REPORT

Pulmonary disease caused by *Mycobacterium xenopi* in HIV-negative patients: five year follow-up of patients receiving standardised treatment

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Abstract The literature concerning the management of pulmonary disease caused by *Mycobacterium xenopi* is scanty and consists of retrospective reports, mostly of small series of patients. Our aim was to document the clinical features and response to treatment of this rare but challenging disease. Patients were treated in a randomised, multi-centre trial with either rifampicin plus ethambutol or rifampicin, ethambutol and isoniazid. Clinical, bacteriological and radiological progress was monitored at set intervals for 5 years. As no differences emerged between the two groups, the results have been combined to provide this prospective survey. Forty-two patients were studied. Mean age was 65 years, three-quarters were male and two-thirds had other lung disease(s). Sputum was positive on direct smear in 62%. Cavitation was present in 81%, mostly large cavities, and disease was extensive in 38%. Despite good clinical response and little toxicity the death rate was high (69%), but less than 10% died primarily because of the *M. xenopi* disease. The *failure of treatment/relapse* rate was 12%. Only 11 (26%) were known to be alive at 5 years of whom seven (17%) were known to be *cured*. There was no correlation between *failure of treatment/relapse* and *in vitro* resistance. Better methods of susceptibility testing and more effective regimens are needed, but it is also evident that improved management of concomitant diseases and better general health will play a major part in increasing survival.

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Keywords pulmonary disease; *Mycobacterium xenopi*, *in vitro* susceptibility, response to treatment.

INTRODUCTION

Pulmonary disease caused by opportunist mycobacteria accounts for approximately 5% of mycobacterial pulmonary disease in U.K. Of the opportunist mycobacterial infections *M. xenopi* is the least common, except in the South East of England, where of 533 new opportunist mycobacterial infections registered at the Mycobacterium Reference Laboratory in Dulwich, 37% were due to *M. xenopi* (1). The symptoms and signs of pulmonary disease caused by *M. xenopi* do not differ from those of *M. tuberculosis* or of the other opportunist mycobacterial pulmonary infections. Radiologically the appearances are indistinguishable from those of pulmonary tuberculosis (2–5).

The British Thoracic Society has conducted a multicentre, randomised trial of two regimens of chemotherapy in the treatment of lung disease caused by *M. xenopi*, the first prospective study of the treatment of this condition. Patients were followed for 3 years after completion of 2 years' chemotherapy with either rifampicin and ethambutol or rifampicin, ethambutol and isoniazid. Patient demographics at entry to the trial and the results of treatment did not differ significantly between the two regimens (6). Combining the results from the two treatment groups provides the first, prospective, controlled survey of the long-term outcome in patients receiving treatment for *M. xenopi* pulmonary disease.

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METHODS

The patients studied were aged 16 years or older, had sputum which was positive on culture for *M. xenopi* on

at least two occasions separated by at least a week, had radiographic changes compatible with mycobacterial pulmonary disease and/or clinical evidence of such disease. Patients known to be HIV+ were not included nor were pregnant women, those with terminal or pre-terminal disease, psychoses, previous intolerance to one or more of the trial drugs or with active co-infection with *M. tuberculosis* or *M. bovis*.

For those in whom anti-tuberculosis chemotherapy had been started before the true diagnosis was known, drugs other than rifampicin and ethambutol were discontinued, except that half the patients continued/received isoniazid as well. The dose of rifampicin was 600 mg daily for patients weighing 50 kg and over and 450 mg daily for those who weighed less than 50 mg. Ethambutol was given in a dose of 15 mg per kg and isoniazid as 300 mg daily. Chemotherapy was continued for 2 years.

Age, sex, weight, BCG status, occupational exposure to dust, previous pulmonary disease(s) and any conditions likely to impair immune defences, e.g. diabetes mellitus, rheumatoid arthritis, lymphoma, leukaemia, therapy with corticosteroids and/or immunosuppressive drugs were recorded. These data were sent to the Co-ordinating Physician, together with the pre-treatment chest radiograph. This and subsequent radiographs were read by the Co-ordinating Physician, using a standard method of grading extent of disease and cavitation (7). *In vitro* sensitivity tests to individual drugs (rifampicin, ethambutol, isoniazid) were performed by the national Mycobacterium Reference Units (MRU) for U.K. and Scandinavia, using the modal resistance method developed for *M. tuberculosis* (8,9).

During the 2 years of chemotherapy, the physician was asked to review the patient every 3 months, judging clinical progress as satisfactory or not, recording also weight, tolerance to chemotherapy and confirmation of its prescription. Two specimens of sputum were requested at each review, to be sent to the MRUs. Chest radiographs were requested at 3, 6, 12 and 24 months from the beginning of the trial regimen. A reminder to discontinue chemotherapy was sent with the review form at 24 months. If the patient's sputum was still positive on culture at 21 months, extra specimens were collected between 21 months and 24 months. If any of these proved positive the patient was categorised as a '*failure of treatment*' and further management was at the discretion of the physician.

After completing chemotherapy patients were reviewed clinically and bacteriologically (two specimens of sputum) every 6 months for 5 years. Chest radiographs were requested annually. Those whose sputum became positive on culture (two specimens separated by at least 2 weeks) were classed as *relapses.* Further management was left to the discretion of the physician.

Patients with negative cultures in the last 3 months of treatment and whose sputum remained negative on culture for the subsequent 3 years were classed as *cured*.

If a patient died during his/her period in the study, the cause of death was ascertained from the physician and/or general practitioner and/or post-mortem report. Using these sources, deaths were classified by the Co-ordinating Physician as primarily caused either by the mycobacterial lung disease or not so caused.

After the trial was completed enquires were made of the consultant and/or general practitioner in order to try to ascertain whether the patients lost from follow-up during the trial were alive at 5 years or not.

RESULTS

Forty-two patients (22 RE, 20 REH) were entered (40 British, 2 Scandinavian) in just over 5 years, three-quarters of whom were male (Table 1). Mean age was 65 years, range 30–84 years. Two-thirds had previous or co-existing lung disease(s), mostly chronic bronchitis and emphysema or asthma (13), healed tuberculosis (5), pneumonia (4) and bronchiectasis (3). Conditions likely to impair immune response were recorded in 11 (26%) and seven (17%) of the 42 had previously worked in dusty occupations. Only one patient was known to have had BCG vaccination. Sputum was positive on direct smear in 26 (62%) patients (Table 1).

Table 1. Pre-treatment characteristics of patients with pulmonary disease caused by *M. xenopi* (*n*=42)

Sex	32 M, 10 F	Direct smear +ve	26 (62%)
Mean age (range)	65 year (30–84 year)	Cavitation	34 (81%)
Previous lung disease	28 (66%)	Unilateral disease	23 (55%)
Reduced immunity	11 (26%)	Upper zone(s) only	19 (45%)
Dusty	7 (17%)	Three zones or more	16 (36%)
BCG	1 (2%)	Other pulmonary diseases evident on CXR	27 (64%)

Clinical and microbiological outcome

Clinical progress was recorded on 256 occasions, on 213 (83%) of which it was graded by the physician as satisfactory. Of the 43 times that clinical progress was regarded as unsatisfactory, 14 (5% of all 256 recordings) were attributed to the *M. xenopi* disease. There were three *failures of treatment* (two of whom died later) and two *relapses* after the end of treatment (Table 2 and Fig. 1). In two patients (5%) outcome is not known. Only seven patients (17%) were known to be alive and *cured* at 5 years. Of the four others alive at 5 years three had earlier been *failures of treatment* or *relapses*. The bacteriological status of the fourth could not be ascertained, but he had not sought treatment again from his original physician for mycobacterial disease. Eight patients (19%) had a poor outcome of their mycobacterial disease (*failure of treatment, relapse* or death because of the mycobacterial disease). No significant association was found for any variable in relation to poor outcome or to survival.

Within 5 years of diagnosis 69% had died, but only three of the 29 deaths (7% of the total entry to the study) were primarily attributed to the mycobacterial disease (Table 2). Of the remaining 26 deaths, six were caused by lung cancer, four by pneumonia, five by respiratory failure not attributable to *M. xenopi*, three by ischaemic heart disease, one by stroke and in seven patients the causes of death were not available.

The results of *in vitro* susceptibility tests were available for 29 patients and indicate that whereas one-third of the organisms were resistant to rifampicin, 86% were resistant to isoniazid and 70% were resistant to

Table 2. *M. xenopi* pulmonary disease: results during and after treatment

	RE	REH	Total	(%)
No. patients	22	20	42	
Outcome unknown	1	1	2	(5%)
No. alive at 5 years	9	2	11	(26%)
No. deaths (all causes)	12	17	29	(69%)
No. died because of *M. xenopi*	0	3	3	(7%)
No. failures of treatment and relapses	4[1D]	1[1D]	5[2D]	(12%)
No. who completed treatment as allocated and were known to be alive and cured at 5 years	5	2	7	(17%)

D, died.

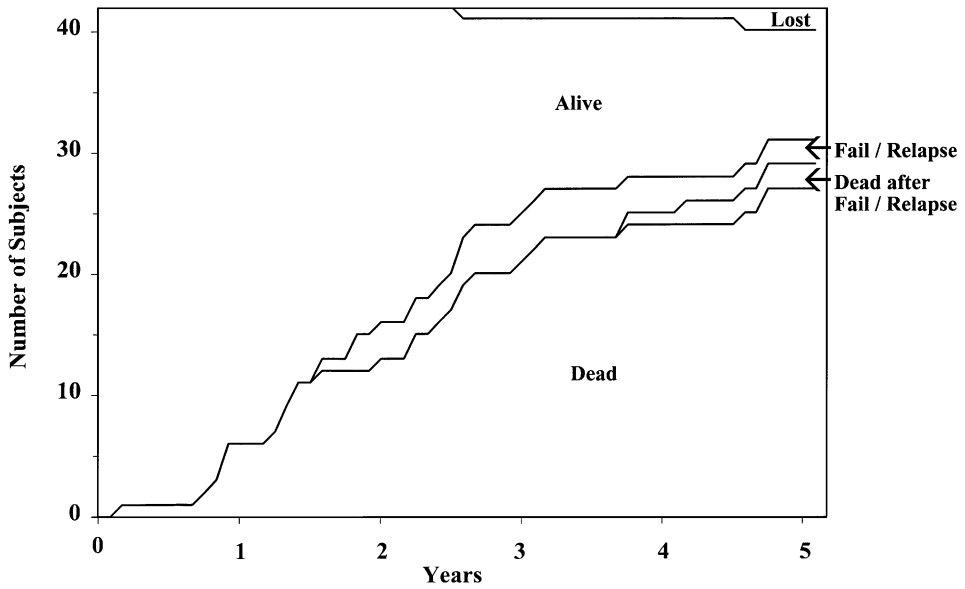

Fig. 1. Outcome over 5 years.

ethambutol. There was no correlation between *failure of treatment/relapse* and *in vitro* resistance to those drugs (Table 3).

Radiological results

Cavitation was found in 34 (81%), and 25 patients (60%) had at least one cavity of 2 cm or more in diameter. Just over half (55%) showed unilateral disease. Three or more lung zones were involved in 36%, whilst in 45% disease was confined to the upper zone(s). In 64% other pulmonary diseases were radiologically evident and in four further patients there were changes indicating combinations of cardiac and pulmonary or pleural and pulmonary disease(s).

At 5 years cavitation was still evident in seven of the ten patients radiographed, slightly less than on entry (81% of all 42 patients), and there had been reductions in the number of lung zones involved by the end results of the disease as compared with the appearances at the beginning of treatment in four of these ten. In eight patients with a complete set of yearly radiographs up to 5 years, 25% were classed as radiologically healed at 3 years, 88% at 4 years and 100% at 5 years (Table 4).

DISCUSSION

This paper reports the results at 5 years of the first prospective survey of the clinical features and response to treatment of patients with pulmonary disease caused by *M. xenopi*. The survey was controlled in that patients received one of two regimens for 2 years, with clinical, bacteriological and radiological information obtained at standard intervals during chemotherapy and for 3 years after the end of chemotherapy. Forty-two patients were studied, a number considerably greater than in the retrospective series reported by Costrini *et al*. (10), Smith and Citron (11) and Contreras *et al*. (12), but slightly less than the number described by Banks *et al*. (13). As the retrospective reports adequately documented the presenting symptoms and signs of this condition, which are much like those of pulmonary tuberculosis (11–13), these were not recorded in the survey.

Clinical progress while alive was on the whole satisfactory, and more so than found in the earlier studies where relatively toxic, multiple-drug regimens, which did not always contain rifampicin and ethambutol, had been used because of the result of *in vitro* sensitivity tests (12,13). The authors of two of the retrospective reports commented on the fact that in their patients the response to treatment appeared not to correlate with the results of susceptibility tests (11,13). We have confirmed that in this disease the results of such tests, performed by the standard modal resistance technique and using single antimycobacterial drugs, do not predict response in the same way as they do for disease caused by *M. tuberculosis*. Synergy between rifampicin and ethambutol, noted by Banks and Jenkins (14), could explain this finding. Nevertheless at 5 years only 17% of the original 42 patients were known to be alive and cured of their *M. xenopi* disease. This is less than Contreras *et al*. reported (29% of 34 patients) (12) and less than that found in the two British reports (72 and 23%) (11,13) but in these three

Table 3. *In vitro* susceptibility in relation to failure of treatment/relapse

		Failure of treatment/relapse	Other	
Rifampicin	Resistant	2	8	$\chi^2 = 0.05$
	Sensitive	3	16	$P = 0.82$
Ethambutol	Resistant	3	17	χ^2 trend = 0.001
	Intermediate	1	0	$P = 0.97$
	Sensitive	1	7	
Isoniazid	Resistant	5	20	χ^2 trend = 0.83
	Intermediate	0	2	$P = 0.36$
	Sensitive	0	2	

Table 4. *M. xenopi* pulmonary disease: radiological healing in the eight patients with a complete set of radiographs to 5 years

Year	One	Two (end of treatment)	Three	Four	Five
Healed	None	None	2	7	8

retrospective studies patients were followed for variable periods which were usually shorter than 5 years.

The death rate of 69% within 5 years was remarkable: it is higher than the 30–40% found in two retrospective series (12,13) and is almost six times that expected in the general population of similar age. *M. xenopi* is associated with much higher mortality than the other species of opportunist mycobacteria (4,15,16), but only 7% of our patients were judged to have died because of the *M. xenopi* disease, less than in the Canadian report (15%) (12) and the earlier British report (20%) (13). It should be appreciated that whilst as good a judgement was made as was possible in the circumstances of the trial, deciding the precise cause of death is not always easy in a population such as this. The generally high death rates in patients with *M. xenopi* pulmonary disease presumably reflect the presence of concomitant diseases. It is likely that the organism opportunistically infects frailer individuals who later succumb to their underlying illnesses rather than to the mycobacterial disease. An alternative explanation could be a systemic effect of this particular organism.

Males predominated (75%) as they had done in the earlier series (80–100%) (10–13). Mean age (65 years) and the range of age (30–84 years) was much as described in three of the previous reports (11–13), but greater than in the fourth (56, range 45–67 years) (10): clearly, the population with this disease is mostly middle-aged to elderly and mostly male, as is the case for the other opportunist mycobacterial species (4,15,16). Underlying lung disease was noted in two-thirds of the patients, fewer than reported in the North American (84%) and Canadian (100%) series (10,12), but much closer to the 74 and 75% in the two British retrospective reports (11,13). Chronic bronchitis and emphysema predominated on both sides of the Atlantic. Costrini *et al.* found diabetes mellitus and/or alcohol abuse in 18 of 19 patients (10) while Contreras *et al*. found alcohol abuse and/or a history of previous gastrectomy in 28 of 34 patients (12). Banks *et al.* commented that six of their 47 patients had previous gastrectomies (13) but the other British report mentioned only one of 15 (11). A quarter of our patients had a condition likely to impair immune response but none were known to be HIV positive. The four retrospective reports antedate the HIV era, but even during the HIV era *M. xenopi* has rarely infected such patients (17).

Cavitation was common: our 81% tallied closely with the percentages quoted in three of the retrospective reports (73–100%) (11–13), but Costrini *et al*. found it in only half of their group of 19 (10). The cavities tended to be large rather than small (60% $>$ 2 cm in diameter). Unilateral disease was present in just over half of our patients, much as it was found by Banks *et al*. (13) but in the North American and Canadian series bilateral disease was more common (60–85%) (10,12). We did not find the predominance of upper zone changes noted by Contreras *et al*. (12) and Smith and Citron (11), but we agree that the radiographic characteristics in *M. xenopi* pulmonary disease are not specific enough to allow differentiation from disease caused by *M. tuberculosis* or by other opportunist mycobacterial infections (2,4,5,18). Comparison of the radiological responses during this study with the previous studies is difficult because those studies were retrospective, had varying durations of follow-up, did not assess radiological changes at set points in time nor use defined methods of categorising changes on the radiograph. All that can be said is that the previous authors noted a general trend towards improvement in the radiological appearances (10,11,13) with one of the reports commenting that cavities rarely closed completely (13). Our findings provide for the first time radiological results in a format that can be used as a basis for future reference.

We were unable to demonstrate a significant association between any variable and survival, but only 42 patients entered the study. Any study on relatively uncommon conditions is always prone to problems with sample sizes which are low, resulting in diminished power to detect associations, or to identify prognostic factors. Additionally, there is the inferential difficulty that many candidate variables for inclusion in examination of associations raise the multiple testing problem, whereby we can expect 1 in 20 of significance tests to give *P*-values less than 0.05 when there are no genuine associations.

The trial has not addressed the place of surgery in management: unilateral disease was present in just over half of our patients, but other data that would provide insight into operability were not recorded. It is likely that respiratory and cardiac co-morbidity would reduce further the number in whom surgery could be undertaken, but it should nevertheless be borne in mind as an option for those who do not respond satisfactorily to chemotherapy. During the period of this study, macrolides and quinolones were shown to have *in vitro* activity against opportunist mycobacteria (19–23). It remains to be seen whether adding one or other or both to rifampicin and ethambutol can improve the results of the treatment of infection with *M. xenopi*. These questions should be answered by the multi-centre trial currently in progress under the auspices of the British Thoracic Society. Our finding that *in vitro* susceptibility to an individual anti-mycobacterial drug does not predict the clinical response to that drug underlines the importance of randomised, controlled clinical trials in assessing the place of any new drug.

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REFERENCES

1. Grange JM, Yates MD. Infections caused by opportunist Mycobacteria: a review. *J Roy Soc Med* 1986; **79:** 226–229.
2. Christensen EE, Dietz DW, Ahn CH, Chapman JS, Murray RC, Anderson J *et al*. Initial roentenographic manifestations of pulmonary *Mycobacterium tuberculosis, M. kansasii, M. intracellulare. Chest* 1971; **80:** 132–136.
3. Evans AJ, Crisp AJ, Colville A, Evans SA, Johnston IDA. Pulmonary infections caused by *Mycobacterium malmoense* and *Mycobacterium tuberculosis:* a comparison of radiographic features. *AJR* 1993; **161:** 733–737.
4. Research Committee, British Thoracic Society. *Mycobacterium kansasii* pulmonary infection: a prospective study of the results of 9 months of treatment with rifampicin and ethambutol. *Thorax* 1994; **49:** 442–445.
5. Evans AJ, Crisp AJ, Hubbard RB, Colville A, Evans SA, Johnston IDA. Pulmonary *Mycobacterium kansasii* infection: a comparison of radiological appearances with pulmonary tuberculosis. *Thorax* 1996; **51:** 1243–1247.
6. British Thoracic Society. First randomised trial of treatment for pulmonary disease caused by *M. avium* intracellulare, *M. malmoense* and *M. xenopi* in HIV negative patients: rifampicin, ethambutol and isoniazid—v-rifampicin and ethambutol. *Thorax* 2001; **56:** 167–172.
7. Simon G. Radiology in epidemiological studies and some therapeutic trials. *BMJ* 1966; **2:** 491–494.
8. Marks J. The design of sensitivity tests on tubercle bacilli. *Tubercle* 1961; **42:** 314–316.
9. Marks J. A system for the examination of tubercle bacilli and other mycobacteria. *Tubercle* 1976; **57:** 205–207.
10. Costrini AM, Mahler DA, Gross WM, *et al*. Clinical and roentogramphic features of nosoconial pulmonary disease due to *Mycobacterium xenopi*. *Am Rev Respir Dis* 1981; **123:** 104–109.
11. Smith MJ, Citron KM. Clinical review of pulmonary disease caused by *Mycobacterium xenopi. Thorax* 1983; **38:** 373–377.
12. Contreras MA, Cheung OT, Sanders DE, *et al*. Pulmonary infection with non-tuberculous mycobacteria. *Am Rev Respir Dis* 1988; **137:** 149–152.
13. Banks J, Hunter AM, Campbell IA, *et al*. Pulmonary infection with Mycobacterium xenopi: review of treatment and response. *Thorax* 1984; **39:** 376–382.
14. Banks J, Jenkins PA. Combined versus single antituberculosis drugs on the *in vitro* sensitivity patterns of non-tuberculous mycobacteria. *Thorax* 1987; **42:** 838–842.
15. British Thoracic Society. Pulmonary disease caused by *Mycobacterium avium-intracellulare* in HIV negative patients: five year follow-up of patients receiving standardised treatment. *Int J Tuber Lung Dis* 2002; **6**(7): 628–634
16. British Thoracic Society. Pulmonary disease caused by *Mycobacterium malmoense* in HIV negative patients: five year follow-up of patients receiving standardised treatment. (ERJ, in press).
17. Shafer RW, Sierra MJ. *Mycobacterium xenopi*, *Mycobacterium fortuitum*, *Mycobacterium kansasii* and other non-tuberculous mycobacteria in an area of endemicity for AIDS. *Clin Infect Dis* 1992; **15:** 161–162.
18. Evans AJ, Crisp AJU, Colville A, *et al*. Pulmonary infections caused by *Mycobacterium malmoense* and *Mycobacterium tuberculosis:* comparison of radiographic features. *AJR* 1993; **161:** 733–737.
19. Fernandez PB, Hardy DJ, McDaniel D, *et al*. *In vitro* and *in vivo* activities of Clarithromycin against *Mycobacteria avium*. *Antimicrob, Agents Chemother* 1993; **37:** 1285.
20. Leysen DC, Haemers A, Pattyn SR. Mycobacteria and the new quinolones. *Antimicrob Agents Chemo ther* 1989; **313:** 1–5.
21. Hoffner SE, Hjelm U, Kallenius G. Susceptibility of *M. malmoense* to anti-mycobacterial drugs and drug combinations. *Antimicrob Agents Chemo Ther* 1993; **37:** 1825.
22. Dantzenberg B, Piperno D, Diot P, *et al*. Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. *Chest* 1995; **107:** 1035–1040.
23. Wallace RJ, Brown BA, Griffiths DE, *et al*. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex—the first 50 patients. *Am J Respir Crit Care Med* 1996; **153:** 1766–1772.