

stereotyped view of these families as extremely anxious and overfocused on the medical needs of their own children rather than the nutritional and social needs of the children and their classmates. In contrast, schools were less positive, relating to training needs, institutional and personal liability, and responsibility, although some schools were positive about the option.

Even with an overall broadly positive response from parents and schools (although the proportion of schools responding was disappointing), the proposed system could not currently be put into action. This is because epinephrine is a prescription medication. However, legislation can be changed, and precedents have been set in related areas such as external automatic defibrillation.

Our study has limitations because of sampling bias. The families recruited had a high rate of having 2 EAIIs available at home and at school and a lower rate of having used of EAIIs to treat anaphylaxis in schools, compared with the available literature.² A lower number of schools reported experience of anaphylaxis in a student. A lower than average number of severe reactions may reflect the local availability of specialized allergy care. These findings may suggest that the life experience of children with food allergy who receive their care from a regional allergy unit⁶ is different from the life experience where such expertise is not so available.⁷

The proposed system has the potential to save the United Kingdom National Health Service a significant amount of money. Parents of children with food allergy are more sensitive to the societal cost of their children's food allergies than many people give them credit for, whereas schools mostly identified major needs for staff retraining and liability coverage if the system were to be introduced. The projected cost savings from the new model of provision could meet some of these costs.

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Biologic IgG level in primary immunodeficiency disease: The IgG level that protects against recurrent infection

To the Editor:

The serum IgG level that protects patients with primary immunodeficiency disease (PID) against recurrent bacterial infection and bronchiectasis remains unknown, despite several decades of debate.¹⁻⁴ Existing studies are limited by small sample size, retrospective study design, and dissimilar outcome variables. Despite these laudable efforts, the serum IgG level that protects patients with PID from infection has not been determined, primarily because the optimal IgG level that prevents bronchiectasis/infection is not likely to be uniform in all patients. However, Medicare/Medicaid generated local coverage determinations for IgG replacement reimbursement in PID based on maintaining a fixed IgG trough, hereafter called level, within a narrow range (400-600 mg/dL).⁵ Thus reimbursement is allocated as if one size fits all. Although they allow for "rare" exceptions to this rule, a description of these exceptions and the documentation required to prove that higher IgG levels are needed are not provided. Thus they do not take into account the wide quantitative and qualitative serum IgG variations that are a hallmark of PID.

The 2006 review by members of the Primary Immunodeficiency Committee⁶ suggests that IgG levels should be at least more than 500 mg/dL for agammaglobulinemic patients and 300 mg/kg greater than the initial IgG level for patients with common variable immunodeficiency (CVID). Furthermore, IgG levels of greater than 500 mg/dL might reduce infection and improve clinical outcomes, and IgG levels of greater than 800 mg/dL might "improve pulmonary outcome." These guidelines infer that different requirements for IgG exist between and within a given PID group. Thus individualizing the amount of IgG given should be the goal to improve clinical outcome, unlike what is dictated by restricted insurance reimbursement. Thus documenting clinical symptoms and serum IgG levels over time, on a case-by-case basis, should improve care and resolve reimbursement dilemmas.

Some patients with PID, such as those with CVID, can present with relatively high IgG levels (400-600 mg/dL), yet show poor qualitative function by failing to mount primary/anamnestic responses to protein or carbohydrate vaccine or both. These patients often require higher quantitative IgG levels than mandated by insurance coverage determinations⁵ to provide adequate protection. As a result, higher IgG serum levels might be required to protect these patients from recurrent sinopulmonary infections and bronchiectasis compared with those who present with lower IgG levels. Thus the goal of IgG replacement, administered intravenously or subcutaneously,⁷ should be to identify and maintain the biologic IgG level of an individual patient with PID within the age-matched control range. We coin the term *biologic IgG level* to represent the minimal serum IgG level that renders a patient as disease free as possible. Because there is a wide (peak trough) variation in serum IgG levels with intravenous IgG replacement versus subcutaneous IgG infusions, it might be easier and more cost-effective to identify and maintain the IgG level at, or just above, the biologic IgG level. We recommend that physicians plot their patients' IgG levels over time against documented infections to identify the biologic IgG level, help optimize care, and address IgG reimbursement queries, should they arise (see patients A and B in Fig 1 below).

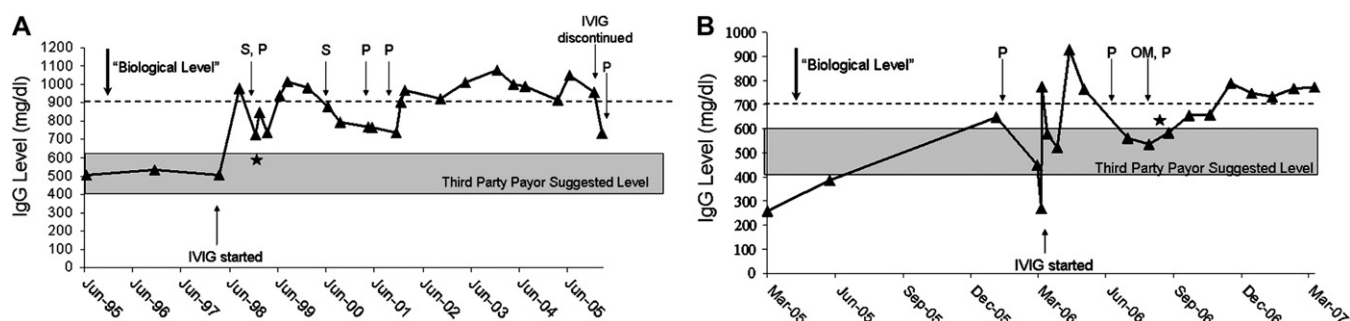


FIG 1. IgG trough levels in patients A and B before, during, and after initiating IVIG therapy and associated infection history. *Time at which our practice assumed the care of this patient. S, Acute sinusitis; P, pneumonia; OM, otitis media.

The cases we provide demonstrate how the biologic IgG level was established in 2 patients from our primary immunodeficiency clinic. This documentation strategy has helped us keep patients infection free and resolve IgG reimbursement issues when payment for maintaining IgG levels outside the recommended range was denied. The biologic IgG level can also be a “moving target,” especially when confounding variables, such as pregnancy and renal disease, are present. Thus careful documentation of symptoms related to IgG levels should help identify the amount of IgG required to keep patients with PID healthy.

Patient A was a 62-year-old woman given a diagnosis of CVID at the age of 57 years. She presented with recurrent pneumonia, an IgG level of 507 mg/dL (normal = 639-1349 mg/dL), an IgA level of 18 mg/dL (normal = 70-312 mg/dL), an IgM level of 23 mg/dL (normal = 56-352 mg/dL), and absent antibody responses to hepatitis B and Pneumovax (Merck & Co., Inc, Whitehouse Station, NJ) (0/12 → 2/12 protective titers) after revaccination. T-cell responses to mitogens and antigens were normal. She was initially managed by another allergist/immunologist who started her on intravenous immunoglobulin (IVIG), 300 mg/kg per dose every 4 weeks. In January 1999, the patient's IgG trough was 727 mg/dL; however, she had 3 separate chest radiograph–documented, blood culture–negative pneumonias. Her IVIG infusions were increased to 400 mg/kg per dose. During 2000-2001, she had 2 episodes of acute sinusitis (the first positive for *Streptococcus pneumoniae* and the second positive for *Haemophilus influenzae*, as documented by sinus tap) and pneumonia (IgG level, 738-879 mg/dL). We increased her IVIG to 500 mg/kg per dose and then to 580 mg/kg per dose, at which time she became asymptomatic. As such, we identified her biologic IgG level as 900 mg/dL. At greater than 900 mg/dL, she remained infection free for greater than 3 years. In November 2005, IVIG therapy was discontinued because of denied insurance reimbursement. As a result, her serum IgG level decreased to less than her biologic IgG level, and subsequently, she developed pneumonia and multiple upper respiratory tract infections.

Patient B was a 4-year-old boy with Jacobson syndrome and CVID. He presented to a pediatric infectious disease specialist with recurrent sinorespiratory infections and pneumonia that required multiple pediatric intensive care unit hospitalizations. His outpatient immunoglobulin levels were: IgG, 257 mg/dL (normal = 441-1135 mg/dL); IgA, less than 15 mg/dL (normal = 25-154 mg/dL); IgM, 25 mg/dL (normal = 43-197 mg/dL). Immunizations were up to date, with nonprotective titers to tetanus toxoid, *H influenzae* B, and *S pneumoniae* (0/14). T-cell/B-cell phenotyping and responses to mitogens and anti-CD3

challenges were normal. He was given 400 mg/kg per dose of IVIG every 4 weeks, with IgG troughs of 500 to 600 mg/dL. He again required admission to the pediatric intensive care unit for pneumonia (positive blood culture: *S pneumoniae*). His IgG level was 561 mg/dL 3 weeks before admission. At that time, we assumed his care, incrementally increased his IVIG dose to 750 mg/kg per dose every 4 weeks, and identified the biologic IgG level (800 mg/dL) that made him infection free.

In summary, the biologic IgG level is likely to be unique for each patient, always in the range of age-matched control subjects, and should be considered to be a moving target that can change with comorbid conditions/diseases. We recommend charting clinical infections against IgG levels over time to identify and maintain each patient's biologic IgG level. We begin with 500 mg/kg (the midpoint of the recommended starting range⁶) as an intravenous loading dose or one quarter of that given subcutaneously weekly and incrementally increase the IgG dose approximately 10% per month as needed to identify the biologic IgG level. Periodic assessment for occult bronchiectasis, even when patients appear to be infection free, is warranted.⁴ Because single IgG levels can be unreliable,⁶ identifying IgG levels over time should provide a biologically relevant benchmark to improve care for patients with PID and provide documentation for IgG insurance company reimbursement as needed.

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An accompanying editorial by Simmons et al provides background and context for clinical pathways and their implementation (**pages 303-4**).

In the April 2008 issue, Scal et al found that financial barriers to treatment resulted in significant delays and unmet needs for young adults with asthma.

Scal P, Davern M, Ireland M et al. Transition to Adulthood: Delays and Unmet Needs among Adolescents and Young Adults with Asthma. *J Pediatr* 2008;152:471-5.

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