

Goals of therapy in antibody deficiency syndromes

Most physicians who care for patients with antibody deficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency would agree that the major goal of immunoglobulin replacement therapy is amelioration of morbidity and mortality resulting from infectious disease. But what does that really mean in practice? Bruton,¹ in 1952, considered the absence of sepsis the indicator of success for gamma globulin injection therapy. In the landmark studies conducted by the Medical Research Council Working Party on Hypogammaglobulinemia in the United Kingdom in the mid to late 1950s through the early 1960s, acute febrile episodes, pneumonia, otitis, and diarrhea were the major recorded outcomes.² In the late 1970s to early 1980s, when immune globulin preparations were first licensed for intravenous use in this country, reduction in the number of acute infections was still used as the criterion for successful therapy in early clinical trials.³⁻⁵ Subsequent to the widespread availability of intravenous immune globulin preparations, investigators began to carry studies of the efficacy of higher-dose therapy beyond simple reduction in the numbers of acute episodes of infection and hospital admissions. They assessed improvement in chest radiographs and in pulmonary function measures such as the forced vital capacity and FEV₁ in patients who were free from acute exacerbations and hence would have previously been considered adequately treated.⁵⁻⁷ This progression of the criteria of successful therapy from prevention of life-threatening sepsis to prevention of clinical pneumonia to prevention of progression of chronic lung disease has been marked by the use of progressively more sensitive diagnostic techniques, from the thermometer and stethoscope to x-ray films and pulmonary function machines. In this issue of the Journal, Kainulainen et al (Kainulainen L, Varpula M, Liippo K, Svedström E, Nikoskelainen J, Ruuskanen O. Pulmonary abnormalities in patients with primary hypogammaglobu-

Abbreviations used

HRCT: High-resolution computed tomography

IVIG: Intravenous Ig

linemia. 1999;104:1031) carry both progressions further by using an even more sensitive diagnostic technique, high-resolution computerized tomography (HRCT), to assess the adequacy of current replacement therapy in preventing progression of subclinical bronchiectasis in patients who would be considered successfully treated by the current criteria of conventional radiography and spirometry.

Although most of the 22 patients in their study already had pulmonary changes demonstrable by x-ray films or HRCT before the institution of intravenous Ig (IVIG) therapy, which was dosed to maintain trough levels greater than 500 mg/dL, pulmonary function tests were normal in most and FEV₁ or forced vital capacity were reduced by >25% of predicted values in only 5 of the 22. The sensitivity of HRCT is indicated by the observation that it revealed bronchiectasis in 16 patients, of whom only 3 had that abnormality demonstrated by conventional radiographs. Similarly, HRCT detected fibrosis in 5 patients whose conventional radiographs were considered normal. The increased sensitivity of HRCT compared with conventional radiography and its use to detect unsuspected bronchiectasis in antibody-deficient patients has been demonstrated previously,⁸⁻¹⁴ but there have been few reports of serial studies with clinical correlations. Of the 14 patients in the study of Kainulainen et al who had repeat studies over a 3-year period, 10 had progression of one or more radiographic or HRCT abnormalities and 5 had progression of bronchiectasis that was regarded as clinically "silent." It is perhaps of greatest concern that 2 of the patients with progressive bronchiectasis are young children and 1 is a young adult, ruling out as an explanation "normal" changes resulting from aging. A useful comparison is provided by an earlier study in which Manson et al⁸ reported that of 7 children who had been given "high-dose" IVIG to maintain serum IgG levels >600 mg/dL and who were followed up with serial computed tomography scans over 5 years, 4 improved but 3 worsened.

These findings raise a number of interesting and important questions. First, what is the significance of observing bronchiectasis or fibrosis on the HRCT of a patient who is asymptomatic, and what are the implications of progression of these findings? Bronchiectasis has been defined as "irreversible dilatation of the

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bronchi,"¹⁵ although we now recognize that repair and resolution can occur. The definition is frequently extended to smaller airways as well. The process is generally considered to be the result of epithelial injury and weakening of the airway wall, primarily as a result of the attack of neutrophil proteinases on structural proteins such as elastin that support the airway. This results in a damaged, dilated airway that is prone to chronic recurrent infection.^{15,16} Most often, this is visualized as a vicious cycle of chronic infection and inflammation in which locally persistent neutrophil activity gradually destroys the airway,¹⁵⁻¹⁷ regardless of whether structural damage and breach of epithelial integrity was initiated by an acute infection in an otherwise normal host, by persistence of bacteria in patients with decreased ability to clear secretions because of immotile cilia or cystic fibrosis, or by inability to efficiently kill bacteria because of an immunologic defect such as antibody deficiency. The presumed role of bacteria as the stimulus for the continuing destructive inflammatory response leads us to consider use of higher doses of IVIG or long-term antibiotic treatment. But is this really necessary when the changes are subclinical and observed only by extremely sensitive new techniques? The answer probably depends on the underlying causes or factors contributing to the chronic inflammation in each situation. In cystic fibrosis, although many patients may have subclinical disease even into their teen years,¹⁸ the rate of progression is clearly such that life is significantly shortened in almost all patients. In ciliary dyskinesia syndromes, patients may develop symptoms but premature mortality is uncommon. Individual patients with antibody deficiency are probably spread across this entire spectrum.

Is the clinical significance of observing changes on HRCT sufficient that prevention of these changes should be adopted as the therapeutic target in all patients with antibody deficiency syndromes? Perhaps not, but there are enough studies demonstrating unexpected bronchiectasis in high percentages of patients otherwise considered adequately treated that HRCT should probably be considered a routine periodic screening test in antibody-deficient patients. To be sure, there are pitfalls in the diagnosis of bronchiectasis by HRCT,^{16,19} and questions about its standardization and reproducibility over time will have to be studied further in these patients. There is certain to be considerable individual variation in the extent of involvement and in rates of progression. If bronchiectasis, fibrosis, or other changes are observed, follow-up HRCT at yearly intervals may help to identify those patients in whom lung injury is progressing at a sufficiently rapid rate that it will become clinically significant. In those patients, one would naturally try to intervene to stop the progressive damage. Although increasing the dose of IVIG may have a role in achieving this goal, selection of dose and interval should not be based on arbitrary criteria such as milligrams per kilograms per month or a target serum IgG level but should be individualized, not only to keep the patient clinically well but also to prevent the progression of disease that may be initially sub-

clinical. However, just as in the management of acute infections, IVIG is not the whole answer. Higher doses increase the risk of complications, are expensive, and may further compromise the availability of what has become a limited commodity. What is the role of antibiotics, and is there a role for anti-inflammatory therapies? In many patients with bronchiectasis, even in those who do not produce purulent sputum, bronchoscopy may yield treatable organisms and specific antibiotic therapy can be used. Certainly diagnostic bronchoscopy should be considered in any patient who repeatedly has crackles in the same area or who has a chronic cough or changes on conventional radiographs, even if pulmonary function test results are all normal. The use of anti-inflammatory therapy, with the goal of preventing tissue damage, is being studied in other chronic lung diseases^{20,21} and frequently allows amelioration of locally excessive inflammatory responses without compromising the ability to eradicate infectious stimuli. Bronchodilators and mechanical aids to airway clearance may also play important adjunctive roles.

Because of individual variation in infection, environmental influences, and inflammatory-reparative responses, it is not likely that studies aimed at evaluating the effects of single interventions such as maintaining higher IgG levels will provide universally applicable results. However, the studies of Kainulainen et al, Manson et al,⁸ and others do provide strong suggestions that the technologic advance of HRCT should modify our current assumptions about the criteria of adequate therapy in antibody deficiency syndromes.

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