The Immune System is designed to specifically and directly recognize foreign proteins such as the diphtheria toxoid (DT) protein in the DT vaccine. Through this direct recognition process, signals can be generated that activate B lymphocytes, which are capable of making anti-DT antibodies. Polysaccharides (carbohydrate or sugar polymers) are commonly found on the surfaces of microorganisms, and are important for immune recognition and targeting of the microorganism. These become the target of antibodies, in part due to a bystander effect: The immune system is responding to a protein from the microorganism, and nearby B lymphocytes capable of making antibodies against a polysaccharide from the same microorganism get stimulated in the mix of lymphocytes in this close proximity. Due to the inherent inefficiency, it may take some time, occasionally years, before adequate anti-polysaccharide antibodies for protection from infection can be made. And, it is known that production of anti-polysaccharide antibodies is critical for the overall prevention and control of bacterial infections; this is one reason why infants and children are so susceptible to streptococcal ear infections.

Streptococcal organisms, also known as pneumococcus, cause many of the severe infections, especially in younger children and in those with antibody deficiencies. To help deal with this, vaccines were developed that attach (i.e., conjugate) the polysaccharide of importance to the DT protein. This results in the immune system undergoing the expected normal response to the DT protein, but it “tricks” the immune system into responding to the polysaccharide with formation of anti-polysaccharide antibodies. These so-called conjugated vaccines are Prevnar (pneumococcal 7-serotype conjugate vaccine to diphtheria CRM197 protein) and the newer Prevnar13 (pneumococcal 13-serotype conjugate vaccine to diphtheria CRM197 protein).

Here is where a dilemma occurs. If anti-polysaccharide antibodies can be detected after immunization with Prevnar13, is this the result of the inherent ability of the patient to respond to polysaccharide antigens, or is this solely an immunologic trickery effect from response with the DT protein?

To make the diagnosis of an antibody deficiency, it is common to perform a pre-/post-immunization study. Response to the non-conjugated pneumococcal vaccine (e.g., Pneumovax23) is thought to provide the most relevant information regarding making the diagnosis of an antibody deficiency. To perform the assay, blood is obtained (for pre-immunization antibody measurement), the vaccine is given, and after four weeks blood is again obtained (for post-immunization antibody measurement). The change in the pre- to post-immunization antibody levels indicates the responsiveness of the immune system. Currently, most immunologists believe that children up to approximately 6 years of age should have half of the anti-pneumococcal antibody levels in the protective range (>1.3 μg/mL) in the post-immunization specimen, and that the antibody levels should have increased more than three times, except for values that were already very high. For those older than 6 years of age, there should be a similar response in 70 percent of the antibodies tested.

Many available assays from commercial laboratories check for 12 to 14 of the 23 specific pneumococcal serotype antibodies from the non-conjugated vaccine. Before the introduction of the Prevnar with seven serotypes, this was fine, since there would be 12 to 14 non-conjugated serotypes to evaluate. After the 7-valent Prevnar, there could still be five to seven serotypes to evaluate. And, many immunologists divided the results in the 1) conjugated and 2) non-conjugated anti-polysaccharide antibody responses. Patients with normal antibody immunity would respond well in both categories. Younger children with otherwise normal immunity may have a somewhat better response in the conjugated category. Patients with an evolving antibody deficiency, that is, one that has not completely presented with all the disease features, may have a reasonable response to the conjugated polysaccharide antigens but poorer responses with the non-conjugated ones. And, patients with a more completely defined or severe antibody deficiency may have poor antibody responses to both conjugated and non-conjugated antigens. Therefore, the predicament is that younger children and those with evolving antibody deficiency may have relatively normal responses with conjugated vaccine.

Now, Prevnar13 is being used. This is wonderful for the
prevention of infections, but it results in more quandaries when considering the evaluation of patients suspected of having antibody deficiencies. If only 12 to 14 pneumococcal serotypes are evaluated, the person with evolving antibody deficiency who has previously received Prevnar13 may seem to have a reasonably good response, since most of the antigens present in Prevnar13 are present in the assay. Therefore, one is not truly assaying the non-conjugated responsiveness, yet the non-conjugated anti-polysaccharide antibody response is likely a better indicator of immune “normalcy” or, alternatively, antibody deficiency. The general solution to this dilemma is to assay for all 23 pneumococcal serotypes from the non-conjugated pneumococcal vaccine. There will then be the possibility of antibodies to 13 serotypes, which may have produced as a result of Prevnar13 vaccination, and antibodies to 10 non-conjugated serotypes. Then a better assessment of the situation can be made. The sticky question that arises from the definition of antibody deficiency is: Does one consider only the 10 non-conjugated for anti-polysaccharide antibody production or all 23? Since the goal is to determine the response to non-conjugated polysaccharide antigens, it makes the most sense to consider the 10 non-conjugated serotypes separately. Yet, if the 13 conjugated antigens produce poor responses, this is suggestive of a more severe antibody deficiency.

We will continue this discussion in the next issue.

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Editor’s Note: This Immunology 101 column, introduced in the April-May 2010 issue of IG Living, is intended to be a basic course in immunology.

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