



Introduction of Medical Care System for Multi-drug Resistant Tuberculosis in Taiwan

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Abstract

Tuberculosis is the most severe infectious disease in the world as well as in Taiwan. Nearly 15,000 new cases are recorded every year in Taiwan. Factors such as the long period required for treatment and medical side effects make some patients take medicine irregularly, which is the main reason for the development of multiple-drug resistant tuberculosis (MDR TB).

The World Health Organization (WHO) warned in 2007 that the spread of MDR TB has become a major public health problem which is threatening the whole world. It thus recommended nations around the world to implement the “Directly Observed Treatment, Short-course, plus” (DOTS-plus) for preventing and controlling this disease.

The “Medical Care System for Multiple-drug Resistant Tuberculosis” was launched in May, 2007, in Taiwan. It consists of 5 medical care teams

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to receive MDR TB patients. Medical resources are provided by Taiwan CDC, and each medical care team is requested to conform to the WHO treatment guidelines for this disease. Each case is placed under rigorous treatment for 2 years. Besides the clinical treatment, social workers have been recruited for carrying out DOTS-plus in the community to provide patients with complete and continuous attention. A total of 171 MDR TB cases had been received and put under treatment as of November 2007.

This medical care system cooperates with the Bureau of National Health Insurance in managing the use of fluoroquinolone medications and in conducting spot-checks of the prescription of anti-tuberculosis medicine. This system also focuses on the management and improvement of quality control in the laboratories and has introduced more second-line anti-tuberculosis medicine into Taiwan. Through this system, we can improve the cure rate for MDR TB patients.

Keywords: multiple-drug resistant tuberculosis, DOTS-plus, medical care system

Introduction

Tuberculosis is the most severe infectious disease in Taiwan. Nearly 15,000 new cases are recorded every year, which is more than the sum of the annual case numbers for all the other reportable communicable diseases. This disease is also the most severe infectious disease in the world, which is the disease causing the largest number of casualties with single pathogen.

A confirmed diagnosis of this disease is usually delayed due to its long incubation period, atypical clinical signs (especially for first-time infections), inconspicuous clinical features (such as fever and cough), and the occurrence of false-negative results from tests of sputum isolates.



Besides, the patients' desire to follow through the treatment may be hindered because of the long period required for therapy (usually longer than 6 months) and the side effects of hyperimmune reaction, such as cutaneous exanthema, skin itching, nausea, vomiting, optic neuritis and joint pain. Furthermore, since the introduction of the national health insurance system in Taiwan, tuberculosis patients have been treated in local hospitals or clinics for convenience reasons rather than being transferred to facilities specialized in tuberculosis treatment. As a result, the quality of medical care varies from place to place, which has led to a decrease in successful disease diagnoses and failures in treatment that in turn aided the development of multiple-drug resistant tuberculosis.

On March 24, 2007, WHO issued a warning about the serious threat posed by the spread of MDR TB to global health. There are over one million MDR TB patients worldwide at the present, and 300 to 600 thousand new cases are recorded every year [1]. In Taiwan the number of MDR TB cases is also increasing due to the aforementioned reasons. Currently, 422 cases are listed in the central infectious disease surveillance system.

MDR TB medical care system was established based on the following considerations: 1). most local medical facilities do not have sufficient capabilities for the treatment of MDR TB; and 2). local medical facilities are unwilling to accept MDR TB cases under the current the national health insurance payment system. On the other hand, the Medical Care System for Multiple-drug Resistant Tuberculosis is a specialized and focused medical system that provides medical resources on a case-by-case basis. This system officially began operating on May 1, 2007, and is expected to help control the epidemic situation of MDR TB.

The Framework of MDR TB Medical Care System

In early 2007, Taiwan CDC announced a subsidy plan for this disease. Taiwan was divided into 6 areas according to the jurisdiction of each of CDC's local branches, and 5 medical teams were subsequently selected as contract medical care centers (Table 1).

Table 1. Members of the “MDR TB Medical Care System”

Area	Name	Collaborating medical facilities
Taipei Area	Wan Fang Medical Team of Taipei City	Taipei Medical University Municipal Wan Fang Hospital, Taipei City Hospital He-Ping Branch, Mackay Memorial Hospital Taipei Branch, Taipei Hospital (Department of Health, Taiwan, R.O.C.).
Northern Taiwan Area	Taoyuan Medical Team, Department of Health, Taiwan, R.O.C.	Taoyuan General Hospital (Department of Health, Taiwan R.O.C.) and Shinwu Branch, Hsin Chu General Hospital (Department of Health, Taiwan, R.O.C.), Chutung Hospital (Department of Health, Taiwan, R.O.C.)
Central Taiwan Area	Taichung Medical Team, Department of Health, Taiwan, R.O.C.	Taichung Hospital (Department of Health, Taiwan, R.O.C.), Chan-Hua Hospital (Department of Health, Taiwan, R.O.C.), Nantou Hospital (Department of Health, Taiwan, R.O.C.), Miao-Li General Hospital (Department of Health, Taiwan, R.O.C.), Tsaotun Psychiatric Center (Department of Health, Taiwan, R.O.C.), Fong Yuan Hospital (Department of Health, Taiwan, R.O.C.), Taichung Veterans General Hospital, Chung Shan Medical University Hospital, China Medical University Hospital.
Southern Taiwan and Kaohsiung Area	Chest Medical Team, Department of Health, Taiwan, R.O.C.	Chest Hospital (Department of Health, Taiwan, R.O.C.), National Chen Kung University Hospital, Tainan Hospital (Department of Health, Taiwan, R.O.C.), Chia-I Wan Cio Veterans Hospital, Chi-Shan Hospital (Department of Health, Taiwan, R.O.C.), Pingtung Hospital (Department of Health, Taiwan, R.O.C.), Chia-I Hospital (Department of Health, Taiwan, R.O.C.), Fooyin University Hospital, Kaohsiung Municipal Min-Sheng Hospital, Kaohsiung Veterans General Hospital.
Eastern Taiwan Area	National Tuberculosis Association Team	Buddhist Tzu Chi General Hospital, Mennonite Christian Hospital, Mackay Memorial Hospital Taitung Branch, Hua-Lien Hospital (Department of Health, Taiwan, R.O.C.), Taitung Hospital (Department of Health, Taiwan, R.O.C.), Fenglin Veterans Hospital.



The Administration Scheme for MDR TB Medical Care System

The treatment for MDR TB not only takes a long time but also has limited effectiveness using the standard TB therapy. As a result, WHO established a MDR TB group in 1999 to assist countries in evaluating the feasibility for implementing DOTS-plus [2]. WHO also set up the “Guidelines for the programmatic management of drug-resistant tuberculosis.”

The MDR TB medical care system follows this concept and requires every MDR TB medical care team to comply with the WHO guidelines. Every MDR TB patient should undergo rigorous treatment for 2 years. Besides the clinical therapy, the medical care teams need to recruit care workers for carrying out DOTS-plus in the community. As a result, the patients receive complete and continuous medical care, which helps overcome the traditional gap between clinical medicine and public health and resolve the difficulties associated with the provision of continuing care for discharged MDR TB patients. The care workers serve the patients by “delivering medicine and supervising its consumption by patients before leaving.” The clinicians will also receive more complete information on patients’ treatment in the community through the care workers. This system may increase MDR TB patients’ compliance with treatment as well as the disease’s cure rate, which in turn helps bring the MDR TB epidemic under effective control.

Taiwan CDC also provides NTD 1 million for every MDR TB patient (a maximum of NTD 2 million for the 2 year treatment period, excluding the cost of medicine) to be used flexibly by the medical team to improve

patient compliance with treatment and achieve the ultimate goal of cure.

The Targets and Procedures for MDR TB Medical Care System

Based on the result of antimicrobial susceptibility as determined by the Kuyang Laboratory of Taiwan CDC, cases with drug resistance against both INH (isoniazid) and RMP (rifampicin), including current patients with positive sputum cultures since January 1, 2007, are the target patients.

MDR TB has been listed as a second class reportable communicable infectious disease since October 15, 2007. According to the Communicable Disease Control Act, upon detection of any suspected cases, medical institutions and local clinics should report them to the health authorities within 24 hours. Non-MDR TB medical teams should follow the standard procedures of specimen testing, in which samples are sent to the Kuyang Laboratory for re-check before transferring target patients to a MDR TB medical team. After a re-check of samples, the confirmed target cases are transferred to a MDR TB medical team with all related disease history records. The MDR TB medical facility should fill out a “MDR TB transferring form” and fax the form to the local health authority as well as to the local branch of Taiwan CDC after receiving the application. The local health authority should offer a “MDR TB therapy notice” and should inform the patient within 3 days to complete the process.

The Present Operation of MDR TB Medical Care System

A total of 171 MDR TB patients had been included in the MDR TB medical care system from May to November 2007, and all patients had been either hospitalized or received outpatient therapy. The average age of

these patients was 50.6 years old (standard deviation: 16.1 years). Among them, 137 were males (80.1% of all patients) and their average age was 51.3 years old, while the average age of female patients was 47.5 years old (p value=0.367). The age of most of these patients lied between 41-60 years old, and the age distribution is showed in Figure 1. Forty-six aborigines were included in this group of 171 patients (28.2%); three of them were residents of correctional facilities while another three lived in a long-term care institute. The age of MDR TB patient was younger in the aboriginal population (45.5 years old) than in other population groups (52.6 years old, p value=0.009).

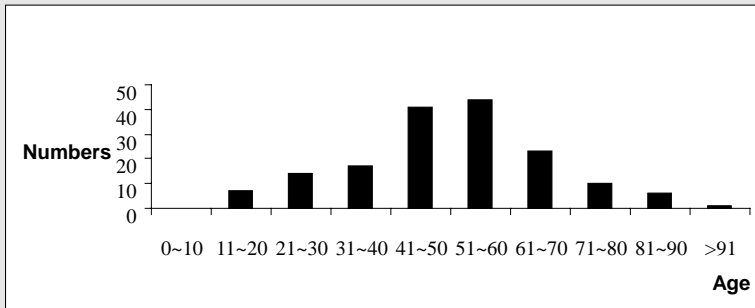


Figure 1. Age distribution of MDR TB patients

According to the WHO definition of MDR TB, a “new patient” has had no or less than 1-month period of anti-tuberculosis treatment after being confirmed as a MDR TB case. Based on this, Taiwan has recorded 41 new patients (24.0% of all patients). Twenty-two cases have been lost (12.9%); 83 are recurring cases or patients with failed therapy (48.5%); and 25 cases have unknown therapy history (14.6%). The average age of new patients was younger than other patients, but the difference is not

statistically significant (new patients: 46.1 years old; other patients: 52.1 years old; p value=0.083).

The time from confirmation of MDR TB to INH/RMP antimicrobial effect is different from case to case. Excluding the new patients, 25 patients (19.8%) experienced INH/RMP antimicrobial effect within 1 year of therapy, whereas 81 patients (64.3%) encountered this effect after at least 2 years of medical therapy.

Fifty-five patients in the MDR TB medical care system have received a complete set of tests for antimicrobial susceptibility, including susceptibility for ethambutol, streptomycin, fluoroquinolone, kanamycin, prothionamide/ethionamide and p-aminosalicylic acid (PAS). These tests were administered by Taiwan CDC's Research and Diagnostic Center or by a contract laboratory. The antimicrobial rate for each anti-tuberculosis medicine is showed in Figure 2, and the high antimicrobial rates for fluoroquinolone and streptomycin between 40-50% deserve special attention. Eleven patients (20%) showed susceptible effects to all anti-tuberculosis drugs listed above. Thirteen patients (23.6%) revealed only anti-ethambutol and/or anti-streptomycin effect.

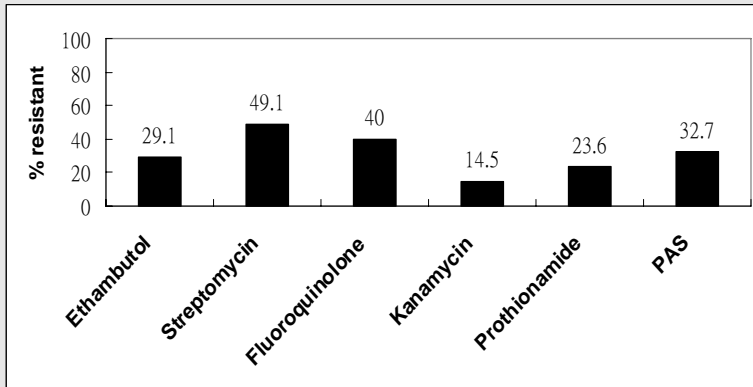


Figure 2. Antimicrobial results of MDR TB patients

The average age of all TB patients in Taiwan was 58 ± 20 years old (median: 60 years old), and the average age of patients in MDR TB medical care system was 50.6 ± 16.1 years old, which was younger than the ordinary TB patients (p value < 0.001). Similar result was also noted in California, USA [3]. From 1998-2002, the data collected from National Taiwan University Hospital revealed that more MDR TB patients were < 65 years old than > 65 years old (7.3% vs. 2.4%, p value < 0.001) [4]. Furthermore, until February 3, 2008, TB surveillance data from Taiwan CDC showed that there were 11877 TB cases in Taiwan, including 972 aborigines (8.2%). Aboriginal patients constituted a large portion of patients in the MDR TB medical care system (28.2%), and the average age of aboriginal patients was obviously younger than other patients. Related literature has indicated that the average age of aboriginal patients in Taiwan is younger than the non-aboriginal patients [5]. This may explain the younger average age of MDR TB patients.

Related articles and reports about risk factors of MDR TB patients

indicated that therapy failure or lost of past medical history are 2 important factors [3, 6]. There are 61.4% patients in the MDR TB medical care system in Taiwan located in this group. Further more, no medical therapy was recorded in 24% of these patients, which may indicates that part of the MDR TB patients are still spreading the pathogens. Therefore, Taiwan CDC should enhance the medical care and management for MDR TB patients.

The epidemiological and clinical data were collected from the patients participating in this system. However, the characteristics of MDR TB in Taiwan may not be completely shown by this statistical information because all these patients were selected by the 5 medical care teams based on the standard procedures. Besides, this system has been running for only six months and the therapy effect may not have been comprehensively evaluated. A large-scale investigation and close monitoring of medical care situations are recommended for further understanding of risk factors and clinical characteristics of MDR TB patients.

Estimation Mechanism of MDR TB Medical Care System

In order to evaluate the effectiveness of the therapy, Taiwan CDC requests each medical care team to submit seasonal reports on their patients. The data in the present article are from these reports. However, there has been no comprehensive evaluation of the therapy effect due to the short period for which this system has been in operation (May-November, 2007). Nonetheless, Taiwan CDC invited Dr. Peter Cegielski, MD, MPH (editor-in-chief of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis, Chief of MDR



TB Team, Division of Tuberculosis Elimination, U.S. CDC) and Dr. Charles L. Daley, M.D., FCCP (Professor of Medicine, National Jewish Medical and Research Center and University of Colorado Health Sciences Center) to Taiwan for field investigation and consultation in June and December 2007 respectively.

Dr. Cegielski and Dr. Daley commended Taiwan's effort in MDR TB control and showed a high level of interest in this policy. They also offered several recommendations, including the introduction of more second-line anti-TB medicine to increase the therapy efficacy for MDR TB patients, a shortening of the established schedule for each TB examination to avoid delayed therapy, and the practice of clinical monitoring of drug concentration in the blood to control the therapy drug concentration and side effects. They also recommended that the MDR TB patients should be encouraged to accept surgery therapy to increase the cure rate. Based on these recommendations, a conference is scheduled for 2008 to improve relevant medical standards by offering the medical care teams a chance to learn from and constructively compete with one another.

Conclusion

WHO believes that a successful introduction DOTS-plus for the prevention and treatment of MDR TB should be based upon an established DOTS program and its 5 major strategies: 1). political commitment to the prevention and treatment of MDR TB; 2). an effective mechanism for case diagnosis; 3). standardized drug prescriptions; 4). sufficient supply of second-line drug; and 5). standardized procedures for case registration and reporting. In addition, DOTS-plus needs to pay special attention to the

diagnosis of MDR TB and the use of second-line anti-TB drugs [1].

The prevention and treatment of MDR TB was not included in the main points of TB prevention in the past. Due to the increasing level of severity of the MDR TB epidemic and in response to WHO's call for action, Taiwan CDC has invested a large amount of funding in the prevention and treatment of MDR TB. Taiwan CDC has also cooperated with the Bureau of National Health Insurance in managing the fluoroquinolone medications and in conducting random checks of anti-TB drug prescriptions. Furthermore, Taiwan CDC has placed an emphasis on improving quality control at its contract laboratories, on introducing less commonly seen second-line anti-TB drugs and on subsidizing clinicians for further training.

Based on the response from clinicians, patients encountering difficulties during treatment are now transferred from regular medical facilities to facilities in this dedicated system at an early stage for specialized treatment. The cure rate of these patients has greatly increased while the chance of patients developing "extensively drug-resistant tuberculosis (XDR-TB)" has greatly reduced. This is exciting news for patients, medical practitioners and the public alike. Although there is still a long way to go, we hope that this system offers new opportunities in medical treatment for MDR TB patients and helps connect Taiwan's effort to the global objective of halving the number of TB cases in ten years.



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