

Table of Contents

Editors and Contributors iv

VOLUME 1

Editors: Alan P. Knutsen, MD, and Larry W. Williams, MD

Part 1: Antibody Deficiency Syndromes 1

Ricardo U. Sorensen, MD, Kenneth Paris, MD, MPH, and Emilio J. Saturno, MD

Introduction 1
Antibody-Mediated Immunity 1
Classification of Antibody Deficiencies 3
Clinical Manifestations of Antibody Deficiencies 4
General Evaluation of Antibody-Mediated Immunity 5
Specific Antibody Deficiency Syndromes 10
Treatment of Antibody Deficiencies 17
Summary 17
References 18

Part 2: Inherited and Acquired Complement Deficiencies. 21

John P. Atkinson, MD, and M. Kathryn Liszewski, BA

Introduction 21
The Complement System 21
Incidence and Genetics 24
Review of Specific Deficiencies with Brief Case Presentations and Commentary 25
Summary 32
References 32

Part 3: Severe Combined Immunodeficiency. 34

Joseph L. Roberts, MD, PhD

Introduction 34
Case 1 34
Case 2 38
References 39

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Antibody Deficiency Syndromes

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INTRODUCTION

Antibodies are an essential component of host defense. The spectrum of antibody deficiencies ranges from severe deficiencies of all immunoglobulins to milder but clinically relevant deficiencies of specific antibodies in patients with normal immunoglobulin concentrations. The International Union of Immunological Societies (IUIS) recognizes several well-defined antibody deficiency syndromes.¹ In clinical practice, however, one encounters many forms of immunoglobulin and antibody deficiencies that do not meet the strict criteria for each syndrome as defined by expert groups.^{2,3} These abnormalities are addressed in this discussion because they require expert advice and intervention. An aggressive search for all antibody abnormalities secures early diagnosis of the severe forms, for which the prognosis depends largely on recognition before severe infections cause permanent sequelae.

Antibody deficiencies are the most frequently reported immunodeficiencies.⁴ The most commonly occurring antibody deficiency syndromes are generally the least severe. For example, IgA deficiency, which may occur asymptotically, is the most common immunodeficiency,⁵ whereas agammaglobulinemias, the most severe immunodeficiencies, are relatively rare. The low frequency of some of the best-defined antibody deficiency syndromes has led to the misconception that these abnormalities are not relevant in clinical practice. One report found that, as a group, antibody deficiencies are the most frequently encountered immunodeficiencies in a clinical immunology practice.⁶ In addition, various immunoglobulin and antibody abnormalities are an integral part of all combined T cell and B cell immunodeficiency syndromes. Antibody function is also affected in some primary complement deficiencies.

ANTIBODY-MEDIATED IMMUNITY

The various forms of antibody deficiency are best understood after a brief review of the development and function of antibody-mediated immunity.

Secreted antibodies attach to infecting microorganisms and enhance opsonization for phagocytosis by polymorphonuclear cells and macrophages. IgM and IgG further activate the complement system through the classic pathway, which leads to lysis of susceptible bacteria and opsonization by C3b. Antibodies are effective against extracellular pathogens (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, bacterial toxins, and viruses) before intracellular infection occurs. Cell-mediated immunity is essential against intracellular pathogens, including viruses, mycobacteria, *Salmonella*, fungi (eg, *Pneumocystis carinii*), and protozoa (eg, *Toxoplasma gondii*). When a patient with known antibody deficiency is infected with these pathogens, an additional defect in cellular immunity must be suspected.

DEVELOPMENT OF MAJOR IMMUNOGLOBULINS

Immunoglobulins

The 3 major immunoglobulins (IgM, IgG, and IgA) contain specific antibodies. IgM remains within the vascular space because of its large size and protects against blood-borne infections. IgM has a short half-life and does not confer long-term protection.

IgG, the immunoglobulin present in the highest concentrations in both intravascular and extravascular spaces, has a special importance in secondary antibody responses and is thus responsible for immunologic memory and long-term protection against infections with viral and bacterial pathogens. IgG has 4 subclasses that differ in structure, concentration, and function.⁷ The relative proportion of each subclass is constant: IgG1 represents 60% to 65% of total IgG, IgG2 20% to 25%, IgG3 5% to 10%, and IgG4 3% to 6%. As is true for total IgG, the concentrations of each subclass vary within a wide range of normal values based on patient age. Antibodies to proteins occur primarily in IgG1 and IgG3, whereas antibodies to polysaccharides occur primarily in IgG2.

IgA is the only immunoglobulin that is normally secreted by the body, primarily in the gastrointestinal (GI) and respiratory tracts in response to luminal antigens. A dimeric form of IgA is transported into epithelial barriers, where it binds to a glycoprotein (secretory