

Directly Observed Therapy-Short-Course (DOTS) at the Makati Medical Center

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ABSTRACT

Setting: Hospital-based Directly Observed Therapy-Short-course (DOTS) Clinic. **Background:** One significant finding of the 1997 nationwide tuberculosis prevalence survey was that more TB symptomatic patients consult the private health sector as compared to the public health sector; therefore, the responsibility of TB control should be shared between private practitioners and the public health sector. **Objective:** This paper describes the first year experience of the Makati Medical Center (MMC) DOTS Clinic, a private-public partnership, which provides subsidized supervised anti-TB treatment using World Health Organization recommendations. **Results:** A total of 163 patients were enrolled in one year. The mean age was 41 years and males comprised 60%. Treatment category I patients comprised 49%, category II 26% and category III 25%. Among 37 new smear-positive pulmonary TB cases, the cure rate was 84%, with no treatment failure noted. Among 22 smear-positive re-treatment cases, the cure rate was only 36%, and the failure rate was 59%. The over-all success rate was 79.5% (108); the failure rate 10%. Seven (5%) patients were lost, 6 (4.5%) died and 1 (1%) transferred out. Among 76 *M. tuberculosis* isolates, 43 (57%) were SHRE susceptible, 14 (18%) were multidrug-resistant, 13 (17%) were H resistant; 3 (4%) were E-resistant; 2 (3%) were HE-resistant, and 1 (1%) was HS-resistant. **Conclusions:** DOTS is effective for new smear-positive pulmonary TB. For re-treatment cases however, the DOTS-Plus strategy appears essential due to the high rate of treatment failure and multidrug-resistant TB. (*Phil J Microbiol Infect Dis* 2000; 29(2):80-86)

Key words: Directly Observed Therapy-Short-course, tuberculosis

INTRODUCTION

During the 1997 nation-wide tuberculosis (TB) prevalence survey, it was noted that more TB symptomatics who consult for treatment go to private practicing physicians than to the public health clinics where anti-TB drugs are free.¹ It then became apparent that for the TB control program in the Philippines to succeed, the private sector should bear an equal responsibility with the public health service. The Makati Medical Center Directly Observed Therapy-Short-Course (MMC DOTS) Clinic was thus established on 24 March 1999, in celebration of the World TB Day. This is a private-public collaborative effort of the Makati Medical Center and the Tropical Disease Foundation representing the private sector, and the Department of Health and Barangay San Lorenzo, representing the public sector.

This preliminary report describes the first year experience of the MMC DOTS clinic. Patient accrual and characteristics and response to therapy are described. Treatment outcomes are compared to the targets for new smear-positive pulmonary TB (PTB) set by the TB Control Service of the Department of Health (DOH) which are 85% cure rate, 5% treatment completed, 1-2% treatment failure, 2-3% deaths, 5% lost, and 5% transfer out.²

MATERIALS AND METHODS

Patient enrolment

Patients referred for TB symptoms or chest x-ray findings of PTB were evaluated. Patients were referred to the clinic by their attending private physicians or from the MMC charity outpatient and inpatient departments. They were interviewed for signs and symptoms of TB, and if symptomatic, at least two sputum specimens, were collected for acid-fast bacilli (AFB) smear and culture. Any previous chest x-rays done were reviewed.

Treatment regimens

Those with at least two positive AFB smears were enrolled in the DOTS program after informed consent. If the patient was symptomatic with negative smears, a chest x-ray was done. If radiographic findings were suggestive of PTB, the patient was enrolled. Patients were categorized according to the World Health Organization (WHO) guidelines.³ Category I are new cases of smear-positive PTB, or smear-negative PTB with extensive x-ray lesion, or severe extrapulmonary TB. Category II are re-treatment cases due to relapse, treatment failure, treatment after loss, or "others," and Category III are new cases of smear-negative PTB with mild x-ray lesion, or less severe extrapulmonary lesion.

Enrolled patients were required to report to the clinic for directly observed therapy daily except Sunday during the first month of the intensive phase and thrice weekly thereafter until the end of therapy. Any defaulter for a scheduled clinic visit was immediately followed up by phone and by domiciliary visit the following day, during which time the DOTS nurse would administer due medications under direct observation. Defaulters were then encouraged to return to the clinic.

Treatment regimens were administered according to the WHO guidelines.³ Patients in Category I were given 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) in the intensive phase followed by 4 months continuation phase of HR daily or thrice a week (TIW). Patients in Category II were given 2 months of HRZE streptomycin (S) then 1 month of HRZE in the intensive phase followed by 5 months continuation phase of HRE daily or TIW. Category III patients were given 2 months of HRZ followed by 4 months of HR daily or TIW.

Case definitions³

A "new case" is a patient who has never taken anti-TB medicines or has previously taken anti-TB drugs for less than one month. A "re-treatment case" is a patient who has previously taken at least one month of anti-TB drugs.

In general, TB patients are classified as pulmonary or extrapulmonary. The former refers to a patient with TB disease involving the lung parenchyma; the latter refers to a patient with TB disease in a site other than the lungs. Extrapulmonary TB can either be "severe," which includes meningitis, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genitourinary, and miliary TB, or "less severe" which includes the lymph node, bone other than the spine, peripheral joint, skin, or unilateral pleural effusion.

"Relapse" is a patient who has gone through a complete course of anti-TB treatment in the past and has been declared cured by a doctor and again presents with smear-positive sputum. "Treatment failure" is a patient who remains smear-positive by the 5th month of therapy or later, or a patient who is initially smear negative and becomes smear positive on the 2nd month of treatment. "Treatment after loss" is a patient who interrupts treatment for > two months. Re-treatment patients who do not fit into any of the above criteria were enrolled under "others."

Monitoring and assessment of outcome

Response to therapy was monitored by sputum smear and culture. After the baseline sputum examination, this was repeated a) towards the end of the intensive phase of therapy, i.e., at the end of the 2nd month for those on the 6-month regimen, and at the end of the 3rd month for those on the 8-month regimen, b) during the continuation phase, i.e., at the 4th month and 5th month, respectively, then c) towards the end of treatment, i.e., at the end of the 5th month and 7th month, respectively.

Based on WHO criteria,³ treatment outcomes were classified as follows: 1) cure defined as the conversion of an initially smear positive to smear-negative sputum on at least two occasions towards the end of therapy; accordingly, this can only be assessed in initially smear-positive PTB; 2) treatment completed is a patient who was initially smear-negative and has remained negative until the end of treatment; 3) treatment failure is the persistence of a smear-positive sputum by the 5th month of therapy, or the conversion of an initially smear-negative to smear-positive sputum on the 2nd month of treatment; 4) transfer out is a patient who elects to pursue therapy elsewhere with the permission and referral of the

clinic; 5) lost is a patient who interrupts treatment for > two months; and 6) death is a patient who dies during the course of treatment regardless of cause.

Sputum smear and culture

Acid-fast smear and culture for *Mycobacterium tuberculosis* were done according to standard procedures. Drug susceptibility testing (DST) to H, R, Z, E and S was done according to proportion methods using standard procedures.⁴ Susceptibility to Z was determined using the pyrazinamidase test.⁵

RESULTS

Treatment category of patients

At the end of the first year of operation, 163 patients were enrolled. The mean age was 41 years. Males comprised 98 (60%) and females 65 (40%). The first two patients were enrolled on February 5, 1999 (Figure 1). Patients were grouped according to the three major treatment categories described above.

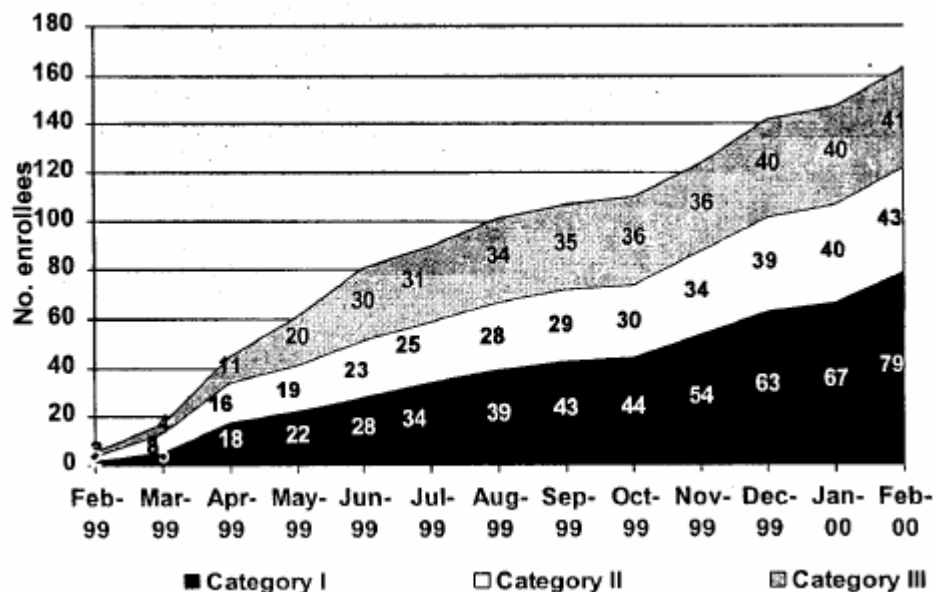


Figure 1. No of enrollees in the MMC DOTS Clinic according to category (Feb 1999–Feb 2000) N= 163

There were 79 (49%) patients enrolled as Category 1, 43 (26%) as Category II (re-treatment), and 41 (25%) as Category III (Table 1). Of the 79 category I patients, 50 were smear-positive PTB, 16 were smear-negative PTB with extensive pulmonary lesion by radiography, and 13 were severe extrapulmonary TB. The 43 category II cases comprised 1 treatment failure, 19 treatment after loss, and 23 "others". Of the 41 category III patients, 25 were smear-negative PTB with mild pulmonary lesion by radiography, and 16 were less severe extrapulmonary TB.

Sputum smears were positive in 50 (76%) of 66 category I PTB cases and in 24 (56%) of 43 re-treatment cases of PTB. Overall, 74 (68%) of 109 PTB cases in category I and category II were sputum smear-positive.

There were 29 extrapulmonary TB cases in all, 13 (45%) of whom were considered severe under category I, which included 4 Pott's disease patients, 3 pleural effusion, 3 gastrointestinal TB, 2 meningitis, and 1 mediastinal lymphadenitis. The 16 (55%) less severe forms included 6 lymphadenitis, 4 non-

extensive pleural effusion, 3 TB of the bone other than the spine, and 1 each of sialadenitis, arthritis and soft tissue abscess (Table 1).

Treatment outcome

By the end of the first year, 136 patients were eligible for outcome assessment. Treatment success was attained in 108 (79.5%), which included 69 smear-negative and 39 smear-positive patients. Overall, 14 (10%) patients had treatment failure; 7 (5%) were lost, 6 (4.5%) died and 1 (1%) transferred out (Figure 2).

Table 1. Treatment categories of patients enrolled in MMC DOTS Clinic

Category	No.	%	Subtypes	No.
Category I	79	49	Smear + PTB	50
			Smear - PTB	6
			Severe EPTB*	13
			Pott's disease	4
			Pleural effusion	3
			Gastrointestinal TB	3
			Meningitis	2
			Mediastinal lymphadenitis	1
Category II	43	26	Treatment failure	1
			Treatment after loss	19
			Others	23
Category III	41	25	Smear - PTB	25
			Mild EPTB*	16
			Lymphadenitis	6
			Pleural effusion	4
			TB of the bone other than spine	3
			Sialadenitis	1
			Arthritis	1
			Soft tissue abscess	1

*EPTS-Extrapulmonary TB

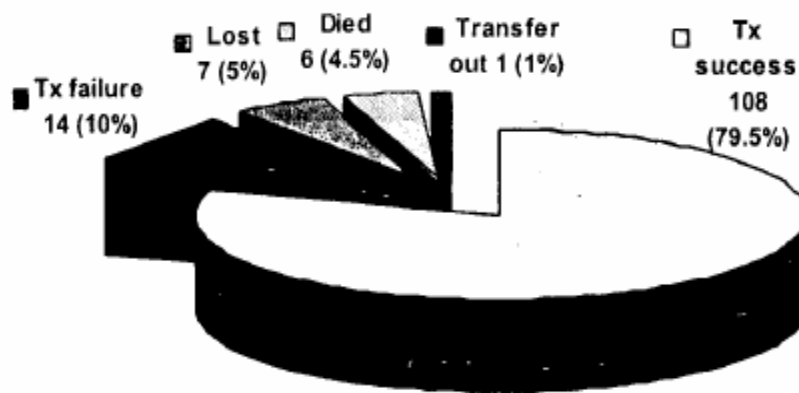


Figure 2. Treatment outcomes in 136 patients (Feb 1999-Feb 2000)

Treatment success

Of the 37 new smear-positive PTB eligible for outcome assessment, the cure rate was 84% (31 out of 37). Among the re-treatment cases, cure rate was at a low of 36% (8 out of 22 evaluables). Overall, cure was noted in 39 (66%) of 59 smear-positive PTB.

Treatment failure

None of the new smear-positive PTB cases had treatment failure. However, one patient who was initially smear and culture negative converted to culture positive on the second month of supervised treatment. This patient was later found out to be HE resistant. Treatment failure was thus noted in 1 (3%) of 37 category I cases.

Among 24 smear-positive re-treatment cases, 22 were eligible for assessment. Eight patients had MDR-TB and were still positive after 5 months of treatment using the WHO recommended empiric re-treatment regimen. An additional 5 patients had susceptibility results of MDR-TB before the 5th month of treatment; hence, these patients were likewise considered treatment failures and were shifted to appropriate second-line anti-TB agents.⁶ Treatment failure was thus noted in 13 (59%) of 22 category II cases. One of these was initially SHRE-susceptible and acquired HRS-resistance 1½ months after start of treatment. All 14 treatment failures are currently receiving supervised individualized treatment regimens (ITRS) in the DOTS clinic.

Other treatment outcomes

The most common reason for default among the 7 patients considered lost was transfer of residence. Of the six deaths, five were due to their underlying illnesses, such as colon cancer, multiple myeloma, multiple sclerosis, arrhythmia, cerebrovascular accident, while only one died of gastrointestinal TB. One (1%) patient with pulmonary TB transferred out then eventually died of TB meningitis four months later.

Drug susceptibility isolates of *M. tuberculosis*

Seventy-six (49%) of 154 patients had positive culture for *M. tuberculosis*. These include 14 cases with extrapulmonary TB. Of these 76 isolates, 43 (57%) were SHRE-susceptible, while 14 (18%) were MDR-TB, including one isolate that was not clinically compatible and was therefore disregarded. The remaining 19 (25%) were resistant to at least one drug: H-resistance was found in 13 (17%), E-resistance in 3 (4%), HE-resistance in 2 (3%), and HS-resistance in 1 (1%) (Figure 3).

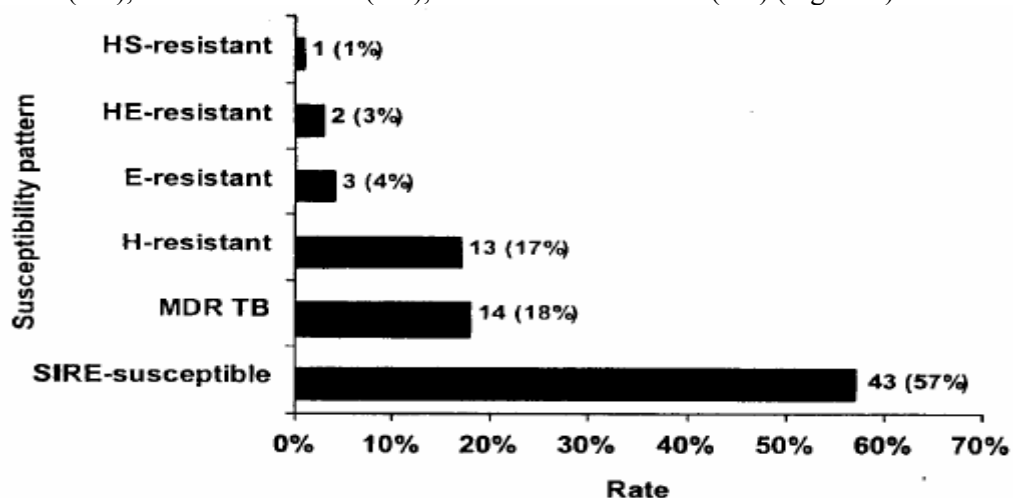


Figure 3. Drug susceptibility of 76 *M. tuberculosis* isolates

There were 51 culture-positive category I and category III (mild extrapulmonary TB) cases. Nine isolates were tested for pyrazinamide susceptibility and all were susceptible. Assuming all isolates were susceptible to pyrazinamide, 37 (72.5%) of 51 patients with HRES-susceptible isolates would have all four drugs in the category I treatment regimen effective (Table 2), 8 (15.7%) which had H-resistance and

3 (5.8%) with E- resistance would have three drugs effective. One (2%) patient who had HS-resistance would also have three drugs (RZE) effective. Another 2% who had HE-resistance would have only 2 drugs effective. One HRES-resistance was noted in a patient who responded to the WHO category I regimen of 2 HRZE + 4HR. Aside from this patient, no primary resistance to rifampicin was noted among the new cases. With respect to the WHO recommended continuation phase of HR, 10 (20%) of the 51 patients would be on monotherapy with rifampicin because of H-resistance.

Table 2. Category I (pulmonary) and Category II (mild extrapulmonary) patients enrolled at MMC DOTS Clinic

Susceptibility pattern	No. (drugs) effective		Patients N=25	
	Intensive phase 2 HRZE	Continuation phase 4HR	No.	%
HRES-susceptible	4 (HRZE)	2 (HR)	37	72.5
H-resistant	3 (RZE)	1 (R)	8	15.7**
E-resistant	3 (HRZ)	2 (HR)	3	5.8
HS-resistant	2 (RZ)	1 (R)	1	2**
HE-resistant	2 (RZ)	1 (R)	1	2**
HRES-resistant	2 (ZE)	0 (None)	1	2*

*Not clinically compatible **Rifampicin monotherapy at continuation phase

Among 25 category II or re-treatment cases enrolled in the MMC DOTS Clinic who were culture-positive, only 7 had Z sensitivity data and all were sensitive. Assuming all *M. tuberculosis* isolates to be Z-susceptible, using the WHO re-treatment regimen of 2HRZES/1HRZE/5HRE as empiric treatment, six (24%) would have all 5 drugs effective; 5 (20%) with H-resistance would have 4 drugs effective; 6 (24%) would have 3 drugs effective during the 1st two months of the intensive phase, 4 (16%) would have 2 drugs effective, and 4 (16%) would have 1 drug effective (Table 3). If at least three effective drugs are sufficient in the intensive phase, then 17 (68%) of the 25 patients would benefit from the regimen and the remaining 8 (32%) would have insufficient treatment. However, of the former, short-course therapy of DOTS would not be appropriate in five patients with HR-resistant TB and only the remaining 12 (48%) may be appropriately treated with short course therapy. Furthermore, the HE-resistant case with RZS effective in the intensive phase may succeed in attaining a negative smear by the end of the intensive phase; however, the continuation phase of HRE would be tantamount to rifampicin monotherapy.

Table 3. Category II patients enrolled in MMC DOTS Clinic

Susceptibility pattern	No. (drugs) effective using WHO re-treatment regimen			Patients N=25	
	Intensive phase		Continuation phase	No.	%
	2HRZES/1HRZE	5HRE			
HRES-susceptible	5 (HRZES)	5 (HRZES)	3 (HR)	6	24
H-resistant	4 (RZES)	3 (RZE)	2 (R)	5	20
HE-resistant	3 (RZS)	2 (RZ)	1(HR)	1	4
HR-resistant	3 (SEZ)	2 (ZE)	1 (R)	5	20
HRS-resistant	2 (ZE)	2 (ZE)	1 (R)	2	8
HRE-resistant	2 (ZS)	1 (Z)	0	2	8
HRES-resistant	1 (Z)	1 (Z)	0	4	16

DISCUSSION

This one-year experience of supervised anti-TB therapy in the MMC-DOTS Clinic demonstrates the acceptance of the DOTS strategy by TB patients. Subsidized medication and response monitoring appear to be strong incentives to patient attendance in the clinic. Defaulters were minimal and patients complied with their scheduled visits even if coming to the clinic entailed long trips. The overall dropout rate was acceptable at 5%.

The overall treatment success of 79.5% is encouraging. In those with initially smear-positive PTB, there was no treatment failure and the cure rate of 84% approximates the DOH target of 85%. Short

course chemotherapy through the DOTS strategy is no doubt effective for susceptible strains of TB. However, because of the prevalence of H resistance, standard continuation phase with HR would be a concern. Drug susceptibility testing is therefore essential. ITRs based on drug susceptibility testing (DST) through the DOTS-Plus strategy would be the ideal approach for patients with drug resistance, particularly those with MDR-TB. Thirteen of the fourteen treatment failures were found in the re-treatment group and these were all attributable to MDR-TB.

MDR-TB is a public health threat in the Philippines. The rate of MDR-TB during the 1997 nationwide tuberculosis prevalence survey (NTPS) was 4.3%; INH-resistance was 14.9%, and resistance to at least one of the first-line anti-TB agents was 17.6%.⁷ In the 1997 Sentinel Surveillance Study involving 4 sites (the National Capital Region, Zamboanga, Cebu, and La Union), the MDR rate was 5.1%, while the Multicenter TB Study done in 1998 covering seven regions reported 9.7%.⁸

With such rates of H-resistance and MDR-TB, the WHO recommended empiric treatment for category II patients may not be adequate, as a good proportion of these patients will have MDR-TB. In our series, 13 (52%) of 25 re-treatment cases had MDR-TB. In fact, the scenario may be worsened by the "amplifier effect" caused by repeated courses of DOTS in re-treatment cases.⁹ The amplification of resistance multiplies the cost of treatment in the long run, and prolongs the duration of communicability, thereby increasing the burden of illness in the community. DOTSPlus, the current approach in the management of MDR-TB through ITRs based on DST, is believed to be the more cost-saving strategy in the final analysis since it will preserve the susceptibility of the *M. tuberculosis* strain to the cheaper first-line drugs and limit the communicability to a short period of time.

After using the WHO recommended re-treatment regimen 'as empiric therapy followed by ITRs based on results of DST, cure, as demonstrated by sputum and culture conversion, is likely in 6 of 15 MDR-TB cases currently undergoing treatment in our clinic. With the high MDR-TB rate of 4.3%-9.7%, the Philippines may be considered a "hot spot" for MDR-TB, warranting the implementation of DOTS-Plus, hand-in-hand with the DOTS strategy.

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