Editorial

Treatment of pulmonary disease caused by opportunist mycobacteria

During the early 1950s it was recognised that mycobacteria other than Mycobacterium tuberculosis could cause pulmonary disease in man. Over 30 years later there is no general agreement about the treatment of patients with these mycobacterial infections. The greatest controversy surrounds the treatment of infection caused by the M avium-intracellulare-scrofulaceum complex (MAIS), for which various treatments have been advocated, including chemotherapy with three or more drugs or, alternatively, surgical resection of the affected lung. Although the treatment of infection caused by M kansasii is less controversial there is no uniform approach to treatment. Disease caused by M xenopi has been described by some as easy to treat with chemotherapy, whereas others have found the response to drug treatment to be unpredictable.

This diversity of opinion and approach to treatment has arisen for two reasons. Firstly, there have been no large prospective studies designed to compare treatment regimens. Secondly, the failure to consider infection caused by M kansasii, the MAIS complex, and other opportunist mycobacteria as entities distinct from infection caused by M tuberculosis has led to inappropriate comparisons with tuberculosis. As a result principles that govern the treatment of tuberculosis, in particular the role of in vitro drug sensitivity tests, and criteria by which response to treatment is assessed have been empirically extended to disease caused by other mycobacterial species. It was realised in early reports that patients with infection caused by M kansasii often remained sputum culture positive and showed persistent cavities on their chest radiographs after a few months' treatment with combinations of isoniazid, para-aminosalicylic acid (PAS) and streptomycin. The results were poor by comparison with the prompt bacteriological and radiographic responses in patients with tuberculosis given the same treatment and raised doubts about the use of chemotherapy in opportunistic mycobacterial disease.

In 1963 the American Thoracic Society recommended that surgical treatment for opportunistic mycobacterial infection should be given to those patients who are suitable surgical candidates. The failure of chemotherapy was often attributed to drug resistance, but the importance of prolonging the duration of chemotherapy in opportunistic mycobacterial disease beyond that which would normally be required in tuberculosis was not appreciated. In several surgically treated series preoperative chemotherapy was given on average for only four to seven months, but some patients receiving as little as eight weeks of treatment before surgery. In contrast, chemotherapy alone, with isoniazid, p-aminosalicylic acid, and streptomycin for 24 months, produced successful results in 80–100% of patients with M kansasii infection despite reports of in vitro resistance to these agents.

In vitro drug sensitivity testing in opportunistic mycobacterial disease

Many studies show that the results of in vitro drug sensitivity tests performed against opportunist mycobacteria bear little relation to the clinical response observed when these drugs are used in treatment. The results of treatment with agents such as cycloserine and ethionamide, which often show good in vitro action, have been disappointing and may reflect drug toxicity and poor compliance by patients. Paradoxically, successful treatment has been achieved with combinations of standard antimycobacterial agents, despite reported in vitro resistance, though the duration of treatment has had to be prolonged in these circumstances. Good in vitro sensitivity to first line agents has allowed the duration of chemotherapy to be shortened—for example, short course chemotherapy for infection caused by M kansasii is possible with regimens containing rifampicin.

Critical levels of in vitro resistance that have clinical importance have been defined for M tuberculosis but not for other mycobacterial species. Nevertheless, isolates of opportunistic mycobacteria are reported as "resistant" if the minimum inhibitory concentrations of drugs that suppress their growth in vitro exceed the minimum inhibitory concentrations for drug sensitive
strains of *M. tuberculosis*. The comparison with *M. tuberculosis* makes the assumption that critical levels of in vitro resistance that predict treatment failure in *M. tuberculosis* infection are the same for all mycobacteria, irrespective of species. Clearly this is not so. Isolates of mycobacteria belonging to the MAIS complex or of *M. xenopi* or *M. malmoense* should not therefore be classified as resistant until in vitro criteria that correlate with the clinical results of treatment of these infections have been established.

Drug resistance cannot be defined simply by relating in vitro minimum inhibitory concentrations to serum drug concentrations as the latter do not necessarily reflect drug concentrations achieved within tissues and macrophages. For example, concentrations of ethambutol in both normal and caseous lung tissue are several times higher than the concentrations in plasma, and even higher drug concentrations are achieved within alveolar macrophages. In addition, concentrations of ethambutol needed to kill phagocytosed bacilli are lower than the bactericidal concentrations required in culture medium. Such factors may account for the effectiveness of some drugs in treatment despite their poor in vitro action.

**Recommendations for treatment**

Pulmonary disease most often results from infection with *M. kansasii*, the MAIS complex, *M. xenopi*, or *M. malmoense*.

**M. kansasii**

Infection with *M. kansasii* should be treated with regimens that include both rifampicin and ethambutol. The combination of rifampicin and ethambutol alone produced successful results in one series. The preliminary results of a prospective multicentre study conducted in the United Kingdom by the British Thoracic Society suggests that nine months' treatment with regimens that include both rifampicin and ethambutol will be adequate. Of 75 patients who had completed treatment by March 1986, 14 had received rifampicin combined with ethambutol and 61 had been given rifampicin and ethambutol combined with one or more additional drugs, usually isoniazid. These additional drugs were given for less than three months at the start of treatment in most patients. One failure of treatment resulted from non-compliance with drug treatment and two deaths occurred from unrelated pneumonia. Successful results were obtained in the remaining patients, 100% sputum conversion to culture negative being achieved within nine months of the start of treatment. Three patients (4%) subsequently relapsed, though relapse in one was associated with the development of laryngeal carcinoma.

**MAIS complex**

There is no consensus about the best treatment for pulmonary infection caused by the MAIS complex. Surgical resection of affected lung is advocated by some, and others have recommended chemotherapy with standard antimycobacterial drugs. The results following surgical treatment have undoubtedly been good, conversion to sputum culture negative being achieved postoperatively in 93–100% of cases in some series, and relapses occurring in only 5% of patients during prolonged follow up. These results are more impressive than those obtained with chemotherapy alone, but comparisons of this nature do not compare like with like. Patients included in surgically treated series are often selected in so far as they have less extensive disease and have sufficiently good cardiopulmonary reserve to withstand thoracotomy and pulmonary resection. Even in centres where surgery is strongly advocated they have comprised no more than 30–40% of all patients treated. In addition, many have received adjunctive chemotherapy, which in some cases has been continued for two or three years. In contrast, patients treated with chemotherapy alone have often had other serious pulmonary conditions, which in some cases were considered to be more important prognostically than the mycobacterial infection itself. Interestingly, 94% of patients in one series who had no coexistent lung disorder, and who were not breathless on admission, converted to sputum culture negative and showed radiographic improvement in response to chemotherapy alone. The median follow up was 22 months, during which time 6% of patients relapsed. These initial results are as good as those obtained with surgery and, although follow up was relatively short, are far better than the results reported in many other medically treated series. Surgical treatment, even in selected patients, has not always been successful. In one series 33% of patients ultimately relapsed after having surgery; in another series complications, including bronchopleural fistula, developed in 24% of patients and there was a 7% postoperative mortality.

Medical treatment is the only therapeutic option available for many patients. Pessimistic reports on the results of chemotherapy have often failed to indicate the duration of treatment given before it was concluded to be unsuccessful. Treatment with rifampicin and isoniazid combined with either ethambutol or streptomycin was successful in 84% of cases, in one series when treatment was prolonged. Two years of treatment appeared to offer the best chance of success. Unfortunately, 16% of patients failed to respond to chemotherapy and 13% relapsed within one year of completing treatment. Treatment with five or six drug regimens has been advocated, particularly for progressive disease, but there have been no
comparative studies showing that such multiple regimens are more effective than those comprising fewer drugs. The British Thoracic Society is at present conducting a prospective study in which 24 months' treatment with rifampicin, ethambutol, and isoniazid is being compared with 24 months of rifampicin and ethambutol; patients treated with other drugs or surgery are also being followed up.

**M. xenopi**

Pulmonary infection with *M. xenopi* has been classified as easy to treat, but reports describing successful treatment have frequently been based on small series or case reports of individual patients with short follow up. The results from larger series indicate that the response to chemotherapy in this condition is unpredictable. Most patients improve while receiving treatment and convert to sputum culture negative. Some are cured, but 26% of patients in one series relapsed and 10% developed progressive disease while receiving treatment with drugs that showed good in vitro activity. The best results were obtained with regimens that included rifampicin, ethambutol, and isoniazid. Surgery has been effective in controlling the disease in a small number of patients; it should be considered for patients who either relapse or fail to respond to initial chemotherapy.

**M. malmoense**

There have been few reports describing the response to treatment of pulmonary infection caused by *M. malmoense*. Successful results have been obtained with a combination of rifampicin, ethambutol, and isoniazid given for 18–24 months but follow up was relatively short. Ethambutol seems to be crucially important in this regimen as its withdrawal was followed by clinical deterioration in several patients.

**Drug synergism**

Synergism between standard antimycobacterial drugs may account for their effectiveness in treatment. In vitro studies have shown that drugs in combination are more effective than single agents in suppressing the growth of *M. kansasii*, MAIS, *M. xenopi*, and *M. malmoense*. Rifampicin combined with ethambutol was particularly effective against strains of *M. malmoense* and *M. xenopi* (figure), and inhibited one third

![Isobolograms for five strains of Mycobacterium malmoense and five strains of M xenopi tested against ethambutol combined with rifampicin. A line or isobol is drawn for each strain, which joins the minimum effective concentration of ethambutol when used alone (on the ordinate) with the minimum effective concentration of rifampicin when used alone (on the abscissa) through the point which represents their minimum effective concentrations when combined. The inset shows three theoretical isobols. Drug combinations that are synergistic produce concave isobols (ESR), antagonistic combinations produce convex isobols (EAR), and additive combinations produce straight lines (EXR). Each strain of M malmoense and M xenopi produced a concave isobol consistent with a synergistic effect between rifampicin and ethambutol. Reproduced from Banks et al.](http://thorax.bmj.com/content/44/6/449)
of strains of the MAIS complex that had shown poor in vitro susceptibility to the single agents. Similar results have been obtained by workers using different techniques for culture and sensitivity testing. A mechanism for synergy between these two agents has been proposed. Rifampicin acts against mycobacteria by inhibiting bacterial DNA dependent RNA polymerase, thus blocking transcription. Rifampicin resistant strains of Mycobacterium tuberculosis have a resistant polymerase, which is not inhibited by the drug. In contrast, rifampicin resistance among opportunistic mycobacteria seems to be due to a failure of the drug to penetrate the bacterial cell wall. The RNA polymerase of rifampicin resistant strains belonging to the MAIS complex is highly sensitive to rifampicin. Ethambutol, even in low concentrations, induces morphological changes in the bacterial cell wall in vitro, probably by interfering with mycolic acid and phospholipid synthesis. This action on the cell wall might facilitate access of rifampicin into the cell, thus exposing its rifampicin sensitive polymerase. A similar action in vivo might explain the effectiveness of the combination of rifampicin and ethambutol in treatment.

Opportunistic mycobacterial disease in patients with human immunodeficiency virus infection

Opportunistic mycobacterial disease in patients with HIV infection differs substantially in its clinical presentation and response to treatment from the localised pulmonary infection seen in patients who do not have HIV infection. Disseminated disease is the most common manifestation and patients frequently present with fever, weight loss, and malaise. Gastrointestinal symptoms may predominate. Fever, enlarged lymph glands, hepatosplenomegaly, and skin lesions are the most common findings. Although physical signs in the chest are less common, the chest radiograph is usually abnormal and may show a wide range of abnormalities, including mediastinal adenopathy, pulmonary nodules, and patchy alveolar infiltrates. The response to chemotherapy has been poor, though the clinical picture is often obscured by other opportunistic infections. Multiple drug regimens that include rifampicin, ansamycin, ethambutol, clofazamine, ethionamide, and streptomycin have been advocated but, despite good in vitro action shown by several of these drugs, the clinical response has been disappointing.

Summary

Opportunistic mycobacterial infections localised to the chest may be treated with combinations of standard antimycobacterial drugs. The combination of rifampicin and ethambutol seems to be particularly effective, both in vivo and in vitro. In vitro sensitivity testing with single drugs may have a role in the future when the levels of in vitro resistance compatible with the clinical response to treatment are eventually established. Sensitivity testing against drugs in combination may prove useful for modifying treatment regimens in those patients who either fail to respond to initial chemotherapy or relapse. Further evidence on this will, it is hoped, emerge from the prospective studies currently in progress.

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