Immunodeficiency in Bronchiectasis

7

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7.1 Immune Deficiency and Bronchiectasis

Immune deficiencies have been identified as the cause of bronchiectasis in 6–14% [1–7] of adult and 20–34% of paediatric cohorts [8–11]. They are the third most common cause of bronchiectasis, after cystic fibrosis and postinfectious bronchiectasis, in children and adults [10, 12]. Therefore, immune deficiency should be considered in all idiopathic bronchiectasis cases, particularly if onset is in childhood [13, 14]. It is important to identify underlying immune deficiencies, as without specific treatments such as immunoglobulin replacement therapy [6, 9], these patients are at greater risk of developing progressive bronchiectasis [15], other infections and immune-mediated complications.

7.2 Immune Deficiencies Associated with Bronchiectasis

Bronchiectasis in immune-deficient patients is predominantly the consequence of chronic respiratory infection punctuated by episodes of exacerbation. Immune dysregulation and chronic inflammation may also have a role in the pathogenesis and progression of bronchiectasis in immune deficiency [16, 17]. Any defect in the

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Table 7.1 Frequency of bronchiectasis reported in various immune-deficient states

Immune-deficient state	Reported frequency of bronchiectasis
CVID	20–68% [15, 22–24]
XLA	32% (adults) [38]
SAD	18% (adults) [33]
APDS	18–60% [56–58]
STAT3 HIES	65% [62]
DOCK8 HIES	37% [63]
CGD	17% [68]
Renal transplant	2.4%
Thymoma with hypogammaglobulinaemia	10% [17]

CVID common variable immune deficiency, *XLA* X-linked agammaglobulinaemia, *SAD* specific antibody deficiency, *APDS* activated PI3-kinase delta syndrome, *STAT3* signal transducer and activator of transcription 3, *HIES* hyper-IgE syndrome, *DOCK8* dedicator of cytokinesis 8, *CGD* chronic granulomatous disease

immune system that predisposes to infection may be complicated by bronchiectasis. Table 7.1 describes the frequency of bronchiectasis reported in various immune deficiencies.

7.2.1 Primary and Secondary Immune Deficiencies

Immune deficiencies are termed primary immune deficiencies (PIDs) if aetiology is genetic or idiopathic rather than acquired or secondary to external cause. Secondary immune deficiencies (SID) are most often 'secondary' to immunosuppressive medications, chemotherapy, transplantation, HIV infection and haematological malignancies. PID that is associated with bronchiectasis development includes primary antibody deficiencies (PAD), combined immune deficiencies with T- and B-cell dysfunction and phagocytic disorders. Before a patient is diagnosed as having a PID however, secondary causes for immune deficiency should be considered and excluded.

7.2.2 Antibody Deficiencies

Defects in immunoglobulin (antibody) production are the most common immune defects identified in patients with bronchiectasis [9, 10]. Bronchiectasis is reported as a concomitant disease in 17.4% (421/2421) of patients with PAD included in the patient registry of the European Society of Immunodeficiencies (ESID) in 2016 [18]. Respiratory tract infections in these patients are most often due to encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Immunoglobulins are important in the immune response to encapsulated bacteria as they opsonise (coat) the encapsulated bacteria activating both the complement system and phagocytes to eradicate the infection. Thus, defects in the quantity or quality of antibody production are associated with recurrent bacterial respiratory tract infections and bronchiectasis.

There are five different isotypes or classes of antibody: IgM, IgD, IgE, IgA and IgG [19]. IgM is the first antibody generated in response to pathogen, IgA is transported to mucosal surfaces, IgE is involved in immune responses to helminths and allergy and IgD is expressed by the surface of naïve mature B cells. IgG crosses the placenta, mainly in the third trimester, with the majority of serum antibody in the newborn being of maternal origin. Antibody levels in all infants fall over the first 3–6 months of life as maternally derived IgG is consumed and the infant's capacity to produce their own immunoglobulin is developed. IgG is the predominant immunoglobulin in the extracellular compartment, and patients with reduced total IgG levels (hypogammaglobulinaemia) or who have defective IgG responses to pathogens or immunisations (specific antibody deficiency) are at risk of developing recurrent chest infections and bronchiectasis. IgG can be further subdivided into subclasses, IgG1, IgG2, IgG3 and IgG4.

Primary antibody deficiencies (PAD) are the most common PID identified in adults and children affecting approximately 2.1/100,000 in the UK population [15]. They are characterised by reduced serum immunoglobulin levels and/or poor antibody responses to immunisation. Antibody deficiency can also occur as part of other PID syndromes including combined immune deficiencies. The genetic conditions underlying PAD are increasingly being recognised; however, at present, most PAD do not have an identifiable genetic aetiology. All PIDs are diagnosed in accordance with European or international diagnostic criteria based on clinical history, immune results and, where available, confirmation of known genetic mutations [20, 21]. These criteria are updated by expert panels at regular intervals reflecting the rapid development in genetics in this field.

Antibody deficiencies may be primary or secondary in aetiology. Secondary antibody deficiency may be due to medications including immunosuppressants and anticonvulsants; thymoma and haematological malignancies including myeloma, chronic lymphocytic leukaemia and non-Hodgkin's lymphoma; bone marrow transplantation; infections such as HIV, EBV, congenital rubella, CMV and *Toxoplasma gondii*; hypercatabolism of immunoglobulin; and excessive loss of immunoglobulins through nephrotic syndrome, severe burns, protein-losing enteropathy and chylous collections (lymphangiectasia) [18].

Below we describe individual PAD that may be complicated by bronchiectasis and how these are investigated. In general however if concerned that a patient with recurrent infection may have an underlying PAD, we would measure immunoglobulin levels, immunisation responses and T-cell and B-cell numbers. Assessment of immunisation responses is described further below in Section: *Determining abnormal immunisation responses and diagnosing SAD*.

7.2.3 Common Variable Immune Deficiency (CVID)

CVID is the most common significant PID representing about 20% of all PID recorded in Europe and has a minimal prevalence of 1.3/100,000 in the UK population [15]. CVID is also the most common PAD and PID to cause bronchiectasis.

CVID is characterised by recurrent infections and marked decrease of IgG and IgA with or without low IgM levels and failure to produce protective serological responses to test immunisation [20, 21]. Bronchiectasis has been reported to occur in 20–68% of individuals with CVID (see Table 7.1) [15, 22–24]. CVID is an idiopathic condition, and its onset can be at any age, though most patients present in the first two decades of life. A significant minority of patients with CVID (20–25%) develop non-infectious, immune-mediated complications such as autoimmunity, particularly autoimmune cytopenias, granuloma formation, enteropathy, polyclonal lymphoproliferation and lymphoid malignancy [25–28]. CVID patients with reduced helper T-cell (CD3+CD4+) numbers of less than 200 cells/mcl have a higher frequency of bronchiectasis and atypical infections than other CVID patients and may therefore be more appropriately classified as late-onset combined immune deficiency (LOCID) [29].

Immune Abnormalities in CVID Reduced IgG and IgA; normal or reduced IgM; poor serological response to polysaccharide pneumococcal or other immunisation; normal or reduced B cells; and normal or reduced T cells.

Genetic Investigations in CVID CVID is a diagnosis of exclusion made in cases of idiopathic reduced IgG and IgA and a history of infection. To date, in most patients with CVID, no underlying genetic cause has been identified. Targeted studies of molecules and receptors important in antibody production have identified a number of rare genetic causes of hypogammaglobulinaemia including ICOS, CD19, CD21, CD81 and BAFF receptor deficiency [30]. Increasingly, whole exome sequencing (WES) studies are being performed on cohorts of CVID patients, revealing many novel genetic findings. All WES identified novel mutations require further investigation, usually using molecular and functional techniques, to confirm if they play a plausible role in the pathogenesis of the CVID. It is anticipated that as new mutations are identified, the proportion of CVID patients who have unexplained hypogammaglobulinaemia will reduce as we increasingly identify subgroups associated with specific genetic mutations.

7.2.4 Specific Antibody Deficiency (SAD)

Specific antibody deficiency (SAD) is characterised by normal total IgG, IgA and IgM levels but failure to make an adequate antibody response to the specific antigens of infectious pathogens or immunisations [20, 21]. Polysaccharide antigen responses, such as to the pneumococcal polysaccharide immunisation (PPV), are predominantly T-cell independent, while protein antigen responses, such as to the tetanus toxoid or other protein-conjugated immunisations, are T-cell dependent. Failure to respond to polysaccharide antigens with intact protein antigen responses may be called specific polysaccharide antibody deficiency, and this implies a functional defect of B-cell function [31]. Poor polysaccharide responses are expected in infants before the age of 2 years. Patients with poor polysaccharide responses are

susceptible to encapsulated bacterial chest infections [32]. Bronchiectasis has been reported to occur in 18% of individuals with SAD (see Table 7.1) [33]. Poor immunisation responses may also be present in other PID including CVID and combined immune deficiencies.

Immune Abnormalities in SAD Normal IgG, IgA and IgM; poor serological response polysaccharide pneumococcal or other immunisations; normal B-cell and T-cell numbers.

Genetic Investigations in SAD No known genetic defects cause isolated SAD.

7.2.5 Determining Poor Immunisation Responses and Diagnosing SAD

Methods applied to assess immunisation responses vary. The most widely used approach is to compare pneumococcal specific antibody levels before and 4 weeks after administration of 23-valent polysaccharide pneumococcal immunisation (PPV-23) [34]. Anti-pneumococcal antibody assays measure either (1) the total anti-pneumococcal IgG titre or (2) multiple pneumococcal serotype-specific antibody (PSSA) levels for a variety of *Streptococcus pneumoniae* serotypes included in PPV-23. There is no universally agreed definition of a normal/poor response to pneumococcal immunisation. A fourfold increase in the total anti-pneumococcal IgG titre is regarded as normal by some, with a less than fourfold response is regarded as suboptimal and 'no response' is regarded as abnormal/poor [35]. However, if an individual has a high baseline anti-pneumococcal IgG titre, due to previous pneumococcal immunisation or infection, they may not achieve a fourfold increase post immunisation despite a normal immune system. Alternatively, a normal immunisation response can be defined as the ability to achieve an IgG titre $\geq$0.35 or 1.3 mg/mL for each *Streptococcus pneumoniae* serotype tested. With this approach, a 'normal' post-PPV-23 response is defined in those older than 6 years as 70% of the serotype-specific anti-pneumococcal IgG responses tested converting from nonprotective to protective after 4–6 weeks. In those less than 6 years, only 50% of serotypes are expected to achieve these levels [35, 36].

7.2.6 X-Linked Agammaglobulinaemia (XLA)

In XLA, formerly known as Bruton's agammaglobulinaemia, mutations in the *BTK* gene cause an X-linked condition with a severe reduction in all immunoglobulins in the blood (agammaglobulinaemia) and profoundly decreased B cells. The *BTK* gene encodes Bruton's tyrosine kinase (BTK), an intracellular tyrosine kinase critical for B-cell development in bone marrow [37]. These *BTK* gene mutations impair BTK protein function resulting in a deficiency of mature B cells and subsequent agammaglobulinaemia. Hypomorphic mutations in *BTK* can result in a partially

functioning BTK protein, and patients may have very low levels of both B cells and immunoglobulins detectable in peripheral blood. Typically, in infancy as maternal IgG disappears, boys with XLA develop severe and recurrent bacterial infections especially affecting the upper and lower airways. In a single, large study, bronchiectasis has been reported to occur in 32% of individuals with XLA (see Table 7.1) [38]. Agammaglobulinaemic patients have also been described to develop chronic enteroviral infections [39]. Less common (15%) autosomal recessive causes agammaglobulinaemia present similarly and is also due to intrinsic defects in B-cell development. They include deficiencies in pre-B-cell receptor components (μ heavy chain, λ5, Igα and Igβ) and the signalling molecules downstream of BTK, B-cell linker (BLNK) and p85α subunit of PI3 kinase (PIK) [39–41].

Immune Abnormalities in XLA Severely reduced IgG, IgA and IgM; severely reduced B cells; normal T-cell numbers. Reduced BTK protein expression on molecular testing.

Genetic Investigations in XLA BTK gene analysis.

7.2.7 IgG Subclass Deficiency

IgG subclass deficiency occurs when the total serum IgG is normal but one or more IgG subclass (IgG1–4) is deficient. Many patients with IgG subclass deficiency are asymptomatic; however, IgG2 subclass deficiency is considered more likely to be clinically significant when associated with poor immunisation responses and/or IgA deficiency. Patients with isolated IgG subclass deficiency and normal immunisation responses usually do not suffer from an increased infection rate or bronchiectasis [42, 43]. Reduced IgG subclasses may also be present in other PID including activated PI3-kinase δ syndrome.

Immune Abnormalities in IgG Subclass Deficiency Normal total IgG; reduced IgG subclass(es); normal IgM; reduced or normal IgA; normal or poor immunisation responses; normal B-cell and T-cell numbers.

Genetic Investigations in IgG Subclass Deficiency There are no known genetic defects described in this condition.

7.2.8 Combined Immune Deficiencies

In combined immune deficiencies, B-cell and T-cell function is impaired. Combined immune deficiencies are often complicated by antibody deficiency, predisposing patients to recurrent bacterial respiratory tract infections and bronchiectasis (see Table 7.1). The additional defects in T-cell-mediated immunity predispose patients to viral and opportunistic infections as well as bacterial infections. In general if

concerned that a patient with recurrent infection may have an underlying combined immune deficiency, immunoglobulin levels, T-cell and B-cell numbers and T-cell or lymphocyte function should be determined.

7.2.9 Class Switch Recombination Defects: Formerly Known as Hyper-IgM Syndromes

This group of disorders are characterised by defects in class switch recombination (CSR) resulting in reduced IgG and IgA levels and T-cell dysfunction with normal or elevated IgM levels [44]. CD40 ligand (CD40L) deficiency was the first CSR defect to be described and remains the most common. It is inherited as an X-linked disorder and is complicated by recurrent and severe bacterial and opportunistic infections, neutropenia, autoimmune disease and less frequently sclerosing cholangitis and cholangiocarcinoma [45, 46]. The related CD40 deficiency is a similar but autosomal recessive condition [47]. In addition to bacterial pneumonias, individuals with CSR defects frequently develop *P. jirovecii* pneumonia [48]. AID (activation-induced cytidine deaminase) and UNG (uracil DNA glycosylase) deficiencies are other rare autosomal recessive CSR defects which are less associated with opportunistic infections but develop more lymphadenopathy [49–52]. Patients with CSR defects are at risk of developing bronchiectasis due to recurrent or severe bacterial respiratory tract infections secondary to antibody deficiency and T-cell dysfunction. The exact prevalence of bronchiectasis in CSR deficiency is unknown but may be decreasing due to early recognition and haematopoietic stem cell transplantation in childhood.

Immune Abnormalities in CSR Defects Severely reduced IgG and IgA; normal or elevated IgM; normal B- and T-cell numbers. Reduced CD40L protein expression on activated T cells and CD40 expression on B cells.

Genetic Investigations in CSR Defects *CD40LG*, *CD40*, *AID* and *UNG* gene analysis.

7.2.10 Activated PI3K-δ Syndrome (APDS)

Phosphoinositide 3-kinase δ (PI3Kδ) is a kinase which generates phosphatidylinositol 3,4,5-trisphosphate (PIP_3). It is a heterodimer comprised of a catalytic subunit, p110δ, and a regulatory subunit, p85. PI3Kδ is expressed predominantly in leukocytes and plays an important role in their proliferation, survival and activation [53–55]. Gain-of-function mutations in *PIK3CD* and *PIK3R1*, the genes for p110δ and p85α, respectively, cause an autosomal dominant primary immune deficiency—activated PI3K-δ syndrome (APDS). Activated PI3K-δ syndrome is associated with recurrent chest and herpes infections, bronchiectasis, lymphoproliferation, hypogammaglobulinaemia and impaired immunisation responses. Studies have reported high rates of bronchiectasis, usually with paediatric onset, in APDS (see Table 7.1) [56–58].

Immune Abnormalities in APDS Normal or reduced IgG and IgA; normal or elevated IgM; normal or reduced IgG subclasses; normal or reduced B- and T-cell numbers.

Genetic Investigations in APDS *PIK3CD* and *PIK3R1* gene analysis.

7.2.11 Ataxia Telangiectasia

Ataxia telangiectasia (AT) is a disorder predominantly of the nervous system with progressive ataxia and neuropathy. It is due to mutations in *ATM* gene which has a role in controlling the cell cycle and DNA repair. AT is complicated by telangiectasia and progressive immune deficiency in some patients with recurrent sinopulmonary infections and decreased T cells and antibody levels. It is unusual for AT patients to survive beyond the second decade of life because of the development of lymphoid malignancy and/or infections.

Immune Abnormalities in AT Normal or reduced IgG and IgA; normal or elevated IgM; normal or reduced IgG subclasses; normal B-cell count; progressively decreased T-cell numbers.

Genetic Investigations in AT *ATM* gene analysis.

7.2.12 Wiskott–Aldrich Syndrome

Wiskott–Aldrich syndrome (WAS) is a X-linked immunodeficiency caused by mutations in the *WAS* gene leading to decreased T-cell responses and antibody levels. Wiskott–Aldrich syndrome protein (WASP) is a cytoskeletal protein involved in T–B-cell interactions. Patients have congenital thrombocytopenia with small platelets and, to a variable degree, recurrent bacterial and viral infections, eczema and autoimmune disease.

Immune Abnormalities in WAS Normal or reduced IgG and IgM; normal or elevated IgA; normal or reduced immunisation responses; normal B-cell count; progressively decreased T-cell numbers. Reduced WASP expression on molecular testing.

Genetic Investigations in WAS *WAS* gene analysis.

7.2.13 CTLA-4 Deficiency

Cytotoxic T lymphocyte antigen-4 (CTLA-4) is an essential negative regulator of immune responses. CTLA-4 deficiency is an autosomal dominant immune

dysregulation syndrome of incomplete penetrance (CTLA haploinsufficiency) characterised by hypogammaglobulinaemia, recurrent infections and autoimmunity including granulomatous–lymphocytic interstitial lung disease (GLILD) [59].

Immune Abnormalities in CTLA-4 Deficiency Reduced IgG and IgA; normal or reduced IgM; reduced B cells; normal T-cell numbers.

Genetic Investigations in CTLA-4 Deficiency *CTLA4* gene analysis.

7.2.14 LRBA Deficiency

LRBA (lipopolysaccharide-responsive beige-like anchor protein) deficiency is an autosomal recessive cause of childhood-onset hypogammaglobulinaemia and autoimmunity [60, 61].

Immune Abnormalities in LRBA Deficiency Reduced IgG and IgA; normal or reduced IgM; normal or reduced B-cell and T-cell numbers.

Genetic Investigations in LRBA Deficiency *LRBA* gene analysis.

7.2.15 Hyper-IgE Syndromes

Hyper-IgE syndromes (HIES) are a group of rare PID characterised by recurrent skin and lung infections, eczema and elevated serum IgE level. Over recent years underlying genetic causes have been identified in HIES. The most common cause of HIES is autosomal dominant signal transducer and activator of transcription 3 (STAT3) deficiency. Multiple forms of autosomal recessive HIES have been identified including DOCK8 (dedicator of cytokinesis 8) deficiency. Less commonly PGM3, SPINK5 and TYK2 deficiencies may cause an autosomal recessive HIES. Bronchiectasis is common in HIES with studies reporting frequencies of bronchiectasis of 65% and 37% in STAT3 deficiency and DOCK8 deficiency, respectively (see Table 7.1) [62, 63].

7.2.15.1 STAT3 Deficiency

STAT3 deficiency impairs T and B lymphocyte function, particularly effecting T-helper 17 (Th17) cells. STAT3 deficiency patients have eczema, raised IgE, eosinophilia, recurrent skin and chest infections. They develop recurrent pneumonia and pulmonary abscesses, most often due to *S. aureus* and *S. pneumoniae*, bronchiectasis, aspergillosis and characteristically pneumatoceles. The skin infections are caused by *S. aureus* and *Candida* species. Patients may also be affected by a variety of connective tissue abnormalities including coarse facial features, defective eruption of permanent teeth, hyperextensibility, scoliosis, pathological fractures and aneurysms [62, 64].

Immune Abnormalities in STAT3 Deficiency Normal IgG, IgA and IgM; normal or reduced immunisation responses; normal B-cell and T-cell numbers; elevated IgE and eosinophils.

Genetic Investigations in STAT3 Deficiency *STAT3* gene analysis.

7.2.15.2 DOCK8 Deficiency

DOCK8 is a regulatory protein involved in actin reorganisation within cells. DOCK8 deficiency causes a combined immune deficiency complicated by recurrent respiratory and skin infections and eczema with raised IgE. Compared to STAT3 deficiency, DOCK8 deficiency has an autosomal recessive inheritance, no skeletal abnormalities and significantly higher rates of viral skin infections, allergies and malignancy [65].

Immune Abnormalities in DOCK8 Deficiency Normal IgG and IgA; normal or reduced IgM; normal or reduced immunisation responses; reduced B-cell and T-cell numbers; decreased NK-cell numbers; elevated IgE and eosinophils.

Genetic Investigations in DOCK8 Deficiency *DOCK8* gene analysis.

7.2.16 Phagocytic Disorders

Chronic granulomatous diseases (CGD) are a rare group of disorders effecting 0.17/100,000 in the UK population [15] caused by X-linked or autosomal recessive mutations in genes encoding components of NADPH oxidase complex, the enzyme responsible for respiratory burst and superoxide production in phagocytes [66]. The defect in NADPH function in CGD leads to impaired killing of organisms such as *S. aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia*, and *Aspergillus* by phagocytic cells. Patients with CGD develop recurrent and severe bacterial and fungal infections predominantly abscesses, lymphadenitis and pneumonias, pneumatoceles and granulomatosis lesions [67]. In a single, large study, bronchiectasis has been reported to occur in 17% of individuals with CGD (see Table 7.1) [68].

Immune Abnormalities in CGD Normal or elevated IgG; normal IgA and IgM; normal immunisation responses; normal B-cell and T-cell numbers; absent or reduced neutrophil oxidative burst on neutrophil functional testing.

Genetic Investigations in CGD *CYBB* (gp91phox), *CYBA* (p22phox), *NCF1* (p47phox), *NCF2* (p67phox), *NCF4* (p40phox) gene analysis.

7.2.17 Mannose-Binding Lectin Deficiency

Mannose-binding lectin (MBL) is a member of the innate lectin family of pathogen-associated molecular pattern receptors that activate complement. MBL deficiency is common affecting about 5–10% of the population with most affected individuals remaining healthy and a minority complaining of an increased frequency of chest infections [69]. However, an increased risk of bronchiectasis has been reported in individuals with CVID or cystic fibrosis and MBL deficiency [70–72]. In patients with bronchiectasis, severely reduced MBL levels (<200 ng/mL) have been associated with more frequent infective exacerbations. Reduced levels of L-ficolin (ficolin-2), another complement activating member of the innate lectin family, have also been reported in bronchiectasis patients and in CVID patients who develop bronchiectasis [73, 74].

Immune Abnormalities in MBL Deficiency Normal IgG, IgA and IgM; normal immunisation responses; normal B-cell and T-cell numbers; reduced MBL level.

7.2.18 Other PID

Bronchiectasis has been described in other PID including immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) and in chronic mucocutaneous candidiasis disease (CMCD) [75, 76].

7.3 Secondary Immune Deficiencies

Secondary immune deficiencies (SID) are more common than PID [14]. The SID most frequently associated with bronchiectasis are 'secondary' to drug therapies including chemotherapy, haematological malignancies, HIV infection and transplantation [9, 10]. With the increasing use of immunomodulatory drugs for cancer and inflammatory disorders particularly in older people, the prevalence of bronchiectasis is increasing. Significant rates of bronchiectasis can develop due to SID, and in a study by Duraisingham et al., 28.2% of patient with secondary antibody deficiency developed bronchiectasis (n = 39) compared to 37.3% of primary antibody-deficient patients (n = 126) [77]. However, as SID is often a predictable complication of specific treatments and diseases, it is important to monitor at risk patient groups and intervene therapeutically with the aim of preventing the development of recurrent chest infections and bronchiectasis. In SID the most common, immunological findings are secondary hypogammaglobulinaemia and lymphopenia.

7.3.1 Drug-Induced Secondary Immune Deficiency

An increased risk of infection is a predictable side effect of many immunosuppressive medications. Medications and chemotherapeutic agents that target lymphocytes are most likely to suppress antibody production. Studies in patients with rheumatoid arthritis and inflammatory bowel disease have shown that immunosuppressants such as sulphasalazine, gold therapy, cyclophosphamide, systemic glucocorticoids and, to a lesser extent, azathioprine and methotrexate have been associated with higher rates of infection, including pneumonia, and the development of antibody deficiencies in these patient groups [78–82]. Rituximab, an anti-B-cell therapy, is used to treat severe autoimmune conditions and some haematological malignancies. Rituximab, especially with multiple treatments, has been associated with hypogammaglobulinaemia complicated by recurrent chest infections and bronchiectasis [83, 84]. Systemic glucocorticoid use, short high dose and low dose over months or years, can also induce hypogammaglobulinaemia [85]. More surprisingly, various anticonvulsants, including carbamazepine, phenytoin and valproate, have been described to induce antibody deficiency which can be complicated by respiratory tract infections [86–92].

Drug-induced immune deficiency often resolves following cessation of the implicated medication. Patients on medications known to be associated with SID should be monitored. If recurrent or severe infections are noted, we would advise patients be investigated and managed as described below.

7.3.2 Haematological Malignancies and Secondary Immune Deficiency

In haematological malignancies, such as multiple myeloma, chronic lymphocytic leukaemia and lymphoma, both the malignancy and the treatment may contribute to a secondary immune-deficient state.

Multiple myeloma is a malignant disorder of plasma cells in which abnormal monoclonal antibody is produced, and conversely normal polyclonal antibody production is often reduced. Dendritic cell, T-cell, NK-cell and B-cell dysfunction has been identified in myeloma patients [93]. Infection is the leading cause of death in patients with multiple myeloma [94, 95]. Myeloma may be complicated by infection, including pneumonia and sepsis, due to *S. pneumoniae*, *H. influenzae*, gram-negative *Bacillus* and *S. aureus* [95, 96].

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the developed world effecting 4.1 in 100,000 individuals [97]. CLL is associated with B-cell dysfunction, hypogammaglobulinaemia and low pneumococcal antibody levels. Patients with CLL and evidence of antibody deficiency have been identified to be more likely to develop infections than individuals with CLL alone [98, 99].

Thymoma can be complicated by hypogammaglobulinaemia with reduced B cells and variable degrees of T-cell defects. Thymoma with secondary hypogammaglobulinaemia, also known as Good's syndrome, was found to be complicated by

bronchiectasis in 10% of cases on a systematic review of 152 cases [17]. Patients with Good's syndrome may also develop autoimmune diseases such as pure red cell aplasia and myasthenia gravis.

The treatments for these haematological malignancies may contribute to the immune deficiency. Older chemotherapeutic agents induced myelosuppression, while newer targeted therapies such as anti-CD20 antibodies (rituximab, ofatumumab and obinutuzumab), proteasome inhibitors (bortezomib) and kinase inhibitors (ibrutinib and idelalisib) are associated with a narrower range of B- and T-cell inhibition. Haematopoietic stem cell transplant is also associated with myelosuppression and a period of significant immunosuppression. As with other forms of drug-induced SID, once therapy ceases, immune function will usually improve over a variable period of time. However, if severe or recurrent chest infections occur during this immunosuppressed period, patients will be at risk of developing bronchiectasis.

7.3.3 Transplantation

Bronchiectasis has been described following solid organ and haematopoietic stem cell transplantation. The bronchiectasis post transplantation has been related to immunosuppressive medications and pulmonary graft-versus-host disease, bronchiolitis obliterans [100–105]. Allogeneic haematopoietic stem cell transplant is also complicated by the loss of memory T and B cells and potentially poor immune reconstitution.

In solid organ transplantation, long-term immunosuppressive therapy is often indicated to prevent allograft rejection. The development of bronchiectasis in adults and children postrenal transplantation has been related to mycophenolate therapy, specifically the development of antibody deficiency due to mycophenolate therapy [106–112]. Mycophenolate inhibits purine synthesis and severely depresses both cell-mediated and humoral immunity by inhibiting T-cell and B-cell proliferation. In paediatric heart transplant recipients, the development of bronchiectasis has been related to transplant before 4 years old and poor pneumococcal immunisation antibody responses [113, 114].

7.3.4 HIV

Untreated HIV infection is characterised by a progressive decrease in helper T-cell (CD3+CD4+) numbers. HIV infection predisposes individuals to lower respiratory tract infections with pathogens such as *S. pneumoniae*, *H. influenzae* and *Pneumocystis jirovecii* and respiratory viruses such as parainfluenza [115]. Lymphocytic interstitial pneumonitis can occur in HIV-positive individuals, though the incidence has declined with increasing access to antiretroviral therapy [116]. Bronchiectasis has been described to occur in 5–16% of children with HIV [115, 117]. The development of bronchiectasis in HIV-positive

children has been associated with lymphocytic interstitial pneumonitis, recurrent pneumonias and reduced helper T-cell (CD3+CD4+) numbers of less than 100 cells/mcl [117, 118].

7.4 Investigations

Immune deficiency is more likely to be the underlying cause of bronchiectasis if the patient has a history of recurrent chest infections and infections affecting non-pulmonary sites. PIDs are more likely in patients with childhood onset of recurrent infections, a family history of PID and other non-infectious features of the particular PID described above. SID is more likely to be the cause of bronchiectasis if the patient is currently or has previously been exposed to immunosuppressants, anticonvulsants or chemotherapeutic agents or is HIV positive, has had a haematological malignancy or previously underwent solid organ or haematopoietic stem cell transplantation.

7.4.1 Investigations We Perform in All Patients with Bronchiectasis [13, 119, 120]

Test	Looking for
Neutrophil count	Neutropenia, lymphopenia and leucocytosis
IgG, IgA and IgM levels	Antibody deficiency
Serum electrophoresis in all adult patients	Multiple myeloma
Anti-pneumococcal IgG levels, pre- and 4 weeks post polysaccharide pneumococcal immunisation	Poor polysaccharide antigen responses
HIV test	HIV infection

7.4.2 Additional Immune Tests that May Be Completed Depending on Clinical History

Neutrophil oxidative burst	Chronic granulomatosis disease
Complement function	Complement deficiency
Mannose-binding lectin level	Mannose-binding lectin deficiency
Lymphocyte subsets	Suspect PID with low B, T or NK cells
Lymphocyte function tests	Suspect PID with abnormal lymphocyte function

7.5 The Management of Bronchiectasis Secondary to Immune Deficiency

The management of bronchiectasis secondary to immune deficiency includes general bronchiectasis management measures such as airway clearance and physiotherapy, patient education, influenza immunisation, antibiotic treatment for infective

exacerbations and the consideration of prophylactic antibiotics, hypertonic saline and bronchodilators where these therapies may be of benefit. Additional specific treatment measures depend on the underlying immune deficiency identified, such as the consideration of immunoglobulin replacement therapy (IRT) in patients with antibody deficiency. It is recommended that the management and monitoring of patients with bronchiectasis and immune deficiency should be provided through a joint respiratory and clinical immunology (±paediatricians) care model with access to physiotherapy and respiratory nursing services with an expertise in bronchiectasis [13, 121]. We have followed this model for a number of years with a dedicated 'Lung Defence Clinic' in which selected patients are seen by just such a multidisciplinary and multi-professional team.

7.5.1 Immunisation

All patients with bronchiectasis secondary to immune deficiency should receive the annual inactivated influenza immunisation including patients on IRT. The seasonal variation in influenza strains means that immunoglobulin products may not have protective titres of antibody against a year's specific pandemic influenza strains. Household and close contacts of immune-deficient individuals should also be offered the annual inactivated influenza immunisation. All indicated inactivated immunisations can be administered to immune-deficient individuals though the immune response to these immunisations could be suboptimal depending on the underlying immune deficiency [122, 123].

Immunisation against the encapsulated bacteria, *S. pneumoniae*, *H. influenzae* and *Neisseria* meningococcal groups A, C, W, Y and B, is recommended in patients with complement deficiencies and patients with asplenia or splenic dysfunction due to their increased risk of bacterial meningitis and overwhelming sepsis, respectively. Antibody responses to these immunisations can be monitored and additional booster immunisations administered.

Due to safety concerns, all live, attenuated immunisations are contraindicated in patients with reduced helper (CD3+CD4+) T-cell numbers less than 200 cells/mcl or impaired T-cell function, as a component of a severe combined immune deficiency, combined immune deficiency or secondary to HIV [124, 125]. In other immunosuppressed individuals, live vaccines should only be administered after consultation with an appropriate specialist [125].

7.5.2 Antibiotic Prophylaxis

As in other forms of non-CF bronchiectasis, antibiotic prophylaxis should be considered in immune-deficient patients with bronchiectasis who have frequent infective exacerbations. Immune-deficient patients however may also be candidates for antibiotic prophylaxis due to chronic rhinosinusitis and other recurrent bacterial infections [126]. Antibiotic prophylaxis is also advised in patients with complement deficiencies or splenic dysfunction. In patients with combined immune deficiencies,

prophylactic co-trimoxazole, antivirals and antifungals may also be indicated to prevent atypical and nonbacterial infections.

7.5.3 Immunoglobulin Replacement Therapy (IRT)

Immunoglobulin replacement therapy (IRT) consists of long-term, regular infusions of pooled donor IgG (normal immunoglobulin) and should be considered in all patients with primary and secondary antibody deficiency and bronchiectasis to reduce their infection frequency. In some primary antibody deficiencies, such as XLA and CVID, IRT is an essential part of the standard of care, and all patients should be commenced on IRT [127]. In addition, all IgG-deficient or specific antibody-deficient (primary or secondary) patients with recurrent chest infections or infective exacerbations of bronchiectasis despite a trial of antibiotic prophylaxis should be considered for IRT [77]. A recent survey of immunologists found that objective evidence of recurrent chest infections (number of proven infections, pharmacy-confirmed prescriptions, etc.) was the most important factor in the decision to commence IRT in antibody-deficient individuals [128].

IRT can be given by intravenous (IVIG) or subcutaneous (SCIG) infusion with the interval between doses varying from a few days to every 3 weeks, depending on immunoglobulin product used and individual patient need and preference. IRT can be administered in the hospital day ward setting or as home therapy. Home therapy IRT is usually self-administered by the patient or by their relatives after a period of training [129].

Our current practice is that IRT is usually commenced at a dose of 0.4 g/kg/month in patients without bronchiectasis and at a higher dose of 0.6 g/kg/month in antibody-deficient patients with bronchiectasis [128, 130, 131]. Patient response to immunoglobulin and clinical requirement to increase immunoglobulin dose is determined by monitoring the patient's frequency of infection in conjunction with their trough (predose) or steady state IgG levels [132, 133]. Studies have suggested that the use of higher doses of immunoglobulins to maintain IgG troughs at up to 10 g/L may reduce frequency of overall infection and pneumonia in particular [133–135].

Normal immunoglobulin is derived from blood donations and is thus a finite resource. Increasingly normal immunoglobulin is administered in the treatment of other medical conditions. To ensure the immunoglobulin supply of patients with PID on long-term IRT in times of storage policies for prioritising demand, such as the Department of Health, UK, *Guidelines for Immunoglobulin Use* (update 2011), place PID as the highest priority indication for IRT [136]. SID is a 'blue' indication which means that IRT is usually made available unless there is a shortage in supply.

7.5.4 Other Treatments for PID

Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative, early treatment option for many combined and all severe PIDs including severe combined immune deficiency (SCID), CGD, CSR defects, APDS, DOCK8

deficiency and LRBA deficiency [44, 57, 61, 65–67]. Various studies have supported gene therapy as a potential curative treatment alternative to HSCT in SCID, CGD and WAS [137–139]. In patients with less severe phenotypes of combined immune deficiency or who have been deemed unsuitable for HSCT, other interventions such as long-term antimicrobial prophylaxis and IRT may be appropriate [57, 61, 62, 66, 67]. In CGD, adjuvant INF-gamma subcutaneous therapy may improve neutrophil and monocyte function [66, 67].

7.6 Long-Term Monitoring

In patients with bronchiectasis and immune deficiency, we aim to maintain or improve their lung function, prevent future infections and infective exacerbations in bronchiectasis, improve quality of life and ensure the normal growth and development in children [13]. We believe that these aims are most effectively achieved through specialist clinics with respiratory medicine, clinical immunology, physiotherapy and respiratory nursing and in children paediatric, involvement, as is our practice [13].

The appropriate monitoring of lung function for bronchiectasis progression is debated. Due to the risk of asymptomatic progression of bronchiectasis, it has been suggested HRCT and spirometry should be periodically performed. *Pasteur* et al. in the BTS guideline for non-CF bronchiectasis recommended the measurement of FEV1 and FVC at least four times each year in bronchiectasis patients with immune deficiency [13, 126].

7.7 Outcomes

Patients with immune deficiency and bronchiectasis have greater morbidity and mortality outcomes than those who do not develop bronchiectasis [25]. Two large studies showed that respiratory failure from chronic lung disease has historically been a major cause of death in CVID [140, 141]. Due to these associated poor outcomes, it is crucial to identify immune deficiency promptly and intervene to prevent the development and progression of bronchiectasis. A delay in the diagnosis or recognition of immune deficiency has been associated with the development of bronchiectasis in CVID patients in some, but not all, cohorts [25, 77, 142].

Conclusions

- Immune deficiency is an important cause of bronchiectasis that should be considered and investigated for in all cases of idiopathic bronchiectasis.
- The identification of an underlying immune deficiency in bronchiectasis may indicate additional therapeutic interventions.
- A delay in recognising an underlying immune deficiency in bronchiectasis may result in otherwise preventable recurrent infectious exacerbations and bronchiectasis progression as well as other infective complications.

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