Controversies in IgG replacement therapy in patients with antibody deficiency diseases

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This Current perspectives article will review and highlight the importance of accurate diagnosis of patients who have failed to produce specific antibodies to naturally encountered foreign proteins or polysaccharides or after vaccination and the appropriate institution of immunoglobulin replacement therapy. The field of primary immunodeficiency disease (PIDD) has expanded remarkably since the early descriptions 6 decades ago. With greater recognition and advanced cellular and molecular diagnostic technology, new entities and single-gene defects in patients with PIDD are rapidly being defined. This, combined with treatment advances and newborn screening for severe combined immunodeficiency, has resulted in improved outcomes and survival and even permanent cures. Awareness of PIDD has also increased, but the guidelines for recognition remain to be validated. The zeal for registering and enrolling patients has potentially created a large body of "patients" treated with immunoglobulin replacement unnecessarily. The complexity, diversity, and availability of laboratory testing have brought awareness of PIDD to the forefront, but because of an absence of standardization of certain assays, concerns about the correct diagnosis and appropriate treatment have increased. We hope to refocus the discussion on identifying clear laboratory and clinical guidelines for the establishment of an accurate diagnosis of antibody deficiency, its rationale, and, where indicated, institution of safe treatment. (J Allergy Clin Immunol 2013;131:1001-5.)

Key words: *Antibody deficiency, immunoglobulin replacement, common variable immunodeficiency, primary immunodeficiency, pneumococcal antibody concentration, specific antibody deficiency*

Abbreviations used
CVID: Common variable immunodeficiency
PIDD: Primary immunodeficiency disease

Major advances in the definition, delineation, diagnosis, and definitive treatment of primary immunodeficiency disease (PIDD) have provided the clinician with the ability to identify holes in the armor of host defense and even restore what nature did not provide.[1] Despite these satisfying developments, which include identification of defective genes in patients with PIDD[2,3] and, in some cases, curative cellular therapy with hematopoietic stem cell reconstitution[4-6] or gene therapy,[7,8] there still remains a murky area of diagnosis and treatment in patients with the most common forms of PIDD: antibody deficiency disorders. These areas of concern center around the laboratory methods and interpretation of antibody test results,[9-11] which often leads to inappropriate placement of individuals on lifelong immunoglobulin replacement therapy. Here we do not address those antibody deficiency diseases with established molecular and genetic lesions causing absent or nonfunctional cellular factors. Our concern is with the more common situation of patients given the presumptive diagnosis of antibody deficiency based on imperfect laboratory tests and nonvalidated interpretation of the results of such assays.

Table I lists antibody deficiencies or combined cellular and antibody diagnoses, including proposed justifications for the use of immunoglobulin replacement therapy (A, established; F, not indicated). It is a very general approach that reflects, to a large degree, the opinion of the authors and is not meant to encompass all clinical situations. In several of the cellular and antibody deficiencies, immunoglobulin replacement has a limited effect because hematopoietic stem cell transplants are needed to restore T-cell numbers and function. We include this table to give readers a sense of the scope of immunoglobulin replacement in patients with PIDD and suggest where it might be considered effective therapy and where it is not.

A majority of patients with proved PIDD have some impairment of humoral or antibody-mediated immunity.[12,13] There are currently a number of laboratory-based methods available for defining the extent of the antibody deficiency. With the advances in knowledge and technology, recognition of single-gene disorders has increased.[3,14] Flow cytometry–based analyses of lymphocyte subpopulations, including B-cell phenotyping, have also become routine, together with quantitation of serum immunoglobulin levels. With a focus on the PIDDs that constitute predominantly antibody deficiencies, combining the 3 approaches of serum immunoglobulin quantitation, evaluation of circulating B-cell numbers and phenotypes, and molecular analyses has revealed important defects leading to arrests of B-cell differentiation at the pre–B-cell or B-cell stage.[15-17] These defects generally result in severe reductions in levels of all serum immunoglobulin isotypes with profoundly decreased or absent numbers of circulating B cells, severe reduction in at least 2 serum immunoglobulin isotypes with normal or low numbers of B cells, low serum IgG and IgA levels with normal to increased IgM levels and normal numbers of total circulating B cells but decreased numbers of memory and/or switched B cells, or rare light chain deficiencies with normal numbers of circulating B cells. Because these conditions are

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TABLE I. Indication of immunoglobulin replacement for antibody deficiency

Score	PIDD entity	Immune defect	Expected response to IVIG/SCIG
A1	Agammaglobulinemia (X-linked, AR)	Lack of B cells	Effective
	HIgM caused by AID and UNG deficiency	Abnormal B-cell signaling resulting in defective CSR and SHM	Effective
A2	HIgM caused by CD40L and CD40 deficiency	Defective T/B-cell interaction resulting in abnormal CSR and SHM; defective macrophage activation	Effective, susceptibility to opportunistic infections not reduced
A3	CVID with normal T-cell function (including deficiencies of CD19, CD20, CD21, CD80, ICOS, TACI, or BAFF-R)	Hypogammaglobulinemia, antibody deficiency, often with CSR defect	Effective
B1	CVID with complications (splenomegaly, granuloma formation, autoimmunity, lymphoma)	Hypogammaglobulinemia, antibody deficiency, CSR and SHM affected, often associated with a T-cell defect (abnormal CD40L expression, decreased CD4/CD8 ratio)	Effective in reducing infections but not granuloma formation, autoimmunity or incidence of malignancy
B2	Thymoma with immune deficiency (Good syndrome)	B- and T-cell defects	Effective in reducing infections
B3	XLP with EBV-induced loss of B cells	Antibody deficiency caused by reduced number of B cells; defective cytotoxic T cells, NK cells	Effective in reducing infections, no effect on EBV-related pathology
B4	SCID after HSCT without B-cell engraftment	Mixed chimera with donor T cells and host B cells	Effective
C1	Selective antibody deficiency	Defective CSR reported; anti-PPS antibodies measured by ELISA do not reflect functionality	Antibiotic prophylaxis might be equally effective
C2	Clinically and genetically well-described syndromes with variable antibody deficiency (WAS, DiGeorge syndrome, STAT3 deficiency, VODI, DKC, ICF, AT, Netherton syndrome)	Abnormal antibody responses associated with other immune defects; characteristic syndromic defects might predominate	Partially effective; other disease-specific strategies required
D1	CID (eg, mutations in *PNP*, *ZAP70*, and genes controlling MHC class I and II expression)	Hypogammaglobulinemia; B- and T-cell defects	Limited benefit; HSCT should be considered
D2	Hypomorphic mutations in *RAG1/2*, *IL2RG*, *ADA*, *RMRP*, *Artemis*, and *DNA ligase IV*	Hypogammaglobulinemia, combined immune deficiency, often normal (but oligoclonal) T-cell numbers, low B-cell numbers (Omenn syndrome)	Limited benefit; HSCT indicated
D3	SCID	Severe B- and T-cell deficiency, lymphopenia	Limited temporary benefit while waiting for and during HSCT
E1	Complement deficiencies (C3, C4, and C5-9), properdin deficiency	Abnormal antibody responses have been described	Might be beneficial; other prophylactic strategies include hyperimmunization, prophylactic antibiotics
E2	Transient hypogammaglobulinemia of infancy with severe recurrent infections	Hypogammaglobulinemia, generally normal antibody production	Immunoglobulin replacement not indicated except if antibody production is demonstrated to be temporarily defective
E3	IgG subclass deficiency	≥1 IgG subclass affected	Immunoglobulin replacement only if a significant antibody deficiency is demonstrated
F	Asymptomatic hypogammaglobulinemia and normal antibody responses; selective immunoglobulin deficiencies	Normal B- and T-cell numbers, normal antibody responses; selective IgM, IgA, and IgE deficiency	Immunoglobulin replacement not indicated

IVIG/SCIG is effective in entities scored A and in most that are scored B. Those entities scored C and D might obtain limited benefit, and those scored E and F are not expected to benefit from immunoglobulin replacement.

ADA, Adenosine deaminase; *AID*, activation-induced cytokine deaminase; *AR*, autosomal recessive; *AT*, ataxia telangiectasia; *BAFF-R*, B cell–activating factor of the TNF family receptor; *CD40L*, CD40 ligand; *CID*, combined immunodeficiency; *CSR*, class-switch recombination; *DKC*, dyskeratosis congenita; *HIgM*, hyper-IgM syndrome; *HSCT*, hematopoietic stem cell transplantation; *ICF*, immunodeficiency with centromeric instability and facial anomalies; *ICOS*, inducible costimulator; *IL2RG*, IL-2 receptor γ; *IVIG*, intravenous immunoglobulin; *NK*, natural killer; *PNP*, purine nucleoside phosphorylase; *PPS*, pneumococcal polysaccharides; *RAG*, recombination-activating gene; *RMRP*, RnaseMRP RNA; *SCID*, severe combined immunodeficiency; *SCIG*, subcutaneous immunoglobulin; *SHM*, somatic hypermutation; *STAT3*, signal transducer and activator of transcription 3; *TACI*, transmembrane activator and calcium modulator and cyclophilin ligand; *UNG*, uracil-N-glycosylase; *VODI*, hepatic veno-occlusive disease with immunodeficiency; *WAS*, Wiskott-Aldrich syndrome; *XLP*, X-linked lymphoproliferative syndrome; *ZAP70*, ζ chain–associated protein of 70 kDa.

associated with a global failure of normal antibody production, immunoglobulin replacement is generally indicated.

The present approach used to determine whether subjects with suspected antibody deficiency require immunoglobulin replacement therapy relies heavily on the performance of antibody tests to both protein and polysaccharide vaccines.[18] A common belief is that these antibody responses to polysaccharide antigens are more meaningful than those to protein antigens, and the use of a 23-valent pneumococcal polysaccharide vaccine has been considered by some as the most informative. There are several problems with the