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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 secondary or primary is important because this has implications for evaluation and management. Prior receipt of

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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;■■■:■■■-■■■.)

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*

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,

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

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 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

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 |

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 cells. Including B-cell enumeration and peripheral B-cell flow cytometry in screening could improve longitudinal monitoring by

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_{1-5} 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.

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 in Fig 2. Of note, the IgG level below which IgG-RT should be started prophylactically in the absence of other laboratory

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.

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 biologic agents, corticosteroids, BCTT, and/or chemotherapy, making it difficult to determine the contribution of individual

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.

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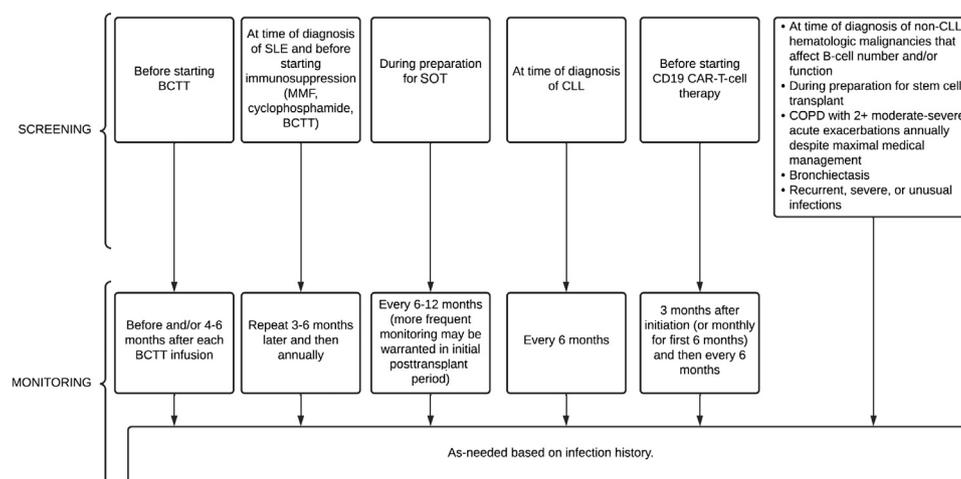
FIG 1. General considerations for screening and monitoring. At a minimum, screening and monitoring should include an IgG level. Non-IgG immunoglobulins and specific antibody responses have also been recommended because IgG levels alone do not indicate normal B-cell function. Lymphocyte subsets for B-cell 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.
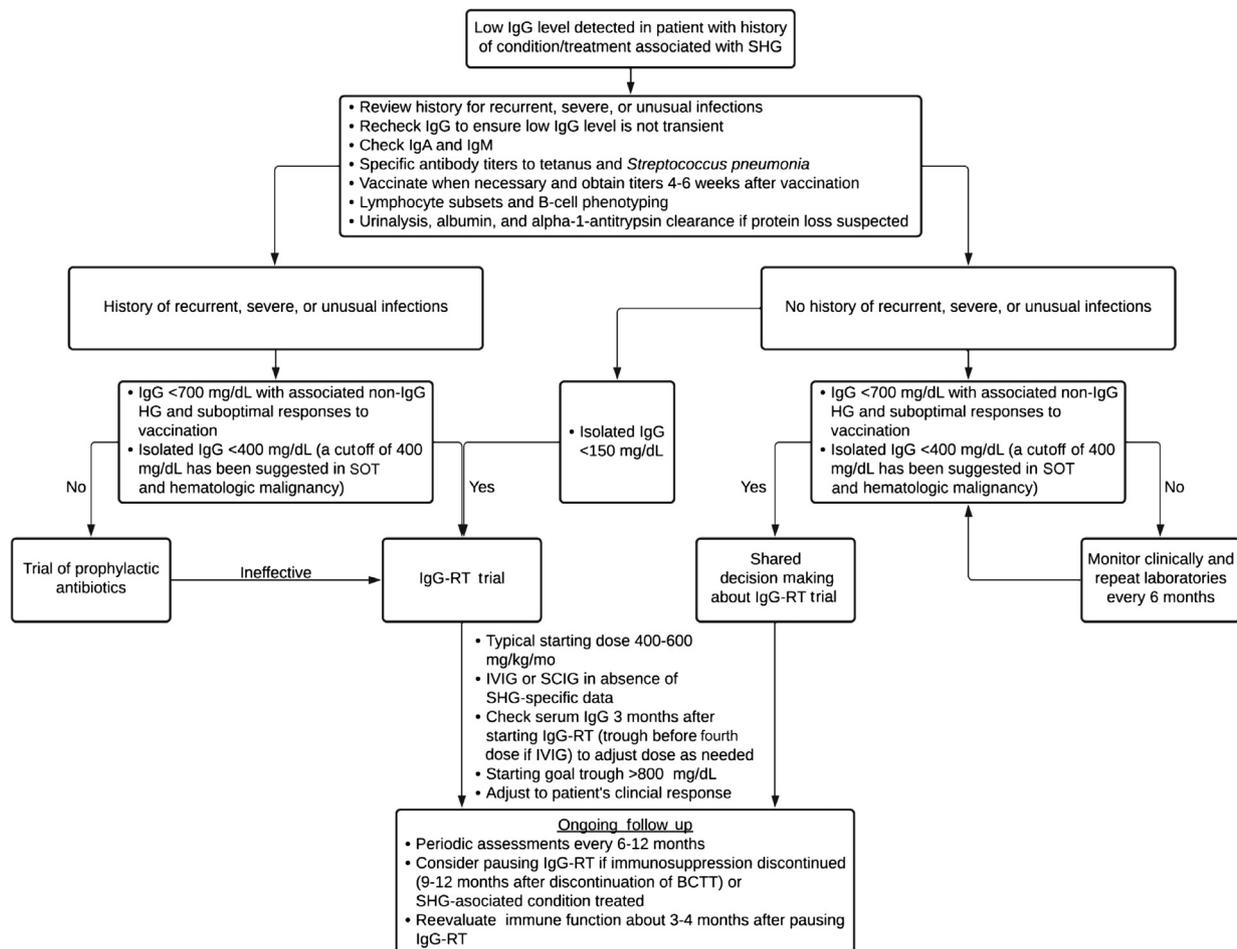
FIG 2. General considerations for evaluation and management. If SHG is uncovered, it is important to assess additional measures of immune function. Infection history is an important piece of determining next steps for management. Given the paucity of SHG-specific data, many recommendations are based 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.

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 identified as a risk factor for developing post-RTX SHG, but this finding

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

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.

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 IgG₁ 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 posttransplant 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 multi-center 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_{1-3} 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 postinfusion 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.

REFERENCES

1. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020;40:24-64.
2. Hoyt KJ, Chatila TA, Notarangelo LD, Hazen MM, Janssen E, Henderson LA. The immunologic features of patients with early-onset and polyautoimmunity. Clin Immunol 2020;211:108326.
3. Lim E, Tao Y, White AJ, French AR, Cooper MA. Hypogammaglobulinemia in pediatric systemic lupus erythematosus. Lupus 2013;22:1382-7.
4. Barsalou J, Saint-Cyr C, Drouin E, Le Deist F, Haddad E. High prevalence of primary immune deficiencies in children with autoimmune disorders. Clin Exp Rheumatol 2011;29:125-30.
5. Spârchez M, Lupan I, Delean D, Bizo A, Damian L, Muntean L, et al. Primary complement and antibody deficiencies in autoimmune rheumatologic diseases with juvenile onset: a prospective study at two centers. Pediatr Rheumatol Online J 2015;13:51.
6. Srivastava S, Wood P. Secondary antibody deficiency—causes and approach to diagnosis. Clin Med (Lond) 2016;16:571-6.
7. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol 2019;10:33.
8. Dhalla F, Lucas M, Schuh A, Bhole M, Jain R, Patel SY, et al. Antibody deficiency secondary to chronic lymphocytic leukemia: should patients be treated with prophylactic replacement immunoglobulin? J Clin Immunol 2014;34:277-82.
9. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk 2013;13:106-11.
10. De Angelis F, Tosti ME, Capria S, Russo E, D'Elia GM, Annechini G, et al. Risk of secondary hypogammaglobulinaemia after rituximab and fludarabine in indolent non-Hodgkin lymphomas: a retrospective cohort study. Leuk Res 2015;39:1382-8.
11. Dhalla F, Misbah SA. Secondary antibody deficiencies. Curr Opin Allergy Clin Immunol 2015;15:505-13.
12. Chan AY, Torgerson TR. Primary immune regulatory disorders: a growing universe of immune dysregulation. Curr Opin Allergy Clin Immunol 2020;20:582-90.
13. Cowan J, Gaudet L, Mulpuru S, Corrales-Medina V, Hawken S, Cameron C, et al. A retrospective longitudinal within-subject risk interval analysis of

immunoglobulin treatment for recurrent acute exacerbation of chronic obstructive pulmonary disease. PLoS One 2015;10:e0142205.

14. Leitao Filho FS, Mattman A, Schellenberg R, Criner GJ, Woodruff P, Lazarus SC, et al. Serum IgG levels and risk of COPD hospitalization: a pooled meta-analysis. Chest 2020;158:1420-30.

15. Berger M, Geng B, Cameron DW, Murphy LM, Schulman ES. Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease. Respir Med 2017;132:181-8.

16. Putcha N, Dransfield MT, LaFon D, Woo J, Azar A, Fawzy A, et al. BAL and serum immunoglobulin G levels are associated with risk for exacerbations, clinical and CT phenotypes, an analysis of SPIROMICS. In: A41 COPD: EPIDEMI-OLOGY. American Thoracic Society; 2019:A1580. Available at: https://www.atsjournals.org/doi/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A1580. Accessed June 5, 2021.

17. McCullagh BN, Comellas AP, Ballas ZK, Newell JD, Zimmerman MB, Azar AE. Antibody deficiency in patients with frequent exacerbations of chronic obstructive pulmonary disease (COPD). PLoS One 2017;12:e0172437.

18. Turner MW, Warner JO, Stokes CR. Immunological studies in cystic fibrosis. Arch Dis Child 1978;53:631-8.

19. Matthews WJ, Williams M, Oliphint B, Geha R, Colten HR. Hypogammaglobulinemia in patients with cystic fibrosis. N Engl J Med 1980;302:245-9.

20. Garside JP, Kerrin DP, Brownlee KG, Gooi HC, Taylor JM, Conway SP. Immunoglobulin and IgG subclass levels in a regional pediatric cystic fibrosis clinic. Pediatr Pulmonol 2005;39:135-40.

21. Proesmans M, Els C, Vermeulen F, De Boeck K. Change in IgG and evolution of lung function in children with cystic fibrosis. J Cyst Fibros 2011;10:128-31.

22. Jain S, Hopkins R, Kiernan M, El-Dahr JM. Is common variable immune deficiency common in cystic fibrosis? J Allergy Clin Immunol 2012;129:AB158.

23. Florescu DF, Kalil AC, Qiu F, Schmidt CM, Sandkovsky U. What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant 2013;13:2601-10.

24. Petrov AA, Traister RS, Crespo MM, Silveira FP, Xie M, Coffey K, et al. A prospective observational study of hypogammaglobulinemia in the first year after lung transplantation. Transplant Direct 2018;4:e372.

25. Kaplan B, Bonagura VR. Secondary hypogammaglobulinemia: an increasingly recognized complication of treatment with immunomodulators and after solid organ transplantation. Immunol Allergy Clin North Am 2019;39:31-47.

26. Kammermeier J, Dziubak R, Pescarin M, Drury S, Godwin H, Reeve K, et al. Phenotypic and genotypic characterisation of inflammatory bowel disease presenting before the age of 2 years. J Crohns Colitis 2017;11:60-9.

27. Hartono S, Ippoliti MR, Mastroianni M, Torres R, Rider NL. Gastrointestinal disorders associated with primary immunodeficiency diseases. Clin Rev Allergy Immunol 2019;57:145-65.

28. Jeffrey Modell Foundation. 10 warning signs of primary immunodeficiency. Available at: http://www.info4pi.org/library/educational-materials/10-warning-signs. Accessed October 7, 2021.

29. Hill JA, Giralt S, Torgerson TR, Lazarus HM. CAR-T - and a side order of IgG, to go? - immunoglobulin replacement in patients receiving CAR-T cell therapy. Blood Rev 2019;38:100596.

30. Los-Arcos I, Iacoboni G, Aguilar-Guisado M, Alsina-Manrique L, Díaz de Heredia C, Fortuny-Guasch C, et al. Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper. Infection 2021;49:215-31.

31. Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012;130:S1-24.

32. Centers for Disease Control and Prevention. COVID-19 vaccines for moderately or severely immunocompromised people. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. Accessed November 7, 2021.

33. Agarwal S, Cunningham-Rundles C. Treatment of hypogammaglobulinemia in adults: a scoring system to guide decisions on immunoglobulin replacement. J Allergy Clin Immunol 2013;131:1699-701.

34. Stump SE, Schepers AJ, Jones AR, Alexander MD, Auten JJ. Comparison of weight-based dosing strategies for intravenous immunoglobulin in patients with hematologic malignancies. Pharmacotherapy 2017;37:1530-6.

35. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 2017;139:S1-46.

36. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. Clin Immunol 2010;137:21-30.

37. Agostini C, Blau I-W, Kimby E, Plesner T. Prophylactic immunoglobulin therapy in secondary immune deficiency— an expert opinion. Expert Rev Clin Immunol 2016;12:921-6.

38. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014; 371:1507-17.

39. Lichvar AB, Ensor CR, Zeevi A, Morrell MR, Pilewski JM, Hayanga JWA, et al. Detrimental association of hypogammaglobulinemia with chronic lung allograft dysfunction and death is not mitigated by on-demand immunoglobulin G replacement after lung transplantation. Prog Transplant 2018;1526924818817028.

40. Cabral P, Kaplan AA, Phachu D, Shah M, Attique HB, Elali I. Impact of prefilter dilution on IgG removal in membrane-based therapeutic plasma exchange. Ther Apher Dial 2021 Nov 14. https://doi.org/10.1111/1744-9987.13757. Epub ahead of print.

41. Orange JS, Belohradsky BH, Berger M, Borte M, Hagan J, Jolles S, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012;169:172-81.

42. Vacca A, Melaccio A, Sportelli A, Solimando AG, Dammacco F, Ria R. Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial. Clin Immunol 2018;191:110-5.

43. Benbrahim O, Viallard J-F, Choquet S, Royer B, Bauduer F, Decaux O, et al. A French observational study describing the use of human polyvalent immunoglobulins in hematological malignancy-associated secondary immunodeficiency. Eur J Haematol 2018;101:48-56.

44. Shankar T, Gribowicz J, Crespo M, Silveira FP, Pilewski J, Petrov AA. Subcutaneous IgG replacement therapy is safe and well tolerated in lung transplant recipients. Int Immunopharmacol 2013;15:752-5.

45. Carbone J, Palomo J, Fernandez-Yañez J, Sarmiento E. Subcutaneous immunoglobulin replacement therapy in a heart transplant recipient with severe recurrent infections. Heart Lung Vessel 2015;7:256-9.

46. Shah SN, Todoric K, Tarrant TK. Improved outcomes on subcutaneous IgG in patients with humoral immunodeficiency and co-morbid bowel disease. Clin Case Rep Rev 2015;1:151-2.

47. Patuzzo G, Tinazzi E, Micheletti M, Puccetti A, Lunardi C. Secondary hypogammaglobulinemia in Waldmann's disease treated with subcutaneous immunoglobulins. Eur Ann Allergy Clin Immunol 2016;48:55-7.

48. Hlavackova E, Liska M, Jicinska H, Navratil J, Litzman J. Secondary combined immunodeficiency in pediatric patients after the Fontan operation: three case reports. Int Arch Allergy Immunol 2016;170:251-6.

49. Yamada Y, Ota T, Nomura Y, Tauchi N, Nishihara E, Kuraishi K. Subcutaneous immunoglobulin (SCIG) home therapy for treatment of hypogammaglobulinemia due to protein-losing enteropathy (PLE) after total cavopulmonary connection. Ped Cardiol Card Surg 2016;32:432-6.

50. Shock A, Humphreys D, Nimmerjahn F. Dissecting the mechanism of action of intravenous immunoglobulin in human autoimmune disease: lessons from therapeutic modalities targeting Fcγ receptors. J Allergy Clin Immunol 2020;146:492-500.

51. Koleba T, Ensom MHH. Pharmacokinetics of intravenous immunoglobulin: a systematic review. Pharmacotherapy 2006;26:813-27.

52. Melamed IR, Borte M, Trawnicek L, Kobayashi A-L, Kobayashi RH, Knutsen A, et al. Pharmacokinetics of a novel human intravenous immunoglobulin 10% in patients with primary immunodeficiency diseases: analysis of a phase III, multi-centre, prospective, open-label study. Eur J Pharmaceut Sci 2018;118:80-6.

53. Mahmood I, Tegenge MA, Golding B. Considerations for optimizing dosing of immunoglobulins based on pharmacokinetic evidence. Antibodies (Basel) 2020; 9:E24.

54. Chinen J, Shearer WT. Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol 2010;125:S195-203.

55. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60-5.

56. Barmettler S, Ong M-S, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open 2018;1:e184169.

57. Makatsori M, Kiani-Alikhan S, Manson AL, Verma N, Leandro M, Gurugama NP, et al. Hypogammaglobulinaemia after rituximab treatment—incidence and outcomes. QJM 2014;107:821-8.

58. Yang N, Farmer J, Barmettler S. Retrospective analysis of the immunologic evaluation in patients receiving ocrelizumab. J Clin Immunol 2020;40:1-163.

59. Tsao L, Otani IM, Bove R. Hypogammaglobulinemia in multiple sclerosis patients receiving disease-modifying immunomodulatory agents. J Allergy Clin Immunol 2019;143:AB16.

60. Hauk M, McGoey B, Michelis M. M255 Persistent hypogammaglobulinemia following obinutuzumab treatment for chronic lymphocytic leukemia. Ann Allergy Asthma Immunol 2019;123:S111.

61. Grigg A, Dyer MJS, Díaz MG, Dreyling M, Rule S, Lei G, et al. Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma. Haematologica 2017;102:765-72.

62. Sharman JP, Forero-Torres A, Costa LJ, Flinn IW, Inhorn L, Kelly K, et al. Obinutuzumab plus CHOP is effective and has a tolerable safety profile in previously untreated, advanced diffuse large B-cell lymphoma: the phase II GATHER study. Leuk Lymphoma 2019;60:894-903.

63. Mahévas M, Azzaoui I, Crickx E, Canoui-Poitrine F, Gobert D, Languille L, et al. Efficacy, safety and immunological profile of combining rituximab with belimumab for adults with persistent or chronic immune thrombocytopenia: results from a prospective phase 2b trial. Haematologica 2021 Sep 1;106(9):2449-57. https://doi.org/10.3324/haematol.2020.259481.

64. Stohl W, Hiepe F, Latinis KM, Thomas M, Scheinberg MA, Clarke A, et al. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with systemic lupus erythematosus. Arthritis Rheum 2012;64:2328-37.

65. Christou EAA, Giardino G, Worth A, Ladomenou F. Risk factors predisposing to the development of hypogammaglobulinemia and infections post-rituximab. Int Rev Immunol 2017;36:352-9.

66. Besada E, Koldingsnes W, Nossent JC. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2014;53:1818-24.

67. Boleto G, Avouac J, Wipff J, Forien M, Dougados M, Roux C, et al. Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: a 12-year longitudinal multi-center study. Semin Arthritis Rheum 2018;48:149-54.

68. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909-20.

69. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306-9.

70. Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, et al. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Rheumatology (Oxford) 2011;50:2311-3.

71. Price V. Auto-immune lymphoproliferative disorder and other secondary immune thrombocytopenias in childhood. Pediatr Blood Cancer 2013;60:S12-4.

72. Stabler S, Giovannelli J, Launay D, Cotteau-Leroy A, Heusele M, Lefèvre G, et al. Serious infectious events and immunoglobulin replacement therapy in patients with autoimmune disease receiving rituximab: a retrospective cohort study. Clin Infect Dis 2021;72:727-37.

73. van Vollenhoven RF, Emery P, Bingham CO, Keystone EC, Fleischmann R, Furst DE, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 2010;37:558-67.

74. Katz Y, Harbeck RJ, DiMichelle D, Mitchell B, Strunk RC. Steroid-treated asthmatic patients with low levels of IgG have a normal capacity to produce specific antibodies. Pediatr Asthma Allergy Immunol 1988;2:309-16.

75. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-33.

76. Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456-73.

77. Thiel J, Rizzi M, Engesser M, Dufner A-K, Troilo A, Lorenzetti R, et al. B cell repopulation kinetics after rituximab treatment in ANCA-associated vasculitides compared to rheumatoid arthritis, and connective tissue diseases: a longitudinal observational study on 120 patients. Arthritis Res Ther 2017;19:101.

78. Barmettler S, Price C. Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab—for how long? J Allergy Clin Immunol 2015;136:1407-9.

79. Roll P, Mahmood Z, Muhammad K, Feuchtenberger M, Dörner T, Tony H-P. Long-term repopulation of peripheral B-cell subsets after single and repeated rituximab infusions in patients with rheumatoid arthritis. Clin Exp Rheumatol 2015;33:347-53.

80. Anolik JH, Friedberg JW, Zheng B, Barnard J, Owen T, Cushing E, et al. B cell reconstitution after rituximab treatment of lymphoma recapitulates B cell ontogeny. Clin Immunol 2007;122:139-45.

81. Baker D, Pryce G, James LK, Marta M, Schmierer K. The ocrelizumab phase II extension trial suggests the potential to improve the risk: benefit balance in multiple sclerosis. Mult Scler Relat Disord 2020;44:102279.

82. Bar-Or A, Grove RA, Austin DJ, Tolson JM, VanMeter SA, Lewis EW, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: the MIRROR study. Neurology 2018;90:e1805-14.

83. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis 2011;15:e2-16.

84. Mitka M. FDA: increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013;310:1664.

85. Evens AM, Jovanovic BD, Su Y-C, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170-80.

86. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834-40.

87. Palazzo E, Yahia SA. Progressive multifocal leukoencephalopathy in autoimmune diseases. Joint Bone Spine 2012;79:351-5.

88. Raisch DW, Rafi JA, Chen C, Bennett CL. Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA's adverse event reporting system. Expert Opin Drug Saf 2016;15:1003-11.

89. Tellez R, Lastinger AM, Hogg JP. Chronic enteroviral meningoencephalitis in a patient on rituximab for the treatment of psoriatic arthritis: a case report and brief literature review. IDCases 2019;17:e00558.

90. Goldberg SL, Pecora AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002;99:1486-8.

91. Byrd JC, Peterson BL, Morrison VA, Park K, Jacobson R, Hoke E, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.

92. Lee M-Y, Chiou T-J, Hsiao L-T, Yang M-H, Lin P-C, Poh S-B, et al. Rituximab therapy increased post-transplant cytomegalovirus complications in non-Hodgkin's lymphoma patients receiving autologous hematopoietic stem cell transplantation. Ann Hematol 2008;87:285-9.

93. Hartmann JT, Meisinger I, Kröber SM, Weisel K, Klingel K, Kanz L. Progressive bicytopenia due to persistent parvovirus B19 infection after immunochemotherapy with fludarabine/cyclophosphamide and rituximab for relapsed B cell lymphoma. Haematologica 2006;91:ECR49.

94. Isobe Y, Sugimoto K, Shiraki Y, Nishitani M, Koike K, Oshimi K. Successful high-titer immunoglobulin therapy for persistent parvovirus B19 infection in a lymphoma patient treated with rituximab-combined chemotherapy. Am J Hematol 2004;77:370-3.

95. Sharma VR, Fleming DR, Slone SP. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. Blood 2000;96:1184-6.

96. Song KW, Mollee P, Patterson B, Brien W, Crump M. Pure red cell aplasia due to parvovirus following treatment with CHOP and rituximab for B-cell lymphoma. Br J Haematol 2002;119:125-7.

97. van der Kolk LE, Baars JW, Prins MH, van Oers MHJ. Rituximab treatment results in impaired secondary humoral immune responsiveness. Blood 2002;100:2257-9.

98. Nazi I, Kelton JG, Larché M, Snider DP, Heddle NM, Crowther MA, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood 2013;122:1946-53.

99. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2014;66:1016-26.

100. Kim W, Kim S-H, Huh S-Y, Kong S-Y, Choi YJ, Cheong HJ, et al. Reduced antibody formation after influenza vaccination in patients with neuromyelitis optica spectrum disorder treated with rituximab. Eur J Neurol 2013;20:975-80.

101. Farez MF, Correale J, Armstrong MJ, Rae-Grant A, Gloss D, Donley D, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2019;93:584-94.

102. Genentech. Rituxan (rituximab) [package insert]. 2020. Available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed June 5, 2021.

103. Genentech. Ocrevus (ocrelizumab) [package insert]. 2021.

104. Bingham CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62:64-74.

105. van Assen S, Holvast A, Benne CA, Posthumus MD, van Leeuwen MA, Voskuyl AE, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum 2010; 62:75-81.

106. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414-22.

107. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. J Cutan Med Surg 2019;23:50-74.

108. Tanrıöver MD, Akar S, Türkçapar N, Karadağ Ö, Ertenli İ, Kiraz S. Vaccination recommendations for adult patients with rheumatic diseases. Eur J Rheumatol 2016;3:29-35.

109. Centers for Disease Control and Prevention. ACIP General Best Practice Guidelines for Immunization. 2021. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed January 5, 2021.

110. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44-100.

111. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1. Arthritis Rheumatol 2021;73:1093-107.

112. Bar-Or A, Calkwood JC, Chognot C, Evershed J, Fox EJ, Herman A, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology 2020;95:e1999-2008.

113. Smets I, Reyes S, Baker D, Giovannoni G. Blunted vaccines responses after ocrelizumab highlight need for immunizations prior to treatment. Mult Scler Relat Disord 2021;50:102851.

114. Cooper N, Davies EG, Thrasher AJ. Repeated courses of rituximab for autoimmune cytopenias may precipitate profound hypogammaglobulinaemia requiring replacement intravenous immunoglobulin. Br J Haematol 2009;146:120-2.

115. Bisogno G. Persistent B-cell depletion after rituximab for thrombocytopenic purpura. Eur J Pediatr 2007;166:85-6.

116. Adeli MMG, Eichner BH, Thornburg C, Williams L. Persistent antibody depletion after rituximab in three children with autoimmune cytopenias. Pediatr Hematol Oncol 2009;26:566-72.

117. Levy R, Mahévas M, Galicier L, Boutboul D, Moroch J, Loustau V, et al. Profound symptomatic hypogammaglobulinemia: a rare late complication after rituximab treatment for immune thrombocytopenia. Report of 3 cases and systematic review of the literature. Autoimmun Rev 2014;13:1055-63.

118. Palacios T, Bartelt L, Scheld W, Lopes MB, Kelting SM, Holland S, et al. Fatal Coxsackie meningoencephalitis in a patient with B-cell lymphopenia and hypogammaglobulinemia following rituximab therapy. Ann Allergy Asthma Immunol 2015;115:148-50.

119. Quartier P, Brethon B, Philippet P, Landman-Parker J, Le Deist F, Fischer A. Treatment of childhood autoimmune haemolytic anaemia with rituximab. Lancet 2001;358:1511-3.

120. Khojah AM, Miller ML, Klein-Gitelman MS, Curran ML, Hans V, Pachman LM, et al. Rituximab-associated hypogammaglobulinemia in pediatric patients with autoimmune diseases. Pediatr Rheumatol Online J 2019;17:61.

121. Ottaviano G, Marinoni M, Graziani S, Sibson K, Barzaghi F, Bertolini P, et al. Rituximab unveils hypogammaglobulinemia and immunodeficiency in children with autoimmune cytopenia. J Allergy Clin Immunol Pract 2020;8: 273-82.

122. Kaplan B, Kopyltsova Y, Khokhar A, Lam F, Bonagura V. Rituximab and immune deficiency: case series and review of the literature. J Allergy Clin Immunol Pract 2014;2:594-600.

123. Rao A, Kelly M, Musselman M, Ramadas J, Wilson D, Grossman W, et al. Safety, efficacy, and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenias. Pediatr Blood Cancer 2008;50:822-5.

124. Labrosse R, Barmettler S, Derfalvi B, Blincoe A, Cros G, Lacombe-Barrios J, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol 2021;148:523-32.e8.

125. Delbe-Bertin L, Aoun B, Tudorache E, Lapillone H, Ulinski T. Does rituximab induce hypogammaglobulinemia in patients with pediatric idiopathic nephrotic syndrome? Pediatr Nephrol 2013;28:447-51.

126. Worch J, Makarova O, Burkhardt B. Immunreconstitution and infectious complications after rituximab treatment in children and adolescents: what do we know and what can we learn from adults? Cancers (Basel) 2015;7:305-28.

127. Zarkhin V, Li L, Kambham N, Sigdel T, Salvatierra O, Sarwal MM. A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. Am J Transplant 2008;8:2607-17.

128. Liang Y, Zhang L, Gao J, Hu D, Ai Y. Rituximab for children with immune thrombocytopenia: a systematic review. PLoS One 2012;7:e36698.

129. Filanovsky K, Miller EB, Sigler E, Berrebi A, Shvidel L. Incidence of profound hypogammaglobulinemia and infection rate in lymphoma patients following the combination of chemotherapy and rituximab. Recent Pat Anticancer Drug Discov 2016;11:228-35.

130. Ferreira I, Isenberg D. Vaccines and biologics. Ann Rheum Dis 2014;73:1446-54.

131. Cheng DR, Barton R, Greenway A, Crawford NW. Rituximab and protection from vaccine preventable diseases: applying the evidence to pediatric patients. Expert Rev Vaccines 2016;15:1567-74.

132. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73:1366-83.

133. Castelino DJ, McNair P, Kay TW. Lymphocytopenia in a hospital population–what does it signify? Aust N Z J Med 1997;27:170-4.

134. Hamilos DL, Young RM, Peter JB, Agopian MS, Iklé DN, Barka N. Hypogammaglobulinemia in asthmatic patients. Ann Allergy 1992;68:472-81.

135. Kawano T, Matsuse H, Obase Y, Kondo Y, Machida I, Tomari S, et al. Hypogammaglobulinemia in steroid-dependent asthmatics correlates with the daily dose of oral prednisolone. Int Arch Allergy Immunol 2002;128:240-3.

136. Wirsum C, Glaser C, Gutenberger S, Keller B, Unger S, Voll RE, et al. Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. J Clin Immunol 2016;36:406-12.

137. Settipane GA, Pudupakkam RK, McGowan JH. Corticosteroid effect on immunoglobulins. J Allergy Clin Immunol 1978;62:162-6.

138. Posey WC, Nelson HS, Branch B, Pearlman DS. The effects of acute corticosteroid therapy for asthma on serum immunoglobulin levels. J Allergy Clin Immunol 1978;62:340-8.

139. Butler WT, Rossen RD. Effects of corticosteroids on immunity in man, I: decreased serum IgG concentration caused by 3 or 5 days of high doses of methylprednisolone. J Clin Invest 1973;52:2629-40.

140. Sharma S, Lichtenstein A. Dexamethasone-induced apoptotic mechanisms in myeloma cells investigated by analysis of mutant glucocorticoid receptors. Blood 2008;112:1338-45.

141. Lanzillotta M, Della-Torre E, Milani R, Bozzolo E, Bozzalla-Cassione E, Rovati L, et al. Effects of glucocorticoids on B-cell subpopulations in patients with IgG4-related disease. Clin Exp Rheumatol 2019;37:159-66.

142. Lee J, Machin M, Russell KE, Pavlidis S, Zhu J, Barnes PJ, et al. Corticosteroid modulation of immunoglobulin expression and B-cell function in COPD. FASEB J 2016;30:2014-26.

143. Lack G, Ochs HD, Gelfand EW. Humoral immunity in steroid-dependent children with asthma and hypogammaglobulinemia. J Pediatr 1996;129:898-903.

144. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis 2002;34:1098-107.

145. Sepkowitz KA, Brown AE, Armstrong D. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome. More patients, same risk. Arch Intern Med 1995;155:1125-8.

146. Mansharamani NG, Balachandran D, Vernovsky I, Garland R, Koziel H. Peripheral blood CD4 + T-lymphocyte counts during *Pneumocystis carinii* pneumonia in immunocompromised patients without HIV infection. Chest 2000;118:712-20.

147. Limper AH, Knox KS, Sarosi GA, Ampel NM, Bennett JE, Catanzaro A, et al. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med 2011; 183:96-128.

148. Cuadrado MJ, Calatayud I, Urquizu-Padilla M, Wijetilleka S, Kiani-Alikhan S, Karim MY. Immunoglobulin abnormalities are frequent in patients with lupus nephritis. BMC Rheumatol 2019;3:30.

149. Smilek DE, Lim N, Ding L, Murray SG, Diamond B, Wofsy D. Correlation of hypogammaglobulinaemia with proteinuria, and the relationship between hypogammaglobulinaemia and infection in active lupus nephritis. Lupus Sci Med 2017;4:e000229.

150. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583-94.

151. Gordon C, Amissah-Arthur M-B, Gayed M, Brown S, Bruce IN, D'Cruz D, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford) 2018;57:e1-45.

152. Yong PFK, Aslam L, Karim MY, Khamashta MA. Management of hypogammaglobulinaemia occurring in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2008;47:1400-5.

153. Erratum: Eular/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1480.

154. Park JK, Lee MA, Lee EY, Song YW, Choi Y, Winthrop KL, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 2017;76:1559-65.

155. Park JK, Lee YJ, Shin K, Ha Y-J, Lee EY, Song YW, et al. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 2018;77:898-904.

156. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol 2019;123:454-60.

157. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States Immune Deficiency Network Registry. J Allergy Clin Immunol 2018;141:1028-35.

158. Tallantyre EC, Robertson NP, Jolles S. Secondary antibody deficiency in neurology. Curr Opin Allergy Clin Immunol 2018;18:481-8.

159. Greenfield AL, Hauser SL. B-cell therapy for multiple sclerosis: entering an era. Ann Neurol 2018;83:13-26.

160. Zoehner G, Miclea A, Salmen A, Kamber N, Diem L, Friedli C, et al. Reduced serum immunoglobulin G concentrations in multiple sclerosis: prevalence and association with disease-modifying therapy and disease course. Ther Adv Neurol Disord 2019;12:1756286419878834.

161. Tsao L, Bove R, Krishnakumar T, Otani I. Hypogammaglobulinemia in patients with neuromyelitis optica (NMO). J Allergy Clin Immunol 2020;145:AB215.

162. Tallantyre EC, Whittam DH, Jolles S, Paling D, Constantinesecu C, Robertson NP, et al. Secondary antibody deficiency: a complication of anti-CD20 therapy for neuroinflammation. J Neurol 2018;265:1115-22.

163. Marcinnò A, Marnetto F, Valentino P, Martire S, Balbo A, Drago A, et al. Rituximab-induced hypogammaglobulinemia in patients with neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflamm 2018;5:e498.

164. Radaelli M, Moiola L, Sangalli F, Esposito F, Barcella V, Ferrè L, et al. Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. Mult Scler 2016;22:511-9.

165. Portaccio E, Zipoli V, Siracusa G, Piacentini S, Sorbi S, Amato MP. Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. Mult Scler 2003;9:446-50.

166. Selter RC, Biberacher V, Grummel V, Buck D, Eienbröker C, Oertel WH, et al. Natalizumab treatment decreases serum IgM and IgG levels in multiple sclerosis patients. Mult Scler 2013;19:1454-61.

167. Lee M, Nguyen J, Fuleihan R, Gundling K, Cunningham-Rundles C, Otani IM. Neurologic conditions and symptoms reported among common variable immunodeficiency patients in the USIDNET. J Clin Immunol 2020;40:1181-3.

168. Reyes S, Ramsay M, Ladhani S, Amirthalingam G, Singh N, Cores C, et al. Protecting people with multiple sclerosis through vaccination. Pract Neurol 2020;20:435-45.

169. Farhat L, Dara J, Duberstein S, De A. Secondary hypogammaglobulinemia after rituximab for neuromyelitis optica: a case report. Drug Saf Case Rep 2018;5:22.

170. Stokmaier D, Winthrop K, Chognot C, Evershed J, Manfrini M, McNamara J, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis (S36.002). Neurology 2018;90. Available at: https://n.neurology.org/content/90/15_Supplement/S36.002. Accessed August 3, 2020.

171. Wing EJ, Bruns FJ, Fraley DS, Segel DP, Adler S. Infectious complications with plasmapheresis in rapidly progressive glomerulonephritis. JAMA 1980;244:2423-6.

172. Chapel HM, Lee M. The use of intravenous immune globulin in multiple myeloma. Clin Exp Immunol 1994;97:21-4.

173. Park S, Jung CW, Jang JH, Kim SJ, Kim WS, Kim K. Incidence of infection according to intravenous immunoglobulin use in autologous hematopoietic stem cell transplant recipients with multiple myeloma. Transpl Infect Dis 2015;17:679-87.

174. Ueda M, Berger M, Gale RP, Lazarus HM. Immunoglobulin therapy in hematologic neoplasms and after hematopoietic cell transplantation. Blood Rev 2018;32:106-15.

175. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v78-84.

176. Oscier D, Dearden C, Eren E, Erem E, Fegan C, Follows G, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. Br J Haematol 2012;159:541-64.

177. Na I-K, Buckland M, Agostini C, Edgar JDM, Friman V, Michallet M, et al. Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies. Eur J Haematol 2019;102:447-56.

178. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143-238.

179. Blombery P, Prince HM, Worth LJ, Main J, Yang M, Wood EM, et al. Prophylactic intravenous immunoglobulin during autologous haemopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications. Ann Hematol 2011;90:1167-72.

180. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma 2009;50:764-72.

181. Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. Br Med Bull 2008;87:49-62.

182. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. Best Pract Res Clin Haematol 2010;23:145-53.

183. Kay NE. Abnormal T-cell subpopulation function in CLL: excessive suppressor (T gamma) and deficient helper (T mu) activity with respect to B-cell proliferation. Blood 1981;57:418-20.

184. Hersey P, Wotherspoon J, Reid G, Gunz FW. Hypogammaglobulinaemia associated with abnormalities of both B and T lymphocytes in patients with chronic lymphatic leukaemia. Clin Exp Immunol 1980;39:698-707.

185. Sampalo A, Navas G, Medina F, Segundo C, Cámara C, Brieva JA. Chronic lymphocytic leukemia B cells inhibit spontaneous Ig production by autologous bone marrow cells: role of CD95-CD95L interaction. Blood 2000;96:3168-74.

186. Dighiero G. An attempt to explain disordered immunity and hypogammaglobulinemia in B-CLL. Nouv Rev Fr Hematol 1988;30:283-8.

187. Chapel H, Dicato M, Gamm H, Brennan V, Ries F, Bunch C, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimens. Br J Haematol 1994;88:209-12.

188. Anaissie EJ, Kontoyiannis DP, O'Brien S, Kantarjian H, Robertson L, Lerner S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 1998;129:559-66.

189. Gottenberg J-E, Dörner T, Bootsma H, Devauchelle-Pensec V, Bowman SJ, Mariette X, et al. Efficacy of epratuzumab, an anti-CD22 monoclonal IgG antibody, in systemic lupus erythematosus patients with associated Sjögren's syndrome: post hoc analyses from the EMBODY trials. Arthritis Rheumatol 2018;70:763-73.

190. Sun C, Tian X, Lee YS, Gunti S, Lipsky A, Herman SEM, et al. Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. Blood 2015;126:2213-9.

191. Sinisalo M, Aittoniemi J, Oivanen P, Käyhty H, Olander RM, Vilpo J. Response to vaccination against different types of antigens in patients with chronic lymphocytic leukaemia. Br J Haematol 2001;114:107-10.

192. Jiang F, Verma P. Management of hypogammaglobulinemia and recurrent infections in a chronic lymphocytic leukemia patient receiving ibrutinib. Ann Allergy Asthma Immunol 2018;120:324-5.

193. Friman V, Winqvist O, Blimark C, Langerbeins P, Chapel H, Dhalla F. Secondary immunodeficiency in lymphoproliferative malignancies. Hematol Oncol 2016;34:121-32.

194. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. N Engl J Med 1991;325:81-6.

195. Besa EC, Klumpe D. Prophylactic immune globulin in chronic lymphocytic leukemia. N Engl J Med 1992;326:139.

196. Takata T, Suzumiya J, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the administration of rituximab-CHOP. J Clin Exp Hematop 2009;49:9-13.

197. Bedognetti D, Zoppoli G, Massucco C, Zanardi E, Zupo S, Bruzzone A, et al. Impaired response to influenza vaccine associated with persistent memory B cell depletion in non-Hodgkin's lymphoma patients treated with rituximab-containing regimens. J Immunol 2011;186:6044-55.

198. Yri OE, Torfoss D, Hungnes O, Tierens A, Waalen K, Nordøy T, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. Blood 2011;118:6769-71.

199. Musto P, Brugiatelli M, Carotenuto M. Prophylaxis against infections with intravenous immunoglobulins in multiple myeloma. Br J Haematol 1995;89:945-6.

200. Frangoul H, Min E, Wang W, Chandrasekhar R, Calder C, Evans M, et al. Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT. Bone Marrow Transplant 2013;48:1456-9.

201. Ashihara E, Shimazaki C, Yamagata N, Hirata T, Okawa K, Oku N, et al. Reconstitution of lymphocyte subsets after peripheral blood stem cell transplantation: two-color flow cytometric analysis. Bone Marrow Transplant 1994;13:377-81.

202. Koehne G, Zeller W, Stockschlaeder M, Zander AR. Phenotype of lymphocyte subsets after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1997;19:149-56.

203. Talmadge JE, Reed E, Ino K, Kessinger A, Kuszynski C, Heimann D, et al. Rapid immunologic reconstitution following transplantation with mobilized peripheral blood stem cells as compared to bone marrow. Bone Marrow Transplant 1997; 19:161-72.

204. Hicks LK, Woods A, Buckstein R, Mangel J, Pennell N, Zhang L, et al. Rituximab purging and maintenance combined with auto-SCT: long-term molecular remissions and prolonged hypogammaglobulinemia in relapsed follicular lymphoma. Bone Marrow Transplant 2009;43:701-8.

205. Lim SH, Esler WV, Zhang Y, Zhang J, Periman PO, Burris C, et al. B-cell depletion for 2 years after autologous stem cell transplant for NHL induces prolonged hypogammaglobulinemia beyond the rituximab maintenance period. Leuk Lymphoma 2008;49:152-3.

206. Lim SH, Zhang Y, Wang Z, Esler WV, Beggs D, Pruitt B, et al. Maintenance rituximab after autologous stem cell transplant for high-risk B-cell lymphoma induces prolonged and severe hypogammaglobulinemia. Bone Marrow Transplant 2005;35:207-8.

207. Shortt J, Spencer A. Adjuvant rituximab causes prolonged hypogammaglobulinaemia following autologous stem cell transplant for non-Hodgkin's lymphoma. Bone Marrow Transplant 2006;38:433-6.

208. Wiegering V, Eyrich M, Winkler B, Schlegel PG. Comparison of immune reconstitution after allogeneic versus autologous stem cell transplantation in 182 pediatric recipients. J Pediatr Hematol Oncol 2019;41:e302-7.

209. Abdel-Azim H, Elshoury A, Mahadeo KM, Parkman R, Kapoor N. Humoral immune reconstitution kinetics after allogeneic hematopoietic stem cell transplantation in children: a maturation block of IgM memory B cells may lead to impaired antibody immune reconstitution. Biol Blood Marrow Transplant 2017;23: 1437-46.

210. Törlén J, Gaballa A, Remberger M, Mörk L-M, Sundberg B, Mattsson J, et al. Effect of graft-versus-host disease prophylaxis regimens on T and B cell reconstitution after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2019;25:1260-8.

211. Abrahamsen IW, Sømme S, Heldal D, Egeland T, Kvale D, Tjønnfjord GE. Immune reconstitution after allogeneic stem cell transplantation: the impact of stem cell source and graft-versus-host disease. Haematologica 2005;90:86-93.

212. Bosch M, Khan FM, Storek J. Immune reconstitution after hematopoietic cell transplantation. Curr Opin Hematol 2012;19:324-35.

213. Manz RA, Thiel A, Radbruch A. Lifetime of plasma cells in the bone marrow. Nature 1997;388:133-4.

214. Storek J. Immunological reconstitution after hematopoietic cell transplantation —its relation to the contents of the graft. Expert Opin Biol Ther 2008;8:583-97.

215. Berger M, Figari O, Bruno B, Raiola A, Dominietto A, Fiorone M, et al. Lymphocyte subsets recovery following allogeneic bone marrow transplantation (BMT): CD4+ cell count and transplant-related mortality. Bone Marrow Transplant 2008;41:55-62.

216. Kim DH, Sohn SK, Won DI, Lee NY, Suh JS, Lee KB. Rapid helper T-cell recovery above 200 x 10 6/l at 3 months correlates to successful transplant outcomes after allogeneic stem cell transplantation. Bone Marrow Transplant 2006;37: 1119-28.

217. Storek J, Gooley T, Witherspoon RP, Sullivan KM, Storb R. Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol 1997;54:131-8.

218. Inaba H, Hartford CM, Pei D, Posner MJ, Yang J, Hayden RT, et al. Longitudinal analysis of antibody response to immunization in paediatric survivors after allogeneic haematopoietic stem cell transplantation. Br J Haematol 2012;156: 109-17.

219. Pohl MA, Lan SP, Berl T. Plasmapheresis does not increase the risk for infection in immunosuppressed patients with severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. Ann Intern Med 1991;114:924-9. https://doi.org/10.7326/0003-4819-114-11-924.

220. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis 2000;30: S29-65.

221. Sundin M, Remberger M, Lindqvist H, Omazic B, Sundberg B, Uzunel M, et al. Hypogammaglobulinemia in children after allogeneic hematopoietic stem cell transplantation: a cytokine mediated immunoglobulin isotype class switch arrest? Pediatr Blood Cancer 2015;62:890-6.

222. Bhella S, Majhail NS, Betcher J, Costa LJ, Daly A, Dandoy CE, et al. Choosing wisely BMT: American Society for Blood and Marrow Transplantation and Canadian Blood and Marrow Transplant Group's list of 5 tests and treatments to question in blood and marrow transplantation. Biol Blood Marrow Transplant 2018; 24:909-13.

223. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. Blood Rev 2019;34:45-55.

224. Bhoj VG, Arhontoulis D, Wertheim G, Capobianchi J, Callahan CA, Ellebrecht CT, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood 2016;128:360-70.

225. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 2018;131:121-30.

226. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.

227. Kochenderfer JN, Somerville RPT, Lu T, Yang JC, Sherry RM, Feldman SA, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. Mol Ther 2017;25:2245-53.

228. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med 2017;377: 2545-54.

229. Cordeiro A, Bezerra ED, Hirayama AV, Hill JA, Wu QV, Voutsinas J, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. Biol Blood Marrow Transplant 2020;26:26-33.

230. Park JH, Romero FA, Taur Y, Sadelain M, Brentjens RJ, Hohl TM, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. Clin Infect Dis 2018;67:533-40.

231. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-48.

232. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.

233. Halliley JL, Tipton CM, Liesveld J, Rosenberg AF, Darce J, Gregoretti IV, et al. Long-lived plasma cells are contained within the CD19(−)CD38(hi)CD138(+) subset in human bone marrow. Immunity 2015;43:132-45.

234. Pescovitz MD, Torgerson TR, Ochs HD, Ocheltree E, McGee P, Krause-Steinrauf H, et al. Effect of rituximab on human in vivo antibody immune responses. J Allergy Clin Immunol 2011;128:1295-302.e5.

235. Centers for Disease Control and Prevention. Pneumococcal vaccine recommendations. 2021. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html. Accessed June 5, 2021.

236. Dransfield MT, Harnden S, Burton RL, Albert RK, Bailey WC, Casaburi R, et al. Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. Clin Infect Dis 2012;55:e35-44.

237. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. JAMA 2017;317:269-79.

238. Tiotiu A, Salvator H, Jaussaud R, Jankowski R, Couderc L-J, Catherinot E, et al. Efficacy of immunoglobulin replacement therapy and azithromycin in severe asthma with antibody deficiency. Allergol Int 2020;69:215-22.

239. Kim JH, Ye YM, Ban GY, Shin YS, Lee HY, Nam YH, et al. Effects of immunoglobulin replacement on asthma exacerbation in adult asthmatics with IgG subclass deficiency. Allergy Asthma Immunol Res 2017;9:526-33.

240. Schwartz HJ, Hostoffer RW, McFadden ER, Berger M. The response to intravenous immunoglobulin replacement therapy in patients with asthma with specific antibody deficiency. Allergy Asthma Proc 2006;27:53-8.

241. Haque S, Boyce N, Thien FCK, O'Hehir RE, Douglass J. Role of intravenous immunoglobulin in severe steroid-dependent asthma. Intern Med J 2003;33: 341-4.

242. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. Clin Immunol 1999;91:126-33.

243. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. J Allergy Clin Immunol 1999;103:810-5.

244. Niggemann B, Leupold W, Schuster A, Schuster R, v Berg A, Grübl A, et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Clin Exp Allergy 1998;28:205-10.

245. Wallwork JC, Brenchley P, McCarthy J, Allan JD, Moss D, Ward AM, et al. Some aspects of immunity in patients with cystic fibrosis. Clin Exp Immunol 1974;18: 303-20.

246. Wheeler WB, Williams M, Matthews WJ, Colten HR. Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels: a 5-year longitudinal study. J Pediatr 1984;104:695-9.

247. Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation 2001;71:242-6.

248. Robertson J, Elidemir O, Saz EU, Gulen F, Schecter M, McKenzie E, et al. Hypogammaglobulinemia: incidence, risk factors, and outcomes following pediatric lung transplantation. Pediatr Transplant 2009;13:754-9.

249. Bentur L, McKlusky I, Levison H, Roifman CM. Advanced lung disease in a patient with cystic fibrosis and hypogammaglobulinemia: response to intravenous immune globulin therapy. J Pediatr 1990;117:741-3.

250. Balfour-Lynn IM, Mohan U, Bush A, Rosenthal M. Intravenous immunoglobulin for cystic fibrosis lung disease: a case series of 16 children. Arch Dis Child 2004;89:315-9.

251. Winnie GB, Cowan RG, Wade NA. Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. J Pediatr 1989;114:309-14.

252. Yip NH, Lederer DJ, Kawut SM, Wilt JS, D'Ovidio F, Wang Y, et al. Immunoglobulin G levels before and after lung transplantation. Am J Respir Crit Care Med 2006;173:917-21.

253. Ohsumi A, Chen F, Yamada T, Sato M, Aoyama A, Bando T, et al. Effect of hypogammaglobulinemia after lung transplantation: a single-institution study. Eur J Cardiothorac Surg 2014;45:e61-7.

254. Chambers DC, Davies B, Mathews A, Yerkovich ST, Hopkins PM. Bronchiolitis obliterans syndrome, hypogammaglobulinemia, and infectious complications of lung transplantation. J Heart Lung Transplant 2013;32:36-43.

255. Sarmiento E, Cifrian J, Calahorra L, Bravo C, Lopez S, Laporta R, et al. Monitoring of early humoral immunity to identify lung recipients at risk for development of serious infections: a multicenter prospective study. J Heart Lung Transplant 2018;37:1001-12.

256. Kawut SM, Shah L, Wilt JS, Dwyer E, Maani PA, Daly TM, et al. Risk factors and outcomes of hypogammaglobulinemia after lung transplantation. Transplantation 2005;79:1723-6.

257. Putcha N, Paul GG, Azar A, Wise RA, O'Neal WK, Dransfield MT, et al. Lower serum IgA is associated with COPD exacerbation risk in SPIROMICS. PLoS One 2018;13:e0194924.

258. Corales R, Chua J, Mawhorter S, Young JB, Starling R, Tomford JW, et al. Significant post-transplant hypogammaglobulinemia in six heart transplant recipients: an emerging clinical phenomenon? Transpl Infect Dis 2000;2:133-9.

259. Yamani MH, Avery RK, Mawhorter SD, Young JB, Ratliff NB, Hobbs RE, et al. Hypogammaglobulinemia following cardiac transplantation: a link between rejection and infection. J Heart Lung Transplant 2001;20:425-30.

260. Mawhorter S, Yamani MH. Hypogammaglobulinemia and infection risk in solid organ transplant recipients. Curr Opin Organ Transplant 2008;13:581-5.

261. Ku G, Varghese Z, Fernando ON, Baillod R, Hopewell JP, Moorhead JF. Serum IgG and renal transplantation. Br Med J 1973;4:702-7.

262. Broeders EN, Wissing KM, Hazzan M, Ghisdal L, Hoang A-D, Noel C, et al. Evolution of immunoglobulin and mannose binding protein levels after renal transplantation: association with infectious complications. Transpl Int 2008;21:57-64.

263. Fernández-Ruiz M, López-Medrano F, Varela-Peña P, Lora-Pablos D, García-Reyne A, González E, et al. Monitoring of immunoglobulin levels identifies kidney transplant recipients at high risk of infection. Am J Transplant 2012;12:2763-73.

264. Augusto J-F, Garnier A-S, Demiselle J, Langs V, Picquet J, Legall R, et al. Hypogammaglobulinemia and risk of severe infection in kidney transplant recipients. Transpl Infect Dis 2016;18:741-51.

265. Pollock CA, Mahony JF, Ibels LS, Caterson RJ, Waugh DA, Wells JV, et al. Immunoglobulin abnormalities in renal transplant recipients. Transplantation 1989;47:952-6.

266. Smolin MR, Rickman W, Hasbargen J. Hypogammaglobulinemia in a renal transplant recipient with antiglomerular basement membrane disease. Am J Kidney Dis 1988;11:267-9.

267. Braun WE, Avery R, Gifford RW, Straffon RA. Life after 20 years with a kidney transplant: redefined disease profiles and an emerging nondiabetic vasculopathy. Transplant Proc 1997;29:247-9.

268. Origüen J, Fernández-Ruiz M, Lumbreras C, Orellana MÁ, López-Medrano F, Ruiz-Merlo T, et al. Potential role of post-transplant hypogammaglobulinemia in the risk of *Clostridium difficile* infection after kidney transplantation: a case-control study. Infection 2015;43:413-22.

269. Fernández-Ruiz M, López-Medrano F, San-Juan R, Aguado JM. Post-transplant hypogammaglobulinemia and risk of infection after kidney transplantation: magnitude matters. Transpl Infect Dis 2017;19.

270. Keven K, Sahin M, Kutlay S, Sengul S, Erturk S, Ersoz S, et al. Immunoglobulin deficiency in kidney allograft recipients: comparative effects of mycophenolate mofetil and azathioprine. Transpl Infect Dis 2003;5:181-6.

271. Boddana P, Webb LH, Unsworth J, Brealey M, Bingham C, Harper SJ. Hypogammaglobulinemia and bronchiectasis in mycophenolate mofetil-treated renal transplant recipients: an emerging clinical phenomenon? Clin Transplant 2011;25:417-9.

272. Dury S, Colosio C, Etienne I, Anglicheau D, Merieau E, Caillard S, et al. Bronchiectasis diagnosed after renal transplantation: a retrospective multicenter study. BMC Pulm Med 2015;15:141.

273. Doron S, Ruthazer R, Werner BG, Rabson A, Snydman DR. Hypogammaglobulinemia in liver transplant recipients: incidence, timing, risk factors, and outcomes. Transplantation 2006;81:697-703.

274. Van Thiel DH, Finkel R, Friedlander L, Gavaler JS, Wright HI, Gordon R. The association of IgA deficiency but not IgG or IgM deficiency with a reduced patient and graft survival following liver transplantation. Transplantation 1992;54:269-73.

275. Carbone J, Micheloud D, Salcedo M, Rincon D, Bañares R, Clemente G, et al. Humoral and cellular immune monitoring might be useful to identify liver transplant recipients at risk for development of infection. Transpl Infect Dis 2008;10:396-402.

276. Zuberi SJ, Siddiqui M, Lodi TZ. Immunoglobulins in liver disease. J Pak Med Assoc 1977;27:391-2.

277. Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant 2011;11:196-202.

278. Bourassa-Blanchette S, Patel V, Knoll GA, Hutton B, Fergusson N, Bennett A, et al. Clinical outcomes of polyvalent immunoglobulin use in solid organ transplant recipients: a systematic review and meta-analysis, part II: non-kidney transplant. Clin Transplant 2019;33:e13625.

279. Claustre J, Quétant S, Camara B, France M, Schummer G, Bedouch P, et al. Nonspecific immunoglobulin replacement in lung transplantation recipients with hypogammaglobulinemia: a cohort study taking into account propensity score and immortal time bias. Transplantation 2015;99:444-50.

280. Carbone J, Sarmiento E, Palomo J, Fernandez-Yañez J, Muñoz P, Bouza E, et al. The potential impact of substitutive therapy with intravenous immunoglobulin on the outcome of heart transplant recipients with infections. Transplant Proc 2007;39:2385-8.

281. Sarmiento E, Diez P, Arraya M, Jaramillo M, Calahorra L, Fernandez-Yañez J, et al. Early intravenous immunoglobulin replacement in hypogammaglobulinemic heart transplant recipients: results of a clinical trial. Transpl Infect Dis 2016;18:832-43.

282. Lederer DJ, Philip N, Rybak D, Arcasoy SM, Kawut SM. Intravenous immunoglobulin for hypogammaglobulinemia after lung transplantation: a randomized crossover trial. PLoS One 2014;9:e103908.

283. Bourassa-Blanchette S, Knoll GA, Hutton B, Fergusson N, Bennett A, Tay J, et al. Clinical outcomes of polyvalent immunoglobulin use in solid organ transplant recipients: a systematic review and meta-analysis. Clin Transplant 2019;33:e13560.

284. Poole JA, Qiu F, Kalil AC, Grant W, Mercer DF, Florescu DF. Impact of immunoglobulin therapy in intestinal transplant recipients with posttransplantation hypogammaglobulinemia. Transplant Proc 2016;48:479-84.

285. Sharma AP, Moussa M, Casier S, Rehman F, Filler G, Grimmer J. Intravenous immunoglobulin as rescue therapy for BK virus nephropathy. Pediatr Transplant 2009;13:123-9.

286. Anyaegbu EI, Almond PS, Milligan T, Allen WR, Gharaybeh S, Al-Akash SI. Intravenous immunoglobulin therapy in the treatment of BK viremia and nephropathy in pediatric renal transplant recipients. Pediatr Transplant 2012;16:E19-24.

287. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation 2006;81:117-20.

288. Vu D, Shah T, Ansari J, Naraghi R, Min D. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. Transplant Proc 2015;47:394-8.

289. Moon J, Chang Y, Shah T, Min DI. Effects of intravenous immunoglobulin therapy and Fc gamma receptor polymorphisms on BK virus nephropathy in kidney transplant recipients. Transpl Infect Dis 2020;22:e13300.

290. Maggiore U, Medici MC, Vaglio A, Buzio C. Increased viral load after intravenous immunoglobulin therapy for BK virus-associated nephropathy. Transpl Infect Dis 2010;12:470-2.

291. Lew J, Casey M, Leard LE, Hays S, Otani IM. Perceptions around lung transplant-associated hypogammaglobulinemia. J Clin Immunol 2021;41:1940-2.

292. Adegunsoye A, Strek ME, Garrity E, Guzy R, Bag R. Comprehensive care of the lung transplant patient. Chest 2017;152:150-64.

293. Rhee Y, Sha BE, Santos CAQ. Optimizing vaccination in adult patients with liver disease and liver transplantation. Clin Liver Dis (Hoboken) 2020;15:63-8.

294. Hull RP, Goldsmith DJA. Nephrotic syndrome in adults. BMJ 2008;336:1185-9.

295. Heslan JM, Lautie JP, Intrator L, Blanc C, Lagrue G, Sobel AT. Impaired IgG synthesis in patients with the nephrotic syndrome. Clin Nephrol 1982;18:144-7.

296. Yokoyama H, Kida H, Abe T, Koshino Y, Yoshimura M, Hattori N. Impaired immunoglobulin G production in minimal change nephrotic syndrome in adults. Clin Exp Immunol 1987;70:110-5.

297. Wells JV, Fudenberg HH. Metabolism of radio-iodinated IgG in patients with abnormal serum IgG levels, II: hypogamma-globulinaemia. Clin Exp Immunol 1971;9:775-83.

298. Shatat IF, Becton LJ, Woroniecki RP. Hypertension in childhood nephrotic syndrome. Front Pediatr 2019;7:287.

299. Kemper MJ, Altrogge H, Ganschow R, Müller-Wiefel DE. Serum levels of immunoglobulins and IgG subclasses in steroid sensitive nephrotic syndrome. Pediatr Nephrol 2002;17:413-7.

300. Warshaw BL, Check IJ. IgG subclasses in children with nephrotic syndrome. Am J Clin Pathol 1989;92:68-72.

301. Han J-W, Lee K-Y, Hwang J-Y, Koh D-K, Lee J-S. Antibody status in children with steroid-sensitive nephrotic syndrome. Yonsei Med J 2010;51:239-43.

302. Harris HW, Umetsu D, Geha R, Harmon WE. Altered immunoglobulin status in congenital nephrotic syndrome. Clin Nephrol 1986;25:308-13.

303. Mathias R, Stecklein H, Guay-Woodford L, Harmon WE, Harris HW. Gamma globulin deficiency in newborns with congenital nephrotic syndrome. N Engl J Med 1989;320:398-9.

304. Fujinaga S, Ozawa K, Sakuraya K, Yamada A, Shimizu T. Late-onset adverse events after a single dose of rituximab in children with complicated steroid-dependent nephrotic syndrome. Clin Nephrol 2016;85:340-5.

305. Fujinaga S, Nishino T, Umeda C, Tomii Y, Watanabe Y, Sakuraya K. Long-term outcomes after early treatment with rituximab for Japanese children with cyclosporine- and steroid-resistant nephrotic syndrome. Pediatr Nephrol 2019;34:353-7.

306. Marzuillo P, Guarino S, Esposito T, Di Sessa A, Orsini SI, Capalbo D, et al. Rituximab-induced IgG hypogammaglobulinemia in children with nephrotic syndrome and normal pre-treatment IgG values. World J Clin Cases 2019;7:1021-7.

307. Parmentier C, Delbet J-D, Decramer S, Boyer O, Hogan J, Ulinski T. Immunoglobulin serum levels in rituximab-treated patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2020;35:455-62.

308. Colucci M, Carsetti R, Serafinelli J, Rocca S, Massella L, Gargiulo A, et al. Prolonged impairment of immunological memory after anti-CD20 treatment in pediatric idiopathic nephrotic syndrome. Front Immunol 2019;10:1653.

309. Fujinaga S, Tomii Y. Profound effect of post-rituximab mycophenolate mofetil administration for persistent hypogammaglobulinemia in young children with steroid-dependent nephrotic syndrome. Clin Exp Nephrol 2020;24:386-7.

310. Ogi M, Yokoyama H, Tomosugi N, Hisada Y, Ohta S, Takaeda M, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. Am J Kidney Dis 1994;24:427-36.

311. Seet RCS, Lau LG, Tambyah PA. Strongyloides hyperinfection and hypogammaglobulinemia. Clin Diagn Lab Immunol 2005;12:680-2.

312. Simon CH, Markusse HM. *Campylobacter jejuni* arthritis in secondary amyloidosis. Clin Rheumatol 1995;14:214-6.

313. Wu HM, Tang J-L, Cao L, Sha ZH, Li Y. Interventions for preventing infection in nephrotic syndrome. Cochrane Database Syst Rev 2012;CD003964.

314. Payne KM, Nelson MR, Petersen MM. Congenital nephrotic syndrome and agammaglobulinemia: a therapeutic dilemma. Ann Allergy Asthma Immunol 2013;111:142-3.

315. Molinaro I, Barbano B, Rosato E, Cianci R, Di Mario F, Quarta S, et al. Safety and infectious prophylaxis of intravenous immunoglobulin in elderly patients with membranous nephropathy. Int J Immunopathol Pharmacol 2014;27:305-8.

316. Luque Y, Anglicheau D, Rabant M, El Karoui K, Jamme M, Aubert O, et al. Renal safety of high-dose, sucrose-free intravenous immunoglobulin in kidney transplant recipients: an observational study. Transpl Int 2016;29:1205-15.

317. Umar SB, DiBaise JK. Protein-losing enteropathy: case illustrations and clinical review. Am J Gastroenterol 2010;105:43-9; quiz 50.

318. Florent C, L'Hirondel C, Desmazures C, Aymes C, Bernier JJ. Intestinal clearance of alpha 1-antitrypsin. A sensitive method for the detection of protein-losing enteropathy. Gastroenterology 1981;81:777-80.

319. Umeno J, Hisamatsu T, Esaki M, Hirano A, Kubokura N, Asano K, et al. A hereditary enteropathy caused by mutations in the SLCO2A1 gene, encoding a prostaglandin transporter. PLoS Genet 2015;11:e1005581.

320. Uchida K, Nakajima A, Ushijima K, Ida S, Seki Y, Kakuta F, et al. Pediatric-onset chronic nonspecific multiple ulcers of small intestine: a nationwide survey and genetic study in Japan. J Pediatr Gastroenterol Nutr 2017;64:565-8.

321. Kelsen JR, Sullivan KE, Rabizadeh S, Singh N, Snapper S, Elkadri A, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Evaluation and Management for Patients With Very Early-onset Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2020;70:389-403.

322. De Giacomo C, Maggiore G, Scotta MS, Ugazio AG. Administration of intravenous immunoglobulin in two children with hypogammaglobulinaemia due to protein losing enteropathy. Clin Exp Immunol 1985;60:447-8.

323. Duraisingham SS, Buckland MS, Grigoriadou S, Longhurst HJ. Secondary antibody deficiency. Expert Rev Clin Immunol 2014;10:583-91.

324. Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. J Clin Immunol 2012;32:1180-92.

325. Isa HM, Al-Arayedh GG, Mohamed AM. Intestinal lymphangiectasia in children. A favorable response to dietary modifications. Saudi Med J 2016;37:199-204.

326. Aroor S, Mundkur S, Kanaparthi S, Kumar S. Waldmann's disease (primary intestinal lymphangiectasia) with atrial septal defect. J Clin Diagn Res 2017;11:SD03-4.

327. Ozen A, Comrie WA, Ardy RC, Domínguez Conde C, Dalgic B, Beser ÖF, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. N Engl J Med 2017;377:52-61.

328. Pazmandi J, Kalinichenko A, Ardy RC, Boztug K. Early-onset inflammatory bowel disease as a model disease to identify key regulators of immune homeostasis mechanisms. Immunol Rev 2019;287:162-85.

329. Stephen J, Vilboux T, Haberman Y, Pri-Chen H, Pode-Shakked B, Mazaheri S, et al. Congenital protein losing enteropathy: an inborn error of lipid metabolism due to DGAT1 mutations. Eur J Hum Genet 2016;24:1268-73.

330. Gluchowski NL, Chitraju C, Picoraro JA, Mejhert N, Pinto S, Xin W, et al. Identification and characterization of a novel DGAT1 missense mutation associated with congenital diarrhea. J Lipid Res 2017;58:1230-7.

331. Johnson JN, Driscoll DJ, O'Leary PW. Protein-losing enteropathy and the Fontan operation. Nutr Clin Pract 2012;27:375-84.

332. Morsheimer MM, Rychik J, Forbes L, Dodds K, Goldberg DJ, Sullivan K, et al. Risk factors and clinical significance of lymphopenia in survivors of the Fontan procedure for single-ventricle congenital cardiac disease. J Allergy Clin Immunol Pract 2016;4:491-6.

333. Chakrabarti S, Keeton BR, Salmon AP, Vettukattil JJ. Acquired combined immunodeficiency associated with protein losing enteropathy complicating Fontan operation. Heart 2003;89:1130-1.

334. Kane JM, Canar J, Kalinowski V, Johnson TJ, Hoehn KS. Management options and outcomes for neonatal hypoplastic left heart syndrome in the early twenty-first century. Pediatr Cardiol 2016;37:419-25.

335. Bernardi AM, Moses S, Barber BJ, Witte MH, Seckeler MD. Higher incidence of protein-losing enteropathy in patients with single systemic right ventricle. Pediatr Cardiol 2021;42:178-81.

336. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. Circulation 2019;140:e234-84.

337. Goldberg DJ, Dodds K, Rychik J. Rare problems associated with the Fontan circulation. Cardiol Young 2010;20:113-9.

338. Rychik J. Protein-losing enteropathy after Fontan operation. Congenit Heart Dis 2007;2:288-300.

339. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE Study Group. J Thorac Cardiovasc Surg 1998;115:1063-73.

340. Feldt RH, Driscoll DJ, Offord KP, Cha RH, Perrault J, Schaff HV, et al. Protein-losing enteropathy after the Fontan operation. J Thorac Cardiovasc Surg 1996;112:672-80.

341. Magdo HS, Stillwell TL, Greenhawt MJ, Stringer KA, Yu S, Fifer CG, et al. Immune abnormalities in Fontan protein-losing enteropathy: a case-control study. J Pediatr 2015;167:331-7.

342. Zaupper LB, Nielsen BW, Herlin T. Protein-losing enteropathy after the total cavopulmonary connection: impact of intravenous immunoglobulin. Congenit Heart Dis 2011;6:624-9.

343. Cheung YF, Leung MP, Yuen KY. Legionella pneumonia and bacteraemia in association with protein-losing enteropathy after Fontan operation. J Infect 2001;42:206-7.

344. Kurolap A, Eshach Adiv O, Hershkovitz T, Tabib A, Karbian N, Paperna T, et al. Eculizumab is safe and effective as a long-term treatment for protein-losing enteropathy due to CD55 deficiency. J Pediatr Gastroenterol Nutr 2019;68:325-33.

345. Kurolap A, Eshach-Adiv O, Hershkovitz T, Paperna T, Mory A, Oz-Levi D, et al. Loss of CD55 in eculizumab-responsive protein-losing enteropathy. N Engl J Med 2017;377:87-9.

346. Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing MG, et al. Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific statement from the American Heart Association. Circulation 2017;136:e348-92.

347. European Medicines Agency. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). 2018. Available at: https://www.ema.europa.eu/en/clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig#current-effective-version-section. Accessed January 5, 2021.

348. Glennie MJ, French RR, Cragg MS, Taylor RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. Mol Immunol 2007;44:3823-37.

349. Taylor RP, Lindorfer MA. Immunotherapeutic mechanisms of anti-CD20 monoclonal antibodies. Curr Opin Immunol 2008;20:444-9.

350. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, Pham HP, Schneiderman J, Witt V, Wu Y, Zantek ND, Dunbar NM, Schwartz GEJ. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J Clin Apher 2019;34:171-354.

351. Dunleavy K, Tay K, Wilson WH. Rituximab-associated neutropenia. Semin Hematol 2010;47:180-6.

352. Tesfa D, Ajeganova S, Hägglund H, Sander B, Fadeel B, Hafström I, et al. Late-onset neutropenia following rituximab therapy in rheumatic diseases: association with B lymphocyte depletion and infections. Arthritis Rheum 2011;63:2209-14.

353. Dörner T, Shock A, Goldenberg DM, Lipsky PE. The mechanistic impact of CD22 engagement with epratuzumab on B cell function: implications for the treatment of systemic lupus erythematosus. Autoimmun Rev 2015;14:1079-86.

354. Dörner T, Goldenberg DM. Targeting CD22 as a strategy for treating systemic autoimmune diseases. Ther Clin Risk Manag 2007;3:953-9.

355. Pan J, Niu Q, Deng B, Liu S, Wu T, Gao Z, et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia 2019;33:2854-66.

356. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373:1207-19.

357. de Weers M, Tai Y-T, van der Veer MS, Bakker JM, Vink T, Jacobs DCH, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol 2011;186:1840-8.

358. Overdijk MB, Verploegen S, Bögels M, van Egmond M, Lammerts van Bueren JJ, Mutis T, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs 2015;7:311-21.

359. Frerichs KA, Bosman PWC, van Velzen JF, Fraaij PLA, Koopmans MPG, Rimmelzwaan GF, et al. Effect of daratumumab on normal plasma cells, polyclonal immunoglobulin levels, and vaccination responses in extensively pre-treated multiple myeloma patients. Haematologica 2020;105:e302-6.

360. Cottini F, Huang Y, Williams N, Bumma N, Khan AM, Chaudhry M, et al. Real world experience of daratumumab: evaluating lymphopenia and adverse events in multiple myeloma patients. Front Oncol 2020;10:575168.

361. Paul Y, Aguirre LE, Basher F, Miao F, Koru-Sengul T, Hoffman JE. Hypogammaglobulinemia and its implications in patients treated with daratumumab: a single institution experience. Blood 2019;134:3131.

362. Salter AI, Pont MJ, Riddell SR. Chimeric antigen receptor–modified T cells: CD19 and the road beyond. Blood 2018;131:2621-9.

363. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-44.

364. Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107:13075-80.

365. Orlowski RZ. The ubiquitin proteasome pathway from bench to bedside. Hematology 2005;2005:220-5.

366. Segarra A, Arredondo KV, Jaramillo J, Jatem E, Salcedo MT, Agraz I, et al. Efficacy and safety of bortezomib in refractory lupus nephritis: a single-center experience. Lupus 2020;29:118-25.

367. Methotrexate [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf. Accessed June 5, 2021.

368. Jeurissen ME, Boerbooms AM, van de Putte LB, Doesburg WH, Mulder J, Rasker JJ, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum 1991;34:961-72.

369. Kogure T, Harada N, Tatsumi T, Fujinaga H. Investigation of clinical characteristics as predictive factors for the humoral immune response to the influenza vaccine in patients with rheumatoid arthritis. Clin Rheumatol 2014;33:323-8.

370. Subesinghe S, Bechman K, Rutherford AI, Goldblatt D, Galloway JB. A systematic review and metaanalysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. J Rheumatol 2018;45:733-44.

371. Kapetanovic MC, Kristensen L-E, Saxne T, Aktas T, Mörner A, Geborek P. Impact of anti-rheumatic treatment on immunogenicity of pandemic H1N1 influenza vaccine in patients with arthritis. Arthritis Res Ther 2014;16:R2.

372. Ribeiro ACM, Guedes LKN, Moraes JCB, Saad CGS, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis 2011;70:2144-7.

373. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis 2016;75:687-95.

374. McMahan ZH, Bingham CO. Effects of biological and non-biological immunomodulatory therapies on the immunogenicity of vaccines in patients with rheumatic diseases. Arthritis Res Ther 2014;16:506.

375. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. Arthritis Rheum 2011;63:3723-32.

376. Chiricozzi A, Gisondi P, Bellinato F, Girolomoni G. Immune response to vaccination in patients with psoriasis treated with systemic therapies. Vaccines (Basel) 2020;8:769.

377. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000;47:85-118.

378. Peter HH, Ochs HD, Cunningham-Rundles C, Vinh DC, Kiessling P, Greve B, Jolles S. Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations. J Allergy Clin Immunol 2020;146:479-91.e5.

379. Goebeler M, Bata-Csörgő Z, De Simone C, Didona B, Remenyik E, Reznichenko N, Stoevesandt J, Ward ES, Parys W, de Haard H, Dupuy P, Verheesen P, Schmidt E, Joly P; ARGX-113-1701 Investigator Study Group. Treatment of pemphigus vulgaris and foliaceus with efgartigimod, a neonatal Fc receptor inhibitor: a phase II multicentre, open-label feasibility trial. Br J Dermatol 2021 Oct 5. https://doi.org/10.1111/bjd.20782. Epub ahead of print.

380. Stevens C, Lipman M, Fabry S, Moscovitch-Lopatin M, Almawi W, Keresztes S, et al. 5-Aminosalicylic acid abrogates T-cell proliferation by blocking interleukin-2 production in peripheral blood mononuclear cells. J Pharmacol Exp Ther 1995;272:399-406.

381. MacDermott RP, Schloemann SR, Bertovich MJ, Nash GS, Peters M, Stenson WF. Inhibition of antibody secretion by 5-aminosalicylic acid. Gastroenterology 1989;96:442-8.

382. Farr M, Tunn E, Bacon PA, Smith DH. Hypogammaglobulinaemia and thrombocytopenia associated with sulphasalazine therapy in rheumatoid arthritis. Ann Rheum Dis 1985;44:723-4.

383. Farr M, Scott DG, Bacon PA. Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. Drugs 1986;32:49-53.

384. Besada E. Risk factors and adverse events poorly predict infections and hypogammaglobulinemia in granulomatosis with polyangiitis patients receiving rituximab. Autoimmune Dis 2016;2016:1-6.

385. Levy J, Barnett EV, MacDonald NS, Klinenberg JR, Pearson CM. The effect of azathioprine on gammaglobulin synthesis in man. J Clin Invest 1972;51:2233-8.

386. Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. Molecules 2018;23:2087.

387. Ponsford MJ, Steven R, Bramhall K, Burgess M, Wijetilleka S, Carne E, et al. Clinical and laboratory characteristics of clozapine-treated patients with schizophrenia referred to a national immunodeficiency clinic reveals a B-cell signature resembling common variable immunodeficiency (CVID). J Clin Pathol 2020;73:587-92.

388. Ponsford M, Castle D, Tahir T, Robinson R, Wade W, Steven R, et al. Clozapine is associated with secondary antibody deficiency. Br J Psychiatry 2018;214:1-7.

389. Ponsford MJ, Pecoraro A, Jolles S. Clozapine-associated secondary antibody deficiency. Curr Opin Allergy Clin Immunol 2019;19:553-62.

390. Abe S, Suzuki T, Hori T, Baba A, Shiraishi H. Hypogammaglobulinemia during antipsychotic therapy. Psychiatry Clin Neurosci 1998;52:115-7.

391. U.S. Food and Drug Administration. Immune Globulin Intravenous (IGIV) Indications. Available at: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulin-intravenous-igiv-indications. Accessed January 5, 2021.

392. Woo P, Pereira RS, Lever AM. Persistent immunoglobulin deficiency after prednisolone and antiepileptic therapy in a C2 deficient patient with lupus-like syndrome. J Rheumatol 1984;11:828-31.

393. Pereira LF, Sanchez JF. Reversible panhypogammaglobulinemia associated with phenytoin treatment. Scand J Infect Dis 2002;34:785-7.

394. Guerra IC, Fawcett WA, Redmon AH, Lawrence EC, Rosenblatt HM, Shearer WT. Permanent intrinsic B cell immunodeficiency caused by phenytoin hypersensitivity. J Allergy Clin Immunol 1986;77:603-7.

395. Travin M, Macris NT, Block JM, Schwimmer D. Reversible common variable immunodeficiency syndrome induced by phenytoin. Arch Intern Med 1989;149:1421-2.

396. Lillie MA, Yang LC, Honig PJ, August CS. Erythroderma, hypogammaglobulinemia, and T-cell lymphocytosis. Occurrence following therapy with phenytoin. Arch Dermatol 1983;119:415-8.

397. Dosch HM, Jason J, Gelfand EW. Transient antibody deficiency and abnormal t-suppressor cells induced by phenytoin. N Engl J Med 1982;306:406-9.

398. Wong JCY, Li PH. Carbamazepine-induced B-cell aplasia: overlooked and overtreated. Ann Allergy Asthma Immunol 2020;124:89-91.

399. Ozaras N, Goksugur N, Eroglu S, Tabak O, Canbakan B, Ozaras R. Carbamazepine-induced hypogammaglobulinemia. Seizure 2012;21:229-31.

400. Gonçalves D, Moura R, Ferraz C, Vitor AB, Vaz L. Carbamazepine-induced interstitial pneumonitis associated with pan-hypogammaglobulinemia. Respir Med Case Rep 2012;5:6-8.

401. Hoshino C, Hoshi T. Carbamazepine-induced agammaglobulinaemia clinically mimicking diffuse panbronchiolitis. BMJ Case Rep 2011;2011:bcr1120103535.

402. Yamamoto T, Uchiyama T, Takahashi H, Himuro K, Kanai K, Kuwabara S. B cell aplasia and hypogammaglobulinemia after carbamazepine treatment. Intern Med 2010;49:707-8.

403. Tamada T, Nara M, Tomaki M, Ashino Y, Hattori T. Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. BMJ Case Rep 2009;2009:bcr2006063842.

404. Rice CM, Johnston SL, Unsworth DJ, Glover SC, Donati M, Renowden SA, et al. Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. J Neurol Neurosurg Psychiatry 2007;78:1011-2.

405. Moreno-Ancillo A, Cosmes Martín PM, Domínguez-Noche C, Martín-Núñez G, Fernández-Galán MA, López-López R, et al. Carbamazepine induced transient monoclonal gammopathy and immunodeficiency. Allergol Immunopathol (Madr) 2004;32:86-8.

406. Go T. Carbamazepine-induced IgG1 and IgG2 deficiency associated with B cell maturation defect. Seizure 2004;13:187-90.

407. Castro AP, Redmershi MG, Pastorino AC, de Paz JA, Fomin AB, Jacob CM. Secondary hypogammaglobulinemia after use of carbamazepine: case report and review. Rev Hosp Clin Fac Med Sao Paulo 2001;56:189-92.

408. Spickett GP, Gompels MM, Saunders PW. Hypogammaglobulinaemia with absent B lymphocytes and agranulocytosis after carbamazepine treatment. J Neurol Neurosurg Psychiatry 1996;60:459.

409. Eom T-H, Lee H-S, Jang P-S, Kim Y-H. Valproate-induced panhypogammaglobulinemia. Neurol Sci 2013;34:1003-4.

410. Maruyama S, Okamoto Y, Toyoshima M, Hanaya R, Kawano Y. Immunoglobulin A deficiency following treatment with lamotrigine. Brain Dev 2016;38:947-9.

411. Australia National Blood Authority. Secondary hypogammaglobulinaemia unrelated to haematological malignancy or haemopoeitic stem cell transplant (HSCT). 2020. Available at: https://www.criteria.blood.gov.au/Medical Condition/View/2628. Accessed June 6, 2021.

412. Australia National Blood Authority. Acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT). 2020. Available at: https://www.criteria.blood.gov.au/Medical Condition/View/2621. Accessed June 6, 2021.

413. National Institute for Health and Care Excellence. Myeloma: diagnosis and management. 2016. Available at: https://www.nice.org.uk/guidance/ng35/evidence/full-guideline-2306487277. Accessed June 6, 2021.

414. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed June 6, 2021.

415. Florescu DF, Kalil AC, Qiu F, Grant W, Morris MC, Schmidt CM, et al. Does increasing immunoglobulin levels impact survival in solid organ transplant recipients with hypogammaglobulinemia? Clin Transplant 2014;28:1249-55.

416. Yamani MH, Avery R, Mawhorter SD, McNeill A, Cook D, Ratliff NB, et al. The impact of CytoGam on cardiac transplant recipients with moderate hypogammaglobulinemia: a randomized single-center study. J Heart Lung Transplant 2005;24:1766-9.

417. Muñoz P, Giannella M, Alcalá L, Sarmiento E, Fernandez Yañez J, Palomo J, et al. Clostridium difficile-associated diarrhea in heart transplant recipients: is hypogammaglobulinemia the answer? J Heart Lung Transplant 2007;26:907-14.

418. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, Gale RP, Chapel HM, Bunch C, Rai KR, Foon K, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 1988;319:902-7.

419. Griffiths H, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989;73:366-8.

420. Jurlander J, Geisler CH, Hansen MM. Treatment of hypogammaglobulinaemia in chronic lymphocytic leukaemia by low-dose intravenous gammaglobulin. Eur J Haematol 1994;53:114-8.

421. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 1995;17:75-80.

422. Sklenar I, Schiffman G, Jønsson V, Verhoef G, Birgens H, Boogaerts M, et al. Effect of various doses of intravenous polyclonal IgG on in vivo levels of 12 pneumococcal antibodies in patients with chronic lymphocytic leukaemia and multiple myeloma. Oncology 1993;50:466-77.

423. Molica S, Musto P, Chiurazzi F, Specchia G, Brugiatelli M, Cicoira L, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81:121-6.

424. Chapel H, Brennan V, Delson E. Immunoglobulin replacement therapy by self-infusion at home. Clin Exp Immunol 1988;73:160-2.

425. Sarmiento E, Rodríguez-Molina J, Muñoz P, Fernández-Yáñez J, Palomo J, Fogueda M, et al. Decreased levels of serum immunoglobulins as a risk factor for infection after heart transplantation. Transplant Proc 2005;37:4046-9.

426. Sarmiento E, Rodriguez-Molina JJ, Fernandez-Yañez J, Palomo J, Urrea R, Muñoz P, et al. IgG monitoring to identify the risk for development of infection in heart transplant recipients. Transpl Infect Dis 2006;8:49-53.

427. Sarmiento E, Jaramillo M, Calahorra L, Fernandez-Yañez J, Gomez-Sanchez M, Crespo-Leiro MG, et al. Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: a multicenter prospective study. J Heart Lung Transplant 2017;36:529-39.

428. Howard JF Jr, Bril V, Vu T, Karam C, Peric S, Margania T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2021;20:526-36.

429. FDA. FDA Approves New Treatment for Myasthenia Gravis. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-myasthenia-gravis. Accessed March 6, 2022.

430. argenx BV. VYVGART (efgartigimod alfa-fcab) [package insert]. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761195s000lbl.pdf. Accessed March 6, 2022.