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REVIEW

Susceptibility to nontuberculous mycobacterial lung disease

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ABSTRACT: The nontuberculous mycobacteria (NTM) exhibit heterogeneous pathogenicity in humans. Articles on known and potential human factors capable of producing susceptibility to NTM lung disease (NTMLD) were identified by a systematic search of the medical literature, and are reviewed in the present study.

Patients with pre-existing structural lung disease are known to be at risk of NTMLD. Other susceptible groups have become recognised since the 1980s, in particular middle-aged nonsmokers without previous lung disease (a group including those with Lady Windermere syndrome) and patients with genetically determined defects of cell-mediated immunity, including abnormalities of the interleukin-12/interferon-γ axis, certain human leukocyte antigen alleles, cystic fibrosis transmembrane conductance regulator mutations, and polymorphisms of solute carrier 11A1 (or natural resistance-associated macrophage protein 1) and the vitamin D receptor.

Information is also accruing about acquired systemic causes of susceptibility to NTMLD, including inhibitory antibodies directed against interferon-γ, post-menopausal waning of endogenous oestrogen levels, coeliac disease and exposure to use of dietary phyto-oestrogens. It is not known whether immunosuppressive factors, such as oral corticosteroid treatment, chronic renal failure, diabetes mellitus and other known risk factors for pulmonary tuberculosis, are also risk factors for the development of NTMLD. Caution is appropriate in managing such patients.

KEYWORDS: Bronchiectasis, immunodeficiency, Lady Windermere syndrome, *Mycobacterium avium–intracellulare* complex, nontuberculous mycobacterial lung disease, susceptibility

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STATEMENT OF INTEREST
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The nontuberculous mycobacteria (NTM) are a group of >100 species of bacteria that are ubiquitous in soil and water, and which exhibit varied pathogenicity. NTM are opportunists, requiring defects in local or systemic host immunity in order to cause disease in humans. The present study reviews the evidence relating to congenital and acquired conditions that may predispose individuals to NTM lung disease (NTMLD).

The classification of NTM has evolved, and the number of organisms involved has increased enormously. Initially, classification of mycobacteria was based on phenotype, and was limited to identification of the known pathogens, *Mycobacterium tuberculosis*, *M. bovis* and *M. avium–intracellulare* complex (MAC). Later, NTM were divided into four groups on the basis of pigment production and growth speed. Runyon groups I–III were slow growers and group IV contained rapid growers [1]. The early history of the classification and identification of mycobacteria has been summarised by WOLINSKY [2].

The development of 16S ribosomal DNA gene sequencing improved the accuracy of species identification and led to the description of many new mycobacterial species. However, the older phenotype-based classification system is still clinically relevant. For example, rapidly growing mycobacteria are generally less virulent than more slowly growing species [3], although their capacity for biofilm formation and tolerance of a wide range of environmental conditions contributes to their capacity to cause nosocomial disease.

METHODS

PubMed was searched for English language articles using combinations of search terms, including ''Mycobacterium'', ''nontuberculous mycobacterium'', ''atypical mycobacterium'', ''Mycobacterium

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avium-intracellulare'', ''Lady Windermere syndrome'', ''bronchiectasis'', ''cystic fibrosis'', ''immunodeficiency'', ''immunosuppression'', ''susceptibility'', ''risk factor'', ''interferon gamma'', ''tumour necrosis factor'', ''human immunodeficiency virus'', ''transplant'', ''cancer'' and ''malignancy''. The initial search identified 1,822 articles. These were screened to ensure relevance to the topic of the review. Article reference lists were then searched for additional relevant articles. Approximately 180 articles were reviewed. Information on the strength of evidence was collected from original research articles. However, estimates of risk of NTM infection and disease are less certain than in diseases such as tuberculosis (TB) because the NTM denominators are unknown in most populations.

SYSTEMIC DEFENCES AGAINST MYCOBACTERIAL DISEASE

The normal host immune response to mycobacterial infection has been described elsewhere [4, 5]. Lipoarabinomannan in the mycobacterial cell wall binds to macrophage Toll-like receptor (TLR)2 [6], inducing production of the cytokines interleukin (IL)-12 and tumour necrosis factor (TNF)-α. IL-12 binds to its receptor (IL-12R) on the surface of activated T-cells and natural killer cells. The IL-12/IL-12R complex upregulates production of interferon (IFN)-γ *via* the signal transducer and activator of transcription 4 (STAT4) signalling pathway.

Interferon-γ and tumour necrosis factor-α

IFN-γ is an extracellular pro-inflammatory cytokine that activates both the innate and adaptive arms of the immune system, principally in response to intracellular microbial infection. Its effects include: stimulating production of other pro-inflammatory cytokines, such as TNF-α and IL-12; inhibiting the production of anti-inflammatory cytokines, such as IL-4; upregulating major histocompatibility complex (MHC) class II expression on the surface of macrophages and other antigen-presenting cells; stimulating immunoglobulin (Ig) production by B-lymphocytes; promoting differentiation of T-helper lymphocytes (Th) into the Th1 phenotype; and promoting apoptosis of anti-inflammatory Th2 lymphocytes [7].

IFN-γ binds to the IFN-γ receptor (IFN-γR). This receptor is a heterodimer, with IFN-γR1 and IFN-γR2 chains, and is present on the surface of many inflammatory cells. Binding of IFN-γ to IFN-γR leads to modulation of nuclear gene expression *via* the Janus kinase (JAK)-STAT signalling pathway as follows. JAK associated with IFN-γR phosphorylates STAT1. This enters the nucleus, where it binds to promoter regions of IFN-γ-inducible genes [7]. The functions of these genes include promotion of MHC-I and -II expression, modulation of leukocyte–epithelial cell interactions, and promotion of inflammatory cytokine synthesis and free radical formation [8]. These functions are key aspects of the innate and acquired immune response to most microbial pathogens, and are pertinent as systemic defences against mycobacterial disease.

TNF-α is released by a variety of inflammatory cells, predominantly macrophages, in response to immune recognition of mycobacterial lipoarabinomannan. TNF-α binds to the macrophage membrane-bound TNF-α receptors 1 and 2, acting through the intracellular nuclear factor (NF)-κB pathway to modulate gene expression [9, 10]. TNF-α recruits and activates other inflammatory cells, and appears essential for granuloma formation [11]. Increased susceptibility to mycobacterial disease is a recognised side-effect of treatment with TNF-α antagonists [12].

Mycobacterial virulence factors

The molecular basis of mycobacterial virulence has recently been reviewed [13, 14]. It mainly resides in the components of the cellular envelope. These include lipoarabinomannan, a polysaccharide that promotes intracellular mycobacterial survival by blocking phagosomal maturation [15]; and trehalose dimycolate (or cord factor), a glycolipid that exerts hyper-inflammatory effects through modulation of IFN-α secretion and is implicated in cavitating disease [16]. Important secreted products include: catalase [17]; protein kinase G, which inhibits lysosomal fusion [18]; and enhanced intracellular survival protein, which inhibits T-cell proliferation *in vitro* [19].

The virulence of NTM varies by species but is generally low in immunocompetent individuals. Given the environmental ubiquity of NTM, either intense exposure or defects in local or systemic host immunity are probably necessary in order for disease to develop [20].

SUSCEPTIBILITY TO NTMLD

Patients with pre-existing structural lung disease are known to be at increased risk of NTMLD. Respiratory diseases associated with risk of NTMLD in multiple cross-sectional and cohort studies include chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis (CF), previous TB, silicosis, pneumoconiosis and alveolar proteinosis [21–30]. Other established risk factors for NTMLD include increasing age, male sex, smoking, alcohol abuse, residence in urban or coastal environments, and participation in mining and smelting [31]. Since the 1980s, other susceptible groups have been identified, in particular middle-aged nonsmokers without previous lung disease (a group which includes those with Lady Windermere syndrome [32]) and patients with genetic defects in cell-mediated immunity. Additionally, information is accruing regarding a number of acquired systemic causes of susceptibility to NTM disease. The remainder of the present study reviews the local and systemic factors that may play a role in increasing susceptibility to NTMLD. For most of the factors discussed, table 1 outlines relevant investigations and states the level of published evidence that supports the association.

Mechanical factors and impaired local immunity

MAC infection begins when the mycobacterial virulence factor, fibronectin attachment protein, adheres to fibronectin within exposed extracellular matrix on damaged mucosal surfaces [70]. *In vitro* studies in human tissue show that NTM are only able to adhere to damaged mucosa, unlike *M. tuberculosis*, which adheres to intact mucosa [71]. Impairment of local immune function due to chronic pulmonary diseases and mucosal damage combine to increase propensity for NTMLD. Factors compromising local immunity include impaired clearance of secretions, abnormal composition of airway surface liquid, abnormal composition of sputum and airway damage caused by persistent inflammation [72]. Theoretically, locally impaired perfusion may lower tissue oxygenation and reduce the accessibility of blood-borne protective factors.

TABLE 1 Summary of investigations used to detect susceptibility to nontuberculous mycobacterial (NTM) lung disease (NTMLD)

Disease	Tests	Evidence linking to NTMLD
Bronchiectasis, COPD, silicosis, pneumoconiosis, previous TB	HRCT	Cohort studies [24, 30], prevalence studies [22, 23, 26–28], case series [25, 29]
Cystic fibrosis	Sweat chloride, CFTR genotyping	Cohort studies [33], case–control studies [34–39], prevalence studies [40–45]
GORD	24-h pH monitoring (and other diagnostic tests)	Two prevalence studies [46, 47]
Deficiencies in IFN-γR1, IFN-γR2, IL-12, IL-12R	Tests of IFN-γ production in response to mycobacterial antigens, other specialised immunological tests, genotyping	Case reports and series [48–52]; no evidence for isolated lung disease
STAT1 deficiency	Tests of cellular response to exogenous IFN	Case reports [53, 54]; no evidence for isolated lung disease
Chronic granulomatous disease	Tests of neutrophil function (*e.g.* nitroblue tetrazolium)	One case report [55]
HLA types associated with NTM disease	HLA genotyping	One prevalence study [56], one cohort study [57]
SLC11A1 polymorphisms	SLC11A1 genotyping	One case series [58]
CFTR heterozygosity	CFTR genotyping	Prevalence studies [59, 60], one case–control study [61]
α_1-AT deficiency	Serum α_1-AT	No direct evidence
VDR polymorphisms	VDR genotyping	One case series [62]
Vitamin D deficiency	Serum vitamin D	No direct evidence
Coeliac disease	Coeliac autoantibodies and serum IgA	No direct evidence
HIV infection	HIV serology	Cohort studies [63], prevalence studies [64], case series [23, 65–68]
Inhibitory anti-IFN-γ antibodies	Anti-IFN-γ antibodies	One case series [69]

Only high-resolution computed tomography (HRCT) of the chest can be regarded as a routine clinically relevant test. Further study is required in order to determine whether or not specific indications can be found for the other tests listed. When interpreting the information regarding the type and strength of evidence for each risk factor, it should be borne in mind that the strength of association between many risk factors and NTM disease is unknown due to the lack of mandatory reporting of NTM infection. COPD: chronic obstructive pulmonary disease; TB: tuberculosis; GORD: gastro-oesophageal reflux disease; IFN-γR: interferon (IFN)-γ receptor; IL: interleukin; IL-12R: interleukin-12 receptor; STAT1: signal transducer and activator of transcription 1; HLA: human leukocyte antigen; SLC11A1, soluble carrier 11A1; CFTR: cystic fibrosis transmembrane conductance regulator; α_1-AT: α_1-antitrypsin; VDR: vitamin D receptor; Ig: immunoglobulin.

Bronchiectasis

Bronchiectasis and NTM lung infection (NTMLI) frequently coexist, and it is often difficult to separate cause from effect. Among patients in the UK with adult-onset bronchiectasis, the prevalence of NTMLI and NTMLD have been reported at 10 and 3%, respectively [24]. No difference was found in age, sex or spirometric results between patients with and without evidence of NTMLI. Peripheral mucus plugging on computed tomography (CT) was more common among patients with NTMLI. This raises the possibility that stagnant secretions provide an important medium for NTM (and other organisms) to proliferate. The present authors postulate that optimal use of airway clearance methods in bronchiectasis may protect against the development or progression of NTMLD. Although bronchiectasis is a risk factor for NTMLI and NTMLD, there is no consistent evidence that NTMLD and the severity of bronchiectasis are correlated [24, 30].

Cystic fibrosis

CF has been associated with an increased prevalence of NTMLI in several cross-sectional and cohort studies [33–45]. It is likely that the mechanisms of susceptibility in CF are similar to those in non-CF bronchiectasis. Peripheral mucus plugging is more common in CF than in non-CF bronchiectasis [24, 59].

The prevalence of NTMLI in CF has increased since the early 1990s [73]. Suggested explanations include increased testing frequency, improved sampling and culture techniques, and the increasing lifespan of CF patients, due to either decades of exposure being required to contract NTM or milder CF lung disease permitting not only longer survival but also somehow providing a more suitable environment for NTM [33].

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) appears to be common among patients with NTMLD [46, 47]. THOMSON *et al.* [46] studied 58 patients with MAC lung disease (MACLD). A clinical diagnosis of GORD was more common among patients with MACLD than among age-matched controls (44 *versus* 28%; $p<0.019$). Since patients with MAC were more frequently prescribed acid suppressive therapy, THOMSON *et al.* [46] speculated that acid suppression may increase risk of NTMLD by promoting survival of NTM in gastric fluid. However, they also point out that acid suppressive therapy may simply reflect more severe GORD.

KOH *et al.* [47] performed 24-h pH monitoring on 58 patients with type 2 NTMLD (MAC and *M. abscessus*); 26% showed evidence of GORD. Those with GORD exhibited more widespread airways disease on CT (bronchiectasis involving a median of four *versus* two lobes; $p=0.008$), and were more likely to show acid-fast bacilli on sputum smear (80 *versus* 44%; $p=0.033$). Only 27% of patients with NTMLD and GORD reported symptoms of reflux.

Thus it is not clear whether GORD symptoms are simply more common among patients who cough, whether GORD is relevant only insofar as it causes airways disease which then predisposes to NTM disease, or whether reflux independently increases the risk of NTMLD, for example by delivering NTM into airways.

Type 2 NTMLD and Lady Windermere syndrome

In 1989, PRINCE *et al.* [74] reported a series of patients with MACLD without apparent predisposing factors; 81% of the patients were female and 76% had a radiographical pattern of fibronodular (type 2) NTMLD, rather than the classic cavitatory (type 1) pattern. It has subsequently become clear that this syndrome is also common amongst those with lung disease caused by NTM other than MAC [73]. Sufferers are usually white, female and post-menopausal [74–76]. REICH and JOHNSON [76] reported that disease commonly occurs in the right middle lobe (RML) and lingula in these individuals. They proposed that this syndrome is related to a fastidious habit of voluntary cough suppression, and named the entity Lady Windermere syndrome [32].

The validity of Lady Windermere syndrome has been challenged. Some authors have pointed out that patients with myopathy, stroke or other conditions associated with impaired cough are not at increased risk of NTMLD [77]. A history of habitual cough suppression was not reported in the patients studied by REICH and JOHNSON [76]. However, there have since been several reports in which cough suppression has been documented [78, 79]. Another question is whether or not NTMLD affects the RML and lingula more often than would be expected by chance; a study of 31 patients with type 2 MACLD by HUANG *et al.* [80] found no predilection for any anatomical location. REICH and JOHNSON [76] found confinement of disease to the RML or lingula in only 21% of cases, which could be due to chance [20].

There are anatomical factors that could make the RML and lingula more susceptible to NTMLD. Both locations exhibit a relative lack of collateral ventilation and have long narrow bronchi that are dependent when upright. Both are features that might impair clearance of secretions [81]. Repeated vibration from the heart (in conjunction with gravity) might also impede the clearance of secretions from these lobes.

Certain physical features appear to be more common among patients with type 2 NTMLD. These include a tall slender body habitus, pectus excavatum, scoliosis and mitral valve prolapse [80, 82, 83]. Many of these features resemble those found in inherited connective tissue disorders such as Marfan's syndrome and the phenotype associated with hyper-IgE syndrome [20]. It is not clear whether this phenotype is an epiphenomenon of a systemic immune defect, or whether the skeletal deformities and consequent alterations in lung anatomy and mechanics might impair clearance of bronchial secretions. Increased susceptibility to bronchiectasis and pneumonia has been noted in Marfan's syndrome [84] and hyper-IgE syndrome [85]. Finally, solute carrier 11A1 (SLC11A1) may be relevant in Lady Windermere syndrome; this is discussed in more detail later.

IMPAIRED SYSTEMIC IMMUNITY AND NTMLD

Since the late 1990s, the molecular basis of susceptibility to mycobacterial disease has become better characterised with the identification of several mutations affecting cell-mediated immunity. Examples are mutations involving IL-12 [48] and IFN-γRs [86]. Nevertheless, only 35% of HIV-negative patients with disseminated NTM disease exhibit an identifiable genetic abnormality [20]. Most patients with NTMLD surveyed by HUANG *et al.* [87] showed no evidence of IFN-γR or SLC11A1 mutations. Granuloma formation appears normal in these patients [88], reflecting intact cell-mediated immunity [89].

Congenital and inherited susceptibility to NTMLD

The term Mendelian susceptibility to mycobacterial disease [90] denotes those inherited disorders causing an immune defect partly or totally restricted to NTMLD. All disorders classified in this category are caused by mutations in the genes encoding cytokines, receptors and downstream signal-transducing proteins of the IL-12/IFN-γ axis. Susceptibility to NTM associated with these conditions is not restricted to lung disease; indeed, most of the NTM infections described in this group have been disseminated or extrapulmonary. However, the literature on these rare disorders is currently confined to case reports and case series [48–54].

A number of genetic defects in the IL-12/IFN-γ/STAT1 signalling pathway have been described. Over 150 individuals have been documented with such defects, most of whom were recognised because of recurrent NTM infection [52]. Clinically relevant mutations have been described in the genes encoding IL-12, IL-12Rβ1, IFN-γR1, IFN-γR2 and STAT1 [4, 48, 50, 86]. Mutations have not been described in IFN-γ itself, although IFN-γ deficiency associated with disseminated *M. tuberculosis* disease has been reported [91].

Most mutations affecting IFN-γR1, IFN-γR2 and STAT1 show an autosomal dominant pattern of inheritance and cause only partial impairment of IFN-γ signalling [86]. Recurrent mycobacterial disease first becomes evident in adolescence or adulthood (mean age 13.4 yrs), and onset appears to be delayed among patients who have received the bacille Calmette–Guérin (BCG) vaccination [86]. Granuloma formation is normal [92]. These patients generally respond to antimycobacterial chemotherapy or exogenous IFN-γ [86]. They show increased susceptibility to Salmonella and Histoplasma infections, but retain resistance to viral infection [4].

In contrast, most patients with autosomal recessive mutations affecting IFN-γ signalling exhibit a complete absence of IFN-γ activity [86]. In the case of recessive STAT1 mutations, activity of other IFNs is also absent, leading to vulnerability to viral infection. Patients with recurrent disseminated infection often present in early childhood and respond poorly to antimicrobial therapy [4, 86]. Granulomas are absent or poorly formed and abundant mycobacteria are present in tissues [92]. Occasional success with haematopoietic stem cell transplantation has been reported [93].

Mutations in the gene encoding the p40 subunit of IL-12 lead to deficiency in, or absence of, IL-12. Mutations in the gene encoding the IL-12Rβ1 subunit lead to impaired IL-12 signalling. PICARD *et al.* [48] reported a series of 13 patients with IL-12 deficiency. The phenotype appears to be variable; 12 out of the 13 patients had a history of mycobacterial disease, and all children given BCG inoculation subsequently developed disseminated infection. However, overall mortality with

IL-12 deficiency was lower than with complete IFN-γR deficiency, and granuloma formation was usually preserved.

The phenotypic abnormality associated with IL-12Rβ1 deficiency is mild. A reported series of affected individuals found an increased incidence of mycobacterial disease (predominantly *M. avium*), but no cases of recurrent disease and low mortality [50]. FIESCHI *et al.* [50] speculated that IL-12 might be a redundant part of the immune response against mycobacteria.

Other primary immunodeficiency disorders

Rare mutations in the NF-κB essential modulator gene are associated with severe X-linked impairment of innate and adaptive immunity. Such patients are susceptible to a wide range of infections, including those caused by NTM [94]. A French family has been described with an X-linked recessive syndrome characterised by recurrent mycobacterial disease (disseminated BCG infection and TB), with no detectable abnormality of NF-κB essential modulator or the IL-12/IFN-γ axis [95].

Chronic granulomatous disease has rarely been associated with NTMLD [55]. X-linked hyper-IgM syndrome has only been associated with susceptibility to TB [96].

Human leukocyte antigen alleles

Some authors have reported an association between human leukocyte antigens (HLAs) and susceptibility to TB, principally the class I antigens A10 and B8 and the class II antigen DR2 (DRB1*1501) [97]. HLA genotyping of HIV-positive patients with disseminated MAC has revealed positive associations with the DR2, DQB1*0601 and DRB1*0701 alleles, and a negative association with the DMA*0102 allele [98]. Two Japanese groups have identified HLA antigens including DR6, DQ4, A33 and A26 as being more common among patients with MACLD without pre-existing lung disease [56, 57]; A26 was associated with progression of disease.

CF transmembrane conductance regulator mutations

Heterozygosity for mutant CF transmembrane conductance regulator (CFTR) is associated with phenotypic manifestations of CF, such as chronic pancreatitis, sinusitis and bronchiectasis [99]. Up to 24% of patients with CF show evidence of NTMLI [33]. In a study of KIM *et al.* [61], there was a greater likelihood of radiological NTMLD progression in patients with single CFTR mutations. Some authors have suggested that type 2 NTMLD might be a *forme fruste* of CF [77]. ZIEDALSKI *et al.* [59] tested 50 patients with idiopathic bronchiectasis or NTMLD (20 patients in the latter group) for CFTR mutations and elevated sweat chloride concentrations. Of the study group, 50% were either heterozygous or homozygous for pathological CFTR mutations, and 20% met diagnostic criteria for CF. In another report, 24% of patients with NTMLD exhibited at least one CFTR mutation [60].

CFTR mutations are common in Europeans [100], and will become more common as additional rare CFTR alleles are added to the >1,500 mutations already described [101]. The clinical relevance of heterozygosity for CFTR alleles largely awaits clarification.

α_1-Antitrypsin

There is scant literature supporting an association between α_1-antitrypsin (α_1-AT) mutations and NTMLD. KIM *et al.* [61] compared NTMLD CT features in patients with normal and abnormal α_1-AT phenotypes and found no differences at diagnosis or during follow-up. KAMINSKA *et al.* [102] studied patients with bronchiectasis and pulmonary infection with rapidly growing NTM; 31% exhibited an abnormal α_1-AT genotype *versus* 27% of patients infected with pyogenic bacteria alone (p-value not reported). It is not clear whether α_1-AT mutations predispose to NTMLD independent of the airways disease associated with α_1-AT deficiency [103].

SLC11A1: natural resistance-associated macrophage protein 1

SLC11A1 or natural resistance-associated macrophage protein 1 (NRAMP1) is an ion transporter that localises to the lysosomal membrane during phagocytosis, where it acts as a divalent cation transporter [104]. The published literature suggests an association between some SLC11A1 polymorphisms and NTMLD. KOH *et al.* [58] compared the prevalence of three SLC11A1 polymorphisms in 41 patients with type 2 NTMLD (with *M. intracellulare* and *M. abscessus*) *versus* 50 healthy controls. Heterozygosity for the intron 4, codon 543 of exon 15 or 3′-untranslated region polymorphisms was associated with increased risk of NTMLD, with odds ratios of 2.78, 5.74 and 9.54, respectively. However, the earlier study of eight patients and four controls of HUANG *et al.* [87] had found no association between SLC11A1 polymorphisms and NTMLD. A meta-analysis found no association between SLC11A1 polymorphisms and TB [105].

Vitamin D receptor polymorphisms

Vitamin D receptors (VDRs) are expressed on the surface of macrophages and activated lymphocytes. Vitamin D is believed to exert a number of immunomodulatory effects on these cells, including suppression of IFN-γ and IL-12 production, with the net effect of favouring the proliferation and activity of Th2 over Th1 [106]. Th1 are thought to produce a cytokine profile that favours granuloma formation and cell-mediated immunity, whereas Th2 activity favours humoral immunity [107]. Imbalance between Th1 and Th2 responses has been implicated in the pathogenesis of a variety of immunological and infectious diseases, including asthma [108, 109], atopy [107], ulcerative colitis [110], leishmaniasis [111], TB [112] and leprosy [113].

Several groups have reported associations between VDR polymorphisms and risk of TB [114]. VDR polymorphisms might therefore be expected to affect susceptibility to NTMLD. GELDER *et al.* [62] tested 56 patients with *M. malmoense* lung disease for three VDR polymorphisms, and found decreased prevalence of the *Flavobacterium okeanokoites* I (FokI) f polymorphism and increased prevalence of the *Acetobacter pasteurianis* subspecies *pasteuranis* I A and *Thermus aquaticus* YTI I (TaqI) t polymorphisms. However, TANAKA *et al.* [115] tested 111 Japanese patients with MACLD and 177 healthy controls for the FokI and TaqI polymorphisms and found no difference in prevalence compared with controls.

Coeliac disease, a chronic inflammatory disorder of the small bowel, has been associated with increased risk of TB (hazard

ratio 3.74) in a Swedish cohort study of 14,335 patients [116]. LUDVIGSSON *et al.* [116] speculate that malabsorption of vitamin D might provide an explanation. There is no published literature on NTM disease among patients with coeliac disease.

Toll-like receptor 2

TLRs, human equivalents of the Toll receptor of Drosophila spp., mediate recognition of bacterial antigens by the innate immune system [117]. TLR2 has been identified as the means by which human macrophages recognise mycobacteria [6].

RYU *et al.* [118] studied 17 patients with NTM lung disease (MAC and *M. abscessus*), measuring production of TLR2 mRNA, TNF-α mRNA, IL-12 mRNA, TNF-α and the IL-12 p40 subunit by peripheral blood monocytes. After exposure to MAC, the levels of these products produced by monocytes from NTM patients were lower than those produced by monocytes from healthy controls. Exposure to MAC in the presence of neutralising anti-TLR2 antibody reduced the measured production of mRNA and cytokines among controls; there was no reduction observed among NTM patients. These results suggest a defect in TLR2 conferring susceptibility to NTM disease.

ACQUIRED SUSCEPTIBILITY TO NTM

HIV

Disseminated MAC has long been recognised as a complication of AIDS [119]. Interestingly, isolated MACLD is uncommon among HIV-positive patients, even in cases in which the CD4 count is very low [120]. This fact highlights the importance of abnormal airway mucosa as an initiating factor for MACLD.

Malignancy

The association between cancer and TB is well recognised [121]. Many reports of pulmonary and extrapulmonary NTM disease among patients with solid and haematological malignancies have been published [122–124]. Any association is probably secondary to defective cell-mediated immunity [125]. NTMLD among patients with cancer is uncommon, but the incidence is probably higher than in the general population [73]. JACOBSON *et al.* [126] found an annual incidence of 2.5 cases of *M. kansasii* disease per 100,000 patient registrations in an oncology centre in southern USA. The estimated annual incidence among the general population is 1.0–1.8 per 100,000 population [73]. It is not known whether these infections were triggered by malignancy, antineoplastic chemotherapy, corticosteroids, indwelling vascular catheters or comorbid conditions, such as diabetes mellitus.

Leukaemia is a stronger risk factor than solid malignancy for NTM disease at various sites [126]. Hairy cell leukaemia is the haematological malignancy most strongly associated with NTM disease in the literature [127]. The incidence of mycobacterial disease is ~5% in this condition [122]. The monocytopenia and impaired monocyte function seen in this disorder may explain this association [123]. There are several reports of NTM disease associated with other acute and chronic leukaemias [124, 128–131].

Infection with rapidly growing mycobacteria occurs among patients with cancer [123, 129, 132–134]. Most are associated with intravenous lines [123].

Organ transplantation

The literature on NTM disease among solid organ and haematopoietic stem cell transplant (HSCT) recipients has been reviewed by DOUCETTE and FISHMAN [135]. The incidence of NTM disease in HSCT is 0.4–4.9% [135, 136], and it usually occurs as a vascular-catheter-related infection; however, 30% of reported cases exhibited pulmonary disease. MAC is the commonest pulmonary pathogen and the commonest pathogen in children [136], whereas rapidly growing mycobacteria are the commonest pathogens overall. Half of all reported cases of NTM disease after HSCT occur in the setting of graft-*versus*-host disease, perhaps because treatment of this condition involves anti-TNF-α antibodies [136].

NTM disease has been reported in heart, lung, liver and kidney transplant recipients. The reported incidences are 0.24–2.8, 0.46–2.3, <0.1 and 0.16–0.38%, respectively [135]. Among heart transplant recipients, the incidence may have been higher prior to widespread use of cyclosporin [137]. Renal and heart transplant recipients usually develop cutaneous disease, whereas lung transplant recipients usually develop pleuropulmonary disease. *M. kansasii* is the most common pathogen overall, MAC is most common following lung transplantation and rapidly growing mycobacteria are less important (although still prominent among renal transplant recipients). When NTM are isolated prior to transplantation, the effect on subsequent risk of NTM disease is unknown, but appears to be low in patients whose infection is treated [135, 138].

Diabetes mellitus

There have been several reports of NTM disease in diabetic patients, including cutaneous infections with *M. chelonae* at insulin injection sites [139–142], MAC pleuritis [143], *M. kansasii* pneumonia [144], MAC suppurative thyroiditis [145], and flexor tenosynovitis with *M. kansasii* [146] and *M. scrofulaceum* [147, 148]. Several risk factors for NTM disease, such as CF and corticosteroid use, are also risk factors for diabetes. There is no literature regarding diabetes mellitus as an independent risk factor for NTMLD.

Chronic renal failure

NTM disease associated with catheter exit sites (cutaneous infection and peritonitis) is a recognised complication of peritoneal dialysis [149]. Cases of bone and joint infection associated with slowly growing mycobacteria have also been reported [150, 151]. Chronic renal failure has been identified as a possible risk factor for NTM disease in retrospective cohort studies and literature reviews [23, 134, 152].

TNF-α antagonists

The TNF-α antagonists include the monoclonal antibodies infliximab and adalimumab and the soluble TNF-α receptor etanercept. They are effective treatments for many inflammatory disorders, including rheumatoid arthritis and inflammatory bowel disease [153, 154]. Infliximab and adalimumab are more potent immunosuppressants than etanercept; besides binding to circulating TNF-α, they also inhibit lymphocyte activation and IFN-γ production [155]. Infliximab also induces apoptosis of immune cells by binding to transmembrane TNF-α [156]. The increased risk of TB associated with TNF-α antagonists is well established [157, 158], and is greater for infliximab than for the

less potent etanercept [159]. Most cases occur within the first 90 days of treatment and so probably represent reactivation of latent TB infection (LTBI) rather than a primary infection [159].

The literature on NTMLD is more limited. In a review of Food and Drug Administration records of US patients treated with TNF-α antagonists, NTMLD was much less commonly reported than TB (10.7 *versus* 108.1 cases per 100,000 patients), and was more common for infliximab than for etanercept (rate ratio 2.08; p=0.023) [159]. The lower rates of NTMLD may occur because *M. tuberculosis* is more virulent than NTM, or because pre-existing LTBI is more common than subclinical NTMLD among patients treated with TNF-α antagonists.

Etanercept therapy has been reported in association with fatal MACLD [160], fatal pulmonary *M. xenopi* infection [161], fatal pulmonary *M. abscessus* infection [162], *M. chelonae* endophthalmitis [163], *M. xenopi* spinal osteomyelitis [164] and pulmonary *M. szulgai* infection [165]. In the latter case, the patient's treatment changed from etanercept to adalimumab after *M. szulgai* was identified.

Current guidelines recommend screening for active or inactive TB, and risk assessment for LTBI before commencing TNF-α antagonist therapy [166]. If possible, treatment for LTBI should be completed before starting TNF-α antagonists, so that active TB is not treated with a regimen designed for LTBI. Expert opinion suggests that patients with active NTM disease should only receive TNF-α antagonists with concurrent antimycobacterial chemotherapy [73].

Anti-IFN-γ antibodies

Following several reports of high-affinity neutralising antibodies directed against IFN-γ in patients with recurrent mycobacterial infection [167, 168], PATEL *et al.* [69] reported the results of screening 35 patients with recurrent disseminated NTM disease or NTMLD. Inhibitory IFN-γ antibodies were detected in six (17%) patients. *In vitro* tests showed that these antibodies prevented IFN-γ from binding to its receptor. PATEL *et al.* [69] were unable to determine whether these antibodies were pathogenic or simply a consequence of prolonged high titres of circulating IFN-γ.

Sex hormones

The prevalence of type 2 NTMLD rises following menopause. Female sex hormones have, therefore, been suggested as protecting against this condition [169]. Both male and female sex hormones exert immunomodulatory effects on murine macrophages. In the study of TSUYUGUCHI *et al.* [169], ovarectomised mice exhibited a higher mycobacterial load following infection with MAC compared with controls. Macrophages from infected mice exhibited enhanced *in vitro* activity against MAC when treated with 17β-oestradiol. The effect of testosterone on susceptibility to NTM is less clear in mice. It induces macrophage apoptosis [170] and slows wound healing [171], but also stimulates macrophage TNF-α production [171]. The role of androgens in mycobacterial infection has not been studied. Finally, CURRAN *et al.* [172] have reported reduced IFN-γ production among MAC-infected mice fed soy or genistein, suggesting that dietary phyto-oestrogens might counteract the antimycobacterial effects of endogenous female sex hormones. There is no literature regarding sex hormones and human susceptibility to mycobacterial disease.

CONCLUSION

The factors implicated in increased susceptibility to NTMLD have been reviewed. These may be local or systemic, congenital or acquired. NTM usually require abnormal airway mucosa in order to initiate bronchopulmonary infection. Local factors that exacerbate damage to the mucosal surface, or that increase the tissue burden of NTM, may promote disease. These include airway inflammation, ciliary dysfunction, abnormal sputum composition, mucus plugging of large or small airways, and the elongated bronchi and absent collateral ventilation that characterise the RML and lingula.

Some primary immunodeficiency conditions cause increased vulnerability to systemic NTM disease. Hereditary defects in the IL-12/IFN-γ/STAT1 axis predispose to disseminated NTM disease. Certain HLA alleles, CFTR alleles, and polymorphisms of SLC11A1 (NRAMP1) and the VDR may increase susceptibility to NTM disease while sparing other aspects of immune function.

It is unclear whether susceptibility to NTMLD may be acquired as an isolated phenomenon; candidate mechanisms include development of anti-IFN-γ autoantibodies, waning of endogenous oestrogen levels following menopause and use of dietary phyto-oestrogens. These last two mechanisms have only been investigated in animal models.

Possible causes of type 2 NTMLD and Lady Windermere syndrome may be found within all of the above categories; they include anatomical peculiarities of the RML and lingula, inheritance of certain SLC11A1 or CFTR genetic variants, and the fall in endogenous oestrogen production following menopause.

Important areas for further study include smoking, oral corticosteroid treatment, chronic renal failure, diabetes mellitus and other known risk factors for pulmonary tuberculosis. From a clinical viewpoint, caution is appropriate in managing such patients, and more frequent monitoring and/or lowering the threshold for treatment may be appropriate. Despite new exciting developments, there is much more to be learnt before understanding of the mechanisms and relative importance of factors associated with susceptibility to nontuberculous mycobacterial lung disease is complete.

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