



Current screening approaches for antibody deficiency

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Purpose of review

Diagnostic delay is a major problem for rare diseases including primary antibody deficiency (PAD). The aim of this review is to discuss the opportunities and challenges of current and future screening approaches for antibody deficiency, to reduce the delay and its impact on patients.

Recent findings

Diagnostic delay in PAD is known to result in increased morbidity, mortality, and permanent functional impairment. Approaches to prevent this have been only partially successful and the delay may still be many years as the clinical presentation of PAD is highly variable and may be at any age, making screening difficult. Patients often have numerous healthcare encounters generating repeated cycles of laboratory and clinical data before the diagnosis is made. Low immunoglobulin levels result in alterations in laboratory tests not directly aimed at measuring immunoglobulins. We describe these and highlight the growing evidence in support of using calculated globulin which is part of the liver function test profile as a screening tool for antibody deficiency. Additional approaches include using embedded algorithms to analyse data generated by repeated clinical encounters (e.g. infections, antibiotics, cytopenias), potentially in combination with laboratory results such as calculated globulin, to help bring forward the diagnosis of PAD in patients in whom this has not yet been considered.

Summary

There is a strong case for the use of calculated globulin in screening for antibody deficiency. Further work is required to integrate laboratory results with clinical data to reduce diagnostic delay in patients with hitherto unsuspected antibody deficiency.

Keywords

algorithm, hypogammaglobulinemia, primary antibody deficiency, screening, secondary antibody deficiency

INTRODUCTION

Antibody deficiency may be either primary or secondary and the most common severe primary antibody deficiency (PAD) is common variable immunodeficiency (CVID). CVID is an important diagnosis not to miss as it is relatively common (estimated at 3.7/100 000) and patients frequently require medical attention and intervention [1–4].

PAD accounts for the majority (57%) of all symptomatic primary immunodeficiency (PID) on the European Society for Immunodeficiencies (ESID) registry (<http://esid.org/Working-Parties/Registry/ESID-Database-Statistics>). Secondary antibody deficiency occurs even more frequently than PAD.

The third national Immune Deficiency Foundation survey of more than 1300 patients with PID found that 27% of patients had been diagnosed with PID by 6 years of age, and only 40% of patients were diagnosed by 18 years of age. In the survey, 49% of

patients reported permanent functional impairment prior to diagnosis, and the number of permanent functional impairments correlated directly with duration of diagnostic delay [5]. Thus, early diagnosis and effective treatment are important to reduce the rate of infection and prevent sequelae [6]. For PAD, median delay in diagnosis of 6 and 4 years has been reported in United Kingdom and USA, respectively [1,7]. For common variable immunodeficiency (CVID), the more recent 2013 analysis of the German National Registry for Primary

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KEY POINTS

- Diagnostic delay is common in PAD, resulting in increased morbidity, mortality and reduced quality of life.
- Low immunoglobulins impact on a number of routine laboratory tests which may have a role in shortening diagnostic delay.
- Of these tests calculated globulin is perhaps the best candidate as it is cheap, widely available and underutilized.
- Calculated globulin cut-off values have been established and their use has been shown to facilitate early diagnosis of patients with unsuspected hypogammaglobulinaemia.
- Studies using patient databases to identify individuals with possible unsuspected immunodeficiency show promise but further work is required.
- Future studies should look at the potential to combine data from multiple sources to identify patients with unsuspected immunodeficiency.

Immunodeficiency reported an average diagnostic delay of 4 years [3] and the U.K. Primary Immunodeficiency Network a median delay of 5 years for the period 2008–2012 [8[•]]. There is high variability between individual patients and between different disorders (Table 1) [1,3,7,8[•],9^{••},10–12]. Diagnostic delay is greater in adults than children, perhaps reflecting a misconception that primary immunodeficiencies are always diseases of childhood (Table 1) [8[•]]. This in combination with the protean manifestations of CVID, the number of specialties to which patients may present and the wide range of noninfectious complications (Fig. 1) all contribute to the delay in recognition of the underlying diagnosis, resulting in recurrent infections and irreversible end organ damage such as bronchiectasis. Alongside this there is also a severe impact on quality of life which makes reducing delay a target for action [1,5,6,10–13].

A number of approaches have been taken to help promote earlier diagnosis. These include raising awareness of physicians and patients, systematic population screening and opportunistic screening. Given the rarity of the immunodeficiency disorders it is conceivably a more difficult task to 'consider the

Table 1. Diagnostic delay in immunodeficiency

Disorder (n)	Age	Average ^a diagnostic delay (range)	Reference
CVID (248)	3–79 years	4 years (NR)	[1]
CVID (465)	NR	4 years	[3]
XLA (70)	NR	1 years	[3]
CGD (75)	NR	1–2 years	[3]
All PAD (15)	Adults	5.5 (2–27) years	[7]
All PAD (16)	Children	2.5 (1–5) years	[7]
CVID (13)	Adults	6.5 (2–27) years	[7]
CVID (5)	Children	3 (1–5) years	[7]
XLA (8)	Children	0 (0–3) years	[7]
CVID (290)	All ages	5 (IQR 1–13) years	[8 [•]]
CVID (83)	≤16 years	2 (IQR 0–5) years	[8 [•]]
CVID (53)	17–29 years	3 (IQR 1–10) years	[8 [•]]
CVID (154)	≥30 years	8 (IQR 2–23) years	[8 [•]]
Agammaglobulinaemia (47)	All ages	1 (IQR 0–2) years	[8 [•]]
SCID (56)	NR	97 (IQR 30–202) days	[8 [•]]
CGD (47)	NR	1 (IQR 0–3) years	[8 [•]]
CVID (8)	All ages	4 (2–30) years	[9 ^{••}]
CVID (224)	2–73 years	8.9 years (NR)	[10]
PAD (87)	6–71 years	2 years (0–41 years, all patients)	[11]
SCID (31)	NR	143 (1–455) days	[12]

CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IQR, interquartile range; NR, not reported; PAD, primary antibody deficiency; SCID, severe combined immunodeficiency; SPAD, specific antibody deficiency; XLA, X-linked agammaglobulinaemia.

^aMedian reported where available, otherwise mean.

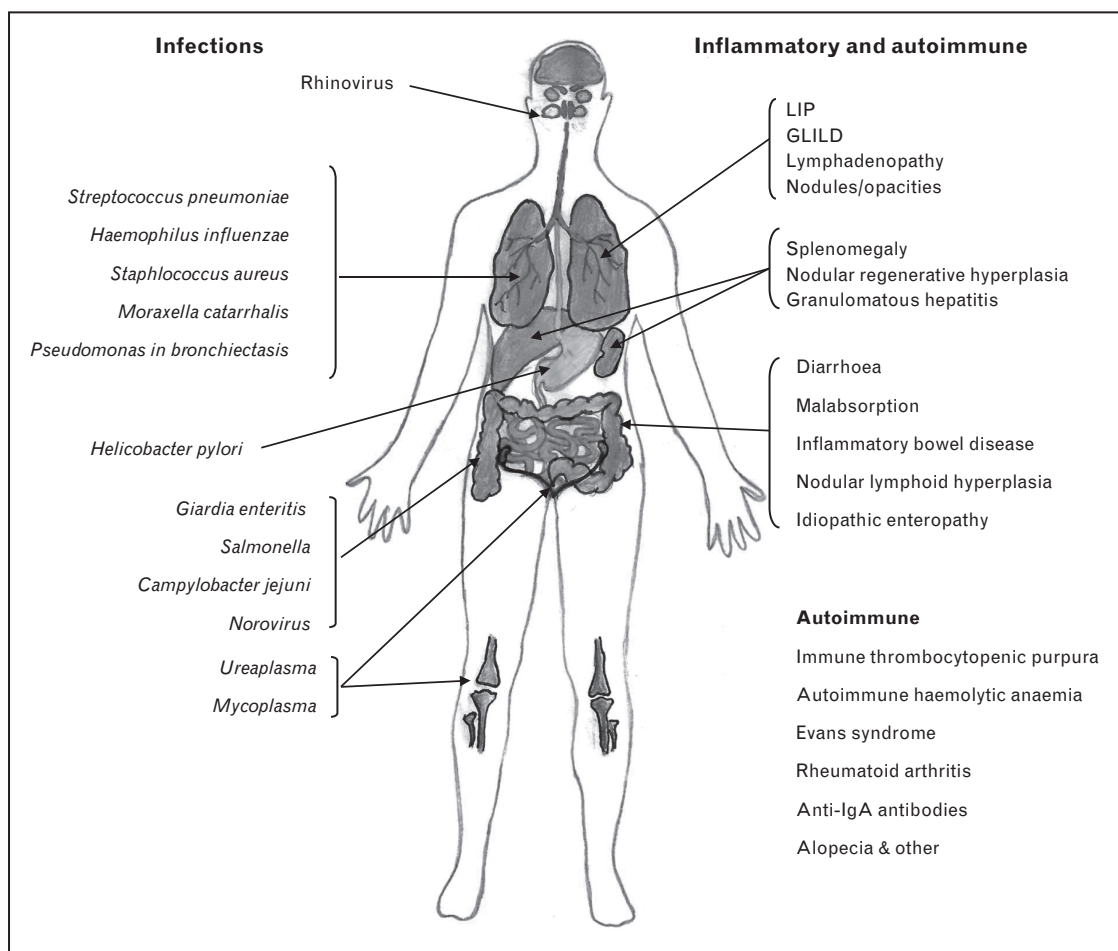


FIGURE 1. Infections and autoimmune and/or inflammatory complications in CVID. The predominant organisms and sites of infection are shown on the left, with the inflammatory and autoimmune complications on the right. Other autoimmune complications include neutropenia, vitiligo, Sjögren syndrome/Sicca syndrome, autoimmune thyroiditis, diabetes mellitus, multiple sclerosis, pernicious anaemia, systemic lupus erythematosus, antiphospholipid syndrome, uveitis, juvenile rheumatoid arthritis, lichen planus, vasculitis, and psoriasis. (Drawn by Pippa Jolles). LIP, lymphocytic interstitial pneumonia; GLILD, granulomatous lymphocytic interstitial lung disease. Reproduced with permission from [4].

diagnosis' rather than 'make the diagnosis' once considered. The majority of patient encounters will be with nonspecialists and it is unreasonable to expect primary care physicians to recall details of approximately 8000 rare diseases (<http://www.rare-disease.org.uk/>).

Significant efforts have been made to reduce diagnostic delay in primary immunodeficiency through education. The European Society for Immunodeficiency (ESID) has developed diagnostic pathways for nonimmunologists [14] and the Jeffrey Modell Foundation (JMF) '10 Warning Signs of Immunodeficiency' are widely available, although limitations in applying these to children have been described (<http://www.info4pi.org/library/educational-materials/10-warning-signs>) [15,16]. If immunodeficiency is not considered as part of the differential diagnosis, these documents will not be consulted and the diagnosis may be overlooked.

Increasing awareness has been shown to be beneficial; JMF initiated a Physician Education and Patient Awareness Campaign in USA and demonstrated increased referrals and diagnoses following the initiative [17]. The J-Project is a Central and Eastern European programme to raise awareness of PID (alongside a similar initiative, the A-Project in Africa). This has shown remarkable results with increased numbers of referrals, diagnoses and treated patients particularly where the baseline has been very low [18]. However, PID databases still demonstrate significant delays in diagnosis for patients with PID and individual education and awareness initiatives may be limited in durability by the need to remind and refresh this knowledge with changes in staffing and competing demands on time.

In this review we consider population and opportunistic screening and additional methods

such as interrogation of patient databases to achieve earlier diagnosis of PAD. We define population screening as systematic testing of all members of a population at a set time, usually based on age, an example would be screening for severe combined immunodeficiency (SCID) by T-cell receptor excision circle (TREC) analysis of Guthrie spots [19,20].

Opportunistic screening refers to testing when the opportunity arises, such as a healthcare encounter for another reason. PAD is said to typically manifest with predominantly sino-pulmonary recurrent infections but presentations may be much more varied. CVID may present not only in primary care but to a range of specialties with noninfectious autoimmune disorders, granulomatous or inflammatory complications [1,4,21,22] (Fig. 1). These patients therefore have often had multiple (sometimes >100) healthcare encounters with laboratory tests performed over long periods before a diagnosis is made. These encounters and tests present an opportunity to identify patients with unsuspected immunodeficiency and hence reduce diagnostic delay.

There is good evidence to support neonatal screening for SCID [23] and successful programmes have been developed in a number of countries [19,20,24–26]. Screening for other immunodeficiencies has not been widely implemented. However, recent studies [9²²,27²²] have shown efficacy for low-cost opportunistic screening for patients with PAD.

POPULATION AND OPPORTUNISTIC SCREENING

The general criteria that should be met to justify systematic screening are well acknowledged and have been widely adopted by healthcare organizations [28,29]. Although antibody defects comprise the majority of PID, most are not single gene defects and present over a wide age range, making the targeting of population screening difficult. Although evidence is limited, it appears that antibody deficiency in CVID can develop over a relatively short period, potentially less than 1 year [9²²]. With this rapid chronology and assuming current average diagnostic delay of around 5 years, screening every 4 years would be required to reduce the average delay to 2 years. Testing at a single set age would have only limited efficacy and would be required at regular intervals throughout life to be effective. Population screening for PAD on this basis would be difficult to justify. A possible exception is X-linked agammaglobulinaemia and the autosomal recessive agammaglobulinaemias (ARAGs) which result in very low B-cell numbers and could be

detected using kappa-deleting recombination excision circles (KRECs) in addition to the SCID newborn screening initiatives for little additional cost [24,30].

Opportunistic, in contrast to population screening, using routine laboratory tests has significant advantages as it is better able to address the issues of the wide age range and varied clinical presentations (Table 2) [9²²,27²²,31,32,33²²,34,35²²,36,37].

PRIMARY ANTIBODY DEFICIENCIES

Low immunoglobulin levels affect a variety of laboratory tests (Table 2). Most of these are not normally remarked upon as the effects noted are not directly relevant to the reason for performing the test, for example serum free light chains [36], or there was no validated lower limit to the reference range, for example until recently for calculated globulin [9²²,27²²].

CALCULATED GLOBULINS

Patients with hypogammaglobulinaemia are recognized to have low calculated globulins, defined as the difference between serum total protein and albumin, which is usually performed as part of a liver function test (LFT) profile [38]. Immunoglobulins comprise about 30% by mass of calculated globulins and so there is potential for changes in other proteins to mask hypogammaglobulinaemia. Acute phase proteins, such as complement and α 1-antitrypsin, increase during bacterial infection causing an increase in calculated globulins. The causes of high and low calculated globulins are shown in Table 3.

Two recent studies [9²²,27²²] in different patient populations (Wales and Hull, UK) have evaluated the efficacy of using calculated globulins to identify hypogammaglobulinaemia. The first study defined method specific cut-off values for the lower limit of the reference range and using a calculated globulins cut-off giving a specificity of about 95% showed sensitivities of 24, 15 and 11% for immunoglobulin G (IgG) below 3, 4 and 5 g/l respectively. Using a calculated globulins cut-off of less than 18 g/l, PPV for low IgG less than 6 g/l was 89% and IgG less than 4 g/l was 56% [27²²]. Following this study, screening for antibody deficiency using calculated globulins has been introduced across all laboratories performing LFT profiles in Wales and if the levels are found to be less than 18 g/l (using bromocresol green methodology for albumin measurement) a comment 'Low calculated globulins may represent antibody deficiency. Consider immunoglobulins if there is a history of recurrent infections' is

Table 2. Impact of low immunoglobulin levels on laboratory tests

Test	Potential disorder identified	References
Serum calculated globulins (total protein minus albumin)	Low – hypogammaglobulinaemia High – hypergammaglobulinaemia (HIV, organ-specific and systemic autoimmune disorders)	[9 [■] ,27 [■]]
ELISA based tests for autoantibodies (e.g. tissue transglutaminase, antinuclear, etc.)	Very low signal compared with negative control suggests reduced immunoglobulin (IgG, IgA or IgM depending on the test target)	[31,32]
Plasma viscosity	Low – hypogammaglobulinaemia High – hypergammaglobulinaemia (lymphoproliferative disorders, HIV, organ-specific and systemic autoimmune disorders)	[33 [■]]
Total IgE	IgE <2 IU/ml – hypogammaglobulinaemia or selective IgE deficiency	[34,35 [■]]
Serum free light chains	Very low values – hypogammaglobulinaemia	[36]
Erythrocyte sedimentation rate (ESR)	Low ESR is seen in hypogammaglobulinaemia	[37]
Indirect immunofluorescence tests for autoantibodies (e.g. antinuclear, mitochondrial, smooth muscle, endomysial, islet cell, etc.)	Very low background immunofluorescence compared with negative control slide suggests low IgG	
Direct immunofluorescence (and other immunoglobulin detection techniques for biopsy samples)	Very low signal compared with negative control – hypogammaglobulinaemia or selective IgA deficiency depending upon the test target	
Serum electrophoresis	Reduced gamma region may indicate primary or secondary immunoglobulin deficiency Polyclonal increase associated with HIV, systemic and organ-specific autoimmune disease	
Blood grouping	Absence of isohaemagglutinins – hypogammaglobulinaemia	

automatically added avoiding the need for retraining of staff. It should be noted that for hospital-based samples a caveat may need to be added as fluid shifts following intravenous fluids or surgery may temporarily reduce calculated globulin levels. This screening program is detecting previously unsuspected primary and secondary antibody deficiencies and also small paraproteins associated with immunoparesis (1.2% of samples).

The second study [9[■]] used specified cut-offs for calculated globulins to calculate sensitivity and positive predictive values (PPV) for hypogammaglobulinaemia. Using a cut-off of calculated globulins based on the first percentile (and hence specificity of 99%) in a prospective screening programme over a period of nearly 6 years found sensitivity of 58, 59 and 50%, and PPV of 8.6, 20 and 30% for an IgG below 3, 4 and 5 g/l, respectively. This compared well with a modelled PPV of (9.4, 25 and 40%, respectively). During 6 years in a patient population of 600 000, the following previously undiagnosed patients were identified: 12 CVID, 10 haematological malignancies [including non-Hodgkins lymphoma, light chain (AL) amyloid, oligosecretory multiple myeloma and light chain myeloma] and 20 drug-related hypogammaglobulinaemias [9[■]].

Both studies found unsuspected antibody deficiency in patients. The majority were secondary hypogammaglobulinaemia, but new patients with CVID were also identified. Both also highlighted that albumin measurement methodology and platform significantly influence calculated globulins and demonstrated the need to use method specific cut-off values and consider calculation of a local calculated globulins cut-off based on a percentile for the population screened.

Taken together, these studies present a compelling case for use of calculated globulins to identify patients with hypogammaglobulinaemia and to promote earlier diagnosis of primary and secondary hypogammaglobulinaemia and unsuspected monoclonal gammopathies at very low cost. It should be noted that this approach will not detect specific antibody deficiency given the normal total immunoglobulin levels.

PLASMA VISCOSITY

Plasma viscosity is used as a marker of an acute phase response and hypogammaglobulinaemia has been shown to result in low plasma viscosity [33[■]]. Although based on small numbers (19 adult

Table 3. Causes of high and low calculated globulin

High calculated globulins	Low calculated globulins
Lymphoproliferative disease: Plasma cell dyscrasias (e.g. multiple myeloma, Waldenstroms macroglobulinaemia) Non-Hodgkin's lymphoma Monoclonal gammopathy of undetermined significance (MGUS)	Primary antibody deficiency, e.g. CVID Plasma cell dyscrasias Small paraproteins with immune-paresis (e.g. multiple myeloma, light-chain disease, oligo/nonsecretory multiple myeloma, AL amyloid) Hodgkin's and non-Hodgkin's lymphoma
Infection Viral infections (e.g. HIV, EBV, HBV) Chronic infection (e.g. TB, osteomyelitis, endocarditis)	Drug therapies Immunosuppressive drugs Chemotherapy Rituximab Anticonvulsants DMARDS
Sarcoidosis	
Connective tissue disease Systemic lupus erythematosus Sjogren's syndrome Rheumatoid arthritis	Increased loss Protein losing enteropathy Renal losses Plasma exchange
Autoimmune liver disease Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis	Fluid therapy/shifts (e.g. perioperatively or in acutely unwell patients such as ITU or medical therapy involving fluid resuscitation)

CVID, common variable immunodeficiency; DMARDS, disease modifying antirheumatic drugs; EBV, Epstein-Barr virus; HBV, hepatitis B virus; TB, mycobacteria tuberculosis.

samples) a plasma viscosity below 1.48 cPa gave a PPV of 74% for one or more immunoglobulin levels to be below the adult reference range. The authors reviewed six patients with plasma viscosity results available before commencement of immunoglobulin replacement therapy and found that 50% had plasma viscosity less than 1.5 cPa. Like calculated globulins, plasma viscosity will be affected by the presence of acute phase proteins, with the addition of fibrinogen present in plasma but not serum. Fibrinogen is the single most important determinant of PV (contributing 57% of the variation in plasma viscosity) but IgG and immunoglobulin M also make a significant contribution (15% of the variation) [39]. However, plasma viscosity is performed relatively infrequently compared with LFTs which will limit utility (in the Hull laboratory the ratio of PV : LFT requests is 1 : 5 and is much lower in Wales).

CELIAC SCREENING

Celiac screening is based on detection of immunoglobulin A (IgA) autoantibody to tissue transglutaminase (TTG) in an ELISA system or endomysial tissue in indirect immunofluorescence (IIF).

However, selective IgA deficiency (IgAD) is common in celiac disease and so total IgA level is often checked to avoid false negative screen results. This may be done by measuring serum IgA level in all patients or in a group selected on the basis of low OD signal in ELISA or background staining in IIF [32]. Our experience of using a 5th percentile cut-off for TTG is that this has a sensitivity of 70% for detection of IgA below the lower limit of our reference interval (0.8 g/l, unpublished data). Sensitivity for complete IgAD (IgA <0.07 g/l) would be expected to be higher. In a commercial Luminex-based celiac screen, use of an IgAD detection bead has shown 100% sensitivity and specificity for IgAD [40]. Most patients with IgAD are asymptomatic but a proportion may suffer from recurrent infection and some of these will have a broader antibody deficiency potentially affecting other major immunoglobulin classes. Detection of IgAD should therefore trigger an appropriate laboratory comment or further investigation. Although there are no published systematic investigations of the efficacy of this approach for the early detection of hypogammaglobulinaemia and PAD there are supportive case reports in the literature [31].

As with low IgA in celiac screening, low IgG levels result in low background staining in indirect

(IIF) and direct immunofluorescence (DIF) tests. Anecdotal evidence from our laboratories and others suggests that this low signal IIF for autoantibody detection has resulted in the identification of patients with low IgG. There are however no systematic studies demonstrating efficacy.

TOTAL IMMUNOGLOBULIN E LEVELS

There is evidence to support the follow-up of patients with undetectable serum immunoglobulin E (IgE) found during investigation of allergic disease. An assessment of the IgE levels in patients with a diagnosis of CVID in a Cardiff cohort revealed 87% to have a total IgE below the reference range (unpublished data). Published studies [34,35^{*}] support follow-up of patients with undetectable total IgE noted during investigations for suspected allergic disease and demonstrate the detection of patients with hypogammaglobulinaemia. In a review of 2622 total IgE results, 85 (3.2%) had IgE level below 2 IU/ml [34]. Of these, six had one or more immunoglobulin levels below the reference interval for age (two children and four adults), leading to a new diagnosis of antibody deficiency in two patients. This gives a PPV of 7.1% for a low immunoglobulin, suggesting potential value in routine practice. However, the limited number of IgE tests performed (less than 1% of the number of LFTs in our experience) does limit its likely impact on diagnostic delay for hypogammaglobulinaemia.

DATABASE MINING

Integrated information management systems that allow easy collating of data from different sources such as history, prescribing information and pathology results would facilitate additional approaches to identifying patients with patterns suggestive of immunodeficiency. Ideally these should allow automated algorithms to run in the background, linking results to identify the particular patterns associated with immunodeficiency. This would allow exclusion of other known causes and so reduce the number of patients identified and increase the PPV from the algorithm. Linking databases in this way would allow identification of patients with patterns of distinct features which might include infections, multiple attendances and courses of antibiotics, cytopenias, gastrointestinal symptoms linked to calculated globulin levels or unusual combinations such as sarcoidosis and low calculated globulins. Healthcare systems with large databases of patient results and records may use data-mining techniques, either patient specific, run at each encounter, or run periodically across the whole database. Defined

patterns could be searched for in primary care from practice databases.

A study from the USA has shown efficacy in using patient ICD-9 discharge codes to identify all hospitalized patients at least 60 years of age with at least two immunodeficiency-related complications for follow-up. From 321 754 in-patient visits, 533 patients were identified for follow-up. It was possible to test 59 of these patients. Of these, 17 were found to have an unsuspected PID and 13 a secondary immunodeficiency [41].

Several studies have looked at the prevalence of immune defects in patients with recurrent pneumonia. Using a definition of recurrent pneumonia as two episodes within 1 year or 3 years in a lifetime, 6–9% of children presenting with pneumonia had recurrent disease and 8–16% of these had an immune defect [42–46]. In adults with three or more episodes of pneumonia, 12% had an immunoglobulin defect and 22% in total were found to have an immune defect [47]. Similarly, a review of 150 adults with bronchiectasis found that 8% had an immune defect [48]. Yarmohammadi *et al.* [49] reviewed clinical records for 237 patients referred for investigation of possible immunodeficiency and identified symptoms found more often in the immunodeficient group – chronic sinusitis, bronchitis, otitis media, and chronic diarrhoea were more common although unexpectedly pneumonia was not. However, they did not comment on recurrent pneumonia. Work in children suggests that family history of PID, parental consanguinity, previous sibling death, use of intravenous antibiotics and failure to thrive are useful indicators of severe PID [15,16,50]. These types of study inform the database search terms which may have the most potential to reduce diagnostic delay in immunodeficiency.

CONCLUSION

Shortening diagnostic delay remains a major challenge for patients with rare disease and antibody deficiency poses specific problems in that patients may present at any age, to a range of specialties, with autoimmune and inflammatory disorders where the underlying diagnosis is far from apparent. We have highlighted the strengths and weaknesses of different approaches in which follow-up of specific laboratory tests which are impacted upon by low immunoglobulin levels may be effective in identifying unsuspected immunodeficiency.

The use of calculated globulin screening in particular has been shown to identify patients with PAD. It is cheap, has a defined reference range, comments may be automated within laboratory

systems and it benefits from the very high numbers of LFT profiles undertaken in primary and secondary care. There is considerable underutilized potential for the laboratory to improve patient outcomes by taking a proactive role in highlighting patients with possible immunodeficiency. A further major opportunity exists in the targeted use of algorithms using key terms in the history, prescription and test results to interrogate the smaller and larger databases which are now ubiquitous in clinical practice across primary and secondary care. As with screening in other settings, such as newborn screening for SCID, the success of some of the approaches described are already raising challenges with increased numbers of patients requiring assessment and treatment; however, this impact on resources needs to be assessed in terms of the overall benefit to the patient.

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Conflicts of interest

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