

Images in Allergy and Immunology

Bruce D. Mazer, MD, Salem Al-Tamemi, MD, Joyce W. Yu, MD, and Qutayba Hamid, MD, PhD, Editors

Immune supplementation and immune modulation with intravenous immunoglobulin

Editor's note: This feature, Images in allergy and immunology, is designed to highlight current concepts of the immunopathology of allergic diseases and other common immunologically mediated diseases. The presentation will appear as sets of images that involve cross-pathology, histopathology, and molecular pathology and will cover a range of topics of interest to allergists and immunologists.

Antibody deficiency is the most common of the immune deficiencies.¹ The discovery by Colonel Ogden Bruton of a method of intramuscular antibody supplementation in the 1950s revolutionized the treatment of these patients. Investigation through the following decade refined the preparation of gamma globulins and led to important work in Europe and landmark studies in the United States by Janeway and Rosen during the 1960s.²⁻⁴ These investigations led to the current commonly used formulation for antibody supplementation, intravenous immunoglobulin (IVIG).² IVIG is produced from pooled serum from more than 10,000 donors and therefore contains a broad spectrum of antibodies.⁵ These antibodies cover a large variety of community-acquired pathogens, making IVIG (400-600 mg/kg administered approximately every 3-4 weeks) first-line therapy for individuals with primary humoral immune deficiency. IVIG is effective in diminishing many of the respiratory complications of antibody deficiencies, including

From Meakins Christie Laboratories, McGill University and the McGill University Health Center-Montreal Children's Hospital.

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Reprint requests: Qutayba Hamid, MD, PhD, McGill University, Meakins-Christie Laboratory, 3626 St Urbain St, Montreal H2X 2P2, Canada. E-mail: qutayba.hamid@mcgill.ca

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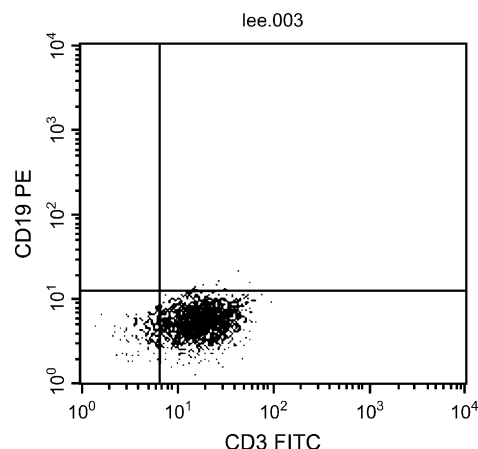


FIG 1. Flow cytometry demonstrating absent B lymphocytes.

sinusitis, pneumonia, and bronchiectasis. Examples of primary immune humoral immune deficiencies include X-linked agammaglobulinemia or Bruton's agammaglobulinemia, characterized by a complete absence of B lymphocytes (Fig 1). Other important examples include X-linked and autosomal recessive hyper-IgM syndromes, deficiency of the inducible costimulator of B cells, common variable immune deficiency, and some individuals with specific antibody (eg, polysaccharide) deficiencies.⁶

Although the majority of immunoglobulin administered in North America is administered through the intravenous route, experience in Europe has shown that subcutaneous infusion provides comparable antibody levels with an extremely low incidence of adverse effects.⁷ There is increasing interest in establishing these programs in both the United States and Canada (Figure 2, showing a patient in training, provided by J. W. Yu, MD, and B. Mazer, MD).⁸

Antibody replacement therapy is also indicated in some individuals with combined immune deficiencies (such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, or DiGeorge syndrome; Fig 3) and some secondary immune deficiencies.⁹ It is also used in patients with severe combined immune deficiency before definitive transplantation therapy and in a significant number of posttransplant patients who have chimerism of their T- and B-cell engraftment.¹⁰⁻¹² Antibodies and antibody networks have long been proposed to regulate normal immune function. This has led to the use of IVIG in inflammatory and autoimmune conditions. High doses of IVIG (1-2 g/kg) are used, in contrast to the dose used for immune deficiency. Although unclear as to the mechanism of action in many of the diseases for which IVIG therapy has been attempted,^{5,13} there are several conditions in which good mechanistic evidence has been determined.

Immune thrombocytopenic purpura (ITP) is a common disorder of antibody-mediated peripheral platelet destruction. Bone marrow examination from affected

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FIG 2. Infusion pump and patient receiving subcutaneous immunoglobulin infusion.

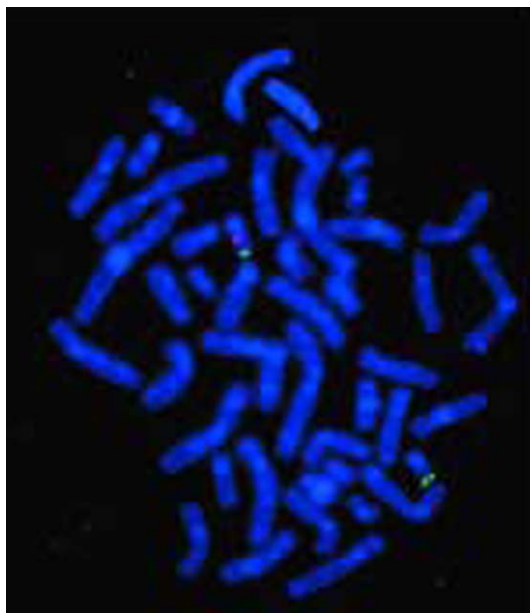


FIG 3. Fluorescent *in situ* hybridization demonstrating DiGeorge syndrome abnormality. (Courtesy of Drs. N. Jabado and Alessandra Duncan, Divisions of Hematology-Oncology and Cytogenetics, Montreal Children's Hospital.)

individuals shows both normal and giant megakaryocytes (Fig 4). IVIG is able to rapidly increase platelet counts in most patients with acute ITP, as well as in patients with chronic ITP. Studies in animal models suggest an effect on diminishing the ability of macrophages to clear platelets, primarily through inhibitory Fc γ RIIb receptors.¹⁴⁻¹⁶

Kawasaki syndrome is an inflammatory disorder of unknown cause. It affects children between the ages of 6 months and 6 years and is characterized by high fever, diffuse amorphous rashes, conjunctivitis, fissuring of the palms and soles, and lymphadenopathy. The most important complication of this disorder is the development of coronary aneurysm or dilatation (Fig 5). IVIG is effective in diminishing the incidence of coronary artery disease, especially if used within the first 7 days of the illness. Potential mechanisms include neutralization of inhibition of cytokine production and staphylococcal endotoxins,¹⁷ and more

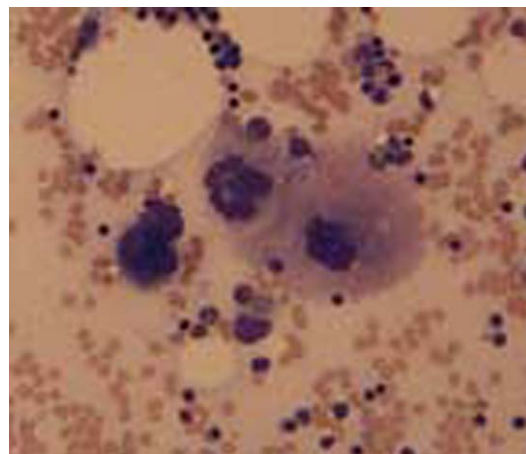


FIG 4. Bone marrow examination from a patient with ITP.

recently, gene array analysis suggested that IVIG downregulates monocyte-related inflammatory proteins, such as adrenomedullin, S100A12, and the chemokine receptor CCR2.^{18,19}

There are a large number of neurologic conditions for which IVIG is used. Controlled trials have demonstrated positive effects in Guillain-Barré syndrome (Fig 6, demonstrating the electromyograph in affected and recovering patients with Guillain-Barré syndrome patients), chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis. Although the mechanism of action is unclear, decreases in levels of circulating cytokines, such as IL-1b, and complement proteins might contribute to the effects.^{20,21}

Attempts to treat severe atopic diseases, such as steroid-dependent asthma, have been reported. There have been numerous encouraging studies, but randomized controlled trials have been both positive and negative. High-dose IVIG (2 g/kg) might be useful in atopic individuals receiving high doses of oral steroid therapy (Fig 7) because of its effect on decreasing total and antigen-specific IgE levels, as well as modifying the expression of steroid receptors.²² *In vitro* IVIG diminishes total C ϵ transcripts in cultured stimulated lymphocytes (Fig 8), contributing to IVIG's effect on IgE levels.²³

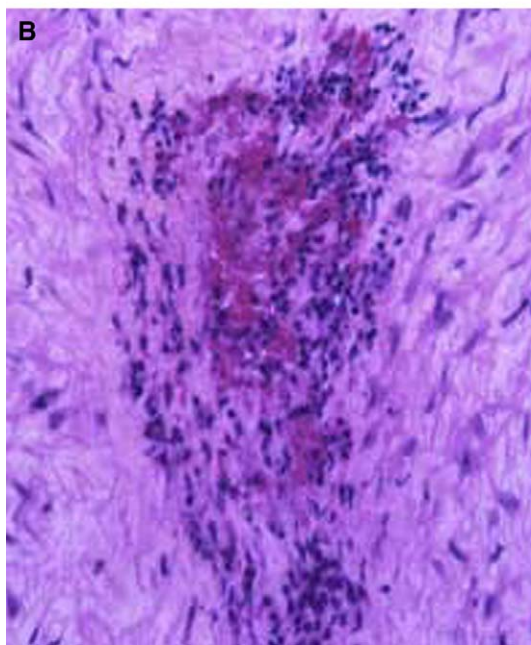


FIG 5. Postmortem specimen (A) and pathology (B) from a patient with a myocardial infarction caused by Kawasaki syndrome. (Courtesy of Drs. Charles Rholicek and Chantal Bernard, Divisions of Cardiology and Pathology, Montreal Children's Hospital.)

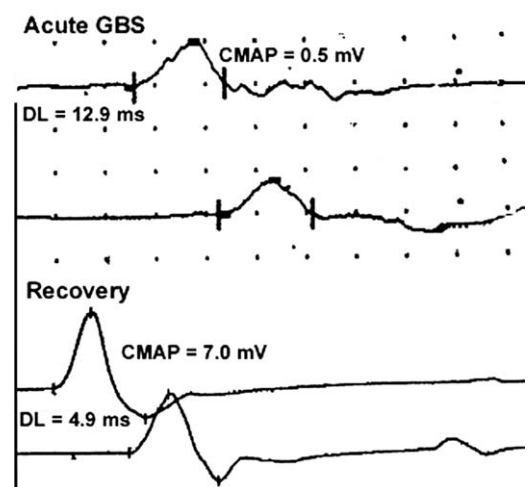


FIG 6. Electromyography in Guillain-Barré syndrome (GBS). CMAP, Compound muscle action potential; DL, distal latency.

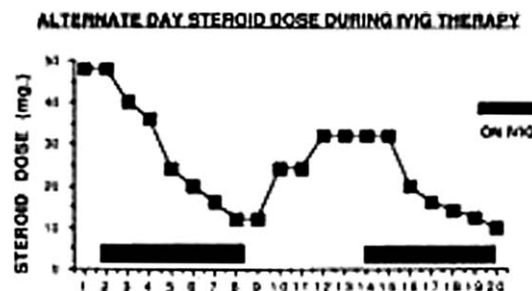


FIG 7. Time course of steroid withdrawal for a patient with severe asthma receiving IVIG.

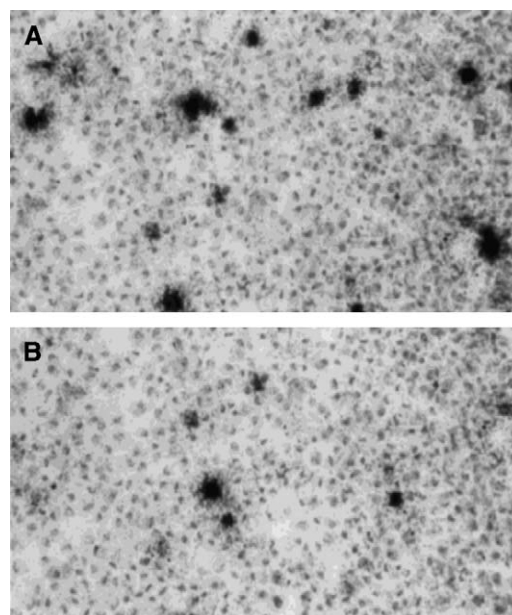


FIG 8. *In situ* hybridization for Cε transcripts.

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