M Chan-Yeung 陳慕華
K Noertjojo
CC Leung 梁子超
SL Chan 陳兆麟
CM Tam 譚卓明

Prevalence and predictors of default from tuberculosis treatment in Hong Kong

香港肺結核患者延誤就醫的比率以及具預測性的因素

Objective. To determine the prevalence and risk factors of default from tuberculosis treatment in Hong Kong.
Design. Retrospective study.
Setting. Data were obtained from programme forms completed by physicians in the Hong Kong Government Tuberculosis and Chest Service and from medical records from Hong Kong chest clinics.
Patients. In all, 5917 patients registered for antituberculous drug therapy in 1996; medical records of 5757 patients were reviewed.
Main outcome measures. Patients who defaulted treatment were defined as those who had failed to collect medication for more than 2 consecutive months after the date of the last attendance during the course of treatment. Demographic and clinical characteristics, including history, treatment, and outcome, were compared between defaulters and non-defaulters, both among the whole group and among those with pulmonary disease.
Results. There were 442 (8%) patients who defaulted from treatment. Forty-five percent of those who defaulted did so in the first 2 months of treatment. Key risk factors associated with non-compliance were a history of default, male sex, and a history of concomitant liver disease or lung cancer. Among patients with pulmonary tuberculosis (381 defaulters and 1537 non-defaulters), multiple drug resistance was also associated with default from treatment. Among defaulters with pulmonary disease, 39% were still bacteriologically positive at the time of default.
Conclusion. Default from treatment may be partially responsible for the persistent high rates of tuberculosis in Hong Kong in the past decade. Health professionals should ensure that all barriers to treatment be removed and that incentives be used to encourage treatment compliance.

目的：確定香港肺結核患者延誤就醫的比率，以及可預測延誤就醫的因素。
設計：回顧研究。
安排：資料取自香港政府胸肺科醫生填寫的醫療方案表格，以及胸肺科診所保存的病歷紀錄。
患者：5917 名在 1996 年登記接受抗結核藥物治療的病人中，本研究檢閱了其中 5757 名患者的病歷紀錄。
主要結果測量：本研究對延誤就醫的定義為，療程內在最後一次就診後連續兩個月以上沒有到診所領藥。研究對象被分為延誤就醫和按時就醫兩組，針對人口統計學和臨床特徵，包括病史、接受的治療以及結果，分別比較這兩組及兩組中的肺病患者。
結果：共有 442 名患者(8%)延誤就醫，其中 45% 在治療期首兩個月已出現這種情況。與拒絕接受治療有關的主要因素包括之前已有延誤就醫的紀錄、男性、曾有伴發肝病或肺癌的紀錄。肺結核患者(延誤就醫者381位，按時就醫者1537位)中，延誤就醫也和身體多次出現抗藥反應有關。在延誤就醫的肺病患者中，39% 在沒有按時就醫期間，對細菌測試仍然呈陽性反應。
結論：患者延誤就醫可能是造成香港過去10年肺結核病發率維持高水平的其中一個原因。醫護人員應盡力掃除患者接受治療的障礙，並推行各種措施鼓勵患者接受治療。

Key words:
Hong Kong;
Treatment refusal;
Tuberculosis

關鍵詞：
香港；
拒絕接受治療；
肺結核

Hong Kong Med J 2003;9:263-8

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
M Chan-Yeung, FRCP, FHKAM (Medicine)
K Noertjojo, MD, MSc
CC Leung, FHKCP, FHKAM (Medicine)
SL Chan, FRCP, FHKAM (Medicine)
Tuberculosis and Chest Service, Department of Health, 99 Kennedy Road, Wanchai, Hong Kong
CM Tam, MRCP, FHKAM (Medicine)

Correspondence to: Prof M Chan-Yeung (e-mail: mmwchan@hkucc.hku.hk)

Introduction

Tuberculosis is a leading cause of morbidity and mortality worldwide.[1] In Hong Kong, the incidence of tuberculosis was very high in late 1940s, at nearly 700.0 cases per 100 000 population. With the effective control programme of the Government Tuberculosis and Chest Service of the Hong Kong Special Administrative Region (Chest Service) and the progressive improvement in the socio-economic situation, the notification rate of tuberculosis decreased to 100.9 per 100 000 in 1995. Since then, the incidence of tuberculosis has increased progressively—to 101.0 in 1996, 109.0 in 1997, and 113.7 per 100 000 in 2000.[2] Although the rise in incidence may merely reflect the increased awareness among the medical profession of the importance of notification,[3] the increase may also be real. Furthermore, the lack of a decline in the notification rate during the past 10 years has to be explained.

Poor case management, often because of non-adherence to treatment, has emerged as the most important factor in the resurgence of tuberculosis and the appearance of multiple drug resistance (MDR).[4] The prolonged duration of treatment, the need for multiple drugs, and socio-economic factors are the main reasons for non-adherence to treatment. The currently recommended minimum duration of treatment is 6 months, which, although much shorter than the previously recommended 12 to 24 months, is still very long. According to the World Health Organization (WHO), directly observed therapy (DOT) ensures successful treatment of patients with tuberculosis. Hong Kong has used DOT since the 1970s and was then one of the few places in the world to have such practice.[5] There are still patients who are not compliant to DOT and default from treatment. In this study, we assessed the prevalence and predictors of default from tuberculosis treatment in Hong Kong.

Methods

We studied all patients who were registered for tuberculosis treatment between 1 January 1996 and 31 December 1996 with the Chest Service, which treats about 80% to 90% of all notified cases in Hong Kong each year. To examine the predictors of default from treatment, we used a nested case-control study design. Default was defined as failure to collect medication for more than 2 consecutive months after the date of the last attendance. For each case of default, four controls were randomly selected (using computer-generated random numbers) from cases of completed treatment.

Data of patients treated by the Chest Service were obtained from programme forms that were submitted by physicians of the Chest Service at the onset of tuberculosis treatment and at 6, 9, and 24 months thereafter. The forms had the following information: patient name, starting date of treatment, age, sex, history of treatment, the type of tuberculosis (pulmonary or extrapulmonary), the extent of disease (if pulmonary), and the case category (new, relapse, treatment after default, and treatment after failure). The forms also listed the type of drug regimen used, the frequency of drug treatment, side-effects, bacteriological status before treatment and at 2 and 5 or 6 months from the start of treatment, drug sensitivity of micro-organisms, and the treatment outcome. The following information was not available: socio-economic status, history of drug misuse, and human immunodeficiency virus (HIV) status. In addition, we reviewed medical records at local chest clinics for patients with missing forms, missing information, and inconsistent information between forms. Altogether, 5757 records were reviewed. The definitions used in this study were modified from those according to the International Union Against Tuberculosis and Lung Diseases (Box).[6]

Data were entered into an Epi-Info database (Windows version 6.0; Centers for Disease Control and Prevention, Atlanta, US) and their accuracy was checked. The data were then analysed using the Statistical Package for the Social Sciences (Windows version 6.0; SPSS Inc., Chicago, US). The differences in clinical features between the cases of default and the controls were tested by Chi squared analysis

Definitions used in this study

Default–failure to collect medication for more than 2 consecutive months after the date of the last attendance during the course of treatment

Pulmonary cases–tuberculosis of the lungs, including sputum smear-positive and smear-negative cases (with a minimum of three sputum examinations). In the absence of positive bacteriology, patients had clinical features (such as fever, cough, sputum, haemoptysis, or weight loss) and radiological features compatible with tuberculosis, which improved on treatment
Extrapulmonary tuberculosis–tuberculosis affecting organs other than the lungs, including cases of tuberculosis pleurisy and miliary tuberculosis

New cases–those in which patients had never previously been treated for as long as 1 month
Relapse cases–those in which patients, who, having previously been treated, were declared cured and then had active disease confirmed either bacteriologically or clinically and radiologically
Treatment failure–cases in which patients who, while receiving treatment, remained or became again smear-positive at 5 months or later
Treatment after default–treatment of patients who returned for treatment with positive sputum after interrupting treatment for more than 2 months
Others–all other cases

Minimal tuberculosis–disease with combined area less than that of the right upper lobe
Moderate tuberculosis–disease with combined area less than that of the right lung but more than that of the right upper lobe
Advanced tuberculosis–disease with combined area more than that of the right lung

Multiple drug resistance–cases in which organisms were resistant to at least isoniazid and rifampicin

Table 1. Time of default and bacteriological status of patients with pulmonary tuberculosis*

Time since start of treatment	Total No. (%)	Smear- and culture-positive	Culture-positive only	Smear-positive only	Smear- and culture-negative	No bacteriology information
No treatment	8 (2.1)	0 (0)	5 (5.8)	0 (0)	2 (0.9)	1 (5.0)
<2 weeks	28 (7.3)	1 (2.0)	9 (10.5)	3 (25.0)	12 (5.7)	3 (15.0)
2 weeks-2 months	133 (34.9)	28 (54.9)	43 (50.0)	6 (50.0)	47 (22.2)	9 (45.0)
2-4 months	85 (22.3)	10 (19.6)	19 (22.1)	2 (16.7)	50 (23.6)	4 (20.0)
>4 months	127 (33.3)	12 (23.5)	10 (11.6)	1 (8.3)	101 (47.6)	3 (15.0)
Total	381 (100)	51 (13.4)	86 (22.6)	12 (3.1)	212 (55.6)	20 (5.2)

* Data shown are No. of patients (%)

Table 2. Characteristics of defaulters and non-defaulters*

Characteristic	Defaulters (n=442)	Non-defaulters (n=1768)	P value†
Age-group (years)			
0-19	19 (4.3)	108 (6.1)	NS‡
20-39	157 (35.5)	568 (32.1)	
40-59	135 (30.5)	503 (28.5)	
⩾60	131 (29.6)	589 (33.3)	
Mean age (SD) [years]	46.9 (19.0)	48.0 (19.4)	NS
Sex			
Female	108 (24.4)	555 (31.4)	0.004
Male	334 (75.6)	1213 (68.6)	
Case category			
New case	339 (76.7)	1501 (84.9)	<0.001
Relapse	51 (11.5)	239 (13.5)	
Treatment after default	49 (11.1)	24 (1.4)	
Others	3 (0.7)	4 (0.2)	
Disease site			
Pulmonary	347 (78.5)	1392 (78.7)	NS
Pulmonary and extrapulmonary	34 (7.7)	145 (8.2)	
Extrapulmonary only	61 (13.8)	231 (13.1)	
Concomitant illnesses	66 (14.9)	261 (14.8)	NS
Diabetes	25 (5.7)	179 (10.1)	0.006
Liver disease	17 (3.8)	14 (0.8)	<0.001
Lung cancer	7 (1.6)	6 (0.3)	0.002
Other cancers	2 (0.5)	4 (0.2)	NS

* Data shown are No. of patients (%) unless otherwise stated
† Chi squared test
‡ NS not significant

or analysis of variance. Multiple logistic regression was used to analyse the association between various risk factors and treatment default. This study was approved by the Ethics Committee of the University of Hong Kong.

Results

Of the 5757 patients who were treated by the Chest Service for tuberculosis in 1996, 442 (8%) refused treatment or failed to attend the clinic for more than 2 consecutive months, thereby fulfilling the criteria for treatment default. Approximately 45% of patients who defaulted did so within the first 2 months of treatment.

Of the 442 patients who defaulted, 381 (86%) had pulmonary tuberculosis. Of those with pulmonary disease, 149 (39%) were still bacteriologically positive (51 smear- and culture-positive, 86 culture-positive only, and 12 smear-positive only) at the time of default (Table 1).

From patients who completed treatment, 1768 were randomly selected as controls. The default group had more men than women and a higher proportion with a history of default compared with the control group (Table 2). There was no significant difference in age between defaulters and non-defaulters. Although a similar proportion of cases and of controls had concomitant illnesses, the proportion with diabetes was lower and the proportion with liver disease or lung cancer was higher among those who defaulted from treatment.

Among the controls, 1537 (87%) had pulmonary disease. The differences between defaulters and non-defaulters among patients with pulmonary disease were similar to the overall differences between defaulters and non-defaulters among the whole group in terms of distribution in age, sex, case category, and presence of concomitant illnesses (not shown). There were no differences between cases and controls with pulmonary disease in the extent of disease or presence of cavitation, and similar proportions had positive bacteriology (Table 3). Whereas the proportion with resistance to one or more drugs was similar between cases and controls, the proportion with MDR (defined as those with resistance to at least isoniazid and rifampicin) was higher among cases than among controls. All seven patients with MDR who defaulted were still culture-positive and three of them were also smear-positive at the time of default.

Multiple logistic regression analyses were performed to determine the risk factors associated with default among all patients and among those with pulmonary disease only. For the whole group, important risk factors associated with default included male sex (odds ratio [OR]=1.5; 95% confidence interval [CI], 1.1-2.1), a history of default (OR=8.2;

Table 3. Extent of disease, cavitation, bacteriology, and drug susceptibility pattern among defaulters and non-defaulters with pulmonary disease

	Defaulters, n=381 No. (%)	Non-defaulters, n=1537 No. (%)	P value*
Extent of disease	380 (100.0)	1529 (100.0)	
Minimal	230 (60.5)	916 (59.9)	NS†
Moderate	109 (28.7)	445 (29.1)	
Advanced	41 (10.8)	168 (11.0)	
Cavitary disease	73 (19.9)	278 (18.9)	NS
Bacteriological status	359 (100.0)	1494 (100.0)	NS
Smear- and culture-positive	99 (27.6)	464 (31.1)	
Culture-positive only	116 (32.3)	456 (30.5)	
Smear-positive only	14 (3.9)	34 (2.3)	
Smear- and culture-negative	130 (36.2)	540 (36.1)	
Drug susceptibility	340 (100.0)	1520 (100.0)	NS
Fully sensitive	313 (92.1)	1424 (93.7)	
Resistant to one first-line drug	18 (5.3)	78 (5.1)	
Resistant to more than one first-line drug	9 (2.6)	18 (1.2)	
Multiple drug resistance (including isoniazid and rifampicin)	7 (2.1)	3 (0.2)	<0.001

* Chi squared test
† NS not significant

Table 4. Odds ratios from multiple logistic regression analysis examining the association between selected risk factors and treatment default*

	Odds ratio	95% Confidence interval	P value
All cases			
Sex			
Male versus female	1.4	1.1 -1.8	0.02
Age (years)	0.99	0.99 -1.00	NS†
Case category			
Relapse versus new cases	0.9	0.7 -1.3	NS
Previous default versus new cases	8.9	5.3 -14.9	<0.001
Concomitant illness			
Lung cancer: yes versus no	5.7	1.9 -17.3	0.002
Liver disease: yes versus no	4.4	2.1 -9.4	<0.001
Diabetes: yes versus no	0.5	0.3 -0.9	0.01
Pulmonary disease			
Sex			
Male versus female	1.5	1.1 -2.1	0.008
Age (years)	0.99	0.98 -1.00	NS
Cavitation			
Yes versus no	1.1	0.8 -1.6	NS
Case category			
Relapse versus new case	0.9	0.6 -1.3	NS
Previous default versus new case	8.2	4.7 -14.3	<0.001
Extent of disease			
Moderate versus minimal	0.9	0.7 -1.3	NS
Advanced versus minimal	0.7	0.4 -1.1	NS
Concomitant illness			
Lung cancer: yes versus no	8.1	2.5 -26.3	<0.001
Liver disease: yes versus no	3.8	1.5 -9.5	0.004
Diabetes: yes versus no	0.6	0.3 -0.9	0.03
Drug susceptibility			
Multiple drug resistance versus fully sensitive	9.4	2.1 -41.8	0.003

* Pseudo R^2=0.06
† NS not significant

95% CI, 4.7-14.3), liver disease (OR=3.8; 95% CI, 1.5-9.5), and lung cancer (OR=8.1; 95% CI, 2.5-26.3) [Table 4]. A history of diabetes mellitus was associated with a reduced likelihood of default (OR=0.6; 95% CI, 0.3-0.9). For patients with pulmonary disease, in addition to the above risk factors, MDR tuberculosis was associated with default (OR=9.4; 95% CI, 2.1-41.8).

Discussion

The Chest Service's policy is to treat all cases of tuberculosis with DOT. There are 18 chest clinics in Hong Kong, and patients are allowed to move freely between them for convenience. The clinics are open from 8:00 am to 7:30 pm during weekdays and for half-days on Saturdays. The cost of drug treatment is not an issue in Hong Kong, because all antituberculous drugs are free of charge. Thus, the infrastructure for DOT in Hong Kong is very good. Nevertheless, 442 (8%) of patients who registered at the Chest Service for treatment of tuberculosis in 1996 defaulted from treatment. Of the 381 who had pulmonary disease at the time of default, 40% had positive results to smear or culture tests, indicating that they were still potentially infectious. However, the treatment completion rate in Hong Kong in 1996 was about 80% at 12 months and 85% at 24 months,[7] which reaches the target set by the WHO for treatment completion.[8]

According to published studies, one smear- and culture-

positive patient with pulmonary tuberculosis infects, on average, about 12 others each year, and while each culture-positive patient infects two others.[9] Hence, the patients who defaulted from treatment in 1996 might have infected 1032 individuals in the first year after default from treatment. Furthermore, about 10% to 15% of infected individuals develop the disease after infection and half of them may be infectious and in turn can transmit the disease to others.[10] Thus, because the rate of default from treatment has varied by 7% to 8% each year during the past decade in Hong Kong,[11] these defaulters might have added substantially to the pool of infectious people.

Because of other factors, such as death, natural remission, retreatment of some cases, and the effect of partial treatment on the viability of the bacilli, it is not possible to delineate exactly the impact of default from treatment to the overall rate of tuberculosis in Hong Kong. We also found that concomitant lung cancer was also a predictor of defaulting from treatment. The high mortality of lung cancer may have shortened the period of infectivity. Because the mean duration of infectivity of each case of tuberculosis is estimated to be 2 years,[12] the additional annual risk of infection attributable to patients who defaulted from treatment in Hong Kong is about 0.03%. Default from treatment is unlikely to be solely responsible for the current stagnant rate of tuberculosis at a relatively high level. Other factors, such as the high rate of tuberculosis among the elderly, together with the ageing population in Hong Kong, are probably also important.[13]

In this study, we found that a history of default from treatment is the strongest predictor of non-compliance, followed by the presence of concomitant lung cancer, liver disease, and male sex. Thus, a history of default should alert the health professional to give special attention to ensure removal of all barriers to treatment. Most published studies have shown that HIV infection, homelessness, smoking, alcohol and drug misuse, psychiatric illness, and poverty are all risk factors for non-compliance to treatment.[14,15] In our study, data on alcohol and drug abuse, HIV status, and socio-economic status were not available in the programme forms of the Chest Service. Additionally, patients with lung cancer and liver disease might have been hospitalised or died, but such information was not available to us.

Among patients with pulmonary disease, the risk of MDR tuberculosis was significantly higher among defaulters than non-defaulters, which is consistent with most of the published results.[14,15] This finding is especially worrisome, because all patients were still bacteriologically positive at the time of treatment default. However, the surveillance of antituberculous drug resistance in Hong Kong between 1986 and 1999 showed a significant decline in overall drug resistance.[16] Multiple drug resistance decreased from 2.7% to 1.0% for new cases and from 15.9% to 8.3% for retreated cases.

Legal sanction against defaulters has been attempted, but only mainly in the United Stated in the mid-1980s, when there was a dramatic rise in the rate of tuberculosis and MDR tuberculosis among HIV-infected individuals.[17] Although there was widespread support for such legal action, there were concerns that these powers might be abused for use as a means of social control, and many believed that it was unfair to detain patients when their ability to comply with treatment was affected by the lack of housing, primary health care, and services for substance users.[17,18] In the United Kingdom, legislation allows for the detention of an individual with a notifiable disease that is a threat to others, but this legislation is rarely used.[19] The moral issues in the use of coercion and detainment in dealing with non-adherence in the diagnosis and treatment of tuberculosis have been widely debated.[19-21] Although coercion and detainment have been found by ethicists to be a morally acceptable strategy to fight the spread of tuberculosis, their use to support strategies that improve treatment compliance must be sensitive to national and cultural differences and not simply be based on perceived successes elsewhere. Due regard must be paid to the possibility that such negative measures may aggravate the social stigma and discrimination that still surround this important airborne disease. Even if we can achieve 100% case-holding, the strategy will still not work unless patients come forward for treatment in the first place.

On the other hand, it has been shown that successful DOT programmes with a high rate of treatment completion (86%-97%) are those that provide incentives such as shelter for the homeless, methadone and rehabilitation programmes for drug abusers, food coupons, and money for transportation; some programmes also provide educational opportunities, while others make use of occupation settings to administer the drugs.[22-28] Directly observed therapy programmes without such incentives are less successful, with treatment completion rate of 85.0% to 87.5%.[29,30]

The current DOT programme in Hong Kong uses a combination of incentives and enablers, which include education for patients and their families, intermittent client-focused regimens, money for food, referrals for other social services, as well as use of outreach teams and the tracing of defaulters. Greater efforts are required in the education of the patients and public to increase their understanding of the importance of treatment completion for patients with tuberculosis.

Conclusion

In Hong Kong, the rate of default from tuberculosis treatment in 1996 was 8%—unchanged from the rate during the past decade. The defaulters probably contributed to the pool of infectious patients in the community and may be partially responsible for the persistent high rate of tuberculosis locally. A history of default from treatment should alert health professionals to ensure that all barriers to treatment be removed, and that incentives be used to encourage treatment compliance.

Acknowledgements

This study was supported by the University of Hong Kong and the Hong Kong Tuberculosis, Chest and Heart Diseases Association. We thank the staff of the chest clinics for their assistance in reviewing medical records.

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