

Letter to the Editor

Pathogen-specific IgG antibody levels in immunodeficient patients receiving immunoglobulin replacement do not provide additional benefit to therapeutic management over total serum IgG

To the Editor

The conventional way of monitoring immunoglobulin replacement in antibody-deficient patients is by measuring the total IgG in serum by nephelometry. Despite adequate levels of total IgG, some patients continue to have upper respiratory tract infections, especially with *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*. Lucas et al¹ reported recently that the optimal dosage of immunoglobulin replacement to prevent infection is not necessarily based on trough IgG levels. One possible explanation for this finding is that pathogen-specific antibody levels do not correlate with total IgG in these patients. We therefore explored the clinical utility of measuring pathogen-specific antibodies with commercially available assays for pneumococcus and *Haemophilus influenzae* in antibody-deficient patients receiving immunoglobulin replacement.

We selected 62 patients, of whom 60 had a diagnosis of primary antibody deficiency and 2 had secondary antibody deficiency. The mean baseline IgG for the patients with documented pretreatment levels was 1.0 g/L. Over a period of 2 years, we collected samples from these patients. Samples were taken 2 to 4 weeks after the patient's last immunoglobulin infusion. The *H influenzae*, pneumococcus, and tetanus antibody levels were measured by using ELISA kits from The Binding Site, Birmingham, United Kingdom (VaccZyme TM MK016, MK012, MK010). The ELISA measures specific IgG antibodies against *H influenzae* type B (HIB), pneumococcal capsular polysaccharides of 23 serotypes (PCP), and tetanus toxoid (TET), respectively. Serum IgG levels were quantified by the immuno-turbidometric assay using Cobas Tina-Quant IgG Gen-2 reagent. To survey the frequency of chest infections and relate this to the level of immunoglobulin replacement, we obtained relevant clinical details from patients' records during the period when the serum samples were taken.

When we included all 75 samples taken from 62 patients, of which 13 were repeat measurements, there was a strong and significant correlation between all 3 pathogen-specific antibodies with total IgG levels (PCP-Ab, $r^2 = 0.5615$; HIB-Ab, $r^2 = 0.4227$; TET-Ab, $r^2 = 0.3081$; Fig 1).

An interesting observation was that a minority of patients had low levels of pathogen-specific antibodies despite adequate IgG levels, which in our unit was defined at ≥ 7.0 g/L. To analyze this finding quantitatively, we assigned thresholds for pathogen-specific antibody levels below which we defined as suboptimal. For HIB-Ab and TET-Ab, these were the accepted protective values of ≥ 1 mg/L and ≥ 0.1 IU/mL, respectively.^{2,3} Because PCP-Ab had no universally defined protective level, we arbitrarily defined the optimal threshold at ≥ 50 mg/L. This figure is between the geometric means (45.8 mg/L and 59.5 mg/L) found in 2 studies^{4,5} of healthy unvaccinated adult subjects by using the same immunoassay kit as our study.

We categorized patients according to their total IgG levels: less than 7.0 g/L, between 7.0 and 9.0 g/L, and greater than 9.0 g/L (Fig 2). The mean values of HIB-Ab were above the protective

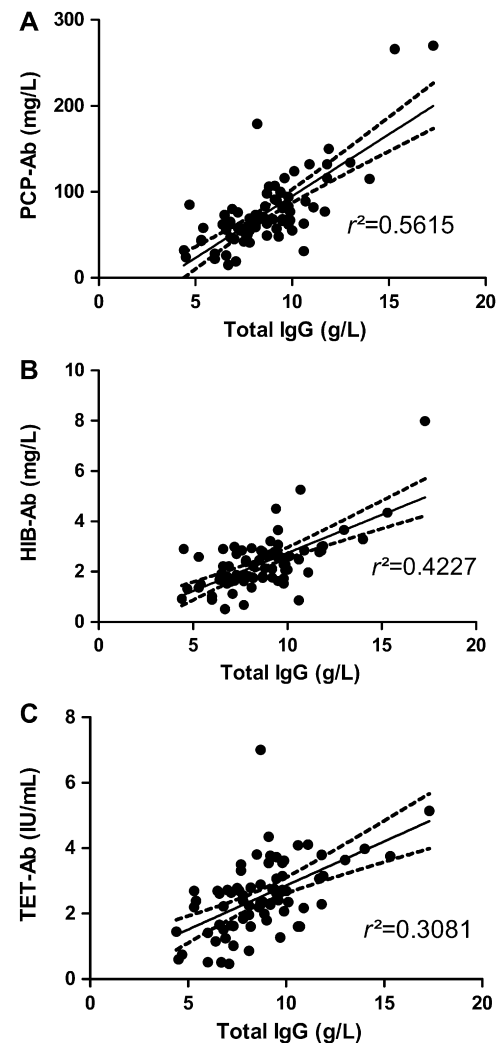


FIG 1. Correlation of total IgG (g/L) levels with pathogen-specific IgG levels. A total of 75 individual antibody level results were taken from 62 patients. Samples were taken 2 to 4 weeks after the patient's last immunoglobulin infusion. Each individual sample was analyzed for total IgG, PCP-Ab, HIB-Ab, and TET-Ab. **A**, Total IgG and PCP-Ab. **B**, Total IgG and HIB-Ab. **C**, Total IgG and TET-Ab. On each graph, the linear regression line is shown with 95% CI in dotted lines.

levels for all categories of IgG (1.7 mg/L, 2.1 mg/L, and 2.6 mg/L, respectively). The patients with total IgG less than 7 g/L had the highest proportion of patients with suboptimal PCP-Ab (9/16; 56%) and suboptimal HIB-Ab (3/16; 19%; Fig 2). However, even for patients with total IgG ≥ 7.0 g/L, 8 patients had suboptimal PCP-Ab (Fig 2, A). In contrast, for HIB-Ab, only 2 patients did not have protective levels (Fig 2, B). The TET-Ab measurements were all well above the protective levels for all the patients (data not shown).

In our cohort of 62 patients, there were equal numbers of patients with and without bronchiectasis. Of 44 patients with known smoking history, 9 had smoked. Of these 9, 8 had bronchiectasis. Of the 35 nonsmokers, only 1 had bronchiectasis. Analysis by Fisher exact test gives a significant association of

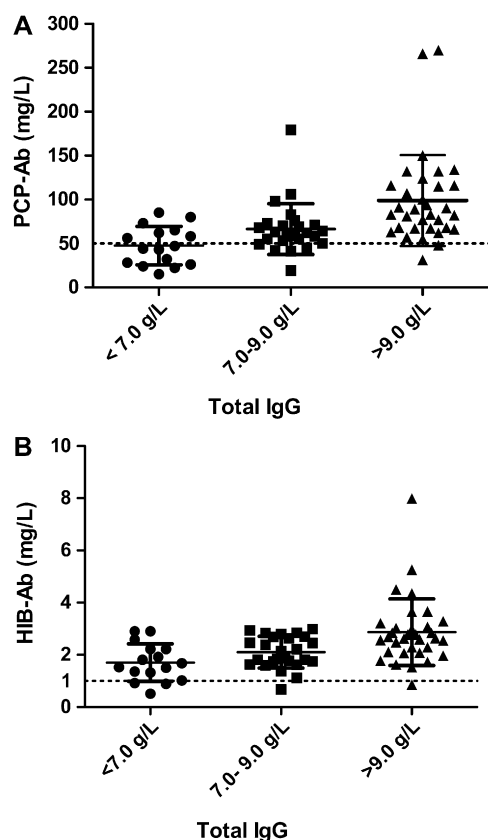


FIG 2. Scatter plot of PCP-Ab and HIB-Ab results grouped according to 3 levels of total IgG (>9.0 g/L, 7.0-9.0 g/L, and <7.0 g/L). The cutoffs for optimal/suboptimal levels for PCP-Ab (50 mg/L) and HIB-Ab (1 mg/L) are shown by a dotted line.

smoking and bronchiectasis ($P = .0214$) with a relative risk of 7.238 (95% CI, 0.9948-52.66) and an odds ratio of 11.08 (95% CI, 1.229-99.81). There was no difference in the diagnostic delay in these 2 cohorts. Patients without bronchiectasis had a diagnostic delay of 7.0 ± 9.688 years, and patients with bronchiectasis had a diagnostic delay of 10.76 ± 12.69 years. This was not statistically significant ($P = .1965$; Mann-Whitney test).

Overall, the annual frequency of chest infections in patients with IgG ≥ 7.0 g/L was between 0 and 3 episodes. There was no difference in the frequency of chest infections whether the patients had optimal or suboptimal pathogen specific antibody titers ($P = .97$; 1-way ANOVA). The patients with total IgG ≥ 7.0 g/L but suboptimal PCP-Ab had less bronchiectasis (2/5; 40%) than those with optimal PCP-Ab (35/61; 57%). This finding may be a result of the small numbers of patients with suboptimal PCP-Ab, or it may be related to 6 of the 8 patients having levels just below the cutoff and within 1 SD of the mean. Prophylactic antibiotics did not account for the similarity in chest infection rates ($P = .80$; 1-way ANOVA).

In this population of mostly primary antibody-deficient patients on immunoglobulin replacement, the burden of chest infections was low. None of the patients had pneumonia

confirmed by chest radiograph, and there were no chest infections requiring hospital admission. There were 4 positive sputum microbiology samples in 4 patients: 2 *H influenzae* infections, 1 *Haemophilus parainfluenzae*, and 1 group A *Streptococcus pyogenes*. The average frequency of minor chest infections, defined as acute symptoms of productive cough without fever or respiratory distress, was 1 episode in 12 months. Finally, there was no difference between intravenous or subcutaneous route of infusion to the profile of PCP-Ab ($P = .90$; 2-tailed Mann-Whitney test) and HIB-Ab ($P = .33$; 2-tailed Mann-Whitney test).

In conclusion, our findings showed a consistent relationship between PCP-Ab and HIB-Ab with total IgG; in general, higher total IgG correlates with higher pathogen-specific antibody levels. The use of PCP-Ab and HIB-Ab measurements did not identify patients more susceptible to chest infections when total IgG was ≥ 7.0 g/L. All except 2 patients had protective HIB-Ab levels if their total IgG was ≥ 7.0 g/L. At this level of total IgG, the mean PCP-Ab level of $66.7 \mu\text{g/mL}$ was above the geometric mean of healthy unvaccinated individuals found in 2 studies ($45.8 \mu\text{g/mL}$ and $59.5 \mu\text{g/mL}$) using the same The Binding Site immunoassay.^{4,5} With total IgG levels ≥ 7.0 g/L, none of our study patients had serious chest infections requiring hospital admissions.

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REFERENCES

1. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol* 2010;125:1354-60.
2. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1984;149:1034-5.
3. Ramsay M, Corbel M, Redhead K, Ashworth L, Begg N. Persistence of antibody after accelerated immunization with diphtheria/tetanus/pertussis vaccine. *BMJ* 1991;330:1489-91.
4. Stead A, Douglas J, Broadfoot C, Kaminski E, Herriot R. Humoral immunity and bronchiectasis. *Clin Exp Immunol* 2002;130:325-30.
5. Schauer U, Stemberg F, Reiger C, Buttner W, Borte M, Schubert S, et al. Levels of antibodies specific to tetanus toxoid, *Haemophilus influenzae* type b, and pneumococcal capsular polysaccharide in healthy children and adults. *Clin Diagn Lab Immunol* 2003;10:202-7.