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MINIREVIEW

Pneumococcal Vaccine: A Tool for the Evaluation of the B-Cell Function of the Immune System (41742)

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The pneumococcal vaccine has been developed to prevent infections caused by the most common of the pneumococcal serotypes. This review will describe the pneumococcal vaccine, its composition, recommended use, and current knowledge of the protective levels of antibody. In addition to the protective effects of the vaccine, however, a new use is becoming important. This new use of the vaccine takes advantage of the fact that bacterial polysaccharide antigens, in general, produce antibody which maintain a stable concentration over a long period of time. Since the half-life of immunoglobulins at best is 3 weeks, a constant level of antibody must result in continued biosynthesis at a rate equivalent to the loss incurred by catabolism. Any decrease in B-cell function which upsets the steady state would result in a lower level of antibody and/or a poorer response to immunization. It is this use of the pneumococcal vaccine, the measurement of antibody levels after immunization, which I term a tool for the evaluation of the B-cell function of the immune system.

Composition of the 23-Valent Vaccine. Although pneumococci are exquisitly sensitive to chemotherapeutic and antibiotic agents, the work of Dr. Robert Austrian (1–5) has conclusively demonstrated that there is a significant mortality associated with pneumococcal infections despite prompt and adequate treatment. The inescapable conclusion therefore is the need for prevention of infection, hence a vaccine. That a vaccine is efficacious has been shown by the work of McLeod *et al.* (6) many years ago. More recent studies of the epidemiology of pneumococcal infections (2, 7–19) indicated that a limited number of pneumococci were responsible for the vast majority of infections. The first commercially available vaccines were discontinued with the advent of chemotherapeutic and antimicrobiol agents but recently a 14-valent vaccine was licensed (20). This vaccine was capable of preventing 80% of pneumococcal infections (4). A new formulation of the vaccine, with 23 serotypes, will be available shortly which should be capable of preventing 90% of pneumococcal infections (21). This new vaccine will contain serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22, 23F, and 33F.

Two major problems in developing the multivalent pneumococcal vaccine were solved by use of a radioimmunoassay (RIA) procedure (22, 23). These two problems concern dosage and antigenic competition or compatibility. There was no practical way in which the doseage of each component could be scientifically arrived at without a rapid sensitive and specific method to measure the antibody response in a series of volunteers given monovalent components over a dose range from 5 to 1000 μg (4). The second problem of compatibility or whether all of the components required for a single antigenic preparation could be given without reducing the immune response to each of the components as measured in the dose–response determination, was also solved by use of the RIA. These questions were answered by using 50 μg of each of the 14 components a dosage and combination which were adequate to produce antibody levels not significantly different from when each of the components were given separately (4). When the number of serotypes were increased to 23 the dosage per type was reevaluated and reduced to 25 μg/component (21), a dosage which was still on the plateau region of the dose–response curve but allowed for a reduction in the total antigenic load.

Antibody Response in High-Risk Individuals. The pneumococcal vaccine released in 1978 consisting of 14 serotypes has been used to prevent pneumococcal infection in high-risk groups. These consist of sickle cell disease (24–27, 76), nephrotic syndrome (28–30), sys-

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temic lupus erythematosus (SLE) (31–32), Hodgkin's disease (33–36), COPD (37), multiple myeloma (38), uremia and diabetes (39–42), bone marrow transplantation (43–44), Wiskott–Aldrich Syndrome (45), Sjogren's syndrome (46), kidney transplant (47–48), hemodialysis (49–50), elderly (51–53) and infants (54–57), and splenectomy (58–63). These results indicated that the extent of antibody response depended upon the clinical syndrome, degree and kind of treatment, and age of the patient. Some of the early findings were indeed surprising. It has always been assumed from the work of Heidelberger and others (64) that antibody to bacterial polysaccharide antigens in humans led to a long lasting response. While this is true in the adult, in the infant immunization with type 3 pneumococcal polysaccharide resulted in a sharp rise in antibody levels, above the 200 ng of antibody N/ml level, but fell rapidly such that within 6 months the levels have essentially returned to that of an unimmunized infant (54–57). A second administration of vaccine at 12 months of age resulted in a second burst of antibody production but this was not an anemestic response since age-matched infants receiving the same amount of vaccine for the first time responded equally well. Once again, however, the antibody levels fell so that at 2 years of age the infants again had antibody levels essentially as high as unimmunized age matched children. Immunization at 2 years of age demonstrated an immune response in all groups tested which was uninfluenced either positively or negatively by previous exposure to immunogen (54). These results were important for several reasons, first, it allowed interpretation of field trial (65–67) data which were obtained for 2 years following immunization, only the first 6 months the infants had the benefit of increased antibody titers. Secondly, these data proved that infants below the age of 2 years could be immunized (27) receiving the benefit of increased titers while not being exposed to condition conducive for immunologic tolerance. In addition to the results of type 3 pneumococcal antigen it was observed that there was a very distinct order to the immunogenicity of the various components in the multivalent vaccine. Type 6A was among the least immunogenic components in the vaccine and infants 2 years of age or less rarely responded to type 6A. The factors responsible for the maturation of the immune system which allows for type 3 to be the most immunogenic and type 6A the least have not been clearly defined. The precise age at which the immune response to bacterial polysaccharide antigens in the human reaches full maturity is not known.

Protective Levels of Antibody. A major question which has been addressed over a period of years relates to how much antibody is required for protection (56–57, 68–71). It is well known that antibody itself will not kill pneumococci. An adequate functioning phagocytic cell aided greatly by the complement system is required to kill invading pneumococci. However, rarely are the white cells so effete and the complement system so depleted as to make the system dependent on these two factors. That is to say in almost all clinical conditions antibody is the limiting factor. If one can define the level of antibody which is required to kill it would greatly aid the evaluation of vaccines for each clinical syndrome. One can then assess whether individuals respond to the vaccine with a protective level and how long they maintain their level before revaccination. By four different methods of evaluation, our current working estimate of the protective level in the pneumococcal system is 200 to 300 ng antibody (16) N/ml. The lower figure of 200 was estimated from work done in collaboration with Sell, Wright, and associates (55–57). These studies were described above.

A second method of evaluating a protective level is the measurement of antibody in the premorbid sera of individuals who develop a pneumococcal bacteremia and whose etiologic agent is known (70). To date, 33 such sera have been analyzed, 32 of which have antibody levels below 300 ng Ab N/ml.

A third method of estimating a protective level of antibody has been used recently. This involves a study of the correlation between opsonic activity, as measured by the reduction of nitroblue tetrazolium, and RIA. A good correlation was obtained with this procedure (71). In children, colonization by pneumococci resulted in a rise in antibody titer by both opsonic measurements and RIA. Sera of young adolescents showed detectable opsonic activity when antibody measurements by RIA

gave values between 200 and 300 ng Ab N/ml. It is assumed that once antibody attains a level in serum where it gives detectable opsonic activity, it will be minimally protective.

The fourth method of estimating a protective level is based on the assumption that healthy adults who, as a group, do not acquire pneumococcal infections, have minimal protective levels of antibody. The pooled human sera analyzed for reference have a geometric mean titer of 216 ng Ab for 12 of the 14 serotypes, and 233 ng Ab for the 14 serotypes presently available in the commercially available vaccine.

If one assumes that 200–300 ng of antibody N/ml is indeed the protective level it is required to demonstrate that the binding of total antibody by RIA to give the 200–300 ng antibody N/ml is composed of equally effective antibody molecules. Many experiments have been performed along these lines. A correlation between RIA and mouse protection was performed by serotypes 1, 2, and 8 (23). This experiment consisted of passively immunizing mice with human antibody assayed by total binding (RIA) and challenging with virulent pneumococci. There was a good coefficient of correlation between the two methods. However, these experiments were conducted using normal healthy young adults as volunteers. A second series of investigations dealt with the question of the difference of protective power of the various isotypes in serum. Separation of IgM from IgG on Sephadex G 200 (72) and passive immunization into mice followed by lethal challenge indicated that IgM and IgG had essentially the same protective ability when standardized by total binding (RIA). Additional studies relating total binding values as measured by RIA to opsonic activity have indicated a good agreement for most types (48, 60, 71, 73, 74). An additional question addressed was whether values measured by RIA of antibody raised after immunization were equally protective if the host had been treated with chemotherapeutic reagents, radiation, suffered from nephrotic syndrome, COPD, was young or old. These determinations carried out by Havas, Katz, and Landesman indicate that there was little or no difference in the ability of antibody as measured by RIA to protect in passive transfer mouse protection assays. These results indicate that measurement by RIA can be used in determining minimal protective levels. One additional aspect has been investigated. Does the high preimmunization levels found in patients with chronic obstructive pulmonary disease (COPD), (37) presumably following repeated infections of nasopharyngeally carried microorganisms, have protective ability equal to that of postimmunization antibody. Work presently in progress by Katz and Davis indicate that this appears indeed to be the case.

Does antibody made by the elderly, as measured by RIA, protect against infection as measured by mouse protection assays? This question has been addressed by Katz and again the answer is that it protects equally (77). These questions all directed at whether RIA can determine a protective level of antibody have been answered affirmatively.

Evaluation of B-Cell Function. In work with Siber (33) and Minor (34) it was seen that the longer the period of time after treatment patients with Hodgkin's disease responded better to the pneumococcal vaccine. Similarly, the more intense the treatment with chemotherapy and/or radiation the poorer the response to the pneumococcal vaccine. Since untreated Hodgkin's patients respond as well as normal healthy adults it is apparent that the treatment impairs the immunocompetent cells ability to respond to the immunogen. The quantitative measure of the response to the vaccine compared to healthy controls was a measure of the recovery of the B-cell function of the immune system. This observation has been followed up in other clinical syndromes such as multiple myeloma (38, 75) and immunodeficiency diseases (45). Having standardized the radioimmunoassay with sera from normal

TABLE I. IMMUNE RESPONSE IN THE INSTITUTIONALIZED ELDERLY[a]

Subject	Pre	Post
G.H.2	22[b]	94
G.H.1	16	197
A.F.	47	751
M.C.	434	1797
R.D.	161	2969
D.D.	753	3515

[a] Unpublished results in collaboration with Dr. David Bentley.

[b] Geometric mean of 12 serotypes of ng Ab N/ml.

TABLE II. IMMUNE RESPONSE IN THE NONINSTITUTIONALIZED ELDERLY[a]

	Elderly	Controls[b]
Pre	167	310
Post	1263	1950
Ratio	7.5	6.3
Percentage responding with twofold or greater	76%	97%

[a] Unpublished results in collaboration with Dr. Maurice F. Mufson and Dr. George Pankey. These data refer to pneumococcal type 3 antibody.

[b] Young healthy controls immunized with 23-valent PNU-IMUNE.

healthy adults one can evaluate the B-cell function of the immune system. This is particularly apparent in results observed in the response of the aged (Table I) which present data obtained from sera of institutionalized elderly. It is obvious that some of these individuals are completely lacking the ability to respond to antigenic stimulus while others respond as well or better than the average normal healthy adult. Work currently being done with Mufson on noninstitutionalized elderly 65 and older in Huntington, West Virginia being attended by a private physician respond well to the pneumococcal vaccine as measured thus far by type 3. Forty-one elderly individuals were immunized and their sera analyzed. Thirty-one individuals responded with a 2-fold or greater anti-type 3 response. Preimmunization level was 167 ng Ab N/ml and a postimmunization level of 1263, for a 7.5-fold rise (Table II). Normal healthy young adults, 30 individuals immunized with a 23-valent PNU-IMUNE vaccine and analyzed consecutively with the elderly, showed a preimmunization level of 310 ng Ab N/ml and a postimmunization level of 1950 for a 6.3-fold rise. These results indicate that for the vast majority of elderly, 76% in this study, responded as well as young healthy controls. The release guidelines for the vaccine (20) require an 80% 2-fold or better response in young healthy individuals. The remaining 10 elderly patients 24% did not respond. The preimmunization level was 293 and the postimmunization level was 326 for a ratio of 1.1. This 10% difference is not considered significant. Further studies will be conducted to determine why the 11 individuals did not respond but it is clear that for a large number of elderly for whom pneumococcal infection is a life threatening risk their B-cell function of the immune system is working adequately to produce protective levels of type 3 antibody. Additional studies are being conducted on the other serotypes.

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