ORIGINAL ARTICLE

Delayed Suspicion, Treatment and Isolation of Tuberculosis Patients in Pulmonology/ Infectious Diseases and Non-Pulmonology/ Infectious Diseases Wards

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Background/Purpose: Delayed diagnosis and isolation increases the risk of nosocomial transmission of tuberculosis (TB). To assess the risk of delayed management of TB, we analyzed the risk factors of prolonged delay in isolation of smear-positive TB patients in pulmonology/infectious diseases and other wards in a tertiary teaching hospital.

Methods: We enrolled smear-positive TB patients aged > 16 years with delayed respiratory isolation following hospitalization. Medical records were reviewed retrospectively. Time intervals between admission, order of sputum acid-fast staining, initiation of anti-tuberculous treatment and isolation were compared between pulmonology/infectious diseases wards (PIWs) and other wards. Risk factors were analyzed in patients with prolonged isolation delay of > 7 days in individual groups.

Results: Isolation was delayed in 191 (73.7%) of 259 hospitalized smear-positive TB patients. Median suspicion, treatment and isolation delays were 0, 3 and 4 days in PIWs and 1, 5 and 7 days in other wards. For patients admitted to non-PIWs, atypical chest radiographs, symptoms without dyspnea or not being admitted from the emergency department (ED) were risk factors for prolonged isolation delay exceeding 7 days. The only risk factor for delayed isolation in patients admitted to PIWs was age ≥ 70 years.

Conclusion: Delays in suspicion, treatment and isolation of TB patients were longer in non-PIWs. Clinicians should be alert to those admitted to non-PIWs with atypical chest radiographs, atypical symptoms, or not admitted from the ED. [*J Formos Med Assoc* 2009;108(3):202–209]

Key Words: cross infection, emergency service, hospital, infection control, tuberculosis

Minimizing transmission of tuberculosis (TB) in health care facilities is vital for controlling tuberculosis. Outbreaks of nosocomial TB have been reported frequently.[1–4] TB is endemic in Taiwan. In 2004, 24,161 TB cases were notified, 17,142 were confirmed, and 957 TB-related deaths occurred.[5,6] The notification rate of TB in that year was 75.6 per 100,000 population, a rate 15.1 times higher than in the United States.[7] In 2003, an outbreak of nosocomial transmission of *Mycobacterium*

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tuberculosis was discovered through screening for severe acute respiratory syndrome (SARS) in a hospital in northern Taiwan.[8]

Guidelines for TB infection control published by the US Center for Disease Control and Prevention (CDC) have been implemented widely in health care facilities in the United States.[9] The results have been readily apparent in the decreased number of TB outbreaks and transmission of *M. tuberculosis* to patients and health care workers (HCWs) in health care facilities.[10–12] The CDC guidelines recommend calculating the time intervals from admission to suspicion, diagnostic procedures, isolation and initiation of effective anti-tuberculous chemotherapy as an important part of infection control programs.[9,10]

The risk of exposure to TB is thought to be higher in pulmonology/infectious diseases wards (PIWs) because of the larger number of contagious patients managed in these departments. In addition, infectious disease specialists and pulmonologists are more familiar with the symptoms of TB, and are more alert to its radiographic findings. As a result, TB patients are more likely to be diagnosed earlier in PIWs. We therefore hypothesized that delayed diagnosis, treatment and isolation may be shorter in these departments.

Here, time intervals were calculated, and risk factors for delayed isolation of adult TB patients with positive sputum acid-fast staining (AFS) were analyzed to evaluate the risk of unprotected exposure to TB in a tertiary hospital in northern Taiwan. The computed intervals in PIWs and non-PIWs were compared, and risk factors for prolonged isolation delay in these two groups were analyzed.

Methods

Patients

At Linkou Chang-Gung Memorial Hospital (CGMH), a 3500-bed tertiary teaching hospital in northern Taiwan, 800–1000 cases of TB are reported annually. Hospitalized smear-positive TB patients aged > 16 years with delayed isolation were included in this study. The patient list was obtained from the Committee for Infection Control of CGMH. Medical records were retrospectively reviewed. There were 1880 patients reported with TB at CGMH between July 2002 and September 2004. As a result of the limited number of available negative-pressure isolation rooms, most of the reported TB patients were not hospitalized and were managed in the outpatient clinics. Only 259 (13.7%) patients with positive sputum AFS and cultures were hospitalized. Delayed isolation was defined as patients with positive AFS and *M. tuberculosis* cultures in respiratory tract specimens who were not transferred to negative-pressure isolation rooms immediately after admission. Prolonged isolation delay was defined as patients with delayed respiratory isolation that exceeded 7 days after admission.

We classified all patients as PIW (pulmonology and infectious diseases wards) and non-PIW (other hospital wards including non-pulmonary/infectious diseases medical wards or non-medical wards). This study was approved by the Ethics Committee of CGMH.

Data collection

The collected demographic data included gender, age, comorbidity, initial symptoms and ward of admission. Chest radiographs at admission were reviewed for the existence of predominant upper lobe lesions, cavitations or miliary lesions. Atypical chest radiographs for TB were defined as those with none of the above findings. Comorbidity included diabetes mellitus, chronic renal insufficiency (serum creatinine > 2.0 mg/dL) or end-stage renal disease, cancer, hematologic diseases, autoimmune diseases, neurologic disorders, and use of immunosuppressive drugs or corticosteroids. The initial symptoms including cough, sputum, fever, shortness of breath, hemoptysis, body weight loss, or fatigue were recorded. Dates of available chest radiograph after admission, ordering of sputum AFS, initiation of anti-tuberculous chemotherapy and date of isolation in negative-pressure room were also collected. The intervals between admission and ordering of AFS, admission

and initiation of anti-tuberculous chemotherapy, admission and respiratory isolation, and between ordering of sputum AFS and isolation were calculated. Whether sputum AFS was ordered at the emergency department (ED) was recorded in patients admitted from the ED. The admission–chest radiograph and admission–AFS intervals were defined as day 0 if chest radiograph or sputum AFS were ordered before admission (e.g. ordered at the ED).

Statistical analysis

The characteristics of patients with delayed isolation in the PIW and non-PIW groups were compared by independent t test for continuous variables and χ^2 or Fisher's exact test for categorical variables. The days between different interventions were non-parametric data and compared by Mann–Whitney U test. The cumulative proportion of patients isolated after admission was calculated by the Kaplan–Meier method. Multiple logistic regression analysis by stepwise procedure was used to explore predictors for prolonged isolation delay in individual groups. The dependent variable was whether delayed isolation exceeded 7 days. Independent variables included age, gender, comorbidity, initial symptoms, findings on chest X-ray, and status of AFS order at the ED. The analysis was performed for all the subjects and for two groups (PIW and non-PIW) separately. In addition, the interaction between admission ward and the above factors was included in the regression model for the whole population. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered statistically significant.

Results

Demographics

One hundred and ninety-one (73.7%) of 259 hospitalized AFS-positive pulmonary TB patients experienced delayed isolation during the study period. Their average age was 65.0 ± 17.0 years and 151 (79.1%) were male (Table 1). The most

frequently associated comorbidity was diabetes mellitus, chronic lung disease, chronic renal insufficiency, cardiovascular diseases, neurologic diseases, and malignancy. Most comorbidity was of a similar proportion between the two groups, except that more patients presented with malignancy and neurologic diseases in the non-PIW group. More patients in the PIW group presented with fever and respiratory symptoms, including cough, hemoptysis and sputum production, but no difference was found in dyspnea, weight loss or fatigue between the two groups.

The most frequent finding on chest radiographs was predominant upper lobe lesions. Nevertheless, there was no statistically significant difference in the proportion of patients with predominant upper lobe lesions, cavitations or miliary lesions on chest radiographs between the PIW and non-PIW patients. Thirty-four percent of patients with delayed isolation presented with atypical chest radiographs without any predominant upper lobe lesions, cavitations or miliary lesions. The percentage of patients who presented with atypical chest radiographs for TB was higher, but not significantly, in the non-PIW group (27.6% vs. 40.9%; $p = 0.07$).

Among the 191 patients with delayed isolation, 170 (89.0%) patients were admitted from the ED. TB was suspected and sputum AFS had been ordered at the ED in 67 of 170 (35.1%) patients. The proportion of patients with sputum AFS ordered at the ED was significantly higher in the PIW group (50.0% vs. 19.4%; $p < 0.001$).

Management intervals before isolation

The median intervals from admission to ordering of sputum AFS, initiating anti-tuberculous treatment, and respiratory isolation were 1, 4 and 5 days, respectively (Table 2). The intervals between admission and different interventions were all shorter in the PIW than in the non-PIW group, including intervals from admission to AFS order, admission to initiation of anti-tuberculous chemotherapy, and from admission to isolation. The interval from chest radiography to ordering sputum AFS was also shorter in the PIW group.

Table 1. Characteristics of 191 patients with delayed respiratory isolation between July 2002 and September 2004 in Linkou CGMH (*p* values indicate the differences between the two groups)

	Total (*n* = 191)	PIW (*n* = 98)	Non-PIW (*n* = 93)	*p*
Age (yr)	65.0 ± 17.0	62.8 ± 18.5	67.3 ± 15.0	0.07
Male gender	151 (79.1%)	73 (74.5%)	78 (83.9%)	0.11
Associated comorbidity				
Diabetes	56 (29.3%)	23 (23.5%)	33 (35.5%)	0.07
Chronic renal insufficiency	30 (15.7%)	12 (12.2%)	18 (19.4%)	0.18
Chronic lung diseases	26 (13.6%)	17 (17.3%)	9 (9.7%)	0.12
Cardiovascular diseases	22 (11.5%)	11 (11.2%)	11 (11.8%)	0.90
Neurologic diseases	20 (10.5%)	6 (6.1%)	14 (15.1%)	0.04
Malignancy	20 (10.5%)	5 (5.1%)	15 (16.1%)	0.01
Liver cirrhosis	9 (4.7%)	2 (2.0%)	7 (7.5%)	0.09
Autoimmune diseases	7 (3.7%)	1 (1.0%)	6 (6.5%)	0.06
Coal miner	3 (1.6%)	2 (2.0%)	1 (1.1%)	0.60
Chronic steroid use	1 (0.5%)	0	1 (1.1%)	0.49
Hematologic diseases	1 (0.5%)	0	1 (1.1%)	0.49
Drug abuser	1 (0.5%)	1 (1.0%)	0	1.00
Symptoms				
Cough	104 (54.5%)	73 (74.5%)	31 (33.3%)	< 0.001
Fever	94 (49.2%)	56 (57.1%)	38 (40.9%)	0.03
Sputum	72 (37.7%)	48 (49.0%)	24 (25.8%)	0.001
Hemoptysis	16 (8.4%)	14 (14.3%)	2 (2.2%)	0.003
Dyspnea	66 (34.6%)	39 (39.8%)	27 (29.0%)	0.12
Body weight loss	43 (22.5%)	21 (21.4%)	22 (23.7%)	0.71
Fatigue	47 (24.6%)	21 (21.4%)	26 (28.0%)	0.30
Chest radiographs				
Predominant upper lobe lesion	114 (60.0%)	64 (65.3%)	50 (54.3%)	0.12
Cavitation	13 (6.8%)	8 (8.2%)	5 (5.4%)	0.57
Miliary lesion	12 (6.3%)	7 (7.1%)	5 (5.4%)	0.77
Atypical for TB (none of the above)	65 (34.0%)	27 (27.6%)	38 (40.9%)	0.07
Sputum AFS ordered at ED				< 0.001
Yes	67 (35.1%)	49 (50.0%)	18 (19.4%)	
No	103 (53.9%)	39 (39.8%)	64 (68.8%)	
Not admitted from ED	21 (11.0%)	10 (10.2%)	11 (11.8%)	

Table 2. Days between different managements, compared between patients admitted to PIWs or non-PIWs*

	All (*n* = 191)	PIW (*n* = 98)	Non-PIW (*n* = 93)	*p*
Ad to CXR	0.3 ± 1.1 (0, 0–10)	0.1 ± 0.6 (0, 0–5)	0.5 ± 1.4 (0, 0–10)	0.004
CXR to AFS	3.3 ± 5.3 (1, 0–33)	2.1 ± 3.5 (1, 0–18)	4.6 ± 6.4 (2, 0–33)	< 0.001
Ad to AFS	2.5 ± 4.8 (1, 0–31)	0.9 ± 2.2 (0, 0–15)	4.2 ± 6.1 (1, 0–31)	< 0.001
Ad to anti-TB	5.8 ± 6.0 (4, 1–39)	4.1 ± 4.0 (3, 1–24)	7.6 ± 7.1 (5, 1–39)	< 0.001
Ad to isolation	6.5 ± 6.2 (5, 1–39)	4.7 ± 4.0 (4, 1–25)	8.3 ± 7.4 (7, 1–39)	< 0.001
AFS to isolation	4.0 ± 3.6 (3, 0–24)	3.9 ± 3.4 (3, 1–24)	4.2 ± 3.8 (3, 0–24)	0.56

*Data presented as mean ± standard deviation (median, range). Ad = admission; CXR = chest radiograph; AFS = acid-fast staining; anti-TB = anti-tuberculous chemotherapy.

Nevertheless, the median delay from suspicion to isolation, i.e. from ordering of sputum AFS to respiratory isolation was 3 days. The median time of delayed isolation (from admission to isolation) by Kaplan–Meier estimate was 4.0 days for the PIW group and 7.0 days for the non-PIW group (Figure).

Risk factors of prolonged isolation delay

Fifty-four (28.3%) patients had delayed respiratory isolation that exceeded 7 days. The percentage of
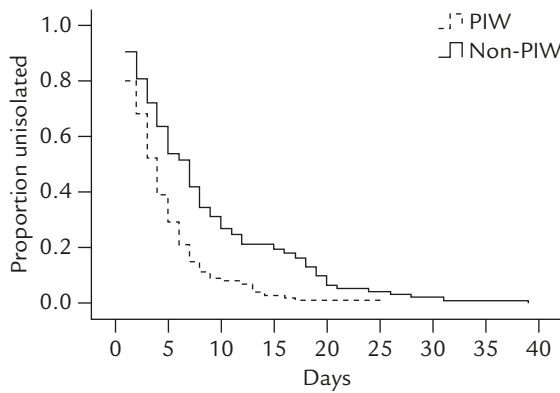
Figure. Cumulative proportion of days of delayed respiratory isolation in PIWs and non-PIWs by life-table analysis.

patients with isolation delays that exceeded 7 days was significantly lower in the PIW group than in the non-PIW group (15.3% *vs.* 41.9%; $p < 0.001$). In the multiple logistic regression model, admission to a PIW or non-PIW was not a significant factor. However, its interaction with other variables was significant, but the confidence intervals were very wide, which indicated an unreliable estimate. Therefore, only the results for PIWs or non-PIWs were presented respectively. In patients admitted to a PIW, age ≥ 70 years was the only significant independent factor associated with increased risk of prolonged isolation delay. In non-PIWs, patients without dyspnea, those with atypical chest radiographs, and those not admitted from the ED had a higher risk for prolonged isolation delay with odds ratios of 4.3, 9.5 and 8.1, respectively (Table 3).

Discussion

The risk of nosocomial transmission of TB from patients to HCWs cannot be entirely eliminated.[13]

Table 3. Results of multiple logistic regression analysis using whether delayed isolation exceeded 7 days as the dependent variable for PIWs and non-PIWs

Variables	Proportion with prolonged isolation delay	Adjusted OR (95% CI)	p
PIW			
Age			
< 70 yr	9.4%	Reference	–
≥ 70 yr	26.5%	3.5 (1.1–10.8)	0.03
Non-PIW			
Dyspnea			
Yes	22.2%	Reference	–
No	50.0%	4.3 (1.1–16.7)	0.04
Chest X-ray typical for TB			
Yes	25.5%	Reference	–
No	64.9%	9.5 (3.1–29.4)	< 0.001
Sputum AFS ordered at ED			
Yes	11.1%	Reference	–
No	48.4%	4.8 (0.9–26.4)	0.07
Not admitted from ED	54.5%	8.1 (1.0–65.7)	0.05

OR = odds ratio; CI = confidence interval; TB = tuberculosis; AFS = acid-fast staining; ED = emergency department.

A Turkish study revealed a 2.71 times higher incidence of TB in HCWs than in the general population between 1991 and 2000.[14] In our hospital, the risk of nosocomial TB transmission was hard to measure directly because the tuberculin skin test was not performed routinely in hospital employees during the study period. Nevertheless, institutional risk of TB transmission is correlated with indicators of patient care such as delayed diagnosis and treatment.[15] TB transmission occurs when patients are not immediately placed in respiratory isolation.[1] Lack of specific presentations may delay suspicion, diagnosis and ultimately, respiratory isolation.[16,17] HCWs with unprotected exposure to infectious TB before suspicion of TB and proper respiratory isolation are at increased risk of contracting TB.[10] The duration of management delays has varied in previous studies. A study in Washington DC, USA, found that 58% of hospitalized TB cases were not identified immediately after admission, 26% were not diagnosed until 4 weeks after admission, and 20% were not diagnosed or treated throughout their entire hospital stay.[18] Another study in St. Louis, USA, reported a median treatment delay of 3 days, and up to one-third of these patients had a management delay of more than 10 days.[19] In a Canadian multicenter study, which included both smear-positive and smear-negative TB patients, the median interval from admission until isolation was 12.5 days in hospitalized patients receiving delayed treatment.[15] The present study showed that 73.3% of hospitalized AFS-positive TB patients were not initially managed properly. The median duration of delayed respiratory isolation in this study was 5 days, and the median treatment delay was 4 days.

Greenaway et al reported that, as the rate of TB admission increases, the risk of TB transmission per hospitalized TB patient decreases.[15] Pulmonologists and infectious diseases specialists treat most TB patients and are the most familiar with its symptoms and radiologic findings. The present study demonstrated that TB patients in PIWs had significantly shorter delays for suspicion,

treatment and respiratory isolation. Fifty-four (28.3%) of 191 patients experienced prolonged delays in respiratory isolation, which exceeded 7 days. The proportion of patients with prolonged delays was significantly higher in the non-PIW group (41.9%, 39/93) than in the PIW group (15.3%, 15/98). However, in the multiple regression model that included all study subjects, the ward of admission was not a significant factor for prolonged isolation delay after we adjusted for other variables. The proportion of patients with atypical chest radiographs did not differ significantly between these two groups. More patients had fever and respiratory symptoms including cough, sputum or hemoptysis in PIWs. A higher percentage of TB patients admitted to PIWs had been suspected of having TB and AFS was ordered at the ED. For patients in non-PIWs, most of the diagnoses were not related to pulmonary disease and fewer patients had been suspected of having TB at the ED. Factors such as symptoms, radiographic presentations or sputum AFS at the ED, but not the ward of admission, were the risk factors for delayed diagnosis and isolation. In the non-PIW group, multiple logistic regression analysis showed that patients without dyspnea, those with atypical chest radiographs, and those not admitted from the ED had a higher risk of delayed isolation of >7 days. On the contrary, respiratory symptoms, systemic symptoms, patterns of chest radiographs or AFS ordering at the ED were not associated with prolonged isolation delay in PIW patients. The only significant risk factor for prolonged isolation delay was age ≥70 years in PIW patients.

A high proportion of hospitalized infectious TB patients are admitted from the ED. Physicians at the ED play a role of "gatekeeper" in providing a first-line defense against nosocomial transmission of infectious diseases including TB, SARS and other communicable respiratory diseases.[20] Eighty-nine percent of our patients with delayed respiratory isolation were admitted to the hospital from the ED. A similar result in a New York City hospital study showed that the percentage of AFS-positive patients admitted from the ED

was 84.7–88.5% between 1992 and 1994.[21] Moran et al found that TB was presumed in 71% of cases admitted from the ED and was significantly associated with shorter delays in isolation and therapy.[22] Here, only 35% of the patients had been suspected of having TB with sputum AFS ordered at the ED. The reason for the low rate of suspicion was probably the lack of typical radiographic findings at the ED. Sokolove et al reported that 25% of active TB patients had atypical chest radiographs at the ED.[16] Our data showed that 34% of smear-positive TB patients had atypical chest radiographs at the ED. Lack of typical symptoms might be another risk factor for delayed suspicion. Sokolove et al also found that only one-third of active TB patients at the ED had chief complaints of pulmonary symptoms, and cough was noted in only 64% of cases and was the chief complaint in <20% of cases.[16] In the present study, cough was noted in 54.5% of hospitalized AFS-positive TB patients, 49.2% of them had fever, and only 37.7% had sputum. Ordering sputum AFS for all patients with pulmonary infiltrates at the ED, but not only for those with typical chest radiographs, might be beneficial for the earlier detection of contagious TB in hospitalized patients.

Only patients with positive AFS in respiratory specimens are isolated in our hospital because of the limited number of negative-pressure isolation rooms. This may result in the delayed isolation of these contagious TB patients. The median delay from suspicion to isolation was 3 days in the present work. If all TB suspects were isolated properly before AFS results become available, the delay of isolation could be shortened for a median of 3 days. An expanded respiratory isolation policy to isolate all TB suspects has been implemented in a US hospital, which led to proper isolation of >95% of patients with TB upon admission, but resulted in an eight-fold overuse of isolation rooms.[23] There were not sufficient isolation rooms to isolate all TB suspects in our hospital, and early suspicion and diagnosis might be the better way to decrease the risk of unprotected exposure to infectious TB.

In conclusion, we documented that 73.3% of hospitalized smear-positive TB patients had delayed isolation with a median isolation delay of 5 days. TB patients in non-PIWs had longer delays in suspicion, treatment and respiratory isolation. The ward of admission was not a significant risk factor for prolonged isolation delay. Patients admitted to non-PIWs with atypical chest radiographs, atypical symptoms for TB, or those not admitted from the ED had a higher risk of prolonged isolation delay that exceeded 7 days. TB should be carefully considered even if the patients have only mild symptoms or present with atypical chest radiographs. All HCWs should be educated continuously in the recognition and prevention of TB transmission in health care facilities.

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