Treatment of pulmonary tuberculosis in patients notified in England and Wales in 1978–9: chemotherapy and hospital admission

MEDICAL RESEARCH COUNCIL TUBERCULOSIS AND CHEST DISEASES UNIT*

ABSTRACT The treatment of adult patients, both white and of Indian, Pakistani, or Bangladeshi ethnic origin, with previously untreated pulmonary tuberculosis who were notified in England and Wales from 1 October 1978 to 31 March 1979 has been surveyed. Chemotherapy was completed as planned by the physician in charge in 820 (65%) of the 1253 patients. Eleven percent of patients died before chemotherapy could be completed, 8% defaulted, and 6% had chemotherapy modified because of drug toxicity, and for 8% there were miscellaneous reasons for failure to complete chemotherapy. Of the 1003 patients who completed chemotherapy, 804 (80%) were prescribed isoniazid and rifampicin throughout, 667 (67%) receiving ethambutol in addition, either in the initial phase (550) or throughout chemotherapy (117). A further 129 (13%) had a regimen based on isoniazid and ethambutol throughout, and the remaining 70 had miscellaneous combinations of drugs. For the 544 patients who received a two phase regimen of isoniazid and rifampicin throughout with one or two additional drugs initially and who completed chemotherapy as planned, the median duration of chemotherapy was 10-8 months, 122 (22%) patients being treated for more than 12 months. For all 1001 patients who completed chemotherapy (whether or not as planned) and for whom the duration was known, the median duration was 11-8 months and 311 (31%) had more than 12 months' treatment. The great majority (79%) of the patients were admitted to hospital initially, the commonest reason being for investigation and diagnosis.

In recent years controlled clinical trials have established that there are several highly effective short course chemotherapy regimens of six to nine months' duration for the treatment of pulmonary tuberculosis1 and these are being increasingly used in both technically advanced and developing countries. In November 1976 the British Thoracic Association (BTA) recommended,2 and in 1980 reiterated,3 that a nine month regimen of isoniazid plus rifampicin, with ethambutol in the initial phase, was the treatment of choice for pulmonary tuberculosis in Britain, a regimen which both the BTA2,3 and a French Cooperative group4 had studied. It is of special interest to know the extent to which short course regimens are being adopted in routine clinical practice. A survey of all new notifications of tuberculosis in England and Wales,5 undertaken in a six month period in 1978–9, provided a unique opportunity to document details of the chemotherapy which the patients actually received. The present investigation was limited to patients with pulmonary tuberculosis, who were being treated for the first time.

Patients and methods

The population for this treatment survey was based on the 2390 adult patients (aged 15 years or more) with respiratory disease (without any non-respiratory lesion) notified from 1 October 1978 to 31 March 1979.6 The study was confined to patients who had a pulmonary lesion on a pretreatment chest radiograph, confirmed at independent assessment,
patients were found to be ineligible by the original criteria and were therefore excluded, and for the other 25 the information required was not available or was incomplete because the notes had been lost or destroyed. Results are presented for the 1277 patients for whom there was adequate information. There are minor differences in the number of patients in some of the analyses below because every item of information was not available for every patient.

**Results**

**ALL PATIENTS**

**Pretreatment characteristics**

Of the total of 1277 patients, 989 (77%) were of white and 288 (23%) of Indian subcontinent ethnic origin (table 1), 74% and 51% respectively being male. The white patients of both sexes were, on average, older than the Indian subcontinent patients, 51% compared with 17% being aged 55 years or more. The difference is likely to be related, at least in part, to the younger age distribution of the Indian subcontinent population from which the patients were drawn.

A positive culture result from a sputum specimen was reported for 78% of the white and 62% of the Indian subcontinent patients, 58% and 44% respectively being positive on smear examination as well.

**Table 1**  
**Pretreatment characteristics of the 1277 patients**

<table>
<thead>
<tr>
<th>Pretreatment characteristic</th>
<th>Ethnic origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
</tr>
<tr>
<td><strong>Male (age (y))</strong></td>
<td></td>
</tr>
<tr>
<td>15–34</td>
<td>115 (16)</td>
</tr>
<tr>
<td>35–54</td>
<td>213 (29)</td>
</tr>
<tr>
<td>55 or more</td>
<td>400 (55)</td>
</tr>
<tr>
<td>Total</td>
<td>728 (100)</td>
</tr>
<tr>
<td><strong>Female (age (y))</strong></td>
<td></td>
</tr>
<tr>
<td>15–34</td>
<td>82 (31)</td>
</tr>
<tr>
<td>35–54</td>
<td>75 (29)</td>
</tr>
<tr>
<td>55 or more</td>
<td>104 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>261 (100)</td>
</tr>
<tr>
<td><strong>Bacteriological results from sputum specimens</strong></td>
<td></td>
</tr>
<tr>
<td>Culture positive</td>
<td>578 (78)</td>
</tr>
<tr>
<td>Smear positive</td>
<td>198 (25)</td>
</tr>
<tr>
<td>Culture negative</td>
<td>213 (22)</td>
</tr>
<tr>
<td><strong>Radiographic characteristics at independent assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Total area affected</td>
<td>167 (17)</td>
</tr>
<tr>
<td>One lung or more</td>
<td>143 (14)</td>
</tr>
<tr>
<td>&lt; One lung, ( \geq ) right upper lobe</td>
<td>679 (69)</td>
</tr>
<tr>
<td>&lt; Right upper lobe</td>
<td></td>
</tr>
<tr>
<td>Cavitation</td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>31 (3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>78 (8)</td>
</tr>
<tr>
<td>Slight</td>
<td>160 (16)</td>
</tr>
<tr>
<td>Nil</td>
<td>720 (73)</td>
</tr>
<tr>
<td><strong>Total patients assessed</strong></td>
<td>989 (100)</td>
</tr>
</tbody>
</table>
Radiographically the disease was, on average, more extensive in the white patients, 17% having a total area equivalent to at least one lung affected, compared with 6% of the Indian subcontinent patients, and a higher proportion of white patients had moderate or extensive caviation—11% compared with 6%.

**Initial drug combinations prescribed**

The great majority of patients—1212 (95%)—received isoniazid plus rifampicin initially. Most (1060) received one additional drug, which was usually ethambutol (in 953 cases), only 71 patients receiving streptomycin and only 36 pyrazinamide. Fifty eight patients were prescribed isoniazid plus rifampicin with two additional drugs, and one with three additional drugs; the remaining 93 had no additional drugs.

There were 50 (4%) patients who were prescribed isoniazid and ethambutol without rifampicin, 22 receiving one additional drug (usually streptomycin), and 28 none. Thirteen (1%) patients had miscellaneous combinations and two started with a single drug.

**Completion of chemotherapy**

Of the 1253 patients for whom the information was recorded (table 2), chemotherapy was completed as planned in 820 (65%). The proportion was lower in the white group than in the Indian subcontinent group, the difference being entirely accounted for by the patients who died. Default or poor compliance (8%) and toxicity (6%) were the other important reasons why chemotherapy was not completed as planned. Other reasons were reported for 103 patients: chemotherapy was given for longer than planned in 65 cases and for shorter than planned in 12, was changed for reasons other than toxicity in 16, and was reported to be different from the physician's usual regimen in 10.

**FINDINGS FOR THE 1003 PATIENTS WHO COMPLETED CHEMOTHERAPY** (patients who died, defaulted, or left the United Kingdom having been excluded).

**Individual drugs prescribed**

Every patient except one had isoniazid, 973 (97%) had rifampicin, 870 (87%) had ethambutol, 121 (12%) had streptomycin and 60 (6%) had pyrazinamide.

**Regimens prescribed**

There were 534 (53%) patients (table 3) who were prescribed isoniazid plus rifampicin supplemented by ethambutol initially (EHR/HR)—that is, the regimen recommended by the BTA. In a further 117 (12%) patients, however, the ethambutol was continued throughout (EHR). Twenty two patients had two additional drugs initially—namely, ethambutol and pyrazinamide (10), streptomycin and etham-

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**Table 3 Regimens prescribed for the 1003 patients who completed chemotherapy**

<table>
<thead>
<tr>
<th>Regimen†</th>
<th>Total No (%)</th>
<th>Completed as planned No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR throughout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHR/HR</td>
<td>534</td>
<td>468</td>
</tr>
<tr>
<td>SHR/HR</td>
<td>37 (60)</td>
<td>33 (64)</td>
</tr>
<tr>
<td>ZHR/HR</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>EHR</td>
<td>117 (12)</td>
<td>93 (11)</td>
</tr>
<tr>
<td>HR + 2 drugs/HR</td>
<td>22 (2)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>HR</td>
<td>67 (7)</td>
<td>60 (7)</td>
</tr>
<tr>
<td>HE throughout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHE/HE</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td>SHE/HE</td>
<td>20 (11)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>ZHE/HE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HE + 2 drugs/HE</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>HE</td>
<td>19 (2)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>70 (7)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Total patients assessed</td>
<td>1003 (100)</td>
<td>820 (100)</td>
</tr>
</tbody>
</table>

*Excluding 133 patients who died, 101 who defaulted, and 16 who left the UK.
†Eighty patients had minor departures from the regimens under which they are categorised.

For the two phase regimens drugs given in the initial phase are shown first and those given in the continuation phase after the oblique (/). H—isoniazid; R—rifampicin; E—ethambutol; S—streptomycin; Z—pyrazinamide.

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**Table 2 Completion of chemotherapy**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Total No (%)</th>
<th>White No (%)</th>
<th>Indian subcontinent No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed as planned</td>
<td>820 (65)</td>
<td>613 (63)</td>
<td>207 (74)</td>
</tr>
<tr>
<td>Not completed as planned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>133 (11)</td>
<td>128 (13)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Default or poor compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left the UK</td>
<td>101 (8)</td>
<td>77 (8)</td>
<td>24 (9)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>16 (1)</td>
<td>6 (1)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>80 (6)</td>
<td>68 (7)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Total patients assessed*</td>
<td>1253 (100)</td>
<td>973 (100)</td>
<td>280 (100)</td>
</tr>
</tbody>
</table>

*Information was not recorded for 24 patients (16 white, eight Indian subcontinent).
butol (5), streptomycin and pyrazinamide (6), and ethambutol and capreomycin (1). A total of 804 (80%) patients received a regimen based on isoniazid and rifampicin. In 129 (13%) the regimen was based on isoniazid and ethambutol, 86 (9%) receiving rifampicin in the initial phase. There remain 70 (7%) patients who had other one or two phase regimens or regimens of three or more phases.

The findings of the 820 patients who completed chemotherapy as planned by the physician in charge are also shown in table 3.

**Duration of chemotherapy**

In all groups (table 4) the median duration of chemotherapy was 10 months or more and almost a third of the patients received more than 12 months' chemotherapy. The distribution of the total duration of chemotherapy was bimodal, with one mode at nine and the other at 12 months, except for the regimen based on isoniazid and ethambutol, whose mode was 12 months.

In all regimen groups there was evidence (lower section of table 4) that the duration of chemotherapy was influenced by the bacteriological result of the initial sputum specimen. The median duration was longest for those with sputum positive on both smear and culture, and shortest for those with sputum negative on both smear and culture.

For the two phase regimens based on isoniazid plus rifampicin or isoniazid plus ethambutol the median durations of the initial phase of chemotherapy (table 5) were 2-5 months and 4-0 months, 22% and 55% respectively having an initial phase of at least four months.

**Intermittent chemotherapy**

Only 21 (2%) patients had intermittent chemotherapy, given in all except one in the continuation phase. It was prescribed by only seven of more than 300 doctors who participated.

**FINDINGS FOR ALL 1277 PATIENTS WHO STARTED CHEMOTHERAPY**

**Adverse reactions**

Details of possible adverse reactions were not...
specifically requested, but were reported for 109 (9%) of the 1277 patients known to have started
chemotherapy, including nine who had two different
reactions. Most (probably all) of the serious re-
arctions leading to interruptions or changes in
chemotherapy are likely to have been reported, but
the drug or drugs causing individual reactions were
often not clearly established.

Of the 953 patients who started treatment with
isoniazid, rifampicin, and ethambutol, possible re-
arctions were reported in 81 (8%), including five with
two different reactions. Twenty nine patients had
hepatic reactions, of whom 14 had hepatitis, includ-
ing 11 with jaundice, and 15 had only abnormal
results from liver function tests. Ten patients had
gastrointestinal, eight hypersensitivity, and four
cutaneous reactions. Possible ocular toxicity was
reported in six patients and neurological reactions in
12, including eight with peripheral neuritis. Throm-
bocytopenic purpura occurred in one patient and
renal failure in another and for 15 patients the type
of reaction was not specified.

Hospital admission
The great majority (79%) of the 1277 patients were
admitted to hospital initially, the proportions being
very similar for the white and Indian subcontinent
ethnic groups—79% of 989 and 76% of 288
patients respectively.

The clinician was asked to indicate one or more of
the following reasons for admission: (1) for investi-
gation; (2) for tuberculosis, either because of routine
policy, severity of disease, infectivity, or social
reasons; (3) for other diseases; (4) for miscellaneous
other reasons. For 55% more than one reason was
indicated. The commonest reason (60%) was for
investigation, other frequent reasons being routine
policy (23%), severity of disease (27%), infectivity
(24%), and social reasons (25%). For the 450
patients in whom only one reason was given the
commonest was investigation (56%), severity of
disease (11%), and routine policy (10%).

Factors affecting management
Stepwise multiple regression and discriminant
analysis techniques were used to look for possible
associations between pretreatment factors and the
management of the patients. The pretreatment
characteristics studied were age, sex, ethnic origin,
radiographic extent of disease and of cavitation at
independent assessment, and the results of smear
examination and of culture of sputum. The findings
in the two groups were initially analysed separately,
but were then combined as there was no evidence
that ethnic origin influenced the management.

The number of drugs prescribed initially for the
1277 patients known to have started chemotherapy
was associated with four significant independent
variables. The most significant was the result of sputum
smear examination, patients with a positive smear
receiving more drugs initially; the other factors, in
order, were younger age, more extensive radio-
graphic disease, and a positive sputum culture.

In the analyses of the total duration of
chemotherapy (based on the 820 patients who com-
pleted chemotherapy as planned by the physician in
charge) a further factor was included—namely,
whether or not the chemotherapy was based on
isoniazid and rifampicin throughout. This was the
most significant factor, patients receiving this regi-
men being treated for a shorter time. The extent of
disease and the sputum culture result were also
significant, patients with more extensive disease or a
positive culture being treated for longer.

It is important to add that in both of the above
analyses less than 10% of the total variation is
accounted for by the significant factors; probably a
high proportion of the remaining variation is due to
differences between the large number of clinicians
concerned in the management of the patients.

Discussion
In the last decade the efficacy of short course regi-
mens of chemotherapy in the treatment of pulmo-
nary tuberculosis has been established beyond all
reasonable doubt.1 A nine month regimen of
isoniazid and rifampicin throughout, with an initial
supplement of streptomycin or ethambutol, is close
to being 100% effective in antibacterial terms2–4
and in November 1976 the BTA recommended this
regimen with ethambutol for the first two months as
the treatment of choice for pulmonary tuberculosis
in Britain. The 1978–9 notification survey in
England and Wales5 provided a unique opportunity
to assess the extent to which short course regimens had
been adopted in routine practice by undertaking the
present survey two years after notification. This sur-
vey was limited to adults who had pulmonary tuber-
culosis only, and who had had no previous treat-
ment, a group eminently suitable for the regimen
recommended by the BTA. Full information was
available for 97% of those eligible. The findings
reflect the management of pulmonary tuberculosis
in England and Wales in a period extending into
1981.

The clinician in charge reported that
chemotherapy was completed as planned in only
65% of the patients. The main reasons for it not
being completed as planned were death, default or
poor compliance, and toxicity. Eleven per cent of
the patients died before completion of
chemotherapy (13% of the white patients, but only 2% of the Indian subcontinent patients). Death was reported to be due to tuberculosis in half of these patients and most deaths occurred soon after the start of chemotherapy, so clearly this remains an important clinical problem. In 8% of patients there were problems of default or poor compliance. A potential advantage of short course chemotherapy over standard regimens of longer duration is that patients who default early are more likely to be already cured when they do so. For example, up to 90% of patients with severe smear positive disease have been reported cured by daily regimens of isoniazid plus rifampicin for only four months, supplemented by streptomycin and pyrazinamide for the first two months. A three month daily regimen of these four drugs has also been reported to cure up to 80% of patients.

In the evaluation of clinical management there are two important aspects of the chemotherapy prescribed to be considered, the drug combinations and the duration. Regimens based on rifampicin and isoniazid were prescribed for most (80%) of the 1003 patients who completed chemotherapy and over half (53%) received this combination with ethambutol in the initial phase, the regimen recommended by the BTA. In a further 12%, however, the ethambutol was continued throughout, a practice which cannot be recommended—firstly, because of the absence of evidence that ethambutol adds any benefit in patients with fully sensitive strains and, secondly, because ocular toxicity due to ethambutol may be serious (although dose related, it may occur even at a dosage of 15 mg/kg). In all, 13% of the 1003 patients had isoniazid and ethambutol throughout and only half of these had rifampicin in the initial phase. The evidence indicates that regimens based on isoniazid and rifampicin are more likely to have already cured patients who default early and also to cure patients with initial resistance to isoniazid. Regimens based on isoniazid and rifampicin throughout are clearly the treatment of first choice.

The second important consideration is the duration of treatment. In 1976 the BTA recommended a duration of nine months' chemotherapy for pulmonary tuberculosis. Only 33% of the 819 patients who completed chemotherapy as the physician had planned received nine months' or less chemotherapy. Forty nine per cent of patients received 12 or more months' chemotherapy and 5% more than 18 months, the median duration being 11.1 months. Indeed only 32% had isoniazid and rifampicin for nine to 12 months, with ethambutol for two to three months, an approximation to the BTA regimen; this compares with 20% in an earlier

survey in South and West Wales. In Scotland, where the Working Party on Tuberculosis set up a surveillance system for pulmonary tuberculosis in 1978, the proportion of patients who had completed chemotherapy as planned by 12 months had increased from 41% for patients notified in 1978 to 46% in 1979 and 51% in both 1980 and 1981. Even for those notified in 1981, however, 29% were continuing treatment on a regular basis into the second year. The problem of major advances in treatment not being adopted by physicians in their routine practice has been discussed by Fox. Treatment for longer than necessary carries social and psychological disadvantages for the patient and his family, exposes the patient to the risks of late drug toxicity, and increases the cost of the treatment. One approach to the problem of treatment continuing for longer than planned might be to ensure that a clinic appointment at the end of the proposed course is booked as a standard procedure at the start of treatment. Although the risk of default from treatment in the early months is likely to be less in short course regimens than in those of longer duration, this important issue needs to be investigated in several countries under widely differing service programme conditions. One such study is currently being undertaken collaboratively between an Algerian group and the Medical Research Council.

The importance of pyrazinamide in the initial phase of short course chemotherapy and its low toxicity in the dosage used is now well established and at the time that patients in the survey started chemotherapy there was already a substantial body of evidence to this effect. Even so it was prescribed for only 6% of the patients. Indeed, in Scotland for patients notified in 1980 the proportion was only 3%. In a study in Britain the BTA concluded in 1982 that a six month regimen of isoniazid and rifampicin, in which pyrazinamide as well as ethambutol or streptomycin is given in the first two months, is as effective as the recommended nine month regimen and no more toxic, confirming earlier reports from Singapore. Possibly therefore the proportion of patients receiving pyrazinamide will increase rapidly over the next few years in Britain.

The use of supervised intermittent chemotherapy, particularly in problem patients, has been widely accepted in many countries and in some as the optimal regimen for service programmes, especially in urban areas. In this survey only 21 (2%) patients were prescribed intermittent chemotherapy and this by only seven of more than 300 clinicians. The problems of treating alcoholics and the homeless middle aged white men and the elderly in Britain are well documented, and we might have expected that
fully supervised intermittent chemotherapy would have been used more frequently.

It has been established for over 20 years that ambulatory outpatient chemotherapy for pulmonary tuberculosis is highly effective and that there are no advantages from hospital admission for treatment as a routine policy, yet 79% of patients were admitted to hospital initially. Several reasons were given, the commonest being investigation and diagnosis; but for 10% of patients the admission was reported to be because of routine policy only, and for 23% this was one of the reasons. Although unnecessary prolongation of chemotherapy results in increased expense, particularly if rifampicin is used, unnecessary hospitalisation is much more costly and wasteful of health service resources. No information was collected on duration of hospital stay, but as the average daily cost of a tuberculosis bed was £72 in England in 1982 even a few days' unnecessary stay is more expensive than the total drug cost of highly effective short course regimens.

Surveys such as the present are important in assessment of the extent to which new advances in management are being adopted. Further surveys from time to time (or, when appropriate, continuous surveillance of all new patients) can lead to improvements in practice, as was first demonstrated in Kenya after a national survey in 1964 of the management of patients in the service programme of that country. The present survey shows that despite the existence of a considerable body of evidence of the efficacy and safety of treatment lasting for six to nine months, and even a recommendation from the BTA, short course regimens had not been widely adopted in clinical practice in the late 1970s or the early 1980s, even though most patients were receiving the recommended drug combinations. In the light of the more recent (1982) conclusion of the BTA that the six month regimen including pyrazinamide, referred to above, is as effective as and no more toxic than the previously recommended nine month regimen, it is hoped that practice in Britain may change rapidly.

The success of this survey was due to the enthusiastic cooperation of the chest physicians, general physicians with special interest in chest diseases, and clinicians in other specialties and of the nursing staff, secretaries, and records officers of many hospitals and chest clinics. We are grateful for the help and support of the Department of Health and Social Security and the Welsh Office and of the British Thoracic Society.

References


*Thorax* 1985 40: 113-120
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