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Pulmonary infection with *Mycobacterium kansasii* in Wales, 1970-9: review of treatment and response

J BANKS, AM HUNTER, IA CAMPBELL, PA JENKINS, AP SMITH

From the Chest Unit, Llandough Hospital, Penarth; and the Mycobacterium Reference Unit, University Hospital of Wales, Cardiff

ABSTRACT Thirty-five patients (88% male) with pulmonary infection caused by *Mycobacterium kansasii* have been reviewed. Sixty-six per cent had pre-existing lung disease, chronic bronchitis and emphysema accounting for half of the disorders. Unilateral lesions were present in 69% of patients whose chest radiographs were reviewed and 90% had cavitating disease. The development of unilateral or bilateral disease appeared to be independent of any delay in starting treatment. Five patients died while receiving treatment, but none of these deaths was due to *M kansasii* infection. The remaining 30 patients were successfully treated with drug regimens, all of which included rifampicin and 86% of which included ethambutol. There was 100% sputum conversion, with no relapses after a mean follow-up period of five-and-a-half years. Rifampicin and ethambutol given for a mean period of 15 months appeared to be a non-toxic, effective combination.

Studies published in the last decade have shown the effectiveness of rifampicin in the treatment of pulmonary infection caused by the non-tuberculous mycobacterium *M kansasii*.[1 2] No uniform approach to treatment, however, has been established. Harris *et al* have recommended that until the rate of relapse is known in patients treated with and without regimens containing rifampicin this drug should be kept in reserve for patients requiring retreatment.[1] Others have recommended various combinations of rifampicin, ethambutol, isoniazid, and streptomycin.[3 4] Some patients are treated with drug combinations which include cycloserine and ethionamide on the basis of in vitro sensitivity results. The aim of this retrospective study was to seek the simplest effective regimen which was well tolerated.

Methods

Cultures from all patients with non-tuberculous mycobacterial infection encountered in Wales are sent to the Mycobacterium Reference Unit in Cardiff for identification and sensitivity testing. From 1970 to 1979 50 patients were registered by the unit as having pulmonary infection due to *M kansasii*.

Address for reprint requests: Dr J Banks, Chest Unit, Llandough Hospital, Penarth, S Glam CF6 1XX.

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We were able to trace the case notes of 35, from which information about age, sex, mode of presentation, treatment, and subsequent progress was obtained. In the remaining 15 patients the records were either unobtainable or too incomplete for review because patients failed to attend follow-up clinics or moved to other areas and were lost to follow-up. Since *M kansasii* may occur as a casual isolate in otherwise healthy people the organism should be cultured repeatedly before it is considered clinically significant. Each of the 35 patients included had at least two positive sputum specimens (average per person 5·7 positive cultures). There were no concurrent isolations of *M tuberculosis*. In 29 cases the chest radiographs were obtained for review. These films were assessed independently by one of the authors, who had no knowledge of the clinical or bacteriological state of the patients. In six patients the radiographs were unobtainable, and descriptions of the radiographic abnormalities were obtained indirectly from reports made by the chest physician in charge of the patients.

The results of treatment were assessed according to the clinical, bacteriological, and radiographic response. A patient was considered cured when satisfactory clinical progress, as documented by the physician in charge, was accompanied by persistently negative sputum cultures and radiographic evidence of healed disease.

Results

The 50 patients registered by the Mycobacterium Reference Unit as having infection due to *M kansasii* represented 1·2% of the total number of pulmonary mycobacterial infections encountered in Wales during the decade 1970–9. Of the 35 patients whose records were reviewed, 31 were men (88·5%). The mean age of the group was 51·6 years (range 30–76 years). Pre-existing lung disease was present in 23 patients (66%)—chronic bronchitis and emphysema in 12 cases and pneumoconiosis in two (table 1). Thirty-one patients were smokers; in another three cases the smoking habits were not documented.

Thirty-one patients presented with a change in symptoms or were referred because of new symptoms. Cough and sputum were present in 30 (86%) of patients. Haemoptysis was a presenting feature in 10 (28%). Three patients were symptomless at the time of diagnosis, two having lesions on routine films from mass miniature radiography and the third an abnormal chest radiograph before elective minor surgery. A fourth patient was found to have an abnormal chest radiograph after admission to hospital with a stroke.

In vitro sensitivity tests were made with a resistance ratio method with wild strains of *M tuberculosis* as standards. All the *M kansasii* strains were sensitive to rifampicin. Two showed borderline resistance (ratio 2–4) to ethambutol, and 33 borderline resistance to streptomycin. All the strains were at least eight times as resistant to isoniazid as the standard strains.

The chest radiographs of 29 patients were available for review. Parenchymal disease consistent with tuberculosis was present in all cases. Twenty (69%) of these showed unilateral disease only. Twenty-six (90%) had cavitating disease. In six of the eight patients in whom there was a delay between diagnosis and the start of treatment the disease remained unilateral. The periods of delay ranged from one month to three years, with a mean interval of 8·25 months.

Table 1 *Pre-existing pulmonary disease in patients with Mycobacterium kansasii infection*

	No of patients
Chronic bronchitis and emphysema	12
Previous *M tuberculosis*	5
Coalworkers' pneumoconiosis	2
Bronchiectasis	1
Multiple pleural plaques (cause undetermined)	1
Background reticular shadowing	1
Ring shadows right lung apex—known to have been present for 10 years	1
Total	23

Of 35 patients treated, five died while receiving treatment but none of these deaths was considered to be due to *M kansasii* infection (carcinoma of the rectum, disseminated prostatic carcinoma, massive haematemesis, and two cases of cor pulmonale). All five patients had become culture negative and had shown initial clinical improvement in response to treatment. As we were interested in the long-term follow-up of patients, they have not been included in the analysis of treatment regimens shown in tables 2 and 3.

The remaining 30 patients were all successfully treated with drug regimens containing rifampicin (tables 2 and 3). Ethambutol was included in all but four of the treatment regimens, and in nine patients this was given with rifampicin alone for 15 months on average.

All patients had satisfactory clinical responses with resolution of symptoms considered due to *M kansasii*. Continuing disability, when it occurred, was due to pre-existing chronic pulmonary disease. The sequential radiographs of 25 patients were reviewed. For the other five patients completing treatment chest radiographs were not available, but the radiographic reports in their case notes were reviewed. Radiographic evidence of healing of lesions with closure of cavities was observed in 24

Table 2 *Treatment regimens used in 30 patients with M kansasii infection*

Drug combination	*No*	*Period of treatment (m)*				*Mean follow-up (m)*
		3–5	*6–12*	*13–18*	*19–24*	
Rifampicin and ethambutol	9		2	5	2	55·6
Rifampicin, ethambutol, and isoniazid	7		3	4		49·1
Rifampicin and isoniazid	2			2		78
Rifampicin, ethambutol, and cycloserine	3			2	1	46
Rifampicin, ethambutol, and ethionamide	2				2	90
Other combinations (see table 3)	7	1	2	1	3	74·5
Total	30*	1	7	14	8	66

*The five patients who died while having treatment are excluded from the analysis.

Table 3 *Other drug combinations (used in single cases only*)*

Drug combination	*Period of treatment (m)*	*Follow-up (m)*
Rifampicin, ethambutol, streptomycin	20	80
Rifampicin, ethambutol, isoniazid, cycloserine, ethionamide	12	48
Rifampicin, ethambutol, isoniazid, thiacetazone, PAS	24	108
Rifampicin, ethionamide	3·5	60
Rifampicin, cycloserine, ethionamide	7	108
Rifampicin, ethambutol, isoniazid, viomycin	16	30
Rifampicin, ethambutol, isoniazid, ethionamide	20	84

*These cases are included in table 2.

(80%) of the 30 cases. Cavitation persisted in four (13%) patients. In three of these the sputum culture was persistently negative and the patients remained well. In the fourth patient the lesions were shown to be cavitating progressive massive fibrosis at necropsy six years later. In two patients (7%) the radiographic appearances remained unchanged and it was considered that they were due to old infection by *M tuberculosis*.

There was 100% sputum culture conversion. The 30 patients treated successfully have been followed up for a mean period of five-and-a-half years and there have been no relapses. During this time eight have died but none of the deaths was due to *M kansasii* infection (cerebrovascular accident, progressive massive fibrosis, myocardial infarction, two cases of cor pulmonale, lobar pneumonia, bronchiectasis, peptic ulcer).

Discussion

M kansasii is the commonest non-tuberculous mycobacterium encountered in Western Europe and accounted for 1·2% of pulmonary mycobacterial infection in Wales during the decade 1970–9. Its predilection for middle-aged men with pre-existing lung disease[5,6] is again apparent in this study. Twenty-three patients (66%) had evidence of underlying pulmonary disease, chronic bronchitis and emphysema accounting for half of the disorders.

The high proportion of patients with unilateral lesions (69%) and cavitary disease (90%) on the chest radiograph have been noted in other studies.[5–7] The corresponding figures for *M tuberculosis* are unilateral disease 23%[8] and cavitation 50%.[9] The radiographic appearances were otherwise no different from those seen in *M tuberculosis*. Delay in starting treatment did not appear to have an influence on whether a patient developed unilateral or bilateral disease. In one patient with unilateral disease three years elapsed between diagnosis and the start of treatment.

Patients with infections due to *M kansasii* generally respond well to antituberculous chemotherapy.[3] The efficacy of rifampicin in treating this condition is well documented.[1,2] Harris *et al*, since they recommend that rifampicin should be kept in reserve for retreatment until we know the relapse rate for regimens containing and not containing this drug, suggest initial treatment with isoniazid, ethambutol, and streptomycin.[1] Others suggest a combination of rifampicin, ethambutol, and isoniazid with three months' initial treatment with streptomycin.[4] Our study confirms the efficacy of regimens containing rifampicin in the treatment of *M kansasii* infection. Since 100% sputum conversion was obtained with no relapses during a mean follow-up period of five-and-a-half years we recommend its inclusion in all treatment programmes.

Nine patients were treated with a combination of rifampicin and ethambutol given for an average of 15 months. This proved to be an effective, non-toxic combination. Rifampicin resistance has, however, developed in patients treated with this drug combined with ethambutol and isoniazid when in vitro sensitivity results have shown resistance to the two latter drugs.[10] Most patients in our study had organisms sensitive to ethambutol but in two there was borderline resistance. One of these two patients was successfully treated with a combination of rifampicin, viomycin, and isoniazid, and the other with rifampicin, cycloserine, and ethionamide. As a counsel of perfection we therefore suggest that cycloserine or ethionamide should be used as a third drug to complement rifampicin and ethambutol at the start of treatment until the results of ethambutol sensitivity tests are available.

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