

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

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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 per cent 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 tuber-

culosis in Britain, a regimen which both the BTA^{2,3} 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 1979.⁵ The study was confined to patients who had a pulmonary lesion on a pretreatment chest radiograph, confirmed at independent assessment,

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Accepted 14 September 1984

who had at least one pretreatment culture result available from a respiratory specimen and were either of white or of Indian subcontinent ethnic origin (Indian, Pakistani, or Bangladeshi) (92% of all cases in the notification survey came from these four groups). Patients known to have had previous treatment for tuberculosis, to have initial resistance to one or more antituberculosis drugs, or to have non-respiratory in addition to pulmonary disease were not included because these factors might have affected management. Patients who died before treatment could be started or in whom the diagnosis was made after death were also excluded. Of the 1411 patients eligible by the above criteria for this treatment survey, 49 were excluded because they had been admitted to a then current BTA chemotherapy study,⁶ so that their regimen had been determined by random allocation. There remained 1362 patients to be followed up.

Two years after the last patient was notified, a form was sent to the clinician in charge of each patient to obtain information on (1) the drugs prescribed in the initial and continuation phases and their durations; (2) whether or not chemotherapy was completed as planned; and (3) whether the patients had been admitted to hospital initially, and the reason for admission. A survey form was returned for 1349 (99%) of the 1362 patients, but 72 were excluded from the analysis. Forty seven

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.⁷

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*

<i>Pretreatment characteristic</i>		<i>Ethnic origin</i>	
		<i>White No (%)</i>	<i>Indian subcontinent No (%)</i>
Male (age (y))	15-34	115 (16)	68 (47)
	35-54	213 (29)	49 (34)
	55 or more	400 (55)	29 (20)
	Total	728 (100)	146 (100)
Female (age (y))	15-34	82 (31)	91 (64)
	35-54	75 (29)	31 (22)
	55 or more	104 (40)	20 (14)
	Total	261 (100)	142 (100)
Bacteriological results from sputum specimens	Culture positive	578	127
	Smear positive	198 } (78)	53 } (62)
	Smear negative	213	108
	Culture negative	213 (22)	108 (38)
Radiographic characteristics at independent assessment	Total area affected		
	One lung or more	167 (17)	17 (6)
	<One lung, ≥right upper lobe	143 (14)	41 (14)
	<Right upper lobe	679 (69)	230 (80)
	Cavitation		
	Extensive	31 (3)	4 (2)
	Moderate	78 (8)	13 (5)
	Slight	160 (16)	44 (15)
	Nil	720 (73)	226 (78)
	Total patients assessed	989 (100)	288 (100)

Radiographically the disease was, on average, more extensive in the white patients, 17% having a total area equivalent to at least one lung affected,⁸ compared with 6% of the Indian subcontinent patients, and a higher proportion of white patients had moderate or extensive cavitation⁹—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,

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

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

*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.

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-

Table 2 Completion of chemotherapy

Chemotherapy	Total No (%)	White No (%)	Indian subcontinent No (%)
Completed as planned	820 (65)	613 (63)	207 (74)
Not completed as planned			
Died	133 (11)	128 (13)	5 (2)
Default or poor compliance	101 (8)	77 (8)	24 (9)
Left the UK	16 (1)	5 (1)	11 (4)
Toxicity	80 (6)	68 (7)	12 (4)
Other reasons	103 (8)	82 (8)	21 (8)
Total patients assessed*	1253 (100)	973 (100)	280 (100)

*Information was not recorded for 24 patients (16 white, eight Indian subcontinent).

Table 4 Total duration of chemotherapy*

Duration (m)†		Completed chemotherapy					
		All patients No (%)	As planned				
			Total No (%)	HR plus 1 or 2 drugs/HR No (%)	EHR No (%)	HR No (%)	HE plus 1 drug/HE No (%)
Total	6 or less	19 (2)	7 (1)	2 (<1)	3 (3)	1 (2)	1 (1)
	7	21 (2)	18 (2)	14 (3)	2 (2)	2 (3)	0 (0)
	8	25 (2)	20 (2)	14 (3)	2 (2)	2 (3)	1 (1)
	9	250 (25)	228 (28)	178 (33)	19 (19)	21 (35)	4 (5)
	10	99 (10)	82 (10)	60 (11)	8 (8)	7 (12)	5 (6)
	11	74 (7)	61 (7)	46 (8)	9 (9)	2 (3)	4 (5)
	12	202 (20)	174 (21)	108 (20)	25 (25)	9 (15)	24 (31)
	13-15	169 (17)	132 (16)	75 (14)	17 (17)	10 (17)	20 (26)
	16-18	83 (8)	58 (7)	29 (5)	12 (12)	3 (5)	9 (12)
	19-21	33 (3)	23 (3)	13 (2)	3 (3)	1 (2)	5 (6)
	22 or more	26 (3)	16 (2)	5 (1)	1 (1)	2 (3)	5 (6)
	Total patients assessed	1001 (100)	819 (100)	544 (100)	101 (100)	60 (100)	78 (100)
Median	Culture + smear +	11.9	11.9	11.5	11.8	11.8	13.0
	Culture + smear 0	10.9	10.8	9.9	11.8	10.8	11.7
	Culture 0	10.0	10.0	9.0	11.0	9.0	12.0
	All patients	11.8	11.1	10.8	11.8	10.0	12.1

*Excluding patients who died, defaulted, or left the UK and two for whom the duration was unknown.

†The duration of chemotherapy has been calculated so that, for example, 7 months represents from 6.5 to 7.5 months. Regimen abbreviations are given in table 3.

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

Table 5 Duration of initial phase of chemotherapy*

Duration (m)†	Regimen	
	HR plus 1 or 2 drugs/HR No (%)	HE plus 1 drug/HE No (%)
<2	38 (7)	6 (8)
2	227 (42)	17 (22)
3	158 (29)	12 (15)
4	48 (9)	8 (10)
5	15 (3)	5 (6)
6	23 (4)	5 (6)
>6	33 (6)	25 (32)
Total	542 (100)	78 (100)
Median	2.5	4.0

*For patients who completed chemotherapy as planned in the two phase regimens, excluding two for whom the duration was unknown.

†The duration of the initial phase has been calculated so that, for example 2 months includes from 1.5 to 2.5 months. Regimen abbreviations are given in table 3.

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 reactions 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 reactions were reported in 81 (8%), including five with two different reactions. Twenty nine patients had hepatic reactions, of whom 14 had hepatitis, including 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. Thrombocytopenic 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 investigation; (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 were 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 radiographic disease, and a positive sputum culture.

In the analyses of the total duration of chemotherapy (based on the 820 patients who completed 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 regimen 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 regimens of chemotherapy in the treatment of pulmonary 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 survey was limited to adults who had pulmonary tuberculosis only, and who had had no previous treatment, 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.¹⁰ 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.¹¹⁻¹² A three month daily regimen of these four drugs has also been reported to cure up to 80% of patients.¹³⁻¹⁴

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/kg¹⁵). 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.¹¹⁻¹⁴ 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.¹⁶ 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 1978¹⁷ to 46% in 1979¹⁸ and 51% in both 1980¹⁹ and 1981.²⁰ 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.²¹ 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,¹⁴ and at the time that patients in the survey started chemotherapy there was already a substantial body of evidence to this effect.²² Even so it was prescribed for only 6% of the patients. Indeed, in Scotland for patients notified in 1980¹⁹ the proportion was only 3%. In a study in Britain the BTA concluded in 1982⁸ 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.¹² 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,²³⁻²⁴ 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,²⁵ 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.²⁶ No information was collected on duration of hospital stay, but as the average daily cost of a tuberculosis bed was £72 in England in 1982²⁷ 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.²⁸ 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.

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