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Primary Immunodeficiency: New Insights and Practical Clinical Approaches

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This issue of the *Journal of Allergy and Clinical Immunology: In Practice* presents a compilation of articles that address current topics in primary immune deficiency, concentrating on practical aspects of diagnosis and management. The articles found here start with reviews of 2 of the more prevalent medical complications of primary immune deficiency: autoimmunity by Walter et al¹ and lung disease by Schussler et al.² In both articles, the central themes concern how immune dysregulation, a common aspect of immune deficiency, leads to additional organ dysfunction, the mechanisms that underlie these events, and how understanding these processes has led to improved treatment and more targeted therapies. In a third clinical management review, de la Morena³ describe her recent compilation of data describing the overall phenotypes found in a large cohort of subjects with the hyper-IgM syndrome, concentrating on the X-linked version of this immune defect. Few large series describing the clinical course of this rare immune deficiency have appeared, making this a valuable and timely update. Looking at another largely X-linked disease, Thomsen et al⁴ provide a comprehensive review of current best practices in the management of chronic granulomatous disease from an expert team, including both standard prophylactic antibiotic regimens and management of the more complex inflammatory complications that occur in these patients.

Since the introduction of adequate immune globulin replacement and standard use of killed polio vaccine, the incidence of central nervous system enteroviral infections in X-linked agammaglobulinemia has largely disappeared; most likely, the great majority of practicing clinical immunologists have never seen a case. However, Bearden et al⁵ remind us that this viral infection has actually not disappeared, and continued vigilance for the manifestations of enteroviral infections is still required. In a somewhat similar vein, Gernez et al⁶ in a Chief Complaint article describe a young immigrant man with a very delayed diagnosis of hyper-IgE syndrome who presented at an allergy clinic with severe hemoptysis and eventually required pneumonectomy. Although some of the patients with immune defects described in this issue are children, Rosenberg et al⁷ remind us that immune deficiencies are not confined to pediatric patients; in fact, as they outline, taking all subjects as a whole, there are more adults with immune defects than infants and children.

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Providing guidance for evaluating immune function, Sobh and Bonilla⁸ review the current use of vaccines and interpretation of laboratory values, essential for estimating humoral immune function before prescribing immune globulin replacement. Continuing the theme of therapy, Wasserman⁹ has contributed a review of the “nuts and bolts” of immune globulin replacement. As most allergist/immunologists are aware, there are a number of new products now available with different formulations, solution concentrations, and routes of administration. Wasserman disentangles this information to provide practical advice for physicians who do not prescribe immunoglobulin on an everyday basis, but who want to pick the most appropriate product and dosing regimen when the occasion arises.

This issue also contains 4 original articles, 2 of these on common variable immune deficiency (CVID) and 2 on rare combined immune defects. For CVID, Bertinchamp et al¹⁰ apply the 2014 European Society for Immune Deficiency definition of CVID to a group of 521 subjects with CVID in the French Registry. About 20 patients in their cohort had severe T-cell defects (low T-cell numbers and opportunistic infections); with these distinct differences, they prefer the term late-onset combined immunodeficiency rather than CVID for these subjects. In a second article on CVID, Quinti et al¹¹ present a 32-item questionnaire to measure specific health-related quality of life for adults with CVID, which they then validated on 118 subjects, identifying main indicators of reduced quality of life in these subjects. The third original article concerns the diagnosis of methylenetetrahydrofolate dehydrogenase deficiency made in 2 brothers who had lymphopenia, opportunistic and bacterial infections, and macrocytosis. Ramakrishnan et al¹² report that with a mixed picture of immune deficiency, but no molecular diagnosis, the boys were managed on immune globulin and antibiotic treatment for some time. However, with the application of whole-exome sequencing, they were found to have a missense methylenetetrahydrofolate dehydrogenase mutation inherited from one parent and a large deletion from the other, which in combination led to the loss of gene function. As for other infants and children with this novel (and very rare) form of nutritionally-based severe combined immunodeficiency (SCID), the immune defect of these children could be cured by folinic acid, with no need for either immune globulin or prophylactic antibiotics. As the final article in this issue, Freeman et al¹³ report a successful haploidentical related donor hematopoietic stem cell transplant from the patient's brother in a very sick young woman with DOCK8 deficiency, treated posttransplant with high-dose cyclophosphamide to ablate alloreactive donor T cells. With now 100% donor chimerism, her clinical manifestations of DOCK8 deficiency stabilized, improved, or resolved within 2 months of transplant. The use of HLA-haploidentical related donors with later cyclophosphamide makes many more transplants available and appears to successfully eliminate graft versus host disease. This strategy will in all likelihood be used in many more subjects with primary immune deficiency.

This issue delves into a number of current facets about the evaluation and care of patients with both well-known and newly described primary immune defects. The central themes of this issue include using larger cohorts to understand the clinical phenotypes and medical complications of these patients, and the increasing need for genetic testing to guide both diagnosis and decision making.

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References

1. Walter JE, Farmer JR, Foldvari Z, Torgerson TR, Cooper MA. Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies. *J Allergy Clin Immunol Pract.* 2016; 4:1089–100. [PubMed: 27836058]
2. Schussler E, Beasley MB, Maglione PJ. Lung disease in primary antibody deficiencies. *J Allergy Clin Immunol Pract.* 2016; 4:1039–52. [PubMed: 27836055]
3. de la Morena MT. Clinical phenotypes of hyper IgM syndromes. *J Allergy Clin Immunol Pract.* 2016; 4:1023–36. [PubMed: 27836054]
4. Thomsen IP, Smith MA, Holland SM, Creech CB. A comprehensive approach to the management of children and adults with chronic granulomatous disease. *J Allergy Clin Immunol Pract.* 2016; 4:1082–8. [PubMed: 27178966]
5. Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-linked agammaglobulinemia: update on epidemiology and therapy. *J Allergy Clin Immunol Pract.* 2016; 4:1059–65. [PubMed: 26883540]
6. Gernez Y, Tsuang A, Smith TD, Shahjehan K, Hui Y, Maglione PJ, et al. Hemoptysis in a patient with elevated immunoglobulin E. *J Allergy Clin Immunol Pract.* 2016; 4:1054–8. [PubMed: 27693026]
7. Rosenberg E, Dent PB, Denburg JA. Primary immune deficiencies in the adult: a previously underrecognized common condition. *J Allergy Clin Immunol Pract.* 2016; 4:1101–7. [PubMed: 27836059]
8. Sobh A, Bonilla FA. Vaccination in primary immunodeficiency disorders. *J Allergy Clin Immunol Pract.* 2016; 4:1066–75. [PubMed: 27836056]
9. Wasserman RL. The nuts and bolts of immunoglobulin treatment for antibody deficiency. *J Allergy Clin Immunol Pract.* 2016; 4:1076–81. [PubMed: 27836057]
10. Bertinchamp R, Gérard L, Boutboul D, Malphettes M, Fieschi C, Oskenhendler E, et al. Exclusion of patients with a severe T-cell defect improves the definition of common variable immunodeficiency. *J Allergy Clin Immunol Pract.* 2016; 4:1147–57. [PubMed: 27522107]
11. Quinti I, Pulvirenti F, Giannantoni P, Hajjar J, Canter DL, Milito C, et al. Development and initial validation of a questionnaire to measure health-related quality of life of adults with common variable immune deficiency: the CVID_QoL Questionnaire. *J Allergy Clin Immunol Pract.* 2016; 4:1169–79. [PubMed: 27665385]
12. Ramakrishnan KA, Pengelly RJ, Gao Y, Morgan M, Patel SV, Davies EG, et al. Precision molecular diagnosis defines specific therapy in combined immunodeficiency with megaloblastic anemia secondary to MTHFD1 deficiency. *J Allergy Clin Immunol Pract.* 2016; 4:1160–6. [PubMed: 27707659]
13. Freeman AF, Shah NN, Parta M, Su HC, Brofferio A, Gradus-Pizlo I, et al. Haploidentical related donor hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for DOCK8 deficiency. *J Allergy Clin Immunol Pract.* 2016; 4:1239–42. [PubMed: 27641484]