


SCREENING PROTOCOLS TO MONITOR RESPIRATORY STATUS IN PRIMARY IMMUNODEFICIENCY DISEASE: FINDINGS FROM A EUROPEAN SURVEY AND SUBCLINICAL INFECTION WORKING GROUP

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Abbreviations:

ARAG	Autosomal recessive agammaglobulinaemia
CRP	C-reactive protein
CVID	Common variable immunodeficiency
ESID	European Society for Immunodeficiencies
FEF 25–75	Forced expiratory flow at 25-75% of forced vital capacity
FEV1	Expiratory volume at 1 second
FVC	Forced vital capacity
GLILD	Granulomatous and lymphocytic interstitial lung disease
HRCT	High resolution computerised tomography
Ig	Immunoglobulin
MRI	Magnetic resonance imaging
PAGID	Pan-American Group for Immunodeficiency

PCR	Polymerase chain reaction
PEFR	Peak expiratory flow rate
PID	Primary immunodeficiency
SPAD	Specific antibody deficiency
TLCO	Transfer factor for carbon monoxide
XLA	X-linked agammaglobulinaemia

Summary

Many patients with primary immunodeficiency (PID) who have antibody deficiency develop progressive lung disease due to underlying subclinical infection and inflammation. To understand how these patients are monitored we conducted a retrospective survey based on patient records of 13 PID centres across Europe, regarding the care of 1,061 adult and 178 paediatric patients with PID on IgG replacement.

The most common diagnosis was common variable immunodeficiency in adults (75%), and hypogammaglobulinaemia in children (39%). The frequency of clinic visits varied both within and between centres: every 1 to 12 months for adult patients and every 3 to 6 months for paediatric patients. Patients diagnosed with lung diseases were more likely to receive pharmaceutical therapies and received a wider range of therapies than patients without lung disease. Variation existed between centres in the frequency with which some clinical and laboratory monitoring tests are performed, including exercise tests, laboratory testing for IgG subclass levels and specific antibodies, and lung function tests such as spirometry. Some tests were carried out more frequently in adults than in children, probably due to difficulties conducting these tests in younger children. The percentage of patients seen regularly by a chest physician, or who had microbiology tests performed following chest and sinus exacerbations, also varied widely between centres.

Our survey revealed a great deal of variation across Europe in how frequently patients with PID visit the clinic and how frequently some monitoring tests are carried out. These results highlight the urgent need for consensus guidelines on how to monitor lung complications in PID patients.

Introduction

Approximately 70–75% of patients with primary immunodeficiency disease (PID) suffer from antibody deficiency [1]. Many of these patients may develop progressive lung disease as a result of underlying subclinical infection and inflammation, despite apparently adequate levels of replacement immunoglobulin G (IgG) [2-6]. Viral and bacterial pathogens have been detected in secretions from the airways of patients with PID with persistent and/or recurrent infections [7-11] and from PID patients with no apparent infections at the time of testing [7]. Consensus of a meeting of EU experts (Paris, June 2013) was that subclinical infection is not adequately monitored, and wide variation may exist between centres in the methods and frequency of monitoring both for evidence of infection and development of chronic lung disease.

Currently, a number of screening measures are used across different centres to diagnose and monitor patients with PID, including lung function tests such as forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), and transfer factor for carbon monoxide (TLCO); imaging techniques such as high resolution computerised tomography (HRCT) and magnetic resonance imaging (MRI); and numerous other tests including cultures from induced sputum, blood gas analysis and exercise testing. However, the frequency with which these are applied is not standardised, and there is currently a lack of local and national guidelines for screening and treating lung disease in PID.

It is expected that differences may exist between the frequency with which some clinical and laboratory monitoring tests are performed in adult and paediatric patients, due to the challenges of performing some of these tests in infants. For instance, infants can require sedation or a general anaesthetic in order for HRCT or MRI to be carried out [12, 13]. In addition, lung function testing, TLCO in particular, can only be reliably performed in children over 6 years of age [14].

To better understand current practice in how PID patients with antibody deficiency across Europe are screened and monitored in both adult and paediatric patients with different

categories of lung disease, a survey was conducted to identify screening tests and their timing in different centres.

Methods

A survey exploring which screening protocols are used in the assessment of PID was conducted from September to November 2015 (Supplement). The survey included 12 questions and was emailed to 13 different centres across eight European countries: Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, and the UK.

Information was requested on the number of paediatric and adult patients with antibody deficiency for 6 patient groups:

- Paediatric/adult PID patients with no apparent lung disease
 - Paediatric/adult PID patients with bronchiectasis
 - Paediatric/adult PID patients with other lung disease, e.g. fibrosing lung disease or granulomatous and lymphocytic interstitial lung disease (GLILD) [group referred to as 'other lung disease']

Respondents were asked to consider only patients treated with IgG replacement therapy. PIDs were defined according to the European Society for Immunodeficiencies (ESID) criteria. Common variable immunodeficiency (CVID) was diagnosed according to the ESID / Pan-American Group for Immunodeficiency (PAGID) criteria or revised ESID criteria [15, 16]. For each patient group described above, information on how frequently patients attended the clinic for monitoring and assessment, which screening and monitoring tests were used and how often, and which treatments were administered at their centre for patients with PID was requested.

Data on how many patients received different therapies (in addition to IgG replacement therapy), including prophylactic antibiotics, steroids and other therapies such as rituximab

was collected. The proportion of patients treated with each therapy was calculated as a percentage.

Survey respondents were asked to consider how frequently they undertake different types of tests for on-going monitoring for each group of patients. Tests were divided into five categories: clinical monitoring and assessment, laboratory monitoring, lung function, imaging, and other monitoring tests. The frequency of testing was recorded as 1) scheduled regularly or at the clinic visit, 2) as required, or 3) never. The proportion of patients included in each frequency group was calculated as a percentage.

A Fischer's exact test was conducted to assess whether there were any statistically significant differences regarding the frequency with which the clinical monitoring and assessment tests were conducted between the different disease groups (without lung disease, with bronchiectasis or with 'other lung disease') for either adult or paediatric patients. Information about which guidelines were followed for screening, treating and monitoring patients with PID, the percentage of patients seen regularly by a chest physician at their institute, and the frequency of microbiology testing in patients with chest and sinus exacerbations was also collected.

Results

Patient characteristics

A total of 1,239 patients with PID presenting with antibody deficiency and receiving IgG treatment were included in this survey (Table 1). The most common underlying PID diagnosis for paediatric patients was hypogammaglobulinaemia (39%), whereas the majority of adult patients had been diagnosed with CVID (75%). Of the patients included in the survey, 24% of children and 36% of adults had been diagnosed with lung disease.

Patients diagnosed with lung diseases were more likely to receive prophylactic antibiotics, steroids, rituximab or other pharmacological treatments than patients without lung disease. A

higher percentage of patients with bronchiectasis or 'other lung diseases' received prophylactic antibiotics as compared to those without lung disease (Figure 1). A higher percentage of clinicians treating paediatric patients reported prescribing prophylactic antibiotics compared to those treating adult patients, regardless of the presence or type of lung disease. The percentages of patients receiving prophylactic antibiotics varied widely in all categories as some respondents stated that they treated all patients with antibiotic prophylaxis, while others never recommended this therapy for these patient categories. In addition, a higher percentage of adult patients received inhaled and/or oral steroids than paediatric patients, regardless of the presence or type of lung diseases. Steroids (inhaled and/or oral) were given most commonly to those with 'other lung diseases' (65% of adult patients and 57% of paediatric patients), followed by patients with bronchiectasis (50% of adult patients and 32% of paediatric patients), and given to 31% of adults and 0% of paediatric patients without lung disease.

Frequency of clinic visits

There was a greater variation between centres in the frequency of clinic visits for adults than paediatric patients. Clinicians routinely saw paediatric patients every 3 to 6 months, whereas adult patients were seen from once every month, to once every 12 months. Variation also existed within centres, with some clinicians seeing patients at fixed intervals (commonly every 3 or 6 months for both adult and paediatric patients) and others seeing patients based on clinical findings; for example, one centre reviewed adult patients every 4 to 12 months. Clinicians commented that patients were seen more frequently if they were particularly unwell; for example, patients with cancer, chronic lung disease or malabsorption may be seen every month. For paediatric patients, respondents generally reported seeing those with bronchiectasis or 'other lung diseases' more frequently than those with no lung disease (mean: 3.7, 3.7 and 5.2 months, respectively). For adult patients, respondents generally reported seeing those with 'other lung diseases' (such as fibrosing lung disease or GLILD)

more frequently than those with bronchiectasis and no lung disease (mean: 3.3, 4.7 and 4.9 months, respectively).

Clinical monitoring and assessment

The frequency with which clinical monitoring and assessment was carried out was similar for adult and paediatric patients for most tests, as shown in Figure 2. In addition, no significant differences were observed between the frequencies of testing for patients without lung disease, with bronchiectasis or with 'other lung disease', for either adult or paediatric patients. The majority of clinical monitoring was performed regularly at clinic visits, where all respondents conducted a clinical examination and recorded frequencies of respiratory tract infection and sinusitis since last visit. For exercise tests, fatigue assessments, and quality of life assessments particularly wide variation was seen in the frequencies of testing at different centres (Figure 2). Exercise tests were less frequently performed in paediatric patients than adult patients (25% versus 44–63%, respectively), regardless of the presence of lung disease.

Laboratory monitoring tests

For patients without lung disease, the frequency of laboratory monitoring varied greatly between the different centres, as did the tests used (Figure 3). However, few differences in the frequency of testing were seen in the monitoring of adult compared to paediatric patients (Figure 3). In addition, there were no significant differences in the frequency of performing laboratory monitoring, including sputum analysis, viral swabs and deep sequencing, for either adult or paediatric patients with and without lung disease.

Testing for elastase in sputum and deep sequencing for detecting pathogens were only carried out by a minority (0%–25%), regardless of patient's age or the presence of lung disease. The frequency of testing for specific antibodies and IgG2 and IgG3 trough levels varied widely between centres. For all groups of patients at least 71% of clinicians reported that IgG trough levels and IgA and IgM levels were assessed routinely at clinic visits; this

was more frequently than for monitoring IgG subclass levels, which were only assessed routinely or as required by around 50% of clinicians, regardless of age or the presence of lung disease. Testing for specific antibodies was conducted slightly more frequently by clinicians monitoring adult patients as compared to those monitoring paediatric patients; depending on the presence of lung disease, these tests were never performed by 38–50% of centres treating children, compared to 22–25% of centres treating adults. Swabs for viral polymerase chain reaction (PCR) testing were mainly carried out as required, regardless of age or lung disease. One respondent commented that obtaining routine viral swabs for PCR testing was recently discontinued at their institute, following an audit, and is now only performed when the patient is symptomatic.

Lung function tests

Lung function tests were carried out routinely at the majority of centres. There were generally only small variations in the frequency of testing between adult and paediatric patients (Figure 4) and no significant differences were observed between different disease groups. However, there was a trend towards more frequent testing in adult vs. paediatric patients with 'other lung disease'. For example, FEV1 and FVC were performed at clinic visits in 50% of paediatric patients with 'other lung disease', compared to 78% of adults. Additionally, for both adult and paediatric patients lung function tests were generally performed more frequently in patients with lung disease than without; for example, FEV1, FVC, peak expiratory flow rate (PEFR), and the forced expiratory flow at 25–75% of FVC (FEF 25–75) were performed routinely at clinic visits by 50–63% of respondents when treating adults with no lung disease, compared to 67–78% of respondents when treating adults with bronchiectasis or 'other lung disease'. The same was true for the frequency of lung function tests for paediatric patients with no lung disease versus bronchiectasis. There was also no significant difference in the frequency of testing for paediatric patients without lung disease and those with 'other lung disease'; however, this may be due to the low number of the latter patient category included in this survey (n=10).

TLCO was performed routinely by fewer clinicians than the other tests for both adult and paediatric patients. In adults the test was performed at routine clinic visits by 38% of clinicians for patients without lung disease, 44% for patients with bronchiectasis and 56% for patients with 'other lung disease'. However, TLCO was performed less routinely in paediatric patients; it was only performed by 13% of clinicians treating those with no lung disease or bronchiectasis, and by 25% of clinicians when treating children with 'other lung disease'. In addition, TLCO was never performed in paediatric patients by 25–38% of clinicians.

Imaging

Although no significant difference between disease groups was observed, there was a trend for all imaging tests to be carried out slightly more frequently in adult than paediatric patients with no lung disease (Figure 5). Additionally, HRCT imaging was performed at least occasionally by all clinicians for paediatric patients with lung disease, whereas 25% never carried out the test in paediatric patients without lung disease. For adult patients, around half of all respondents regularly performed HRCT imaging and the other half performed HRCT imaging as required, regardless of the presence or type of lung disease. When asked which imaging techniques were used to assess which organs, HRCT was the predominant imaging modality used for the lungs.

MRI was used by some respondents for imaging of the brain and central nervous system; however, this was rarely performed. In patients without lung disease, MRI was never performed by 63% of clinicians treating paediatric patients, and was performed as needed by the remainder (Figure 5). MRI was more frequently performed in adult patients; it was performed routinely by 13% of clinicians and as needed by approximately half of respondents. Only minimal variations were seen in the frequency of MRI for patients with and without lung disease.

X-rays of the lungs were carried out as needed by the majority of respondents, and this frequency was largely independent of disease state.

Other monitoring tests

The percentage of all PID patients regularly seen by a chest physician varied widely, with answers ranging from 30–100%. The percentage of chest and sinus exacerbations which did not have microbiology tests performed also varied; 69% of respondents stated that 50% or more of their patients had no microbiology tests performed.

Guidelines

Centre guidelines were followed when available. Only three respondents out of thirteen, from centres in Italy and Sweden, stated that they follow national guidelines; respondents from centres in the UK, Germany, Spain, Belgium and the Netherlands specifically reported a lack of national guidelines. Guidelines followed included those from the Immune Deficiency Foundation [17], Italian Primary Immunodeficiency Network [18], UK Primary Immunodeficiency Network, and additional published guidelines [5, 19-22].

Discussion

Our survey has revealed a great deal of variation across Europe in how frequently PID patients attend clinics and how frequently some monitoring tests are carried out in PID patients with and without lung disease, reflecting the lack of guidelines or standardised routines for respiratory monitoring in patients with PID [3].

The frequency at which patients' quality of life should be monitored is also not standardised, which was reflected in the wide range of frequencies indicated by the survey respondents.

However, results from a self-reported survey of 1,526 patients with PID showed that recognising the factors that drive perceived health is key for delivering appropriate treatment to individual patients with PID [23]. These findings highlight the importance of selecting the most appropriate methods and standardising quality of life and perceived health assessments in PID patients.

Variation in the frequency with which some monitoring tests were performed may be due to differences in health care services provided in different countries. Moreover, international guidelines are not yet available to harmonise disparities in monitoring between different countries. Also, the availability of some laboratory tests, as well as access to physiotherapy and pulmonary rehabilitation, may be influenced by expertise and funding available at different centres; these factors may also influence the frequency of clinic visits, the availability of respiratory physicians and the use of some monitoring protocols/tests.

As mentioned in the introduction, some differences existed between the frequency with which some clinical and laboratory monitoring tests were performed in adult versus paediatric patients, which may be due to the challenges of performing tests such as MRI, HCRT and TLCO in very young children. Conversely, it should be noted that other variables, such as the rate of growth and weight gain (not investigated in this survey) form important aspects of assessment and monitoring in children but are not an issue in adults.

High resolution CT scan is a valuable tool for diagnosing and also monitoring, and can lead to early detection of lung abnormalities. In this study, participants were in agreement that adult patients should have a baseline HRCT, but the exact frequency of CT evaluation for follow up is less well defined. Most experts suggest HRCT should be performed every 2–4 years for patients with proven and potentially progressive lung abnormalities and less frequent in patients with normal lung findings, as demonstrated in the literature [5, 20, 24, 25]. However, its use must carefully consider a small risk associated with the ionizing radiation exposure required for CT scans [26]. This consideration is particularly pertinent to children; thus, although HRCT should be considered in paediatric patients to monitor disease progression [1], it should not be used on a regular basis in children without lung disease. The cost of CT scans and whether the results will affect patient management should also be considered. The expectation that imaging studies can be used to monitor patients may be misplaced; if there is accelerated disease progression the achievable interval is too long and other approaches are required to help optimise the timing of

interventions. MRI provides an alternative to HRCT but is not yet widely used for diagnosis and monitoring of lung disorders in PID.

As expected, results from our survey suggested that there is an increase in the perceived prevalence of lung disease in adult PID patients compared to paediatric patients, which appeared to occur despite current monitoring and treatment interventions. Respondents reported that while lung disease is less commonly seen in patients less than 10 years old, this may depend on the level of screening, and children diagnosed with PID when they were older were more likely to have already established lung disease. Differences in the prevalence of lung disease may reflect the increased duration of infection in the presence of poor antibody function and of exposure to pathogens in adults, and delayed diagnosis and/or under-treatment. In addition, lung disease may be caused by inflammation secondary to immune dysregulation over an extended period of time [20], and co-morbidities including sinus disease, airflow obstruction, and gastro-oesophageal reflux disease may influence infective exacerbation rates of bronchiectasis and potentially disease progression. Thus, adults are more likely to be affected than paediatric patients due to their increased duration of exposure. Improvements in the quality of care over the last 20–30 years may also have an impact on the prevalence of lung disease in adult patients. Children with PID currently receive better care and may be less ill than those treated some time ago, who are now the adults included in this survey. Further investigation is needed to determine whether opportunities exist to improve monitoring and treatment to prevent progression.

The types of PID diagnosed also differed between adult and paediatric patients. This may be in part due to the difficulty in distinguishing between transient hypogammaglobulinaemia and CVID in some young children until the immune system is sufficiently mature, with the opportunity to reassess this over time. For patients with hypogammaglobulinaemia, subclinical infection and inflammation represent an important concern that can lead to persistent immune activation and chronic lung disease [3]. Some antibody deficiency syndromes in children may resolve or improve with age and maturation of the immune

system, especially transient hypogammaglobulinaemia of infancy (THI) [27]; however only a small proportion of such patients are likely to require immunoglobulin replacement. Large clinical studies are currently underway to assess the impact of microbiology and virology testing, and it is hoped that their results will inform relevant guidelines in the near future.

Our survey has highlighted a lack of local, national and European guidelines for screening and treating lung disease in PID. There is a strong need for evidence-based consensus guidelines on how to monitor and treat patients both with no lung disease, with different types of lung disease encountered in PID with antibody deficiencies, and in different age groups — especially as emerging therapeutic modalities may be different (for example, IgG replacement therapy and antibiotics as compared to corticosteroids, rituximab and other immunosuppressive therapies). Such guidelines will also likely need to accept that monitoring and treatment of any lung disease that is discovered will need to be individualised, and provide guidance as to how this should be carried out. Moreover, there are no standardised protocols for the use of biomarkers to predict disease course and complications, nor record the presence or progression of lung disease [3]. In addition, there is currently no formal tool validated or accepted specifically for use in PID patients for the measurement of changes in overall health, in particular the importance of evaluating the patients' general well-being, such as quality of life or fatigue assessment. The development of formal tools or scoring systems, such as the St. George's respiratory questionnaire or validated quantitative scales for monitoring sinus and chest infections, could be beneficial for monitoring the progression of symptoms in patients with PID. Tools used to monitor lung disease in other settings, such as the British Thoracic Society quality standard [28], the Bronchiectasis Severity Index [29] or the FACED score [30], may have utility in the setting of PID.

Current guidelines focus mainly on diagnosis over the treatment of lung disease in PID patients. The lack of consensus on assessment, and preventive and therapeutic measures for lung disease in PID patients, may be due to factors such as small patient cohorts,

variation in the criteria used for diagnosis, different aetiologies of PID, and differing doses of replacement IgG. In addition, although IgG replacement therapy effectively reduces infections in PID patients (particularly severe infections such as pneumonia) [4], the effect of different doses of IgG on chronic lung disease, mucosal infections, bacterial colonisation, pathogen persistence, upper airway infections (especially viral infections), and inflammation, is less clear.

Some important limitations of this survey should be mentioned. First, this was not a prospective study; our report represents a snapshot of the way patients are treated across different centres at one point in time. As such, we did not assess the use of diagnostic and baseline tests, such as HRCT. Also, there is a possibility that some results could be confounded by conditions such as autoimmune cytopenia, which occur more frequently in patients with lung disease. In patients with these conditions immunosuppressive therapy is given for reasons not directly related to lung disease, meaning that these patients are more likely to require different therapies and may be required to attend the clinic more often. In addition, comorbidities which influence the management of lung disease may differ between adults and children.

In conclusion, our survey has shown differences in how frequently various monitoring methods are carried out at different European centres in PID patients with or without lung disease. Results from this survey define current practice and clearly highlight the need for consensus guidelines on how to monitor and treat lung complications in patients with PID. This would allow the application of agreed standards and the use of key performance indicators to harmonise care and utilise these as outcome measures; an approach that has been successfully used in the clinical accreditation of Immunodeficiency Centres. There is also a need for standardised biomarkers and assessment tools to monitor disease progression, which would allow data to be compared between centres. It is hoped that evidence from well-planned and controlled clinical studies will allow the development of

evidence-based guidelines for monitoring and treatment of different groups of patients with PID, which would help to ensure that all PID patients receive optimal care.

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Figures and Tables

Table 1. Number of patients treated by participating physicians, with diagnoses

	Paediatric patients	Adult patients
Patients and centres		
Number of centres treating patients (n=13)	8	9
Total number of patients treated (n=1,239)	178	1061
Patients with and without lung disease, number of patients (%)		
Without lung disease	133 (75)	539 (51)
With bronchiectasis	38 (21)	358 (34)
With 'other' lung disease	7 (4)	164 (15)
Diagnoses		
Diagnoses for all patients, number of patients (%)		
CVID	57 (32)	798 (75)
XLA	33 (19)	42 (4)
SPAD	13 (7)	37 (3)
ARAG	6 (3)	4 (0.4)
Hypogammaglobulinaemia	69 (39)	180 (17)
Diagnoses for patients with progressive lung disease*, number of patients (%)		
CVID	18 (42)	307 (80)
XLA	7 (16)	18 (5)
SPAD	2 (5)	9 (2)
ARAG	2 (4)	4 (1)
Hypogammaglobulinaemia	14 (33)	40 (12)

*Lung disease that worsens over time, including bronchiectasis and other lung disease

ARAG, autosomal recessive agammaglobulinaemia; CVID, common variable immune dysfunction;

SPAD, selective or partial antibody deficiency; XLA, X-linked agammaglobulinaemia

Figure 1. Percentage of PID patients receiving prophylactic antibiotics, rituximab, steroids, and other treatments, with and without lung disease.

■ Adult patients ■ Paediatric patients

Figure 2. Frequency with which clinical monitoring tests are performed in patients with PID.

■ Performed at clinic visit ■ Performed as required ■ Never performed

P = paediatric patients (8 centres)

A = adult patients (9 centres)

Figure 3. Frequency with which laboratory monitoring tests are performed in patients with PID.

■ Performed at clinic visit ■ Performed as required ■ Never performed

P = paediatric patients (8 centres)

A = adult patients (9 centres)

CRP, C-reactive protein; PCR, polymerase chain reaction

Figure 4. Frequency with which lung function tests are performed in patients with PID.

■ Performed at clinic visit ■ Performed as required ■ Never performed

P = paediatric patients (8 centres)

A = adult patients (9 centres)

FEV1, forced expiratory volume at 1 second; FVC, forced vital capacity; TLCO, transfer factor for carbon monoxide; PEFR, peak expiratory flow rate; FEF 25–75, the forced expiratory flow at 25–75% of FVC

Figure 5. Frequency with which imaging is performed in patients with PID.

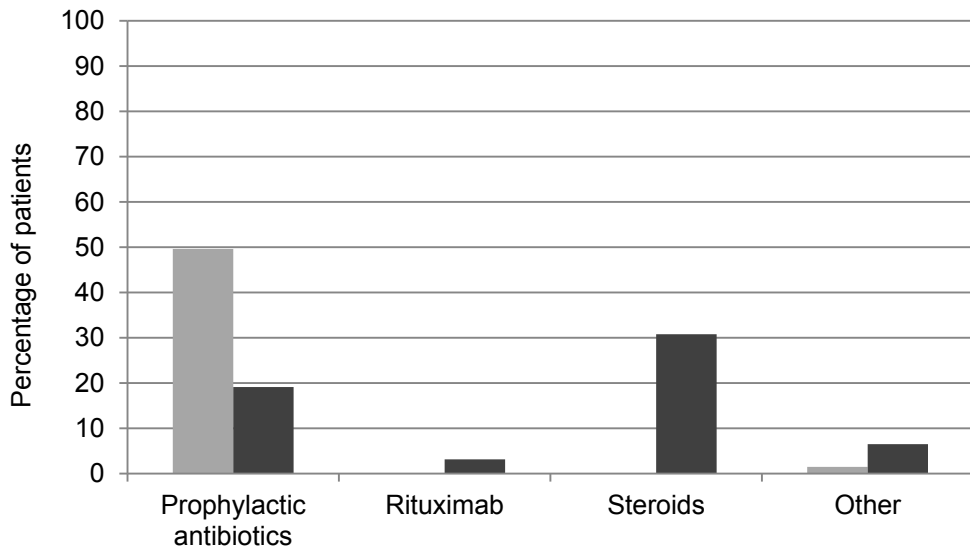
■ Performed at clinic visit ■ Performed as required ■ Never performed

P = paediatric patients (8 centres)

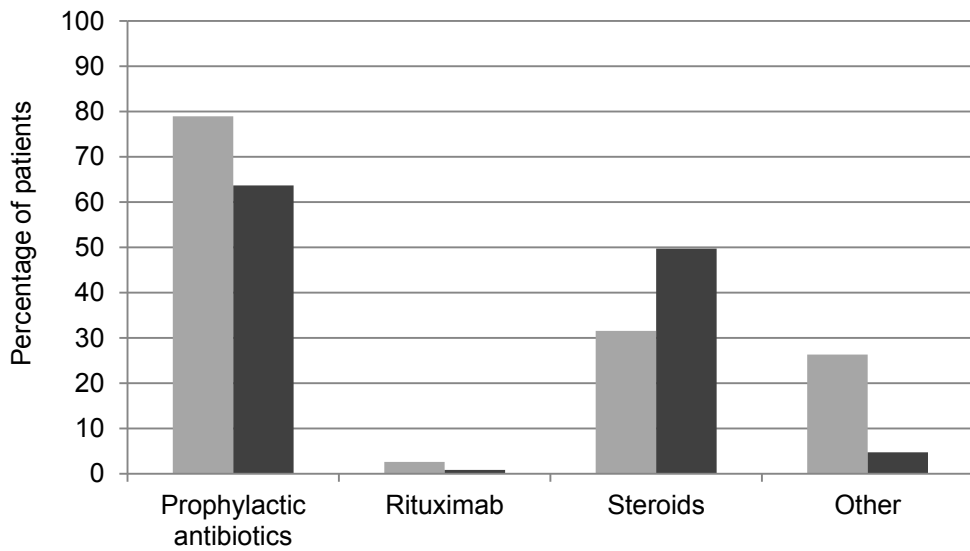
A = adult patients (9 centres)

CT, computed tomography; MRI, magnetic resonance imaging

A. No lung disease



B. Bronchiectasis



C. Other lung diseases

