# Primary and Secondary Immunodeficiency

## A Case-Based Guide to Evaluation and Management

Jonathan A. Bernstein
*Editor*

Springer

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*Editor*
Jonathan A. Bernstein
College of Medicine
University of Cincinnati
Cincinnati, OH
USA

ISBN 978-3-030-57156-6 ISBN 978-3-030-57157-3 (eBook)
https://doi.org/10.1007/978-3-030-57157-3



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

*I carry your heart with me (I carry it in*
*my heart) I am never without it (anywhere*
*I go you go, my dear; and whatever is done*
*by only me is your doing, my darling)*
*From "I carry your heart with me," by*
*E. E. Cummings*
*This book is dedicated in loving memory of*
*Liv Rose Meisterman*
*(daughter of Ali and Danny Meisterman)*
*4/22/2019 to 7/11/2019*
*The specialty of immunodeficiency requires*
*that we appreciate the complexity of the*
*human body and the fragility of life. Liv was*
*a blessing and will always be in our hearts.*

# Contents

# Contributors

**Yuliya Afinogenova, MD** Department of Rheumatology, Allergy & Immunology, Yale New Haven Hospital and Yale School of Medicine, New Haven, CT, USA

**Caroline Allan, MBChB** Department of Immunology, Auckland City Hospital, Auckland, New Zealand

**Taha Al-Shaikhly, MBChB** Department of Medicine, Penn State College of Medicine, Hershey, PA, USA

**Rohan Ameratunga, BHB, MBChB, PhD** Department of Clinical Immunology, Auckland City Hospital, Auckland, New Zealand

**Peter D. Arkwright, MB BS, D Phil** Department of Pediatric Allergy and Immunology, Lydia, Manchester, UK

Becker Institute, Manchester, Lancashire, UK

**Danielle E. Arnold, MD** Immune Deficiency – Cellular Therapy Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

**Mark Ballow, MD** Division of Allergy and Immunology, Johns Hopkins All Children's Hospital/USF Department of Pediatrics, St. Petersburg, FL, USA

**Jonathan A. Bernstein, MD** College of Medicine, University of Cincinnati, Cincinnati, OH, USA

**Joel P. Brooks, DO, MPH** Department of Allergy and Immunology, George Washington University School of Medicine and Health Sciences, Children's National Health System, Washington, DC, USA

**Natalia S. Chaimowitz, MD, PhD** Section of Immunology, Allergy and Retrovirology, Department of Pediatrics, Texas Children's Hospital, Houston, TX, USA

**Irina Dawson, MD** Division of Allergy and Immunology, Johns Hopkins All Children's Hospital/USF Department of Pediatrics, St. Petersburg, FL, USA

**William K. Dolen, MD** Medical College of Georgia at Augusta University, Augusta, GA, USA

**Rachel Eisenberg, MD** Children's Hospital at Montefiore, Division of Allergy and Immunology, Montefiore Medicial Center, Bronx, NY, USA

**James M. Fernandez, MD, PhD** Department of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, OH, USA

**Lauren Fine, MD** Department of Medicine, VA Medical Center Miami, Miami, FL, USA

**Lisa R. Forbes, MD** Texas Children's Hospital, Section of Immunology, Allergy and Retrovirology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

**Ramsay L. Fuleihan, MD** Department of Allergy and Immunology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

**Jessica Galant-Swafford, MD** Department of Medicine, Division of Rheumatology, Allergy and Immunology, University of California, San Diego, San Diego, CA, USA

**Melissa D. Gans, MD** Children's Hospital at Montefiore, Division of Allergy and Immunology, Montefiore Medicial Center, Bronx, NY, USA

**Bob Geng, MD** University of California, San Diego, and Rady Children's Hospital, Division of Allergy and Immunology, San Diego, CA, USA

**Laura S. Green, MD** The Allergy, Asthma and Sinus Center, Knoxville, TN, USA

**Justin Greiwe, MD** Division of Immunology, Allergy, and Rheumatology, University of Cincinnati, Cincinnati, OH, USA

**Jennifer R. Heimall, MD** Immune Deficiency – Cellular Therapy Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

**Vivian Hernandez-Trujillo, MD** Allergy and Immunology Care Center of South Florida, Nicklaus Children's Hospital, Miami Lakes, FL, USA

**Saara Kaviany, BS, DO** Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

**Nofar Kimchi, MD** Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

**Heather K. Lehman, MD** University of Buffalo Jacobs School of Medicine and Biomedical Sciences, Department of Pediatric Allergy and Immunology, Buffalo, NY, USA

**Andrew W. Lindsley, MD, PhD** Department of Allergy and Immunology, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**Rebecca A. Marsh, MD** Bone Marrow Transplantation and Immune Deficiency, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**John McDonnell, MD** Department of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, OH, USA

**Thomas F. Michniacki, MD** Division of Pediatric Hematology/Oncology, C.S. Mott Children's Hospital/University of Michigan, Ann Arbor, MI, USA

**S. Shahzad Mustafa, MD** Division of Allergy, Immunology, Rheumatology, Rochester Regional Health, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

**Camile Ortega, DO** Department of Medical Education, Nicklaus Children's Hospital, Miami, FL, USA

**Christine A. Royer, MD** Department of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, OH, USA

**Parteet Sandhu, MD** Division of Allergy and Clinical Immunology, University of Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA

**Jenny Shliozberg, MD** Department of Allergy and Immunology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA

**Kristin C. Sokol, MD, MS, MPH** Schreiber Allergy, Rockville, MD, USA

**Robert Tamayev, MD, PhD** New York Allergy and Sinus Center, Glendale, NY, USA

**Kelly Walkovich, MD** Division of Pediatric Hematology/Oncology, C.S. Mott Children's Hospital/University of Michigan, Ann Arbor, MI, USA

**Betty B. Wray, MD** Medical College of Georgia at Augusta, Augusta, GA, USA

**David T. Yang, MD** Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, USA

# Chapter 1
# An Overview of Primary Immunodeficiencies


**Jonathan A. Bernstein**

## Introduction

Immunodeficiency, whether primary or secondary, is a serious disorder that requires early diagnosis and intervention to prevent comorbidities and potential death. The majority of primary immunodeficiency (PID) cases are rare monogenic defects that present in infancy or early childhood. However, with improved screening recommendations (e.g., T-cell receptor excision circle (TREC) screening for severe combined immunodeficiency (SCID)) and diagnostic testing as well as advanced therapies, these patients are surviving longer into adulthood, requiring systems that allow transitioning to adult care more seamless. However, some of the more common PID (IgA deficiency, common variable immunodeficiency (CVID)) and secondary immunodeficiencies (SID) present in adults but often go unrecognized as uneventful recurrent sinus infections or chronic bronchitis with intermittent pneumonia. Early warning signs of possible PID such as recurrent otitis media, recurrent sinusitis or pneumonia, severe infections requiring intravenous antibiotics, failure to thrive or growth retardation in an infant or a child, recurrent skin or organ abscesses, persistent oral or skin candidiasis, severe infections leading to septicemia, or a family history of PID should alert additional workup or referral to an immunodeficiency specialist. However, many cases are identified serendipitously, such as when a patient being evaluated for celiac disease is found to have an undetectable IgA level, prompting referral to an immunologist for further assessment. As most patients with PID and SID present to their primary care physician or a community specialist without specialized immunodeficiency training, it is imperative that resources like this casebook are available that can provide guidance for their initial clinical evaluation and management.

J. A. Bernstein (✉)
College of Medicine, University of Cincinnati, Cincinnati, OH, USA
e-mail: bernstja@ucmail.uc.edu



J. A. Bernstein (ed.), *Primary and Secondary Immunodeficiency*,
https://doi.org/10.1007/978-3-030-57157-3_1

Ultimately, it is hoped that the clinician will develop a fundamental knowledge of immunodeficiency conditions outlined in this book so they can become more comfortable in the diagnosis and treatment of these disorders. For those interested in a more in-depth understanding of the immune system, *Stiehm's Immune Deficiencies* is a useful reference.

## Overview of Casebook

This book uses a case-based approach that focuses on our current understanding of specific B- and T-cell immunodeficiencies, immune dysregulation syndromes, innate immune defects, and secondary immunodeficiencies. Although there may be some rarer disorders that have been omitted or topics not discussed in sufficient detail, the major conditions encountered by clinicians and their appropriate management are reviewed clearly and succinctly in each chapter.

The first section of this book addresses B-cell immunodeficiency conditions, which include common variable immunodeficiency (CVID), hypogammaglobulinemia, specific antibody deficiency, agammaglobulinemia, immunoglobulin class-switch defects, transient immunodeficiency of infancy, selective isotype immunodeficiency, and CVID-like disorders. The second section focuses on T-cell immunodeficiency, which includes severe combined immunodeficiency, idiopathic CD4 lymphopenia, hyper-IgE syndromes, and genetic syndromes with associated immunodeficiencies. The third section centers on immune dysregulation syndromes including autoimmune lymphoproliferative syndrome, auto-inflammatory syndromes, immune dysregulation leading to autoimmunity, and dendritic cell immunodeficiency conditions. The fourth section addresses innate immune defects and includes congenital neutropenia and migration defect disorders, chronic granulomatous disease, primary immunodeficiencies of complement, natural killer cell defects, and mucocutaneous candidiasis. Finally, the fifth section addresses immunodeficiency secondary to malignancies and biologics, immunodeficiency secondary to prematurity, pregnancy, and aging as well as the appropriate approach to vaccinations in primary and secondary immunodeficiencies, including in asplenic patients. Each chapter provides two case presentations nested with a discussion of the essential elements of a proper medical history, differential diagnosis, diagnostic testing, treatment options, and long-term management. Each chapter concludes with a "Clinical Pearls and Pitfalls" summary that emphasizes the important take-home messages for the reader. It is clear from each chapter that evaluation of PID requires much more than ordering a Complete blood count (CBC) with differential, quantitative immunoglobulins, and B- and T-cell vaccination responses. Therefore, it is advisable to involve a clinical immunologist, who may be trained in hematology or allergy, to determine whether a more in-depth evaluation is required.

## Immunodeficiency Comorbidities

Some notable important observations can be gleaned from reading the various chapters in this book that are worth emphasizing. In addition to severe life-threatening infections which can affect multiple organ systems, primary immunodeficiency patients are at increased risk for several comorbid conditions including malignancies and autoimmune diseases. Therefore, careful monitoring of these patients over time is a necessary component of their management. For example, DNA breakage disorders such as ataxia telangiectasia, Bloom's syndrome, and Nijmegen breakage syndrome are all at increased risk for leukemias and lymphomas [1]. However, carcinomas and brain tumors can also occur in Bloom's syndrome and Nijmegen breakage syndrome, respectively [1]. CVID patients are at increased risk for lymphoma, gastric, thyroid, and skin cancers, whereas patients with immune dysregulation syndromes like Autoimmune lymphoproliferative syndrome (ALPS) are at increased risk for Hodgkin's and non-Hodgkin's lymphoma. In addition, GATA2 patients are at increased risk for myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), as well as Epstein Barr Virus (EBV)- and Human Papillomavirus (HPV)-induced tumors [1, 2]. Patients with other immunodeficiencies such as Wiskott-Aldrich syndrome are at increased risk for MDS, lymphomas, and acute lymphocytic leukemia [1, 2]. It is important to note that while many of these malignancies occur in children and adolescents, they also are known to occur in adult CVID patients [2].

Autoimmune disorders are the most frequent noninfectious complications occurring in 20–30% of CVID patients [3]. In one registry study, autoimmune cytopenias were 700 times more common in CVID patients than in the general population [3]. The most common autoimmune cytopenias are immune thrombocytopenia and hemolytic anemia and less commonly autoimmune neutropenia which in up to 60% of the time precede the onset of CVID [3]. CVID patients with interstitial lung disease are more likely to have autoimmune cytopenias [3]. CVID patients are also at increased risk for splenomegaly, granulomatous and lymphoproliferative disease, organ-specific autoimmune disease, and malignancy. In addition, other autoimmune disorders reported in less than 5% of CVID patients include inflammatory arthritis, systemic lupus erythematosus, Sjogren's, Behcet's, psoriasis, alopecia areata, vitiligo, type I diabetes mellitus, inflammatory bowel disease, autoimmune enteropathy, and gastritis [3].

## Technological Advancements in Immunodeficiency

Another important observation worth discussing is the rapidity with which the specialty of immunodeficiency has evolved. Since 1971, when the term "common variable immunodeficiency" was first proposed to describe a heterogeneous group of patients with recurrent infections characterized primarily by late-onset antibody failure unrelated to any other underlying cause, it has expanded exponentially as a

direct result of immunophenotyping and genotyping technologies [4]. As patient phenotyping has improved, it has been possible to use cellular and molecular techniques such as flow cytometry, next-generation sequencing (NGS), whole exome sequencing (WES), and gene editing to identify monogenic defects in many of these patients never previously characterized [1, 3–6]. By 2016, the International Union of Immunological Societies (IUIS) has classified more than 400 inborn errors of immunity (IEI), which have doubled since 2009 [5]. For example, NGS has identified monogenic defects such as transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), signal transducer and activator of transcription 3 gene (STAT3) and phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit delta gene (PIK3CD), gain-of-function (GOF) mutations, nuclear factor kappa beta (NFkB), lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and their associated risk for autoimmune or malignancy complications [1, 3, 7]. In addition, deep intronic mutations such as UNC13D-associated hemophagocytic lymphohistiocytosis (HLH), IL-7R and Janus kinase 3 for severe combined immunodeficiency (SCID), zeta chain–associated protein kinase (ZAP70) in children with T-cell immunodeficiencies, signal transducer and activator of transcription-3 (STAT3) in hyper-IgE syndrome, and NF-kB essential modulator (NEMO) in ectodermal dysplasia and immunodeficiency have been identified [5]. RNA sequencing has been useful for identifying partial or complete loss of gene expression in probands compared to controls which otherwise never would have been recognized using older methodologies [5]. Furthermore, flow cytometric assays are now routinely being used to assess for hemophagocytic lymphohistiocytosis (HLH) which can be a primary IEI (i.e., perforin deficiency) or secondary to infections, malignancies, or autoimmune disease without a genetic cause [6]. Specifically, functional flow cytometric 107a assays have been found to be increasingly useful to measure whether NK and cytotoxic T-lymphocytes (CTLs) can release lysosomes after stimulation with K562 cells (NK cells), anti-CD16 antibodies (NK cells), or anti-CD3 antibodies (CTLs) to evaluate for primary and secondary HLH [6].

## Novel Therapeutic Advancements

Intravenous immunoglobulin replacement therapy has been the mainstay of treatment for immunodeficiencies with impaired B-cell function resulting in hypogammaglobulinemia. However, this treatment is frequently associated with systemic side effects that require pretreatment with H1-antihistamines, nonsteroidal anti-inflammatory agents, or glucocorticoids. Even with these pretreatment approaches and changing from one preparation to another, these therapies are still intolerable for many patients. The development of subcutaneous immunoglobulin products has made it possible for patients to self-administer immunoglobulin treatment in their home and is associated with significantly fewer side effects [8].

Not surprisingly, advancements in molecular technology have also led to the development of novel biologic therapies and small molecules that target very

**Table 1.1** Targeted therapies for primary immunodeficiencies [7]

| Molecular structure | Molecular target | Drug | Indication |
|---|---|---|---|
| Macrolide compound | mTOR | Sirolimus | NLCR4 GOF<br>POMP deficiency<br>CTLA-4 Haploinsufficiency<br>APDS |
| CTLA-4 IgG fusion protein | B7-1 (CD80),<br>B7-2 (CD86) | Abatacept<br>Belatacept | CTLA-4 haploinsufficiency,<br>LRBA deficiency<br>CTLA-4 haploinsufficiency |
| Antihuman IL-1 IgG1 mAb<br>IgG1 linked to IL-1R and IL-1R accessory protein | IL-1beta | Canakinumab<br>Rilonacept | CAPS<br>FCAS<br>MWS<br>DIRA |
| IgG1k recombinant humanized mAb | IL-6R | Tocilizumab | STAT3 GOF |
| Fusion protein<br>Chimeric mAb<br>Humanized mAb | TNF-alpha | Etanercept<br>Infliximab<br>Adalimumab | SAVI<br>CANDLE syndrome<br>POMP deficiency |
| Small molecule inhibitor | JAK1 and JAK2<br>JAK1 and JAK3<br>P110 | Ruxolitinib,<br>Tofacitinib<br>Baricitinib<br>Tofacitinib<br>Leniolisib | STAT3 GOF<br>STAT1 GOF<br>CANDLE syndrome<br>APDS |
| Recombinant IL-18 binding protein | IL-18 binding protein | Tadekinig-alpha | NLCR4 GOF |

*CTLA4* cytotoxic T-lymphocyte–associated antigen 4, *STAT* signal transducer and activator of transcription, *GOF* gain of function, *APD* activated phosphoinositide 3-kinase delta syndrome, *CAPS* cryopyrin-associated periodic syndrome, *CANDLE* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, *POMP* proteasome maturation protein, *FCAS* familial cold autoinflammatory syndrome, *LRBA* lipopolysaccharide (LPS)-responsive and beige-like anchor protein, *MWS* Muckle-Wells syndrome, *DIRA* deficiency of IL-1 receptor antagonist, *SAVI* STING-associated vasculopathy with onset in infancy

specific checkpoints important for regulating immunity, inflammation, and cancer (Table 1.1) [5, 9]. Genetic sequencing has been successful in identifying point mutations that have led to precision, targeted therapies such as the CTLA-4 immunoglobulin fusion proteins, Abatacept and Belatacept, used as replacement therapy for CTLA-4 haploinsufficient and LRBA-deficient patients. These therapies have also been effective for treating their associated autoimmune complications [9]. Other cytokine therapies such as Tocilizumab, an anti-IL6 receptor antagonist, have been effective for treating STAT3 GOF mutations [9].

In addition, hematopoietic stem cell transplantation and novel forms of conditioning strategies, which are gradually replacing conventional chemotherapies, have been curative for many of these IEI disorders [5, 10]. Even more astonishing are the advancements in gene therapy to cure IEIs, which has become more feasible as safer lentiviral vectors are being used to correct the molecular defect in vitro by gene addition [5]. This has reduced the risk for graft versus host disease after autologous stem cell infusion and is currently being used in clinical trials to treat Recombination activating gene (RAG)-SCID, X-linked lymphoproliferative disease, and perforin deficiency [5]. Gene editing using CRISPR/Cas9

technology appears promising; however, due to lower transfection efficiency as a result of increased cell mortality compared to gene editing methods, this technique still requires further refinement [5, 10]. Early trials using CRISPR/Cas9 technology to treat gain-of-function (GOF) mutations associated with X-linked SCID and agammaglobulinemia, chronic granulomatous disease (CGD), and hyper-IgM syndrome are ongoing [5, 10]. Other approaches, such as T-cell gene therapy and base editing for use in correcting T-cell defects and single point mutations, also appear promising [5].

As a result of the advancements achieved in patient phenotyping and subsequent identification of specific monogenic defects, strong consideration should be given to obtain a limited immunology exome sequencing panel for all confirmed CVID patients that includes primers for known mutations so they can be risk-stratified for future complications like malignancy and autoimmune diseases which require closer monitoring so precision therapies can be implement if and when they manifest.

## Conclusion

The management of patients with immunodeficiencies involves many stakeholders, including the patient's families and friends, primary care clinicians, patient advocacy groups and foundations, insurance companies, specialty pharmacies, hospitals, immunodeficiency centers of excellence for patient care and research, immunodeficiency reference laboratories, and immunodeficiency professional organizations. In many instances, finding resources in one's community to refer a patient for an immunodeficiency workup can be very challenging and may require travel for many of these patients because not all academic centers have this expertise. The Jeffrey Modell Foundation (http://www.info4pi.org/village/patient-organizations) and the Immune Deficiency Foundation (https://primary-immune.org/about-primary-immunodeficiencies) have many available patient resources, physician referral information, and research initiatives. Table 1.2 lists many of the immunodeficiency centers primarily at major university medical centers that have immunodeficiency specialists where patients can be sent for consultation. Many of these centers also have immunodeficiency laboratories where specialized testing can be performed.

Ultimately, it is hoped that this casebook illustrates the great strides made in understanding and treating PID and SID disorders. However, while reading the cases and current algorithms for management for many of these conditions, it should become increasingly clear that amidst all of the technical and therapeutic advancements made over the past 50 years, diagnoses of immunodeficiency disorders are still frequently delayed, and there remain many knowledge gaps that require further investigation.

**Table 1.2** List of transplant centers with immunodeficiency laboratories in the United States, Canada, and United Kingdom (from the Rare Disease Network Organization; https://www.rarediseasesnetwork.org/cms/pidtc/Learn-More/Participating-Clinical-Centers)

| State | Center | Immunologist | Transplanter | Address |
|---|---|---|---|---|
| *UNITED STATES* | | | | |
| Alabama | The Children's Hospital of Alabama | Prescott Atkinson | Fred Goldman | Children's Hospital of Alabama<br>ACC 512<br>1600 7th Ave S<br>Birmingham AL 35233 |
| Arizona | Phoenix Children's Hospital<br>Center for Cancer and Blood Disorders | Holly Miller | Roberta H. Adams | 1919 E. Thomas Rd.<br>Phoenix, AZ 85016 |
| California | | | | |
| | Children's Hospital LA | Michael Pulsipher | Neena Kapoor | Division of Research Immunology and Bone Marrow Transplant<br>4650 Sunset Boulevard - Mail Stop 62<br>Los Angeles, CA 90027 |
| | Lucile Packard Children's Hospital Stanford | Katja Weinacht | Matthew Porteus | 265 Campus Drive<br>Building G3040B MC 5462<br>Stanford, CA 94305 |
| | Mattel Children's Hospital UCLA | Caroline Kuo | Theodore Moore | Division of Hematology/Oncology<br>10833 Le Conte Avenue; Rm A2-410 MDCC<br>Los Angeles, CA 90095-1752 |
| | UCSF Benioff Children's Hospital | Jennifer Puck | Christopher Dvorak | 505 Parnassus Ave, Rm M674<br>San Francisco, CA 94143-1278 |
| Colorado | Children's Hospital Colorado | Ralph Quinones | John Craddock | 13123 East 16th Avenue, B115<br>Aurora, CO 80045 |
| Washington, D.C. | Children's National Medical Center | Michael Keller | Blachy Davila Saldana | Center for Cancer and Blood Disorders<br>111 Michigan Avenue, NW<br>Washington DC 20010-2970 |

(continued)

**Table 1.2** (continued)

| State | Center | Immunologist | Transplanter | Address |
|---|---|---|---|---|
| Delaware | Alfred I. duPont Hospital for Children/ Nemours | Magee DeFelice | Emi Caywood | 1600 Rockland Road Wilmington, DE 19803 |
| Florida | Johns Hopkins All Children's Hospital | Jennifer Leiding | Benjamin Oshrine | Blood and Marrow Transplant Program All Children's Hospital 601 5th Street South 3rd Floor St. Petersburg, FL 33701 |
| Georgia | Children's Healthcare of Atlanta | Lisa Kobrinski | Elizabeth Stenger | AFLAC Cancer Center 4th Floor, Tower 1 1405 Clifton Road NE Atlanta, GA 30322 |
| Illinois | Ann & Robert H. Lurie Children's Hopsital of Chicago | Ramsay Fuleihan | Morris Kletzel | Ann & Robert H. Lurie Children's Hopsital of Chicago Division of Pediatric Hem, Onc and Stem Cell Transplant 2300 Children's Plaza, Box 30 Chicago, IL 60614 |
| Louisiana | Children's Hospital, LSUHSC | Ken Paris | Lolie Yu | 200 Henry Clay, Suite 4109 New Orleans, LA 70118 |
| Massachusetts | Boston Children's Hospital | Craig Platt | Sung-Yun Pai | Karp Family Research Labs, Rm 08214 300 Longwood Avenue Boston, MA 02115 |
| Maryland | NIAID/NIH | Harry Malech | Elizabeth Kang | Building 10-CRC, Room 6W-3752 9000 Rockville Pike: 10 Center Drive MSC 1456 Bethesda MD 20892-1456 |
| Michigan | University of Michigan Health System | Mark Vander Lugt | Gregory Yanik | 1500 E Medical Center Drive SPC 57 Ann Arbor, MI 48109 |
| Minnesota | University of Minnesota Medical Center | | Angela Smith | Pediatric Blood and Marrow Transplant 420 Delaware Street SE, MMC 484 Minneapolis, MN 55455 |
| Missouri | | | | |

**Table 1.2** (continued)

| State | Center | Immunologist | Transplanter | Address |
|---|---|---|---|---|
| | Cardinal Glennon Children's Medical Center | Deepika Bhatla | Alan P. Knutsen | 1465 South Grand Blvd. St. Louis, MO 63104 |
| | Washington University School of Medicine | Jeffrey Bednarski | Shalini Shenoy | Box 8116 1 Children's Place St. Louis, MO 63110 |
| North Carolina | Duke University Medical Center | Rebecca Buckley | Suhag Parikh | Pediatric Stem Cell Transplant Program Duke University Medical Center Box 3350, Durham, NC 27710 |
| New Jersey | Hackensack University Medical Center | Alfred P. Gilli | | Pediatric BMT Program 30 Prospect Avenue Hackensack, NJ 07601 |
| New York | | | | |
| | Memorial Sloan Kettering Cancer Center | Susan Prockop | | 1275 York Avenue New York, NY 10065 |
| | Maria Fareri Children's Hospital/ NYMC | Subhadra Siegel | Cori Abikoff | 40 Sunshine Cottage Road Skyline IN-H09 Valhalla, NY 10595 |
| | University of Rochester Medical Center | Maria Slack | Jeffrey Andolina | 601 Elmwood Avenue, Rochester, NY 14642 |
| Ohio | Cincinnati Children's Hospital Medical Center University of Cincinnati and Bernstein Allergy Group | Jack Bleesing Jonathan Bernstein | Rebecca Marsh | 3333 Burnet Avenue, MLC 11027 Cincinnati, OH 45229-3039 8444 Winton Road, Cincinnati, Ohio 45231 |
| Oregon | Oregon Health & Science University Doernbecher Children's Hospital | | Evan Shereck | 3181 SW Sam Jackson Park Road, CDRC-P Portland, OR 97239 |
| Pennsylvania | | | | |
| | The Children's Hospital of Pennsylvania | Kathleen Sullivan Jennifer Heimall Soma Jyonouchi | | 3615 Civic Center Blvd. Philadelphia, PA 19104 |
| | Children's Hospital of Pittsburgh of UPMC | Hey Jin Chong | Paul Szabolcs | 4401 AOB Suite 3300 Pittsburgh, PA 15232 |

(continued)

**Table 1.2** (continued)

| State | Center | Immunologist | Transplanter | Address |
|---|---|---|---|---|
| Tennessee | St. Jude Children's Research Hospital | Jay Lieberman | Ewelina Mamcarz | 262 Danny Thomas Place, Memphis, TN 38105 |
| Texas | | | | |
| | Texas Children's Hospital/Baylor | Imelda Celine Hanson | William Shearer | 1102 Bates Street, Suite 330 Houston, TX 77030-2399 |
| | Methodist Children's Hospital of South Texas | | Troy C. Quigg | Pediatric Blood and Marrow Transplantation Program Texas Transplant Institute, Methodist Physician Practices, PLLC 4410 Medical Drive, Suite 550 San Antonio, TX 78229 |
| | University of Texas Southwestern Medical Center Dallas | | Victor Aquino | Pediatric Hematology Oncology 5323 Harry Hines Blvd Dallas, TX 75390-9263 |
| Utah | Primary Children's Medical Center University of Utah School of Medicine | David Shyr | Michael Boyer | 100 N. Mario Capecchi Drive Salt Lake City, UT 84113 |
| Washington | Seattle Children's Hospital Fred Hutchinson Cancer Research Center | | Lauri Burroughs Aleksandra Petrovic | 1100 Fairview Avenue North Mailstop D1-100 Seattle, WA 98109 |
| Wisconsin | | | | |
| | Medical College of Wisconsin Children's Hospital of Wisconsin | John M. Routes | Monica Thakar | 8701 Watertown Plank Road Milwaukee, WI 53226 |
| | University of Wisconsin, American Family Children's Hospital | Christine Seroogy | Ken Desantes | 1111 Highland Ave, 4103 WIMR Madison, WI 53705-2275 |
| *CANADA* | | | | |
| Alberta | Alberta Children's Hospital | Nicola Wright | Victor Lewis | 2888 Shaganappi Trail NW Calgary, AB, Canada T3B 6A8 |

**Table 1.2** (continued)

| State | Center | Immunologist | Transplanter | Address |
|---|---|---|---|---|
| British Columbia | Children's & Women's Health Centre of British Columbia | Stuart Turvey | Jeffrey H. Davis | 4480 Oak Street Vancouver BC, Canada V6H 3V4 |
| Manitoba | CancerCare Manitoba | | Geoff Cuvelier | 675 McDermot Avenue Winnipeg, MB, Canada R3E 0V9 |
| Quebec | CHU Sainte-Justine | | Elie Haddad | Centre de Cancérologie Charles-Bruneau, A484 3175, chemin de la Côte-Sainte-Catherine Montréal, QC (Canada) H3T 1C5 |
| Toronto | SickKids/The Hospital for Sick Children | Eyal Grunebaum | | 555 University Avenue Toronto Ontario, Canada M5G 1X8 |
| *UNITED KINGDOM* | | | | |
| Tyne and Wear | The Great North Children's Hospital, Newcastle | | Andrew Gennery | |

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# Part I
# B-Lymphocyte Immunodeficiency

# Chapter 2
# Common Variable Immunodeficiency, Hypogammaglobulinemia, and Specific Antibody Deficiency


**Heather K. Lehman and Parteet Sandhu**

## Introduction

Antibody deficiencies are a group of primary immune deficiencies caused by defects in B-cell development, B-cell activation, or antibody synthesis. They account for more than half of all diagnosed cases of primary immune deficiencies [1, 2]. Immune deficiencies that are considered primarily antibody deficiencies include agammaglobulinemia (X-linked and autosomal recessive), combined variable immunodeficiency (CVID), specific antibody deficiency (SAD), unspecified hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, selective IgA deficiency, and immunoglobulin class-switch defects. While IgG subclass deficiency has also been recognized as an antibody deficiency, there is some controversy regarding its significance in the absence of associated functional defects in specific antibody production [3]. The focus of this chapter will be on the diagnosis and management of CVID, SAD, and unspecified hypogammaglobulinemia.

There is uncertainty regarding the exact prevalence of CVID; however, it is agreed that it affects at least one in 30,000 persons worldwide [2]. The prevalence of SAD differs between different populations; it has been found to be present in 6–23% of children with recurrent infections [4–7]. In adults, SAD was diagnosed in 12–24% of patients with chronic rhinosinusitis and 8% of patients with recurrent pneumonia [8]. Females have a higher prevalence of antibody deficiencies as compared with males [1]. Complicating prevalence estimates of these conditions is the concern that primary

H. K. Lehman (✉)
University of Buffalo Jacobs School of Medicine and Biomedical Sciences, Department of Pediatrics, Division of Allergy and Clinical Immunology, Buffalo, NY, USA
e-mail: hkm@buffalo.edu

P. Sandhu
Division of Allergy and Clinical Immunology, University of Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA



J. A. Bernstein (ed.), *Primary and Secondary Immunodeficiency*,
https://doi.org/10.1007/978-3-030-57157-3_2

immune deficiencies are likely underdiagnosed [1]. Diagnostic delay also occurs, with multiple studies of patients with CVID demonstrating a mean delay ranging from 5 to 9 years between the onset of symptoms and disease diagnosis [9–12].

Classification schema for antibody deficiencies has evolved over time, beginning in 1966 when Rosen and Janeway grouped them by their mode of inheritance [13]. Currently, there has been a focus on classifying CVID subgroups based on B-cell phenotype via flow cytometry [12].

Antibody deficiencies can have infectious and noninfectious disease presentations. While infectious complications are common in all three diseases discussed in this chapter, noninfectious features are common in CVID and are rare in SAD and hypogammaglobulinemia. Overall, these antibody deficiencies have a good prognosis. Morbidity related to infectious complications has decreased drastically after the introduction of immunoglobulin (Ig) replacement [11]. However, noninfectious complications remain a burden and are the major cause of morbidity and mortality in CVID (Table 2.1). These noninfectious symptoms require close monitoring and a multidisciplinary approach.

**Table 2.1** Noninfectious complications of CVID

| |
|---|
| Pulmonary |
| Lymphocytic interstitial pneumonitis |
| Nodular lymphoid hyperplasia |
| Granulomatous lymphocytic interstitial lung disease (GLILD) |
| Dermatologic |
| Psoriasis |
| Vitiligo |
| Lichen planus |
| Alopecia |
| Gastrointestinal |
| Atrophic gastritis |
| Gastric carcinoma |
| Pernicious anemia |
| Autoimmune enteropathy |
| Small bowel villous flattening |
| Primary biliary cirrhosis |
| Primary sclerosing cholangitis |
| Rheumatologic |
| Lupus |
| Rheumatoid arthritis |
| Vasculitis |
| Hematologic |
| Immune thrombocytopenia |
| Hemolytic anemia |
| Autoimmune neutropenia |
| Evan's syndrome |
| Lymphoid |
| Lymphoid hyperplasia |
| Splenomegaly |
| Non-Hodgkin's lymphoma |

## Case Presentation 1

A 2-year-old male with a history of controlled allergic rhinitis and mild intermittent asthma presented to immunology clinic for the evaluation of frequent infections. He had been suffering from frequent upper respiratory infections, including bilateral otitis media, sinusitis, and pharyngitis. His symptoms started when he was 6 months old, and he required antibiotic courses every 2–4 weeks. He had bilateral tympanostomy tubes placed without improvement in symptoms. He did not have a history of pneumonia or skin infections. On physical exam, he was a well-nourished male with bilateral tympanostomy tubes present, pink nasal mucosa without turbinate swelling, and normal lung exam. There was no lymphadenopathy or organomegaly present. His laboratory evaluation showed normal complete blood count (CBC) with differential. He had a low IgA level (<5 mg/dL) but had normal levels of IgG (850 mg/dL) and IgM (29 mg/dL) for his age. His baseline pneumococcal titers (following primary pneumococcal conjugate vaccine series) showed 4 out of 23 serotypes protective (≥1.3 μg/mL), and he had protective titers against tetanus. He received pneumococcal polysaccharide vaccine, and repeat pneumococcal titers 1 month following vaccination were protective against only 8 out of 23 serotypes. A diagnosis of specific antibody deficiency (SAD) was made. He took trimethoprim-sulfamethoxazole prophylaxis for 3 months, and the frequency of infection improved; however, he continued to have a significant burden from infections. Subsequently, he was started on 0.5 g/kg of intravenous immunoglobulin (IVIG) every 4 weeks with control of infections.

### *Clinical Presentation*

Differentiating frequent infections due to common risk factors such as day-care attendance or passive smoke exposure from primary immune deficiency should be based on a detailed history and physical examination. It is crucial to determine the location, timeline, and severity of the infections. On average, a healthy child will have four to six upper respiratory infections per year, and it is typical for children attending day care to have an increased number of infections [14]. Children with intact immune systems typically handle these infections well, either without antibiotics or with rapid resolution of bacterial infections using appropriate antibiotics.

The clinical presentation of hypogammaglobulinemia and specific antibody deficiency consists mostly of increased frequency and severity of sinopulmonary infections as seen in the case above. In contrast, common variable immune deficiency (CVID) is a clinical disease label that encompasses a heterogeneous group of disease presentations. A substantial subset of patients with CVID have noninfectious complications that drive much of the morbidity and mortality related to the diagnosis, while others may have isolated infectious complications without evidence of

immune dysregulation. Patients with hypogammaglobulinemia and specific antibody deficiency will generally present with mild bacterial infections, including sinusitis, bronchitis, and otitis media. Severe infections such as meningitis, sepsis, osteomyelitis, and skin abscesses are rare in SAD. In contrast, patients with CVID are at higher risk of developing pneumonia and invasive infections such as meningitis and sepsis.

Common respiratory organisms implicated in upper and lower respiratory infections in CVID, SAD, and hypogammaglobulinemia include encapsulated bacteria (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*) and atypical bacteria (*Mycoplasma* sp.) [9, 15, 16]. These patients are also at risk for recurrent viral infections with common pathogens such as human rhinovirus [17]. Ten to fifteen percent of patients with CVID may have symptoms consistent with allergic asthma, despite negative specific IgE to common aeroallergens [18].

Patients with antibody deficiencies also have an increased incidence of gastrointestinal infections, sometimes resulting in chronic diarrhea and malabsorption. The most common pathogens include *Giardia* spp., *Campylobacter jejuni*, and *Salmonella* spp. However, *Helicobacter pylori*, *Shigella* spp., *Norovirus*, *and Parechovirus* can also be implicated in these diseases [9]. Rarely, patients with CVID can also have recurrent urinary tract infections with *Ureaplasma* spp. [16, 19].

Physical appearance can provide clues regarding disease syndromes that may be associated with antibody deficiencies. These include Down syndrome, Kabuki syndrome, trichohepatoenteric syndrome, and Wolf-Hirschhorn syndrome [20–23]. Structural abnormalities in the nasal, otic, and respiratory pathways should be assessed on physical exam, as may be underlying causes of recurrent sinusitis, otitis media, or pneumonia. On examination of the lungs, localized inspiratory or expiratory wheezes may reveal bronchial obstruction, while crackles or rhonchi may elucidate lung parenchymal damage. Lymphadenopathy or organomegaly are found in some CVID patients. Imaging should be obtained when the diagnosis of bacterial infection is unclear, when structural abnormalities are suspected, and as baseline evaluation for bronchiectasis or interstitial disease in CVID, but it should be used judiciously as patients with CVID have been found to be radiosensitive [24].

## *Diagnostic Criteria*

CVID is largely a clinical diagnosis, and the diagnostic criteria have varied over time and from different sources. The widely accepted definition of CVID is proposed by the International Consensus Document (ICON). It defines CVID as low IgG (compared to age-specific norms) along with either low IgA or IgM (low IgA preferred), and an impaired vaccine response, with other causes of hypogammaglobulinemia being excluded [25]. Clinical manifestations such as infections or autoimmunity are not required for the diagnosis, though most patients will have at least one characteristic manifestation of CVID at the time of diagnosis.

Low functional antibody response to vaccines has to be present for a patient to be diagnosed with CVID, SAD, or hypogammaglobulinemia. The exception to the rule is when a patient is found to have an extremely low IgG level of <100 to 300 mg/dL in the absence of protein-losing enteropathy. Given such low IgG levels, there is a high likelihood of these patients having a clinically significant antibody deficiency and being at risk of severe invasive infections. It is recommended to start immunoglobulin replacement without waiting for the evaluation of immune response to vaccines when the IgG level is extremely low [26, 27].

Hypogammaglobulinemia diagnoses include both transient hypogammaglobulinemia of infancy (THI) and unspecified hypogammaglobulinemia that can persist through adulthood. Maternal IgG is transferred to infants transplacentally and has a half-life of 21 days [28]. Maternally acquired IgG remains in an infant for the first 3–6 months of their life [29]. In some children, there is delayed antibody production and do not develop a normal humoral immune system until early childhood. Due to this delay, they have recurrent upper respiratory infections in infancy and early childhood. The diagnosis of THI is a diagnosis of exclusion and is made after immunoglobulin levels have normalized. In patients with THI, IgG levels normalize at 27 months of age on average, and all THI patients reach normal levels by 59 months. Those patients that have persistent infections and low immunoglobulins past this age are given alternative diagnoses of CVID or unspecified hypogammaglobulinemia. Generally, patients with THI can produce specific antibodies to antigens; however, some may have a suppressed response until 36–48 months [30]. Hypogammaglobulinemia beyond 60 months of age is termed unspecified hypogammaglobulinemia. For this diagnosis, the patient needs to have increased infections consistent with antibody deficiency, along with low IgG levels (normal IgA and IgM levels) and abnormal vaccine response [31].

A patient with recurrent respiratory infections, normal immunoglobulin levels, and abnormal vaccine response to the unconjugated polysaccharide *Streptococcus pneumoniae* vaccine is diagnosed with SAD. Patients with SAD will have a normal response to protein and protein-conjugated polysaccharide vaccines [27]. SAD is often identified in children and may represent a subtle developmental delay of the humoral immune system. As seen with other humoral immune deficiencies, these patients develop infections sometime after 7–9 months of age, once maternal IgG has been lost by the infant [32]. However, the diagnosis cannot be given to patients younger than two years of age as the immune system is unable to respond to polysaccharide antigens before this age. In a study of pediatric patients with SAD by Wolpert et al., 44% outgrew the immune defect, developing normal antibody responses after an average of 3.1 years [33]. Ruuskanen et al. reported eight of ten children with initial diagnosis of SAD eventually responded to revaccination with pneumococcal vaccine [34]. However, SAD has also been described in adult patients [35].

The presence of low total immunoglobulins but intact functional responses to vaccines is not indicative of a primary immune deficiency, and the immunoglobulin levels should be repeated. These patients should be evaluated for other causes of low immunoglobulins such as medications, AIDS/HIV, protein-losing enteropathy, and

nephrotic syndrome. Stool testing for alpha-1-antitrypsin is used to screen for protein-losing enteropathy, and urinalysis is performed when nephrotic syndrome is suspected. Medications commonly known to lead to hypogammaglobulinemia include, among others, anticonvulsants (carbamazepine, phenytoin, valproic acid), antimalarials, chemotherapeutics (gold salts, thiopurines), and anti-B–cell monoclonal antibodies [25, 36]. RT-PCR should be used to evaluate HIV/AIDS, and referral to hematology should be made when bone marrow failure or B-cell lymphoma are suspected.

## *Laboratory Findings*

Initial evaluation for antibody deficiency includes complete blood count (CBC) with differential to screen for lymphopenia, and serum immunoglobulin IgA, IgM, and IgG concentrations along with measurement of T-cell–dependent and –independent vaccine response. If the patient has lymphopenia on CBC with differential or extremely low total serum immunoglobulins, flow cytometry for lymphocyte subsets should be obtained. As mentioned earlier, to be diagnosed with CVID, patients must present with low IgG concentrations associated with either low IgA or IgM concentration. Patients with nonspecific hypogammaglobulinemia have low IgG concentrations with normal IgA and IgM concentrations, while patients with SAD have normal total immunoglobulin levels. It is critical to compare immunoglobulin concentrations to age-specific norms during evaluation [37]. In the EUROclass trial, 24% of the patients diagnosed with CVID had a low IgA level, and 50% had an undetectable level. Low and undetectable IgM levels were present in 49% and 30% of patients with CVID, respectively [12]. Some patients with CVID may also present with elevated IgM levels, and this may be associated with poorer prognosis. In one series, for every 100 mg/dL increase in IgM concentration, there was 16% and 31% higher risk of developing polyclonal lymphocytic infiltrate and lymphoid malignancy, respectively [38].

## *Vaccine Response*

Vaccines are used to gain insight into the functional capacity of the adaptive immune system. Vaccines containing protein, polysaccharide, and protein-conjugated polysaccharide antigens are used for this evaluation. The humoral immune response to a protein vaccine, such as tetanus or diphtheria, and to a polysaccharide vaccine, such as 23-valent unconjugated pneumococcal polysaccharide vaccine, should be assessed during evaluation for immune deficiency. Protein and protein-conjugated polysaccharide vaccines produce T-cell–dependent antibody responses, while polysaccharide vaccines produce T-cell–independent immune responses, which are weaker and more short-lived.

Protein antigens in protein and protein-conjugated polysaccharide vaccines are presented by dendritic cells to CD4+ T cells via major histocompatibility complex (MHC) class II, leading to helper T-cell activation. These antigens are also recognized by B-cell receptors (BCRs), leading to receptor-mediated endocytosis of the antigen by B cells. These B cells then engage with antigen-specific helper T cells via CD40:CD40L interactions. This T:B cell interaction leads to isotype switching, affinity maturation, and production of memory B cells. Polysaccharides, glycolipids, and nucleic acids cannot be presented to T cells via MHC molecules; hence, T-cell help is not engaged when developing an antibody response to these antigens. These non-protein antigens are multivalent and instead lead to B-cell activation through BCR crosslinking. B-cell activation can be further enhanced by complement proteins and toll-like receptors in this T-cell–independent antibody response, there are low levels of isotype switching: no affinity maturation and limited memory B-cell production [39].

There are two types of pneumococcal vaccines: 23-valent unconjugated pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccine (PCV13). PPV23 formulation contains 23 serotypes of pneumococcal polysaccharide capsule: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. The PCV13 vaccine includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, and 19F. Conventionally, unconjugated polysaccharide vaccines such as PPV23 are reserved for ages 2 and older [40]. However, some data suggest that infants over the age of 6 months can produce an adequate response to polysaccharide antigens [41, 42].

Specific antibody responses are measured 4–8 weeks following vaccination. When using PPV23, specific antibodies to at least six serotypes only present in PPV23 (not common to PCV13) should be checked. There have been controversies surrounding what constitutes an adequate response to PPV23 vaccination. An adequate serotype-specific titer to prevent invasive pneumococcal disease following PPV is considered to be ≥1.3 μg/mL [27]. Most immunocompetent patients will have a twofold increase in antibody titers from baseline in response to vaccination. However, the higher the pre-vaccination titers, the lesser the magnitude of increase after vaccination. Expert opinion suggests that a normal response to PPV23 for children 2–5 years old is conversion of 50% or more serotypes with at least a twofold increase in the titers. For patients ages 6–65 years, a normal response is considered to be conversion of at least 70% of serotypes with at least a twofold increase in the titers [27]. If normal response is not achieved, repeat doses of PPV23 vaccine in close succession are not recommended as it can lead to a diminished response to the vaccine [27].

SAD can be classified into phenotypes based on degree of response to the unconjugated PPV23 vaccine. For patients less than 6 years of age, a response of ≤2 protective antibody titers is considered to be a severe phenotype, <50% of serotypes protective is considered a moderate phenotype, and failure of a twofold increase in 50% of serotypes is considered mild phenotype. For patients over 6 years of age, a response of ≤2 protective titers is considered severe, <70% of serotypes protective is considered moderate, and failure of a twofold increase in 70% of serotypes is considered mild. For all patients, loss of response within 6 months following

vaccination is considered to be a memory-deficient phenotype of specific antibody deficiency [27].

Other vaccines can also be used in the assessment of humoral immune deficiency in place of pneumococcal and tetanus vaccines. *Haemophilus influenzae* type b conjugate, meningococcal conjugate, pneumococcal conjugate, and rabies vaccines can be used to assess T-cell–dependent responses. The coupling of saccharides to proteins converts the polysaccharides to T-cell–dependent antigens, which are capable of eliciting a more robust B-cell immune response. In contrast, unconjugated meningococcal polysaccharide vaccine can be used to assess T-cell–independent responses. Alternatively, isohemagglutinin titer concentrations can also be used to check for IgG and IgM polysaccharide-specific antibody responses [43]. It is also possible to measure antibody function in an opsonophagocytic assay as wells as antibody avidity; however, these tests are not commercially available [44, 45].

## Case Presentation 2

A 6-year-old female with a history of asthma and chronic rhinitis developed chronic vomiting, iron deficiency anemia, and hypoalbuminemia. Endoscopy and colonoscopy demonstrated nodularity in the gastric bulb, gastric antrum, esophagus, ileum, and colon. Pathology was significant for multiple lymphoid nodules in the GI tract and eosinophils in the distal esophagus and stomach. She had an infectious history of frequent otitis media, bronchitis, sinusitis, and pneumonia, but never exhibited severe enough infections that warranted hospitalization.

Her CBC with differential was significant only for microcytic anemia. Immunoglobulin levels were IgG 239 (nl 591–1597), IgA 22.6 (nl 52–329), and IgM 38 (nl 28–115). She had protective antibody responses against rubella and tetanus but was not protected against measles, despite being up-to-date on vaccinations. Her baseline pneumococcal titers were 0/23 protective, and her titers 1-month post-PPV23 were again 0/23 protective. Flow cytometry for lymphocyte subsets showed normal numbers of CD4, CD8, CD3, CD19, and NK cells, but B-cell phenotyping revealed low switched memory B cells (1.8%) (Table 2.2). She was diagnosed with CVID and was started on IVIG 0.6 g/kg every 4 weeks, with the improvement of

**Table 2.2** B-cell subpopulation surface markers

| B-Cell Subpopulation | B-Cell Surface Markers |
|---|---|
| Mature naïve B cell | CD27− |
| Activated B cell | $CD21^{lo}CD38^{lo}$ |
| Marginal zone B cell | CD27+ IgM+ IgD+ |
| Switched memory B cell | CD27+ IgG+ IgM− IgD− |
| Transitional B cell | $CD38^{hi}IgM^{hi}$ |
| Plasmablast | $CD38^{hi}IgM-$ |
| Plasma cell | CD27+, CD138+ |

Data from [12, 39]