Chapter 12

Immunodeficiencies associated with bronchiectasis

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Summary

Bacterial infection of the lung is a cause of bronchiectasis and also the main clinical problem in patients with bronchiectasis. As a consequence, inherited or acquired immunodeficiencies that allow repetitive lung infection with respiratory pathogens (such as Streptococcus pneumoniae and Haemophilus influenzae) can drive the development and progression of bronchiectasis. The immune defects most strongly associated with bronchiectasis are those resulting in hypogammaglobulinaemia. These include the primary immunodeficiencies, common variable immunodeficiency and X-linked agammaglobulinaemia and the secondary immunodeficiencies caused by lymphoproliferative malignancy, allogeneic bone marrow transplantation and chemotherapeutic interventions. Identifying hypogammaglobulinaemia is important and allows patients to be given immunoglobulin replacement, reducing exacerbation frequency and probably progression of bronchiectasis. Conditions resulting in T-cell dysfunction (such as chronic HIV infection or immunosuppression), reduced bacterial opsonisation (such as complement deficiencies), failure of phagocyte migration (leukocyte adhesion deficiency) and impaired intracellular killing of bacteria (chronic granulomatous disease) may also predispose to bronchiectasis. In this chapter we describe the main immunodeficiencies associated with bronchiectasis and suggest a staged approach to immunological investigations.

Keywords: Antibody, bronchiectasis, haematopoietic stem cell transplant, HIV, immunodeficiency, T-helper cell type 17

Bronchiectasis is characterised by damage and dilatation of the bronchi allowing chronic colonisation with significant numbers of bacterial pathogens. The initial damage to the bronchi can be caused by infection. It is therefore not surprising that a range of immunodeficiencies predisposing to recurrent respiratory tract infections can lead to the development of bronchiectasis.
Immunodeficiencies are defined as primary immunodeficiencies (PIDs), resulting from deleterious genetic mutations, or secondary immunodeficiencies (SIDs), where acquired insults have compromised immune function. The pathogens usually associated with milder bronchiectasis include *Streptococcus pneumoniae* and *Haemophilus influenzae*. Both are common nasopharyngeal commensals in adults and children that also cause acute bronchitis and pneumonia. It is probable that impaired host immunity to these pathogens initiates the development of bronchiectasis, which then further compromises mucosal defences permitting infection and sometimes colonisation with environmental bacteria, such as *Pseudomonas aeruginosa*.

Existing data on the causes of bronchiectasis is derived from relatively low numbers of patients, usually from specialist centres, who have been immunologically investigated to a variable extent as discussed by Bilton and Jones [1] in the first chapter of this Monograph. As a consequence, the true proportion of bronchiectasis patients with a definable immunodeficiency is unclear (and will certainly increase with modern molecular diagnostic approaches). From published reports, up to 7% of adults and up to a third of children presenting with bronchiectasis will have a PID [2–6]. Reported rates of SID are lower but are likely to increase in line with more frequent use of immunotherapy, solid organ and bone marrow transplantation and improved survival from HIV. In this chapter we will discuss each of the major PIDs and SIDs that have been associated with bronchiectasis (table 1), before drawing some more general conclusions about mucosal immunity to bacterial infection.

**Primary immunodeficiencies**

**Antibody deficiency syndromes**

In most case series the commonest immune disorders associated with bronchiectasis are antibody deficiencies [2–7]. Antibody deficiency can be inherited or acquired and can be caused by a range of specific defects in antibody production, leading to several distinct immunological phenotypes the most important of which are discussed below. *S. pneumoniae* and *H. influenzae* are both surrounded by an antigenic polysaccharide capsule which is a major virulence determinant for invasive infection. The close association of antibody deficiencies as causes of bronchiectasis perhaps indicates that antibody-mediated immunity is a non-redundant mechanism for airways immunity to these pathogens. Since antibody deficiency syndromes are responsible for significant numbers of patients with bronchiectasis [3, 5, 6] and require specific management strategies including antibody replacement, it is important that patients presenting with bronchiectasis should be appropriately investigated for these conditions by measuring total serum antibody levels, specific antibody titres and antibody responses to vaccination.

Failure of any of the steps involved in antibody production can potentially lead to defective humoral immunity. Gene mutations affecting early pre-B-cell development (such as recombination-activating gene) will usually also impair T-cell production and lead to severe combined immunodeficiencies which almost always present in childhood. In contrast, adults may present de novo (although with a long history) with a block in pre-B-cell to immature B-cell development giving rise to: X-linked agammaglobulinaemia (XLA) (usually caused by mutations in Bruton’s tyrosine kinase (Btk)); defects in class switch recombination and/or somatic hypermutation (which are necessary to generate high-affinity immunoglobulin (Ig)G, IgA and IgE) resulting in hyper IgM syndromes; and defects (which are currently only partially characterised) in generating functional antibody responses leading to common variable immunodeficiency (CVID), IgA or IgM deficiency, IgG subclass deficiency and isolated specific antibody deficiency. The most common of these conditions are discussed below.

**Common variable immunodeficiency**

CVID is the most common adult primary immunodeficiency, with an estimated prevalence of 1 in 25,000 in Caucasians [8]. Although many patients with CVID develop bronchiectasis, CVID is...
relatively rarely identified as the cause of bronchiectasis in most published data for adult patients, varying from 0.7% to 2.4% of cases [3, 4, 6], and in 2–10% of childhood cases [2, 5].

CVID is characterised by reduced circulating Ig concentrations of one or more isotypes, with IgG levels two standard deviations below normal [9] and poor responses to immunisation. The mean age at diagnosis has two peaks of around 30 years and in younger children [10, 11]. Adult patients with CVID have often had symptoms for many years before diagnosis [11]. Familial CVID
accounts for 10–20% of cases, generally with an autosomal dominant inheritance pattern (often with partial penetrance); although many of the more recently identified genetic defects associated with CVID have an autosomal recessive inheritance pattern. For the majority of patients the molecular defects causing CVID are not known, but in 10–15% mutations affecting Ig production have been described. These include mutations of the inducible T-cell surface expressed CD28 co-stimulatory molecule (<1% CVID); the B-cell activating factor receptor (<1% CVID); the CD19 component of the co-receptor for the B-cell antigen receptor (<1% CVID); the transmembrane regulator, calcium modulator and cyclophilin ligand interactor (10–15% CVID); and a B-cell surface receptor involved in B-cell proliferation [8, 12]. These mutations affect quite different parts of the immunological response required for antibody production, suggesting that the molecular causes of CVID are heterogeneous and perhaps explaining why there is a large range of clinical associations with CVID that only affect a proportion of patients [13]. For example, up to 25% of patients with CVID also develop autoimmune and lymphoproliferative complications including granulomatous disease, lymphocytic infiltrations of the lungs or lymphoma [7, 10, 11, 14]. Although these complications have been particularly associated with known genetic polymorphisms, variations in gene dosage and penetrance has frustrated attempts to generate robust clinical phenotype–genotype classifications [15–17]. Most patients seem to be susceptible to respiratory and gastrointestinal infections, although selection bias and small numbers means that the precise incidence of respiratory tract complications in CVID varies between publications. In a large French series encompassing the national experience of patients with CVID, pneumonia occurred in 58% (31% due to *S. pneumoniae* and 12% due to *H. influenzae*), bronchitis in 69% and sinusitis in 63% of patients [11]. In total, 37% of patients were diagnosed with bronchiectasis. The pattern of bronchiectasis in CVID tends to be diffuse lower and middle lobe disease associated with chronic upper respiratory tract symptoms, similar to idiopathic bronchiectasis [5–7].

CVID is characterised by reduced serum IgG concentrations, so finding levels of serum IgG below the normal range will identify nearly all potential cases. Patients with low IgG levels (even if just above the bottom of the normal range) should be further evaluated initially by measuring: 1) serum IgA, IgM and IgE; 2) IgG subclasses; and 3) levels of specific antibodies (against for example, tetanus toxin, pneumococcal serotype-specific capsular polysaccharide and *H. influenzae* capsular polysaccharide B) before and following vaccination if appropriate. More detailed investigations, usually conducted by clinical immunologists, include B-cell and T-cell immunophenotyping and T-cell proliferative responses to common mitogens (to subclassify CVID and exclude T-cell immunodeficiency). Patients will most likely require lifelong Ig replacement therapy. The main complications of therapy are fever, headache and chills, which are managed through pre-medication with anti-histamines and hydrocortisone. Anaphylactic reactions are rare. Ig replacement may be given by intravenous infusion (i.v. Ig (IVIG), 400 mg·kg⁻¹ every 3–4 weeks) or by subcutaneous injection (100 mg·kg⁻¹ weekly). Although there are few data on the long-term consequences of IVIG treatment, IVIG reduces the incidence of respiratory tract infections [18–20] and computed tomography (CT) scores of inflammation associated with bronchiectasis [21], so is likely to prevent or slow the progression of bronchiectasis. Early identification of CVID cases is therefore important, and measuring serum IgG levels in all cases of bronchiectasis is recommended in the recent British Thoracic Society guidelines [22]. CVID patients are often given prophylaxis with continuous low-dose oral antibiotics as well as IVIG therapy. The long-term prognosis of bronchiectasis in CVID patients is not known, but chronic lung disease is a prominent cause of death for CVID patients [23]. Historically, the dose of replacement IVIG given is based on a trough IgG level with the objective of keeping this within the normal range (7–15 g·L⁻¹). Generally, this results in most patients running a trough IgG at the lower end of the normal range, but recent data suggests that for some patients this is inadequate to keep them free of infection. Individualised Ig therapy using a dose that prevents infection has therefore been advocated to minimise the risk of progressive lung disease [24].

Long-term management of patients with CVID should also include: 1) optimised treatment of their bronchiectasis focusing on appropriated oral and/or nebulised antibiotic prophylaxis
(as discussed by Haworth [25]), anti-inflammatory therapy (described by Smith et al. [26]) and airway clearance strategies (described by Bye et al. [27]); 2) vigilance for the development of lymphoma, lymphoproliferative lung infiltration and granulomatous disease (although there is no consensus on the type or frequency of screening [28]); 3) a low threshold for investigation of gastrointestinal symptoms or B12/folate deficiency to pick up CVID-associated inflammatory enteropathy and Giardia infection; and 4) specialist management of associated idiopathic thrombocytopenic purpura and other autoimmune disease if present.

**X-linked agammaglobulinaemia**

XLA is a rare disorder of B-cell development characterised by absent serum antibodies and no circulating B-lymphocytes. It is usually caused by inherited mutations in the Btk gene, although clinically similar autosomal recessive diseases have been described due to other mutations affecting B-cells [7]. Patients present with recurrent bacterial and viral infections in early childhood. Similar to CVID, patients with XLA are particularly susceptible to infections caused by encapsulated bacteria such as *S. pneumoniae* and *H. influenzae*. As a consequence of recurrent lung infection, lung disease can develop bronchiectasis; in one survey 32% of adult patients with XLA had chronic lung disease, mainly bronchiectasis [29]. The relative risk of developing structural lung damage is, however, reported to be less with XLA compared with CVID [20]. XLA has been associated with up to 3% of cases of childhood bronchiectasis [5] but is only a rare cause in adults. No specific pattern of bronchiectasis in patients with XLA has clearly been described. The long-term prognosis has improved with aggressive treatment with IVIG and antibiotic therapy, although there are few data on the rate of progression of bronchiectasis and chronic lung disease remains a significant cause of death [29].

**IgA, IgM and IgG subclass deficiencies**

In case series of paediatric and adult patients with bronchiectasis, small numbers of patients have selective IgM (<1%), IgA (2%) [3] or IgG subclass deficiency [30–32]. However, the clinical significance of deficiency of IgM or IgA with normal IgG remains unclear. The incidence of isolated IgM deficiency in the normal population is not known and whether IgM can mediate immunity at the mucosal surface has not been clarified. IgA is present at mucosal surfaces including the airway lining fluid [33] and is thought of as an important component of mucosal immunity. IgA deficiency is relatively common [3, 9], with a prevalence of 1 in 600 of the population, but may be more likely to lead to lung damage if combined with IgG subclass deficiencies or specific antibody responses to carbohydrate antigens (see later) [34]. IgG subclass deficiency, especially IgG2, has been associated with bronchiectasis, particularly in children. However, the incidence of IgG subclass deficiency varies widely in patients with bronchiectasis, from 4% to 48% [3, 6, 30, 35, 36] and the significance of subclass deficiency has been questioned as it is relatively common in a normal population [37]. IgG2 deficiency may be associated with reduced natural or vaccine-induced specific antibody to *S. pneumoniae* or *H. influenzae* as discussed later. As such, IgG2 deficiency may reflect poor antibody responses to the bacteria that are associated with bronchiectasis and thus represent a risk factor for disease [38]. Overall, at present there is no clear consensus that identification of isolated IgA, IgM or IgG subclass deficiency in a patient with bronchiectasis is necessarily clinically relevant [6].

**Specific antibody deficiency**

The high incidence of bronchiectasis in patients with hypogammaglobulinaemia is probably related to lack of antibody-mediated immunity to the encapsulated respiratory pathogens *S. pneumoniae* and *H. influenzae*. Antibody responses to *S. pneumoniae* and *H. influenzae* that recognise capsular polysaccharides are protective, and hence a number of groups have explored whether selective deficiencies in antibody responses to polysaccharide antigens could also cause bronchiectasis. Antibody responses to polysaccharide antigens are described as being T-independent and generated
through mechanisms that are different from T-dependent antigens [39]. Distinct B-cell sub-populations respond to polysaccharide antigens and patients who have poor responses to capsular polysaccharide vaccines or who lack particular B-cell subpopulations are particularly susceptible to \textit{S. pneumoniae} pneumonia [40] and perhaps the development of bronchiectasis [41]. Antibody responses to polysaccharide antigens can be tested by evaluating capsule-antigen specific responses after vaccination against \textit{S. pneumoniae} or \textit{H. influenzae}, and can be compared with antibody responses to a protein antigen vaccine, such as diphtheria or tetanus [42]. Specific antibody deficiency has been identified in 58% of patients with idiopathic bronchiectasis [38], but this was a small study in which the immunological criteria used for specific antibody deficiency has been queried [43]. Other larger series of adult patients with bronchiectasis suggest specific antibody deficiency has an incidence varying from 4% to 11% [3, 41]. In some cases, an impaired specific antibody response was associated with selected IgG subclass deficiencies [36]. However, antibody responses to vaccination with polysaccharide antigens are variable and affected by age. Up to 10% of the normal population may be nonresponders [44, 45]. Hence it is difficult to evaluate the significance of specific antibody deficiency as a cause of bronchiectasis without further studies involving large numbers of bronchiectasis patients and matched controls. Furthermore, naturally acquired immunity to at least \textit{S. pneumoniae} may actually be partially dependent on antibody responses to protein rather than capsular antigens [46], undermining the reasoning why a specific defect in carbohydrate responses could cause bronchiectasis.

Other PIDs and bronchiectasis

There are many other immunodeficiencies reported to lead to recurrent lung infection, many of which have been associated with bronchiectasis. Although often very rare, these diseases are of importance as they indicate which components of the immune response are necessary for preventing recurrent bacterial infections of the lung.

\textbf{Transporter antigen peptide deficiency syndrome}

Transporter antigen peptide (TAP) proteins are required for the transfer of peptide antigens from the cytosol into the endoplasmic reticulum where they associate with human leukocyte antigen (HLA)-1 for presentation on cell surfaces. Autosomal recessive mutations in the \textit{TAP1} or \textit{TAP2} genes result in reduced HLA-1 expression and CD8 lymphocyte numbers, but with an increase in natural killer (NK) and $\gamma\delta$ T-cells [47, 48]. The majority of subjects with TAP deficiency have recurrent sino-pulmonary infections with common respiratory tract bacterial pathogens and develop bronchiectasis [47, 48]. Only a handful of families with TAP deficiency have been described, and this genetic defect will be responsible for a vanishingly small proportion of cases of bronchiectasis. However, the association of TAP deficiency and other very rare familial T-cell disorders [49, 50] with bronchiectasis demonstrates that there are previously unsuspected mechanisms of immunity to extracellular bacterial pathogens involving CD8 lymphocytes that requires further investigation. In addition, it has been suggested that an excess of NK and $\gamma\delta$ T-cells might promote bronchiectasis due to a dysregulated inflammatory response in reply to infection with bacterial pathogens [48].

\textbf{Disorders of macrophage or neutrophil function}

There are a wide range of inherited disorders affecting neutrophil function such as chronic granulomatous disease (CGD), leukocyte adhesion deficiency and Chediak–Higashi syndrome [51]. Although these disorders are extremely rare, making it difficult to accurately evaluate their clinical associations, neutrophil disorders classically lead to recurrent pneumonia and abscesses but are not necessarily closely associated with bronchiectasis. In relatively large series of adult patients with bronchiectasis, tests of neutrophil function only occasionally identify patients with abnormal responses and even in these patients the relationship of the defect to bronchiectasis is not clear [2, 3, 5]. CGD has been associated with cases of bronchiectasis in some paediatric case
reports or case series but these reports are likely to have been affected by selection bias as they originate from specialist centres [2, 5, 52]. The seemingly weak association of neutrophil defects with bronchiectasis may also reflect the range of pathogens these patients are most susceptible to, which include *Staphylococcus aureus, Nocardia, Aspergillus* and *Candida* species but excludes *S. pneumoniae* and *H. influenzae*, the pathogens most closely associated with development of bronchiectasis in Ig deficiencies [51]. Primary defects of macrophage function generally affect intracellular killing and lead to increased incidences of infection with intracellular pathogens such as mycobacteria, *Histoplasma, Listeria* and *Salmonella* species [51] but again are generally not directly associated with the development of bronchiectasis. What is unclear is the extent to which functional polymorphisms of phagocytic receptors (such as Fc gamma RIIA H/R 131) or pattern recognition receptors (such as Toll-like receptors) may predispose to bronchiectasis through impaired phagocytosis of opsonised/non-opsonised bacteria or aberrant inflammatory responses.

**Hyper IgE syndrome**

Hyper IgE syndrome is a rare autosomal dominant inherited syndrome that causes susceptibility to a range of infections as well as bone, dental, vascular and joint abnormalities [53]. Most patients have the classical clinical triad of massively raised IgE levels, recurrent pneumonia and soft tissue abscesses (hence the condition is also called Job’s syndrome). The majority of cases are caused by mutations affecting the signal transducer and activator of transcription 3, an intracellular signalling protein important for regulating cellular responses to cytokines [53, 54]. Patients have both an exaggerated and reduced cytokine response to infection. In particular, patients with hyper IgE syndrome have an impaired T-helper cell type 17 (Th17) CD4 response [55], which seems to be important for mucosal immunity to some respiratory pathogens such as *Klebsiella pneumoniae* and *S. pneumoniae* [56, 57], as well as *S. aureus* [58] and *Candida* species [59]. Th17 CD4 immune responses assist neutrophil recruitment to sites of infection as well as local mucosal immunity [56, 57]. Pneumonia in patients with hyper IgE syndrome is often complicated by pneumatoceles, but can also lead to bronchiectasis in a significant proportion of patients [53]. Although hyper IgE syndrome is a rare disease that is only occasionally found in cases series of patients with bronchiectasis [2, 5], the identification that the underlying genetic defect of a Th17 response demonstrates the importance of this pathway for immunity to common bacterial pathogens of the lung.

**Other PIDs associated with bronchiectasis**

Patients with inherited disorders of DNA repair such as ataxia telangiectasia are more susceptible to infections as the development of adaptive immunity is impaired. Many of these patients are antibody deficient and have bronchiectasis [60]. Similarly Wiskott–Aldrich syndrome, an X-linked immunodeficiency caused by mutations in the WASP gene leading to low levels of T- and B-lymphocytes, NK cells and serum IgM, develop infections with encapsulated organisms and therefore are at risk of bronchiectasis [61]. Both these disorders are rare causes of bronchiectasis in paediatric case series [2, 5]. A major component of immunity to extracellular bacterial pathogens is the complement system, and inherited complement deficiencies such as C2 or mannose-binding lectin (MBL) deficiency are associated with recurrent respiratory infections [62, 63]. However, although MBL deficiency is a relatively common condition affecting up to 25% of the normal population [62] there are only occasional reports linking isolated MBL deficiency with bronchiectasis [5]. MBL deficiency may increase the likelihood of bronchiectasis in patients with CVID [64–66] and is associated with more severe disease in patients with cystic fibrosis (CF) [67], suggesting MBL may help control disease progression in other immunodeficiencies associated with bronchiectasis. Lower levels of L-ficolin, another MBL pathway opsonin, has also been found in patients with bronchiectasis compared with controls [68], although these data need to be replicated. Other complement deficiencies are very rare and there are no data linking them to bronchiectasis.

The majority of patients with CF and ciliary dyskinesias will develop bronchiectasis and clearly have impaired physical immune defences of the lung through the effects of the gene defects on
mucociliary clearance. Neither are usually characterised as immunodeficiencies. However, recent data suggest mutations of the CF transmembrane conductance regulator in CF also cause a variety of defects in mucosal innate immunity. These include impaired phagocyte function, reduced efficacy of antibacterial peptides, and failure of bacterial internalisation by epithelial cells, as well as an exaggerated inflammatory response to infection [69, 70]. This constellation of multiple defects in innate immunity could make a significant contribution to the development of bronchiectasis in patients with CF, but this will be difficult to establish conclusively.

Secondary immunodeficiencies

Good clinical data on the associations of different secondary immune deficiencies with bronchiectasis are more limited than the available data for PIDs. In general an accurate assessment using the published data of the importance of SIDs as causes of bronchiectasis is not possible. However, recognised causes of SIDs are probably relatively rare causes of bronchiectasis, with the potential exception of children in areas with a high incidence of HIV infection.

Haematological malignancies

Many haematological malignancies result in B-cell and/or T-cell dysfunction and predispose to recurrent lung infection and subsequent development of bronchiectasis. In addition, profound immunodeficiency may occur as a result of treatment for these conditions. Case reports or case series have described bronchiectasis complicating chemotherapy, acute and chronic leukaemias, myeloma and lymphomas [5, 71–73]. In particular, due to the combination of prolonged survival and the high frequency of secondary hypogammaglobulinaemia, multiple myeloma and chronic lymphocytic leukaemia (CLL) seem to be relatively commonly associated with bronchiectasis, although the exact incidence has not been reported [72]. CLL and myeloma patients with proven bronchiectasis and hypogammaglobulinaemia should be assessed for IVIG therapy. Bronchiectasis has also been reported to develop in association with more acute haematological malignancies, perhaps as a consequence of severe lung infections and/or due to the affects of leukaemia or chemotherapy on host immunity [71]. However, there are no precise data on the incidence and rate of progression of bronchiectasis in patients with haematological malignancies.

Post-transplantation

Haematopoietic stem cell transplantation (HSCT) is associated with an increased incidence of respiratory infections and potentially prolonged defects in cellular and humoral immunity in survivors [74]. These factors could predispose to bronchiectasis [75] and, in the authors’ experience, serial CT scans after allograft HSCT can demonstrate rapidly developing bronchiectasis over a period of weeks to months. In addition, up to 10% of HSCT allograft recipients will develop bronchiolitis obliterans (the main pulmonary manifestation of graft versus host disease) which precedes the appearance of diffuse bronchiectasis in ~40% of cases [76, 77]. Hence, although there are no precise prevalence data on bronchiectasis post-HSCT, it is probably a relatively common complication, especially in allograft recipients. Similarly, patients who develop bronchiolitis obliterans after lung transplantation may also have CT evidence of bronchiectasis [78], and there are case reports of bronchiectasis developing after transplantation of other solid organs [79], presumably because of damage caused by intercurrent pneumonias and/or impaired pulmonary immunity due to prolonged immunosuppressive therapy.

HIV

HIV infection in most patients leads to a progressive T-cell defect characterised by a fall in CD4 T-helper cells. HIV-infected subjects suffer recurrent infections with conventional and opportunistic pulmonary pathogens, including mycobacteria species and S. pneumoniae. With the increasing duration of long-term survival after HIV infection it is therefore perhaps not surprising that up to
16% of HIV-infected children develop bronchiectasis [80, 81]. The incidence of bronchiectasis in HIV-infected adults may also be significant [82, 83]. The aetiology of HIV-related bronchiectasis is not well understood but may include direct effects of HIV infection on T-cell-dependent immunity and local macrophage- and monocyte-dependent pulmonary immunity, secondary effects on humoral responses, as well as direct effects of bronchial wall damage due to intercurrent pneumonia or tuberculosis, and possibly the association of HIV in adults with chronic obstructive pulmonary disease (COPD) [84]. The limited available publications suggest that in children bronchiectasis is more likely in subjects with CD4 counts <100 mm$^3$, or who have had recurrent pneumonia [80]. Interestingly, there is also a specific association with lymphocytic interstitial pneumonitis (LIP), with up to 40% of HIV-infected children with LIP developing bronchiectasis [80, 85]. Whether this reflects accelerated bronchial wall damage due to the lymphocytic infiltrate or reduced mucosal immunity in LIP is not clear. There are no comparative data on the pattern and progression of bronchiectasis in HIV-positive patients compared with patients with bronchiectasis due to other causes. More studies are required on the prevalence and associations of HIV infection with both adult and paediatric bronchiectasis to allow specific risk groups to be defined and managed aggressively to prevent progressive bronchiectasis. In addition, in areas with significant levels of HIV infection whether patients diagnosed with bronchiectasis warrant a HIV test as part of the diagnostic work-up needs consideration.

**COPD and asthma**

There is a high incidence of bronchiectasis in patients with severe asthma and COPD according to CT criteria [86, 87], although the exact incidence is not known and is confounded by both asthma and irreversible airways obstruction being complications of bronchiectasis. Bronchiectasis could be associated with asthma and COPD due to the cycles of recurrent infection and localised bronchial wall inflammation associated with both conditions. The clinical importance of bronchiectasis in patients with airways disease is not clear at present, but as bacterial infections frequently drive exacerbations of COPD, significant bronchiectasis could be clinically highly relevant. Patients with asthma and COPD may have altered mucosal immune responses to microbial pathogens and impaired macrophage function that, along with the marked airway inflammation that characterises both diseases, might contribute towards the development of bronchiectasis [88, 89]. The effects of asthma and COPD on pulmonary immunity need further investigation. Due to the rising incidence of COPD and more extensive use of CT scanning, severe COPD is likely to become an increasingly common association in series of adult patients with bronchiectasis.

**Biological therapies**

Therapies that inhibit tumour necrosis factor-$\alpha$ (such as infliximab) or deplete B-cells (rituximab) are increasingly used to treat rheumatological and other autoimmune conditions. Both therapies are associated with increased risks of infection [90, 91]. These therapies may make management of existing bronchiectasis more challenging and, in our experience, usually require an escalation of antibiotic prophylaxis. Furthermore, they could potentially trigger the development of bronchiectasis by increasing the frequency and/or severity of respiratory infections. Repeated administration of rituximab is often associated with the development of hypogammaglobulinaemia, which in the context of recurrent infection, should be managed by immunoglobulin replacement [92]. The effects of biological therapies are discussed in detail in the chapter by Dhasmana and Wilson [93].

**What information do PIDs and SIDs provide about immunity to airways infection?**

The identification of patients with bronchiectasis due to PIDs provides clear evidence for which aspects of the immune system are required for protection against bacterial infections of the lung.
The close association of bronchiectasis with CF, primary ciliary dyskinesia and antibody deficiency syndromes such as CVID and XLA demonstrate that physical defences and IgG (and perhaps IgA, specific IgG subclasses or anti-polysaccharide antibody responses) are required for the prevention of chronic bacterial infection of the lungs, as discussed in the chapter by Lambrecht et al. [94]. Although the mechanisms remain poorly defined, the clinical manifestations of TAP deficiency and hyper IgE syndrome with bronchiectasis suggest there is also an important and previously unsuspected role for CD8 and Th17 CD4 lymphocytes for the prevention of bacterial lung infection. Conversely, despite the prominence of neutrophil and macrophage infiltration in pneumonia and bacterial bronchitis, defects of phagocyte and complement function are only loosely associated with bronchiectasis. Humoral immunity therefore seems to be more important for bacterial clearance from the bronchial tree than phagocytes. This is perhaps a surprising observation as the main mechanism by which antibody assists pulmonary immunity to bacterial infection would have been predicted to be through promoting bacterial phagocytosis. Despite these clues provided by PIDs and SIDs, large gaps remain in our knowledge on the immune mechanisms required to prevent bacterial infections of the lung. Specific important areas of future research include the mechanisms by which antibody promotes clearance of bacteria from the lung, the bacterial target antigens for these antibody responses, and the role of different T-cell subsets for lung immunity.

A strategy for immunological investigation of patients with bronchiectasis

We recommend a sequential approach to investigation of immune function in patients with bronchiectasis or recurrent infection summarised in table 2. First-line investigations involve measurement of total serum Ig, IgG subclasses and specific antibody levels before and after vaccination (to detect CVID, XLA, IgA/IgM and IgG subclass deficiency) and, where appropriate, test for HIV infection. Further testing can then be initiated (following discussion with a clinical immunologist). Second-line tests include T- and B-cell immunophenotyping (to examine for defects in lymphocyte differentiation), neutrophil superoxide measurements (to look for CGD) and complement (to check for deficiency). A number of third-line tests involving gene sequencing and functional assays (examples shown in table 2) may also be indicated. One important clue to the type of immunodeficiency is the type of infections affecting the patient which can direct

| Table 2. Suggested staged immunological investigations of patients with bronchiectasis |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| **First-line tests** | **Second-line tests** | **Third-line tests** |
| Serum IgG, IgA, IgM, IgE | Immunophenotyping (including B-cell subsets) | Specific gene sequencing (e.g. ICOS, TACI, STAT) |
| IgG subclasses | Targetted genotyping (MBL, FcγRIIa) | TCR Vβ usage |
| Levels of specific antibodies against: pneumococcal serotype specific capsular polysaccharide, tetanus toxin | Neutrophil superoxide | TCR spectratyping |
| Autoantibody screen | Complement levels | Functional assays (e.g. chemotaxis, cytokine release assays, phagocytosis and bacterial opsonisation assays) |
| White cell differential count | HIV test | |

Ig: immunoglobulin; MBL: mannose-binding lectin; ICOS: inducible T-cell surface expressed CD28 co-stimulatory molecule; TACI: transmembrane regulator, calcium modulator and cyclophilin ligand interactor; STAT: signal transducer and activator of transcription 3; TCR: T-cell receptor.
laboratory investigations: encapsulated bacteria in B-cell immunodeficiencies; fungi, viruses and mycobacteria in T-cell immunodeficiencies and catalase-positive organisms (e.g. Staphylococcus, Aspergillus) in neutrophil disorders.

Future directions

26–53% of patients with bronchiectasis have no defined cause [3, 4]. Many of these patients also have upper respiratory tract disease such as sinusitis, suggesting they may have a global defect in preventing chronic bacterial infection of the respiratory tract. Recently, there has been increasing evidence that unsuspected immune defects may underpin many childhood infectious diseases [95] and intensive screening of children with idiopathic bronchiectasis may identify additional PIDs. For example, as untreated patients with primary ciliary dyskinesia and CF almost always develop significant bronchiectasis, other more minor defects in physical defences could be important causes of idiopathic bronchiectasis in adults and children. However, redundancy may limit the role of immunological defects as causes of bronchiectasis. For example, even with significant IgG deficiency the clinical phenotype of bronchiectasis has only partial penetrance and a significant proportion of subjects do not develop chronic lung infection. Hence, in adults, bronchiectasis could be a multifactorial disorder requiring two or more immune defects or a combination of an immune defect with a specific environmental insult in order to develop. The role of many aspects of lung immunity such as mucosal anti-bacterial peptides and proteins have yet to be investigated, and the complexity of the respiratory immune system could make identifying novel immune defects associated with bronchiectasis difficult. Despite this, polymorphisms affecting NK cell function or TAP and HLA associations with bronchiectasis have been described [96–98]. Further genetic studies of large numbers of patients with bronchiectasis are likely to identify additional polymorphisms or mutations affecting different aspects of immune function which could be related to the development of bronchiectasis.

Conclusions

Characterisation of patients with bronchiectasis has demonstrated close associations with a wide range of PIDs and SIDs, confirming that effective pulmonary immunity is necessary to prevent chronic bronchial damage due to bacterial infection. PIDs associated with bronchiectasis provide clear evidence for the vital role of physical defences for preventing lung infection, with important supportive roles from antibody and T-cell. SIDs causing bronchiectasis are less well characterised, but the effects of long-term HIV infection, the new biological therapies and perhaps chronic airways disease on pulmonary immunity are likely to be increasingly associated with the development of bronchiectasis. Patient with SID should be monitored for the development of recurrent lung infections and, where appropriate, the development of hypogammaglobulinaemia. Despite intense investigation for all the known causes of bronchiectasis, a large proportion of patients will still have idiopathic disease. An even more detailed immunological assessment of patients with idiopathic bronchiectasis combined with investigations for novel gene defects and polymorphisms will probably reveal a range of minor defects that affect immune function in a significant proportion of these patients. Although the challenge will then be to confirm that these minor immune defects actually contribute to the development of bronchiectasis, we would predict that increasing numbers of immunodeficiencies associated with bronchiectasis will be identified in the future.

Statement of interest

H. Baxendale has received research grant funding from Biotest and GlaxoSmithKline PLC to explore natural and vaccine related immunity to Streptococcus pneumoniae. Travel to ESI 2010 biannual meeting was funded by Grifols UK, Ltd.
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