



CME Review

Management of primary antibody deficiency syndromes

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- Discuss non Immunoglobulin G adjunct therapies that can be used for management of immunodeficiency patients

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Introduction

Antibody deficiency syndromes can manifest as primary or secondary immunodeficiency diseases. Relatively few of the primary immunodeficiency diseases (PIDDs) clinically manifest exclusively as B-cell immune defects. For example, X-linked agammaglobulinemia (XLA), due to Bruton tyrosine kinase (BTK) deficiency, is commonly thought to be an exclusive B-cell defect. However, on occasion, XLA can present in infancy with neutropenia¹ or evidence of T-cell dysfunction.^{2,3} The molecular cause of this combined cellular defect is unknown.⁴ Thus, the management of patients with antibody deficiency syndromes is not limited to IgG antibody replacement therapy. Rather, the therapeutic approach requires prior characterization of the cellular and molecular defects associated with the presenting clinical symptoms, followed by the institution of a combined IgG replacement and antimicrobial regimen to maintain these patients as infection free as possible. These patients may require long-term antibiotic, antifungal, and, on occasion, antiviral medications in addition to IgG replacement therapy (IgRT). This scenario can also be pertinent for patients with secondary immune deficiency syndromes caused by cancer or autoimmune disease and in others with secondary immunodeficiency from the respective therapeutic regimens used to treat these diseases.^{5–7}

The proposed mechanisms by which IgRT can modulate humoral immune dysregulation in patients with B-cell–defined PIDD has been summarized.^{8,9} Commercially available IgG products contain not only antibodies that neutralize bacteria and viruses but also immunomodulatory molecules that can alter immune function, such as anti-idiotypic antibodies; free CD4, CD8, and HLA molecules; natural antibodies to CD4, CD8, and HLA molecules; cytokines; and antibodies that neutralize activated complement components and proinflammatory cytokines.^{8–11} Thus, IgG products must be considered immunomodulation therapy that can regulate immunocyte function in addition to restoring humoral immunity by passive transfer. Nonetheless, the primary goal of IgRT in patients with primary B-cell defects is to restore antimicrobial antibody function. In this review, we provide a short summary of

selected B-cell–defined PIDDs in which IgRT is the primary therapeutic intervention, the use of adjuvant antimicrobial therapy for patients with these diseases (including those with bronchiectasis), and the IgRT strategies used to restore humoral immunity. Of note, milder humoral immunodeficiencies (eg, select IgA deficiency, transient hypogammaglobulinemia of infancy) that are not usually treated with IgRT are not discussed in this review. For a comprehensive list and discussion of the defined B-cell PIDDs, see the most recent practice parameters for the diagnosis and management of PIDD.¹²

Overview of B-Cell Development, Differentiation, and Function

To focus the reader on those B-cell–defined PIDDs, we begin with a brief review of some of the best defined B-cell defects, including defects in pre-B-cell receptor (BCR) and BCR signaling that limit or markedly reduce antibody expression. Figure 1 summarizes some of the known B-cell genetic defects that give rise to primary humoral immunodeficiencies.¹¹ The immunophysiologic mechanisms of B-cell development have recently been summarized.^{13,14}

PIDDs Arising From Defective B-Cell Development

BTK is a key cytosolic signaling molecule downstream of the pre-BCR and mature BCR. BTK ties pre-BCR and mature BCR activation to calcium influx, activation of the mitogen-activated protein kinase cascade, and modulation of transcription factors, such as nuclear factor- κ B.¹⁵ More than 600 mutations in the *BTK* gene have been described, which result in XLA with pre-B cells arrested at the pro-B-cell stage.^{16,17} XLA is a leaky defect in B-cell development, and many patients have a small amount of serum IgG and a few B cells in the peripheral circulation.¹⁸ Up to 90% of patients with early-onset hypogammaglobulinemia have a *BTK* mutation, whereas approximately half of the remainder have defects in components of the BCR itself or the downstream scaffold protein B-cell linker protein (BLNK).¹⁸ BLNK-deficient patients also demonstrate B cells arrested at the pro-B-cell stage, with a clinical phenotype similar to XLA.¹⁸

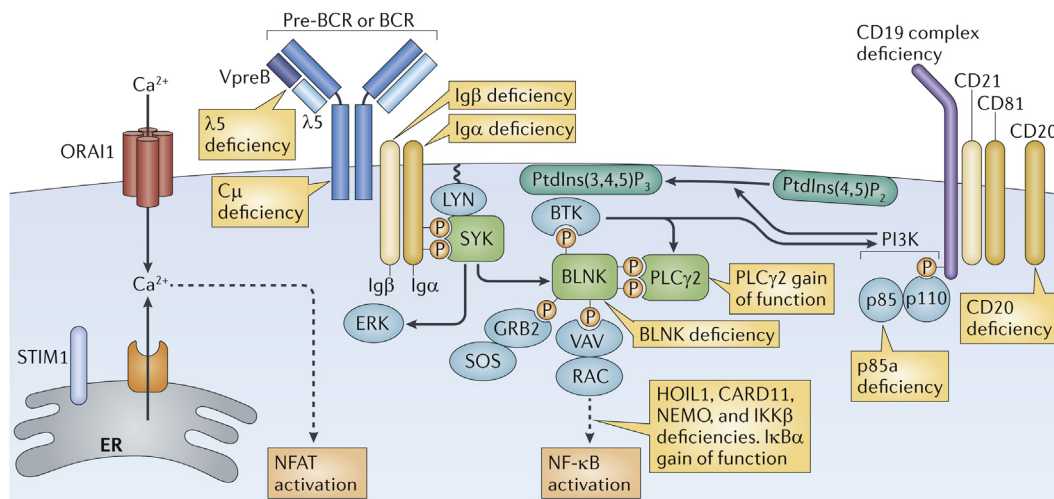


Figure 1. Pre-B-cell receptor (BCR) and BCR signaling defects in primary antibody deficiencies (PADs). The pre-B cell receives proliferation and differentiation signals through the pre-BCR and the coreceptors Igα and Igβ. Signaling from the pre-BCR involves the immunoreceptor tyrosine-based activation motifs of the coreceptors Igα and Igβ, which scaffold and activate the tyrosine kinase SYK. SYK either activates the extracellular signal-regulated kinase (ERK) pathway or phosphorylates (P) (together with LYN) the adaptor protein B-cell linker (BLNK) and Bruton tyrosine kinase (BTK), leading to the activation of phospholipase Cγ2 (PLCγ2) and the phosphoinositide-3-kinase (PI3K) pathway. Defects in this pathway affect the pre-BCR (in Cμ or pseudo light chain λ5); the pre-BCR signal transduction molecules Igα and Igβ; the downstream molecules BTK, BLNK, and PI3K; components of the costimulatory CD19 complex (CD19, CD21, and CD81); and the B-cell marker CD20. The BCR triggers the canonical nuclear factor-κB (NF-κB) pathway through the scaffolding protein CARD11 and activation of the IκB kinase (IKK) complex (comprising IKKα, IKKβ, and NEMO). IKK activation leads to the phosphorylation and degradation of NF-κB inhibitor α (IκBα) and the subsequent release of the p50-p65 NF-κB heterodimer, which then translocates to the nucleus to regulate gene transcription (not shown). After antigen binding to antigen receptors (such as the BCR), endoplasmic reticulum (ER) Ca²⁺ stores are depleted, STIM1 is activated, and ORAI1 Ca²⁺ release-activated Ca²⁺ channels open, resulting in store-operated Ca²⁺ entry. This influx results in activation of the transcription factor NFAT. The dashed arrows indicate downstream signaling events. PtdIns(4,5)P₂ indicates phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P₃, phosphatidylinositol-3,4,5-trisphosphate. Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Immunol*. 2013;13:519–533¹³, copyright 2013.

Patients with mutations that affect proteins of the BCR complex, such as μ chain (IGHM), Igα (CD79A), and Igβ (CD79B), have severe hypogammaglobulinemia.¹⁹ Mutations that affect other components of the BCR present with a less severe phenotype. Patients lacking CD19,²⁰ CD21,²¹ or CD81²² appear to have normal peripheral B-cell numbers. However, they have aberrant affinity maturation and reduced antibody responses, hypogammaglobulinemia, and increased susceptibility to infections.

Homozygous deletion of the CARD11 protein also leads to blocked B-cell differentiation, resulting in hypogammaglobulinemia.²³

PIDDs Arising From Defects in Peripheral B-Cell Survival

In addition to expression of a functional BCR, peripheral B-cell survival depends on signals generated by B-cell activator of the tumor necrosis factor α family (BAFF) binding to its cognate receptor BAFF-R, which is initially expressed by immature B cells in the bone marrow (BM).²⁴ BAFF binding to BAFF-R provides survival signals for immature and mature B cells.²⁴ BAFF also binds 2 other receptors, B-cell maturation factor (BCMA) and transmembrane activator calcium modular and cyclophilin ligand interactor (TACI). APRIL is a proliferation-inducing ligand that binds to TACI and BCMA but not BAFF-R. Expression of BAFF-R, TACI, and BCMA differs, depending on stage of maturation. BAFF-R expression increases when transitional B cells differentiate into the marginal zone (MZ) and follicular B cells. Long-lived plasma cells in the BM express BCMA.²⁴ MZ and switched memory B cells express TACI.²⁴ BAFF-R deficiency blocks B-cell development at the transitional B-cell stage and is associated with decreased MZ and switched memory B cells, reduced IgM and IgG, and abnormal T-cell-independent immune response against pneumococcal polysaccharides.²⁵ TACI deficiency is associated with hypogammaglobulinemia, aberrant development of IgA- and IgG-secreting plasma cells, reduced T-cell-independent polysaccharide

responses, and increased risk of developing autoimmunity. Furthermore, approximately 5% to 10% of patients with common variable immunodeficiency disorder (CVID) have TACI deficiency.^{26,27}

Common Variable Immunodeficiency Disorder

CVID, the most frequent, predominantly B-cell-deficient PIDD in adults, is a genotypically and phenotypically heterogeneous group of disorders.²⁸ CVID is a diagnosis of exclusion. Specifically, no single laboratory test or clinical feature establishes the diagnosis, and no diagnostic criteria have been universally accepted to make this diagnosis.²⁹ However, an international consensus document was recently published that provides a definition of CVID put forth by representatives from international allergy and immunology professional organizations.³⁰ Multiple genes have been implicated in CVID pathogenesis that are reviewed elsewhere.^{30,31} Although many patients have recurrent infections, some are at increased risk for autoimmunity and malignant tumors because of immune dysregulation.^{30,32}

IgRT for Patients With B-Cell Immunodeficiency Disease

IgRT for patients with PIDD is relatively recent. Beginning in 1952, Ogden Bruton used serum-derived IgG to treat B-cell-deficient patients subcutaneously, specifically XLA, a disease that now bears his name.³³ Soon after, patients with PIDD were treated with intramuscular IgG injections that provided limited protection against infection because of the relatively low serum IgG levels that could be attained by this route.³⁴ In addition, these intramuscular injections were painful, and as a result, only small amounts of IgG could be administered in a single injection. Only since the 1980s have IgG preparations been made available for intravenous use. This permitted the administration of much larger

IgG doses in a single infusion, thus enabling clinicians to attain much higher serum IgG levels in patients with PID. ³⁵

Although subcutaneous immunoglobulin (SCIG) infusions were preferred in Europe for financial reasons, only recently has this IgRT modality become common place in the United States. ³⁶ Moreover, both intravenous immunoglobulin (IVIG) and SCIG are now interchangeable IgRT options for patients with PID in the United States. Selecting one IgRT route over another should be based on the patient and family or caregiver preferences, taking into consideration their lifestyle needs. For example, SCIG can be ideal for some infants with difficult intravenous access and ample subcutaneous tissue. ³⁷ However, during school age, the same child may develop needle phobia, thus requiring a change from SCIG to IVIG infusions to improve tolerability for the child and the family. Furthermore, patients who have experienced adverse effects while undergoing IVIG therapy or have other concerns about IVIG (eg, need for pre-medication, desire for more autonomy instead of relying on an infusion nurse) may benefit from SCIG. ³⁸ Thus, the route of IgRT should take into consideration the needs and wishes of both patient and caregivers.

In addition, there is an ongoing debate about whether a change in IgG dose is necessary when switching a patient from IVIG to SCIG infusions. The US Food and Drug Administration requires that the monthly dose of SCIG be adjusted to provide equivalent total monthly systemic exposure to IgG compared with that achieved during previous IVIG treatments, using the area under the curve of serum IgG concentration over time. ³⁹ Thus, a patient can end up receiving more IgG (eg, 137% of the original IVIG dose if using a 20% SCIG product). However, there is evidence that using a 1:1 (IVIG to SCIG) dose is not inferior to using the recommended dose adjustment. These observations compared clinical end points, such as reduced rates of serious bacterial infections, and found comparable outcomes for 1:1 dosing vs dose adjustment when transitioning patients with PID from IVIG to SCIG infusions. ^{38–40} Moreover, using 1:1 dosing is likely more cost-effective because less IgG is needed to achieve comparable clinical outcomes. Clinical immunologists in the United States and Europe who care for B-cell-deficient patients commonly use 1:1 dosing. ⁴⁰

In B-cell deficient patients who also have clinically diagnosed autoimmune disease, the IgG dose may need to be transiently increased above that required to attain the biological IgG level required to prevent recurrent or serious infections. ⁴¹ Up to 25% of patients with CVID have signs of autoimmune disease, including immune thrombocytopenia purpura, autoimmune hemolytic anemia, or both (Evans syndrome). Greater doses of IgG (1 g/kg body weight) given weekly for a short time can be used to supplement baseline therapy if autoimmune disease persists. ⁴¹ Clearly, other therapeutic interventions (eg, gradual taper of corticosteroids and the concomitant use of other immunomodulators) are often required to resolve autoimmune conditions. ⁴¹ However, these higher IgG doses are not indicated to minimize serious bacterial infections required to keep these patients relatively infection free.

Individualizing IgRT for Patients With PID

Personalized medicine is an evolving and innovative trend in modern medicine. This concept of individualized IgRT in PID gained popularity when the concept of identifying a given PID patient's biological IgG level was introduced ⁴¹ and the choice of IVIG vs SCIG replacement therapy became more widespread. ^{42–45} This concept was based on the realization that (1) normal age-specific serum IgG levels varied widely in children and adults ^{46,47} (Fig 2) and (2) patients with PID with B-cell defects, who do not produce adequate immunoglobulins, rarely, if ever, require IgG levels greater than those expressed by age-matched controls.

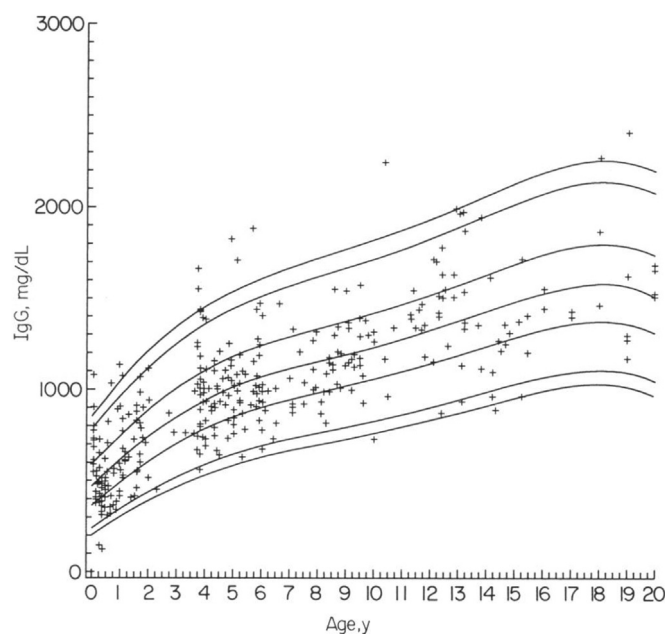


Figure 2. Percentile ranges of IgG. Individual reference ranges of IgG using the Box-Cox method ($\lambda = 0.47$). Percentiles are 2.5%, 5%, 25%, 50%, 75%, 95%, and 97.5%. Reprinted with permission from Lau et al. ⁴⁶

Therefore, clinical immunologists caring for patients with PID must define what the biological IgG level of a given patient should have been if they had been able to express immunoglobulins.

In the 1980s, we began to plot serum IgG levels at the time we documented infections in individual patients with XLA and CVID. This approach helped us identify the serum biological IgG level, which is the minimum IgG level that kept these individuals as free as possible from serious infections ⁴⁸ (Fig 3). To identify the biological IgG level, patients with PID were given 400 to 600 mg/kg every 4 weeks to achieve a starting serum IgG level greater than 650 mg/dL. Thereafter, by plotting IgG serum levels against infections over time, we identified and maintained the biological IgG level that kept a patient with PID as free of infection as possible. As shown in Figure 3, increasing IgRT in increments of 10% to 15% per dose, while monitoring each patient's infection history, ultimately identified a patient's biological IgG level. Each patient's biological IgG level was identified relatively easily, and the level was never outside the normal IgG serum range for age-matched healthy controls.

Some patients with PID continued to develop infections because they missed IgG infusions; some insurance companies failed to provide IgG products based on non-evidence-based projections, specifically internal projections by company physicians or administrators who designated what they believed to be sufficient to keep a patient with PID healthy. These policies also failed to consider the need for greater IgG doses when there was accelerated IgG loss from gastrointestinal or renal disease or when there was clear evidence of an increased frequency of serious and/or frequent sinorespiratory infections at serum IgG levels above 400 to 600 mg/dL, which was the target range thought to be acceptable to keep these patients free of infection. The common practice at that time was to institute concurrent antimicrobial therapy rather than titrate up serum IgG levels. Thus, the concept and documentation of the biological IgG level became important for many reasons, including lobbying insurance companies to widen their adequate serum IgG level targets above 400 to 600 mg/dL. This concept allowed clinicians to individualize IgRT for patients with PID and provide larger IgG doses, when needed, to attain an individual patient's biological IgG

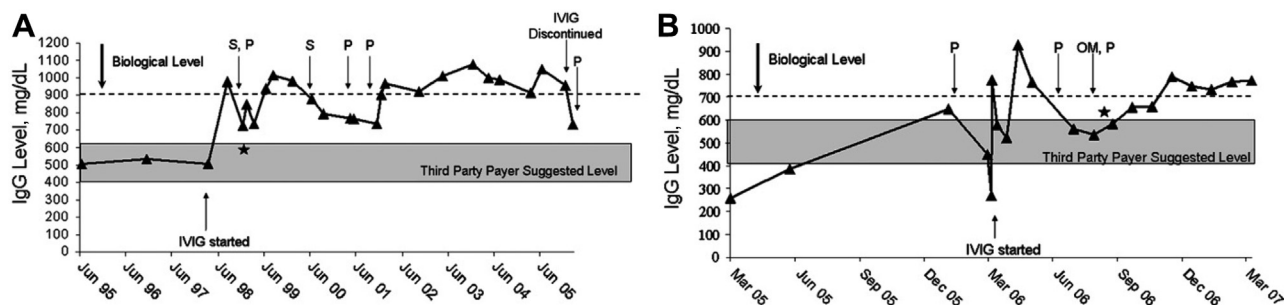


Figure 3. IgG trough levels in patients A and B before, during, and after initiating intravenous immunoglobulin (IVIG) therapy and associated infection history. Time at which our practice assumed the care of this patient. S indicates acute sinusitis; P, pneumonia; OM, otitis media. Reprinted from *J Allergy Clin Immunol*, Vol 122, Bonagura VR, Marchlewski R, Cox A, Rosenthal DW, Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection, Pages 210–212.⁴⁸ Copyright 2008, with permission from Elsevier.

level.^{49,50} It is important to stress that in our practice during the past 30 years we have never had to attain a serum IgG level in a patient with B-cell–deficient PIDD above the 95th percentile for IgG levels identified in age-matched controls. This observation underscores the concept that patients with PIDD are essentially like other individuals except that they cannot produce adequate concentrations of IgG to stay infection free.

Support for Individualizing IgRT in Patients With B-Cell–Deficient PIDD

Further studies have confirmed the concept that finding and maintaining the serum biological IgG level of B-cell–deficient patients is critical in decreasing pneumonia incidence.⁵⁰ In a study of patients with XLA and CVID that spanned 3 decades, Lucas et al⁵⁰ found that the range of serum IgG levels required to keep these patients free of pneumonia and serious lung infections was similar to a Gaussian distribution (Fig 4).⁵⁰ Many, but not all, of these patients required higher IgRT doses, some greater than 600 mg/kg, to stay pneumonia free. Thus, our original concept of individualizing IgRT for patients with PIDD by identifying and then maintaining their biological IgG level⁴⁸ was confirmed independently in a different patient population.⁵⁰ These observations are in contrast to the meta-analyses that looked at IVIG or SCIG replacement therapy dosing that found that (1) the more IVIG or SCIG given, the higher the serum IgG levels, and (2) the higher the IgG levels, the lower the incidence of pneumonia among patients.⁴⁹ Although these concepts are clearly correct, these studies do not take into account that individual patients with PIDD with the same diagnoses likely have unique serum IgG biological levels and require different IgG replacement doses to stay pneumonia free. Taken together, optimal IgRT for any patient with B-cell–deficient PIDD must be individualized, with the burden of identifying and maintaining a given patient's biological serum IgG level clearly resting with the clinical immunologist.

The biological IgG level in an individual patient can be a moving target, especially given the development and resolution of confounding clinical variables that perturb IgG homeostasis, such as pregnancy, weight changes, and the development of gastrointestinal or renal disease. Furthermore, periodic reassessment and adjustment of the IgG dose of a given patient with PIDD is an important part of ongoing clinical care. During long disease-free periods, the clinician might also consider whether a modest dose reduction is appropriate. However, care must be taken not to decrease the serum IgG level below the biological IgG level, thus putting the patient at risk for infection. The overall therapeutic goal of IgRT is always to provide a patient with the best quality of life, using the lowest amount of IgG associated with the least complications of this therapy for the underlying disease.

Requirement of Higher IgG Levels in Patients With B-Cell–Deficient PIDD and Bronchiectasis

Current practice in patients with B-cell–deficient PIDD and bronchiectasis is to give more IgG, even though there are limited data indicating that the serum IgG level associates with the prevention, development, or progression of small airway destruction in PIDD. Patients with XLA and CVID and bronchiectasis may require twice the IgRT dose compared with patients without bronchiectasis, to achieve comparable serum IgG levels.⁵⁰ Increased catabolism or loss may be the reasons for these findings. Furthermore, infection scores were similar in patients with and without bronchiectasis who were receiving IgRT, suggesting that higher IgG dosing was sufficient to prevent excess infections, regardless of underlying structural damage.⁵⁰ There are also limited data to suggest that higher doses of IgG may decrease the rate of decline in lung function in patients with XLA and CVID without bronchiectasis.⁵¹ There is no direct evidence that there is an optimal dose or route of IgRT that prevents the development or progression of bronchiectasis or lung function decline.

Use of Episodic or Long-Term Antibiotic Treatment as Adjunct Therapy in Patients With PIDD

Although IgRT is the cornerstone of therapy for B-cell–deficient patients, the use of long-term antibiotic, antifungal, and antiviral therapy is an important component of the comprehensive treatment regimen for patients with PIDD along with attaining the biological serum IgG level.¹² Antibiotic prophylaxis without IgRT is also commonly used in patients with PIDD with milder humoral immunodeficiencies, such as selective antibody deficiency, IgG subclass and/or IgA deficiency, and symptomatic transient hypogammaglobulinemia of infancy, who demonstrate recurrent respiratory infections. Adjunct antibiotic therapy is used in immunodeficiency patients who continue to have recurrent infections despite optimal IgRT who have bronchiectasis. Although there is no consensus or universally accepted guidelines on antibiotic use in immunodeficiency, a 2009 web-based survey by the PIDD Committee of the American Academy of Allergy, Asthma, and Immunology found that 90.2% of clinical immunologists (those devoting >10% of their clinical practice to PIDD) use prophylactic antibiotics as an adjunct to IVIG in some patients with PIDD. These immunologists considered this therapy strategy to be clinically relevant.⁵²

Bronchiectasis and sinusitis are the most common reasons for using adjunctive antibiotics. Intermittent, seasonal (winter months), continuous, and/or rotating antibiotic regimens are also used by clinical immunologists in addition to IgRT. There are no comparative studies to confirm that one regimen is superior to another. In recent decades, multiple studies have found that prophylaxis with macrolide antibiotics in patients with non–cystic fibrosis bronchiectasis

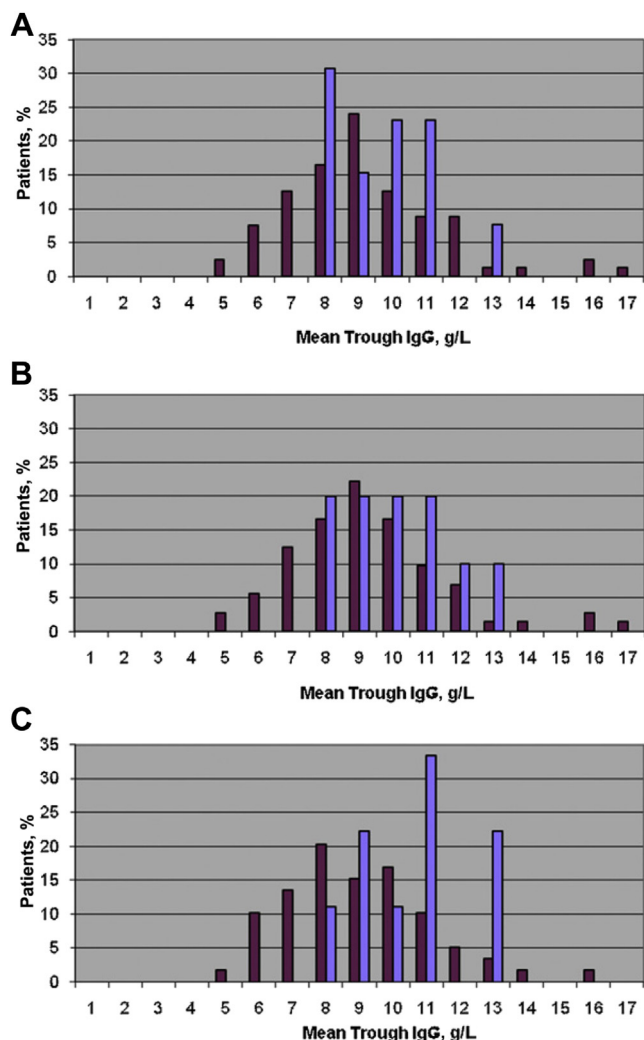


Figure 4. Mean trough IgG levels to keep individual patients infection free. Mean IgG trough levels are shown relative to the total percentage of patients with common variable immunodeficiency disorders (CVIDs) or X-linked agammaglobulinemia (XLA). Red bars represent patients with CVIDs; blue bars represent patients with XLA. A, Periods using a threshold of infection score at 4.5 or less per year. B, Periods using a threshold of infection score at 2.5 or less per year. C, Periods using a threshold of infection score at 0 per year. Reprinted from *J Allergy Clin Immunol*, Vol 125, Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H, Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years, Pages 1354–1360.e4⁵⁰, Copyright 2010, with permission from Elsevier.

leads to a significant decrease in the frequency of infection exacerbations in some patients.^{53–55} Antibiotic resistance remains the main complication of prophylactic antibiotic use. Macrolide resistance of 88% was found in patients with non-cystic fibrosis bronchiectasis who were treated with 250 mg of azithromycin daily for 1 year compared with 26% in the placebo group.⁵⁵

Conclusion

Providing appropriate and therapeutic IgRT for patients with PIDD is the goal and state-of-the-art therapy used by clinical immunologists who care for these patients. Although our knowledge of B-cell–defined PIDD syndromes arising from mutations in genes that control B-cell development, maturation, and function continues to increase, the challenge to clinical immunologists remains to restore the biologically relevant serum IgG level that protects a B-cell–deficient patient from developing severe and/or recurrent infections. Data from

our group and others have indicated that IgRT needs to be individualized and not limited to attaining a serum IgG level of 400 to 600 mg/dL. Individualizing therapy to determine the patient's biological level results in optimal patient outcomes^{48,50} and parallels the wide variation of serum IgG levels found in individuals without PIDD.

In line with the modern concept of personalized medicine, there is increasing evidence to suggest that each individual, regardless of PIDD status, expresses IgG levels that are adequate in the context of the sum of that person's cellular (both innate and adaptive) and other humoral immune responses. Clinical immunologists must consider the kind and frequency of infections and the confounding variables, such as the presence and extent of their lung, renal, or gastrointestinal disease, that are associated with their specific PIDD. In addition, clinical immunologists need to consider flexibility in the replacement modality (ie, IVIG vs. SCIG infusions) and frequency (ie, monthly, weekly, or daily push regimens). Individualizing IgRT and incorporating the preferences of the patient and their caregivers can improve their quality of life.

IgG levels fluctuate in response to infections and other immune stress events in both healthy individuals and patients with PIDD. Thus, closely monitoring serum IgG levels and the incidence of infections should ensure that optimal, personalized IgRT is provided for patients who require functional B-cell reconstitution. Although several studies have found that the more IgG given, the higher the serum IgG levels attained and the lower the incidence of pneumonia,^{49,50} not all patients with PIDD require high IgG doses, and some do very well on lower doses. Using the biological level concept as the modern paradigm, personalized IgRT facilitates the judicious use of available IgG products that gives patients with PIDD the minimal IgG dose they need to stay relatively infection free. Our patient experience reveals that none of the patients with B-cell–defined PIDD whom we have treated ever required IgG doses greater than that defined by the age-matched control levels. This observation supports the contention that each individual has his/her own biological IgG level, including patients who cannot express serum IgG adequately. Thus, the burden is on the clinical immunologist is to find that level as described in this review.⁴⁸

Finally, clinical immunologists sometimes use adjunctive antimicrobial therapy in combination with IgRT for patients with acute or chronic infection or underlying bronchiectasis when IgRT may be insufficient to control these infections or prevent the progression of lung disease. However, evidence-based recommendations are lacking, and more studies are needed. Of note, although outside the scope of this review, effective IgRT for secondary B-cell immune defects caused by some biologics or other immunomodulators used for autoimmune disease or malignant tumors should be studied to determine whether there are any key differences in IgG restoration.

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