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Restrictive treatment policy for pulmonary tuberculosis in a low prevalence country

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ABSTRACT: In Denmark, treatment of tuberculosis is generally recommended only if the diagnosis is confirmed bacteriologically. This policy may cause a delay in treatment, if the patients are smear negative. We investigated the duration of the treatment delay, and whether the delay would cause any serious health problems for the individual, or risk of contact infections, in a retrospective examination of 324 cases of pulmonary tuberculosis.

The mean treatment delay was longer in the oldest age group. Concerning death due to delay, we found no risk for those patients who were not weakened by other disease or old age. Only 11 patients (3.6%) over the age 10 yrs were treated without bacteriological confirmation (1% for Danes).

The infection risk from the smear negative but culture positive patients was minimal, as only one subject was definitely infected from a smear negative patient. However, a risk of transmission exists from patients who are initially culture negative but later become smear positive.

In conclusion, we find the epidemiological and individual risks sufficiently low to continue our rather restrictive treatment policy.

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The indication for starting chemotherapy for tuberculosis varies widely in different countries. If resources for culture or X-ray examinations are not available, only smear positive patients are treated. An aggressive treatment policy has recently been recommended even in countries with resources for culture of *M. tuberculosis* [1]. These recommendations are based on studies from high prevalence areas, where about 60% of patients have been found to become positive during follow-up [2], which is not the case in low prevalence areas [3, 4]. A restrictive treatment policy for tuberculosis may be of advantage in such areas [5].

In Denmark, treatment is generally recommended only in case of positive smear for acid-fast bacilli, or positive culture for *M. tuberculosis,* or if the clinical diagnosis seems completely indisputable. In this study, we have investigated whether this policy has caused any serious health or epidemiological problems, by examining all cases of pulmonary tuberculosis in Copenhagen, in a 3 yr period.

As the severity of disease is difficult to quantify, we have used delay in treatment and number of deaths as the primary indicators of the health risk. The epidemiological problems were quantified by the treatment delay in known disease sources.

Materials and method

In Denmark it is obligatory to register all cases of tuberculosis. Four hundred and five cases were registered in Copenhagen (population approximately 1.2 million) from 1986 to 1988. The records from the hospitals which had diagnosed the cases were examined. If the patient had had contact with other hospitals, and that contact was possibly because of tuberculosis, those records were also examined. The records for three surviving patients could not be found, and three patients were incorrectly notified. Only the data from the 324 (81%) cases of pulmonary tuberculosis are presented.

The following data were registered from each hospital contact: time, age, sex, nationality, alcohol consumption, employment, tuberculous contact during the last 10 yrs, concomitant severe diseases, and smear and culture for tuberculosis. We defined foreigners as first or second generation of non-Danish extraction living in Denmark (Greenland included), irrespective of citizenship. Patients with a daily alcohol consumption of more than 60 g of pure alcohol (approximately five beers) were regarded as alcoholics.

Treatment delay was counted as the number of weeks from the time that suspicion of tuberculosis was

raised until the start of treatment or death. The patient's delay and the primary physician's delay were not registered.

Epidemiological risk was evaluated by a separate registration of the treatment delay in known contacts treated for tuberculosis. This information was available for 42 out of 84 cases. The missing cases were mostly either infected many years earlier or foreigners.

Treatment consisted of isoniazid, rifampicin, pyrazinamide and ethambutol for 3 months, followed by isoniazid and rifampicin for 3 months. Isoniazid preventive therapy is only used in children with a known contact, who develop a positive skin test.

Statistical analysis

Chi-squared was used to compare frequencies. Mann-Whitney and Kruskal-Wallis tests were used to compare treatment delay in the different groups.

Results

Basic description

Two hundred and twenty three of the 324 patients were Danes. The nationality is presented according to age in figure 1. Of the 324 patients, 98 (30%) were alcoholic. Sixty six of 145 (45%) male patients and 30 of 67 (45%) female patients between 20 and 70 yrs of age were working (NS). Forty five (14%) patients were known to have had tuberculosis previously. Eight of the 11 patients who relapsed less than 5 yrs after their last treatment were alcoholics. Three (1%) patients suffered from acquired immune deficiency syndrome (AIDS), and 26 (8%) from another severe disease (mostly malignancies). Nationalities of the 101 foreigners were: Asian (25), African (15), Turkish (20), Yugoslavian (16), Western Europe (10), and from other countries (15).

Treatment policy

Thirteen (4%) patients died before diagnosis, one was left untreated, and 310 were treated. Treatment was started before a definite diagnosis was established in 77 (24%) patients (16 children, 39 foreign adults, and 22 Danish adults). One hundred and fifty six (48%) patients were treated because of positive smear and 77 (24%) because of positive cultures. In two patients, treatment was stopped due to an other diagnosis being established. In only 22 (6.7%) patients was the diagnosis not confirmed bacteriologically later. Of these, 11 were children. Of 305 patients above the age of 10 yrs, 11 (3.6%) were treated without a bacteriologically confirmed diagnosis. As 9 of these were foreigners, the separate percentages for foreigners was 9.7%, and for Danes 0.9%.

Treatment delay

The median treatment delay in smear positive treated patients was 1 week, compared to 6 weeks in the culture positive cases (table 1). In smear positive cases, there was no significant difference in delay according to nationality, age, or alcohol consumption. In the culture positive cases the delay was longer in Danes (than in foreigners), in alcoholics, and in the age group above 50 yrs (compared to the younger age groups) ($p<0.05$).

Table 1. – Treatment delay in 310 treated patients according to smear and culture results

	Delay weeks				Total
	≤1	2–8	9–16	>17	n
Smear positive	143	25	3	6	177
Culture positive	30	67	7	5	109
No positive culture	22	2	0	0	24
All	195	94	10	11	310

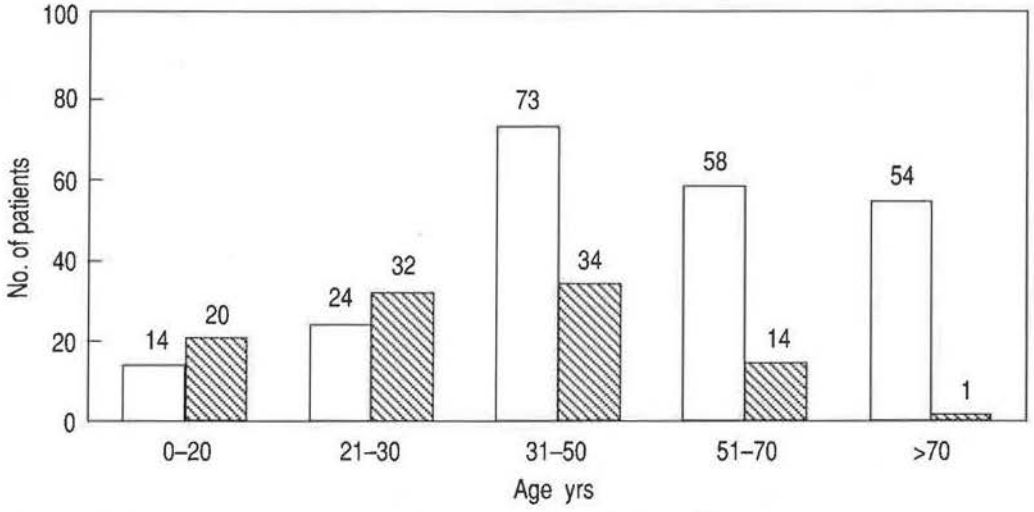

Fig 1. – Age grouping of the 324 patients according to nationality. ☐: Danes; ▨: foreigners.

Complications to delay

Four patients, (three alcoholics) were seriously ill due to treatment delay. No other severe sequelae could be registered. No case of treatment failure was observed.

Death

Two out of 13 patients who died before treatment, died solely because of tuberculosis. One was an alcoholic, who did not seek medical attention before death. The other was treated for recurring pneumonia, and tuberculosis was not suspected before death. The median delay in the other 11 who died before start of treatment was 1 week (range 1–6 weeks). In 10 patients, who died during the first month after treatment start, the delay was 2 weeks (range 1–8 weeks). All of these 21 patients suffered from another severe disease or were old. In three cases, the treatment delay was evaluated to be a contributory cause of death. The ratio between smear positive and smear negative cases in those who died was similar to the ratio in the total patient population.

Transmission

To investigate whether the treatment policy causes any epidemiological risk, we examined the patients who had reported a close tuberculous contact. We examined the treatment delay in these sources of infection. We found five people to have been infected by two smear positive patients, who had a more than 1 yr delay in treatment due to initial negative cultures (table 2). None of these seven patients were severely ill from the disease. In only three cases, the presumed sources were not smear but culture positive. However, as the true infection route was not definite in two of these cases, only in one was the definite infection source smear negative.

Five patients (one physician) employed in hospital or nursing home were treated. This equals the yearly incidence in the general population of Copenhagen (12 out of 100,000). Only one of these subjects had a known tuberculous contact.

Table 2. – Treatment delay in patients who were known sources to secondary infections

	Delay weeks				
	≤1	2–8	9–52	>52	All
Smear positive	30	2	2	5	39
Culture positive	0	2	1	0	3
All	30	4	3	5	42

Numbers are actually diseased patients

Discussion

This retrospective study should be regarded as a supplement to the prospective studies, which are very few from low prevalence areas [3, 4].

Our survey indicates that only 3.6% of patients above the age of 10 yrs treated for tuberculosis did not have the diagnosis confirmed bacteriologically. This shows that a restrictive policy has actually been practised. A much higher proportion had, however, started treatment before a positive smear or culture was obtained. This was mainly the case among foreigners, known to have a much higher incidence of tuberculosis than Danes [6]. The proportion of bacteriologically confirmed cases is definitely higher than in many parts of Europe and in the USA [1, 7].

Concerning death due to delay, we found no risk for the patients who were not weakened by other disease or old age. We found only two patients to have died solely because of tuberculosis; a lower percentage of deaths caused by tuberculosis than in a former autopsy study [8]. Complicating diseases are frequent in the older age groups [9]. This causes a delay in diagnosis and treatment, which can contribute to death [10].

We find the epidemiological problems with the present treatment strategy to be small but not negligible. Alcoholics constitute the greatest problem, because they do not attend follow-up and are often smear positive when they present at hospital. Because of their low treatment compliance and weakened immune-system, they often have relapse of tuberculosis [11]. The epidemiological risk from the initial smear negative but culture positive patients appears to be small. We also found a low incidence of tuberculosis among the hospital employees, as has been found previously [12]. This gives little support to the laboratory finding that the tubercle bacilli are more infectious than usually assumed [13].

The risk of harmful effects to the individual, due to treatment delay, is small if the person can be followed. In alcoholics this surveillance is often difficult, and primary treatment can be preferable.

An international working group has recently presented pertinent proposals for the elimination of tuberculosis. These include use of preventive therapy [14, 15]. However, as the incidence of tuberculosis varies by a factor of 10 even in the industrialized countries of Europe, the treatment policy does not need to be the same throughout Europe.

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