The management of pulmonary and lymph node tuberculosis notified in England and Wales in 1998

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ABSTRACT – The management of 1,337 cases of pulmonary tuberculosis and 422 cases of lymph node tuberculosis reported to the 1998 national notification survey was compared with the recommended standards of treatment. Most patients (84%) were under the care of thoracic physicians. Culture confirmation was obtained in 67.5% of pulmonary cases and 52% of lymph node cases. Drug resistance was reported in 7%, ranging from 3.3% in white patients to 7.9–8.2% in other ethnic groups. Only a minority of non-white ethnic patients received the recommended four-drug initial phase of therapy. Non-standard durations of initial and/or continuation therapy were used in 35% of cases on recommended drug combinations. Thirty-nine (2.9%) pulmonary cases were diagnosed only at post-mortem and a further 96 died before the end of the survey period, 55 (4.3%) due to tuberculosis. The outcome for pulmonary disease, with 80% cured or completing treatment, compare favourably with European outcome data. Although overall outcome data were satisfactory, more patients should have received a four-drug initial phase, with more combination tablet use and better compliance monitoring. Outcome monitoring will henceforth be based mainly on the continuous enhanced surveillance system introduced since 1999.

KEY WORDS: outcome, treatment, tuberculosis

The national survey of tuberculosis notifications in England and Wales in 1993[1] was followed by national audits of management,[2,3] using the 1990 recommendations of the Joint Tuberculosis Committee (JTC) of the British Thoracic Society as the audit standard.[4] A further national survey of tuberculosis notifications was conducted in England Wales in 1998,[5] and in the same year the JTC also published updated evidence-based guidelines,[6] which recommended that both pulmonary and non-respiratory tuberculosis should be treated with six months' rifampicin (R) and isoniazid (H), supplemented by pyrazinamide (Z) for the first two months (2HRZ/4HR) where there was a low incidence of isoniazid resistance, or with both Z and ethambutol (E) for the first two months (2HRZE/4HR) where there was a higher risk of isoniazid resistance. The recommendations for pulmonary and lymph node disease were based on 'A' category data.[7]

This survey reports the treatment given to patients of all ages notified with pulmonary and lymph node tuberculosis in England and Wales in the first six months of 1998, the associated problems and morbidity, and the outcome. The outcome criteria for pulmonary disease in 1998 were modified from those used in 1993[2] to the standardised outcome criteria for Europe which had been published in 1998.[8] This allowed outcome to be described in a manner easily comparable with data from other European countries, something which had previously not been possible.

Methods

This report describes patients notified to the Public Health Laboratory Service Communicable Disease Surveillance Unit between 1 January and 30 June 1998 inclusive. Doctors were asked to use special notification forms, giving enhanced clinical and epidemiological data. Twelve months after notification, the doctors who had returned forms notifying patients with pulmonary tuberculosis (excluding pleural effusion and isolated mediastinal lymphadenopathy) and with peripheral lymphadenopathy were sent a questionnaire on treatment and outcome.

Information sought from the notification form included age, sex and ethnic group of the patient, and the name of the responsible clinician. The bacteriological status at diagnosis was recorded, and for lymph node disease whether histological confirmation was obtained. The drug susceptibility results of those with positive cultures were also obtained. Starting and stopping dates for each drug, and whether treatment was given intermittently, were noted. The clinician reported if recommended or other treatment was started, the reason for any amendment or interruption, for example drug toxicity (suspected or proven), drug resistance, patient failure to attend, prescription error or deliberate decision.

Status at 12 months after notification was classified as death due to tuberculosis, death not due to tuber-

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Clin Med 2003;**3**:57–61

culosis, or alive. For pulmonary disease, outcome was also recorded as one of the following:

- cured (negative cultures in continuation phase)
- cured (negative smears in continuation phase)
- treatment completed
- treatment interrupted (greater than 2 months)
- treatment failure (positive cultures at 5 months)
- transfer out (moved to another clinical unit)
- lost to follow-up.

The clinician was also asked if the patient had been discharged back to the care of the general practitioner at the completion of treatment.

The questionnaires were returned to the audit centre where each patient was given a unique patient identifier known only to those responsible for data entry and cleaning. Data were entered in numerical or coded form onto an electronic database. At the completion of data collection, the numerical/coded data were sent to the Medical Statistics Unit, Edinburgh University, for analysis. As in the previous audits[2,3] and the report on treatment of pulmonary tuberculosis in the 1988 notification survey,[9] fairly wide ranges were allowed as fulfilling the criteria for standard durations of treatment: 6–12 weeks for the initial phase, and 22–30 weeks for total duration for the 2HRZ/4HR and 2 HRZE/4HR regimens.

Results

Exclusions

Of 1,694 pulmonary cases notified, 357 were excluded, 177 because of altered diagnosis (120 with opportunist mycobacteria on culture) and 180 because of non-return of data. Fifty-nine out of 481 lymph node cases were excluded, 12 with altered diagnosis and 47 because of data non-return.

Patient characteristics

Of the 1,337 pulmonary patients, 793 were male, 595 were white and 449 were of Indian Subcontinent (ISC) ethnic origin, 140 were Black-African, and 153 were from other ethnic groups. The 422 lymph node patients showed a female preponderance ($n = 250$), 69 were white, 230 ISC, 70 Black-African and 53 from other ethnic groups. The methods of diagnosis and bacteriology data are given in Table 1.

Eighty-five percent (1,139/1,337) of the pulmonary patients and 82% (345/422) of lymph node patients were under the care of thoracic physicians (84% overall).

Treatment

Forty-two of 1,337 pulmonary patients were not treated, 39 with post-mortem diagnosis, one died pre-treatment, and two moved before treatment. Of those receiving treatment:

- 834 (64.8%) received HRZ
- 373 (28.8%) received HRZE
- 12 (0.9%) received HRE
- 70 (5.4%) received other regimens.

These treatments were modified in 301 (23%) cases, 120 due to drug reactions, 52 due to drug resistance, three for both reasons, and no reason was given in 126. Of 993 receiving unmodified standard treatment:

- 931(93.7%) had this as self-administered treatment
- 63 (6.3%) had directly observed treatment.

Table 1. Method of diagnosis and bacteriology data.

	Pulmonary		Lymph node
Sputum microscopy and culture positive	596	Positive histology and bacteriology	111
Sputum microscopy negative culture positive	307	Positive histology only	122
Sputum microscopy and culture negative	247	Positive bacteriology only	116
Sputum microscopy positive culture negative	51	Clinical diagnosis	73
No Samples	136		
Drug susceptibility data available on 844/903		*Drug susceptibility data available on 227/227*	
Fully susceptible	782 (93%)	Fully susceptible	212 (93%)
Isoniazid resistance	37	Isoniazid resistance	10
Pyrazinamide resistance	9	Pyrazinamide resistance	2
Rifampicin resistance	2	Rifampicin resistance	1
Ethambutol resistance	8	Ethambutol resistance	0
Streptomycin resistance	22	Streptomycin resistance	0
Combined rifampicin/isoniazid resistance (MDR-TB)	15	Combined rifampicin/isoniazid resistance (MDR-TB)	2
Isoniazid resistance by ethnic group			
White	13/377 (3.4%)	White	0/20
ISC	22/267 (8.2%)	ISC	10/132 (8%)
Black-African	8/101 (7.9%)	Black-African	2/47 (4%)
Other	8/99 (8.1%)	Other	0/28

MDR = multi-drug resistant; ISC = originating from Indian Subcontinent.

Of those on self-administered treatment:

- 103 (11%) did not receive fixed drug combination tablets
- 398 (41%) had monthly compliance checks
- 279 (28.1%) did not have compliance checks
- 310 (31%) had no compliance data.

Of the 807 on recommended drugs, 282 (34.9%) received inappropriate durations of initial and/or continuation phases of treatment, almost invariably too long.

Of the 421/422 lymph node cases receiving treatment:

- 263 (62.4%) received HRZ
- 128 (30.4%) received HRZE
- 5 (1.2%) received HRE
- 25 (5.9%) received other combinations.

Treatment was modified in 64, for drug reaction in 29 and resistance in 15 but not stated in 20. Of the cohort:

- 211 (68.5%) had self-administered treatment
- 19 (6.2%) had directly observed therapy
- 78 (25.3%) had no treatment data.

Of those on self-administered treatment:

- 8.3% did not receive fixed drug combination tablets
- 180 (42.6%) had monthly compliance checks,
- 123 (29.1%) did not have compliance checks
- 119 (28.2%) had no compliance data.

Of 308 who completed treatment with recommended drugs, 107 (34.7%) had inappropriate durations of initial and/or continuation phases, again almost always for too long.

The regimens for the various ethnic groups are given in Table 2 for the pulmonary and the lymph node patients.

Drug toxicity

Drug(s) were stopped because of definite or suspected adverse reactions in 123 (9.5%) pulmonary and 31 (7.4%) lymph node patients. The drugs suspected were pyrazinamide (69), rifampicin (46), isoniazid (24), ethambutol (11), others (7) and not recorded (14).

Key Points

Only a minority of non-white ethnic patients received the recommended four-drug initial combination

Drug resistance was found in 8% of non-white and 3% of white patients

Eighty percent of pulmonary patients were cured or completed treatment which compares favourably with European data

Improvements can still be made in tuberculosis treatment and monitoring

Outcome monitoring will now be based on the continuous enhanced surveillance system

Outcome

Of the pulmonary patients, 39 were diagnosed at post-mortem and one patient died before treatment started. Of the 1,297 who started treatment, 96 (7.4%) died before completion of treatment, in 24 (1.9%) of whom tuberculosis was the reported cause of death and in a further 31 (2.4%) it was reported as a contributory factor.

Treatment outcome is given in Table 3. Of those cured or completing treatment, 715 of 1,064 were discharged back to their general practitioner (GP) at completion of treatment, 277 were not and in the remaining 72 the information was not recorded. With the lymph node patients, there was one post-mortem diagnosis and 13 patients left the country. Of the remaining 408 patients, 320 were discharged to the care of their GP on completion of treatment.

Table 2. Initial and final drug treatment regimen by ethnic group.

	Pulmonary					Lymph node				
Regimen	White	Indian/ISC	Black-African	Chinese	Other	White	Indian/ISC	Black-African	Chinese	Other
Initial										
HRZ	414	270	63	15	77	51	150	29	5	28
HRZE	113	143	67	9	41	5	70	36	5	12
HRE	3	4	1	2	2	3	2	0	0	0
Other	35	21	9	1	4	9	8	5	1	2
Final										
HRZ/HR	308	231	45	9	69	38	117	19	4	27
HRZE/HR	79	120	54	7	30	5	52	26	4	12
HRE/HR	3	1	1	2	2	3	1	0	0	0
Other	175	86	40	9	23	22	60	25	3	3

ISC = originating from Indian Subcontinent; H = isoniazid; R = rifampicin; Z = pyrazinamide.

Discussion

This survey reflects the increase in tuberculosis in England and Wales between 1993[1] and 1998,[5] with 1,337 pulmonary cases and 422 lymph node cases in the first six months of 1998, compared with 995 pulmonary[2] and 219 lymph node[3] cases in 1993. The proportion of patients reported here is approximately 80% of those notified to the national survey,[5] as in 1993.[2,3] The bacteriological status of the pulmonary cases reported was representative of the 1998 notification survey,[5] but our ethnic proportions suggest a greater level of non-return of forms from physicians managing patients in ethnic minority groups. 93% of isolates in both pulmonary and lymph node disease showed fully susceptible organisms, with drug resistance higher in those from ethnic minority groups. Incidences were consistent with reported whole year isoniazid resistance of 6% and multi-drug resistant (MDR)-TB of 1.3%.[10]

The 1990 JTC Treatment Guidelines[4] recommended 2HRZ/4HR with the addition of ethambutol in the initial phase in those at higher risk of isoniazid resistance, an 'opt-in' strategy. While some of the patients reported here were on treatment, the JTC updated their Guidelines and recommended 2HRZE/4HR, with ethambutol (E) omitted only in those defined as at low-risk of isoniazid resistance, an 'opt-out' strategy.[6] Applying this, the majority of ethnic minority patients for whom a four-drug initial phase would have been recommended by the JTC, did not receive appropriate initial treatment.

Treatment was modified from standard in 23% of pulmonary and 16% of lymph node cases, sometimes because of drug reactions or resistance, but 40% of alterations were unexplained by these factors. The duration of drug treatment was inappropriate in 29% of both pulmonary and lymph node patient groups, the majority receiving treatment for too long. Of those with non-modified treatment, 93.7% of pulmonary and at least 64.5% of lymph node cases had self-administered treatment. Of the self-administering patients 8–11% did not receive fixed-drug combination therapy and at least 28% of all cases did not receive minimum monthly compliance checks, both of which measures are recommended by the JTC.[4,6]

Only one patient with lymph-node tuberculosis died, but of the 1,337 in the pulmonary cohort, 39 (2.9%) were post-mortem diagnoses, and a further 96 patients died before completion of treatment. Of these, 24 died directly from tuberculosis (1.9%), and in a further 31 (2.4%) tuberculosis contributed to death, making a total of 94 (7.2%) in whom disease caused or contributed to death. A further 45 (3.5%) died before completion of treatment from causes other than tuberculosis. Only 67% of pulmonary patients regarded as cured or having completed treatment,[8] and 78% of lymph node cases, were discharged to their GP the end of treatment, although the JTC Guidelines[4,6] have consistently recommended that such patients with good compliance should be returned to the care of their GP.

When judged by the European outcome criteria, at least 79.6% of cases were in the cured or completed categories (Table 3). Some of the 40 patients transferred to other units are likely to have been in those categories but could not be traced. This figure rises to 82% if pre-treatment deaths are excluded and to 88.6% if all deaths are excluded. Since the European criteria[8] report outcome for whole cohorts without exclusions, the figure of 79.6% is more appropriate for comparison. The paper by Veen *et al*[8] setting out the European outcome criteria also gives outcome data for surveys or surveillance from European countries between 1988 and 1996 (Table 4: Refs 11–18). From these data it can be seen that results in England and Wales (80% cure/completion) compare favourably with those in Europe.

Whilst these data are encouraging in comparative terms, there are still areas of concern. Only a minority of non-white ethnic patients received the four-drug initial phase of treatment which has been recommended on the basis of drug resistance data.[4,6] Such under-treatment increases the chances of developing further drug resistance and even MDR-TB. Not all patients on self-administered treatment received combination tablets which are strongly advised to help compliance and prevent monotherapy, and at least 28% of such patients did not have the minimum monthly compliance monitoring, although compliance is a major determinant of outcome.[19] The 1998 JTC guidance set out why the correct initial regimen, combination tablets, and at least monthly drug compliance monitoring were essential. The failure to carry out compliance monitoring as recommended may in part have been due to inadequate tuberculosis nursing provision in 86% of the 42 high-incidence districts of England and Wales.[20] Treatment was also unnecessarily prolonged in over 20% of cases.

Determining what treatment is given for tuberculosis in England and Wales has previously had to be based on cohorts identified in national notification surveys performed at five-yearly intervals.[2,3,9] Since 1999, tuberculosis notifications

Table 3. Pulmonary TB: outcome of treatment.

Outcome category	Whole cohort		Excluding pre-treatment deaths	Excluding all deaths
Cured: negative cultures	167			
Cured: negative smears	16	79.6%	82.0%	88.6%
Completed treatment	881			
Treatment interrupted	11	0.8%	0.8%	0.9%
Treatment failure	12	0.9%	0.9%	1.0%
Transfer out	40	3.0%	3.1%	3.3%
Lost to follow-up	74	5.5%	5.7%	6.2%
Death (on treatment 96, pretreatment 40)	136	10.2%	7.4%	
TOTAL	1,337		1,297	1,201

Table 4. Reported outcomes of TB programmes in Europe 1988–98: pulmonary TB.

Country	Year(s)	Sample (*n*)	Cured/completed (%)	Data collection	Ref
Italy	1995–6	1,120	83	Survey	11
Netherlands	1995	1,469	82	Survey	12
Slovakia	1994	421	81	Surveillance	13
England and Wales	1998	1,337	80	Survey	**This paper**
Norway	1995	101	77	Surveillance	8
Switzerland (Zurich)	1991–3	428	73	Survey	14
Russian Fed (Ivanova)	1995	119	71	Survey	8
Germany	1994–5	1,000	68	Survey	8
France (Paris)	1992	122	66	Survey	15
Switzerland (Vaud)	1988–92	120	63	Survey	16
Israel	1990–92	877	54	Survey	17
Czech Republic	1994	509	53	Surveillance	13
Turkey	1990	404	15	Survey	18

have been continuously monitored by enhanced surveillance at the Public Health Laboratory Service Centre for Disease Surveillance and Control. From 2002, the outcome of tuberculosis will be monitored on a retrospective basis, one year after notification, with a module based on this survey method and the European criteria,[8] but concentrating on outcome. Some intermittent monitoring of 'process' may also be needed to assess the appropriateness of the regimens used, treatment durations, and the completeness of combination tablet use and compliance monitoring.

Acknowledgement

The study was funded by the Morriston Davies Trust.

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