

**Bronchiectasis and deteriorating lung function in agammaglobulinemia despite immunoglobulin replacement therapy**

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Thank you to you the Editors and Reviewers for assessing our revised manuscript.

Point by point response:

1. Figure legends for Figure 1 and 2 are already provided - page 21 of R2 revision.
2. Units (mg/kg/month) have now been corrected - now page 12 of R2 revision.

For Peer Review

1 **Bronchiectasis and deteriorating lung function in agammaglobulinemia despite immunoglobulin**  
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3 **replacement therapy**  
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**Short title:** Progressive lung disease in agammaglobulinemia

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## Summary

Immunoglobulin replacement therapy enhances survival and reduces infection risk in patients with agammaglobulinemia. We hypothesized that despite regular immunoglobulin therapy some patients will experience ongoing respiratory infections and develop progressive bronchiectasis with deteriorating lung function. 139 (70%) of 199 patients aged 1 to 80 years from nine cities in the UK with agammaglobulinemia currently listed on the UKPID registry were recruited to this retrospective case study and their clinical and laboratory features analyzed. 94% were male of whom 78% had *BTK* gene mutations. All patients were on immunoglobulin replacement therapy and 52% had commenced therapy by the time they were two years old. 60% were also taking prophylactic oral antibiotics. 56% of patients had radiological evidence of bronchiectasis, which developed between the ages of 7 to 45 years. Multi-variate analysis showed that three factors were significantly associated with bronchiectasis: reaching 18 years old (relative risk (95% CI) 14.2 (2.7 – 74.6)), history of pneumonia (3.9 (1.1 – 13.8)) and IVIG rather than SCIG (3.5 (1.2 – 10.1)), while starting immunoglobulin replacement after reaching two years old, gender and recent serum IgG concentration were not significantly associated. Independent of age, patients with bronchiectasis had significantly poorer lung function (predicted FEV<sub>1</sub> 74% (50 – 91)) than those without this complication (92% (84 – 101)) ( $p < 0.001$ ). We conclude that despite immunoglobulin replacement therapy, many patients with agammaglobulinemia can develop chronic lung disease and progressive impairment of lung function.

**Key words:** agammaglobulinemia, infection, bronchiectasis, lung function, immunoglobulin, IVIG, SCIG

1       **Abbreviations:** *BTK* Bruton tyrosine kinase, *BLNK* B cell linker, 95% CI 95% confidence interval, CVID  
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3       Common Variable Immunodeficiency; IG immunoglobulin; *IGHM* immunoglobulin heavy constant  
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5       mu, *IgLL1* immunoglobulin lambda like polypeptide 1, IQR interquartile range, IVIG intravenous  
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7       immunoglobulin, RR relative risk, SCIG subcutaneous immunoglobulin, UKPID UK Primary Immune  
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9       Deficiency; UK-PIN UK-Primary Immunodeficiency Network  
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## Introduction

Agammaglobulinemia is a group of inherited antibody immunodeficiency diseases, which unlike common variable immunodeficiency (CVID), usually present in the first few years of life. Males are more commonly affected than females, with mutations most commonly detected in the *BTK* gene on the X-chromosome.[1] Less frequently, mutations are found in genes coding for the immunoglobulin heavy mu chain (*IGHM*), pre-B cell and B-cell receptor (*IGLL1*, *CD79A*, *CD79B*) and the scaffold protein BLNK of both males and females.[2-6] Respiratory tract and other deep-seated infections caused particularly by encapsulated bacteria account for much of the morbidity and mortality.[7,8]

Since the initial description of inherited agammaglobulinemia by Ogden Bruton in 1952 the mainstay of treatment has been immunoglobulin (IG) replacement therapy to reduce this infection risk.[9] With early diagnosis and IG replacement therapy, clinicians currently expect that chronic lung damage and bronchiectasis might be prevented, more so than in other antibody deficiencies presenting more insidiously and later in life i.e. CVID.[10-13] However there is evidence that bronchiectasis can develop in over half and progress in a third of the patients despite carefully monitored IG replacement.[14-18]

Using data from the UK-PIN national primary immunodeficiency registry, this study aimed to determine if IG replacement therapy protects patients with agammaglobulinemia developing recurrent respiratory infections and in particular bronchiectasis with concomitant impairment of lung function. The findings of this study should help clinicians to more accurately advise their patients as to the natural history of agammaglobulinemia and its potential complications, even with modern, well monitored IG therapy.

## Methods

### *Patient definition and identification*

Patients with agammaglobulinemia excluding CVID, were identified from large clinical immunology referral centres across the United Kingdom contributing patients to the national UK-Primary Immune Deficiency (UKPID) registry.[19] The UKPID registry was established in 2009 and recruits patients prospectively after obtaining written consent. The registry currently contains 4,460 patients with primary immunodeficiency diseases, 199 of whom are classified as having agammaglobulinemia.

Data from nine UK cities with patients registered with agammaglobulinemia were approached. The study had multi-centre ethical approval (04/MRE07/68). After requesting permission from Centre Principle Investigators, data were collated into a single SPSS database (IBM SPSS Statistics 22.0) for analysis. Clinical information included demographics, past medical history of acute or recurrent respiratory tract infections. UKPID registry entries are updated on an annual basis by CB who personally visits each of the centres to ensure that subsequent morbidity and mortality, as well as latest laboratory parameters are recorded. For the purposes of this survey, registry entries were rechecked with source data by AS, CB and centre investigators and missing data points filled. LRTI was defined as respiratory symptoms associated with consolidation noted on chest-x-ray. Bronchiectasis was diagnosed when radiological abnormalities were identified by high-resolution chest CT imaging. Date of diagnosis of bronchiectasis was recorded. Timing of the CT imaging depended on the clinician. Spirometry was not routinely recorded within the PIDUK registry database. For the purposes of this study, the patient's most recent FEV<sub>1</sub> and FVC results were requested from individual site investigators. There is currently no UK-wide protocol for performing chest CT scans or pulmonary function tests. Frequency of monitoring of lung function amongst



1 patients in the study is not known. Therapies, including IG replacement and antibiotic prophylaxis  
2  
3 were also recorded. None of the patients were documented to have spent any time off infusions.  
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### 8 *Laboratory investigations*

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10 Laboratory data included routine hematology (hemoglobin, white blood count (WBC), absolute  
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12 neutrophil and lymphocyte counts, and platelets) and immunology (lymphocyte subsets: absolute  
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14 CD3, CD4, CD8, CD19, CD56) and serum immunoglobulin (Ig) concentrations) taken at diagnosis and  
15  
16 on IG replacement therapy. Immunoglobulin subclasses and vaccine antibody responses were not  
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18 available for most patients in this cohort. Lymphocyte subsets were assessed using standard  
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20 immunofluorescent staining and flow cytometry was performed in accredited regional clinical  
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22 immunology laboratories. Serum immunoglobulin concentrations were measured by nephelometry.  
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24 For patients on 3 – 4 weekly intravenous immunoglobulin replacement (IVIG), trough IgG  
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26 concentrations were checked just prior to administering the next dose; for patients on weekly  
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28 subcutaneous immunoglobulin therapy (SCIG) levels were checked at scheduled clinic visits which  
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30 did not necessarily occur just prior to administration of next dose.  
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### 41 *Statistical Analysis*

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43 Analysis was conducted using the IBM SPSS Statistics 22 program. Continuous variables are quoted  
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45 as medians and interquartile ranges. Statistical differences between groups were determined by  
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47 Chi-square, Mann Witney or Kruskal-Wallis tests. Differences were considered statistically significant  
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49 with a  $p$  value  $<0.05$ . Multi-variate analysis was calculated using Binominal Logistic and Cox  
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51 Regression.  
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## Results

### *Demographics*

One hundred and thirty nine of 199 patients (70%) classified as having agammaglobulinemia on the PIDUK registry were recruited from nine cities treating patients for primary immunodeficiency diseases within the United Kingdom. Twenty seven percent were from Manchester, 18% in London, 12% in Newcastle, 12% in Belfast and 11% in Glasgow, with smaller numbers of patients from Aberdeen, Cardiff, Leeds and Nottingham. Eighty percent were white European. Only 9 (6%) were female. A *BTK* gene mutation was found in 109 (78%) of the 130 males. Two males had *IGHM* mutations. No specific genetic cause was available in the remainder. The median age of the cohort was 27 (range 1 - 80) years. Eighty five percent of patients' symptoms commenced by three years old. The median age of diagnosis was three years (93% by five years old). The median (interquartile range) duration of follow-up was 21 (13 - 32) years, with an overall follow-up for the total cohort of 2,922 years. Three patients (2%) had died (Table I).

### *Clinical and laboratory correlates with infectious complications: bacterial respiratory tract infections and bronchiectasis*

Seventy eight percent of patients had suffered from bacterial infections; 74% from pneumonia, 70% chronic sinusitis, 38% otitis and 23% conjunctivitis. Fifty six percent had bronchiectasis (Table I). Bronchiectasis was associated with a history of bacterial infection at any site (relative risk (95% CI) 2.6 (1.0 - 6.3)), particularly with pneumonia (4.6 (1.8 - 11.8)) and otitis (4.2 (1.6 - 11.0)), but not sinusitis (1.4 (0.6 - 3.1)) or conjunctivitis (0.4 (0.2 - 1.1)) (Table I, Figure 1). Patients with bronchiectasis were significantly older (34 (28 - 48) years) than those without this complication (20 (12 - 34) years) ( $p < 0.001$ ) (Table I) and there was a linear increase in the proportion of patients

1 with bronchiectasis from 18 to 60 years of age ( $r = 0.81$ ,  $p < 0.001$ ) (Figure 2.A). Spirometry was  
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3 available on 73 patients (52%). Twenty of the remaining patients (14%) were too young to perform  
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5 lung function tests. Patients with bronchiectasis ( $n = 46$ ) had significantly lower FEV<sub>1</sub> (74% (50 - 91))  
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7 than those without this complication ( $n = 24$ ) (92% (84 - 101),  $p < 0.001$ ). Fifty five percent of  
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9 patients (25 of 46) with bronchiectasis had an FEV<sub>1</sub> of  $< 70\%$  compared with 8% (2 of 24 patients)  
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11 without bronchiectasis, ( $p < 0.001$ ). Using Cox regression multivariate analysis, the association  
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13 between FEV<sub>1</sub> and bronchiectasis (relative risk (95% confidence interval) 3.2 (1.8 - 5.4)) was  
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15 independent of age. FVC was not significantly different between the two groups (89% (68 - 100)  
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17 versus 96% (81 - 106),  $p = 0.2$ ).  
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23 The most common bacteria isolated from respiratory secretions was *Haemophilus influenzae*  
24 (46% of total isolates), followed by *Streptococcus pneumoniae* (18%), *Staphylococcus aureus* (12%)  
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26 and *Mycoplasma pneumoniae* (8%). There was no association between a particular bacterial species  
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28 and bronchiectasis. Extra-respiratory tract infections in order of frequency were septic arthritis,  
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30 osteomyelitis, skin infections, meningitis, septicemia and gastroenteritis. Only one patient was  
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32 reported to have echovirus encephalitis.  
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38 All but one patients had low or absent B-cells and normal CD56 NK cells. Absolute T-cell  
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40 numbers (CD3, CD4 and CD8) were within the normal range in all patients. None of the patients had  
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42 evidence of a persistent neutropenia (absolute neutrophil count  $< 1.0 \times 10^9/L$ ).  
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#### 48 *Treatment*

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50 Fifty two percent of patients had started on immunoglobulin replacement therapy by two  
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52 years old. The current median (interquartile) immunoglobulin dose was equivalent to 538 (459 -  
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54 705) mg/kg/month. Fifty five percent were on intravenous therapy while 45% were having the  
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1 therapy administered subcutaneously. Patients on IVIG therapy were significantly older (median age  
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3 34 years) than those on SCIG (median age 22 years),  $p < 0.001$  (Table II). A significantly greater  
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5 proportion of patients on IVIG than on SCIG had bronchiectasis and this association remained  
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7 significant after adjusting for patient's age (3.5 (1.2 – 10.1),  $p = 0.02$ ).  
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10 Patients with bronchiectasis started on IG therapy at a significantly older age than those  
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12 without this complication (Table I, Figure 2.B). However, using Binominal Regression multi-variate  
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14 analysis the three key variables associated with bronchiectasis were (i) reaching adulthood (>18  
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16 years old) (14.2 (2.7 – 74.6)), (ii) history of previous pneumonia (3.9 (1.1 – 13.8)) and (iii) treatment  
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18 with IVIG rather than SCIG (3.5 (1.2 – 10.1)). Factors that were not significant in this multi-variate  
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20 analysis were having started IG supplementation after 2 years old, gender and recent serum IgG  
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22 concentration. Regarding serum IgG concentration, patients with bronchiectasis were more likely to  
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24 have been prescribed larger doses of Ig (equivalent to 598 (498 - 848) mg/kg/month) than those  
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26 without this complication (equivalent to 511 (436 - 584),  $p < 0.01$ ) and subsequently had  
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28 significantly higher serum IgG concentrations (10.8 (8.7 - 12.9) versus 9.7 (8.5 - 11.1) g/L,  $p < 0.03$ )  
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30 (Table I, Figure 2.C), with nearly one in five patients with bronchiectasis having an IgG concentration  
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32 above 14.0g/L. Eighty three percent of patients in the cohort had been on immunoglobulin  
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34 replacement therapy for more than seven years (range 0 - 43 years) prior to their diagnosis with  
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36 bronchiectasis. There was no significant association between history of pneumonia or otitis and  
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38 recent serum IgG concentrations above 4.0, 7.0, 10.0 or 14.0 g/L.  
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48 Sixty percent of patients had been prescribed prophylactic antibiotics (Table I). Although the  
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50 use of prophylactic antibiotic use did not increase significantly with age or with history of respiratory  
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52 infections (pneumonia, otitis or bronchiectasis), their use was associated with poorer lung function  
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54 (FEV1 75 (49 – 93) vs 90 (83 – 93),  $p = 0.004$ ). These patients were also more likely to be on a higher  
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1 dose of IG replacement therapy (580 (508 – 788) vs 497 (428 – 582) equivalent mg/kg/month,  $p =$   
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3 0.002) and have higher serum IgG concentrations (11.1 (9.3 – 12.4) vs 9.4 (8.4 – 10.4) g/L,  $p = 0.003$ ).  
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6 Patients recruited from London were significantly older than those from other UK cities. All  
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8 patients recruited from Newcastle upon Tyne and Belfast were white European, in contrast to 64 -  
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10 73% of patients from London, Manchester and Glasgow ( $p < 0.005$ ). There were no significant  
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12 regional differences in age of commencement of IG therapy, dose of IG therapy, use of prophylactic  
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14 antibiotics, serum IgG concentration or prevalence of bronchiectasis. However, London and Glasgow  
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16 centres prescribed IVIG rather than SCIG more frequently than other centres ( $p < 0.005$ ) (Table III).  
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## Discussion

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3 In contrast to the relatively large number of retrospective case studies on CVID, there are only a few  
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5 previously published studies with over 100 agammaglobulinemia patients.[20-21] This is the largest  
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7 study of patients with agammaglobulinemia focusing on chronic lung disease and lung function. Since  
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9 Sweinberg *et al* suggested in 1991 [22] that IG replacement could prevent chronic lung damage, the  
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11 perceived dogma of many patients and clinicians is that optimal IG therapy, good compliance and  
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13 close monitoring can prevent lung disease.[23,24] This retrospective case study shows that over  
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15 half of the patients with agammaglobulinemia in our UK registry developed radiological evidence of  
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17 bronchiectasis and poor lung function. Furthermore, these measures of lung disease occurred many  
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19 years after starting IG replacement therapy. Three independent factors were associated with risk of  
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21 bronchiectasis: attaining adulthood, history of previous pneumonia and treatment with IVIG rather  
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23 than SCIG therapy. Gender, age at starting IG therapy and species of bacterial pathogen isolated  
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25 from respiratory secretions were not significant risk factors after adjusting for age.  
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33 A major difference between our study and the small study of 22 patients (10 with XLA)  
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35 performed by Sweinberg *et al* is that over the last 25 years, high resolution chest CT scans rather  
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37 than chest x-rays have become the standard and a much more sensitive test for bronchiectasis. This  
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39 is likely to at least partly explain the higher prevalence of bronchiectasis in our study.[24-25] An  
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41 important question not addressed here is whether the observed radiological evidence of  
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43 bronchiectasis and the poorer lung function corresponds to deterioration in patients' quality of life.  
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45 Bryan *et al* in their survey of 15 patients with agammaglobulinemia from the North of England  
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47 suggested that there may well be a significant impact on patients' respiratory and overall quality of  
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49 life.[26] Larger studies are required to understand more fully the overall burden of disease.  
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1 There is ongoing debate as to the optimal serum IgG concentration in patients with  
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3 agammaglobulinemia.[27-29] with some clinicians suggesting that a trough [IgG] of >4g/L is  
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5 adequate, while others recommending a [IgG] of >10g/L to prevent the development of subclinical  
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7 lung damage. We found no significant association between the proportion of patients with  
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9 bronchiectasis, pneumonia, otitis or poor lung function and serum IgG cut-off concentrations of 4.0,  
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11 7.0 or 10.0 g/L. Nineteen percent of patients, all with bronchiectasis, had an IgG concentration  
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13  $\geq 14.0$ g/L suggesting that in a subset of patients with bronchiectasis high dose IG supplementation is  
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15 used to try and prevent further deterioration. In this regard, patients with poorer lung function were  
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17 on more treatment, both in terms of dose of IG supplementation and use of prophylactic antibiotics.  
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19 Whether this escalation in therapy is beneficial is not possible to determine from this study.  
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26 There were some regional differences, particularly in the age of the patients with the longer  
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28 established London centers having older patients with a higher prevalence of bronchiectasis. This  
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30 may also explain the preferential use of IVIG in London compared with most other regional centres,  
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32 as the use of SCIG has been largely introduced into the UK over the last 20 years. Serum IgG  
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34 concentrations were significantly lower in patients on SCIG than IVIG but, after taking the age of the  
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36 patient into account, IVIG rather than SCIG was associated with an increased risk of bronchiectasis.  
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38 This is a novel finding, as no previously published studies having directly compared the efficacy of  
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40 IVIG and SCIG in preventing lung disease. Independent studies from other countries are required to  
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42 determine if this finding can be generalized, as if confirmed it may lead to SCIG being recommended  
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44 as the preferred route of treatment for patients with agammaglobulinemia in the future.  
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51 There are a number of limitations of this study. The retrospective nature is inevitable as a  
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53 prospective study to look at the natural history of these patients is difficult. As the PIDUK registry  
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55 has only been collecting data since 2009, deaths prior to that time would not have been recorded  
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1 and therefore the study may well underestimate the severity of the clinical course. It may be that  
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3 followed up for longer, most of these patients will eventually develop chronic lung damage and  
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5 respiratory impairment. Alternatively, with more patient-friendly infusion modalities,[30] and more  
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7 precise and regular monitoring, less patients would develop these pulmonary complications. The  
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9 criteria used by clinicians in each center to order CT scans were not recorded and may have affected  
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11 the timing of diagnosis of bronchiectasis. Quality of life data and smoking history were not collected  
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13 as part of our survey or the PIDUK registry. It would be useful for registries to consider collecting  
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15 smoking history and "patient experience" as part of future routine data collection, particularly in  
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17 view of the potential impact and confounding effects of smoking on lung function. Lung function  
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19 data is currently not recorded routinely as part of the PIDUK registry and had to be requested  
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21 directly from the center investigators. Recording of lung function data by the PIDUK and other  
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23 registries could potentially provide an additional useful outcome measure, particularly as  
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25 deterioration in lung function is a recognized important complication of agammaglobulinemia.  
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33 In conclusion, this study suggests that even with IG replacement therapy, many patients with  
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35 agammaglobulinemia develop chronic lung disease and reduced lung function. Patients at higher  
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37 risk are those that have reached adulthood, have a previous history of pneumonia and are on IVIG  
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39 rather than SCIG therapy. It is important for clinicians to counsel their patients appropriately to  
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41 avoid unrealistic expectations and promote careful long-term monitoring of lung disease particularly  
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43 in those with higher risks.  
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**Declaration of interests**

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**Author Contribution**

PDA conceived of and led the study. Each regional centre lead was in charge of recruiting patients with agammaglobulinemia onto the UKPID registry, which was maintained and updated by CB. AS collated all the data into the centralized database. All authors contributed to the writing of the manuscript and approved the final version.

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**Figure legends**

**Figure 1** Association between bronchiectasis and other respiratory tract infections. Orange = patients with no bronchiectasis, Blue = patients with bronchiectasis. \*  $p < 0.05$ , \*\*  $p < 0.005$  Chi-square test.

**Figure 2** Factors associated with bronchiectasis. **A.** Current age of patients with bronchiectasis. **B.** Age at which patients with (blue) and without (orange) bronchiectasis commenced immunoglobulin replacement therapy. **C.** Recent serum IgG concentration in patients with (blue) and without (orange) bronchiectasis. **Insert:** Percentage of patients with serum IgG concentrations  $>4.0$ ,  $>7.0$ ,  $>10.0$  and  $>14.0$  g/L. \*\*  $p < 0.005$  using Breslow or Chi-square statistics.

Table I Demographic, clinical and laboratory parameters of 139 patients with agammaglobulinemia

| Parameter                          | Total cohort          | No bronchiectasis     | Bronchiectasis        | P value |
|------------------------------------|-----------------------|-----------------------|-----------------------|---------|
| Number                             | 139                   | 61                    | 78                    |         |
| Age (years)                        | 27 (18 - 40)          | 20 (12 - 34)          | 34 (28 - 48)          | 0.001   |
| Gender                             | 94% male              | 91% male              | 93% male              | 0.5     |
| Ethnicity                          | 80% white European    | 82% white European    | 81% white European    | 1.0     |
| Family history                     | 54%                   | 59%                   | 53%                   | 0.6     |
| Age of onset of symptoms (years)   | 0 (0 - 1)             | 0 (0 - 1)             | 0 (0 - 2)             | 0.2     |
| Age at diagnosis (years)           | 3 (1 - 14)            | 3 (1 - 4)             | 7 (1 - 43)            | 0.5     |
| Bacterial infections               | 78%                   | 69%                   | 85%                   | 0.05    |
| Bronchiectasis (on chest CT scan)  | 56%                   | 0%                    | 100%                  |         |
| Bacterial pneumonia                | 74%                   | 60%                   | 87%                   | 0.001   |
| Chronic sinusitis                  | 70%                   | 67%                   | 71%                   | 0.7     |
| Otitis                             | 38%                   | 20%                   | 50%                   | 0.004   |
| Conjunctivitis                     | 23%                   | 36%                   | 18%                   | 0.07    |
| Died                               | 2%                    | 0%                    | 4%                    | 0.1     |
| FEV1 (% predicted for age)         | 84 (56 - 94)          | 92 (84 - 101)         | 74 (50 - 91)          | 0.001   |
| FVC (% predicted for age)          | 89 (78 - 103)         | 96 (81 - 106)         | 89 (68 - 100)         | 0.2     |
| Pre-treatment IgM (g/L)            | 0.0 (0.0 - 0.05)      | 0.1(0.0 - 0.2)        | 0.1 (0.0 - 0.2)       | 0.9     |
| Pre-treatment IgG (g/L)            | 1.0 (0.1 - 2.8)       | 0.9 (0.1 - 2.6)       | 1.1 (0.0 - 2.9)       | 0.9     |
| Pre-treatment IgA (g/L)            | 0.0 (0.0 - 0.0)       | 0.0 (0.0 - 0.1)       | 0.0 (0.0 - 0.2)       | 0.9     |
| CD19 (B-cells) (cells/microlitre)  | 0 (0 - 6)             | 1 (0 - 42)            | 0 (0 - 2)             | 0.2     |
| CD3 (T-cells) (cells/microlitre)   | 1,504 (1,143 - 1,980) | 1,470 (1,195 - 1,945) | 1,539 (1,159 - 2,049) | 0.7     |
| Neutrophils (X 10 <sup>9</sup> /L) | 4.5 (3.3 - 6.8)       | 4.3 (3.0 - 6.5)       | 4.9 (3.5 - 7.5)       | 0.06    |
| Latest IgG (g/L)                   | 10.1 (8.5 - 11.9)     | 9.7 (8.5 - 11.1)      | 10.8 (8.7 - 12.9)     | 0.02    |
| Latest IgG ≥ 4.0 g/L               | 136 (98%)             | 59 (96%)              | 76 (98%)              | 0.6     |

|    |                                      |                    |                    |                    |       |
|----|--------------------------------------|--------------------|--------------------|--------------------|-------|
| 1  | Latest IgG $\geq$ 7.0 g/L            | 131 (94%)          | 55 (90%)           | 74 (95%)           | 0.5   |
| 2  | Latest IgG $\geq$ 10.0 g/L           | 75 (54%)           | 28 (46%)           | 46 (59%)           | 0.2   |
| 3  | Latest IgG $\geq$ 14.0 g/L           | 14 (10%)           | 0 (0%)             | 14 (18%)           | 0.001 |
| 4  |                                      |                    |                    |                    |       |
| 5  |                                      |                    |                    |                    |       |
| 6  |                                      |                    |                    |                    |       |
| 7  | IG replacement                       | IVIG 55%, SCIG 45% | IVIG 58%. SCIG 42% | IVIG 34%, SCIG 66% | 0.008 |
| 8  | Dose IG (mg/kg/month)                | 538 (459 - 705)    | 510 (438 - 584)    | 598 (495 - 848)    | 0.006 |
| 9  | Age IG replacement commenced (years) | 3 (1 - 6)          | 1 (0 - 3)          | 4 (2 - 8)          | 0.02  |
| 10 |                                      |                    |                    |                    |       |
| 11 | IG started when $\geq$ 2 years old   | 72 (52%)           | 20 (32%)           | 52 (67%)           | 0.002 |
| 12 | Prophylactic antibiotics             | 60%                | 54%                | 64%                | 0.3   |
| 13 |                                      |                    |                    |                    |       |
| 14 |                                      |                    |                    |                    |       |
| 15 |                                      |                    |                    |                    |       |
| 16 |                                      |                    |                    |                    |       |

17 Continuous variables are displayed as median (interquartile range) IG = immunoglobulin replacement, IVIG intravenous  
 18 immunoglobulin, SCIG subcutaneous immunoglobulin. Subgroups with and without bronchiectasis are compared using Chi-square test  
 19 for discrete variables and Mann-Whitney U test for continuous variables.  
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Table II Clinical and laboratory features of patients receiving immunoglobulin replacement intravenously and subcutaneously

|                               | IVIG            | SCIG           | <i>P value</i> |
|-------------------------------|-----------------|----------------|----------------|
| Number (%)                    | 73              | 63             |                |
| Age (years)                   | 34 (23-47)      | 22 (13-32)     | 0.001          |
| Males (%)                     | 96%             | 93%            | 0.7            |
| white European (%)            | 85%             | 75%            | 0.2            |
| [IgG] on IG replacement (g/L) | 10.8 (9.2-12.3) | 9.4 (8.0-11.2) | 0.004          |
| Prophylactic antibiotics (%)  | 69%             | 48%            | 0.02           |
| Bacterial sepsis (%)          | 81%             | 76%            | 0.5            |
| Bronchiectasis (%)            | 68%             | 44%            | 0.02           |
| LRTI (%)                      | 75%             | 74%            | 1.0            |
| Otitis (%)                    | 42%             | 35%            | 0.5            |
| Sinusitis (%)                 | 74%             | 67%            | 0.5            |
| Conjunctivitis (%)            | 19%             | 29%            | 0.3            |

Immunoglobulin replacement therapy: IVIG = intravenous, SCIG = subcutaneous. LRTI = history of bacterial lower respiratory tract infections. Continuous variables represent medians/interquartile ranges. Mann-Whitney U test was used for continuous variables and Chi-square test for discrete variables to compare groups with and without complications.

Table III Demographics, clinical features and treatment of patients with agammaglobulinemia from major UK cities

|   | London          | Manchester      | Newcastle      | Belfast        | Glasgow        | <i>P</i> value |
|---|-----------------|-----------------|----------------|----------------|----------------|----------------|
| <b>Number (%)</b>                           | 24              | 44              | 17             | 17             | 15             |                |
| <b>Age (years)</b>                          | 39 (28-53)      | 22 (13-37)      | 29 (14-36)     | 22 (18-27)     | 22 (12-34)     | 0.002          |
| <b>White European (%)</b>                   | 71%             | 64%             | 100%           | 100%           | 73%            | 0.004          |
| <b>Bronchiectasis (%)</b>                   | 87%             | 46%             | 53%            | 44%            | 38%            | 0.01           |
| <b>Age bronchiectasis diagnosed (years)</b> | 19 (16-29)      | 16 (14-35)      | 23 (20-23)     | -              | 18 (18-18)     | 0.8            |
| <b>Age IG commenced (years)</b>             | 4 (1-6)         | 3 (0-5)         | 7 (1-7)        | 2 (0-12)       | 2 (2-6)        | 0.8            |
| <b>Percentage on SCIG</b>                   | 21%             | 62%             | 47%            | 60%            | 20%            | 0.004          |
| <b>Dose of IG (mg/kg/month equivalent)</b>  | 661 (461-1048)  | 511 (436-559)   | 612 (460-612)  | 584 (443-869)  | 518 (492-815)  | 0.2            |
| <b>Latest [IgG] (g/L)</b>                   | 11.1 (9.4-13.4) | 10.2 (8.4-11.8) | 9.3 (8.4-10.5) | 8.5 (7.4-12.4) | 10.8 (10-11.4) | 0.054          |
| <b>Prophylactic antibiotics</b>             | 59%             | 70%             | 47%            | 42%            | 50%            | 0.3            |

Numbers for continuous variables represent medians/interquartile ranges. Kruskal-Wallis test was used for continuous variables and Chi-square test for discrete variables to compare groups. IG = immunoglobulin replacement therapy.

Figure 1

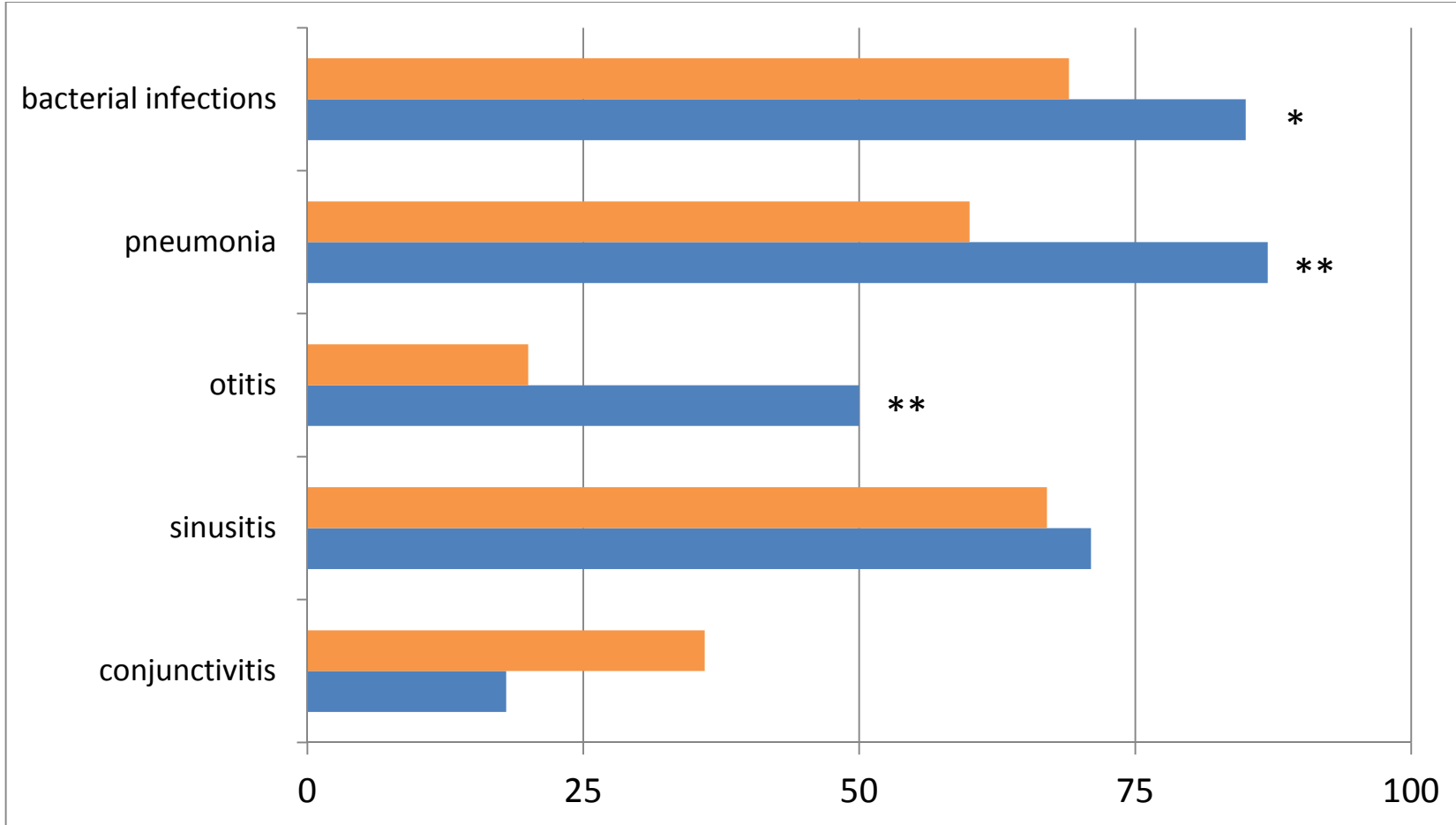
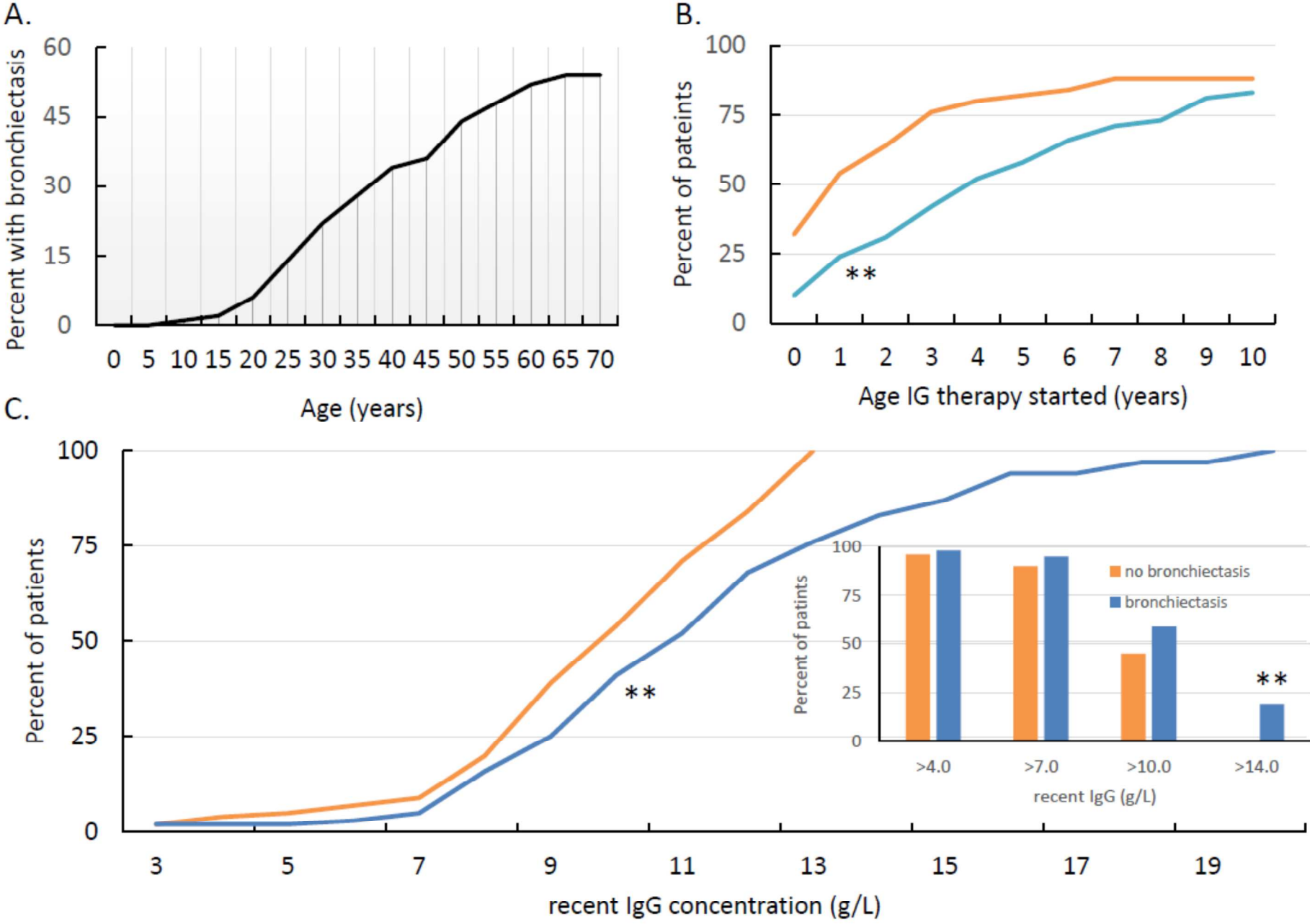


Figure 2



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