Published in final edited form as:

Ann Allergy Asthma Immunol. 2017 July ; 119(1): 83–85. doi:10.1016/j.anai.2017.04.020.

Frequency of untreated hypogammaglobulinemia in bronchiectasis

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Disclosures: Authors have nothing to disclose.

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Bronchiectasis is found in approximately one fourth of patients with common variable immune deficiency, with 14% in 1 study having bronchiectasis at the time of diagnosis,¹ and lower respiratory tract symptoms are associated with a lower quality of life and require increased immunoglobulin (Ig) usage.^{2,3} Additional primary immune deficiencies also are associated with a high rate of bronchiectasis, including IgA deficiency, IgG subclass deficiency, and specific antibody deficiency against polysaccharide antigen despite normal levels of quantitative immunoglobulins.^{4,5} Thus, the development of bronchiectasis with immune deficiency is well described. Nevertheless, despite case reports and small series, little is known about the potential overall frequency of hypogammaglobulinemia in patients with bronchiectasis. We also were interested in examining the incidence of overall hypogammaglobulinemia because historically hypogammaglobulinemia has been described to complicate severe pulmonary diseases, such as cystic fibrosis (CF), post-lung transplantation, and advanced chronic obstructive pulmonary disease.^{6–8} In these settings, hypogammaglobulinemia has been associated with poor outcomes.^{7,8} The purpose of this study was to define the frequency of untreated hypogammaglobulinemia in a large bronchiectasis cohort. The diagnostic delay from development of symptoms to diagnosis for common variable immune deficiency is 6 to 8 years, and we hypothesized that some patients with bronchiectasis might have hypogammaglobulinemia, a cardinal sign of immune deficiency.

To examine this possibility, we used the Bronchiectasis and Nontuberculous mycobacteria (NTM) Research Registry. The Bronchiectasis and NTM Research Registry is a physician-reported, longitudinal registry of more than 2,114 adults with non-CF bronchiectasis and/or NTM followed by pulmonologists at 1 of the 13 US academic medical centers participating in the registry.⁹ The goal of the registry is to support collaborative research and assist in the planning of multicenter clinical trials for the treatment of non-CF bronchiectasis and/or NTM lung disease. Data are collected on an annual basis from medical records and/or patient interviews. To date, the registry has collected up to 9 years of data on some patients.

One thousand two hundred fifty-four patients in the Bronchiectasis and NTM Research Registry had immunoglobulin levels tested from September 13, 1994 through February 22, 2017, representing an initial baseline immunoglobulin assessment at the time of registry entry. Antibody functional analysis was not available from the registry. Figure 1 displays the immunoglobulin levels from the analysis of this registry-based dataset. The overall prevalence of untreated hypogammaglobulinemia (IgG < 500 mg/dL) was 1.4%. We divided the cohort into a group with bronchiectasis (not due to CF) and a group with a history of NTM and having bronchiectasis (NTM + bronchiectasis). One thousand nine patients had bronchiectasis alone and 245 had NTM + bronchiectasis. The bronchiectasis group had a

prevalence of untreated hypogammaglobulinemia of 1.3% and the NTM + bronchiectasis group had a prevalence of 1.6%. Clinical data were available for 15 of 17 of those patients and 10 patients had at least 1 episode of pneumonia in the low IgG group (8 of 12 in bronchiectasis group and 2 of 3 in NTM + bronchiectasis group). We also examined IgA and IgM levels. Six of 1,009 in the bronchiectasis group had an IgM level lower than 20 mg/dL and 0 of 245 in the NTM + bronchiectasis group had a low IgM level. Three of 1,009 in the bronchiectasis group had an IgA level lower than 5 mg/dL and 0 of 245 in the NTM + bronchiectasis group had a low IgA level. IgG subclasses were available for 68 patients. Four of 43 patients in the bronchiectasis group had an IgG2 subclass level lower than 100 mg/dL. There were no patients in the NTM + bronchiectasis group with a low IgG2 level. None of the differences observed between the bronchiectasis and NTM + bronchiectasis groups were statistically significant. Increased immunoglobulin levels also have been described in bronchiectasis; therefore, we examined increased levels as a secondary analysis.^{4,5} In the bronchiectasis group, 9.2% had an IgG level higher than 1,600 mg/dL, 6.4% had an IgM level higher than 230 mg/dL, and 9.8% had an IgA level higher than 400 mg/dL. In the NTM + bronchiectasis group, 9.0% had a high IgG level, 3.2% had a high IgM level, and 1.1% had a high IgA level.

This study of a tertiary care center-derived population with bronchiectasis has several potential limitations because it is a retrospective registry study and there might be referral bias because tertiary care patients are more likely to have complicated case and be medically fragile. In addition, we anticipate that the incidence of hypogammaglobulinemia in our study likely does not fully correlate with the prevalence of immunodeficiency. There might be treated patients with common variable immune deficiency, specific antibody deficiency, or other immune deficiencies with normal immunoglobulin levels. Patients diagnosed with an antibody deficiency and on adequate doses of immunoglobulin replacement would not appear to have hypogammaglobulinemia based on the laboratory results in this database. In a recent meta-analysis of children with non-CF-related bronchiectasis, 16% were found to have an underlying immunodeficiency, with 10% having a B-cell disorder.¹⁰ Our findings demonstrate that only 1% of adult patients with bronchiectasis have detectable un- or undertreated hypogammaglobulinemia. This is the largest dataset of patients with bronchiectasis ascertained for lung disease and not after referral by an immunologist. The identified hypogammaglobulinemia might be due to immune deficiency or might be secondary to corticosteroids or possibly even loss or catabolism.^{7,8} Our findings are reassuring in that only 1.4% of the cohort was found to have a level of hypogammaglobulinemia for which immunoglobulin replacement could be considered, which is of significance because uncorrected humoral immunodeficiency has been demonstrated to be a risk for poor outcome in many types of structural lung disease, including bronchiectasis.^{7,8} Therefore, we continue to recommend screening for humoral immunodeficiency in patients with bronchiectasis, especially when the diagnosis of bronchiectasis is first determined.

Acknowledgment

The authors acknowledge the COPD Foundation Bronchiectasis Research Registry.

Funding Sources: This study was supported in part by PCORI (support to PI CONNECT), and the Wallace Chair of Pediatrics (K.E.S.).

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Figure 1.

Immunoglobulin levels in patients with bronchiectasis and nontuberculous mycobacteria, with mean and SD (red) for the population. Reference ranges are 700 to 1,600 mg/dL for immunoglobulin G (IgG), 40 to 230 mg/dL for immunoglobulin M (IgM), and 70 to 400 mg/dL for immunoglobulin A (IgA).