

Treatment of pulmonary infections caused by mycobacteria of the *Mycobacterium avium-intracellulare* complex

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ABSTRACT Sixty-four patients with pulmonary infection caused by mycobacteria of the *M avium-intracellulare* complex have been reviewed. Patients who were asymptomatic on presentation often had a benign course but some developed progressive disease. Symptomatic patients who were not treated usually deteriorated. Various treatment regimens were used. Successful treatment was achieved in the majority of patients using a combination of isoniazid, rifampicin, and either ethambutol or streptomycin given for 24 months. Other forms of treatment given including multiple drug regimens were not as effective.

Of the many nontuberculous mycobacteria only two cause frequent significant pulmonary disease in man. *M kansasii* infection is more often seen in this country but is not a major clinical problem as there is a good response to antituberculosis drugs. Mycobacteria of the *M avium-intracellulare* complex however present a management problem to the clinician as the disease they cause varies from low grade colonisation of lung to a progressive destruction of lung and death. There are numerous reports of poor response to therapy.¹ Strains within the complex are usually sensitive to ethionamide, often to cycloserine and clofazamine, and show borderline resistance to ethambutol. There is resistance in vitro to all other drugs. Thus when he encounters a patient with this infection a physician is faced with the problem of whether to treat the patient and which drugs to use.

Methods

In England and Wales virtually all nontuberculous mycobacteria isolated in local bacteriology laboratories are sent to the Mycobacterium Reference Laboratory in Cardiff for identification and sensitivity testing.

From the records of the unit an attempt has been made to trace all patients with pulmonary infection caused by the *M avium-intracellulare* complex in England and Wales in the decade 1969-78 inclusive. To be considered significant at least two isolations were required. From the 94 patients with significant positive cultures 64 have been traced and their notes and radiographs reviewed. The progress of the patient was assessed from the clinical and bacteriological details recorded in the notes by the doctor in charge of the case. The radiographic assessments were made by one of the authors without knowledge of the clinical and bacteriological status. Patients were assigned to one of five groups according to the treatment they had received. Each of the groups was subdivided into two subgroups. Those in the first subgroup had been referred because of recent symptoms and subsequent sputum cultures were positive. These were classified as *symptomatic*. The second subgroup comprised those patients who had sputum sent for a routine check often while being seen at the clinic for another reason—for example, coal workers with pneumoconiosis. They were classified as *asymptomatic*.

Three indices were used to assess progression of disease or response to therapy. These were clinical progress, chest radiographs, and sputum culture results. The most important index was the clinical

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progress recorded by the physician in the notes. Initial and follow-up films were assessed for progression of disease or for improvement. If the film showed resolution, closure of cavities, and calcification then the patient was considered to be radiographically cured.

Progressive disease was defined as clinical and radiographic deterioration. The disease was considered to be stable when the clinical and radiographic pattern remained unchanged irrespective of sputum culture results. A patient was considered cured if satisfactory clinical progress was accompanied by radiographic cure and negative sputum cultures with no relapse on cessation of therapy. If the independent review of the chest radiograph revealed improvement but there was no calcification or closure of cavities at a time when the patient was clinically well off therapy with negative sputum cultures he was considered to be bacteriologically cured. When the radiograph showed healing, calcification, and closure of cavities in a patient who was clinically stable off therapy but with occasional positive sputum cultures he was considered to be radiographically cured.

Results

NO TREATMENT GROUP

Thirteen patients received no specific anti-tuberculosis chemotherapy at any time in their illness. There were seven men and six women with a mean age of 61 years (range 37–76 years).

Seven were *symptomatic* at presentation; six had progressive disease, of whom three have subsequently died. The seventh is stable but has only been followed up for two years.

Six patients were *asymptomatic* at the time of diagnosis. All appeared to be stable on follow-up, but four have been under review for only two years, a relatively short period in the natural history of the disease.

INADEQUATE TREATMENT GROUP

At the time of clinical presentation a number of patients were thought to have an infection with *M. tuberculosis* because of the clinical history, radiographic appearance, and often a sputum smear positive for acidfast bacilli. They were initially given first line anti-tuberculosis drugs either in the form of streptomycin, PAS and isoniazid, or rifampicin, isoniazid, and either ethambutol or streptomycin. When the organism was identified on culture the drugs were stopped because of the

in vitro sensitivity results. These patients were therefore classified as having had an inadequate period of chemotherapy.

There were 14 patients in this group (nine men and five women) with a mean age of 63 years (range 30–81 years). Ten were *symptomatic* at presentation and in eight of these the disease has progressed, four dying of it. Four were *asymptomatic* at presentation; one of these has had progressive disease and has died while the other three are stable although none has been under review for more than three years.

ADEQUATE TREATMENT GROUP

Patients in this group received full anti-tuberculosis chemotherapy continuing treatment for at least nine months with rifampicin and isoniazid and for at least 18 months if a combination of PAS and isoniazid was used.

There were 26 patients in this group (20 men) with a mean age of 54 years (range 28–76 years). Nineteen had isoniazid and rifampicin with either ethambutol or streptomycin as a third drug; three had PAS, isoniazid, and initial streptomycin, and four started PAS, isoniazid, and streptomycin but then continued treatment for the appropriate period with isoniazid, rifampicin, and ethambutol.

Twenty-two of these 26 patients were *symptomatic* at presentation and all 26 had chest radiographs suggesting active disease. Nineteen out of 22 *symptomatic* patients and three out of four *asymptomatic* patients were considered to have responded satisfactorily to therapy (table 1). This

Table 1 Adequate treatment group

Outcome	Number	Treatment period (mo)	Follow-up period (yr)
Cure	11	9–24	1–9
Bacteriological cure	4	6–18	4–8
Radiographic cure	4	9–24	3–7
Relapse with subsequent radiographic cure	3	12–18 initially	2–5
Failure	4*	12–18	Up to 9

*Three have died, one slowly progressive over nine years.

gave a response rate of 84%. Three patients relapsed within one year of stopping treatment, having received chemotherapy for between 12 and 18 months. Further courses of the same treatment for between two and four years have been given and the patients remain clinically and radiographically cured, although sputum cultures are intermittently positive.

OTHER DRUGS REGIMENS USED

Because of the *in vitro* sensitivities, ethionamide, clofazamine, cycloserine, and ethambutol were sometimes given in various combinations. There were eight patients who received some combination without any previous drug therapy. There were seven men and one woman with a mean age of 59 years (range 47–76 years). All were *symptomatic* at the time of diagnosis and three seemed to respond initially. However, one of them died of another cause and the other two, together with the five non-responders developed progressive disease, and four have subsequently died. All patients had significant side-effects (especially depression and gastrointestinal upset). Despite unstable or progressive disease, therapy was stopped in the majority because of these side effects.

Multiple drug therapy with five or six drugs in combination was given to four patients in a manner similar to that described by Yeager and Raleigh.² This is too small a number to give a definite answer about the efficacy of this type of therapy. Of two patients with no previous drug therapy one has been cured but one has had progressive disease and has died. Two patients who had failed with other therapy were given multiple drug therapy. One had progressive disease despite adequate therapy with isoniazid, rifampicin, and ethambutol, and he died. The other failed on prothionamide, cycloserine, and thiacetazone, and he has been cured.

Table 2 Results of treatment in symptomatic patients

	Number	Stable	Progressive and alive	Progressive and died
No treatment	7	1	3	3
Inadequate treatment	10	2	4	4
Adequate treatment	22	19*	0	3
Ethionamide, clofazamine, cycloserine, and ethambutol	8	1*	3	4
Multiple drug regimen	2	1	0	1
Total	49	24	10	15

*Died of other cause.

Table 3 Results of treatment in asymptomatic patients

	Number	Stable	Progressive and died
No treatment	6	6	0
Inadequate treatment	4	3	1
Adequate treatment	4	3	1
Surgery alone	1	1	0
Total	15	13	2

Another patient who was retreated had previously been treated with rifampicin, isoniazid, and ethambutol for 12 months but his sputum remained positive despite clinical and radiographic cure. He was then treated with ethionamide, cycloserine, and clofazamine for two years. His sputum still remained positive although his disease by other criteria remained stable.

SURGICAL TREATMENT

Three patients had surgical excision of the bulk of the disease in addition to various drug regimens. Two did well but the third, receiving cycloserine and ethionamide, had surgery in an attempt to control progressive disease. He deteriorated and died six months later. One *asymptomatic* patient with minimal apical disease had surgery without drug cover. He has been cured.

Results of therapy in symptomatic and asymptomatic patients

The results for all patients have been combined and are given in tables 2 and 3. Table 2 shows that in *symptomatic* patients the natural history is that of progressive disease. Effective therapy appears to have been achieved with isoniazid and rifampicin plus either ethambutol or streptomycin as a third drug but not with other regimens. In view of the relapse of three patients given between 12 and 18 months therapy it would seem advisable to give 24 months therapy to all patients.

The disease in *asymptomatic patients* did not necessarily progress but could do so, and both those who did so died of their disease. In some the follow-up period was short and we cannot be certain that progression will not occur.

Discussion

Nontuberculous mycobacteria may cause pulmonary disease similar to that produced by *M. tuberculosis*. Such infections represent two to three per cent of all mycobacterial diseases seen in England and Wales. Patients who are infected tend to have pre-existing lung damage such as pneumoconiosis, chronic obstructive airways disease, bronchiectasis, or an immune deficiency.¹ Some of the nontuberculous mycobacteria may colonise the respiratory tree without causing disease but the natural history of patients with the *M. avium-intracellulare* complex in their sputum would suggest that they are usually pathogenic. The process may be so indolent that it does not produce significant deterioration over many

years, but it may lead to lung destruction and death from respiratory failure.

In this retrospective study we have attempted to establish the outcome of pulmonary infection caused by the *M avium-intracellulare* complex and its response to treatment so that the most appropriate form of therapy may be chosen.

Asymptomatic patients did not always progress but could do so with fatal outcome. *Symptomatic* disease nearly always progressed and unless adequately treated could be fatal. Adequate treatment appeared to be achieved by isoniazid, rifampicin, and either ethambutol or streptomycin for at least nine months but more reliably by giving 24 months' therapy. Other drugs used because of in vitro sensitivity results were not successful and produced unpleasant unwanted side-effects. Multiple drug regimens and surgery were used too infrequently for any conclusion to be reached.

Combined aggressive medical therapy (four to six drugs) and surgical resection is recommended as the treatment of choice by Yeager and Raleigh.² Out of 45 patients, 43% responded to therapy, with surgery increasing the chances of achieving stability. There was a 20% relapse rate over a five-year follow-up period. Rosenzweig³ felt that no particular combination of chemotherapy appeared particularly effective. In 82 patients treated with various combinations of drugs, sustained sputum conversion was attained in 45%. Dutt and Stead⁴ reported 80% initial sputum conversion with multiple drug chemotherapy, 46% of patients with pulmonary disease remaining bacteriologically stable after three to eight years of follow-up.

Patients in England and Wales treated with adequate chemotherapy with isoniazid and

rifampicin, together with either ethambutol or streptomycin, have responded well to therapy. The response rate of 84% compared favourably with that seen in other series.¹⁻⁴ The combination of isoniazid, rifampicin, and ethambutol would seem to be the best as it is effective and acceptable to both physician and patient. Twenty-four months' therapy would appear to give the greatest probability of cure.

Ideally a prospective trial of isoniazid, rifampicin, and either ethambutol or streptomycin given for various durations between nine and 24 months would be useful but it would be impossible to get sufficient numbers of patients in Britain alone. The combination of isoniazid and rifampicin would appear to be the most important part of any planned chemotherapy trials.

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References

- 1 Wolinsky E. Nontuberculosis mycobacteria and associated diseases. State of the art. *Am Rev Respir Dis* 1979; **119**:107-59.
- 2 Yeager H, Raleigh JW. Pulmonary disease due to *Mycobacterium intracellulare*. *Am Rev Respir Dis* 1973; **108**:547-52.
- 3 Rosenzweig DY. Pulmonary mycobacterial infections due to *Mycobacterium intracellulare-avium* complex. *Chest* 1979; **75**:115-9.
- 4 Dutt AK, Stead WW. Long term results of medical treatment in *Mycobacterium intracellulare* infections. *Am J Med* 1979; **67**:449-53.