Specific Antibody Response Against the 23-Valent Pneumococcal Vaccine in Patients With α₁-Antitrypsin Deficiency With and Without Bronchiectasis*

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Objective: To assess the specific antibody response against polyvalent pneumococcal vaccine in patients with α₁-antitrypsin deficiency (AATD) and respiratory infections.

Design and participants: We investigated specific IgG, IgG1, and IgG2 antibody responses against the 23-valent antipneumococcal vaccine in 18 patients with AATD phenotype PizZ, 9 of whom had bronchiectasis and 4 a history of recurrent pneumonia, and compared them with a control group of 40 healthy volunteers.

Interventions: Blood samples were drawn just prior to and 3 weeks after immunization.

Measurements and results: Quantification of specific IgG and its subclasses was performed by an enzyme-linked immunosorbent assay. For patients with AATD, mean increases in specific antipneumococcal titers were 4.7-fold (25 to 75% quartiles, 2.5- to 6.8-fold) for total IgG, 3.2-fold (1.2- to 4.9-fold) for IgG1, and 2.1-fold (1.8- to 3.7-fold) for IgG2. For the control group, the values were 3.3-fold (1.8- to 5.8-fold) for total IgG, 2.5-fold (1.9- to 3.4-fold) for IgG1, and 3.1-fold (1.9- to 4.5-fold) for IgG2; differences were not significant. Patients with bronchiectasis showed a tendency toward higher levels of IgG subclasses than both control subjects and patients without bronchiectasis; however, there was a tendency toward lower postvaccination serum levels of specific antipneumococcal IgG, IgG1, and IgG2 in patients with bronchiectasis compared with patients without bronchiectasis, but this trend did not reach statistical significance. Three of the four patients with recurrent pneumonia did not show an appropriate IgG2 response.

Conclusions: These results suggest that, as a group, patients with AATD have a preserved antibody response against pneumococcal polysaccharides. Patients with bronchiectasis show a tendency toward a decreased antibody response, even with increased serum levels of most Ig types. Individuals with an impaired IgG2 response seem to be at increased risk of recurrent pneumonia. Considering the pernicious effect of pulmonary infections on these patients and the preserved antibody response in a majority of them, pneumococcal vaccination should be recommended to patients with AATD.

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Key words: antibody response; α₁-antitrypsin deficiency; bronchiectasis; IgG subclasses; pneumococcal vaccine

Abbreviations: AAT = α₁-antitrypsin; AATD = α₁-antitrypsin deficiency; ELISA = enzyme-linked immunosorbent assay; NHLBI = National Heart, Lung and Blood Institute; TI2 = thymus-independent type 2

Individuals with severe α₁-antitrypsin deficiency (AATD), particularly those homozygous for the Z allele, are at increased risk of developing pulmonary emphysema due to excessive neutrophil-derived proteases, often in the third and fourth decades of life.¹ In addition to its inhibition against neutrophil elastase and other proteases, α₁-antitrypsin (AAT) has other important biological effects, including a modulatory effect on lymphocyte function; deficient patients exhibit a marked serum-mediated increase in lymphocyte activation, which can be demonstrated by marked acceleration in delayed hypersensitivity responses.² This alteration in lymphocyte function has been proposed as a reason for the increased susceptibility of AATD patients to immune disorders.²,³

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The connection between AATD and immunologic disorders has been emphasized by isolated reports of families with hypogammaglobulinemia and deficient phenotypes of AAT, which have suggested that some form of hypogammaglobulinemia could be determined by a regulatory gene probably linked with the Pi locus.  

Despite the evidence of immunologic and inflammatory roles of AAT and the deleterious effect of respiratory infections in the natural history of pulmonary disease, no studies have so far addressed the possible effect of AATD on the humoral antibody response against specific antigens such as pneumococcal polysaccharides. The impaired antibody response against polysaccharides was first included as a well-characterized syndrome in the World Health Organization’s 1995 review of humoral immunodeficiencies. In most cases, this impaired antibody response is associated with respiratory infections, such as recurrent purulent bronchitis, bronchiectasis, or recurrent pneumonia.

In this study, we analyzed specific antipneumococcal antibody response in a group of patients with AATD and attempted to ascertain whether an impaired response may be associated with the presence of recurrent respiratory infections, namely bronchiectasis or recurrent pneumonia. Furthermore, demonstration of an adequate immune response against polysaccharides in patients with AATD is relevant to justify the administration of pneumococcal vaccination in this population.

**Materials and Methods**

**Study Population**

The study population consisted of patients with severe AATD, phenotype PiZZ, seen at our center. Their results were compared with those of a control group comprised of 40 healthy, nonrelated volunteers (20 women, 20 men; age range, 21 to 48 years; mean age, 30 years), whose characteristics have been described previously.

None of the patients in either group had a history of prior pneumococcal immunization or known immunodeficiency. All subjects gave informed consent, and the study was approved by the Ethics Committee of the Vall d’Hebron Hospitals.

**Ig Quantification**

IgG, IgA, and IgM levels were determined by kinetic nephelometry (Array Protein System; Beckman Instruments, Inc; Brea, CA). Reference values established in our laboratory were as follows: IgG, 8.5 to 16 g/L; IgA, 0.75 to 3.5 g/L; and IgM, 0.58 to 2.5 g/L. IgG subclasses were determined by enzyme-linked immunosorbent assay (ELISA). Reference values in our laboratory were as follows: IgG1, 2.61 to 10.81 g/L; IgG2, 1.12 to 4.08 g/L; IgG3, 0.22 to 2.85 g/L; and IgG4, 0.05 to 1.56 g/L.

**Immunization**

All individuals were vaccinated with the same lot of PNU-Immune 23 polyvalent antipneumococcal vaccine (Lederle Laboratories; Pearl River, NY), 0.5 mL administered IM in the deltoids. This vaccine contained 25 μg of each of the 23 specific capsular polysaccharides. Blood samples were obtained from each individual prior to and 21 days after vaccine administration. These samples were centrifuged at 3,000 rpm for 15 min and the sera obtained were stored in aliquots frozen at −20°C until studied.

**Specific IgG and IgG Subclasses to Pneumococcal Vaccine**

Total IgG, IgG1, and IgG2 levels specific to Streptococcus pneumoniae were determined by an ELISA test based on the method described by Metzger et al., but modified by using the pneumococcal vaccine as antigen as described by silver et al. This technique has been described extensively elsewhere. Because the polyvalent pneumococcal vaccine may be contaminated with nonspecific cell wall polysaccharide, antibodies detected with this assay are not all necessarily protective against pneumococcal infection. However, the aim of the present study was to investigate patients’ ability to respond against polysaccharides in general, as a lack of specific antipolysaccharide response has been recognized as a humoral immunodeficiency that may promote recurrent respiratory infections.

The results of total antipneumococcal IgG were expressed as arbitrary units using a reference serum of 2.240 U/mL calibrated against a pneumococcal reference preparation, labeled PN-A, with the assigned value of 70 pneumococcal IgG antibody U/mL from the European Quality Scheme for specific antibodies (Oxfordshire Health Authority, John Radcliffe Hospital; Oxford, UK), kindly donated by Dr. N. Matamoros (Hospital Son Dureta; Palma de Mallorca, Spain).

The amounts of specific antipneumococcal IgG1 and IgG2 were determined by the same ELISA method used for specific total IgG, using HRP-labeled anti-human IgG1 (clone MH161–1) and IgG2 (clone HP6014), and the results expressed as A490 units.

For specific total IgG, the minimal amount of antibody detectable with this assay was 0.11 U/mL. Within-run and day-to-day coefficients of variation were 7.6 and 10.5%, respectively.

For IgG subclasses, the minimal amount of antibody detectable with these assays was 0.200 A490 above the blank. Within-run and day-to-day coefficients of variation were 6.5 and 10.6% for IgG1, and 10.3 and 11.3% for IgG2.

This assay was not sensitive enough to quantify specific antipneumococcal IgG3 and IgG4. These subclasses were only detected in eight and one control subjects, respectively, and thus were not further analyzed.

Specificity of the antibodies detected to the vaccine was demonstrated by inhibition experiments, in which increasing concentrations of pneumococcal vaccine (range, 0 to 80 ng/mL) were added to two pools of sera with high (9.250 U/mL) and low (150 U/mL) specific antipneumococcal IgG concentrations, and effective competition with the coated pneumococcal polysaccharides for antibody binding was observed.

Specificity was further demonstrated by a lack of cross-reactivity between anti-S pneumoniae and anti-Hemophilus influenzae type b (Hib) antibodies. The criterion for a patient to be considered a “responder” with any antibody isotype has been described elsewhere. In brief, a responder for each of the isotypes evaluated was defined as an individual who showed an increase in his/her antibody titers > 395 U/mL, 0.350 A490 units, and 0.314 A490 units for specific antipneumococcal IgG, IgG1, and IgG2, respectively.
values correspond to the lower limit of the 90% probability intervals (two-tailed) of the log-transformed specific IgG, IgG1, and IgG2 postimmunization titers of the control group.

Data Analysis

Results of specific antipneumococcal IgG, IgG1, and IgG2 were expressed as the median and 25% and 75% quartiles of the pre- and postimmunization antibody titer. The same expression of results was used for fold-increases in antibody titer. Undetectable levels of antipneumococcal antibodies were assigned the value of the lower limit of detection.

The nonparametric rank-sum test was used to compare differences in Ig concentrations between the control group and the study group and subgroups. The rank-sum test was also used to compare antibody titers and fold-increases in antibody titers between different groups. Fisher’s Exact Test was used for frequency data to compare percentages.

Statistical analysis was performed using computer software (Statistical Analysis System; SAS Institute; Cary, NC). A p value < 0.05 was considered significant.

RESULTS

Patient Characteristics

The characteristics of the study population consisting of 18 AATD individuals with the PiZZ phenotype are shown in Tables 1 and 2. On CT examination, 15 had pulmonary emphysema and nine had bronchiectasis. Fourteen (78%) suffered from recurrent exacerbations with increased dyspnea, sputum volume, and sputum purulence. Six patients (33%) had a history of previous pneumonia, which was recurrent in four (one of them with small diffuse bronchiectasis). Eight patients were receiving augmentation therapy with IV AAT (Prolastin; Bayer Pharmaceutical; West Haven, CT) at a dose of 180 mg/kg every 21 days. The characteristics of these patients have been described elsewhere. This treatment was discontinued 1 month before the study as well as during the study period. Patients with bronchiectasis showed more preserved pulmonary function, represented by higher FVC, FEV1, FEV1/FVC, and diffusion of carbon monoxide corrected for alveolar volume, and lower values of total lung capacity and residual volume than patients without bronchiectasis, with the majority of them having pulmonary emphysema with greater airflow obstruction, air trapping, and decreased diffusing capacity (Table 2).

Ig Concentrations

Serum Ig concentrations of patients with AATD and comparisons with the control group are shown in Table 3. Only serum concentrations of IgA were significantly increased in patients with AATD.

Patients with bronchiectasis showed a tendency toward higher Ig concentrations than control subjects and patients without bronchiectasis. These differences were significant for IgA and IgG4 (p < 0.05 vs control subjects) and for IgG4 (p < 0.05 vs non-bronchiectasis patients). Serum levels of IgM were lower for patients with bronchiectasis compared with the control group and patients without bronchiectasis (p < 0.05 in both cases).

Antibody Response to the Vaccine

Table 4 shows values of specific antipneumococcal IgG, IgG1, and IgG2 pre- and postimmunization in the study population and in the control group, as well...
as fold-increases in antibody titers. No significant differences were observed between specific antibody concentrations and fold-increases between groups.

When considering patients with bronchiectasis, we observed reduced serum levels of specific antipneumococcal IgG, IgG1 and IgG2 after immunization compared with patients without bronchiectasis; these differences neared statistical significance for IgG1 (p = 0.06). Differences were not so evident for fold-increases because preimmunization levels were also lower, although not significantly, for patients with bronchiectasis.

The percentages of responders with the different isotypes among the whole group of AATD patients and control subjects are shown in Figure 1. Thirty-two control subjects (80%) showed an adequate IgG response; among the rest, four (10%) responded only with IgG1 and four (10%) did not respond with any of the isotypes studied. Again, no differences were observed between AATD patients and the control group.

Two patients with AATD were considered nonresponders: one was a corticosteroid-dependent 45-year-old man with end-stage pulmonary emphysema, two previous episodes of pneumonia, and frequent acute exacerbations (three or more per year), and the other was a 27-year-old man who had no evidence of emphysema, four episodes of pneumonia since the age of 6 years, frequent bouts of purulent bronchitis (two to three per year), and small diffuse bronchiectasis on CT examination.

Two patients with AATD had recurrent pneumonia. Two of these were the nonresponders previously described; the third did not respond with IgG2 but had a normal IgG and IgG1 response; and the fourth patient displayed a normal antibody response for the three isotypes.

### Discussion

Patients with AATD often develop infectious respiratory complications. Half of the patients described here had bronchiectasis seen on CT examination. One third had a history of documented pneumonia, which was recurrent in four cases. The

### Table 3—Mean Serum Ig Concentrations in Patients With AATD and the Control Group*

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>No.</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>40</td>
<td>11.04 (2.20)</td>
<td>1.90 (0.88)</td>
<td>1.49 (0.67)</td>
<td>6.32 (1.46)</td>
<td>3.64 (1.90)</td>
<td>0.53 (0.30)</td>
<td>0.46 (0.44)</td>
</tr>
<tr>
<td>AATD</td>
<td>18</td>
<td>10.13 (2.72)</td>
<td>2.57 (1.25)</td>
<td>1.44 (0.79)</td>
<td>6.23 (2.49)</td>
<td>3.43 (1.45)</td>
<td>0.53 (0.25)</td>
<td>0.50 (0.32)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>9</td>
<td>10.21 (2.13)</td>
<td>2.93 (1.56)</td>
<td>1.05 (0.41)</td>
<td>7.23 (2.68)</td>
<td>3.85 (1.53)</td>
<td>0.64 (0.24)</td>
<td>0.80 (0.55)</td>
</tr>
<tr>
<td>No bronchiectasis</td>
<td>9</td>
<td>10.06 (3.33)</td>
<td>2.22 (0.76)</td>
<td>1.82 (0.91)</td>
<td>5.11 (1.81)</td>
<td>2.93 (1.26)</td>
<td>0.40 (0.19)</td>
<td>0.17 (0.19)</td>
</tr>
</tbody>
</table>

*Data expressed as mean (SD). All concentrations expressed in grams per liter.

†p < 0.05 between study groups and control group, rank-sum test.

‡p < 0.01 between study groups and control group, rank-sum test.

§p < 0.05 between bronchiectasis and no bronchiectasis, rank-sum test.

### Table 4—Specific Antipneumococcal Antibody Titers and Fold-Increases in the Study Population and Control Group*

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Control Group</th>
<th>AATD</th>
<th>AATD with Bronchiectasis</th>
<th>AATD without Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 18</td>
<td>n = 9</td>
<td>n = 9</td>
</tr>
<tr>
<td>Total IgG</td>
<td>Preimmunization 575 (275–950)</td>
<td>717 (153–1,008)</td>
<td>595 (150–1,760)</td>
<td>880 (205–1,190)</td>
</tr>
<tr>
<td></td>
<td>Postimmunization 1,575 (975–2,550)</td>
<td>2,200 (1,500–4,550)</td>
<td>1,720 (1,500–2,400)</td>
<td>3,400 (2,100–5,470)</td>
</tr>
<tr>
<td></td>
<td>Fold-increase 3.35 (1.85–5.87)</td>
<td>4.72 (2.55–6.83)</td>
<td>4.03 (2.04–6.83)</td>
<td>4.85 (4.44–6.66)</td>
</tr>
<tr>
<td>IgG1</td>
<td>Preimmunization 0.299 (&lt; 0.200–0.466)</td>
<td>&lt; 0.200 (&lt; 0.200–0.302)</td>
<td>&lt; 0.200 (&lt; 0.200–0.264)</td>
<td>&lt; 0.200 (&lt; 0.200–0.306)</td>
</tr>
<tr>
<td></td>
<td>Postimmunization 0.828 (0.609–1.350)</td>
<td>0.888 (0.408–1.112)</td>
<td>0.464 (0.300–0.830)</td>
<td>1.086 (0.947–1.334)</td>
</tr>
<tr>
<td></td>
<td>Fold-increase 2.5 (1.35–3.4)</td>
<td>3.27 (1.27–4.95)</td>
<td>2.32 (1.35–3.83)</td>
<td>3.97 (1.27–5.43)</td>
</tr>
<tr>
<td>IgG2</td>
<td>Preimmunization 0.322 (&lt; 0.200–0.501)</td>
<td>0.440 (0.223–0.639)</td>
<td>0.437 (0.249–0.613)</td>
<td>0.541 (0.223–0.683)</td>
</tr>
<tr>
<td></td>
<td>Postimmunization 1.143 (0.622–1.735)</td>
<td>1.254 (0.766–1.644)</td>
<td>1.192 (0.844–1.422)</td>
<td>1.527 (0.603–1.838)</td>
</tr>
<tr>
<td></td>
<td>Fold-increase 3.1 (1.9–4.5)</td>
<td>2.19 (1.85–3.71)</td>
<td>2.15 (1.85–4.75)</td>
<td>2.23 (1.97–2.45)</td>
</tr>
</tbody>
</table>

*Data expressed as median (25 to 75% quartiles).

†p < 0.05 compared with control group, Wilcoxon rank-sum test.

‡p = 0.06 compared with patients with bronchiectasis, Wilcoxon rank-sum test.
majority (14/18; 78%) frequently experienced infectious exacerbations of their COPD.

However, the specific IgG, IgG1, and IgG2 antipneumococcal antibody responses in most patients with AATD did not differ significantly from the responses observed in healthy adult volunteers. Some findings related to pulmonary infections were of interest: patients with bronchiectasis showed a tendency toward decreased postimmunization antipneumococcal antibody levels compared with patients without bronchiectasis, even with increased serum concentrations of immunoglobulins; and patients with recurrent pneumonia frequently had an associated lack of response of IgG2 isotype.

Impaired antibody response against polysaccharides with normal serum Ig levels has recently been recognized as a primary humoral immunodeficiency. The diagnosis of this syndrome requires demonstration of a lack of specific antibody production in response to immunization with polysaccharide vaccines such as the 23-valent pneumococcal vaccine.

The humoral response against polysaccharides has been classically defined as a thymus-independent type 2 (TI2) response, and thus not mediated by T-lymphocyte cytokines. However, the magnitude of antibody responses to TI2 antigens, the differentiation of specific antibody responses from production of IgM to the IgG subclasses, and the demonstration of some antigen priming in the response to TI2 antigens are all dependent on T cell activity. Thus, the functional alterations of T-lymphocytes that have been described as associated with AATD could occasionally have repercussions on the specific antibody production against some antigens, including bacterial capsular polysaccharides.

Another link between AATD and impaired antibody production stems from the observation of a patient with hypogammaglobulinemia and phenotype PiZZ. From the study of relatives, the presence of individuals with low Ig levels was associated with the phenotypes PiZZ or PiMZ, while those with phenotype PiMM showed normal Ig levels in all cases, which suggests some genetic linkage between both deficiencies.

The lack of antibody response to polysaccharides has been associated with recurrent sinopulmonary infections, particularly in children, but its importance in adults has only recently been addressed. We observed that patients with AATD as a group had a preserved antibody response against the capsular polysaccharides of \textit{S pneumoniae}. Specific antipneumococcal IgG, IgG1, and IgG2 concentrations after immunization with pneumococcal vaccine were similar to those observed in healthy control subjects. In both the study group and the control group, we classified 11 and 10% of individuals as nonresponders, respectively. This finding concurs with a recent meta-analysis of 23 studies assessing the antipneumococcal antibody response in healthy subjects. The results showed that not all normal subjects responded with a significant increase in antibody titers. In fact, it has been suggested that approximately 10% of the population has a genetically-mediated failure to make specific IgG after pneumococcal vaccination; the clinical significance of this finding in asymptomatic individuals remains unclear.

The cause of impairment in specific antibody responses might have been attributed to chronic airflow obstruction; however, there is no evidence at present for this. Musher et al studied a group of 11 bronchitic patients and 15 healthy adults, reporting somewhat lower levels of postvaccination antipneumococcal antibodies among patients, although differences were only significant for one serotype. Because we demonstrated that patients with AATD, some having severe airflow obstruction, showed no significant impairment in antibody responses, airway obstruction per se is unlikely to be a cause of impaired response. Furthermore, one of only two nonresponders was a young patient who had recurrent pneumonia and normal lung function.

Pneumonia has recently been recognized as a common problem in patients with AATD; the National Heart, Lung and Blood Institute (NHLBI) Registry of AATD identified a medical history of pneumonia in 42% of their 1,088 enrollees.
larly, six of our patients had a history of pneumonia; it was recurrent in four of them. The increased burden of neutrophil elastase associated with pulmonary infection may lead to increased pulmonary destruction.\textsuperscript{23} Thus, the NHLBI Registry strongly recommends pneumococcal vaccination in AATD patients,\textsuperscript{22} although, to our knowledge, no previous studies had demonstrated an adequate anti-pneumococcal antibody response in these patients.

Interestingly, both of our nonresponding patients had recurrent pneumonia. However, recurrent pneumonia was especially associated with the failure to respond with IgG2; of note, three of the four patients with recurrent pneumonia were not able to respond with IgG2, although one of them showed an adequate IgG response. The importance of IgG2 in the defense against pneumonia was emphasized in previous works; Shackelford et al\textsuperscript{24} observed that six out of seven children with IgG2 deficiency suffered from recurrent pneumonia. In adults, Herer et al\textsuperscript{25} observed that patients with community-acquired pneumonia exhibited lower serum levels of IgG2 than control subjects, although they produced a normal increase in specific IgG antibodies after immunization with pneumococcal vaccine; unfortunately, the specific IgG2 response was not assessed. In another study, De Gracia et al\textsuperscript{9} observed that the only difference between patients with bronchiectasis with or without IgG subclass deficiencies was the increased frequency of recurrent pneumonia among those with lower levels of IgG2. These results emphasize the importance of IgG2 in the defense against capsulated bacteria such as \textit{S pneumoniae}, the most frequent causative agent of community-acquired pneumonia.\textsuperscript{26} Based on these results, we suggest that patients with recurrent pneumonia should have their IgG2 serum levels tested and, if normal, should be investigated for a deficient IgG2 specific antibody response against polysaccharides, even in the presence of an adequate IgG response, because a normal IgG may be related to an increase in IgG1 and may hinder an inability to respond with specific IgG2.

Half of our patients had bronchiectasis noted on CT examination. The association of bronchiectasis with AATD has been controversial\textsuperscript{27}; unfortunately, its frequency in large series such as the NHLBI Registry\textsuperscript{22} and the different European Registries\textsuperscript{28–30} has not been assessed. It is interesting to observe that patients with bronchiectasis showed a tendency toward increased levels of all IgG subclasses compared with control subjects, and particularly compared with patients without bronchiectasis; this finding has only rarely been reported in the literature\textsuperscript{9,31} and is probably related to polyclonal IgG stimulation as a result of chronic or repeated colonoization. However, these higher serum Ig concentrations are accompanied by lower levels of specific antipneumococcal antibody titers, particularly total IgG and IgG1. In the study by De Gracia et al,\textsuperscript{9} among 65 adults with bronchiectasis of unknown etiology, 31 (48\%) were found to have low levels of one or more IgG subclasses, mainly IgG2. Moreover, patients with IgG subclass deficiencies showed an impaired antibody response against a conjugated \textit{H influenzae} type b vaccine even in the presence of high Ig serum concentrations. These results suggest that polyclonal B-cell activation by recurrent pulmonary infections with consequently high Ig concentrations may hide a specific defect in antibody response against polysaccharide antigens that can only be diagnosed by specific stimulation and could explain a deficient immunologic defense and eventually the development of bronchiectasis. These findings emphasize the need to investigate the antibody response against specific antigens in patients with bronchiectasis of unknown etiology, even in the presence of normal or increased IgG serum concentrations.

Although our study population was older than the control group, this factor did not appear to influence the antibody response. Antibody production has been classically considered to diminish with age. However, recent experimental evidence has proved that even elderly people can produce an adequate response against polysaccharides.\textsuperscript{32,33}

From our results, it can be concluded that pneumococcal vaccination must be recommended in AATD patients because they show, as a group, a preserved antibody response against polysaccharides included in the vaccine. Patients with decreased postimmunization antipneumococcal titers seem to be at increased risk for the development of bronchiectasis, even if they have normal or increased serum Ig levels, and lack of response with IgG2 seems to confer an increased risk for recurrent pneumonia. Study of the specific antibody response in larger series of patients with AATD would be required to confirm these tendencies. Completion of such a study would be hampered, however, by the low frequency of the disease, which makes it difficult to gather enough subjects for definitive conclusions to be drawn.

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