



Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases

Nontuberculous mycobacterial pulmonary diseases (NTM-PD) are increasingly recognised as opportunistic infections of humans. Nodular/bronchiectatic disease and fibrocavitary disease are the most frequent manifestations [1]. Although guidelines have been published [1], there are few data on diagnostic and treatment practices outside of reference clinics. A recent survey in the USA suggested limited adherence to guidelines for diagnosis and treatment of NTM-PD [2].

We performed a survey on diagnostic and treatment practices for NTM-PD in five European countries (EU5) (France, Germany, Italy, Spain and the UK) and Japan, using previously published methods [2]. We randomly selected and contacted 3590 physicians (EU5: 2970; Japan: 620) from databases of each country [3, 4]; of these, 3154 (EU5: 2585; Japan: 569) participated. A total of 997 (EU5: 757; Japan: 240) physicians proved eligible for inclusion in round two, *i.e.* they managed at least one patient who 1) was diagnosed with NTM-PD, as defined by the participating physician; 2) was currently under the physician's care; 3) had active NTM-PD at some point during the past 12 months, regardless of whether treatment was provided; and 4) had complete information available. Of these eligible physicians, 619 (62%; EU5: 446; Japan: 173) participated and entered data on 1429 NTM-PD cases, 1012 from the EU5 (France: 206; Germany: 211; Italy: 210; Spain: 230; UK: 155) and 417 from Japan. Most study physicians were pulmonologists (36%; EU5: 29%; Japan: 54%), followed by internal medicine specialists (23%; EU5: 21%; Japan: 29%) and general practitioners (23%; EU5: 30%; Japan: 5%). They entered demographic, laboratory and treatment data from the patient records in an online questionnaire (33 questions with subquestions).

Mycobacterium avium complex (MAC) predominated as the causative agent of NTM-PD (EU5: 79.4%; Japan: 85.1%), followed by *Mycobacterium abscessus* (EU5: 20%; Japan: 14.9%). The patient groups were different in Japan and the EU5. Of all patients for whom information was entered in the EU5, 37% were females, the mean age was 55.7±15.8 years, 25% were never-smokers, 33% had chronic obstructive pulmonary disease (COPD) and 22% had bronchiectasis. In Japan, 65% of the patients were female, their mean age was 67.0±11.5 years, 65% were never-smokers, 13% had COPD and 25% had bronchiectasis. Cough (86%), sputum production (46%), fatigue (52%) and malaise (39%) were the most frequently reported symptoms at diagnosis; fever was reported by 61% of the EU5 patients *versus* 26% of the Japanese patients.

Sputum sampling was the predominant microbiological diagnostic test for 63.5% of the EU5 patients and for 83.3% of the Japanese patients. Bronchial wash or lavage was performed in 52.6% of the EU5 patients *versus* 21.6% of the Japanese patients.

71% of all patients reported from the EU5 had a (high-resolution) computed tomography (CT) scan to aid in the diagnosis of NTM-PD, ranging from 63.7% in the UK to 79.3% in Italy; in Japan, 80.5% of the patients had a CT scan. Chest radiographs were used for the diagnosis in 71.7% of all patients from the EU5 and 85.4% of all patients from Japan. CT revealed nodular/bronchiectatic disease in 39.2% of the EU5 patients, ranging from 33.2% in the UK to 45.5% in Spain, and in 59.8% of the Japanese patients.

Most patients in Japan were considered by their physicians to have mild disease (67%; compared with 31% moderate, 2% severe), whereas most patients in the EU5 had moderate (59%) or severe disease (19%).



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In the EU5, 68% of the reported patients received antibiotic treatment for NTM-PD, whereas only 43% of patients reported from Japan received treatment. The percentage of patients receiving treatment differed by disease severity. 47% of patients with mild disease received treatment (EU5: 56%; Japan: 40%), *versus* 66% (EU5: 70%; Japan: 51%) of patients with moderate disease and 77% (EU5: 79%; Japan: 29%) of patients with severe disease. Symptomatic improvement was the most frequently cited goal of treatment (EU5: 46%; Japan: 48%), followed by sputum culture conversion (EU5: 31%; Japan: 25%).

Binary logistic regression analysis indicated that the country was the most influential factor for whether a patient was treated for NTM-PD. Patients in Spain and Italy are more than six times as likely to be treated than patients in France. Symptom severity and patient age were second and third most influential factors (table 1).

Oral antibiotics were the most frequently used treatment modality; for 27% of all patients, intravenous antibiotics were reported to be part of the treatment plan (EU5: 31%; Japan: 11%) and for 6% of the patients inhaled antibiotics were reported to be part of treatment (EU5: 7%, Japan: 1%). Both intravenous and inhaled antibiotics were more frequently prescribed for *M. abscessus* than for MAC pulmonary disease (MAC-PD) (intravenous 42.5% *versus* 21.6%; inhaled 11.7% *versus* 4.0%).

For MAC-PD, patients mostly received macrolides (76%), rifamycins (67%), ethambutol (56%) and fluoroquinolones (56%; EU5: 45%; Japan: 71%). Only 16.9% of all 746 treated MAC-PD patients received >6 months of a rifamycin-ethambutol-macrolide regimen: 41.9% of the treated patients in Japan but only 9.2% in the EU5. Within the EU5, this percentage differed by country: 17.8% in the UK, 8.4% in Spain, 8.0% in France, 7.6% in Italy and 4.3% in Germany. In the EU5, female patients were more likely than males to receive this regimen (25 out of 272 females *versus* 26 out of 740 males; $p=0.001$) and it was more often received by patients reported by pulmonologists (9%) or infectious disease physicians (8%) than by general practitioners (4%) or general internal medicine physicians (3%). In all participating countries, access to all these drugs is unrestricted, with physician prescription.

Oral antibiotic treatment for *M. abscessus* pulmonary disease involved use of macrolides (67% of patients), fluoroquinolones (54.3%), rifamycins (32.5%), ethambutol (20%), tetracyclines (10%) and co-trimoxazole (5%).

As only 9.2% (EU5) and 41.9% (Japan) of the treated MAC-PD patients received >6 months of the recommended rifamycin-ethambutol-macrolide regimen, published treatment guidelines seem to have had a limited impact on clinical practice. The EU5 data resemble those reported from the USA, where in a cohort of 915 patients, 80% had MAC-PD and only 13% of these MAC-PD patients received the guideline-compliant regimen [2]. These differences between the EU5, Japan and the USA could be related to the percentage of the reported patients seen by pulmonologists (54% in Japan, 29% in the EU5), the

TABLE 1 Variables influencing the treatment decision

Variables	Odds ratio [#]	Wald score	p-value
Country		114.034	0.001
Spain	6.248	33.366	0.001
Italy	6.032	20.015	0.001
UK	4.005	2.960	0.085
Germany	2.665	2.910	0.088
Japan	1.441	2.346	0.126
France (referent)	1.000		
Physician-assessed symptom severity at presentation		8.229	0.016
Severe	1.932	6.750	0.001
Moderate	1.356	1.954	0.003
Mild (referent)	1.000		
Age		6.275	0.012
>60 years	1.641	5.205	0.023
Sputum specimens for AFB analysis used in diagnosis	1.420	6.819	0.009
Fever a symptom at first presentation	1.413	6.294	0.012
Physician rating of patient's overall health		6.003	0.050
Poor or very poor	1.606	5.697	0.017
Fair	1.382	3.943	0.047
Good or very good (referent)	1.000		


AFB: acid-fast bacilli. [#]: exponentiation of the beta coefficient.

level of acquaintance with the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines or availability of national guidelines promoting similar or different regimens, but this was not captured in the survey.

The predominance of nodular/bronchiectatic disease in Japan, as opposed to the EU5, probably drives the reported differences in disease severity and, as a result, the lower percentage of patients receiving treatment in Japan. Differences in likelihood of treatment within the EU5 may reflect the different rates of antibiotic consumption in European countries [5, 6]. Less frequent use of CT scanning in the EU5 probably results from the predominance of fibrocavitary disease, but it may have hampered the recognition of nodular/bronchiectatic NTM-PD [7].

67% of all treated patients in the EU5 received a macrolide, compared with 98% in Japan and 43% in the USA [2]. Relatively few MAC-PD patients received a rifamycin and/or ethambutol. A regimen of ethambutol-clarithromycin in mild nodular/bronchiectatic disease proved non-inferior to rifampicin-ethambutol-clarithromycin in a recent study in Japan [8], so omitting the rifamycin might be an option for some patients. This may not hold true for ethambutol, as another recent study in Japan showed that not receiving ethambutol was an important risk factor for acquired macrolide resistance and failure [9]. Many patients used fluoroquinolones for both MAC-PD and *M. abscessus* pulmonary diseases, despite a lack of *in vitro* and *in vivo* efficacy [10–13]. The use of macrolide-quinolone regimens has been associated with the emergence of macrolide resistance [13].

In summary, proper diagnosis and treatment of NTM-PD require more attention by clinicians. Current treatment practices are likely to be ineffective and potentially hazardous, as they may induce further drug resistance. Significant educational efforts by professional societies are warranted to improve practices, starting with the implementation of the ATS/IDSA guidelines [1].

Jakko van Ingen ^{1,13}, **Dirk Wagner**^{2,13}, **Jack Gallagher**³, **Kozo Morimoto**⁴, **Christoph Lange**^{5,6,7,8}, **Charles S. Haworth**⁹, **R. Andres Floto**⁹, **Jennifer Adjemian**^{10,11}, **D. Rebecca Prevots**¹⁰ and **David E. Griffith**¹² for the NTM-NET

¹Dept of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands. ²Division of Infectious Diseases, Dept of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. ³Clarity Pharma Research LLC, Spartanburg, SC, USA. ⁴Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan. ⁵Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany. ⁶German Center for Infection Research (DZIF), Clinical Tuberculosis Unit, Borstel, Germany. ⁷International Health/Infectious Diseases, University of Lübeck, Lübeck, Germany. ⁸Dept of Medicine, Karolinska Institute, Stockholm, Sweden. ⁹Cambridge Centre for Lung Infection, Papworth Hospital and Dept of Medicine, University of Cambridge, Cambridge, UK. ¹⁰National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ¹¹United States Public Health Service, Commissioned Corps, Rockville, MD, USA. ¹²University of Texas Health Science Center, Tyler, TX, USA. ¹³Both authors contributed equally.

Correspondence: Jakko van Ingen, Dept of Medical Microbiology, Radboud University Medical Center, P.O. Box 9101, Nijmegen, 6500 HB, The Netherlands. E-mail: jakko.vaningen@radboudumc.nl

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