AUDIT, RESEARCH AND GUIDELINE UPDATE

Non-tuberculous mycobacteria: a retrospective review of Scottish isolates from 2000 to 2010

Clark D Russell,[1,2] Pauline Claxton,[2] Christine Doig,[2] Amie-Louise Seagar,[2] Alan Rayner,[2] Ian F Laurenson[2]

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[1]College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK
[2]Department of Clinical Microbiology, Scottish Mycobacteria Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, UK

Correspondence to
Dr Clark D Russell, College of Medicine and Veterinary Medicine, University of Edinburgh, c/o Department of Clinical Microbiology, Scottish Mycobacteria Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, UK; clarkdrussell@gmail.com

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ABSTRACT

There is growing recognition of the clinical importance of non-tuberculous mycobacteria (NTM), a group of versatile opportunistic bacterial pathogens. We describe the characteristics of NTM isolates in Scotland over an 11-year period using data held by the Scottish Mycobacteria Reference Laboratory. American Thoracic Society microbiological criteria were used to evaluate the clinical significance of isolates. Data presented include analysis of trends across time, species/body site associations, gender and age differences, geographical variations and the association between cystic fibrosis and *Mycobacterium abscessus*. We emphasise the need for standardised reporting criteria for NTM isolates to ensure optimal surveillance of NTM disease.

INTRODUCTION

The non-tuberculous mycobacteria (NTM) are a group of opportunistic bacterial pathogens numbering >120 species. Infection is acquired from environmental reservoirs and usually manifests as pulmonary disease, although lymphadenitis, soft tissue infection and bacteraemia may also result.

Disease caused by NTM is not generally notifiable and, as a result, its epidemiology is not well described. The ubiquity of NTM in the environment makes contamination of samples a problem. In addition, distinguishing pulmonary colonisation from infection can be difficult. Recent work describes the epidemiology of NTM in England, Wales and Northern Ireland; however, such data are currently lacking for Scotland.[1] In this paper we use data held by the Scottish Mycobacteria Reference Laboratory (SMRL) to describe the characteristics of NTM isolates in Scotland over an 11-year period.

METHODS

Data collection

Scottish hospital laboratories submit mycobacterial isolates to the SMRL for speciation, susceptibility testing and typing. Patient age, sex and sample details are routinely included with submitted isolates. Submitted clinical, radiological and HIV information is variable, although patients with cystic fibrosis (CF) are reliably identified. We analysed data from January 2000 to December 2010 inclusive.

Definitions

We used the 'microbiological' criteria of the American Thoracic Society 2007 NTM guidelines to estimate the clinical significance of pulmonary isolates. These were therefore only included in the analysis if a patient had ≥2 positive sputum cultures of the same organism on separate days or a single positive culture from bronchial specimens. In the case of multiple pulmonary isolates of the same species, all of those within 12 months were regarded as representing the same episode of infection. All subsequent isolates within 12 months of the first were not considered further. Samples which grew *Mycobacterium gordonae* were excluded, given the high likelihood that these represented contamination or colonisation. *M gordonae* is usually a non-pathogenic coloniser, even in immunocompromised patients.[2] For extrapulmonary sites, a single positive isolate was considered significant as these were generally from biopsies or sterile sites.

Analysis of data

When calculating population rates, population estimates and NHS Health Board sizes were obtained from the General Register Office for Scotland. A χ^2 test was used to analyse the relationship between species and sample details.

RESULTS

Between 2000 and 2010 a total of 4193 positive NTM isolates from humans were recorded. There were 2176 clinically significant isolates from 1370 episodes of infection, with 2017 representing contamination or colonisation (see online supplementary figure S1); 806 were positive pulmonary isolates from within 12 months of a previous one from the same patient so were considered to represent the same episode of infection. Specimens came from 931 patients.

Trends across time

The rate of all NTM episodes varied year by year and no clear trend was seen (see online supplementary figure S2). A mean rate of 2.43 episodes per 100 000 of the population (range 2.06–2.71) was found. *Mycobacterium avium* complex was most frequently identified, accounting for 48.1% (n=659) of all episodes with a mean rate of 1.18 episodes per 100 000 each year. A 45% increase in the incidence of *M avium* complex was seen over the 11 years. Table 1 shows the most common species, sites and gender ratios of episodes.

Gender

Mean rates of NTM episodes for males and females were 2.53 and 2.33 per 100 000,

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Table 1 Most common *Mycobacterium* species, sites and gender ratios of episodes of infection

			% of episodes from clinically important sites caused by named NTM species			
			Pulmonary n=933	Adenitis n=92	Cutaneous n=53	Blood n=46
Species	% all episodes (n)	Male:female ratio*	% episodes (n)	% episodes (n)	% episodes (n)	% episodes (n)
M. avium complex	48.1 (659)	1.09	**44.8**† (418)	**75.0**† (69)	**20.8**† (11)	**67.4**† (31)
M. malmoense	17.7 (242)	1.04	**21.7**† (202)	**22.8** (21)	**9.4** (5)	**0.0** (0)
M. abscessus	9.8 (134)	0.70*	**13.7**† (128)	**0.0** (0)	**0.0** (0)	**0.0** (0)
M. kansaii	4.4 (60)	1.00	**3.9** (36)	**0.0** (0)	**1.9** (1)	**0.0** (0)
M. chelonae	4.2 (57)	1.48	**2.6**† (24)	**0.0** (0)	**28.3**† (15)	**15.2**† (7)
M. xenopi	3.6 (49)	4.19*	**4.5**† (42)	**0.0** (0)	**0.0** (0)	**0.0** (0)
M. fortuitum	1.8 (24)	1.0	**1.4** (13)	**0.0** (0)	**1.9** (1)	**0.0** (0)
M. simiae	1.5 (21)	0.75	**1.8** (17)	**0.0** (0)	**1.9** (1)	**2.2** (1)
M. marinum	1.5 (21)	1.1	**0.0** (0)	**0.0** (0)	**32.1**† (17)	**0.0** (0)
M. celatum	1.1 (15)	1.5	**1.5**† (14)	**0.0** (0)	**0.0** (0)	**0.0** (0)
M. mucogenicum	0.8 (11)	0.83	**0.2** (2)	**0.0** (0)	**0.0** (0)	**10.9**† (5)
M. peregrinum	0.8 (11)	0.83	**0.3** (3)	**1.1** (1)	**0.0** (0)	**0.00** (0)
M. szulgai	0.7 (10)	1.5	**1.0** (9)	**0.00** (0)	**0.0** (0)	**0.00** (0)
Other	4.1 (56)	–	**2.7** (25)	**1.1** (1)	**3.8** (2)	**4.3** (2)

*denotes p<0.05 by exact binomial test of goodness of fit for male:female ratio
†denotes p<0.05 by Fisher's exact test for association between species and body site
NTM: non-tuberculous mycobacteria.

respectively, with a male:female ratio of 1.08 : 1 (table 1). A ratio of 1.09 was seen when pulmonary episodes were considered alone. *Mycobacterium abscessus* episodes were more common in females (male:female ratio 0.7, p=0.004).

Site and mycobacterial species

The majority of NTM episodes were pulmonary (68.1%, n=933) (see online supplementary figures S3 and S4). These 933 pulmonary episodes occurred in 557 patients, with 209 patients having more than one episode of infection during the study period (94% with the same species, representing either relapse or reinfection) and an average of 1.6 episodes per patient. Renal, adenitis, bloodstream and cutaneous episodes contributed 8.7% (n=119), 6.7% (n=92) 3.4% (n=46) and 3.9% (n=53) of the total, respectively. *M avium* complex were the most frequently isolated organisms from pulmonary (44.8%), adenitis (75%) and bloodstream episodes (67.4%). *Mycobacterium marinum* was the most commonly isolated species from cutaneous episodes and was associated with this site (32.1% of episodes, p<0.0001); 81% of *M marinum* episodes came from cutaneous specimens. *Mycobacterium chelonae* accounted for 28.3% of cutaneous episodes and 15.2% of bloodstream episodes, being associated with both sites (p<0.0001 and p=0.0022, respectively). *Mycobacterium mucogenicum* was associated with bloodstream episodes (causing 10.9%, p<0.0001), with 45.5% of *M mucogenicum* episodes grown from blood cultures.

Age

The majority of all NTM episodes came from patients over the age of 50 (64.0%, n=875), and an even higher proportion of pulmonary episodes were from this age group (72.2%, n=672) (see online supplementary figure S5). However, 73.9% (n=68) of adenitis episodes came from children aged up to 5 years. Mycobacteraemias peak at 35 years (20%, n=46), being rare in later life. In contrast to other species, the incidence of *M abscessus* peaks between the ages of 11 and 25 years, with only 33.6% of episodes occurring in patients aged ≥25 years, probably due to patients with CF (see below).

Geographical variation

Greater Glasgow and Clyde and Lothian Health Boards had average rates of NTM of 3.25 and 3.63 episodes per 100 000 Health Board population, respectively, which were consistently higher than the national average (ratios of 1.34 and 1.49, respectively, compared with the national average for the study period). From 2007 the Borders Health Board also reported rates above the national average (average of 4.64 episodes per 100 000 Health Board population; ratio 1.91). There were no geographical trends in the distribution of NTM species.

Cystic fibrosis

A total of 129 episodes came from patients with CF, and all of these were from the pulmonary site (see online supplementary figure S6). The mean age of the patients was 22 years and the median age was 19 years (range 6–52 years), with 63% (n=81) coming from women. CF was associated with the isolation of *M abscessus* (p<0.0001), which was isolated in 68.2% (n=88) of CF episodes compared with 5.0% (n=40) of pulmonary episodes from patients without CF; 75% (n=66) of *M abscessus* episodes in patients with CF occurred in females. In addition, 68.75% of our *M abscessus* pulmonary episodes occurred in patients with CF.

DISCUSSION

These data gathered over an 11-year period are the first to describe the epidemiology of NTM across the whole of Scotland. A previous retrospective study in south-east Scotland suggests that up to 75% of NTM isolates reported were associated with episodes of clinical disease, whereas this larger nationwide study found that figure to be 52%.[3] The previous study included a review of available case notes, which the current report does not.

We found a mean annual rate of 2.43 NTM episodes per 100 000 of the population, with no clear trend visible between

2000 and 2010. Moore *et al* described similar data from England, Wales and Northern Ireland during the period 1995–2006. They found a 250% increase in NTM reports, from 0.9 per 100 000 in 1995 to 2.9 in 2006.[1] This increase may have occurred earlier in Scotland, and may be related to different laboratory methods used in different centres at different times or heterogeneous case definitions.

Consistent with the work of others, we found the majority of episodes were pulmonary, *M avium* complex was the most common species and episodes were more likely to come from older patients. The clinical significance of NTM found in urine is unclear and may frequently represent urethral colonisation. *M marinum* is primarily a fish pathogen and, following contamination of trivial skin lesions, can cause skin and soft tissue infections in man ('fish-tank' granuloma). Indeed, we found *M marinum* was associated with cutaneous infection, and this was the species most often isolated from this site. *M chelonae* usually causes localised infection but may spread haematogenously, often in immunocompromised patients. Consistent with this, our study found *M chelonae* to be associated with both cutaneous and bloodstream episodes. There are some reports in the literature of *M mucogenicum* bloodstream infections, [4] and our study confirms the association of *M mucogenicum* with NTM bacteraemia.

Approximately 13% of patients with CF have NTM isolated from pulmonary specimens.[5] We found an association between CF and the isolation of *M abscessus*, and this association has been described previously in both American and French cohorts.

Variable referral and reporting of isolates is a significant limitation of this work. We know that some laboratories submit all isolates to the SMRL whereas others use local experience to only submit 'first patient isolates' over a variable period. This practice not only confounds laboratory-based surveillance but relies on local expertise to differentiate between species from the same patient. This may occasionally be dangerous if two species are present in the same patient, especially if *Mycobacterium tuberculosis* complex is included. We believe that standardised referral and reporting criteria for isolates as well as clinical disease are required to ensure optimal patient care and surveillance of NTM disease. Relying on laboratory data alone is insufficient, and our data therefore probably underestimate the true incidence of NTM disease. Only with mandatory reporting of full clinical data can disease caused by NTM be clearly evaluated.

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