# Efficacy of the Conventional Diagnostic Approach to Pulmonary Tuberculosis

N K Chin, G Kumarashinge, T K Lim

## ABSTRACT

<u>Objective:</u> The aim of this study was to evaluate the efficacy of the current clinical approach to the diagnosis of culture positive pulmonary tuberculosis (PTB) in hospitalised adult patients.

<u>Method:</u> We examined the case records and chest X-rays (CXR) of 199 adult patients with culture positive PTB diagnosed from 1993 to 1995. Patients were divided into two groups: early treatment (ET) and delayed treatment (DT) of PTB. DT were patients who received treatment only after respiratory specimens had returned with positive culture results. We also compared the CXR of the DT group with a group of age, sex matched patients who did not have PTB (control). Usual CXR pattern for PTB was defined as : upper lobe acinar shadows, upper lobe cavitation or miliary pattern.

<u>Results:</u> There were 199 patients with a mean age of 56 (19). One patient was HIV antibody positive and 27% were diabetics. There were 143 (72%) patients in the ET group and 56 (28%) in the DT group. The ET group was significantly younger and more likely to show usual features and cavitary disease on the CXR than the DT group. The diabetic patients had significantly more frequent cavitation than non-diabetics. When compared to a control group without PTB, the DT group was significantly more likely to show usual CXR pattern and less likely to have a clear CXR.

<u>Conclusions:</u> The conventional approach to the diagnosis of PTB is reasonably accurate and efficient enough for the majority of patients. The delay in the diagnosis and treatment of PTB was more common among elderly patients, patients with negative smear results and atypical CXR features. If PTB is suspected in elderly patients, an early decision should be made between empiric treatment and further diagnostic testing.

Keywords: pulmonary tuberculosis, delayed diagnosis, radiographic findings, elderly

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## INTRODUCTION

The global impact of the resurgence of tuberculosis in the past decade is well documented and should be widely appreciated[1,2]. Tuberculosis is the leading infectious disease causing deaths among adults in the world, accounting for 25% of avoidable adult deaths in the developing world[3]. The World Health Organisation estimates in its 1995 report on tuberculosis, that one-third of the world's population is already infected with it, an additional 300 million people will be infected in the coming decade and 30 million will die from it[4].

In Singapore, the problem may not appear to be of epidemic proportion with the incidence of new cases at about 50/100,000 population per year in 1990[5]. This annual incidence had decreased at about 5.8% each year from 1960 to 1990[5]. The rate of decline in annual incidence however had slowed down over the past five years and is a cause for concern[6]. The two main reasons for this slow down in the decrease of new case incidence are firstly, demographic change with reactivation of disease among a rapidly aging local population (and its attendant loss of cell-mediated immunity) which had acquired the infection decades earlier (when the disease prevalence was much higher) and secondly, an increase in the proportion of new cases from non-residents seeking employment in Singapore's rapidly expanding economy, who arrive from neighbouring countries with a much higher prevalence of tuberculosis than Singapore (increasing from 14% in 1990 to 27% in 1995)[6-8].

Tuberculosis is an airborne infection. The respiratory tract is the primary site of infection and also the most important route for transmission of the disease. Thus the key to overall control of tuberculosis is early detection and effective treatment of pulmonary tuberculosis (PTB). While a number of molecular techniques for the rapid amplification of nucleic acids from mycobacteria have been developed, their role in the routine diagnosis of PTB is undefined[9-12]. They incur additional costs, introduce new types of errors and have not been thoroughly evaluated in clinical studies[13]. The current approach to the diagnosis of PTB will therefore continue to rely upon the traditional instruments of clinical assessment, plain chest X-rays (CXR) interpretation, microbiological and histological examination of tissue from patients for *Mycobacterium tuberculosis*[14].

This study describes the efficiency of the current diagnostic approach to PTB in adult in-patients in Singapore. We also examined the factors associated with delay in the diagnosis and treatment of culture positive cases of PTB.

## METHODS

We reviewed the case notes and CXRs of all adult in-patients with culture positive PTB who had been admitted to the National University Hospital from

January 1993 to August 1995. The patients were identified from the records of the Microbiology Department. Patients who registered positive cultures for *Mycobacterium tuberculosis* from respiratory tract specimens were studied. These included specimens from sputum, broncho-alveolar lavage, pleural fluid, lung, pleural and relevant lymph node biopsies. All patients with diagnosis made from cervical lymph node and liver specimens also had pulmonary disease consistent with PTB. All routine cultures for mycobacteria in Singapore were performed at a single laboratory using the Bactec 460 radiometric system (Becton Dickinson Diagnostic Instrument Systems, Towson, MD)[15]. This is a rapid, automated culture technique in liquid medium which yields positive results within 3 weeks in almost all cases. The Bactec culture system was however located in another hospital and the transfer of specimens and collation of results by two microbiology departments in different hospitals entailed additional 2 – 3 weeks (a total delay of 5 – 6 weeks) before positive cultures were noted by the house doctor, the patients recalled and appropriate treatment started.

The following items were collated for each patient: (1) The dates when the first culture positive specimens were sent; (2) the dates of commencement of anti-tuberculosis treatment, and (3) the basis on which the anti-tuberculous treatment was started. The patients were divided into two groups: early treatment (ET) and delayed treatment (DT). The ET group consisted of patients who were treated for PTB before cultures were returned positive. The ET group included patients who had positive results on Ziehl-Neelsen staining(Z-N) or granuloma demonstrated on tissue biopsies and patients who were started on anti-tuberculous treatment on an empiric basis. The DT group consisted of patients who received anti-tuberculous treatment only after return of positive culture results.

All CXRs were reviewed by the two authors (NKC and TKL). Usual CXR features for PTB were defined as : upper lobe acinar shadows, upper lobe cavitation or miliary pattern. Since not all patients had lateral views, we only assessed the radiologic features from the standard postero-anterior CXR films.

Since CXR is a key screening test for the presence of PTB, we looked for radiologic features in the DT group of patients which might differentiate them from those patients who did not have PTB. We thus compared the CXR features of patients in the DT group with an equal number of randomly selected, age and sex matched patients (control) admitted over the same period who did not have PTB. The control group was selected from patients who had respiratory specimens taken for mycobacterial culture, and who were suspected to have tuberculosis, but returned negative results and did not have tuberculosis on review of their case notes.

**Statistics**

All results were expressed as mean (SD) values. Continuous variables were compared with unpaired Student's t-tests where appropriate while the chi square was used to test for differences between proportions. The conventional value of 5% was accepted as statistically significant.

**RESULTS**

There were 199 patients with PTB confirmed on culture during the study period. Their mean age was 56 (16) years with a median of 61 years ranging from 17 – 93 years; 28% were women. Only one patient, a 25-year-old man from a neighbouring country with diffuse lymphadenopathy and disseminated disease was HIV antibody positive. No other patient showed features of acquired immunodeficiency syndrome or a concurrent opportunistic infection. The different sensitivities of microscopic examination for Z-N positive bacilli in lung secretions and granuloma in pleural biopsy specimens are shown in Table I Caseating granuloma (with or without positive Z-N staining) were also demonstrated in cervical lymph nodes (n = 3), lung and liver tissue biopsied from other patients. The sensitivity of direct microscopic examination for the whole group was 47% (93/199): 79 patients had positive Z-N staining (40%) and 14 patients (7%) had granulomas.

There were 143 patients (72%, the ET group) who received anti-tuberculous drug treatment before results of positive cultures were available. In this ET group, 89 patients (45% of all 199 cases) were administered treatment on the basis of either positive Z-N staining and/or granulomas demonstrated on examination of respiratory tissue while another 54 (27% of all 199 cases) patients received treatment on an empiric basis without definitive bacteriological confirmation of infection. Ten patients in the ET group had pleural tuberculosis. The remaining 56 patients (28%, DT group) received treatment only after their culture results returned positive. Four patients in this group had positive Z-N stains in the sputum but did not receive appropriate treatment until positive cultures were noted many weeks later. This was the result of errors in transcription of information from the microbiology department. Thus while 147 patients (74%) had an early diagnosis of PTB, due to clerking errors, only 143 patients (72%) actually received early treatment (the ET group). Nine patients in the DT group (4.5%) died before treatment commenced.

All patients in the ET group received specific treatment within 21 days from the date when the first culture-positive specimen was collected. This interval was above 21 days for all DT group of patients. The mean (SD) number of days between the date when the first culture positive specimens were collected and the date when anti-tuberculosis treatment was started was 1.6 (3.6) days for the ET group and 45 (20) days for the DT group.

Fig 1 shows the relationship between delay in diagnosis of PTB with increasing age. There was a marked rise in the proportion of patients in whom the diagnosis of PTB was delayed among the elderly. Table II shows the demographic data, incidence of diabetes mellitus, results of Z-N staining and CXR

## Table I – Sensivity of Z-N staining (lung secretions) and histology (pleural biopsy)

|  | Positive | No. of patients | Sensivity |
|---|---|---|---|
| Expectorated sputum | 62 | 171 | 36% |
| Induced sputum | 5 | 31 | 16% |
| Broncho-alveolar lavage | 14 | 29 | 48% |
| Pleural biopsy | 9 | 10 | 90% |

Positive test: Acid fast bacilli shown on Z-N (Ziehl-Neelsen) staining for lung secretions and granuloma demonstrated in pleural biopsies.
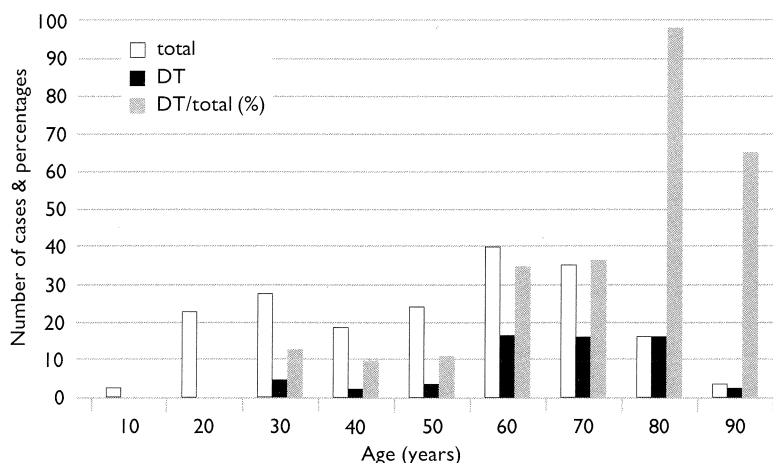


Fig 1 – This figure shows the incidence of PTB in the different decades of life (open bars). The number of patients in each decade in whom the treatment of PTB was delayed until mycobacteria was isolated in culture (DT group) are represented by the black bars. The percentage of patients in the DT group in each decade are represented by the gray bars.

## Table II – Demographic data, incidence of diabetes, positive Z-N stain and CXR features

|  | Total | ET group |  | DT group |
|---|---|---|---|---|
| Numbers | 199 | 143 |  | 56 |
| Age (years) | 56 (19) | 52 (18) | * | 68 (14) |
| Sex ratio (M:F) | 143:56 | 103:40 |  | 40:16 |
| Incidence of diabetes (%) | 27 | 28 |  | 23 |
| Positive Z-N stain (%) | 40 | 53 | * | 7 |
| Cavitation on CXR (%) | 24 | 30 | * | 7 |
| Usual CXR (%) | 50 | 62 | * | 20 |

Z-N : Ziehl-Neelsen (expectorated, induced sputum and broncho-alveolar lavage specimens), CXR : chest X-rays, ET : early treatment, DT : delayed treatment. Usual CXR : upper lobe acinar shadows, upper lobe cavitation or miliary pattern.
* : statistically significant difference between the ET and DT groups at the 5% level. The comparison was made with unpaired Students' t-test for age and the chi-square test for percentages.

features for the whole group (n = 199), ET (n = 143) and DT (n = 56) groups of patients. The ET group was significantly younger, had significantly higher incidence of the usual radiologic features of PTB and cavitary disease on the CXR than the DT group.

There were 81 (41%) elderly patients aged ⩾ 65 years. This elderly group of patients were significantly less likely to show positive Z-N staining (31% vs 46%, $\chi^2$ p = 0.034) and usual features of PTB on CXR (30% vs 46%, $\chi^2$ p < 0.001) in comparison with the group of patients aged < 65 years.

There were 53 patients (27%) with diabetes mellitus. There was no significant difference between diabetic and non-diabetic patients in age and sex ratios. The diabetic patients had significantly higher incidence of cavitation on CXR (38% vs 19%, $\chi^2$ p = 0.007) but a similar incidence of usual pattern for PTB on CXR (57% vs 65%) and also similar proportion of patients in the DT group (25% vs 29%) when compared to non-diabetics. The diabetic patients did not show a higher incidence of mid or lower zone disease on CXR than non-diabetics.

When compared with a sex and age matched group of patients who were initially suspected to have PTB but eventually found not to have active disease (control), the DT group was significantly more likely to show the usual CXR pattern for PTB and less likely to have a clear CXR (Table III).

## DISCUSSION

The conventional approach resulted in early diagnosis of PTB in 147 (74%) patients. This included 143 patients in the ET group where treatment was started early and four patients with positive sputum smear results which were not acted upon. Overall however, there was minimal delay and treatment was instituted in this group well within the first week in the vast majority of patients.

We found that clinically, the diagnosis was initially missed in nearly 30% of hospitalised patients with culture-positive PTB. A missed diagnosis resulted in a delay on the average of over 6 weeks before appropriate treatment was instituted following notification of positive culture results from the laboratory. This delay, with its attendant risks of increasing patient morbidity, mortality and disease transmission in the hospital and community, would have been even greater if the rapid Bactec isolation technique had not been employed routinely. This was despite the broad awareness among housestaff and attending physicians in our hospital, that tuberculosis is a relatively common disease and may have non-specific clinical and radiological presentation. Patients with sputum smear-negative PTB however, are less infectious than those with stain-positive culture and thus may pose less of a threat to the community. There are many factors which may be responsible for delay in the diagnosis and treatment of PTB. The two main reasons are failure to obtain a positive Z-N stain on examination of respiratory secretions (usually sputum) and failure to institute early empiric anti-tuberculous treatment in patients with suspected PTB.

The incidence of positive Z-N staining in this study (40%) was lower than in some other similar studies which reported positive results in 50% – 80% of hospitalised patients[16,17]. This is partly accounted for by the low incidence of cavitary lung disease in our patients (24%) since positive smear results are associated with advanced cavitary disease and high bacterial density. Another reason for the relatively lower sensitivity of the Z-N test in our patients is the poor quality of sputum specimens obtained from patients.

**Table III** – Radiographic features of DT and control groups (n = 56 for both groups, percentages in parenthesis)

|  | DT group | Controls | p |
|---|---|---|---|
| Incidence of diabetes | 23% | 28% | ns |
| Usual CXR | 11 (20) | 3 (5) | 0.03 |
| Mid-lower zone disease | 11 (20) | 15 (27) | ns |
| "Old" PTB | 9 (16) | 7 (12.5) | ns |
| Mass lesion | 7 (13) | 3 (5) | ns |
| Diffuse infiltrates | 10 (18) | 10 (18) | ns |
| Pleural effusion | 4 (7) | 5 (9) | ns |
| Clear lungs fields | 4 (7) | 13 (23) | 0.02 |

Z-N : Ziehl-Neelsen, CXR : chest X-rays, DT : delayed treatment. Controls : Patients who did not have PTB (look under Methods), Usual CXR : Upper lobe acinar shadows, upper lobe cavitation or miliary pattern, "Old" PTB : fibrotic scars (with/without calcification) consistent with healed and inactive PTB. The chi-square was used to test for differences between proportions.

While at least 3 sputum specimens were routinely requested, precautions were not instituted to ensure that only sputum was collected and processed instead of saliva. Moreover, many elderly patients had little cough or were unable to produce a well expectorated specimen. Lower respiratory tract secretions may be obtained non-invasively, safely and relatively inexpensively by using the inhalation of hypertonic saline to induce sputum production and provoke the cough reflex[18,19]. We found however, that Z-N staining of induced sputum specimens had a relatively low sensitivity (16%, Table I). This concurs with the 19% reported by Anderson et al[19]. We are therefore uncertain if more widespread application of sputum induction would increase the overall sensitivity of the sputum smear test. Sampling of lower respiratory tract secretions with fiber-optic bronchoscopy is another alternative[19-24]. In this study, Z-N staining of lung lavage specimens obtained by fiber-optic bronchoscopy was positive in 48%. The sensitivity of staining for mycobacteria in bronchoscopically obtained specimens is highly variable and dependent upon the stage of the disease. It may even be lower than staining induced sputum as in the study reported by Anderson et al who compared sputum induction with bronchoscopy (19% versus 12% respectively)[19] In general, the diagnostic yield of bronchoscopy is higher in patients with more advanced disease. Charoenratanaukul et al, in a study of patients with mild disease, suggested that the diagnostic yield of bronchoscopic examination may be increased with transbronchial biopsy of suspected lung segments (the sensitivity of staining lung lavage specimens in their study was only 7.5%)[24]. Bronchoscopy is an expensive, invasive procedure with potential risks of serious complications. We do not feel that the routine use of fiberoptic examination is appropriate in all patients with suspected PTB who return negative smear results. Fiberoptic bronchoscopy may be considered however in patients with more advanced disease.

With regards to processing the sputum, we did not use any concentration technique such as digestion and centrifugation nor did we use fluorescent microscopy. It has not been proven conclusively however that these more expensive and time-consuming technical refinements are superior to direct microscopy for sputum examination. A wide range of molecular techniques which amplify mycobacterial nucleic acids are currently under evaluation for the rapid diagnosis of tuberculosis[9-13]. Inter-laboratory quality control studies suggest that these tests are poorly standardised and may not be reliable enough for routine application[25-27]. Their role in the routine diagnosis of PTB thus remains undefined.

Empiric treatment without bacteriologic confirmation was administered in 27% of patients in this study. The decision to treat empirically was made early in the clinical course of the patients, usually within the first week. This readiness to treat presumptively for PTB is encouraging[17,28]. The key to early empiric treatment is accurate interpretation of CXR findings. There were highly significantly differences in CXR findings between the ET and DT groups of patients (Table II). There were also significant differences between the CXR findings of the DT group and a group of sex, age matched patients who did not have PTB (Table III). The differences in CXR findings between patients who did not have PTB and the DT group of patients were small, relevant only to a minority of the patients and there was considerable overlap between the two groups (Table III). Even in retrospect, 80% of our patients in the DT group did not present with the usual features suggestive of PTB on their CXRs. For most patients who had a delayed diagnosis, the probability of active PTB, based primarily upon interpretation of CXR features, had obviously not reached the threshold at which treatment should be started and further testing was no longer appropriate[29-31]. It is not known if more sophisticated imaging techniques, in particular computed tomography (CT), would improve the radiologic diagnosis of PTB. Cavitary disease is more easily detected on CT examination than CXR. Hatipoglu et al showed recently that high resolution CT examination discriminated active broncho-pulmonary tuberculosis from post-tuberculous fibrosis better than CXR[32]. High resolution CT may be particularly useful in patients who show intermediate CXR features at the early stage of the disease. Im et al have shown in a study of patients with early active PTB, that 2 – 4 mm nodular branching structures in the centrilobular areas are seen in over 90% of cases[33].

The tuberculin skin test has limited value in the diagnosis of active PTB in Singapore. The BCG vaccine is universally administered to infants and school children. This results in false positive tests in young adults. By contrast, the older population grew up in an environment where PTB was highly prevalent. Thus, positive tuberculin tests are common in older healthy people in Singapore who had acquired the infection in their youth but do not suffer from the disease.

In this study, we found that the diagnosis of PTB was very frequently delayed or missed completely in elderly patients. This is an observation which had been made by many previous studies[34-38]. The clinical

manifestations of tuberculosis in the elderly are varied, atypical and often confounded by poor recall of history and signs of co-existing chronic cardio-respiratory illnesses. We have also shown that the elderly patients were significantly less likely to return positive results on Z-N staining and more likely to present with atypical features on the CXRs. All these factors contribute to a high degree of uncertainty in the diagnosis of PTB in many older patients. A high index of suspicion should be maintained for the possibility of PTB in older patients who present with abnormalities on the CXRs. Repeat samples of properly expectorated sputum should be examined for acid-fast bacteria. With the exception of patients with minimal disease on the CXRs, in elderly patients who return negative smears, a choice should be made between starting empiric anti-tuberculous treatment and further diagnostic testing early in the clinical course of the disease. These additional tests should be selected on an individual basis and may include high resolution CT scanning for patients with early disease or fiber-optic bronchoscopy for more advanced disease. There is a place however, for patients with non-progressive and mild disease to wait 3 to 4 weeks for the results of Bactec cultures.

Kim et al have shown that diabetic patients are five times more likely to acquire active PTB than non-diabetics[39]. Conversely, as seen in this study, diabetes mellitus is a common co-morbid condition among patients with PTB. It had been suggested that atypical radiographic features of PTB such as lower lung field predominance are more frequently encountered among diabetic than non-diabetic patients[40-43]. More recent reports, and the results of this study show that diabetic patients do not present more frequently with CXR features which are atypical of PTB[44,45]. Moreover, we have also confirmed the findings made by Ikezoe et al using CT imaging that cavitary disease is more common among diabetic patients[46]. The presentation of PTB with typical CXR features among diabetic patients account for the observation that the diagnosis of PTB was made with comparable ease between diabetic and non-diabetic patients in this study.

Co-infection with HIV has a major impact on the epidemiology, bacteriology, immunology, clinical manifestations and prognosis of PTB. Only one of our patients was HIV antibody positive, thus the results of this study are representative of patients infected with *Mycobacterium tuberculosis* alone.

We conclude that the conventional approach in the diagnosis of PTB is reasonably accurate and efficient enough resulting in early treatment for the majority of patients. The diagnosis and treatment of PTB is however often delayed in older patients who tend to show negative results on Z-N staining of sputum and findings on the CXR which are not typical of PTB. There should be a high index of suspicion for the presence of active PTB in elderly patients with abnormal CXRs. A decision on whether to start empiric treatment, proceed with more testing or await the results of culture studies should be made early in the course of their illness.

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