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## Primary immunodeficiency disorders: Antibody deficiency

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As a group, antibody deficiencies represent the most common types of primary immune deficiencies in human subjects. Often symptoms do not appear until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. As with the T-cell immune deficiencies, the spectrum of antibody deficiencies is broad, ranging from the most severe type of antibody deficiency with totally absent B cells and serum Igs to patients who have a selective antibody deficiency with normal serum Ig. In addition to the increased susceptibility to infections, a number of other disease processes (eg, autoimmunity and malignancies) can be involved in the clinical presentation. Fortunately, the availability of intravenous immune serum globulin has made the management of these patients more complete. Recently, molecular immunology has led to identification of the gene or genes involved in many of these antibody deficiencies. As discussed in this review, this has led to a better elucidation of the B-cell development and differentiation pathways and a more complete understanding of the pathogenesis of many of these antibody deficiencies. (*J Allergy Clin Immunol* 2002;109:581-91.)

**Key words:** Primary immune deficiencies, antibody deficiencies, B-cell development and differentiation

Unlike patients with T-cell deficiencies, patients with antibody deficiencies usually are free of infection until 7 to 9 months of age, when maternal antibodies that have passed through the placenta during the third trimester of pregnancy have decreased to below protective levels. Individuals with humoral immune or antibody deficiencies usually have infections with encapsulated bacterial organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Usually, patients with antibody deficiencies have few if any problems with fungal or viral pathogens, except patients with X-linked agammaglobulinemia (XLA), who have an unusual susceptibility to enteroviruses and may have chronic enteroviral

### Abbreviations used

AID:	Activation-induced cytidine deaminase
BCR:	B-cell antigen receptor
BLNK:	B-cell linker protein
CVID:	Common variable immunodeficiency
Hib:	<i>Haemophilus influenzae</i> type b
HIGM:	Hyper-IgM
Ig:	Immunoglobulins
IVIG:	Intravenous immune serum globulin
PEG-IL-2:	Polyethylene glycol IL-2
THI:	Transient hypogammaglobulinemia of infancy
XLA:	X-linked agammaglobulinemia

encephalomyelitis.<sup>1</sup> Generally, one does not see growth failure in patients with antibody deficiency in contrast to that seen in patients with severe T-cell deficiencies. Most patients with antibody deficiency can lead normal lives with the use of replacement intravenous immune serum globulin (IVIG) therapy, particularly if a diagnosis is made early before severe infections have damaged tissues (eg, pneumonia and bronchiectasis).

### B-CELL DEVELOPMENT AND DIFFERENTIATION

Pluripotent hematopoietic stem cells progress through an irreversible cascade of differentiation steps as they commit to a particular cell lineage in a complex process influenced by the microchemical environment and a number of soluble factors. There are 2 phases of B-cell development: an initial phase that is antigen independent, in which a diverse repertoire of antigen-specific B cells develops in the bone marrow, and a second phase that occurs when B cells are stimulated by antigen to undergo clonal expansion in the peripheral lymphoid tissues. During clonal expansion, further diversity in the repertoire and increased antibody specificity develops through somatic mutation. It has been important to delineate the process of B-cell differentiation and maturation so that we can better understand the pathogenesis of some of the newly recognized humoral immune deficiencies (Table I). With advances in molecular biology, it is now possible to delineate in more detail, on a molecular basis, some of the antibody deficiencies that heretofore were poorly understood.

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A number of events precede the release of B cells from the bone marrow. Five different classes of Ig molecules are generated from the genetic loci for the Ig heavy chain located on chromosome 14; the gene loci for the light chains  $\lambda$  and  $\kappa$  are located on chromosomes 22 and 2, respectively. The variable-region genes of the Ig heavy-chain ( $V_H$ ,  $D_H$ , and  $J_H$ ) and light-chain gene ( $V_L$  and  $J_L$ ) loci are responsible for the specificity and affinity of the antigen-binding region of the antibody molecule. The constant-region genes associated with the Ig heavy-chain loci on chromosome 14 are located downstream of the variable region genes and dictate the Ig isotype and subclass. A discussion of the mechanism of these DNA recombinatorial events that are responsible for the construction of the Ig molecule and generation of the diversity in the antibody repertoire is beyond the scope of this review. The reader can read more about these processes in recent reviews.<sup>2</sup> However, it is important to discuss the various stages of B-cell differentiation and development because abnormalities in this process can result in certain antibody immunodeficiencies. The scheme for B-cell development and differentiation is shown in Fig 1.

The earliest recognized precursor B cell is the pro-B cell that has both heavy-chain and light-chain gene loci in the germ-line configuration. However, pro-B cells have all the specific elements of the V-D-J recombinatorial machinery (eg, terminal deoxyribonucleotidyl transferase) and the recombinases (eg, recombination activity gene 1 and 2 [Rag-1 and Rag-2]). At the next stage of B-cell development, early pre-B cells express the same intracytoplasmic and surface markers as pro-B cells, as well as the surrogate light chains (eg, Vpre-B and  $\lambda_5/14.1$ ) that are structurally homologous to the  $\kappa$  and  $\lambda$  light chains but have invariant sequences. The genes that are responsible for the Ig heavy chain undergo DNA rearrangement of  $V_H \rightarrow DJ_H$  to form cytoplasmic  $\mu$  heavy chains. Unlike in the mouse, in which IL-7 is critical for B-cell development, IL-7 appears to be less important in human B-cell development. Patients with severe combined immunodeficiency disease who have mutations in the common  $\gamma$ -chain receptor ( $\gamma_c$ ), which is shared between IL-2, IL-4, IL-7, IL-9, and IL-15, and those patients that have a mutation in the IL-7 $\alpha$  receptor chain appear to have normal B-cell development.<sup>3</sup>

At the next stage of B-cell development, the late pre-B-cell stage, terminal deoxyribonucleotidyl transferase expression is lost, and the majority of cells do not express CD34. In addition to the expression of  $\mu_H$  chains, CD25, the receptor for the growth factor IL-2, is also expressed. In the late pre-B-cell stage, the pre-B-cell receptor is expressed.<sup>4</sup> It is probably at this stage that there is an allelic exclusion of the second Ig heavy-chain allele to prevent further heavy-chain loci rearrangements. The pre-B-cell receptor complex is associated with Ig $\alpha$ /Ig $\beta$ , which functions as the signal transduction unit for the receptor and is required for the transition between pro-B to pre-B cells. The Ig $\alpha$  and Ig $\beta$  proteins that are encoded by the mb-1 and B-29 genes, respectively, are structurally similar to the CD3 $\gamma$ , CD3 $\delta$ , and CD3 $\epsilon$  molecules on T

cells. Each has an intracytoplasmic signaling region with an immunoreceptor tyrosine-based activation motif.

Crossed linkage of the B-cell antigen receptor (BCR) activates a distinct family of cytoplasmic protein tyrosine kinases.<sup>5</sup> These kinases phosphorylate enzymes that are required for the generation of second messengers in the cytoplasm. Linker or adaptor molecules play an important role in linking the BCR to cytoplasmic secondary messengers. A B-cell linker protein (BLNK, also known as SLP-65) is phosphorylated by Syk after BCR activation.<sup>6</sup> This leads to the activation of other enzymes, including phospholipase C $\gamma$ , Btk, and Vav. BLNK is expressed in peripheral B cells but not in T lymphocytes. The highest expression of BLNK is in early B-cell development, with progressively lower expression during B-cell maturation.

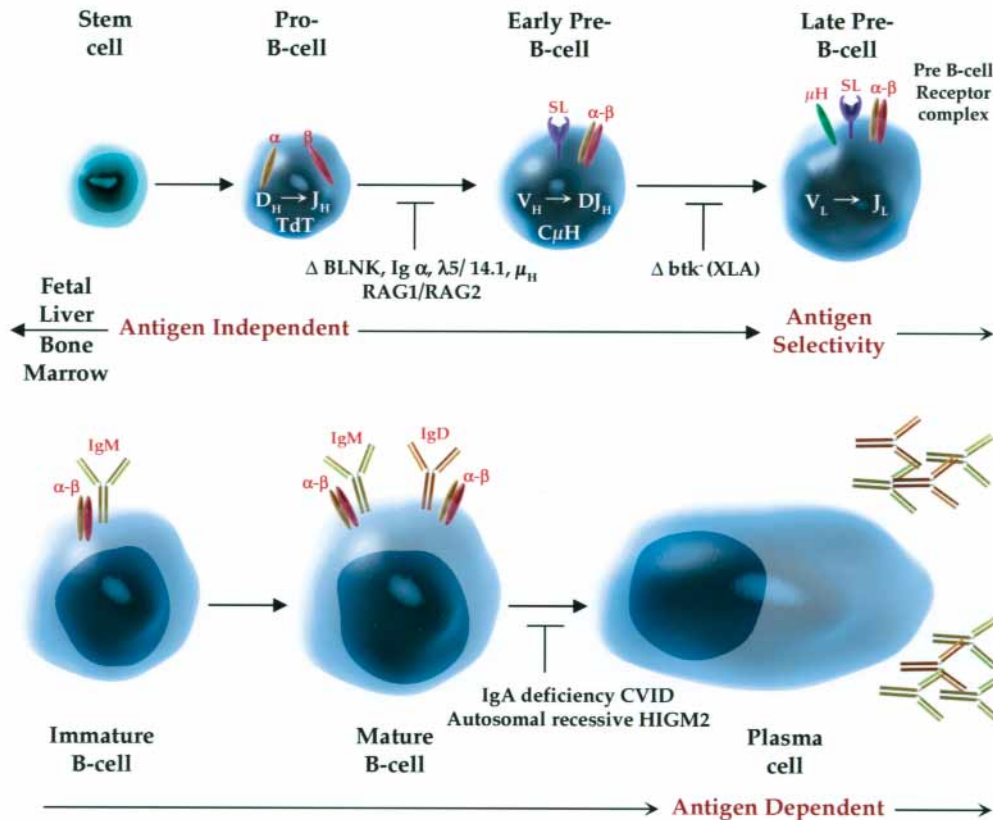
In a late transitional pre-B-cell stage just before becoming an immature B cell, surrogate light-chain expression is lost. The large cycling pre-B cells become small and undergo rearrangement of their light-chain gene loci ( $\kappa$  and  $\lambda$ ) after Rag-1 and Rag-2 expression is turned back on. With a productive light-chain rearrangement in these small transitional late pre-B cells, surface (s)IgM<sup>+</sup> immature B cells appear. Those pre-B cells that have not successfully rearranged their light-chain gene loci undergo an apoptotic cell death. The majority of immature B cells die within 3 to 4 days, whereas only a few cells (ie, 5%-10%) become long-lived mature B cells. This change from an immature B cell to a mature B cell is characterized by the downregulation of sIgM and the upregulation of sIgD expression. Mature B cells also express the L-selectin lymph node homing receptor, complement receptors 1 and 2, CD21, and CD23.

## EARLY-ONSET HYPOGAMMAGLOBULINEMIA AND ABSENT B CELLS

### X-linked agammaglobulinemia

Approximately 85% of patients with early-onset hypogammaglobulinemia and absent B cells are male and have XLA or Bruton's disease.<sup>7</sup> These patients have been demonstrated to have mutations in the gene that encodes tyrosine kinase (Btk or Bruton's tyrosine kinase) and is expressed mainly in lymphocytes of the B lineage.<sup>8</sup> The genetic defect underlying XLA has been located on the midportion of the X chromosome (Xp22) by using polymorphic chromosome markers.<sup>9</sup> Obligate carriers show selective use of the normal X chromosome in B-lineage cells, whereas other cell types show lyonization of the X chromosome.<sup>10,11</sup> A number of distinct mutations of the Btk gene have been described in patients with XLA, most of which involve the kinase domain.<sup>12</sup> Defects in the Btk gene affect the early stages of B-cell differentiation.<sup>13</sup>

The onset of recurrent bacterial infections is typically during the latter part of the first year of life, when maternal antibodies passively acquired through the placenta are reduced below protective levels. The sinopulmonary



**FIG 1.** B-cell development and the mutations that lead to antibody deficiencies. Deletions or mutation in the  $\mu$  heavy chain ( $\mu H$ ), the surrogate light chain ( $SL$ ), or  $Ig\alpha$  ( $\alpha\beta$ ) lead to a block in B-cell development and severe agammaglobulinemia. Similarly, defects in the B-cell signaling pathways mediated by Btk and the adaptor protein BLNK leads to an arrest at the pro-B-cell stage of development and suggests that a functional pre-B-cell receptor is critical for the progression of the pre-B cell to an immature B cell. Mature B cells undergo class switching and somatic hypermutation of the variable-region genes to increase receptor affinity and differentiation into memory B cells or plasma cells. Abnormalities in these latter processes of B-cell differentiation lead to IgA deficiency and CVID, although the molecular basis for these antibody deficiencies is unknown.

tract is a frequent site of infection (60% of patients).<sup>14</sup> Other types of infection include pyoderma (25%), chronic conjunctivitis (8%), gastroenteritis (35%), arthritis (20%), meningitis-encephalitis (16%), and, less commonly, osteomyelitis (3%) and septicemia (10%). *H influenzae* and *S pneumoniae* are commonly associated with these infections. Poorly treated pulmonary infections eventually lead to bronchiectasis. Because cellular immunity is intact, most viral infections, fungal infections, and tuberculosis do not seem to be a problem in patients with XLA. Exceptions to this include viral hepatitis,<sup>15</sup> disseminated polio,<sup>16</sup> and chronic enteroviral encephalitis.<sup>17</sup> *Pneumocystis carinii* infection is rare in patients with XLA but can occur.

Repeated bacterial infections of susceptible target organs, such as the middle ear, sinuses, and lungs, leads to positive physical findings of active inflammation, with eventual scarring or damage to the site. The lymphoid tissues (eg, adenoids, lymph nodes, and spleen) are reduced in size, unlike tissues in patients with common variable immunodeficiency (CVID), who often have lymphoid hyperplasia. Arthritis,<sup>18</sup> a dermatomyositis-like syn-

drome,<sup>19</sup> and meningoencephalitis<sup>20</sup> can also occur in patients with XLA. Chronic meningoencephalitis may occur in association with dermatomyositis or independently. Both are manifestations of chronic enterovirus infections, including the echoviruses and occasionally the Coxsackie virus.<sup>1,20</sup> Infections caused by enteroviruses or *Ureaplasma urealyticum* may cause joint inflammation.<sup>21</sup> Symptoms usually improve or resolve with IVIG therapy. Vaccine-associated poliomyelitis can also occur in patients with XLA.<sup>16</sup> Autoimmune disorders do not seem to be a frequent problem in patients with XLA, unlike in patients with CVID. It is less clear whether patients with XLA have the same predisposition for malignancy as other patients with immune deficiency.<sup>12</sup> Filipovich and Shapiro<sup>22</sup> reported that 4.2% of patients in an immune deficiency cancer registry had XLA. Lymphoreticular and gastrointestinal malignancies were the most common types of cancer.

Early diagnosis, broad-spectrum antibiotics, and replacement therapy with IVIG has changed the outcome of this disease.<sup>14</sup> Infections, especially chronic enteroviral infections and chronic pulmonary disease, are still the

2 major complications in XLA.<sup>14</sup> In a retrospective study of 31 patients with XLA, Quartier et al<sup>23</sup> reported that early IVIG replacement therapy and nadir serum IgG levels of greater than 500 mg/dL were important in preventing severe acute bacterial infections and bronchiectasis. Trough serum IgG levels of greater than 800 mg/dL may be necessary to fully prevent chronic sinusitis, bronchiectasis, and enteroviral infections.

There is a total absence or marked deficiency of serum Igs. Antibodies to even potent protein antigens, such as tetanus toxoid, are absent. Percentages of circulating B cells or surface membrane Ig<sup>+</sup> lymphocytes are extremely low (<2%) or absent.<sup>24</sup> However, pro-B cell numbers in the bone marrow are normal or even increased in number.<sup>13,25</sup> T lymphocytes and other lymphoid subpopulations are normal, and delayed skin reactivity to recall antigens is present. The response of PBMCs to mitogens and allogeneic cells is normal. Lymphoid tissues show absence of plasma cells, lymphoid follicles, and germinal centers. Some patients with Btk mutations may not present until later in life,<sup>26,27</sup> which may reflect different types of Btk mutations. In patients with XLA presenting later in life, the block in B-cell differentiation may be leaky, resulting in some Ig synthesis. A subgroup of patients with CVID may also present with profound hypogammaglobulinemia and markedly reduced numbers of B cells. Molecular analysis for mutations in Btk is necessary to distinguish these patients with CVID from patients with XLA. More details can be found in the review by Conley.<sup>28</sup>

Some patients with the clinical phenotype and laboratory findings of XLA do not have mutations in Btk (Table I). Furthermore, 5% to 10% of patients with early-onset hypogammaglobulinemia and absent B cells are girls. Mutations in several genes in the B-cell differentiation pathway can lead to a profound antibody deficiency. Minegishi et al<sup>29</sup> screened 25 patients with early-onset hypogammaglobulinemia and absent B cells with a normal Btk gene for other genes that encoded components of the pre-B-cell receptor complex. A 2-year-old girl was found to have a homozygous splice defect in the Ig $\alpha$  molecule. CD19<sup>+</sup> B cells were undetectable in the peripheral circulation; there was an almost complete absence of pre-B cells in the bone marrow but normal numbers of pro-B cells. Minegishi et al<sup>30</sup> reported a mutation in the  $\lambda$ 5/14.1 gene encoding the pre-B-cell receptor surrogate light chain that resulted in antibody deficiency and agammaglobulinemia. These female patients who presented with absent B cells and agammaglobulinemia had more severe disease than the boys with Btk mutations.<sup>28,30</sup>

Minegishi et al<sup>31</sup> reported a patient with BLNK deficiency. This patient presented at 8 months of age with recurrent otitis media and subsequently had 2 episodes of pneumonia. At 16 months of age, he was found to have no detectable serum Igs and had less than 1% CD19<sup>+</sup> B cells in the peripheral blood. Bone marrow aspiration showed normal numbers of pro-B cells but no pre-B cells or mature B cells. This patient and associated studies in the mouse indicate that BLNK plays a critical role in orches-

trating the pro-B-cell to pre-B-cell transition and indicates that other adaptor or linker proteins (eg, SLP-76) associated with this intracytoplasmic signaling pathway may also lead to an immune deficiency. Yel et al<sup>32</sup> studied 2 families in which children presented with early-onset hypogammaglobulinemia and absent B cells. These patients were initially referred for the evaluation of mutations in Btk. In 6 patients from these 2 families, 4 different mutations were identified in the  $\mu$  heavy-chain gene on chromosome 14. One of the 2 patients in one family had chronic enteroviral encephalitis, as seen in patients with XLA.

These patients with various mutations in the  $\mu$  heavy chain, the Ig $\alpha$  molecule, the adaptor protein BLNK, and the  $\lambda$ 5/14.1 surrogate light chain illustrate that the pro-B-cell to pre-B-cell process marks an important transition from intrinsically driven B-cell maturation and differentiation to a B-cell receptor, signal-dependent, developmental process. Before the stages of V<sub>H</sub> → DJ<sub>H</sub> rearrangement, there is little, if any, requirement for a B-cell receptor complex or for the molecules that act downstream from the B-cell receptor. However, the appearance of the pre-B-cell receptor complex on the cell surface allows B cells to undergo further development and differentiation.

### Immunodeficiency with hyper-IgM

This syndrome mainly affects boys (55%-65%) and is characterized by severe recurrent bacterial infections with decreased serum levels of IgG, IgA, and IgE but elevated IgM levels.<sup>33</sup> The molecular basis for the X-linked form of immunodeficiency with hyper-IgM (HIGM) has now been identified as a T-cell deficiency in which mutations in the gene that encodes the CD40 ligand molecule are present. However, not all patients are male, and recently, the molecular abnormality of the autosomal recessive form of HIGM has been reported.<sup>34,35</sup> Family consanguinity is frequent. These patients express CD40 ligand normally, and the surface expression of CD40 on B cells is also normal.<sup>36</sup> Molecular studies have shown that the defect in the autosomal variant of HIGM syndrome (HIGM2) is a mutation in the gene that encodes activation-induced cytidine deaminase (AID).<sup>35</sup>

Recurrent bacterial infections of the sinopulmonary and gastrointestinal tracts usually begin in childhood but somewhat later than those in patients with mutations in the CD40 ligand gene (eg, HIGM1). Opportunistic infections with *P carinii* are unusual, unlike in patients with HIGM1,<sup>33,37,38</sup> and autoimmune hematologic diseases do not occur as in patients with HIGM1. A characteristic feature of HIGM2 is lymphoid hyperplasia and adenopathy. Unlike patients with XLA, there is marked hypertrophy of the lymphoid tissues, including the tonsils, lymph nodes, and spleen. In contrast to the lymph nodes in HIGM1 that lack germinal centers,<sup>39</sup> the germinal centers in the nodes of patients with HIGM2 are very large, with highly proliferating B cells. Serum levels of IgM are markedly increased and may reach levels in excess of 1000 mg/dL. After antigen exposure, these patients can produce IgM antibody, and IgM isohemagglutinins are present, but the secondary IgG response is usually



markedly diminished or absent. Peripheral blood B-cell (CD19<sup>+</sup>) counts are normal, and all B cells express sIgM and sIgD. T-lymphocyte numbers and proliferative responses to mitogens and antigens are normal.

In addition to abnormalities in the process of Ig class switch recombination (eg, switching from IgM to IgG, IgA, or IgE), the V-region genes from the CD19<sup>+</sup>CD27<sup>+</sup> B cells do not contain the expected somatic mutations typical of memory B cells. The role for AID in the generation of somatic hypermutation and Ig class switching is not understood. Nevertheless, AID is involved in several crucial steps in terminal B-cell differentiation and antibody production. The AID gene product has homology with APOBEC-1, an mRNA editing enzyme, and raises the question of whether mRNA modification is an important mechanism for the final steps in B-cell maturation.<sup>40</sup>

Recently, another rare form of X-linked HIGM syndrome associated with hypohydrotic ectodermal dysplasia characterized by the absence or hypoplasia of hair, teeth, and sweat glands has been described.<sup>41</sup> Unlike patients with X-linked HIGM, these patients did not have a history of opportunistic infections. This disorder is related to mutations in the gene that encodes the nuclear factor κB essential modulator that is required for activation of the transcription factor nuclear factor κB. Zonana et al<sup>42</sup> described more of a dysgammaglobulinemia with very poor specific antibody production in their patients than an HIGM phenotype.

### Common variable immunodeficiency

Common variable immunodeficiency (CVID), also called acquired hypogammaglobulinemia, adult-onset hypogammaglobulinemia, or dysgammaglobulinemia, is a heterogeneous group of disorders involving both B-cell and T-cell immune function, the predominant manifestation of which is hypogammaglobulinemia. CVID is characterized by recurrent bacterial infections, decreased serum Ig levels, and abnormal antibody responses. The variable in CVID denotes variability in the age at presentation (eg, early childhood, adolescence, or as young adults) and variability in the degree and type of hypogammaglobulinemia. The average age of onset of symptoms is 25 years, and the average age at diagnosis is 28 years.<sup>43</sup> In a subsequent study by Cunningham-Rundles and Bodian,<sup>44</sup> the mortality rate over a 25-year period was 24%, mostly because of lymphoma (18%) and chronic pulmonary disease (11%). Lower levels of serum IgG at the time of diagnosis and poor T-cell function were associated with an earlier age of death. The 20-year survival rate after the diagnosis of CVID is made was 64% for male patients and 67% for female patients compared with 92% to 94% for the general population.

In the respiratory tract recurrent otitis media, chronic sinusitis, and recurrent pneumonia, often with resulting bronchiectasis, are the most frequent presenting infections in adults with CVID.<sup>45</sup> The bacterial pathogens involved are similar to those described in XLA. Other unusual infections in patients with CVID include *Mycoplasma hominis* and *U urealyticum* and are often

associated with arthritis.<sup>21,46,47</sup> In approximately half the patients with CVID, the gastrointestinal tract is affected, presenting with malabsorption or chronic diarrhea.<sup>43,45</sup> Lactose intolerance, protein-losing enteropathy, or superimposed infection of the small bowel with *Campylobacter* or *Yersinia* species or the parasite *Giardia lamblia* contribute to the gastrointestinal symptoms.<sup>48</sup> Atrophic gastritis with achlorhydria may lead to pernicious anemia. Nodular lymphoid hyperplasia (eg, hypertrophy of the Peyer's patches in the small bowel), diffuse lymphoid infiltration, and loss of villi are characteristic in patients with CVID.<sup>49</sup> Hypertrophy of other lymphoid tissues, including peripheral lymph nodes, the spleen, and occasionally the liver, are frequently seen.<sup>45</sup> Secondary neutropenia or thrombocytopenia may result from the hepatosplenomegaly.

Autoimmune disorders occur frequently in patients with CVID (approximately 22% of patients) and include rheumatoid arthritis; autoimmune hematologic disorders, such as hemolytic anemia, idiopathic thrombocytopenic purpura, and pernicious anemia<sup>11</sup>; autoimmune neurologic diseases, such as Guillain-Barré syndrome<sup>50</sup>; chronic active hepatitis often related to hepatitis C virus; and autoimmune endocrinopathies, particularly involving the thyroid.<sup>45</sup> The incidence of malignancy is increased (11%-13%) in CVID during the fifth and sixth decades of life.<sup>43,51</sup> The majority of these malignancies involve the gastrointestinal tract and the lymphoid tissues. An interesting clinical feature of patients with CVID is non-caseating granulomatous lesions infiltrating organs such as the liver, lymph nodes, lung, and skin.<sup>52</sup> These lesions are often confused with sarcoidosis. Although the causes of these granulomas are not known, they occur more frequently in CVID patients with T-cell perturbations and autoimmune disorders.<sup>52</sup>

The serum Ig levels are markedly diminished but are usually higher than those found in patients with XLA. There can be tremendous variability in the degree of hypogammaglobulinemia. Any or all isotypes of Ig can be affected, thus the term *dysgammaglobulinemia*.<sup>53</sup> Specific antibodies are absent or reduced, and isohemagglutinin titers are usually diminished. The proportions of circulating B cells in the peripheral blood are usually normal, but a subset of patients may lack circulating B cells.<sup>54</sup> T-cell function can be quite variable. Cunningham-Rundles et al<sup>43,44</sup> reported that half of the patients had absent delayed skin hypersensitivity to recall antigens, low numbers of circulating peripheral blood T cells, and depressed in vitro responses to mitogens and specific antigens.

Several mechanisms have been proposed to explain the immune abnormalities in patients with CVID, including an intrinsic B-cell defect, excessive T-suppressor cell activity,<sup>55</sup> deficient T-cell helper function,<sup>56</sup> cytokine deficiencies,<sup>57,58</sup> and suboptimal T cell-B cell interactions through deficient expression of the CD40 ligand.<sup>59</sup> These abnormalities reflect the variability of CVID and support the concept that more than one gene is probably responsible for the immune abnormalities in CVID. The

TABLE I. Antibody deficiency disorders

Disease	Serum Ig	Circulating B cells	Abnormality	Inheritance
XLA	All isotypes absent	<2%	Mutations in Btk	X linked
Abnormality in pre-B-cell receptor complex				
I $\alpha$ defect	All isotypes absent	<2%	Splice defect in Ig $\alpha$ molecule	AR
Surrogate light chain	All isotypes absent	<2%	Mutation in $\lambda$ 5/14.1 gene	AR
BLNK defect	All isotypes absent	<2%	Mutations in BLNK	?
$\mu$ Heavy chain	All isotypes absent	<2%	Mutations in $\mu$ heavy chain	AR
AR immunodeficiency with HIGM	Normal or increased IgM, other isotypes decreased	IgM/IgD-bearing cells only	Mutations in AID gene	AR
NEMO	Low IgG, some patients have increased IgM	Normal	Mutations in IKK- $\gamma$	X linked
$\kappa$ -Chain deficiency	Ig with $\lambda$ light chains	Normal; decreased or absent $\kappa$ -bearing B cells	Mutations at chromosome 2p11	AR
Common variable immunodeficiency	Variable, some or all isotypes	Normal or decreased	Unknown, probably not a single abnormality	Variable
IgA deficiency	Very low or absent IgA	Normal	Switch to IgA, defect unknown	Variable
Transient hypogammaglobulinemia of infancy	IgG and IgA decreased	Normal	Delayed maturation	?
IgG subclass deficiency	Decrease in IgG subclass	Normal	Switch to specific IgG subclass, defect unknown	?
Selective antibody deficiency	Normal Ig isotypes	Normal	Defect in response to polysaccharide antigens	?

number of immune deviations described in patients with CVID underscores the heterogeneous nature of this disease. Family members of patients with CVID have an unusually high incidence of IgA deficiency, autoimmune diseases, autoantibodies, and malignancy.<sup>60</sup> Patients and families with CVID or IgA deficiency have an unusually high frequency of an extended MHC haplotype encompassing the region between HLA-DQB1 and HLA-A.<sup>61,62</sup> One or more genes within the MHC class III region on chromosome 6 may be involved in the pathogenesis of CVID and IgA deficiency.<sup>63</sup>

### IgA deficiency

IgA deficiency is one of the most common antibody deficiencies, with an approximate incidence of 1 in 400 to 3000 individuals in the general population.<sup>64</sup> IgA deficiency is defined as a serum IgA concentration of less than 7 mg/dL with normal serum IgM and IgG levels. Both IgA subclasses, IgA1 and IgA2, are usually markedly reduced or absent, although isolated deficiencies of each subclass have been described. IgA deficiency may be found in association with other immune abnormalities, including ataxia-telangiectasia<sup>65</sup> and IgG subclass deficiencies.<sup>66</sup> IgA deficiency may occur in association with the administration of drugs, such as phenytoin, sulfasalazine, hydroxychloroquine, and D-penicillamine.<sup>67,68</sup> IgA deficiency has also been described in association with a number of chromosomal abnormalities, especially on chromosome 18 (18q syndrome or ring chromosome 18).<sup>69</sup> The occurrence of IgA deficiency in both male and female patients and its clustering in families suggest an autosomal inheritance.<sup>70</sup> In some families IgA deficiency appears to be inherited as

a recessive trait, whereas in others it appears to be dominant with variable penetrance.

Many individuals with selective IgA deficiency are clinically asymptomatic. Those IgA-deficient patients with symptoms have sinopulmonary infections and involvement of the gastrointestinal tract with giardiasis and nodular lymphoid hyperplasia.<sup>71</sup> An increased frequency of autoimmune disorders has also been associated with IgA deficiency, including arthritis, a lupus-like illness, autoimmune endocrinopathies, chronic active hepatitis, ulcerative colitis, Crohn's disease, a sprue-like disease, and autoimmune hematologic disorders.<sup>72-76</sup> Selective IgA deficiency is strongly associated with atopy.<sup>72,77</sup> The variability in clinical expression may be related to several factors. Those IgA-deficient patients who have a compensatory increase in secretory monomeric IgM in their upper respiratory tract secretions and gastrointestinal fluids tend to be less symptomatic.<sup>72</sup> IgA-deficient patients with more severe and recurrent sinopulmonary infection tend to have an associated IgG2/IgG4 or IgG4 subclass deficiency.<sup>68,78</sup>

IgA-deficient patients are at risk for the development of anti-IgA antibodies on receipt of blood products.<sup>79</sup> Precaution must be exercised in the administration of IVIG for replacement of IgG subclass deficiency in IgA-deficient patients because IVIG preparations contain small amounts of IgA.<sup>80</sup> However, this risk does not appear to be a problem in those patients with partial IgA deficiency (ie, IgA levels >2 SDs below the normal value for age but greater than 7 mg/dL).

Peripheral blood B cells coexpress IgA, IgM, and IgD, which is similar to the expression seen in the IgA-bearing

B cells found in cord blood.<sup>81</sup> These cells fail to mature into IgA-secreting plasma cells. The pathogenesis of IgA deficiency is not known, although abnormalities in Ig class switching and the cytokines involved in isotype switching have been implicated. Studies of T-cell function have been normal in most patients with selective IgA deficiency. IgA deficiency shares with CVID the inheritance of a restricted MHC extended haplotype.<sup>60,62,63</sup> The pathogenesis of IgA deficiency is still unknown but may share a common cause with CVID because these 2 disorders share many immune aspects.<sup>62,63</sup>

### Transient hypogammaglobulinemia of infancy

Some infants have an abnormal delay in the onset of Ig synthesis, such that the normal physiologic hypogammaglobulinemia that occurs between 2 and 4 months of age is exaggerated and prolonged.<sup>82</sup> This exaggerated physiologic hypogammaglobulinemia may occasionally extend into the second or third year of life.<sup>83</sup> Affected patients usually have recurrent upper respiratory tract infections, including otitis media, sinusitis, and, less commonly, pneumonia.<sup>82</sup> Serum IgG and IgA levels are usually low, but the IgM level is normal or increased. Circulating Ig<sup>+</sup> surface lymphocytes are normal. Antibody responses to protein antigens are normal, but the antibody response to viral respiratory agents may be reduced.<sup>84</sup> Transient hypogammaglobulinemia of infancy is a self-limited disorder, with recovery between 18 and 36 months of age.<sup>82</sup> Long-term follow-up and reevaluation of Ig and B-cell responses are necessary to rule out primary immune deficiency disorders, such as CVID.

### IgG subclass deficiencies

Yount et al<sup>85</sup> in the 1960s and Schur et al<sup>86</sup> in the early 1970s described patients with imbalances of their IgG subclasses and recurrent sinopulmonary infections. Despite the availability of highly specific antisera and more sensitive assays, there is controversy over the clinical significance of the laboratory findings of low levels of serum IgG subclasses. Healthy individuals without recurrent infections can have low serum IgG subclass levels; clinical immunologists have questioned whether IgG subclass deficiency represents a true immunodeficiency disease.<sup>87</sup>

IgG subclass deficiency is defined as a serum IgG subclass level that is more than 2 SDs below the normal mean for age. The age at which each of the IgG subclasses reaches adult levels varies.<sup>88,89</sup> Gm allotype also influences serum concentrations of certain IgG subclasses, particularly IgG2 and IgG3.<sup>90</sup> In adults deficiencies in IgG3 subclass are most common, whereas in children IgG2 is the most prevalent IgG subclass deficiency.<sup>91</sup> IgG subclass deficiency may be seen in conjunction with other primary immune deficiency disorders, such as ataxia-telangiectasia and IgA deficiency.<sup>85,92</sup> IgG subclass deficiency occurs in approximately 15% to 20% of IgA-deficient patients.<sup>93</sup> An IgG subclass deficiency might occur as an isolated single IgG subclass deficiency or as a deficiency of 2 or more IgG sub-

classes (eg, IgG2 and IgG4 deficiency). However, there have been reports of a few patients with homozygous deletions of the constant region genes causing absence of specific IgG subclasses.<sup>94,95</sup>

IgG subclass deficiency can be associated with recurrent infections of the upper and lower respiratory tracts. Pathogens are generally limited to bacteria and respiratory viruses.<sup>96</sup> Because IgG2 is important in the response to polysaccharide antigens, IgG2 subclass-deficient patients typically have infections with *H influenzae* or *S pneumoniae*. Most patients are unable to produce specific antibodies after immunization with purified (unconjugated) polysaccharide antigens (eg, Pneumovax). However, other individuals with IgG2 subclass deficiency can be asymptomatic.<sup>87</sup> In part, this may be due to the shifting of the antibody response to another IgG subclass or Ig isotype, which compensates for the selective IgG subclass deficiency. Also, antibody responses to a conjugate polysaccharide vaccine occur mainly within the IgG1 subclass instead of the IgG2 subclass.<sup>97</sup>

### Selective antibody or antigen-specific antibody deficiency

Ambrosino et al<sup>98,99</sup> described patients with normal serum Ig and IgG subclass concentrations but who have abnormal responses to immunization with (unconjugated) polysaccharides, such as Hib capsular antigen, or to the pneumococcal polysaccharide antigens. Granoff et al<sup>100</sup> described a group of children who had Hib infections despite prior immunization with Hib vaccine. These patients also failed to respond adequately to reimmunization with Hib. A similar group of children with poor antibody responses to Hib vaccine was described by Herrod et al.<sup>101</sup>

In patients with recurrent acute sinusitis and selective antibody deficiency to polysaccharide antigens, immunization with conjugate vaccines to Hib or pneumococcal polysaccharide can be very helpful in decreasing the frequency of infection<sup>102,103</sup> because antibody responses to conjugate polysaccharide vaccine tend to fall within the IgG1 subclass instead of the IgG2 subclass. Immunization with the newer conjugate vaccine may be important because of the emerging antibiotic resistance to *S pneumoniae*. Selective antibody deficiency appears to be a disorder of young children; we seldom identify such patients in adolescence. Most of these patients are between 3 and 6 years of age. This abnormality may therefore reflect a maturational delay of the humoral immune system.

### EVALUATION

Table II outlines an approach to the evaluation of patients with suspected B-cell deficiency. In patients with lung disease, pulmonary function testing should be performed at least once every 6 months; sputum cultures should also be obtained routinely. High-resolution chest computed tomography may be helpful in identifying early bronchiectasis. As discussed above, diarrhea is a

**TABLE II.** Evaluation of B-cell immune function

Quantitative serum Igs: IgG, IgA, IgM
Quantitative IgG subclasses: must be interpreted in conjunction with the ability to produce specific antibodies
Specific antibodies
Isohemagglutinins: IgM antibodies to ABO blood group determinants
Tetanus toxoid
Pneumococcal polysaccharide antigens (with unconjugated vaccine)
Antibodies to other vaccine antigens
Varicella
Hepatitis B
Measles
Antibodies to respiratory viral agents
Respiratory syncytial virus
Mycoplasma
Parainfluenza
Influenza virus A/B
B-cell quantification and phenotyping with mAbs
CD19 (CD20, CD21)
Surface Ig <sup>+</sup> B cells
Molecular studies for known gene abnormalities
Btk and others*

\*See Table I and text.

frequent symptom in patients with antibody deficiency. Stool examinations for ova and parasites and bacterial cultures should be obtained with special attention for identification of *G lamblia* and *Campylobacter* and *Yersinia* species. *G lamblia* responds to metronidazole, as does bacterial overgrowth of the small bowel. One should be aware of the risk of *Clostridium difficile* overgrowth with toxin-induced diarrhea in patients on chronic antibiotic therapy. Blood chemistries, including hepatitis screens and liver function tests, should be obtained on a regular basis (every 6 months or yearly). Blood counts and differentials should be determined at least every 6 months because some patients, such as those with CVID, may have autoimmune cytopenias. A physical examination for abnormalities of lymphoid tissues in patients with CVID is important for surveillance of lymphomas.

Serum Ig concentrations should be measured with quantitative techniques (nephelometry). Values in children must be compared with normal values for age.<sup>104</sup> Immunoelectrophoresis is semiquantitative and should not be used to evaluate a patient with suspected antibody deficiency. Immunoelectrophoresis should only be used to examine serum for paraproteins, such as those found in Waldenstrom macroglobulinemia or multiple myeloma. IgG subclass quantification may be helpful, although there is continuing debate over the utility of these measurements.<sup>105</sup> A careful history and physical examination are important to determine the clinical significance of an Ig subclass abnormality. In addition, the measurement of functional or specific antibodies is critically important to determine the clinical relevance of an Ig deficiency.

Isohemagglutinins are naturally occurring IgM antibodies to the ABO blood group substances. By 1 year of age, 70% of infants have positive isohemagglutinin titers, depending, of course, on their blood type.<sup>106</sup> One can assess the production of specific antibodies after immunization with tetanus, diphtheria, pneumococcus, and other vaccines. Responses to protein antigens generally fall in the IgG1 subclass, whereas the immune response to polysaccharide antigens resides within the IgG2 subclass.<sup>107</sup> Conjugate polysaccharide vaccines may not be helpful in the functional evaluation of an IgG2 subclass deficiency or a selective polysaccharide antibody deficiency. Fortunately, the vaccine for unconjugated pneumococcal polysaccharides is still available for evaluating patients with a selective antibody deficiency. Because a common complaint of many of these patients is recurrent upper respiratory tract infections, one can test serum for the presence of antibodies to common respiratory viral agents, such as influenza A and B, mycoplasma, respiratory syncytial virus, adenovirus, and the parainfluenza viruses.<sup>84</sup> These antibodies fall into both the IgG1 and IgG3 subclasses.<sup>107</sup>

Flow cytometry is important in evaluating peripheral blood for the numbers of B cells and their expression of surface Ig in patients with profound hypogammaglobulinemia. Patients with less than 2% B cells (CD19<sup>+</sup>) will need further molecular evaluation for Btk mutations, or abnormalities in the pre-B-cell receptor complex and secondary intracytoplasmic signaling pathways. Approximately half of the patients with CVID may have reduced T-cell numbers and diminished lymphocyte proliferative responses to mitogens and antigens.

## TREATMENT

The approaches used in the treatment of patients with antibody deficiency include several basic principles. Supportive care, including antibiotics and good pulmonary hygiene measures to improve the mobilization of secretions, are very important. IVIG has been a major advance in the treatment of patients with antibody deficiencies. The transmission of hepatitis C by means of IVIG in 1994 led manufacturers and the US Food and Drug Administration to apply more strict controls in the processing of IVIG and to add additional viral inactivation steps to the purification process (eg, solvent-detergent or pasteurization). These newer IVIG products with additional viral inactivation steps are safe and effective therapies for IgG replacement in patients with antibody immune deficiencies.<sup>108-111</sup> Dosage regimens range from 300 to 600 mg/kg every 3 to 4 weeks. Roifman et al<sup>112</sup> showed that doses of 600 mg/kg every 4 weeks achieved serum IgG trough levels of greater than 500 mg/dL. Even higher doses may be necessary for patients with severe chronic sinopulmonary infections and to prevent bronchiectasis.<sup>23</sup>

Serum IgG trough levels need not be measured with each infusion. After a dose change, equilibration of the serum IgG level may take 3 months. The clinical status of



the patient, including improvement in pulmonary function, decrease in missed days of work or school, and antibiotic use, provides an important indicator of successful replacement therapy. A number of commercial preparations are available in the United States. With the more recently developed commercial products, adverse effects have been markedly reduced. Most adverse reactions are related to the rate of infusion and can be controlled by careful monitoring and slowing the rate when necessary. Other symptoms unrelated to rate can often be controlled by means of pretreatment with acetaminophen or nonsteroidal anti-inflammatory drugs. The most serious adverse reactions to IVIG, although rare, are the anaphylactic reactions caused by anti-IgA antibodies in IgA-deficient patients.<sup>113</sup> Particular caution needs to be exercised in those patients with serum IgA levels of less than 7 mg/dL. An IVIG preparation with a very low level of IgA contamination should be used if IVIG replacement therapy is indicated in this group of immune-deficient patients (eg, IgG subclass deficiency).

Forty percent of patients with CVID can have impaired T-cell function.<sup>43,44</sup> Cunningham-Rundles et al<sup>114</sup> reported the long-term treatment of patients with CVID with low-dose recombinant IL-2 coupled to polyethylene glycol and administered subcutaneously on a weekly basis. T-cell proliferative responses to mitogens and specific antigens increased, and 4 of 8 subjects showed increased antibody responses to a neoantigen, bacteriophage  $\phi\chi$  174. These investigators suggested that IL-2 might be useful as adjunct therapy in some patients with CVID, but further studies are needed to determine whether this type of treatment results in fewer autoimmune disease and malignancies.

Unlike T-cell immune deficiencies, bone marrow transplantation and gene therapy have not become important therapeutic modalities in antibody deficiencies thus far. Newer improved strategies of stem cell transplantation and minitransplants that minimize the use of bone marrow-ablative regimens are being explored for use in certain antibody deficiencies. With the identification of the gene responsible for the immune defect in some patients with antibody disorders (eg, Btk for XLA and AID for HIGM2), gene therapy as an option has become an intriguing concept. However, many barriers to gene therapy remain to be solved (see review by Candotti<sup>115</sup>). Nevertheless, IVIG has made a major difference in the lives of our patients with antibody deficiencies.

## SUMMARY

It has been almost 50 years since Colonel Ogden Bruton described an 8-year-old boy with recurrent bacterial infections who had absence of the "gamma" proteins on serum electrophoresis. Major advances in basic immunology with the availability of monoclonal antibodies and the instrumentation to count and phenotype peripheral blood lymphocytes has made it easier for the clinical immunologist to evaluate for and make diagnoses of immune deficiency. Early diagnosis is critical in

preventing tissue damage from infection and inflammation. In the early 1980s, intravenous preparations of gamma globulin became available to allow more adequate replacement therapy in patients with antibody immune deficiencies. However, there are still many challenges in clinical immunology for the young investigator to address. Although molecular biology has made major advances in our understanding of the pathogenesis of many immune deficiencies, the molecular abnormalities and pathogenesis for many of the antibody deficiencies still remain unknown.

## REFERENCES

1. McKinney R, Katz S, Wilfert C. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. *Rev Infect Dis* 1987;9:334-56.
2. Schroeder HW Jr, Radbruch A, Berek C. B-cell development and differentiation. In: Rich R, Fleisher TA, Shearer WT, Kotzin BL, Schroeder HW Jr. *Clinical immunology: principles and practice*. 2nd ed. New York: Mosby; 2001. p. 9.1-9.14.
3. Puel A, Ziegler S, Buckley RH, Leonard WJ. Defective IL7R expression in T(-)B(+)NK(+) severe combined immunodeficiency. *Nat Genet* 1998;20:394-7.
4. Matsuuchi L, Gold MR. New views of BCR structure and organization. *Curr Opin Immunol* 2001;13:270-7.
5. Wienands J. Signal transduction elements of the B cell antigen receptor and their role in immunodeficiencies. *Immunobiology* 2000;202:120-33.
6. Pappu R, Cheng AM, Li B, et al. Requirement for B cell linker protein (BLNK) in B cell development. *Science* 1999;286:1949-54.
7. Bruton O. Agammaglobulinemia. *Pediatrics* 1952;9:722-8.
8. Tsukada S, Saffran DC, Rawlings DJ, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 1993;72:279-90.
9. Parolini O, Hejtmancik J, Allen R, et al. Linkage analysis and physical mapping near the gene for X-linked agammaglobulinemia. *Genomics* 1993;15:342-56.
10. Fearon E, Winkelstein J, Civin C, Pardoll D, Vogelstein B. Carrier detection in X-linked agammaglobulinemia by analysis of X-chromosome inactivation. *N Engl J Med* 1987;316:427-31.
11. Conley M, Brown P, Pickard A, et al. Expression of the gene defect in X-linked agammaglobulinemia. *N Engl J Med* 1986;315:564-7.
12. Sideras P, Smith CI. Molecular and cellular aspects of X-linked agammaglobulinemia. *Adv Immunol* 1995;59:135-223.
13. Conley ME. B cells in patients with X-linked agammaglobulinemia. *J Immunol* 1985;134:3070-4.
14. Lederman H, Winkelstein J. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine* 1985;64:145-56.
15. Good R, Page A. Fatal complications of virus hepatitis in two patients with agammaglobulinemia. *Am J Med* 1960;29:804-10.
16. Wright P, Hatch M, Kasselberg A, Lowry S, Wadlington W, Karzon D. Vaccine-associated poliomyelitis in a child with sex-linked agammaglobulinemia. *J Pediatr* 1977;91:408-12.
17. Wilfert C, Buckley R, Mohanakumar T, et al. Persistent and fatal central nervous-system ECHO virus infections in patients with agammaglobulinemia. *N Engl J Med* 1977;296:1485-9.
18. Janeway C, Gitlin D, Craig J, Grice D. Collagen disease in patients with congenital agammaglobulinemia. *Trans Assoc Am Physicians* 1956;69:93-7.
19. Gotoff S, Smith R, Sugar O. Dermatomyositis with cerebral vasculitis in a patient with agammaglobulinemia. *Am J Dis Child* 1972;123:53-6.
20. O'Neil K, Pallansch M, Winkelstein J, Lock T, Modlin J. Chronic group A coxsackievirus infection in agammaglobulinemia: demonstration of genomic variation of serotypically identical isolates persistently excreted by the same patient. *J Infect Dis* 1988;157:183-6.
21. Mohiuddin A, Corren J, Harbeck R, Teague J, Volz M, Gelfand E. Ureaplasma urealyticum chronic osteomyelitis in a patient with hypogammaglobulinemia. *J Allergy Clin Immunol* 1991;87:104-7.
22. Filipovich AH, Shapiro RS. Tumors in patients with common variable immunodeficiency. *J Immunol Immunopharmacol* 1991;11:43-6.
23. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous

- immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;134:589-95.
24. Cooper M, Lawton A. Circulating B-cells in patients with immunodeficiency. *Am J Pathol* 1972;69:513-28.
  25. Campana D, Farrant J, Inamdar N, Webster AD, Janossy G. Phenotypic features and proliferative activity of B cell progenitors in X-linked agammaglobulinemia. *J Immunol* 1990;145:1675-80.
  26. Vihinen M, Brandau O, Branden LJ, et al. BTKbase, mutation database for X-linked agammaglobulinemia (XLA). *Nucleic Acids Res* 1998;26:242-7.
  27. Vorechovsky I, Luo L, Hertz JM, et al. Mutation pattern in the Bruton's tyrosine kinase gene in 26 unrelated patients with X-linked agammaglobulinemia. *Hum Mutat* 1997;9:418-25.
  28. Conley ME. Autosomal recessive agammaglobulinemia. In: Ochs HD, Smith CIE, Puck J, editors. *Primary immunodeficiency diseases: a molecular and genetic approach*. New York: Oxford University Press; 1999. p. 285-91.
  29. Minegishi Y, Coustan-Smith E, Rapalus L, Ersoy F, Campana D, Conley ME. Mutations in Ig (CD79a) result in a complete block in B-cell development. *J Clin Invest* 1999;104:1115-21.
  30. Minegishi Y, Coustan-Smith E, Wang Y-H, Cooper MD, Campana D, Conley ME. Mutations in the human h5/14.1 gene result in B cell deficiency and agammaglobulinemia. *J Exp Med* 1998;187:71-7.
  31. Minegishi Y, Rohrer J, Coustan-Smith E, et al. An essential role for BLNK in human B cell development. *Science* 1999;286:1954-7.
  32. Yel L, Minegishi Y, Coustan-Smith E, et al. Mutations in the mu heavy chain gene in patients with agammaglobulinemia. *N Engl J Med* 1996;335:1486-93.
  33. Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). *Immunodef Rev* 1992;3:101-22.
  34. Minegishi Y, Lavoie A, Cunningham-Rundles C, et al. Mutations in activation induced cytidine deaminase in patients with hyper IgM syndrome. *Clin Immunol* 2000;97:203-10.
  35. Revy P, Muto T, Levy Y, et al. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper-IgM syndrome (HIGM2). *Cell* 2000;102:565-75.
  36. Oliva A, Quinti I, Scala E, et al. Immunodeficiency with hyperimmunoglobulinemia M in two female patients is not associated with abnormalities of CD40 or CD40 ligand expression. *J Allergy Clin Immunol* 1995;96:403-10.
  37. Levy J, Espanol-Boren T, Thomas C, et al. The clinical spectrum of X-linked hyper IgM syndrome. *J Pediatr* 1997;131:47-54.
  38. Kraakman MEM, de Weers M, Espanol T, Shuurman RKB, Hendriks RW. Identification of a CD40L gene mutation and genetic counseling in a family with immunodeficiency with hyperglobulinemia M. *Clin Genet* 1999;48:46-8.
  39. Facchetti F, Appiani C, Salvi L, Levy J, Notarangelo LD. Immunohistologic analysis of ineffective CD40-CD40 ligand interaction in lymphoid tissues from patients with X-linked immunodeficiency with hyper-IgM. *J Immunol* 1995;154:6624-33.
  40. Puck JM. A disease gene for autosomal hyper-IgM syndrome: more genes associated with more immunodeficiencies. *Clin Immunol* 2000;97:191-210.
  41. Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohidrotic ectodermal dysplasia. *Nat Immunol* 2001;2:223-8.
  42. Zonana J, Elder ME, Schneider LC, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000;67:1555-62.
  43. Cunningham-Rundles C. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol* 1989;9:22-33.
  44. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34-48.
  45. Hermans P, Diaz-Buxo J, Stobo J. Idiopathic late-onset immunoglobulin deficiency: clinical observations in 50 patients. *Am J Med* 1976;61:221-37.
  46. Jorup-Ronstrom C, Ahl T, Hammarstrom L, Smith CIE, Rylander M, Hallander H. Septic osteomyelitis and polyarthritis with ureaplasma in hypogammaglobulinemia. *Infection* 1989;17:301-3.
  47. Roifman CM, Rao CP, Lederman HM, Lavi S, Quinn P, Gelfand EW. Increased susceptibility to Mycoplasma infection in patients with hypogammaglobulinemia. *Am J Med* 1986;80:590-4.
  48. Ament M, Ochs H, Davis S. Structure and function of the gastrointestinal tract in primary immunodeficiency syndromes. A study of 39 patients. *Medicine* 1973;52:227-48.
  49. Hermans P, Huizenga K, Hoffman H, Brown A. Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. *Am J Med* 1966;40:78-89.
  50. Conley M, Park C, Douglas S. Childhood common variable immunodeficiency with autoimmune disease. *J Pediatr* 1986;108:915-22.
  51. Cunningham-Rundles C, Siegal F, Cunningham-Rundles S. Incidence of cancer in 98 patients with common variable immunodeficiency. *J Clin Immunol* 1987;7:294-9.
  52. Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. *Ann Intern Med* 1997;127:613-7.
  53. Fudenberg H, Good R, Goodman H, et al. Primary immunodeficiencies: report of a World Health Organization committee. *Pediatrics* 1971;47:927-46.
  54. Geha R, Schneeberger E, Merler E, Rosen F. Heterogeneity of "acquired" or common variable agammaglobulinemia. *N Engl J Med* 1974;291:1-6.
  55. Waldmann T, Durm M, Broder S, Blackman M, Blaese M, Strober W. Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinemia. *Lancet* 1974;2:609-13.
  56. Reinherz E, Geha R, Wohl M, Morimoto C, Rosen F, Schlossman S. Immunodeficiency associated with loss of T4+ inducer T-cell function. *N Engl J Med* 1981;304:811-6.
  57. Sneller M, Strober W. Abnormalities of lymphokine gene expression in patients with common variable immunodeficiency. *J Immunol* 1990;144:3762-9.
  58. Eisenstein EM, Chua K, Strober W. B cell differentiation defects in common variable immunodeficiency are ameliorated after stimulation with anti-BD40 antibody and IL-10. *J Immunol* 1994;152:5957-68.
  59. Farrington M, Grosmaire LS, Nonoyama S, et al. CD40 ligand expression is defective in a subset of patients with common variable immunodeficiency. *Proc Natl Acad Sci U S A* 1994;91:1099-103.
  60. Schaffer F, Palermos J, Zhu Z, et al. Individuals with IgA deficiency and common variable immunodeficiency share complex polymorphisms of major histocompatibility complex class III genes. *Proc Natl Acad Sci U S A* 1989;86:8015-9.
  61. Volanakis J, Zhu Z, Schaffer R, et al. Major histocompatibility complex class III genes and susceptibility to IgA deficiency and common variable immunodeficiency. *J Clin Invest* 1992;89:1914-22.
  62. Schroeder HW Jr. Genetics of IgA deficiency and common variable immunodeficiency. *Clin Rev Allergy Immunol* 2000;19:127-40.
  63. Ashman R, Schaffer F, Kemp J, et al. Genetic and immunologic analysis of a family containing five patients with common variable immune deficiency or selective IgA deficiency. *J Clin Immunol* 1992;12:406-14.
  64. Bachmann R. Studies on the serum g-A-globulin level. III. The frequency of a g-A-globulinemia. *Scand J Clin Lab Invest* 1965;17:316-20.
  65. Peterson R, Kelly W, Good R. Ataxia-telangiectasia: its association with defective thymus, immunological deficiency disease and malignancy. *Lancet* 1964;1:1189-93.
  66. Oxelius V, Laurell A, Lindquist B, et al. IgG subclasses in selective IgA deficiency. *N Engl J Med* 1981;304:1476-7.
  67. Seager J, Jamison D, Wilson J, Hayward A, Soothill J. IgA deficiency, epilepsy, and phenytoin treatment. *Lancet* 1975;2:632-5.
  68. Proesmans W, Jaeken J, Eeckles R. D-penicillamine-induced IgA deficiency in Wilson's disease. *Lancet* 1976;2:804-5.
  69. Stewart J, Go S, Ellis E, Robinson A. Absent IgA and deletions of chromosome 18. *J Med Genet* 1970;7:11-9.
  70. Nell P, Ammann A, Hong R, Stiehm E. Familial selective IgA deficiency. *Pediatrics* 1972;41:71-9.
  71. Gryboski J, Self T, Clemett A, Herskovic T. Selective immunoglobulin A deficiency and intestinal nodular lymphoid hyperplasia: correction of diarrhea with antibiotics and plasma. *Pediatrics* 1968;42:833-7.
  72. Ammann A, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. *Medicine* 1971;50:223-36.
  73. Cunningham-Rundles C. Physiology of IgA and IgA deficiency. *J Clin Immunol* 2001;21:303-9.
  74. Heneghan MA, Stevens FM, Cryan EM, Warner RH, McCarthy CF. Celiac sprue and immunodeficiency states: a 25-year review. *J Clin Gastroenterol* 1997;25:421-5.
  75. Schaffer FM, Monteiro RC, Volanakis JE, Cooper MD. IgA deficiency. *Immunodeficiency* 1991;3:15-44.

76. Strober W, Sneller MC. IgA deficiency. *Ann Allergy* 1991;66:363-75.
77. Hammarstrom L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). *Clin Exp Immunol* 2000;120:225-31.
78. Bjorkander J, Bake B, Ozelius V, Hanson L. Impaired lung function in patients with IgA deficiency and low levels of IgG2 or IgG3. *N Engl J Med* 1985;313:720-4.
79. Vyas G, Perkins H, Fudenberg H. Anaphylactoid transfusion reactions associated with anti-IgA. *Lancet* 1968;2:312-5.
80. Bjorkander J, Hammarstrom L, Smith C, Buckley R, Cunningham-Rundles C, Hanson L. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol* 1987;7:8-15.
81. Conley M, Cooper M. Immature IgA B cells in IgA deficient patients. *N Engl J Med* 1981;305:495-7.
82. Tiller T, Buckley R. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. *J Pediatr* 1978;92:347-53.
83. McGeady S. Transient hypogammaglobulinemia of infancy: need to reconsider name and definition. *J Pediatr* 1987;110:47-50.
84. Cano F, Mayo D, Ballow M. Absent specific viral antibodies in patients with transient hypogammaglobulinemia of infancy. *J Allergy Clin Immunol* 1990;85:510-3.
85. Yount W, Hong R, Seligmann M, Good R, Kunkel H. Imbalances of gamma globulin subgroups and gene defects in patients with primary hypogammaglobulinemia. *J Clin Invest* 1970;49:1957-66.
86. Schur P, Borel H, Gelfand E, Alper C, Rosen F. Selective gamma-G globulin deficiencies in patients with recurrent pyogenic infections. *N Engl J Med* 1970;283:631-4.
87. Shackelford P, Granoff D, Madassery J, Scott M, Nahm M. Clinical and immunologic characteristics of healthy children with subnormal serum concentrations of IgG2. *Pediatr Res* 1990;27:16-21.
88. Schur P, Rosen F, Norman M. Immunoglobulin subclasses in normal children. *Pediatr Res* 1979;13:181-3.
89. Morell A, Skvaril F, Steinberg A, Loghem EV, Terry W. Correlations between the concentrations of the four subclasses of IgG and Gm allotypes in normal human serum. *J Immunol* 1972;108:195-206.
90. Ambrosino D, Schiffman G, Gotschlich E, et al. Correlation between G2m(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. *J Clin Invest* 1985;75:1935-42.
91. Soderstrom T, Soderstrom R, Avanzini A, Brandtzeq P, Karlson G, Hanson L. Immunoglobulin G subclass deficiencies. *Int Arch Allergy Appl Immunol* 1987;82:476-80.
92. Oxelius V. Quantitative and qualitative investigations of serum IgG subclasses in immunodeficiency diseases. *Clin Exp Immunol* 1979;36:112-6.
93. Plebani A, Monafa V, Avanzini M, Ugazio A, Burgio G. Relationship between IgA and IgG subclass deficiencies: a reappraisal. *Monogr Allergy* 1986;20:171-8.
94. Migone N, Oliviero S, de Lange G, et al. Multiple gene deletions within the human immunoglobulin heavy-chain cluster. *Proc Natl Acad Sci U S A* 1984;81:5811-5.
95. Depiero A, Kaminski DA, Halsey JF, Briles D, Burrows PD, Hostoffer RW. Immunologic compensation in a patient with a large IgH constant region deletion. *J Allergy Clin Immunol* 2001;107:1051-5.
96. Stanley P, Corbo G, Cole P. Serum IgG subclasses in chronic and recurrent respiratory infections. *Clin Exp Immunol* 1984;58:703-8.
97. Insel R, Anderson P. IgG subclass distribution of antibody induced by immunization with the isolated and protein conjugated polysaccharide of *H. influenzae* b and G2m(n) distribution of serum IgG2 in man. *Monogr Allergy* 1988;23:128-37.
98. Ambrosino D, Siber G, Chilmonczyk B, Jernberg J, Finberg R. An immunodeficiency characterized by impaired antibody responses to polysaccharides. *N Engl J Med* 1987;316:790-3.
99. Ambrosino D, Umetsu D, Siber G. Selective defect in the antibody response to *H influenzae* type b in children with recurrent infectious and normal serum IgG subclass levels. *J Allergy Clin Immunol* 1988;81:1175-9.
100. Granoff D, Shackelford P, Suarez B, et al. *Haemophilus influenzae* type b disease in children previously vaccinated with type b polysaccharide vaccine. *N Engl J Med* 1986;315:1584-90.
101. Herrod H, Gross S, Insel R. Selective antibody deficiency to *Hemophilus influenzae* type b capsular polysaccharide vaccination in children with recurrent respiratory tract infection. *J Clin Immunol* 1989;9:429-34.
102. Gandhi A, Brodsky L, Ballow M. Benefits of antibiotic prophylaxis in children with chronic sinusitis: assessment of outcome predictors. *Allergy Proc* 1993;14:37-43.
103. Shapiro G, Virant F, Furukawa C, Pierson W, Bierman C. Immunologic defects in patients with refractory sinusitis. *Pediatrics* 1991;87:311-6.
104. Stiehm E, Fudenberg H. Serum levels of immune globulins in health and disease. A survey. *Pediatrics* 1966;37:715-27.
105. Morell A. IgG subclass deficiency: a personal viewpoint. *Pediatr Infect Dis J* 1990;9:S4-8.
106. Stiehm E. Immunodeficiency disorders: general considerations. In: Stiehm E, editor. *Immunologic disorders in infants and children*. 3rd ed. Philadelphia: WB Saunders Company; 1989. p. 157-95.
107. Ferrante A, Beard L, Feldman R. IgG subclass distribution of antibodies to bacterial and viral antigens. *Pediatr Infect Dis J* 1990;9:S16-24.
108. Thampakkul S, Bellow M. Replacement intravenous immune serum globulin therapy in patients with antibody immune deficiency. *Immunol Allergy Clin North Am* 2001;21:165-84.
109. Ballow M, editor. Therapeutic applications of intravenous immune serum globulin. *Clin Rev Allergy* 1991;10:1-146.
110. Buckley R, Schiff R. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med* 1991;325:110-7.
111. Cunningham-Rundles C. Intravenous immunoglobulin treatment in the primary immunodeficiency diseases. *Immunol Allergy Clin North Am* 1988;8:17-49.
112. Roifman C, Levison H, Gelfand E. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;1:1075-7.
113. Burks A, Sampson H, Buckley R. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia: detection of IGE antibodies to IgA. *N Engl J Med* 1986;314:560-4.
114. Cunningham-Rundles C, Bodian C, Ochs HD, Martin S, Reiter-Wong M, Zhuo Z. Long-term low-dose TL-2 enhances immune function in common variable immunodeficiency. *Clin Immunol* 2001;100:181-90.
115. Candotti F. The potential for therapy of immune disorders with gene therapy. *Pediatr Clin North Am* 2000;47:1389-407.