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Clinical relevance of *Mycobacterium malmoense* isolation in the Netherlands

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ABSTRACT

Uncertainty exists about the clinical relevance of *Mycobacterium malmoense* isolation, especially in pulmonary samples. We therefore determined clinical relevance, treatment and outcome of *M. malmoense* isolation in the Netherlands.

A retrospective medical file study was conducted for all patients in the Netherlands from whom *Mycobacterium malmoense* had been isolated between January 2002 and January 2006. Diagnostic criteria for nontuberculous mycobacterial (NTM) disease published by the American Thoracic Society (ATS) were used to determine clinical relevance. Treatment was compared with guidelines published by the British Thoracic Society.

In total, 51 patients were found from whom *M. malmoense* was isolated. Forty patients (78%) had pulmonary isolates, 32 of them met the ATS diagnostic criteria (80%). Cavitary disease was most common (n=28; 88%). Patients with pulmonary disease were mostly males, with an average age of 56 years and pre-existing chronic obstructive pulmonary disease. Cervical lymphadenitis was the most common extrapulmonary disease type. Adherence to treatment guidelines was poor. A good clinical response to treatment was observed in 70% and 73% of patients treated for pulmonary and extrapulmonary disease, respectively.

In conclusion, *M. malmoense* is a clinically highly relevant NTM in the Netherlands causing serious pulmonary morbidity. Adherence to treatment guidelines is not satisfactory.

Keywords: atypical mycobacteria, atypical mycobacterium infections, *Mycobacterium malmoense.*

INTRODUCTION

First described as a respiratory tract pathogen in 1977 by Schroder and Juhlin [1], *Mycobacterium malmoense* is among the most frequently isolated and clinically relevant nontuberculous mycobacteria (NTM) in northern Europe [2, 3, 4]. The environment is the suspected source of transmission of NTM to humans through aerosols and ingestion. Person-to-person transmission or transmission from animal sources has not been proven [3, 5, 6]. The presence of NTM in the environment implies that a NTM cultured from a non-sterile body site, such as the respiratory tract, may result from contamination or occasional presence of the NTM in a sample. Hence, it is important to distinguish contamination from true NTM disease. The American Thoracic Society (ATS) has published guidelines to assist in this distinction [3]. The clinical relevance of a NTM species can be quantified by assessing the percentage of patients with positive cultures of the respective NTM who meet the ATS diagnostic criteria.

In this study, we quantified the clinical relevance of *M. malmoense* isolation in the Netherlands between 2002 and 2006 by applying the ATS diagnostic criteria, and evaluated treatment and outcome.

MATERIAL AND METHODS

Study subjects

Patients were identified by reviewing the database of the Dutch National Institute for Public Health and the Environment (RIVM) for *M. Malmoense* positive cultures. The RIVM is the national mycobacteria reference laboratory that provides identification and drug susceptibility testing for all hospitals in the Netherlands. We reviewed

medical records of the identified patients from whom *Mycobacterium malmoense* was cultured in the January 2002 to January 2006 period.

Study design and setting

The present study was a retrospective observational study concerning all patients with *M. malmoense* positive cultures identified at the RIVM. The local ethics committee approved the study. We recorded demographic data, clinical data, drug susceptibility, treatment and outcome. The 2007 ATS diagnostic criteria were used to determine clinical relevant infections (Box 1) [3].

Treatment was compared with guidelines published by the British Thoracic Society: a NTM based treatment regimen was defined as consisting of rifampicin or rifabutin and ethambutol [7]. An adequate response to treatment was defined as symptomatic improvement and reversion to at least three subsequent negative cultures.

The RIVM subjected isolates of most patients to laboratory diagnosis. All patients isolates were subcultured in both liquid and solid media and identified using the Inno-Lipa Mycobacteria v2 (Innogenetics, Gent, Belgium) reverse line blot assay which has specific probes for *M. malmoense*. Prior to 2004, 16S rDNA gene sequencing (151bp hypervariable region A) was performed, after ruling out membership of the *M. tuberculosis* or *M. avium* complex using the AccuProbe assays (GenProbe, San Diego, USA). Remaining isolates were identified at local hospitals, by 16S sequencing.

Drug susceptibility was tested using the agar dilution method [8]. Drugs included in the test panel were isoniazid, rifampicin, ethambutol, streptomycin, cycloserine, prothionamide, amikacin, ciprofloxacin, clofazimine, clarithromycin, and rifabutin.

Data analysis

Pearson χ^2 and Fisher exact tests were used for statistical correlations.

RESULTS

Mycobacterium malmoense was isolated from 51 patients in the study period. Forty patients (78%) had pulmonary isolates, in 11 cases (22%) these were of extra-pulmonary origin. No patients in the study group were HIV-infected.

During the study period, no increase in notification of *M. malmoense* isolation was observed each year.

Pulmonary isolates

Of all 40 patients with pulmonary *M. malmoense* isolates, 32 (80%) met the ATS diagnostic criteria and were likely to suffer *M. malmoense* lung disease. The baseline patient characteristics are detailed in Table 1.

The predominant patient profile is a male with pre-existing pulmonary disease, mainly chronic obstructive pulmonary disease (COPD). The seven patients without a previous diagnosis of pre-existing pulmonary disease were mostly smokers, with radiographic features suggestive of pulmonary disease. Most patients reported productive cough (n=37; 93%), weight loss (n=24; 60%), and fatigue (23; 58%). Night sweats (n=10; 25%), hemoptysis (n=7; 8%) or fever (n=11; 28%) were infrequently reported. Only patients who reported weight loss were more likely to meet the ATS diagnostic criteria (p=0.048; OR 7.333; 95%CI 1.072-50.145). In the group of the patients that did not meet the ATS diagnostic criteria, four failed to meet the bacteriological criteria (three because only one sputum sample was collected) and four failed to meet the bacteriological and radiological criteria. Seventy-five percent

(n=24) of the 32 patients that met the ATS criteria for pulmonary NTM disease presented with cavitary lesions visible on chest radiographs. Additional computed tomography scanning revealed 4 extra cases of cavitary disease (total n=28; 88%), not identified as such using plain chest radiographs. Two patients presented with multiple nodular opacities on chest radiograph; two had a single pulmonary mass.

Thirty patients who met the ATS diagnostic criteria for pulmonary NTM disease started treatment. Figure 1 summarizes treatment and outcome in the study group. The mean duration of antimycobacterial treatment was 12 months (range 1–26 months). Macrolides were added in 22 patients (18 clarithromycin, 4 azithromycine; 92%), fluoroquinolones in 6 (4 ciprofloxacin, 2 moxifloxacin; 25%). Nine patients received therapy for presumed tuberculosis, prior to the diagnosis of NTM disease, for a mean duration of 48 days (range 2-123 days), and completed a NTM based regimen afterwards. Six patients with *M. malmoense* pulmonary disease only received a complete first-line tuberculosis treatment.

Of 30 patients treated, twenty-one patients showed an adequate response (70%), five suffered a failure or relapse (17%; mean time to relapse 13 months, range 5-24 months) and four died (13%) (Figure 1). Although the percentage of patients with an adequate response was lower in those receiving macrolide containing regimens (43 vs. 63%), this difference was not statistically significant (p=0.344). The mean duration of treatment among patients who later relapsed was shorter than for patients with an adequate response, though not significantly (320 vs. 358 days; p=0.709). The frequency of adequate response was not significantly different between patients treated with a TB based regimen and those treated with a NTM regimen (p=0.260). Two patients who met the ATS criteria refused treatment, one patient died, the other showed progressive disease. Follow-up of patients not meeting ATS diagnostic

criteria was uneventful; no more positive cultures have been recorded. Symptoms regressed in absence of antimycobacterial treatment.

Six (20%) patients received the 24 months of rifampicin and ethambutol regimen based on the British Thoracic Society (BTS) trials. This did not affect the percentage of patients with an adequate response (BTS regimen vs. other: 83% vs. 71%; p=0.426).

Contact-tracing studies were initiated for two patients with pulmonary *M. malmoense* isolates; both were presumed to have pulmonary tuberculosis. Some contacts received six months of isoniazid, based on a tuberculin skin test conversion.

In this study, one case of disseminated *M. malmoense* disease was noted in a patient who received immunosuppressive treatment after kidney transplantation. He presented with pulmonary *M. malmoense* disease, which extended to histologically and bacteriologically proven lymphadenitis and mediastino-esophageal fistula, with blood cultures yielding *M. malmoense*. Interestingly, this patient had strong epidemiological links to a patient diagnosed with smear positive pulmonary *M. malmoense* disease one year before.

Extra-pulmonary isolates

Eleven patients had extra-pulmonary *M. malmoense* isolates; we noted ten cases of cervicofacial lymphadenitis, including two in elderly patients. One case of tenosynovitis of the 2nd and 3rd digit of the right hand was observed in a plant handler with a history of multiple wounds to the right wrist. He had an adequate response after surgical debridement followed by a macrolide based regimen of 13 months duration. The eight pediatric cases of lymphadenitis were 3 boys and 5 girls without predisposing conditions, with a mean age of 36 months (range 22-46 months). All

presented with painless cervical or submandibular swelling, without fever or other symptoms. Surgical excision was the most frequent treatment and resulted in an adequate response in all patients. One of the elderly patients had a relapse after surgery, the other had an adequate response. Overall, 8 patients (73%) with extra-pulmonary isolates had an adequate response after the initial therapy.

In vitro drug susceptibility testing was performed on the primary isolates from 46 patients. Isolates were resistant to isoniazid (all), streptomycin (70%), amikacin (70%), ciprofloxacin (61%); intermediately susceptible (39%) or resistant (46%) to ethambutol; and susceptible to rifampicin (72%), rifabutin (96%), clarithromycin (all), cycloserine (98%), prothionamide (96%) and clofazimine (all).

Relapse or treatment failure among patients with pulmonary *M. malmoense* disease was not associated with *in vitro* rifampicin or ethambutol resistance (p=0.327 and p=0.405 respectively).

DISCUSSION

Mycobacterium malmoense is one of the most clinically relevant NTM in the Netherlands. Eighty percent of patients with pulmonary isolates met the ATS diagnostic criteria, compared to 21 (47%) relevant infections among 45 patients with pulmonary *M. xenopi* isolates, and 11 (73%) among 15 patients with pulmonary *M. szulgai* isolates [9, 10]. We observed *M. malmoense* disease exclusively in HIV-negative patients, which is in contrast to *M. avium*, *M. kansasii*, *M. xenopi* and *M. szulgai* [3, 9, 10]. Patients are mainly males with pre-existing pulmonary disease. The ATS diagnostic criteria were designed for infections with *M. avium*, *M. kansasii* and *M. abscessus*; they may be less applicable to *M. malmoense.* Because of the high

degree of true pulmonary *M. malmoense* infections observed, judgment on the clinical relevance of pulmonary *M. malmoense* isolates could probably be based on less strict criteria, as is advocated for *M. kansasii* [3], to prevent a prolonged period of inadequate treatment. The high degree of clinical relevance is in accordance with previous observations from northern Europe, varying from 70% to 84% using either ATS criteria or a modification of these criteria [11-14].

Interestingly, a dramatically lower clinical relevance of 10% was found in a retrospective case study of 73 patients in the USA [15]. There is no explanation for this difference, however it suggests less pathogenic strains of *M. malmoense* in northern America compared to northern Europe. There are no known bacterial virulence factors for *M. malmoense.* Phylogenetically related *M. szulgai* and *M. kansasii*, both of which are suggested to be among the most pathogenic NTM [3, 9] are known to harbor a region of difference 1-like genetic element (including *esat-6* and *cfp-10* genes) which is a well-known virulence factor for *M. tuberculosis* [16]. *Mycobacterium malmoense*, however, lacks this element [17]. To date, immunological studies have focused on *M. avium* and *M. abscessus* [18, 19], rather than *M. malmoense*. Studies of *M. malmoense* pathogenesis and virulence in murine models are warranted, as are studies on the role of host genetic factors in *M. malmoense* disease.

In a recently published retrospective study of the prevalence of all NTM in Ontario, Canada, between 1997-2003, *M. malmoense* was not isolated [20]. This observation is in contrast with the increase in *M. malmoense* notification in Europe since 1980, including increasing numbers of countries reporting isolation of *M. malmoense* [21]. This contrast suggests environmental niches favoring transmission to humans in

Europe. Whether this observation can be linked with the lower clinical relevance observed in the United Sates needs to be studied.

Human transmission has never been proven, even in a setting of geographic clustering of cases. In a study published by Doig and coworkers, small differences observed using pulsed-field electrophoresis were sufficient to show a lack of correlation between strain type and epidemiological or patient characteristics, making person-to-person spread unlikely [22].

The BTS treatment guidelines for pulmonary *M. malmoense* disease were not well adhered to including choice of antimycobacterial therapy and duration of therapy. Treatment of *M. malmoense* disease was often preceded by or consisted only of TB treatment. This observation reflects the similar clinical presentation of pulmonary *M. malmoense* and *M. tuberculosis* complex infection and is a cause of concern. Increasing the use of PCR to rule out *M. tuberculosis*, providing a quick and definite NTM diagnosis, will probably decrease morbidity and mortality and prevent initiation of unnecessary contact tracing studies. Although hampered by our limited study group size and duration of follow-up, successful clinical response in this study in the optimally treated group (83%) is comparable with a 75% successful outcome found by Henry *et al* [23]. The failure and relapse rates found in the recently published BTS trial (12% in the group treated with R and E, 5% in the group treated with R and E combined with clarithromycine or ciprofloxacin) are lower compared to the rate found in our study (17%) [24]. Probably, the shorter mean duration of antimycobacterial therapy negatively influenced treatment outcome in our population.

The mortality rate found among adequately treated patients in this study (13%) is comparable to that found by Banks *et al* (15%) [12], and Henry *et al* (11%) [23]. The NTM disease related mortality after 5 years of follow-up is found to be low (3,6%)

[24]. Mortality has been related to the length of delay between diagnosis and start of the treatment, while the occurrence of relapse has previously been associated with total time span of treatment [11]. Other factors suggested to independently affect mortality are *in vitro* resistance to ethambutol and the involvement of more than one lung zone [15]. In our study population, there was no significant association between ethambutol resistance and treatment failure.

The recently published BTS trial showed no additional benefit of adjunctive clarithromycin or ciprofloxacin over the 24RE regimen for pulmonary *M. malmoense* disease. Addition of clarithromycin even led to more side-effects [24]. These data are clinically important considering the extent of adjunctive macrolide and/or fluorquinolone use in our study group.

The frequency and types of extrapulmonary disease in our study are similar to those found in a survey in Sweden in which 21% of 221 patients had extra-pulmonary isolates, mainly lymphadenitis [14]. Pediatric cases of cervicofacial lymphadenitis are most frequent and tend to affect children in a limited age range, which may be related to environmental exposures specific to this age category [25], or the state of development of the immune system in children. Contrary to pulmonary disease, *M. malmoense* lymphadenitis is a relatively benign condition. Surgery is considered to be the optimal treatment and yields good results [3, 26].

Tenosynovitis due to *M. malmoense* is rare, though case reports are available in the international literature [27]. Extra-pulmonary infection with *M. malmoense* is rare and dissemination is only observed in patients with severely impaired immunity, although rarely in HIV/AIDS.

In conclusion, pulmonary *Mycobacterium malmoense* isolation is clinically relevant in 80% of all patients in the Netherlands, reflecting a level of virulence unmatched by other NTM species. Pulmonary disease resembling tuberculosis, and pediatric lymphadenitis are the most common types of *M. malmoense* disease. Some patients are incorrectly treated for tuberculosis for a lengthy period. We recommend the use of molecular diagnostic tools for every sample positive for mycobacteria to enable quick initiation of adequate therapy. Treatment outcome is relatively favourable when compared to other NTM infections. Future studies are necessary to optimize treatment regimens and to discern host and pathogen factors determining virulence and transmission to humans.

REFERENCES

1. Schröder KH, Juhlin I. *Mycobacterium malmoense* sp. nov. *Int J Syst Bacteriol* 1977; 27: 241-246.
2. Martín-Casabona N, Bahrmand AR, Bennedsen J, Thomsen VO, Curcio M, Fauville-Dufaux M, Feldman K, Havelkova M, Katila ML, Köksalan K, Pereira MF, Rodrigues F, Pfyffer GE, Portaels F, Urgell JR, Rüsch-Gerdes S, Tortoli E, Vincent V, Watt. Spanish Group for Non-Tuberculosis Mycobacteria. Non-tuberculous mycobacteria: patterns of isolation. A multi-country retrospective survey. *Int J Tuberc Lung Dis* 2004; 8: 1186-1193.
3. Griffith DE, Aksamit T, Brown-Elliot BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367-416.
4. Subcommittee of the Joint Tuberculosis Committee of the Britisch Thoracic Society. Management of opportunistic mycobacterial infections: Joint Tuberculosis Committee guidelines 1999. *Thorax* 2000; 55: 210-218.
5. Portaels F. Epidemiology of mycobacterial diseases. *Clin Dermatol* 1995; 13: 207-222.
6. Primm TP, Lucero CA, Falkinham III JO. Health impacts of environmental mycobacteria. *Clin Microbiol Rev* 2004; 17: 98-106.
7. Research committee of the British Thoracic Society. Pulmonary disease caused by *M. malmoense* in HIV negative patients: 5-yr follow up of patients receiving standard treatment. *Eur Respir J* 2003; 21: 478-482.

8. van Klingeren B, Dessens-Kroon M, van der Laan T, Kremer K, van Soolingen D. Drug susceptibility testing of *Mycobacterium tuberculosis* complex by use of a high-throughput, reproducible, absolute concentration method. *J Clin Microbiol* 2007; 45: 2662-2668.
9. van Ingen J, Boeree MJ, de Lange WCM, de Haas PE, Dekhuijzen PN, van Soolingen D. Clinical relevance of *Mycobacterium szulgai* in the Netherlands. *Clin Infect Dis* 2008; 46: 1200-1205.
10. van Ingen J, Boeree MJ, de Lange WCM, Hoefsloot W, Bendien SA, Magis-Escurra C, Dekhuijzen R, van Soolingen D. *Mycobacterium xenopi* clinical relevance and determinants, the Netherlands. *Emerg Infect Dis* 2008; 14: 385-389.
11. Banks J, Jenkins PA, Smith AP. Pulmonary infection with *Mycobacterium malmoense,* a review of treatment and response. *Tubercle* 1985; 66: 197-203.
12. Bollert FGE, Watt B, Greening AP, Crompton GK. Non-tuberculous pulmonary infections in Scotland: a cluster in Lothian? *Thorax* 1995; 50: 188-190.
13. Thomson VØ, Andersen ÅB, Miörner H. Incidence and clinical significance of non-tuberculous mycobacteria isolated from clinical specimens during a 2-y nationwide survey. *Scand J Infect Dis* 2002; 34: 648-653.
14. Henriques B, Hoffner SE, Petrini B, Juhlin I, Wåhlén P, Källenius G. Infection with *Mycobacterium malmoense* in Sweden: report of 221 cases. *Clin Infect Dis* 1994; 18: 596-600.
15. Buchholz UT, McNeil MM, Keyes LE, Good RC. *Mycobacterium malmoense* infections in the United States, January 1993 through June 1995. *Clin Infect Dis* 1998; 27: 551-558.

16. Lewis KN, Liao R, Guinn KM, Hickey MJ, Smith S, Behr MA, Sherman DR. Deletion of RD1 from *Mycobacterium tuberculosis* mimics Bacille Calmette-Guerin attenuation. *J Infect Dis* 2003;187:117-23.
17. Sorensen AL, Nagai S, Houen G, Andersen P, Andersen AB. Purification and characterization of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. *Infect Immun* 1995;63:1710-7.
18. Rottman M, Catherinot E, Hochedez P, Emile JF, Casanova JL, Gaillard JL, Soudais C. Importance of T cells, gamma interferon, and tumor necrosis factor in immune control of the rapid grower *Mycobacterium abscessus* in C57BL/6 mice. *Infect Immun* 2007; 75: 5898-5907.
19. Doherty TM, Sher A. Defects in cell-mediated immunity affect chronic, but not innate, resistance of mice to *Mycobacterium avium* infection. *J. Immunol* 1997; 158: 4822-4831.
20. Marras TK, Chedore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997-2003. *Thorax* 2007; 62: 661-666.
21. Hoefsloot W, Boeree MJ, van Ingen J, Bendien S, Magis C, de Lange W, Dekhuijzen PN, van Soolingen D. The rising incidence and clinical relevance of *Mycobacterium malmoense*. *Int J Tuberc Lung Dis* 2008; 12: 987-993.
22. Doig C, Muckersie L, Watt B, Forbes KJ. Molecular epidemiology of *Mycobacterium malmoense* infections in Scotland. *J Clin Microbiol* 2002; 40: 1103-1105.
23. Henry MT, Inamdar L, O'Riordain O, Schweiger M, Watson JP. Nontuberculous mycobacteria in non-HIV patients: epidemiology, treatment and response. *Eur Respir J* 2004; 23: 741-746.

24. Research Committee of the British Thoracic Society. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in the treatment of Opportunist Mycobacterial pulmonary diseases and an assessment of the value of immunotherapy with *M.vaccae*: a pragmatic, randomised trial by The British Thoracic Society. *Thorax* 2008; 63: 627-634.

25. Lindeboom JA, Prins JM, Bruijnesteijn van Coppenraet ES, Lindeboom R, Kuijper EJ. Cervicofacial lymphadenitis in children caused by *Mycobacterium haemophilum*. *Clin Infect Dis* 2005; 41: 1569-1575.

26. Lindeboom JA, Kuijper EJ, Bruijnesteijn van Coppenraet ES, Lindeboom R, Prins JM. Surgical excision versus antibiotic treatment for nontuberculosis mycobacterial cervicofacial lymphadenitis in children: a multicenter, randomized, controlled trial. *Clin Infect Dis* 2007; 44: 1057–1064.

27. Olsen RJ, Cernoch PL, Land GA. Mycobacterial synovitis caused by slow-growing nonchromogenic species: eighteen cases and a review of the literature. *Arch Pathol Lab Med* 2006; 130: 783-791.

BOX AND TABLE

BOX 1: SUMMARY OF THE 2007 AMERICAN THORACIC SOCIETY DIAGNOSTIC CRITERIA

American Thoracic Society Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease

Clinical criteria

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules.

and

2. Appropriate exclusion of other diagnoses.

Microbiological criteria

1. Positive culture results from at least two separate expectorated sputum samples. (If the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures.)

or

2. Positive culture results from at least one bronchial wash or lavage.

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

Abbreviations: AFB = Acid-Fast bacilli, CT = Computed tomography, HRCT = High resolution computed tomography

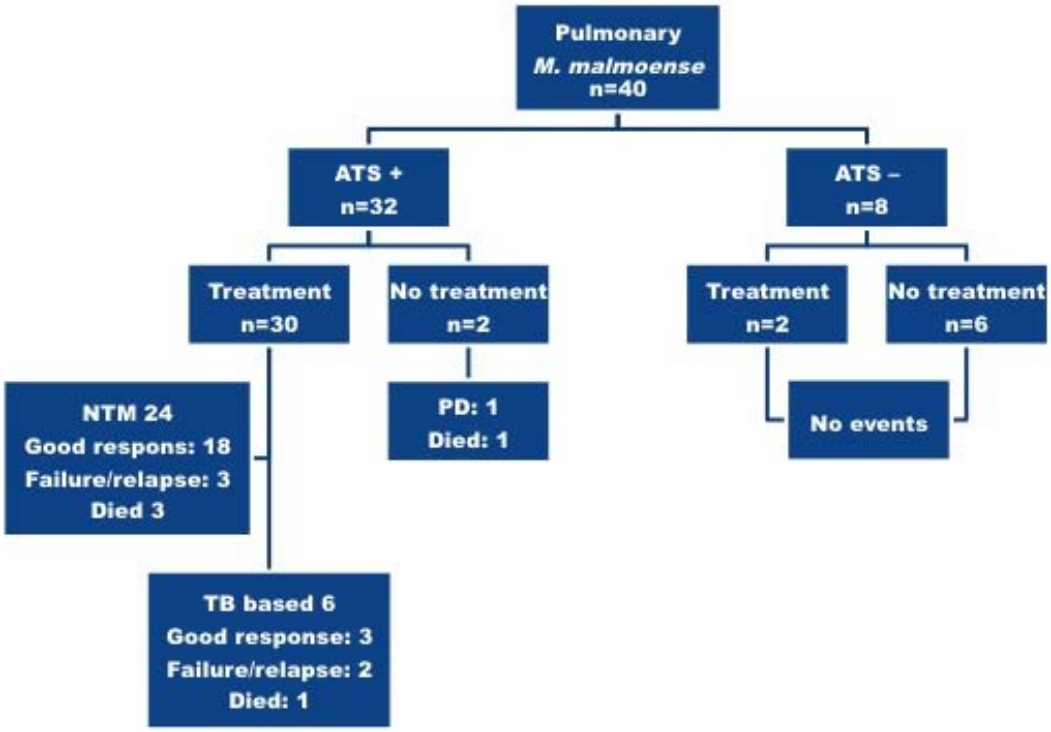
TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WITH PULMONARY *M. MALMOENSE* ISOLATES.

	ATS criteria met	ATS criteria not met	Total	P value
N	32	8	40	
Males	21 (66)	7 (88)	28	0.67
Mean age (range)	56 (28-81yr)	57 (33-83yr)	56 (28-83yr)	0.84
Pre-existing pulmonary disease	26 (81)	7 (88)	33	0.57
COPD	21 (66)	5 (63)	26	0.59
Prior TB	2 (6)	2 (25)	4	0.18
AFB smear positive	27 (84)	2 (25)	29	0.03
Cavitary lesion	28 (88)	1 (13)	29	< 0.001
Nodular lesion(s)	4 (13)	1 (13)	5	0.74

Data are presented as n or n (%). ATS: American Thoracic Society; COPD: Chronic obstructive pulmonary disease; TB: tuberculosis; AFB: acid fast baccilli

FIGURE LEGENDS

FIGURE 1: Frequency, treatment and outcome of pulmonary M. malmoense disease in the Netherlands between 2002 and 2006.



NTM based: treatment given to treat nontuberculous mycobacteria; TB based: group of patients treated only for a presumed tuberculosis infection; ATS+: fulfilment of the criteria of the American Thoracic Society; PD: progressive disease.