG-RT in severe asthma. Although open-label trials examining the effects of high-dose IVIG on corticosteroid-dependent or severe asthma without known antibody deficiency demonstrated reductions in corticosteroid dose as well as improvements in peak flows, symptom scores, and hospitalizations,[238-241] 3 double-blind placebo-controlled asthma studies did not find that IVIG provided significant clinical benefits.[242-244] One trial was terminated prematurely after all 3 patients receiving higher IVIG doses of 2 g/kg were hospitalized with symptoms consistent with aseptic meningitis.[242] No subsequent trials have emerged.

Summary of previously published literature: Asthma

The literature does not support routine screening for antibody deficiency in asthma or use of IgG-RT in severe asthma.

- *Evaluation:* The literature does not support routine screening for antibody deficiency in asthma.
- *Vaccination:* Routine vaccination has been recommended without dose adjustment of corticosteroids if the daily corticosteroid dose is or is equivalent to prednisone less than 20 mg daily.[111]
- *Management:* The literature does not support the use of IgG-RT in severe asthma without antibody deficiency and severe sinopulmonary infections.
- *Areas of uncertainty:* A large number of SHG cases in asthma are likely due to corticosteroid-associated SHG, and further studies clarifying the association between high-dose corticosteroid use (≥20 mg/d) and the effect of corticosteroid-associated SHG on vaccination responses and infection outcomes will help guide evaluation and management.

Cystic fibrosis

Although CF is commonly associated with progressive hypergammaglobulinemia, a subset of patients can develop low IgG levels for age.[18-21] Prevalence rates of SHG in pediatric CF range between 1.9% and 10.8%.[19,20,245] The clinical significance of this is unclear. Although functional antibody responses have not been evaluated in most reports describing SHG in CF, a few series describe normal specific antibody response to protein vaccine.[19,246] SHG in CF has been associated with milder lung disease, whereas hypergammaglobulinemia has been correlated with worsened pulmonary function, clinical status, and mortality.[19,246] Inverse correlation between FEV_1 and IgG level has been reported in pediatric cohorts with CF.[19,21] Both pediatric and adult patients with CF can develop SHG after lung transplant (LT),[247,248] and this is discussed further in the Transplant section. In addition, the possibility of a PI in patients with a CF diagnosis and low IgG levels cannot be discounted.[22]

Case series and reports have suggested a possible benefit of IVIG in CF.[249,250] A small RCT of low-dose IVIG (300 mg/kg over 3 days) during acute pulmonary exacerbations in CF without HG showed no effect on length of hospitalization, although pulmonary function transiently improved.[251] A work group report from the AAAAI on the use of IgG-RT determined that IVIG may provide benefit in CF with HG (Category III-C evidence) but is unlikely to be beneficial in CF without HG (Category Ib-A evidence).[35]

Summary of previously published literature: CF

SHG is observed in CF although the clinical significance is unclear outside of posttransplant settings.

- *Evaluation:* Screening for humoral immune defects in select patients with CF, particularly those being considered for LT, may identify an underlying PI.
- *Vaccination:* Routine vaccinations per CDC guidelines are recommended for patients with CF.
- *Management:* Apart from patients who are diagnosed with underlying PI and select post-LT patients as discussed in the SOT section, there is insufficient evidence to recommend the routine use of IgG-RT in patients with CF.
- *Areas of uncertainty:* Further investigation into SHG evaluation and management is largely needed for transplant-associated SHG and is covered in the Transplant section.

SOLID ORGAN TRANSPLANT

SHG occurs frequently after SOT, and is associated with worse clinical outcomes, including increased infections and 1-year all-cause mortality.[23] In a meta-analysis of 18 studies (1756 recipients of lung, heart, kidney, and liver transplants), 45% of SOT patients developed HG (IgG < 700 mg/dL) and 15% developed severe SHG (IgG < 400 mg/dL) during the first year posttransplant.[227] SHG occurs most commonly after LT, followed by heart transplant (HT), KT, and liver transplant (OLT), with higher rates in adults compared with children (Table VII).[23]

Evaluation

Screening for the underlying PI in conjunction with a consulting clinical immunologist before SOT has been recommended[25,277] because 7% of KT recipients[263] and up to 15% of LT recipients have preexisting HG.[24,247,248,252] Monitoring every 6 to 12 months posttransplant with serum IgG, IgA, and IgM levels as well as specific antibody titers to tetanus, *Haemophilus influenza* type B, and Streptococcus pneumonia has also been recommended.[25,277]

Management

IgG-RT has been studied for SHG post-LT and post-HT with evidence that, when initiated and dosed appropriately, it may mitigate the adverse outcomes associated with SHG (Table VI).[35,278-281] Of note, IVIG did not provide benefit in studies in

which IVIG was underdosed or given sporadically.[24,39,282] Data are limited and inconclusive regarding the benefit of IVIG for post-KT SHG.[283] IgG-RT has not been found to provide significant survival benefit in intestinal (including liver) transplant.[278,284]

IVIG is also used for non-SHG indications, adding nuance to the decision-making around whether or not to treat post-SOT SHG. IVIG is used to decrease donor-specific antibodies post-LT and for HLA-sensitized patients as well as antibody-mediated rejection post-KT.[35,277] IVIG has also been investigated with some variable success as a supportive treatment for BK virus, particularly in cases resistant to antiviral therapy and reduction of immunosuppression.[285-290]

There are no side-by-side comparisons of SCIG versus IVIG for post-SOT SHG. The same considerations and shared decision making applied in PI can be applied in post-SOT SHG in the absence of studies comparing SCIG and IVIG specifically in the SOT patient population.[35] In limited case series/reports, SCIG was well tolerated and efficacious at increasing IgG levels or preventing infections in 10 LT recipients and 1 HT recipient with SHG.[44,45] Insurance has been cited as a barrier to initiating IgG-RT in LT patients with SHG,[291] and it must be noted that both IVIG and SCIG are currently not FDA-approved for post-SOT SHG.

Lung transplant

SHG (IgG < 700 mg/dL) and severe SHG (IgG < 400 mg/dL) occur frequently post-LT and are associated with worse survival and infectious outcomes (Table VII). Severe SHG in particular has been associated with increased 1-year all-cause mortality, chronic lung allograft dysfunction, increased antibiotic use, and increased risk of respiratory, bacterial, cytomegalovirus, and fungal infections.[23,24,39] In adult but not pediatric LT recipients, lower pretransplant IgG levels predict post-LT SHG but not infection or 1-year mortality post-LT.[24,248,252]

In addition to IgG, IgA and IgM decrease significantly post-LT.[253-255] Pre- and post-LT low IgA and IgM levels with and without concomitant IgG HG have been associated with increased infections and hospitalization days.[247,248,254]

Risk factors for post-LT SHG include basiliximab induction or mycophenolate use.[24,252] Risk factors for post-LT severe SHG include female sex, COPD/emphysema, bronchiolitis obliterans, and less than 30% of pretransplant pneumococcal antibody levels being protective.[24,252-254,256]

Immune evaluation may be particularly warranted for patients undergoing LT for CF and COPD. As discussed in the Pulmonary section, both CF and COPD can be associated with antibody deficiencies, and there is a recognized interplay between humoral immune function and outcomes in these 2 patient populations.[14,17,19,22,246,257] Indeed, COPD has been associated with lower pretransplant IgG levels and increased risk of pretransplant HG compared with other pulmonary diseases independent of corticosteroid use and age.[24,252] COPD/emphysema is also a risk factor for post-LT severe SHG.[24]

As discussed in the Medications section, the effect of corticosteroids on IgG levels does not appear to correlate with the effect of corticosteroids on increasing infections. Prednisone dose has not been associated with posttransplant SHG.[13,24] However, corticosteroid use during the first month post-LT has been correlated with recurrent bacterial infections,[255] and another study found that a combination of age, number of acute steroid courses, and severe SHG at any time during the first year post-LT was predictive of total days of pneumonia.[24]

Heart transplant

The interplay between SHG and infections post-HT was first reported in a case series of 6 patients found to have IgG levels less than or equal to 310 mg/dL.[258] Subsequent studies reported that SHG (IgG < 600 mg/dL) and severe SHG (IgG < 350 mg/dL) are observed post-HT and associated with increased infections (Table VI).

Use of parenteral steroid pulse therapy has been associated with post-HT severe SHG, and post-HT severe SHG has been associated with an increased risk of opportunistic infections and cellular rejection episodes.[259] It is possible that increased episodes of cellular rejection may have been causal rather than a result of SHG because cellular rejection is treated with heightened immunosuppression, which could lead to decreased IgG levels and increased risk of opportunistic infections.[260] Studies are needed to clarify the association between post-HT severe SHG, infection risk, and cellular rejection risk.

Kidney transplant

Post-KT SHG is more pronounced in patients with lower creatinine clearance[261] and appears to recover with time (Table VI).[262-264] Additional risk factors for post-KT SHG include baseline HG[263] and longer duration but not higher doses of immunosuppression.[265] KT recipients may also have SHG due to RTX and/or nephrotic syndrome, and this needs to be taken into consideration when evaluating and managing post-KT SHG (see BCTT and Nephrotic syndrome sections).

Decreased IgG levels are associated with increased infectious complications (Table VII).[261,264-269] Interestingly, in 1 study, post-KT SHG was associated with increased infections only if IgA and/or IgM levels were also low.[262]

Azathioprine appears to be less immunosuppressive than mycophenolate and cyclosporine in KT recipients. Mycophenolate, but not azathioprine, has been associated with post-KT SHG, increased infections,[270] and bronchiectasis.[271,272] Interestingly, in 7 patients who were switched from mycophenolate to azathioprine, infections decreased, and immunoglobulin levels normalized in all but 1 patient.[270] Cyclosporine, but not azathioprine, has been associated with depressed antibody responses to influenza vaccine.[250]

Liver transplant

HG (IgG < 560 mg/dL) has been observed in up to 26% (29 of 112) of patients after OLT.[273] The effect of HG on clinical outcomes remains unclear. Post-OLT HG was associated with both increased 1-year and 5-year mortality in 1 study.[273] However, the same study showed that post-OLT HG was not associated with any of the specific infectious outcomes studied (cytomegalovirus, bacteremia, invasive fungal infection) or with rejection, making it unclear why mortality was increased.[273] Another study found that post-OLT SHG was not associated with increased mortality or infection, but that a low IgA level was.[274] Interestingly, high rather than low pretransplant IgG and IgA levels have been associated with increased risk for infections post-OLT.[275] This may reflect the fact that patients with liver disease can

have elevated immunoglobulins.[275,276] Increased infections in this patient population may reflect more severe liver disease or possibly a deficiency in quality rather than quantity of immunoglobulins.

Summary of previously published literature: SOT

Post-SOT SHG is associated with increased infections and mortality, particularly in LT, HT, and KT recipients.

- *Evaluation:* Published expert opinion has recommended screening of humoral immunity before SOT to identify the underlying PI, which would have implications for management and to identify patients with lower baseline IgG levels at risk for developing post-SOT SHG posttransplant.[25,277] Published expert opinion has recommended monitoring for decreasing IgG levels, loss of specific antibody titers, and recurrent and/or severe bacterial infections every 6 to 12 months after SOT.[25,277] More frequent monitoring may be warranted in the initial posttransplant period when patients are particularly susceptible to infections. Published expert opinion has proposed that screening and monitoring evaluations include serum IgG, IgG subclasses, IgA, IgM, and specific antibody titers to tetanus, *Haemophilus influenza* type B, and Streptococcus pneumonia.[25,277]
- *Vaccination:* Completing recommended vaccinations before SOT is an important piece of infection prophylaxis because the multiple immunosuppressive agents administered after transplant can attenuate vaccine responses.[292,293]
- *Management:* The decision to initiate IgG-RT in SHG post-SOT should be made by a clinical immunologist to allow for optimal patient selection and adequate dosing. IgG-RT doses need to be adequate and consistent to reach steady state and adjusted to maintain IgG trough levels that achieve clinical effectiveness.[35,36] Based on the PI literature, IgG-RT could be considered even in the absence of infections if IgG levels are persistently below 350 mg/dL with documented lack of antibody response. Because SOT patients receive well-defined infection prophylaxis regimens, patients are typically already on antibiotic and other antifungal/antiviral prophylaxis at time of SHG detection.[292]
- *Areas of uncertainty:* Further investigation in specific SOT patient populations (LT, HT, KT, OLT) is needed to identify the most predictive and cost-effective screening immunology laboratories, as well as ideal time points for immune monitoring pretransplant and posttransplant. Further investigation is needed to refine criteria for whether and when to initiate IgG-RT. IgG levels fluctuate significantly post-SOT, with some patients developing severe but transient HG, and specific investigation into whether IgG-RT provides benefit in patients with transient versus persistent SHG is also needed. Finally, there is a need to identify whether SCIG is comparable or superior to IVIG in these patients with multiple comorbidities and often significant protein losses.

PROTEIN-LOSING CONDITIONS

Nephrotic syndrome

Nephrotic syndrome occurs in approximately 3 in 100,000 adults annually and is caused by an extensive number of primary glomerular causes and secondary causes (diabetic nephropathy, SLE, amyloidosis, myeloma, lymphoma, medications, infections, congenital syndromes).[294] SHG can occur because of urinary protein loss in nephrotic syndrome and is exacerbated by impaired IgG synthesis and use of BCTT. In addition to urinary loss, SHG in nephrotic syndrome has been associated with impaired IgG synthesis.[295-297] A comparison of 62 nephrotic patients with 18 healthy control patients found that immunoglobulin synthesis measured by pokeweed mitogen–stimulated lymphocytes was significantly decreased in nephrotic patients, and decreased IgG synthesis was reversed when minimal change disease was in remission.[295]

Nephrotic syndrome is one of the most common pediatric kidney diseases, with a reported incidence of 2 to 16.9 in 100,000 children.[298] In a study of 44 pediatric patients with steroid-sensitive nephrotic syndrome, IgG_1 was decreased at the onset of relapse, followed by decreases in $IgG_{1\text{-}3}$ during relapse, and then persistence of low IgG_2 levels for 12 months after remission.[299] IgG_1 and IgG_2 but not IgG_3 and IgG_4 levels have been found to be significantly decreased during relapse compared with remission.[300,301] Antibody responses to diphtheria and tetanus have been found to be significantly decreased during relapse in nephrotic patients.[301] In pediatric patients with congenital and steroid-sensitive nephrotic syndrome, dysgammaglobulinemia with low IgG and elevated IgM levels has been observed.[299,301-303]

Evaluation. Evaluation of HG in nephrotic syndrome is complicated by the immunosuppressive effects of BCTT; this has been observed in a number of pediatric studies. SHG (IgG < 500 mg/dL) has been observed in 15% to 67% of pediatric patients with steroid-dependent nephrotic syndrome on RTX.[304,305] It is unclear to what degree the observed SHG is due to RTX, non-RTX oral immunosuppression such as steroids, and urinary protein loss from the underlying disease process itself. However, RTX is contributing to some degree because SHG has been observed *de novo* after RTX therapy in 29% to 55% of nephrotic patients with normal baseline IgG levels.[306,307] In addition, more profound B-cell suppression and SHG is seen in nephrotic patients on RTX versus non-RTX oral immunosuppression (prednisone, mycophenolate, calcineurin inhibitors).[308] RTX has also been implicated in contributing to persistent SHG, perhaps in a dose-dependent manner.[125,306]

As with SHG in other settings, HG and RTX use in nephrotic syndrome appears to be associated with increased infections but is not the only factor that determines infection risk. Use of mycophenolate post-RTX may increase the risk for more severe infections in pediatric patients with steroid-dependent nephrotic syndrome.[309] HG (IgG < 600 mg/dL) has been associated with increased risk for bacterial infections (sepsis, acute respiratory distress syndrome, pneumonia, miliary tuberculosis, urinary tract infections, enterocolitis, panniculitis) with 5 fatalities among 86 adult patients with nephrotic syndrome,[310] and there have been case reports of Strongyloides and *Campylobacter jejuni* infections in nephrotic patients with SHG.[311,312] It has also been postulated that SHG is responsible for the high rate of neonatal sepsis in congenital nephrotic syndrome.[303] In pediatric studies, infections have been reported in 9% to 28% of nephrotic patients with post-RTX SHG.[304,306,307]

Management. The utility of IgG-RT in SHG due to nephrotic syndrome remains unclear. In a study of 86 adult patients with IgG levels less than 600 mg/dL due to nephrotic syndrome at

increased risk for infections, IVIG 10 to 15 g every 4 weeks administered to 18 patients to maintain IgG levels above 600 mg/dL led to a decrease in the rate of bacterial infections to a rate similar to that in patients without baseline HG.[310] In pediatric patients, a Cochrane Review found that IVIG could have benefit in preventing infections in pediatric nephrotic syndrome without any noted adverse effects.[313] However, the authors noted that the poor quality and small sample sizes of the reviewed studies did not allow them to draw strong conclusions about risk-to-benefit ratio.

In nephrotic syndrome, IgG-RT is complicated because the IgG administered is quickly lost in the urine. For example, although IVIG is typically administered every 4 weeks, in 1 case report, 55% of the IgG administered via IVIG was lost in the urine over 30 hours.[302] Using SCIG was not found to ameliorate urinary losses in a case report of 1 patient with congenital nephrotic syndrome in whom IgG levels remained low despite receiving supratherapeutic doses of subcutaneous IgG-RT.[314]

The safety of IgG-RT is also called into question in patients with tenuous renal status. Sucrose-free IVIG formulations have been used safely without adverse renal side effects in patients with renal compromise.[315,316]

Summary of previously published literature: Nephrotic syndrome

Special considerations for nephrotic patients with SHG include the contribution of BCTT and the difficulty of adequate repletion due to urinary protein loss when IgG-RT is deemed necessary. The contribution of SHG in infectious complications of nephrotic syndrome remains unclear.

- *Evaluation:* IgG_2 appears to be disproportionately affected in nephrotic syndrome. Interestingly, diphtheria and tetanus but not polysaccharide antibody responses are decreased.
- *Vaccination:* Vaccine responses may be decreased during relapse.
- *Management:* There is insufficient evidence to recommend the routine use of IgG-RT in SHG associated with nephrotic syndrome.
- *Areas of uncertainty:* Studies are needed to identify whether and when IgG-RT is needed in patients with SHG due to nephrotic syndrome. RCTs are needed to identify whether IgG-RT can prevent infections in patients with defined immunophenotypes and whether SCIG is comparable or superior to IVIG in these patients with compromised renal function and urinary protein losses.

Protein-losing enteropathy

SHG can occur in PLE due to net enteral protein loss exceeding the body's ability to synthesize enough protein to replace what was lost. PLEs have diverse etiologies but occur when intestinal leakage of plasma proteins occurs through 1 of 3 pathologic mechanisms: (1) presence of mucosal injury due to erosive or ulcerative gastrointestinal disorders, which enables inflammatory exudates to cross the compromised epithelium; (2) increased mucosal permeability due to compromised mucosal integrity, which allows protein to leak into the lumen; and (3) intestinal loss of lymphatic fluid secondary to lymphatic obstruction (Table I). Primary and secondary intestinal lymphangiectasia are discussed further in a separate section.

Evaluation. SHG, lymphopenia, and increased risk for frequent infections may occur in PLE.[317] SHG due to PLE should be suspected in edematous patients with low albumin for whom other causes of protein loss (eg, proteinuria), suboptimal synthesis, or malnutrition have been excluded.[317]

Increased clearance of alpha-1 antitrypsin, which resists proteolysis and degradation in the intestinal lumen and is excreted intact in the stool, is consistent with a diagnosis of PLE.[318] In addition to decreased immunoglobulins, reduced serum concentrations of albumin, fibrinogen, cholesterol, transferrin, ceruloplasmin, and fat-soluble vitamins are also variably observed.[318]

Genetic testing for monogenic causes of VEO-IBD should be considered in the evaluation of pediatric patients with enteropathy and HG, as well as loss-of-function mutations in SLCO2A1, which encodes a prostaglandin transporter.[319,320] However, it is important to note that many commercially available targeted panels for PI or VEO-IBD do not necessarily include the relevant genes. Thus, whole-exome or genome sequencing may be more useful but harder to access outside of a research setting.[321]

Management. There is limited information on the utility of IgG-RT in the treatment of SHG due to PLE. In a report of 2 pediatric patients with severe SHG due to PLE, an infusion of 200 mg/kg IVIG was effective at increasing serum IgG levels to approximately 700 mg/dL. However, IgG levels fell faster post-infusion than in patients with non-PLE HG, with levels slightly above 350 mg/dL by 7 days post-infusion.[322] It has been suggested that IgG-RT be considered if prophylactic antibiotics are inadequate at preventing infections.[323]

SCIG may possibly be preferable for patients with protein-losing conditions as it is for PI patients with protein-losing conditions.[324] In a case series of 3 patients with PLE, SCIG led to decreased infections and more stable IgG levels than IVIG, suggesting that SCIG may have a more favorable pharmacokinetic profile in PLE.[46] However, SCIG use for non-PI protein-losing conditions would be considered off-label use because it is not FDA-approved for this condition.

Summary of previously published literature: PLE

There is insufficient evidence to recommend the routine use of IgG-RT in PLE.

- *Evaluation:* Increased alpha-1 antitrypsin clearance is consistent with a diagnosis of PLE. In addition, decreased concentrations of albumin, fibrinogen, cholesterol, transferrin, ceruloplasmin, and fat-soluble vitamins can be observed. Genetic testing for VEO-IBD and loss-of-function mutations in SLCO2A1 can also be considered.
- *Vaccination:* Vaccination per CDC guidelines is recommended.
- *Management:* There is insufficient evidence to recommend the routine use of IgG-RT in PLE.
- *Areas of uncertainty:* SCIG may possibly be preferable and lead to more stable IgG levels than IVIG in protein-losing conditions. This hypothesis needs to be investigated with RCTs.

Lymphangiectasias

Intestinal lymphangiectasias are characterized by dilated small intestinal lymphatic channels with impaired lymph drainage and lymphatic obstruction, resulting in leakage of lymph into the

intestinal lumen, with consequent loss of proteins and lymphocytes.[325,326]

Evaluation. In addition to SHG, these patients can present with variable degrees of lymphopenia and altered cellular immunity, which can also be associated with frequent and opportunistic infections. For both primary and secondary intestinal lymphangiectasia, quantitative immunoglobulins and lymphocyte subset enumeration should be checked.

Patients with primary intestinal lymphangiectasias tend to present in childhood and young adulthood, and the underlying etiologies can be sporadic or genetic. Genetic causes include loss-of-function mutations in CD55, which encodes complement decay-accelerating factor,[327,328] and DGAT1, which results in errors of lipid metabolism.[329,330] If CD55 deficiency is suspected, complement evaluation should also be considered. Because many commercially available targeted genetic panels rarely include the relevant genes, whole-exome or genome sequencing may be more useful but difficult to access outside of a research setting.

Acquired intestinal lymphangiectasias are most commonly caused by structural heart disease (eg, atrial septal defect)[326] and surgical repair of congenital heart disease (eg, Fontan repair for single-ventricle heart disease).[331-333] Other causes include infectious or neoplastic or iatrogenic (eg, chemotherapy and radiation), retroperitoneal lymphadenopathy, and liver pathology (eg, cirrhosis, portal hypertension, and hepatic venous outflow obstruction).[317,325,326] The degree of immunologic compromise varies greatly depending on the etiology.

Of the congenital structural heart defects, hypoplastic left heart syndrome raises particular concern for PLE. Hypoplastic left heart syndrome is characterized by a small left ventricle and left-sided structures unable to support appropriate systemic circulation.[334] A recent retrospective administrative database review demonstrated a higher incidence of PLE in patients with hypoplastic left heart syndrome and a younger age of onset compared with patients with tricuspid atresia.[335]

A 3-staged surgical palliation can be performed at different ages, which leads to symptomatic improvement but does not restore the normal biventricular anatomy. The Fontan procedure is the third procedure, usually performed between age 2 and 5 years, that connects the inferior vena caval flow into the pulmonary arteries, resulting in a system with a single ventricle pumping blood into separate, in-series systemic and pulmonary circulations, thereby relieving cyanosis.[334]

PLE is estimated to occur weeks to years after the Fontan operation in 3% to 18% of patients.[48,336-340] Patients who have undergone a Fontan procedure and related surgeries demonstrate variable degrees of T-cell lymphopenia, SHG, and decreased or negative specific vaccine titers.[48,331-333,341,342] The use of immunomodulators such as corticosteroids may increase the risk of infection in these patients.[343]

Management. Treatment of the underlying pathologic mechanism using a multidisciplinary approach is recommended. In general, a high-protein, low-fat diet with medium-chain triglycerides is preferred, resulting in improvement of abnormal laboratory findings and symptomatology.[325,326] For CD55 deficiency, treatment with eculizumab has been shown to be effective in improving general (eg, albumin) and immunologic (eg, membrane attack complex deposition on leukocytes) laboratory parameters and clinical outcomes (eg, diarrhea).[344,345]

There is limited information on the utility of IgG-RT in the treatment of SHG arising from intestinal lymphangiectasia. Patients who have undergone Fontan repair rarely experience clinically significant infection, nor do they routinely require prophylactic antibiotics or IgG-RT.[332,341,346] Case reports suggest that IVIG can improve SHG in post-Fontan patients,[342] but adequately powered RCTs are lacking, and IgG-RT is not routinely recommended.

SCIG has led to clinical and IgG level improvement in a patient in whom IVIG had previously failed to provide adequate IgG levels[47] and in 4 patients with SHG post-Fontan.[48,49]

Summary of previously published literature: Lymphangiectasias

There is insufficient evidence to recommend the routine use of IgG-RT in lymphangiectasias.

- *Evaluation:* For both primary and secondary intestinal lymphangiectasia, quantitative immunoglobulins and lymphocyte subset enumeration should be checked. Underlying genetic causes include loss-of-function mutations in CD55 and DGAT1. Complement evaluation should be considered if CD55 deficiency is suspected. Acquired intestinal lymphangiectasias have a broad differential to be considered.
- *Vaccination:* Vaccination per CDC guidelines is recommended. Patients who have undergone a Fontan procedure have variable degrees of low vaccine titers.
- *Management:* Treatment of the underlying pathologic mechanism is recommended. A high-protein, low-fat diet with medium-chain triglycerides is preferred. Eculizumab can be effective for CD55 deficiency. Often, clinically significant infection does not occur in acquired intestinal lymphangiectasis, and these patients do not routinely require prophylactic antibiotics or IgG-RT.
- *Areas of uncertainty:* Powered RCTs are needed to investigate whether IgG-RT provides clinical benefit. SCIG may possibly be preferable and is likely at least equivalent to IVIG in terms of stabilizing IgG levels in protein-losing conditions. This hypothesis needs to be investigated with RCTs.

FUTURE DIRECTIONS

A review of the existing literature regarding SHG reveals a cornucopia of existing but heterogeneous findings. SHG is associated with increasing infection and mortality risk in some patient populations, but to what degree and whether the association is causal remains unclear in many areas.

We have used the word SHG throughout this report for both HG secondary to medications and HG observed in association with non-PI conditions, because SHG has been traditionally and historically defined in this way. However, there is a case for further subcategorizing SHG. The term SHG could be used specifically for iatrogenic HG due to medications to differentiate from HG detected at time of diagnosis before use of immunosuppressive medications. HG detected at time of diagnosis before use of immunosuppressive medications could be classified further into defined PI antibody syndromes, incidental HG that is not clinically significant, and HG directly caused by the underlying

disease process (most often seen in hematologic and protein-losing conditions). Improved screening practices for HG in the appropriate patient populations at time of diagnosis and before immunosuppression would inform how to differentiate these subcategories.

Well-designed and coordinated clinical trials are hindered by the lack of standardization of what IgG level threshold is considered HG, how investigators categorize mild/moderate/severe HG, transient/persistent SHG, and the definitions used for clinically significant HG. Consensus definitions need to be reached before large-scale studies can be conducted. To aid in standardizing future studies, we have proposed the definition of HG in adult patients to be a serum IgG level below 700 mg/dL, with further stratification into the following brackets of 400 to 699 mg/dL, 200 to 399 mg/dL, and 0 to 199 mg/dL. Age-appropriate reference ranges for pediatric patients and variability between laboratories in the reference ranges of immunoglobulins must be taken into consideration. We have also proposed standard stratification of SHG duration into SHG lasting 3 months, 6 to 12 months, 12 to 24 months, and lasting more than 24 months. It must be stressed that these criteria are not meant to dictate clinical care or be used in diagnostic criteria, merely to standardize studies for the purposes of allowing more generalizable conclusions and creation of meaningful diagnostic criteria. Associations between IgG level thresholds and infection risk are needed in each subpopulation to aid in this effort.

To standardize research efforts toward defining clinically significant in heterogeneous SHG patient populations for clinical practice, it may be helpful first to reach a consensus research definition of a severe and recurrent infection. Based somewhat on the fact that these outcomes are possible to extract from large data sets, a research definition of clinically significant infection could be an infection requiring emergency department visit or hospitalization, requiring intravenous antibiotics, or requiring antibiotic/antiviral/antifungal therapy specifically for the purposes of treatment (vs prophylaxis). The research definition of recurrent could be based on Jeffrey Modell Foundation criteria: 4 or more new ear infections, 2 or more serious sinus infections, 2 or more pneumonias, and 2 or more deep-seated infections including septicemia.[28]

Finally, concerted efforts to obtain FDA approval for IgG-RT in SHG and to conduct any studies needed to gain FDA approval are essential to make advances in SHG care possible. Multiple guidelines have recommended IgG-RT (both IVIG and SCIG) for SHG due to different causes (Table V), and IVIG has been approved in Europe for SHG in patients with secondary immunodeficiencies (IgG < 400 mg/dL or specific antibody failure defined as <2-fold increase in antibody titers to pneumococcal polysaccharide and polypeptide antigen vaccines) with severe or recurrent infections and ineffective antimicrobial treatment.[347] However, IVIG is FDA-approved only for SHG associated with B-cell CLL,[35] and SCIG is not currently FDA-approved for any SHG indication.

CONCLUSIONS

Consensus criteria and future investigations in these important areas are needed to

- determine when and how often screening and monitoring for SHG is needed.
- determine the optimal laboratory evaluations to include in screening and monitoring.
- determine reliable measures for humoral immune recovery versus continued humoral immunodeficiency/immunosuppression.
- identify mechanisms of persistent B-cell functional defects following immunosuppression.
- define clinically significant SHG for which IgG-RT should be started.
- compare IVIG and SCIG, including determination of whether SCIG is equivalent or preferable for patients with SHG with a history of venous thromboembolism, renal disease, or protein loss, as it is in patients with PI.
- determine goal IgG trough levels required to maximize clinical benefit.
- understand timing of immune recovery following immunosuppressive or ablative treatment to assess for immune function/recovery in patients who have and have not started IgG-RT.

Given the heterogeneity of the underlying conditions and causes, future studies need to be designed with clearly defined patient populations. A registry dedicated to SHG would be helpful to gather data and better investigate risk factors and outcomes. Concerted efforts are needed for well-designed RCTs that take into consideration the multiple clinical factors and pharmacokinetics that can affect IgG-RT efficacy.

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