THE MANAGEMENT OF LUNG DISEASE CAUSED BY OPPORTUNIST MYCOBACTERIA*

I.A. Campbell†

This group of organisms is known by many names, i.e. Mycobacteria Other Than Tuberculosis (MOTT), Non-tuberculous Mycobacteria, Atypical Mycobacteria, Anonymous Mycobacteria, Environmental Mycobacteria or Opportunist Mycobacteria. As *M. leprae* is not included in this grouping, the use of the first two names is inappropriate. The organisms are not atypical of the mycobacterial genus nor are they without name or unknown - thus the third and fourth terms are inappropriate. Of the last two names, I prefer Opportunist Mycobacteria because that term better describes their pathological relationships to the human than does the term Environmental Mycobacteria.

These organisms are ubiquitous in the environment and are low-grade pathogens. Cross-infection between patients is very rare indeed. Notification to the Public Health Authorities and contact tracing are unnecessary. Clinically, radiologically and on direct smear the organisms are indistinguishable from *M. tuberculosis*. Diagnosis is based on culture (Löwenstein Jensen or Middlebrook media) and special methods of identification such as temperature range, oxygen preference, sensitivity pattern, pigment production, hydrolysis of Tween 80 and chromatography. DNA probes are available for *M. avium*, *M. intracellulare*, *M. kansasii* and *M. gordonae*. *M. kansasii*, *M. avium intracellulare* (*MAC* or *MAIS*), *M. malmoense* and *M. xenopi* cause pulmonary disease in humans more than all the other species (Table 1).

LUNG DISEASE

As these mycobacteria are widespread, they may exist transiently in the respiratory tract or may contaminate specimens in the laboratory; and thus false positive diagnoses may occur. The diagnosis of lung disease is conventionally made when positive cultures are obtained from two specimens of sputum, taken more than seven days apart, from a patient whose chest X-ray suggests mycobacterial infection, and who may or may not have symptoms of pulmonary infection. The majority of patients are middle-aged to elderly males, of whom over half have pre-existing pulmonary disease (usually chronic bronchitis and emphysema or old tuberculosis). Current (though not past) dust exposure seems to pre-dispose to *M. kansasii* infection. Symptoms are non-specific, e.g. cough, sputum, malaise, breathlessness, haemoptysis and weight loss. Onset of illness is gradual rather than acute and indeed some patients may be asymptomatic. Physical signs are also non-specific or absent. Radiologically, the infiltrates and cavities caused by *M. tuberculosis* and the various opportunist species are indistinguishable from each other. Cavitation occurs in 70-90% of infected patients.

The results of standard *in vitro* sensitivity testing to single anti-mycobacterial drugs, carried out by the method of modal resistance, correlate well with clinical response in *M. kansasii* pulmonary infection but for the other species this is not so. Confusion has arisen because many clinicians and researchers have assumed that the relationships between *in vitro* sensitivity results and clinical response in *M. tuberculosis* also apply to opportunist mycobacteria.

Good information on optimum methods of treating these infections is bedevilled by their rarity and the fact that controlled clinical trials are lacking. The literature consists mainly of small, retrospective series the results of which indicated that ethambutol and rifampicin were important in treatment. The efficacy of regimens containing ethambutol and rifampicin probably results from synergistic interaction beween these two drugs. Streptomycin can also work synergistically with ethambutol and with rifampicin but the place of isoniazid in treatment is not clear.

RESPONSE TO TREATMENT

M. kansasii

Three of five retrospective studies have been based on around 30 patients, and only one of the two prospective studies has included more than 100 patients (Table 2). Relapse rates of between 0% and 9% have been reported. Ten to 25% of patients died within five years of diagnosis, although less than 1% did so directly because of *M. kansasii* pulmonary infection. In the prospective study of 173 patients which was conducted by the British Thoracic Society (BTS), clinical progress was good in two-thirds of the patients throughout their nine months of treatment with rifampicin and ethambutol, and during the subsequent follow-up to five years. Patients gained around 3 kg in weight over this period but 15 relapsed. In eight of these, underlying factors were identified which could have explained the relapses. In three the disease occurred in a different lung or a different pulmonary lobe, and it is possible that these three patients were not relapses but had become reinfected. In four patients, genuine relapse was thought to have occurred. Relapse rates were no different with or without isoniazid treatment initially; many patients had been started on standard anti-tuberculosis therapy before the identity of the mycobacteria was known and thus received between two and four months of isoniazid in addition to rifampicin and ethambutol.

On the basis of the available evidence, the majority of patients can safely be treated with a nine-month course of rifampicin and ethambutol, but for those with overtly compromised defences it would appear sensible to continue therapy with those two drugs for 15-24 months. If *in vitro* resistance to rifampicin or ethambutol is detected, then

*Based on a lecture delivered at the Symposium on Emerging Problems in Respiratory Medicine held in the College on 6 November 1998

†Consultant Chest Physician, Llandough Hospital, Cardiff

TABLE 1
Opportunist mycobacteria that can cause pulmonary disease.

Usually		Rarely	
M. kansasii		*M. szulgai*	*M. gordonae*
M. avium	*MAIS*	*M. simiae*	*M. terrae*
M. intracellulare	Complex	*M. fortuitum*	*M. triviale*
M. scrofulaceum	or *MAC*	*M. chelonei (abscessus)*	*M. gastri*
		M. asiaticum	*M. nonchromogenicum*
M. malmoense			
M. xenopi			

TABLE 2
M. kansasii: response to treatment. Retrospective studies: R. Prospective studies: P.

No. of Patients	Duration of Rx	Regimens	Follow-up	Relapses
28 (R)	12-18 mo.	ERH	12-30 mo.	4%
30 (R)	3-24 mo.	90% ER	≤10 yrs	0
32 (R)	≤24 mo.	Various	6 mo.-16 yrs	0
47 (R)	0-22 mo.	ERH, ± Z initially	5 mo.-9 yrs	0
471 (R)	9-12 mo.	Various	≤5 yrs	8%
40 (P)	12 mo.	ERH	50% for 3 yrs 30% for 5 yrs	2.5%
173 (P)	9 mo.	ER, ± H ± Z ± S initially	5 yrs	9%

E: ethambutol; R: rifampicin; H: isoniazid; Z: pyrazinamide; S: streptomycin

prothionamide or streptomycin should be substituted. Non-compliant patients should be followed-up indefinitely, and relapses should be retreated with 15-24 months of rifampicin and ethambutol. Clarithromycin has *in vitro* activity but as yet there are no prospective, controlled trials defining its place in treatment.

Mycobacterium avium intracellulare (MAC or MAIS)
Between 1971 and 1986 three series were published in the United States from which it could be gleaned that when patients were treated with five or six anti-mycobacterial drugs, with or without surgery, a 40-80% response could be expected. Of those responding, 50% would relapse thereafter. In 1981 a retrospective report which included 64 patients from England and Wales indicated that if treatment was not given 30% of patients would die; if reserve drugs were used 50% would die whereas, if the anti-tuberculosis regimens standard at that time (EHR/HR or SPH/PH*) were given for 18-24 months, 15% died and 85% were considered successfully treated. In the recently-completed, prospective, multicentre study run by the British Thoracic Society, 75 patients received either rifampicin and ethambutol or rifampicin, ethambutol and isoniazid for two years. Results at five years revealed that 31% had died, 3% directly as a result of their *MAC* infection. Twenty-eight percent either failed to convert to being culture-negative by the end of treatment or relapsed in the three years after treatment. Only 27% were known to be alive and culture-negative at five years (Table 3).

M. malmoense
From two retrospective studies it became evident that treatment for 18-24 months with ethambutol and rifampicin was likely to be more effective than regimens in which second- or third-line drugs were used, principally because the second- or third-line drugs were poorly tolerated, and

*Definitions can be found in Table 2, except for P:para-aminosalicylic acid.

TABLE 3
MAC, *M. malmoense* and *M. xenopi*: response to two years' chemotherapy with rifampicin and ethambutol or with rifampicin, ethambutol and isoniazid.

Outcome	*MAC* (75)	*M. malmoense* (106)	*M. xenopi* (42)	All (223)
Died	31%	24%	55%	32%
Failure of chemotherapy or relapse	28%	10%	10%	16%
Cured and alive	27%	41%	19%	32%
Deviated from protocol and outcome unknown	14%	25%	16%	20%

patient compliance consequently bad. If response to chemotherapy was unsatisfactory, and if the disease was limited to one lobe or lung in a reasonably fit patient, surgery, in addition to chemotherapy, sometimes offered the prospect of cure. In the recent BTS study of 106 patients treated with two years of rifampicin and ethambutol or of rifampicin, ethambutol and isoniazid, one quarter were dead within five years, 4% dying because of the *M. malmoense* pulmonary infection. Ten percent either failed to convert to being culture-negative during treatment or relapsed after treatment. Forty-one percent were alive and culture-negative at the end of five years (Table 3).

M. xenopi

Two small, retrospective studies from Britain, and one from the United States, showed that when patients were treated for 8-24 months with rifampicin, ethambutol and isoniazid, or streptomycin, isoniazid and rifampicin, 25-70% might be cured but 10-20% died as result of their *M. xenopi* infection. In these studies it was noted clearly that response was not related to the results of *in vitro* sensitivity testing to single drugs. Second- or third-line drugs and multi-drug regimens of five or six drugs did not improve results. On the rare occasions that surgery was possible it proved a useful adjunct to chemotherapy. In the BTS study, 42 patients started treatment with two years of rifampicin and ethambutol or rifampicin, ethambutol and isoniazid. Within five years 55% were dead, 7% due to *M. xenopi*, whilst 9.5% failed to convert to culture-negative or relapsed after treatment. Only 19% were known to be alive and culture-negative at the end of five years (Table 3).

SUMMARY OF THE OVERALL (CLINICAL AND RADIOLOGICAL) FEATURES OBSERVED IN THE RECENT BTS STUDY OF THE TREATMENT OF *MAC, M. MALMOENSE* AND *M. XENOPI*

In the total of 223 patients with these infections, the ratio of male-to-female incidence was 3:2, and mean age was 61 years (Table 4). Sixty-five percent of these patients had histories of other lung diseases and 21% had been engaged in dusty occupations at some time during their lives. Sputum was positive for organisms on direct smear in two-thirds of the patients. Disease was present in both lungs in 39%. In just under a quarter of the patients, three or more zones of the lungs were affected. In less than 40% the disease was confined to just the upper zones. Cavitation was present in 85%, and in two out of three patients there was radiological evidence of other lung disease(s). By the end of five years, one third of patients had died although only 4% had died directly because of their mycobacterial lung disease. A third were alive and culture-negative but 16% had failed to convert to culture negativity during treatment, or had relapsed after treatment (Table 3). Those surviving to five years gained an average of 1.2 kg in weight but only 25% showed a reduction and closure of their cavities and/or reduced the extent of radiological disease. Records of clinical progress were available from 1,707 clinical encounters during and after treatment: in 88% these records indicated satisfactory clinical progress. Unsatisfactory progress was recorded on 12% of occasions but only a third of these were directly attributable to the opportunist mycobacterial lung disease.

OTHER OPPORTUNIST MYCOBACTERIA

Treatment of the species that rarely cause pulmonary disease is even less well documented in the literature, but from what there is it is evident that disease caused by *M. abscessus* is not curable. *M. fortuitum* probably should be treated with ethambutol and rifampicin for two years plus or minus one or more of ciprofloxacin, clarithromycin, amikacin, cefoxitin and imipenen. For the remaining species evidence is very scanty indeed. A possible regimen would be ethambutol, rifampicin, ciprofloxacin and clarithromycin for two years, remembering that if surgery is possible it should be considered as an adjunct to chemotherapy.

PULMONARY INFECTION BY OPPORTUNIST MYCOBACTERIA IN AIDS

Such infection is most commonly caused by *MAC*, is frequently bacteraemic and is only rarely confined to the lung. Anti-mycobacterial chemotherapy reduces symptoms and prolongs survival, with the median survival after starting treatment varying between six and nine months. Successful response depends more on the restoration of immunocompetence than on anti-mycobacterial therapy. Rifamycins interact unfavourably with protease inhibitors (enhanced drug metabolism leads to a loss of effect of protease inhibitors), whilst rifabutin in combination with clarithromycin can cause uveitis. One alternative is to omit the protease inhibitor from the immune-restoring regimen during the course of anti-mycobacterial therapy with rifampicin, ethambutol and clarithromycin. Another is to

TABLE 4
MAC, *M. malmoense* and *M. xenopi*: overall clinical and radiological features.

Clinical		Radiological	
Male:female	3:2	Bilateral disease	39%
Mean age (SD)	61 (13) yrs	>3 zones	23%
Other lung diseases	65%	Upper zone(s) only	37%
History of dusty occupation(s)	21%	Cavitation	85%
Positive direct smear	65%	Other pulmonary diseases	66%

use rifabutin instead of rifampicin, and substitute ciprofloxacin for clarithromycin. Further studies are ongoing in this field.

In HIV-positive patients it has been shown that prophylactic therapy with clarithromycin or azithromycin prevents disease due to *MAC* and prolongs survival. Monotherapy does carry the risk of induction of bacterial resistance but with clarithromycin this does not have the serious implications that monotherapy with a rifamycin would carry: co-infection with *M. tuberculosis* is not unusual in HIV positive and AIDS patients and, theoretically cross-infection with *M. tuberculosis* is greater in patients with HIV and/or AIDS. Thus rifamycin-resistant strains of *M. tuberculosis* could emerge and spread.

SUMMARY

Opportunist mycobacterial pulmonary infection is a disease of middle-aged to elderly males which doubles expected mortality. *M. xenopi* carries the highest death rate whereas *MAC* is hardest to eradicate. The easiest to cure are *M. kansasii* and *M. malmoense*. Standard *in vitro* sensitivity tests to single anti-mycobacterial drugs correlate poorly with clinical response, except in the case of *M. kansasii* infection. In general, treatment for *M. kansasii* should be with rifampicin and ethambutol for nine months. For *MAC*, *M. malmoense* and *M. xenopi*, in the current state of knowledge, two years of rifampicin and ethambutol, possibly with the addition of isoniazid, appears the regimen of choice. The British Thoracic Society is currently evaluating whether clarithromycin or ciprofloxacin as a third drug would improve the efficacy of rifampicin and ethambutol. In the same trial the role of immunotherapy with *M. vaccae* is also being investigated.

ACKNOWLEDGEMENTS

I am grateful to the physicians, microbiologists and supporting staff who participated in the BTS studies of *M. kansasii*, *MAC*, *M. malmoense* and *M. xenopi*: their efforts and the dedicated work of Elizabeth Lyons, who has co-ordinated the studies over 16 years, have made this presentation possible.

FURTHER READING

1 Campbell IA, Jenkins PA. Opportunistic mycobacterial infections. In: Brewis RAL, Corrin B, Geddes DM, Gibson GJ (eds). *Respiratory Medicine. 2nd edition* London: WB Saunders & Co Ltd, 1995; 840-7.

2 Banks J, Campbell IA. Environmental mycobacteria. In: Davies PDO (ed.). *Clinical tuberculosis. 2nd edition* London: Chapman & Hall, 1998; 521-33.

3 Campbell IA, Jenkins PA, Wallace RJ. Chemotherapy of non-tuberculous mycobacterial disease. In: Gangadharam PRJ, Jenkins PA (eds). *Mycobacteria* New York: Chapman & Hall, 1998; 279-96.

4 Campbell IA, Jenkins PA. *Mycobacterium kansasii*. In: Schlossberg D (ed.). *Tuberculosis and non-tuberculous mycobacterial infections. 4th edition* Philadelphia: WB Saunders & Co. Ltd, 1999; 380-5.