

Influenza immunization in patients with common variable immunodeficiency



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Influenza virus infections are associated with significant morbidity and mortality, particularly in high-risk populations, such as immunocompromised patients, the elderly, patients with cardiopulmonary conditions, and patients with primary immunodeficiency diseases (PIDDs). In all these patients, immunization with inactivated influenza virus vaccines is recommended.¹ In patients with PIDDs treated with IgG replacement therapy, the childhood immunization series is not indicated because their antibody response to immunization might be impaired and antibodies to vaccine pathogens are expected to be well represented in IgG products. Inactivated influenza virus vaccines are an exception to this rule and are indicated in patients whose cellular immunity is preserved, including all predominant antibody deficiency syndromes.²⁻⁴ This indication for yearly influenza immunization is justified because human IgG preparations might not contain antibodies to the latest variants of the influenza virus. Furthermore, influenza vaccines can trigger cellular immunity, generating influenza-specific CD4 and CD8 T lymphocytes in patients unable to generate anti-influenza IgG antibodies.

In adults the predominant antibody deficiency is common variable immunodeficiency (CVID). Although yearly influenza immunization is generally recommended, many assumptions about the vaccine response are not well documented; therefore further studies are important. In this issue of the *Journal*, Gardulf et al⁵ attempted to identify disease markers that would predict a humoral immune response to influenza vaccination in patients with CVID. Forty-eight patients with CVID (29 female and 19 male patients) were vaccinated with 2 doses of the A(H1N1) influenza vaccine Pandemrix (GlaxoSmithKline, Research Triangle Park, NC) administered 1 month apart. Eight (16.7%) of the patients had an antibody response based on titer increases greater than preimmunization levels. In the relatively small percentage of patients who had antibodies, this response was associated with higher serum IgG₁ and lower serum IgM. Response was also associated with a higher level of

plasmablasts and lower CD21^{low} B-cell counts compatible with a specific EUROclass and a post-germinal center B-cell pattern. However, not all responders were in this EUROclass, and not all patients in this class had antibodies. Clinically, the majority of responders had a history of past or present enteropathies. On the other hand, bronchiectasis and autoimmune cytopenias were found exclusively among antibody nonresponders. Further details of responders and nonresponders are presented in the article, but none of these predictors would allow a comprehensive selection of who should and should not be immunized because the majority of all patients did not mount an antibody response.

Cytokine production by cultured cells stimulated with PHA revealed that antibody nonresponders secreted more IL-12 than responders, suggesting stronger T_H1 production in this group. Lower secretion of IFN- γ , IL-2, IL-5, and IL-10 was observed in nonresponders. However, for each of these cytokines, there was a large overlap of values in both responders and nonresponders. The significance of these findings in terms of antibody- and cell-mediated immunity to influenza could not be determined from these results.

All patients in this study were treated with weekly subcutaneous IgG infusions. Different brands were used, but each patient received the same brand and batch of immunoglobulins at least 3 months before and until the last blood sampling. Of note, monogenic forms of PIDDs with a CVID phenotype were excluded from the study. Cellular immunity to influenza antigens was not assessed. During the study period and the 1-year follow-up period, no influenza-like symptoms and/or negative vaccine side effects other than local reactions at the injection site were reported. Exposure of study subjects to subjects affected by influenza was not documented.

Similar results had been reported earlier in a smaller group of patients with CVID.⁶ The study by Gardulf et al⁵ confirms that testing the antibody response in patients with CVID and other predominant antibody deficiency syndromes will often produce negative results. Cell-mediated immunity has been measured in a small group of patients with a much higher response rate, with development of cellular immunity in 7 of 8 patients with CVID and 6 of 8 control subjects.⁷ Therefore studies of antibody responses only, including the study by Gardulf et al,⁵ do not offer information that would support evidence-based recommendations for the use of the influenza vaccine. Similarly, no recommendations can be made regarding immunization of CVID-like patients with different known molecular abnormalities.⁸

Furthermore, no evidence for the superiority of 2 doses given 1 month apart instead of 1 dose, as presently recommended,⁴ is presented in the study by Gardulf et al.⁵ The number of vaccine doses given on a yearly basis needs to be evaluated considering limited evidence that annual influenza vaccination might hamper the development of virus-specific CD8 T-cell responses.⁹

Patients with CVID in whom a disease causing genetic abnormality was already identified were excluded from the study

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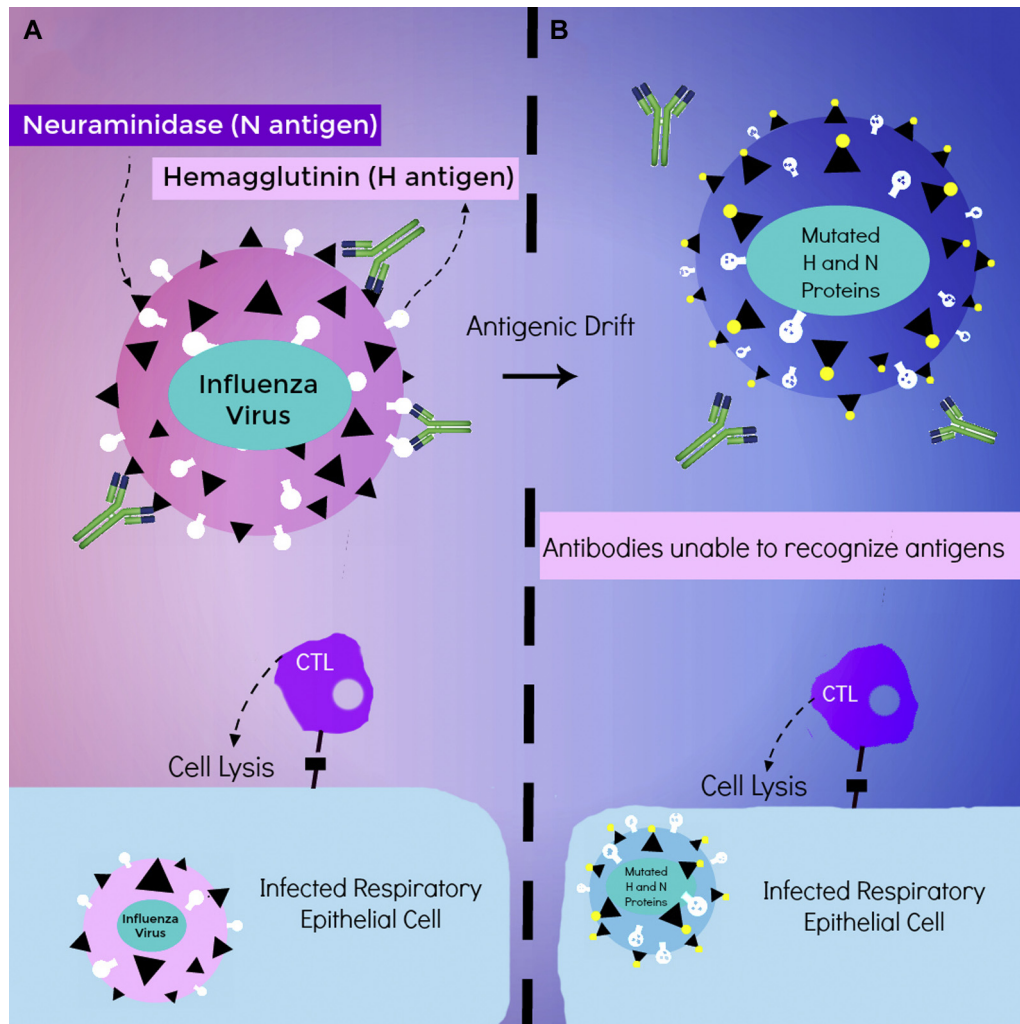


FIG 1. The adaptive immune response to influenza. Antibodies against influenza surface antigens represent those produced by a subject after immunization/natural infection or antibodies passively transferred through IgG replacement in a patient with CVID. **A**, Antibodies (especially those against the H antigens) aid in the prevention of infection, whereas cytotoxic T lymphocytes (CTLs) mediate lysis of infected host cells. **B**, On viral antigenic drift, although antibodies might no longer recognize surface proteins, CTLs continue to play a role by recognizing conserved viral epitopes expressed by infected cells. Image art by Janin Pierce, RN.

by Gardulf et al.⁵ This important variable that can influence the ability to develop specific antibody-mediated or cellular immunity against the influenza virus was not analyzed. Because it is predicted that more and more patients with CVID will be moved from the large CVID group into various forms of molecular abnormalities, resulting in a CVID-like immunologic phenotype, identifying influenza-associated molecular pathways of immunity related to the genetic defect will be important in the future.

Gardulf et al.⁵ indirectly define aspects of the influenza immunization programs that need further study, both in the general population and in patients with primary and secondary immunodeficiencies. For instance, are the antibodies that are present in human gammaglobulin preparations¹⁰ contributing to some immunity against cross-reactive influenza antigens? Are anti-H1N1 IgG antibodies measured with methods assessing weight-by-volume concentrations a reliable measure of immunity because these assays do not assess the functional ability to inhibit viral infection? Does immunization induce a broader spectrum of

immunity against different H and N antigens than the highly specific antibody response (Fig 1)?

Most importantly, how can the effect of immunization be assessed when little is known about the frequency and severity of influenza infections in unimmunized patients with PIDDs receiving IgG replacement therapy?

The specificity and cross-reactivity of both antibody- and cell-mediated immunity against antigenic components that might be present in different influenza strains and the possibility that cellular immunity might have a broader antigenic spectrum are not known. The fact that most years influenza infections are caused by several cocirculating influenza strains and the need to select one of the different available inactivated vaccines have not been addressed. The Centers for Disease Control and Prevention, World Health Organization, and ultimately US Food and Drug Administration select strains for vaccines each year. From the point of view of the immune response in patients with different forms of immunodeficiencies, there is no information to suggest that the single or repeated use of the trivalent versus

quadrivalent vaccines or the high-dose formulation recommended for senior citizens would be preferable. Further studies will require large numbers of patients, prolonged follow-up, basic studies of cell-mediated immunity to influenza infections, and careful monitoring of exposure and influenza infection data.

In summary, annual influenza vaccination in patients is recommended for patients with all immunodeficiencies that do not have or have only a mild deficiency of cellular immunity. Household contacts of these patients should also be immunized. Ideally, the immunology community should set up a reporting system for influenza infections in patients with PIDDs, noting the exact clinical and molecular abnormality present, the IgG replacement therapy, the severity of influenza infections, the strain causing it, and the recent influenza immunization history. Such clinical information, combined with laboratory evaluation of the patient's antibody and cellular response to the specific strain of influenza, would provide a powerful tool for further research and improved clinical practice.

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