

Empirical treatment for Tuberculosis: Survey of Cases treated over 2 years in a London Area

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Abstract

Objective: To determine factors influencing the decision to treat tuberculosis empirically and its outcome.

Methods: A retrospective survey was done to assess the factors influencing the decision to treat tuberculosis empirically and the effectiveness of such treatment, within a London area. Data on tuberculosis cases treated during 1995-96 (n=218) was collected and analysed.

Results: One hundred and fifty-eight (72.5%) cases of tuberculosis were treated empirically, that is, in the absence of positive smear or histology. Factors suggesting tuberculosis were clinical suspicion, abnormal radiology, elevated Erythrocyte Sedimentation Rate (ESR) and/or C-reactive Protein (CRP), grade 3 or 4 Heaf test, contact or family history, and Heaf conversion. Significantly more Asian [79 of 105 (75.2%); $p < 0.02$] and African patients [61 of 81 (75.3%); $p < 0.05$] were treated empirically as compared to West European patients [14 of 28 (50%)]. Based on logistic regression, any non-European ethnicity carried a significant risk for being treated empirically [OR: 2.7, CI: 1.7-20.8; $p < 0.05$]. Patients requiring revision of diagnosis (n=9) were older [55.7 (s.d. 10.1) vs 32.8 (s.d. 16.0) years; $p < 0.001$]; 6 of them had neoplastic conditions.

Conclusion: In this survey, frequent use of empirical treatment for tuberculosis in non-European patients reflects the physicians' high index of suspicion. Although such therapy is justifiable in selected cases, the proportion requiring revision of diagnosis may be reduced by more thorough investigation, especially in older patients (JPMA 54:88;2004).

Introduction

Empirical therapy for suspected tuberculosis is a common practice worldwide. Local disease prevalence is an important factor linked to the high index of suspicion. True estimates of empirical treatment for tuberculosis are not known. Many cases of suspected tuberculosis in the developed countries are also treated empirically; however, it is not clear as to what factors influence such a decision. Furthermore, factors associated with a clinical response to empirical therapy have not been elucidated. Overwhelming disseminated disease such as military tuberculosis should be treated promptly (empirically) as delay of even a few days adversely affects survival. 1,2 Empirically therapy of less advanced disease may also be appropriate in selected cases.3 Sometimes it is given as a 'last resort' therapeutic trial after extensive negative investigations in a patient with pyrexia of unknown origin. 4,5 This retrospective survey of empirically-treated cases over a period of two years in an area of London with a large ethnic minority seeks to identify the factors related to the decision to give anti-tuberculous chemotherapy on an empirical basis. It also assesses the rationale and success of such practice.

Methods

Study population: All patients treated for tuberculosis at Central Middlesex Hospital, and at Willesden and Wembley chest clinics during 1995 and 1996 were identified from the available case summaries and clinic lists. These years predated the merger in 1998 of Central Middlesex Hospital and Northwick Park Hospital. The patients' medical notes were drawn from the archives by the staff at the 2 clinics and by the administrative staff of the department of respiratory medicine at Central Middlesex Hospital. After excluding those who had chemoprophylaxis against tuberculosis ($n = 130$) and those who were lost to follow-up or moved elsewhere during therapy ($n = 12$), 218 patients treated for tuberculosis through 1995 and 1996 were found suitable for this survey. Three patients who had confirmation of infection with non-tuberculous mycobacterial infection were also excluded. Two patients who developed cervical lymphadenopathy while taking chemoprophylaxis were switched to full treatment. These patients were entered into the study.

Data collection: A case record form was created for data collection. Apart from demographic data, symptoms and signs of disease, and baseline investigations [full blood count, biochemistry, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) level, radiology] additional information regarding response to treatment was gathered. Details of further investigations and revision of diagnosis were recorded for those who did not respond to empirical treatment. The data was entered into the case-record forms and screened for any errors and omissions. To ensure confidentiality, personal details (name, address, phone number, name of the general practitioner) were not included.

Definitions of terms

Ethnic origin: The ethnic origin was assigned to one of the following groups: West European, Asian, African (including Black African, Sub-Saharan African and Afro-Caribbean) and Arabs. Asians comprised the largest group ($n = 105$, with 100 from the Indian Sub-continent) followed by Africans ($n = 81$), West Europeans ($n = 28$) and Arabs ($n = 4$). One patient from Bosnia did not fall into any of the 4 main categories given above. For statistical analysis he was considered 'non-West-European' and placed in the ethnic minorities group along with the Asians, Africans and Arabs. For the sake of clarity, West European patients were simply termed 'European' and patients from other ethnic backgrounds were called 'non-European'.

Empirical treatment of tuberculosis: All patients who were started on treatment for tuberculosis on clinical suspicion in the absence of a positive smear for acid fast bacilli or a biopsy specimen showing caseating granuloma were classed as being treated empirically. Based on the initial 'intention-to-treat', the classification of empirical treatment was not altered if tuberculosis was later confirmed on culture. Two patients who developed cervical adenopathy while receiving chemoprophylaxis and were switched to full treatment were also included in the empirically-treated group. Five patients with initial Heaf grade 0 or 1 were given a repeat Heaf test; three of them with baseline Heaf grade 0 achieved grade 3 on the second test. This was considered by the treating physicians as Heaf conversion (increase of at least 2 grades from the baseline test). These 3 patients were given empirical treatment for tuberculosis after their second Heaf test, hence the new Heaf grade was used for statistical analysis.

Response to treatment: According to the case notes, the treating physicians had taken a number of factors as indicators of a satisfactory response to treatment. These factors, albeit non-specific, included:

- Symptomatic

improvement, such as cessation of fever and night sweats, or decrease in cough, size of lymphadenopathy or cold abscess. • Weight gain. • Resolution of radiographic abnormalities. • Reduction in ESR and/or CRP. Statistical analysis: The data was transferred from the completed case record forms to a computer file (SPSS for Windows, Version 4, SPSS Inc., Chicago, USA). The impact of various factors supporting a provisional diagnosis of tuberculosis [ethnic origin, family or contact history, abnormal radiology, Heaf skin test grade 3 or 4, elevated ESR or CRP, previously treated tuberculosis] on the practice of empirical treatment of tuberculosis and on a successful outcome of such treatment was assessed using Pearson's Chi square test. For dichotomous variables with less than 10 cases in any cell, the Fisher's Exact test was employed. Continuous variables were analysed by Mann-Whitney U test. Multivariate logistic regression was employed to estimate an independent association of factors on the decision to treat patients empirically. These factors included a non-European origin, contact or family history of tuberculosis, abnormal radiology, grade 3 or 4 Heaf test, past history of tuberculosis and a high ESR (children >12mm/hour, adults >20mm/hour) or CRP (>7mmol/L). The cut-off levels for elevated ESR and CRP were according to the respective reference ranges of Central Middlesex Hospital's laboratory.

Results

Of 218 patients who received chemotherapy for tuberculosis during 1995 and 1996, 158 (72.5%) were commenced on treatment empirically, that is, in the absence of a positive smear for acid fast bacilli or histology of a biopsy specimen showing caseating granuloma. The standard treatment regimen consisted of four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) for the first 2 months followed by two drugs (rifampicin and isoniazid) for at least 4 more months. There were 5 cases with drug resistant tuberculosis -4 with isoniazid resistance and one with multi-drug resistance (resistant to rifampicin, isoniazid and streptomycin). The treatment regimens for these cases were modified appropriately following the availability of culture and sensitivity results. Fifteen (9.5%) empirically treated patients subsequently had confirmation of *Mycobacterium tuberculosis* on culture. Based on the principle of 'intention-to-treat', these patients were kept within the empirically treated group. Table I compares the characteristics of patients started on treatment empirically with those who received treatment only after a positive smear or histology. There were no differences between the two groups regarding gender, mean age at presentation, positive Heaf test (grade 3 or 4), history of tuberculosis in the family, previous contact with tuberculosis, or an abnormal chest radiograph. Regarding non-specific disease symptoms, fever as a presenting complaint was less common in the empirically treated group. [(0)] The ESR and/or CRP results were available in 171 cases. One hundred and seventeen (68.4%) of them had elevated values. Only 27 cases had CRP measured; 16 had elevated values. As CRP results were available in a minority, its associations were not analysed separately. The ESR and/or CRP was elevated more often among the confirmed cases (Table 1). There was no significant difference between the two groups regarding the type of disease, with pulmonary disease [108 of 158 (68.4%) versus 41 of 60 (68.3%)] being the most common followed by glandular tuberculosis [63 of 158 (39.9%) versus 25 of 60 (41.7%)]. Five patients had erythema nodosum at presentation, 4 of them were from Indian Sub-

continent and 1 was Black African. Erythema nodosum was associated with pulmonary disease in 4 whereas one had suspected tuberculous dactylitis. Only one of these 5 patients, who had pulmonary disease, was treated after confirmation of diagnosis. Six patients had a history of previous treatment for tuberculosis ranging from 6 months to 27 years ago. Five of them were from India and one was European. All these patients were considered to have relapse of tuberculosis because of new pulmonary and systemic symptoms, and abnormalities suggestive of tuberculosis on the chest radiograph. One of them had confirmation of diagnosis before embarking on anti-tuberculous chemotherapy. Sputum sample of a second patient was culture positive. A majority of patients in this survey ($n = 190$) were of non-European origin. Table 2 highlights the characteristics of European patients and those from other Ethnic backgrounds. There were no differences regarding gender, presence of fever, night sweats or weight loss at presentation, history of contact with tuberculosis, and family history of tuberculosis. The proportion of patients [(1)] who had previous BCG vaccination was similar between the two groups. European patients were significantly older and their Heaf test response was more often grade 0-2. An abnormal chest radiograph at presentation was found more frequently among the European patients. There was a trend for more pulmonary tuberculosis, whether confirmed or suspected, among European patients [22 of 28 (78.5%)] as compared to the non-Europeans [127 of 190 (66.8%)]. In contrast, glandular involvement was significantly more common among the non-Europeans [85 of 190 (44.7%) versus 3 of 28 (10.7%), $p < 0.01$]. Fever as a presenting symptom was associated with pulmonary tuberculosis as compared to non-pulmonary disease (59.3% versus 28.6%, $p < 0.01$). Among non-European patients, 99 of 117 (85.3%) with Heaf grade 3 or 4 and 26 of 31 (83.9%) with a lower Heaf grade were given empirical therapy (NS). In the European group 20 of 28 cases were given a Heaf test. Nine of 11 Europeans with a Heaf grade 3 or 4 were treated empirically as compared to 5 of 9 who had a lower Heaf grade (NS). A significantly higher proportion of patients from non-European ethnic background were treated empirically (Figure). Based on logistic regression analysis, any non-pond to empirical treatment for tuberculosis ($n = 9$). Table 4. Characteristics of patients who did not respond to empirical treatment for tuberculosis ($n = 9$). European ethnicity carried a significant probability of being treated empirically for tuberculosis with Asian patients having a 3-fold risk as compared to Europeans (Table 3). None of the other factors traditionally associated with active tuberculosis showed a statistically significant association with the decision to treat empirically. These included fever or weight loss at presentation, elevated ESR or CRP, a positive Heaf test (grade 3 or 4), family history or contact history of tuberculosis and an abnormal chest radiograph. Patients from ethnic minorities were also compared with European patients regarding the performance (where indicated) of invasive diagnostic tests such as bronchoscopy, pleural aspiration, and lymph node or abscess aspiration. The authors considered bronchoscopy to be of diagnostic value in the presence of an abnormal chest radiograph if: a) sputum was smear-negative, or b) no sputum was available. Six of 18 (33.3%) European patients who apparently needed a diagnostic bronchoscopy had this test as compared to 12 of 111 (10.8%) non-European patients ($p < 0.03$, Fisher's Exact test). For these patients the treating physicians did not include induced sputum sampling in their diagnostic repertoire. There was no statistically significant ethnic difference for the proportion who had diagnostic pleural aspiration (5 of 6 Europeans versus 19 of 26 non-Europeans) and

node biopsy or abscess aspiration (1 of 3 Europeans versus 34 of 60 non-Europeans). Patients from ethnic minorities were similar to the Europeans concerning the recorded chest radiograph abnormalities of pleural effusion, and calcified lesions. However, apical shadowing [16 of 28 (57.1%) versus 61 of 189 (32.3%); $p < 0.05$] and cavitory lesions [8 of 28 (28.6%) versus 10 of 189 (5.3%); $p < 0.001$] were more common among the European patients. Nine empirically treated patients had apparent lack of response leading to a revision of diagnosis, whilst in 5 patients the outcome was unclear from the notes. Table 4 gives the characteristics of these cases along with their revised diagnoses. Of these 9 cases, 6 had neoplastic disease. In 3 patients a new diagnosis was made only after they had completed a standard 6-month course of anti-tuberculous chemotherapy (Table 4). There were no differences between the cases requiring revision of diagnosis and those ($n = 144$) who had apparent clinical response to empirical therapy for tuberculosis regarding non-European ethnicity, fever, history of sweats or weight loss, and presence of abnormalities on chest radiograph (data not shown). However, the non-responders were significantly older [55.7 $\pm$ 10.1 versus 32.8 $\pm$ 16.0 years (mean $\pm$ standard deviation); $p < 0.001$], whilst there was a trend for more sputum positivity [124 of 160 (77.5%) versus 4 of 8 (50%), NS] among those exhibiting a clinical response. Three of 9 cases with revision of diagnosis were current or ex-smokers. Tobacco smoking among the remaining patients was similar (20.1%). Data on the follow-up and outcome of these cases after revision of diagnosis ($n = 9$) was not included in this survey.

Discussion

Although empirical therapy for tuberculosis is a common practice worldwide, there are no reported large studies assessing its prevalence and apparent success or failure. It has been described in case reports or small series.^{4,5} To our knowledge this is the first ever reasonably large survey looking at the practice of empirical treatment for tuberculosis. The area covered by the survey is in Northwest London with a large ethnic minority comprising mainly of Asians from the Indian Sub-Continent, East Africans from Somalia and Ethiopia, and a number of subjects from other parts of Africa. The guidelines for management of tuberculosis, both current and past, give recommendations on investigation of suspected cases, and standard treatment regimens as well as regimens suitable for certain sub-groups.⁶⁻⁹ Although empirical therapy of disseminated, overwhelming infection is universally accepted, such treatment for local or less advanced disease remains controversial.¹⁻³ Hence, respiratory physicians and other specialists treating tuberculosis give empirical therapy to some cases according to their own knowledge, belief and experience, which could lead to considerable variations in practice. The primary aim of this study was to assess whether empirical treatment for tuberculosis could be justified, based on the proportion subsequently requiring a revision of diagnosis. Overall, its justification may be argued as only 9 of 158 (5.7%) empirically treated patients had revision of diagnosis. However, of these 9 cases, 6 had a neoplastic condition where any undue delay in diagnosis could significantly worsen the prognosis. The chances of success of empirical therapy for tuberculosis may be improved by better selection of suitable cases, that is, after more thorough investigation especially of elderly patients, as those who had their diagnosis revised had older mean age compared to those who had an apparent response. The United Kingdom tuberculosis guidelines published

through the early 1990s recommended that in view of increasing incidence of drug-resistance, all suspected tuberculosis patients should be investigated thoroughly for confirmation of diagnosis and for assessment of drug susceptibility. 6,7 In this survey, the level of investigations before resorting to empirical therapy seems inadequate. Certainly, those patients in whom invasive tests such as bronchoscopy, and needle aspiration or biopsy were apparently indicated did not always have these tests. In the current era of guidelines ensuring safe and effective practice, this is perhaps difficult to justify especially in a developed country, even in patients from ethnic backgrounds known to have high disease prevalence. The number of local white cases also treated empirically probably reflects the treating physicians' overall high index of suspicion within an area of a large ethnic mix from countries endemic for tuberculosis. Detection of *Mycobacterium tuberculosis* DNA by amplification techniques, such as the polymerase chain reaction (PCR), have recently become available and offer high levels of sensitivity and specificity. 10,11 None of the cases in this survey had their bacteriological specimens tested by PCR as this technique was undergoing clinical evaluation at the time. The use of PCR in smear-negative patients may increase the diagnostic yield and should now be considered as part of the diagnostic work-up. Certainly, all patients treated empirically for tuberculosis should be followed closely for response. In the event of a lack of response, an alternative diagnosis should be sought within 2 months.³ This simple rule was apparently not adhered to, as only 3 of the 9 cases who did not respond to empirical tuberculosis treatment had revision of diagnosis by 2 months. Worse still, 3 of the remaining 6 patients received a full course (6 months) of anti-tuberculous drugs before a new diagnosis was made. Six of the 9 patients who had revision of diagnosis were given more than 2 months of empirical anti-tuberculosis therapy. According to the case records, there was an apparent lack of response in all of them. Only one patient who was later diagnosed as asthmatic had minor weight gain which may erroneously have been taken as evidence of response. Some of the empirically treated patients may have been given treatment inappropriately, as it is possible they had a self-limiting intercurrent illness, and recovery was erroneously ascribed to the use of anti-tuberculous drugs. For example, 4 of the 5 cases with erythema nodosum at presentation who were treated empirically, might well have had sarcoidosis or even a bacterial respiratory infection. The aims of this study did not include the assessment of validity or likelihood of the diagnosis. Being a retrospective survey, such an assessment would not have been possible anyway. In general, once a patient has been committed to empirical tuberculosis therapy, it is difficult for the treating physician to stop it prematurely. A majority [190 (87.1%)] of patients with a diagnosis of tuberculosis (whether provisional or confirmed) were from non-European ethnicity. This is in keeping with a number of other surveys. A recent survey for England and Wales reported a high annual incidence of tuberculosis among the population from the Indian Sub-continent (121 per 100,000) as compared to the white population (4.38 per 100,000). 12 Another study highlighted a significant risk for tuberculosis among Asians if they were originally born in their home country of either India or Pakistan. 13 Parslow and colleagues raised concern that the high incidence of tuberculosis among ethnic minorities in the United Kingdom is linked to deprivation and population density. 14 However, none of these surveys addressed the issue of empirical treatment for tuberculosis, especially in relation to ethnicity. In this survey, based on logistic regression analysis, a non-European ethnicity had a significant independent

association with empirical therapy (Table 3). In the absence of any other significant difference between the patients who had therapy after confirmation of diagnosis and those who were treated empirically, a non-European ethnicity assumes prime importance in the physician's index of suspicion for tuberculosis. It is likely that a similar strong association between ethnicity and clinical suspicion of tuberculosis resulting in more frequent empirical treatment exists in other areas of United Kingdom with large ethnic minorities. A Heaf test response of grade 3 or 4 had a significant association with non-European ethnicity on univariate analysis but it did not achieve statistical significance in the logistic regression model. There was no significant difference between the European and non-European patients regarding family or contact history for tuberculosis, and raised ESR or CRP. These results may in part be due to the fact that this survey is retrospective and there is incomplete data concerning these variables (Tables 1 and 2) causing an apparent lack of effect. There was a trend for cough recorded more often among the European patients. This is in keeping with the fact that Europeans were more likely to have pulmonary disease whereas patients from other ethnic backgrounds often had non-pulmonary involvement. All the 9 patients who had revision of diagnosis were over 40 years of age (range 41 to 73, Table 4) and had a significantly higher mean age as compared to those who improved on empirical therapy (55.7 versus 32.8 years). Atypical disease presentations, often with non-specific symptoms, are well recognised in the older patients resulting in a wide differential diagnosis.^{5,15} Hence it is not surprising that those requiring a revision of diagnosis in this study were older, 6 of them aged 55 or over. Of greater concern is the fact that on re-investigation internal malignancy was a common finding among them. In contrast to these observations, a delay in diagnosis of tuberculosis in the elderly has also been highlighted previously.¹⁶ The data analysed in this study is not very recent. Nevertheless, the authors believe that factors associated with empirical therapy for suspected tuberculosis in areas of United Kingdom with high proportions of ethnic minority populations would not have altered over the years. Certainly, guidelines, as they have evolved, have become more elaborate but they still do not clearly define the place of empirical therapy except in cases with overwhelming or life-threatening infection.^{6,7} One would, however, expect improvements in diagnostic work-up and in follow-up for therapeutic response within the current practice. In conclusion, this survey suggests that empirical treatment for tuberculosis may be a common practice in the United Kingdom in areas with large ethnic minority populations. Empirical therapy among non-European patients seemed to reflect the treating physicians' high index of suspicion, as it could not be explained by differences in other historical and clinical disease parameters. It may be justified in selected cases after exclusion of other possible diagnoses to a reasonable degree. Older patients suspected of tuberculosis are more likely to have an alternative diagnosis and need thorough investigation.

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