

**MARK E. ROSE, MD**

Section of Adult Allergy and Immunology,
Department of Pulmonary, Allergy,
and Critical Care Medicine,
The Cleveland Clinic Foundation

DAVID M. LANG, MD*

Head, Section of Adult Department of
Allergy and Immunology, Department of
Pulmonary, Allergy, and Critical Care
Medicine, The Cleveland Clinic Foundation

Evaluating and managing hypogammaglobulinemia

ABSTRACT

If a patient has frequent or recurrent bronchopulmonary or sinus infections, they may be due to low levels of immunoglobulins. This article describes common primary (idiopathic) and secondary forms of hypogammaglobulinemia and how to evaluate and manage them.

KEY POINTS

Common variable immune deficiency is characterized by severely reduced levels of immunoglobulin (Ig)G and typically manifests as frequent and recurrent sinus and lung infections. Monthly intravenous infusions of pooled immunoglobulins to maintain total serum IgG levels above 500 mg/dL help reduce the infection rate and preserve pulmonary function.

Selective IgA deficiency should be managed by treating infections, if they occur. Daily doses of antibiotics may be helpful as prophylaxis.

Patients with hypogammaglobulinemia should be evaluated to detect possible causes of the condition, including chronic protein-losing gastrointestinal disorders, renal disease, and certain malignancies.

*The author has indicated that he has received honoraria from, has served as a consultant for, or has carried out clinical research with the AstraZeneca, Aventis, Genetech, GlaxoSmithKline, Ivax, Merck, Novartis, Pfizer, and Schering/Key corporations.

A MAN is hospitalized with shortness of breath and a productive cough. He has had four episodes of lobar pneumonia, in different locations, over the past 5 years. He also has had chronic sinusitis since age 10, which was treated with multiple courses of antibiotics, as well as endoscopic sinus surgery 4 years ago. In addition, he has a history of allergic rhinitis and atopic dermatitis, which is now quiescent. He received a polyvalent pneumococcal vaccine 1 year ago because of recurrent infections.

Previous serologic testing for human immunodeficiency virus was negative.

The patient currently takes no medications and has never smoked or used illicit drugs. A review of systems is negative for musculoskeletal, neurologic, cardiovascular, renal, or gastroenterological complaints.

Lobar pneumonia is confirmed by chest radiography. Antibiotic treatment for encapsulated organisms is started. A consultation with the allergy and immunology department is requested.

EVALUATING PATIENTS WITH RECURRENT INFECTIONS

Patients with frequent and recurrent respiratory infections should be tested for immune system abnormalities (FIGURE 1). Recurrent infection includes acute sinusitis three or more times a year or pneumonia two or more times a year. However, immune deficiency diseases are uncommon in the general population. Therefore, the negative predictive value of laboratory tests is greater than their positive predictive value. This makes it important to only test immune function in patients with a

Five types of immunoglobulins

The study of immunoglobulins (antibodies) began in the 1890s when Emil von Behring described “antitoxic activity” in animals immune to diphtheria. Investigators have since described the structure of immunoglobulins and their critical purpose in the adaptive immune response.

Immunoglobulins are the secreted form of the B-cell antigen receptor. They are Y-shaped proteins consisting of two identical heavy polypeptide chains and two identical light chains. There are two types of light chains—kappa and lambda, which are functionally identical. In contrast, there are five types of heavy chains, for which each class of immunoglobulin is named: alpha, found in immunoglobulin (Ig)A, gamma (IgG), delta (IgD), epsilon (IgE), and mu (IgM).

The light and heavy chains each contribute to form a variable and a constant region. The variable region recognizes and binds to a specific anti-

gen, and the constant region confers the effector function of the antibody, ie, its subsequent biologic activity after binding to the antigen.

Antibodies play three critical roles in adaptive immunity:

- They neutralize foreign antigens through direct binding
- They alter antigens so they are more readily engulfed by phagocytes (opsonization)
- They recruit immune effector cells and trigger the release of cytokines and chemokines to destroy foreign antigens.

All of the immunoglobulins fall into the category of serum proteins called gamma globulins, and a low level of any or all of them is called hypogammaglobulinemia. The term is somewhat imprecise, however, because the categorization is based on electrophoresis, and gammaglobulins also include some proteins that are not immunoglobulins.

Immune deficiency diseases are uncommon, so the negative predictive value of tests is high

history of frequent or recurrent infections and who therefore have a high pretest probability of an abnormality.

Basic laboratory tests should be done, including a complete metabolic panel and complete blood count. Then, the physician should evaluate immunoglobulin levels and function.

Immunoglobulin levels. Serum immunoglobulin (Ig)G, IgA, and IgM concentrations are measured using rate nephelometry (total cost \$90), a sensitive, reliable test that quantifies antibody levels. The IgE concentration is measured with an enzyme-linked immunosorbent assay (\$57). Levels are reported with normal values in units of milligrams per deciliter (TABLE 1).

Humoral immune function should be assessed by measuring antibodies to polysaccharide antigen before and after immunization (\$574). First, blood should be obtained for antibodies to polysaccharide antigens such as pneumococcus. Then, if the patient has not recently received a pneumococcal vaccine, he or she should receive unconjugated polyvalent pneumococcal vaccine. Four weeks after vaccination, blood should be tested again for pneumococcal antibodies.

The antibody response to the polysaccharide antigens is reported with corresponding normal values. There is a range of antigens to which normal individuals will respond. While no controlled study has determined the number of antigens to which one should respond, a lack of response to all antigens is consistent with impairment of the humoral immune system. This information is helpful when determining how best to manage a patient with recurrent infections and will be discussed in more detail later in this article.

The recently developed pneumococcal conjugate protein vaccine (Pneumovax) has complicated the evaluation of humoral immune function. Its use for testing is controversial and is not generally recommended, as people may develop antibodies to the conjugated protein but not to the capsular antigens.

Cellular immune function may be compromised in patients with recurrent viral or fungal infections. In such cases one may consider specifically determining T-lymphocyte subsets by flow cytometry and the T-lymphocyte response to protein antigens through mitogen stimulation or by performing delayed hypersensitivity skin testing.



Testing for immune system abnormalities

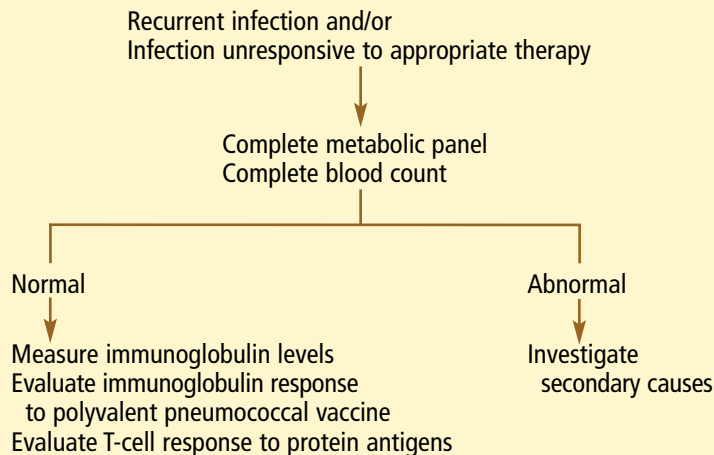


FIGURE 1

■ PRIMARY HYPOGAMMAGLOBULINEMIA

Primary hypogammaglobulinemia by definition is without a known cause. In adults the two most common forms are common variable immune deficiency (CVID) and selective IgA deficiency. Two others, IgG subclass deficiency and deficiency of antibody to a specific antigen, are of unclear clinical significance. TABLE 2 summarizes the different features of immunoglobulin deficiency.

In all immune-deficient states, physicians should attempt to rapidly identify complicating infections and initiate appropriate therapy against the specific microbe. Prophylactic therapy may be of value in some patients.

Common variable immune deficiency

CVID, a heterogeneous immune disorder, is characterized by frequent and recurrent infections and decreased concentrations of multiple classes of immunoglobulins. IgG levels are more than 2 standard deviations below the mean, and the humoral immune response to polysaccharide antigens is impaired.

More than 80% of patients have normal numbers of B lymphocytes, but when the lymphocytes are presented with an antigen, they fail to differentiate into antibody-secreting plasma cells.¹ Some patients may also have increased apoptosis of helper T cells and decreased T-cell function and signaling.^{2,3}

Siblings of patients with CVID are at

increased risk of developing the disorder.⁴ No definitive genetic cause has been identified; susceptibility loci within the major histocompatibility complex of chromosome 6 have been associated with CVID in familial studies,⁵ but these loci are also seen in many autoimmune diseases.

The estimated prevalence of CVID is 1 in 20,000 to 100,000.⁶ It may be diagnosed in childhood, but more often presents in adults.⁷

Consequences of CVID. Patients generally have recurrent and frequent upper and lower respiratory tract infections (eg, sinusitis, otitis, bronchitis, pneumonia) from encapsulated organisms.⁸ In several series of patients with either recurrent sinusitis or pneumonia, the prevalence of hypogammaglobulinemia was greater than in the general population.⁹ From 25% to 48% of patients have splenomegaly.¹⁰

Patients with CVID are also at increased risk for a number of noninfectious diseases and should periodically undergo a thorough history and physical examination to evaluate for their presence. In 1999, Cunningham-Rundles and Bodian found that patients with CVID had a 20-year life expectancy of only 65%, compared with more than 90% in age-matched controls.¹¹

The risk of non-Hodgkin B-cell lymphoma and gastric cancer is particularly high.¹¹ Hypogammaglobulinemia-associated thymoma (Good syndrome) has also been

TABLE 1

Normal serum immunoglobulin concentrations

IMMUNOGLOBULIN TYPE	NORMAL VALUES IN ADULTS (MG/DL)
IgG	717–1,411
IgG ₁	344–966
IgG ₂	133–622
IgG ₃	12–138
IgG ₄	1–115
IgA	78–391
IgM	53–334

CVID generally presents with recurrent and frequent respiratory infections

TABLE 2

Laboratory evaluation of hypogammaglobulinemia

DISORDER	TOTAL IgG	IgA	IgM	IgG SUBCLASS	PNEUMOCOCCAL ANTIBODY RESPONSE
Common variable immune deficiency	Low	Variable	Variable	Low	Impaired
Selective IgA deficiency	Normal	Low	Normal	Variable*	Normal
IgG subclass deficiency	Normal	Normal	Normal	Low*	Variable
Selective antibody deficiency	Normal	Normal	Normal	Variable	Impaired
Secondary hypogammaglobulinemia	Low	Variable	Variable	Low	Variable

*Most commonly IgG₂ subclass

**Cost of IVIG:
\$10,000 to
\$15,000 per
infusion**

reported. It is important that lymphoma not be confused with benign lymphoid hyperplasia, which is also seen in patients with CVID. Patients may develop chronic diarrhea, with or without *Giardia* infection.

CVID is associated with systemic lupus erythematosus, juvenile rheumatoid arthritis, idiopathic thrombocytopenia purpura, and autoimmune hemolytic anemia.^{12,13} The relationship between connective tissue diseases and CVID is not fully understood. Some patients initially present with an immune cytopenia or other autoimmune disease that eventually progresses to CVID.¹⁴

Patients with IgG deficiency have not been found to be at increased risk for bronchiectasis,¹⁵ but they are more likely to develop interstitial lung disease.¹⁶

IVIG is the cornerstone of managing CVID. Regularly scheduled treatment with high doses of intravenous immunoglobulins (IVIG) leads to improved outcomes, including fewer hospitalizations and severe infections.

In the early 1940s, Edwin J. Cohn developed immunoglobulin fractionation methods. Soon after, Charles Janeway identified patients with recurrent infections and reduced concentration of immunoglobulins. By the early 1950s, Janeway was treating his patients

with hypogammaglobulinemia using intramuscular immunoglobulin injections.¹⁷

Since then, techniques have improved, including intravenous administration. Subcutaneous injection is less common but is equally effective.¹⁸

Immunoglobulins are pooled from the sera of thousands of screened donors and typically given through a peripheral catheter either at home or in a physician's office—at a cost of \$10,000 to \$15,000 per infusion. A dose of 400 mg/kg is recommended every 3 to 4 weeks.¹⁹

The dosage is adjusted on the basis of symptomatic improvement and IgG trough levels, which should be measured every 6 months or more often if infections persist. Serum IgG levels should be maintained above 500 mg/dL to help eliminate serious infections and preserve pulmonary function.

Side effects of IVIG. Since IVIG is a blood product, its administration may raise concerns of viral transmission. Although no case of human immunodeficiency virus transmission through IVIG has been reported, hepatitis C transmission occurred in the early 1990s.²⁰ Donor screening and IVIG purification techniques have since improved,²¹ and no known transmission of viral or other infec-



tion has since been reported.

Reactions to treatment with IVIG include headache in up to 50% of patients, and chills, nausea, fatigue, or myalgia in 5% to 10%. Other reported reactions include increased blood pressure,²² aseptic meningitis 24 to 72 hours after the infusion,²³ and acute renal failure in older, diabetic patients after receiving high-glucose, high-osmolar preparations.²⁴ Infusion-related side effects may diminish with slower infusion rates.

Anaphylaxis to IgA in the IVIG preparation can also occur: patients who are IgA-deficient and are exposed to IgA in pooled sera may develop IgE antibodies against IgA. The use of IgA-depleted IVIG has greatly reduced this risk and is safe for patients who are IgA-deficient, even after long-term use of IVIG.²⁵

Because the frequency of IgA deficiency is relatively high in the population, one should check the IgA level prior to initiating IVIG therapy. If low, one should utilize IgA-depleted IVIG, with the first dose given in a monitored, controlled setting.

Selective IgA deficiency

Selective IgA deficiency is characterized by low to nondetectable levels of IgA with normal levels of other immunoglobulin classes. Some regard it as being on a continuum with CVID, with patients diagnosed with selective IgA deficiency occasionally progressing to CVID.²⁶

Selective IgA deficiency is the most common immune deficiency. Its estimated prevalence in whites is 1 in 300 to 1 in 800²⁷; in Asians the prevalence is lower at 1 in 15,000.²⁸ It is inherited in an autosomal-dominant pattern with variable penetrance.

Most patients with IgA deficiency have no symptoms.²⁹ Others have recurrent upper and lower respiratory tract infections. They are also at increased risk for giardiasis and other gastrointestinal infections, autoimmune diseases such as systemic lupus erythematosus and ulcerative colitis, and lymphoproliferative disorders.^{30,31} In one series,¹⁰ the risk of concomitant autoimmune disease was reported at 22%.

Patients who also have low levels of the IgG₂ subclass or low pneumococcal-specific antibody levels are at higher risk for upper and lower respiratory tract infections than are

those with IgA deficiency and normal levels of IgG₂.³² T-cell mediated immunity is not impaired.

Management of selective IgA deficiency is limited to treating associated infections. Some advocate prophylactic daily doses of antibiotics for patients with multiple, recurrent infections. No intervention is available to either replace IgA via infusion or increase production of native IgA.

IgG subclass deficiency: Clinical relevance uncertain

IgG exists as four subclasses. IgG₁ normally has the highest serum concentration, followed by IgG₂, IgG₃, and IgG₄, respectively. IgG₂ is specific for polysaccharide antigens, and IgG₁ and IgG₃ are specific for protein antigens. When the IgG level is reported, the level of each subclass is measured and added to form a total. Therefore, patients may have a normal level of total IgG despite a markedly reduced IgG subclass. IgG₂ is the subclass that is most often low.³³

Subclass deficiency is frequently associated with atopy and can occur in healthy people. However, a deficiency of either IgG₁, IgG₂, or IgG₃ is associated with more frequent and severe infections.³⁴ IgG₂ subclass deficiency is also more common in patients with selective IgA deficiency and those who are homozygous for C2 deficiency.³⁵

Many experts debate the clinical relevance of IgG subclass deficiency—and the use of IVIG to treat it. In a prospective, randomized placebo-controlled crossover study of 43 adult patients with symptomatic IgG subclass deficiency, treatment with IVIG was associated with significantly fewer days of infection.³⁶ However, no other studies have been conducted to confirm these findings.

We recommend that patients suspected of having a deficiency of an IgG subclass and recurrent infection be referred to a clinical immunologist for further evaluation and management.

Specific antibody deficiency with normal immunoglobulins

Deficiencies of specific antibodies are also associated with recurrent infections.³⁷ The condition was discovered when investigators

**Experts
debate the
clinical
relevance
of IgG subclass
deficiency**

evaluated humoral immune function with pneumococcal vaccine and observed that some patients with recurrent infections had normal IgG concentrations but did not form antibodies to some or all of the antigens in the vaccine.

This condition is difficult to definitively diagnose because the pneumococcal antibody response is variable. The number of antigens that a person's immune system recognizes increases from childhood to adulthood,³⁸ and no reliable standard for age-appropriate response has been validated.³⁹

Reports have described patients with a specific antibody deficiency who improved after being treated with IVIG,⁴⁰ but no placebo-controlled study has been conducted.

■ SECONDARY HYPOGAMMAGLOBULINEMIA

Secondary hypogammaglobulinemia can be due to a variety of conditions, which can be divided into diseases of immunoglobulin loss, diseases of immunoglobulin production, drug-induced states, and high-stress states.

No studies to date have had sufficient power to determine the incidence of secondary hypogammaglobulinemia. Thus, if you detect hypogammaglobulinemia, you should take a history to try to rule out potential causes. In addition, laboratory surveillance as described at the beginning of this article should be undertaken when managing patients with infection and known causes of hypogammaglobulinemia such as nephrotic syndrome or chronic lymphocytic leukemia.

Diseases of immunoglobulin loss

The two most common conditions that can result in low immunoglobulin levels are protein-losing enteropathies and renal disorders.

Protein-losing enteropathies that commonly present with decreased immunoglobulins include autoimmune enteropathy and intestinal lymphangiectasia.

Autoimmune enteropathy is characterized by protracted diarrhea, villous atrophy, and enterocyte autoantibodies. It is mostly seen in children but also occurs in adults.⁴¹

Intestinal lymphangiectasia is caused by blocked interstitial lymphatics with resultant

loss of lymph fluid and immunoglobulins in the gastrointestinal tract.⁴² A low-fat, high-protein diet can help return circulating immunoglobulin concentrations to normal.⁴³ Infusion of IVIG successfully reduced the rate of infection in two patients with protein-losing enteropathy.⁴⁴

Chronic renal disease. Nephrotic syndrome is commonly associated with reduced but functionally normal immunoglobulins.⁴⁵ In adults with nephrotic syndrome, hypogammaglobulinemia increases the risk of bacterial infection. Ogi et al⁴⁶ treated 18 patients with nephrotic syndrome and secondary hypogammaglobulinemia with IVIG every 4 weeks to maintain serum IgG levels to above 600 mg/dL, which reduced the infection rate.

Children undergoing dialysis may develop hypogammaglobulinemia across multiple immunoglobulin classes. Isolated IgA deficiency has been reported in adults on dialysis.^{47,48}

Diseases of immunoglobulin production

A number of malignancies, including chronic lymphocytic leukemia (CLL),⁴⁹ lymphoma,⁵⁰ and multiple myeloma,⁵¹ are associated with secondary hypogammaglobulinemia.

A known complication of CLL is an increased risk of infections because of reduced immunoglobulin synthesis.⁵² Patients with CLL who have more frequent infections tend to have lower immunoglobulin levels than patients with CLL without recurrent infections.⁵³

In multiple myeloma, enhanced T-cell suppression of B cells appears to play an important role in promoting hypogammaglobulinemia.⁵⁴

The use of IVIG for treating secondary hypogammaglobulinemia is under investigation, particularly for prophylaxis against infection in patients with hypogammaglobulinemia secondary to malignancy.⁵⁵

Medications

Medications that can cause reversible secondary hypogammaglobulinemia include:

Disease-modifying antirheumatic drugs such as sulfasalazine and gold^{56,57}

Systemic steroids for asthma, as well as for bronchopulmonary dysplasia in children.⁵⁸

If immunoglobulins are low, look for a cause



Steroid-induced hypogammaglobulinemia is unique in that immunoglobulin levels are diminished while function is preserved.

Phenytoin may lead to a CVID-like syndrome⁵⁹ or selective IgA deficiency.⁶⁰

Carbamazepine has been implicated in IgA and IgM deficiency.⁵³

Androgen replacement therapy can cause secondary hypogammaglobulinemia, but its clinical significance is uncertain.⁶¹

High-stress states

Physical stress can reduce immunoglobulin production. During extreme physical activity, athletes can develop reduced concentrations of immunoglobulins and increased risk of infection.⁶² Military recruits who undergo periods of strenuous exercise, reduced calorie intake, and sleep deprivation tend to have lower concentrations of IgG, IgA, and IgM.⁵⁴

■ CASE REVISITED

The allergy and immunology consultant determines that the patient has no family history of recurrent infection, CVID, or selective IgA deficiency.

Laboratory evaluation (lower limit of normal values in parentheses):

- IgG \leq 6.6 mg/dL (565)
- IgG₁ \leq 9 mg/dL (450)

- IgG₂ \leq 12 mg/dL (180)
- IgG₃ \leq 6 mg/dL (13)
- IgG₄ \leq 9 mg/dL (8)
- IgA \leq 7.8 mg/dL (85)
- IgM 9.9 mg/dL (45)

Pneumococcal antibody titers: no antibody response to any of the 12 pneumococcal antigens evaluated.


Complete blood cell count and complete metabolic panel: normal.

Computed tomography of the sinuses: consistent with chronic sinusitis.

There is no evidence of a disease causing hypogammaglobulinemia.

The patient's clinical picture and laboratory evaluation are consistent with CVID. He is treated with IgA-depleted IVIG 400 mg/kg, which is well tolerated.

He is discharged with recommendations for outpatient follow-up in the allergy and immunology clinic and to be maintained at a total serum IgG level of more than 500 mg/dL.

Over the last 5 years, the patient has tolerated his monthly infusions of IVIG with no significant adverse reactions. He has experienced no further episodes of pneumonia and has had sinusitis only once every 2 years. No secondary lymphoproliferative or rheumatologic conditions have developed, and computed tomography scans of the chest have been normal. 

■ REFERENCES

1. **Cunningham-Rundles C.** Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol* 1989; 9:22–33.
2. **Di Renzo M, Zhou Z, George I, Becker K, Cunningham-Rundles C.** Enhanced apoptosis of T cells in common variable immunodeficiency (CVID): role of defective CD28 co-stimulation. *Clin Exp Immunol* 2000; 120:503–511.
3. **Kondratenko I, Amlot PL, Webster AD, Farrant J.** Lack of specific antibody response in common variable immunodeficiency (CVID) associated with failure in production of antigen-specific memory T cells. *MRC Immunodeficiency Group. Clin Exp Immunol* 1997; 108:9–13.
4. **Vorechovsky I, Zetterquist H, Paganelli R, et al.** Family and linkage of selective IgA deficiency and common variable immunodeficiency. *Clin Immunol Immunopathol* 1995; 77:185–192.
5. **Schroeder HW Jr, Schroeder HW 3rd, Sheikh SM.** The complex genetics of common variable immunodeficiency. *J Investig Med* 2004; 52:90–103.
6. **Baumgart KW, Britton WJ, Kemp A, French M, Robertson D.** The spectrum of primary immunodeficiency disorders in Australia. *J Allergy Clin Immunol* 1997; 100:415–423.
7. **Kainulainen L, Nikoskelainen J, Ruuskanen O.** Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J Clin Immunol* 2001; 21:145–149.
8. **Pettit SJ, Bourne H, Spickett GP.** Survey of infection in patients receiving antibody replacement treatment for immune deficiency. *J Clin Pathol* 2002; 55:577–580.
9. **Ekdahl K, Braconier JH, Svanborg C.** Immunoglobulin deficiencies and impaired immune response to polysaccharide antigens in adult patients with recurrent community-acquired pneumonia. *Scand J Infect Dis* 1997; 29:401–407.
10. **Curtin JJ, Murray JG, Apthorp LA, Franz AM, Webster AD.** Mediastinal lymph node enlargement and splenomegaly in primary hypogammaglobulinemia. *Clin Radiol* 1995; 50:489–491.
11. **Cunningham-Rundles C, Bodian C.** Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999; 92:34–48.
12. **Michel M, Chanet V, Galicier L, et al.** Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. *Medicine (Baltimore)* 2004; 83:254–263.
13. **Uluhan A, Sager D, Jasin HE.** Juvenile rheumatoid arthritis and common variable hypogammaglobulinemia. *J Rheumatol* 1998; 25:1205–1210.
14. **Swaak AJ, van den Brink HG.** Common variable immunodeficiency in a patient with systemic lupus erythematosus. *Lupus* 1996; 5:242–246.
15. **Stead A, Douglas JG, Broadfoot CJ, Kaminski ER, Herriot R.** Humoral immunity and bronchiectasis. *Clin Exp Immunol* 2002; 130:325–330.
16. **Popa V, Colby TV, Reich SB.** Pulmonary interstitial disease in Ig deficiency. *Chest* 2002; 122:1594–1603
17. **Berger M.** A history of immune globulin therapy, from the Harvard crash program to monoclonal antibodies. *Curr Allergy Asthma Rep* 2002; 2:368–378.
18. **Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J.** The comparison of the efficacy and safety of intravenous versus subcutaneous



- immunoglobulin replacement therapy. *J Clin Immunol* 2000; 20:94–100.
19. Sewell WA, Buckland M, Jolles SR. Therapeutic strategies in common variable immunodeficiency. *Drugs* 2003; 63:1359–1371.
 20. Bjoro K, Froland SS, Yun Z, Samdal HH, Haaland T. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N Engl J Med* 1994; 331:1607–1611.
 21. Chandra S, Cavanaugh JE, Lin CM, et al. Virus reduction in the preparation of intravenous immune globulin: in vitro experiments. *Transfusion* 1999; 39:249–257.
 22. Lemm G. Composition and properties of IVIg preparations that affect tolerability and therapeutic efficacy. *Neurology* 2002; 59(suppl 6):S28–S32.
 23. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin: frequency and risk factors. *Ann Intern Med* 1994; 121:259–262.
 24. Sati HI, Ahya R, Watson HG. Incidence and associations of acute renal failure complicating high-dose intravenous immunoglobulin therapy. *Br J Haematol* 2001; 113:556–557.
 25. Cunningham-Rundles C, Zhou Z, Mankarious S, Courter S. Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with IgA antibodies. *J Clin Immunol* 1993; 13:272–278.
 26. Johnson ML, Keeton LG, Zhu ZB, Volanakis JE, Cooper MD, Schroeder HW Jr. Age-related changes in serum immunoglobulins in patients with familial IgA deficiency and common variable immunodeficiency (CVID). *Clin Exp Immunol* 1997; 108:477–483.
 27. Mila Llambi J, Etxagibel Galdos A, Matamoros Flori N. The Spanish Registry of Primary Immunodeficiencies (REDIP) [in Spanish]. *Allergol Immunopathol (Madr)* 2001; 29:122–125.
 28. Kanoh T, Mizumoto T, Yasuda N, et al. Selective IgA deficiency in Japanese blood donors: frequency and statistical analysis. *Vox Sang* 1986; 50:81–86.
 29. Weber-Mzell D, Kotanko P, Hauer AC, et al. Gender, age and seasonal effects on IgA deficiency: a study of 7293 Caucasians. *Eur J Clin Invest* 2004; 34:224–228.
 30. Curzio M, Bernasconi G, Gullotta R, Ceriani A, Sala G. Association of ulcerative colitis, sclerosing cholangitis and cholangiocarcinoma in a patient with IgA deficiency. *Endoscopy* 1985; 17:123–125.
 31. Hermaszewski RA, Ratnavel RC, Denman DJ, Denman AM, Webster AD. Immunodeficiency and lymphoproliferative disorders. *Baillieres Clin Rheumatol* 1991; 5:277–300.
 32. French MA, Denis KA, Dawkins R, Peter JB. Severity of infections in IgA deficiency: correlation with decreased serum antibodies to pneumococcal polysaccharides and decreased serum IgG2 and/or IgG4. *Clin Exp Immunol* 1995; 100:47–53.
 33. Gross S, Blais MS, Herrod HG. Role of immunoglobulin subclass and specific antibody determinations in the evaluation of recurrent infection in children. *J Pediatr* 1992; 121:516–522.
 34. Ekdahl K, Braconier JH, Svanborg C. Immunoglobulin deficiencies and impaired immune response to polysaccharide antigens in adult patients with recurrent community-acquired pneumonia. *Scand J Infect Dis* 1997; 29:401–407.
 35. Alper CA, Xu J, Cosmopoulos K, et al. Immunoglobulin deficiencies and susceptibility to infection among homozygotes and heterozygotes for C2 deficiency. *J Clin Immunol* 2003; 23:297–305.
 36. Soderstrom T, Soderstrom R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. *Cancer* 1991; 68(6 suppl):1426–1429.
 37. Follin P, Ulanova M, Hahn-Zoric M, Hanson LA. Invasive Haemophilus influenzae type b (Hib) infection in an adult patient with a selective deficiency of antibody to the Hib capsular polysaccharide. *Clin Infect Dis* 1997; 25:915–917.
 38. Sorensen RU, Leiva LE, Javier FC 3rd, et al. Influence of age on the response to Streptococcus pneumoniae vaccine in patients with recurrent infections and normal immunoglobulin concentrations. *J Allergy Clin Immunol* 1998; 102:215–221.
 39. Go ES, Ballas ZK. Anti-pneumococcal antibody response in normal subjects: a meta-analysis. *J Allergy Clin Immunol* 1996; 98:205–215.
 40. Zora JA, Silk HJ, Tinkelman DG. Evaluation of postimmunization pneumococcal titers in children with recurrent infections and normal levels of immunoglobulin. *Ann Allergy* 1993; 70:283–288.
 41. Leon F, Olivencia P, Rodriguez-Pena R, et al. Clinical and immunological features of adult-onset generalized autoimmune gut disorder. *Am J Gastroenterol* 2004; 99:1563–1571.
 42. Fuss IJ, Strober W, Cuccherini BA, et al. Intestinal lymphangiectasia, a disease characterized by selective loss of naive CD45RA+ lymphocytes into the gastrointestinal tract. *Eur J Immunol* 1998; 28:4275–4285.
 43. Lester LA, Rothberg RM, Krantman HJ, Shermeta DW. Intestinal lymphangiectasia and bilateral pleural effusions: effect of dietary therapy and surgical intervention on immunologic and pulmonary parameters. *J Allergy Clin Immunol* 1986; 78:891–897.
 44. De Giacomo C, Maggiore G, Scotta MS, Ugazio AG. Administration of intravenous immunoglobulin in two children with hypogammaglobulinemia due to protein losing enteropathy. *Clin Exp Immunol* 1985; 60:447–448.
 45. Fikrig SM, Schiffman G, Philipp JC, Moel DI. Antibody response to capsular polysaccharide vaccine of streptococcus pneumoniae in patients with nephrotic syndrome. *J Infect Dis* 1978; 137:818–821.
 46. Ogi M, Yokoyama H, Tomosugi N, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. *Am J Kidney Dis* 1994; 24:427–436.
 47. Neu AM, Lederman HM, Fivush BA. Hypogammaglobulinemia and fatal sepsis in an infant maintained on peritoneal dialysis. *Pediatr Nephrol* 1993; 7:455–456.
 48. Kuo MC, Hwang SJ, Chang JM, Tsai JC, Tsai JH, Lai YH. Recurrent infections in haemodialysis patients—do not forget selective immunoglobulin A deficiency. *Nephrol Dial Transplant* 1998; 13:3220–3222.
 49. Aittoniemi J, Miettinen A, Laine S, et al. Opsonising immunoglobulins and mannan-binding lectin in chronic lymphocytic leukemia. *Leuk Lymphoma* 1999; 34:381–385.
 50. Castellano G, Moreno D, Galvao O, et al. Malignant lymphoma of jejunum with common variable hypogammaglobulinemia and diffuse nodular hyperplasia of the small intestine. A case study and literature review. *J Clin Gastroenterol* 1992; 15:128–135.
 51. Perri RT, Oken MM, Kay NE. Enhanced T cell suppression is directed toward sensitive circulating B cells in multiple myeloma. *J Lab Clin Med* 1982; 99:512–519.
 52. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP. Infection and immunity in chronic lymphocytic leukemia. *Mayo Clin Proc* 2000; 75:1039–1054.
 53. Moreno-Ancillo A, Cosmes Martin PM, Dominguez-Noche C, et al. Carbamazepine induced transient monoclonal gammopathy and immunodeficiency. *Allergol Immunopathol (Madr)* 2004; 32:86–88.
 54. Boyum A, Wiik P, Gustavsson E, et al. The effect of strenuous exercise, calorie deficiency and sleep deprivation on white blood cells, plasma immunoglobulins and cytokines. *Scand J Immunol* 1996; 43:228–235.
 55. Stiehm ER. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. *Pediatr Infect Dis J* 1997; 16:696–707.
 56. Farr M, Tunn E, Bacon PA, Smith DH. Hypogammaglobulinaemia and thrombocytopenia associated with sulphasalazine therapy in rheumatoid arthritis. *Ann Rheum Dis* 1985; 44:723–724.
 57. Snowden N, Dietch DM, Teh LS, Hilton RC, Haeney MR. Antibody deficiency associated with gold treatment: natural history and management in 22 patients. *Ann Rheum Dis* 1996; 55:616–621.
 58. Hamilos DL, Young RM, Peter JB, Agopian MS, Ikle DN, Barka N. Hypogammaglobulinemia in asthmatic patients. *Ann Allergy* 1992; 68:472–481.
 59. Travin M, Macris NT, Block JM, Schwimmer D. Reversible common variable immunodeficiency syndrome induced by phenytoin. *Arch Intern Med* 1989; 149:1421–1422.
 60. Braconier JH. Reversible total IgA deficiency associated with phenytoin treatment. *Scand J Infect Dis* 1999; 31:515–516.
 61. Yesilova Z, Ozata M, Kocar IH, et al. The effects of gonadotropin treatment on the immunological features of male patients with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2000; 85:66–70.
 62. Reid VL, Gleeson M, Williams N, Clancy RL. Clinical investigation of athletes with persistent fatigue and/or recurrent infections. *Br J Sports Med* 2004; 38:42–45.
-
ADDRESS: David M. Lang, MD, Department of Allergy and Immunology, C22, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.