Comparison of Modified Directly Observed Therapy versus Conventional Treatment for Active Pulmonary Tuberculosis at Veterans Memorial Medical Center

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Objectives: To compare the effectiveness of a modified direct observation therapy program versus conventional treatment in achieving treatment completion for patients with active pulmonary tuberculosis in Veterans Memorial Medical Center.
Design: 12-month prospective randomized trial.
Setting: In and outpatients seen at VMMC.
Subjects: A total of 166 patients diagnosed with active pulmonary tuberculosis according to WHO and ATS.
Main outcome measures: Improvements in clinical signs and symptoms, stable radiographic lesions, conversion to AFB sputum negative smears were noted from baseline, 2nd month, 4th month and 6th month of treatment. Emphasis on 6 month completion of anti- TB medications was made.
Results: Both groups (modified DOT versus conventional therapy) produced significant improvements in sputum conversion to negative (p value of .001), stable radiographic lesions (p value of .000) and clinical signs and symptoms: cough (p value .000), fever (p value .000), hemoptysis (p value of .000 and .004 respectively), body malaise (p value .000) and weight loss (p value .000) from baseline to 6 month treatment completion. There were no significant differences between outcome measures in both groups. Percentages of treatment completion for Group 1 and Group 2 were 100 and 96 % respectively. However, between group analysis showed no significant difference between the two (p value 0.623).
Conclusion: Modified DOT had comparable results as regards to treatment completion rates, improvements with radiologic findings, clinical signs and symptoms and conversion to sputum AFB negative smears versus conventional treatment in subjects with active PTB in VMMC. *Phil Journal of Chest Diseases. Vol 12 No. 1 pp: 1-6*

Keywords: PTB, Therapy, DOTS

Introduction

Pulmonary tuberculosis is a major public health problem, which has made a remarkable resurgence in the world today. The World Health Organization reports that every year almost- nine million people develop tuberculosis and three million people die from the disease globally.[1] Almost one third of the total global infectious cases are detected in the Western Pacific region where the cases have doubled in the last decade.[1]

In the Philippines, which have a population of 77 million, over 22 million are infected by *Mycobacterium tuberculosis,* and 234,000 develop the disease annually.[3] Tuberculosis burden reported in the WHO Western Pacific Region was 73 per 100,000 population, much higher than the regional average.[1]

The key factors to this devastating public health problem are frequent treatment interruptions and poor adherence resulting in relapse and ongoing transmission despite development of highly efficacious treatment regimens for active tuberculosis.[2] The significant increase in number of cases is due to recent transmission of infection.[3] The untreated cases serve as reservoirs to infect others and even one active case can produce a mini-epidemic.[6]

According to the Center for Disease Control and Prevention, in order to achieve cure rates greater than 90% of active tuberculosis patients and < 5% relapse rate, 90% of all cases should complete a recommended six-month three to four drug course of therapy within one year.[7] A strategy to improve adherence and completion rates for tuberculosis treatment is through Direct Observation Therapy.[1] DOT is a program

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wherein a health worker or a delegate sees the patient taking their anti-TB medication.[7]

There are several DOT programs that have different approaches in their implementation. One South African study reported that patients could choose their supervisor and the emphasis was on the patient's convenience.[8] A Thailand study also gave supervision.options and focused on convenience, which contributed to its favorable results.[9]

DOT programs are complex and varied, which is influenced by culture and the community. The task of this study is to investigate effectiveness of a modified DOT program and to compare it with conventional (self-administered TB treatment). The emphasis will be based on patient's convenience since most of the patients are in the geriatric age group.

Methodology

This study is a prospective randomized control one comparing effectiveness of a modified direct observation therapy versus conventional treatment for active pulmonary tuberculosis patients at the Veterans Memorial Medical Center (VMMC) in achieving treatment completion. All patients who were diagnosed to have PTB III (active) according to the ATS Classification or Category I or III according to the WHO guidelines, were included.[5] These are patients with clinical, bacteriological, and radiographic evidence of current tuberculosis disease. Those with new pulmonary smear positive and new pulmonary smear negative with parenchymal involvement were also included.

Patients who were excluded were those diagnosed to have multiple-drug resistance or severe illness (with liver or kidney disease), pregnant patients and patients who have started treatment elsewhere for more than two weeks.

Subjects were grouped into Group I: DOT, and Group II: Conventional Treatment (Self Administered Treatment or SAT). All patients who have extensive parenchymal lesions noted radiographically were admitted for at least two weeks. Those with sputum positive smears were admitted for two months or until sputum sero-converts to negative. Both groups were given weight-adjusted 3 or 4-drug therapy depending on the extent of the disease. *Table I* shows the recommended treatment dosage used in both groups.

Group I subjects (Modified DOT) were assigned their chosen supervisors (family members) to delegate watching intake of medication. Both patient and supervisor were educated regarding the DOT program. Subjects were required to sign the medication sheet upon intake. The supervisors were tasked to visit their physician every two weeks during the intensive phase for drug supply and for checking of signed medication sheet.

Table I Weight-Adjusted Fixed Dose Combination

ADULT	Initial Phase (2 months daily)	Continuation Phase (4 months daily)
Weight (kg)	RHZE 150mg + 75mg + 400mg + 275mg	RH 150mg + 75mg
30-37	2	2
38-54	3	3
55-70	4	4
71-90	5	5

R-Rifampicin H-Isoniazid Z-Pyrazinamide E- Ethambutol

Subjects were followed up monthly. Group II subjects were followed up at the Out-patient Department where their weight-adjusted monthly medications were provided. Supervision was not required. Both groups were monitored monthly. Chest X-ray films were evaluated prior to treatment (baseline) and 6 months after completion of medications. Clinical signs and symptoms were noted and recorded as baseline, on the second month, 4th month, and 6thmonth. Sputum AFB smears were collected and analyzed prior to initiation of anti-TB therapy, on the 2nd, 4th, and 6th month. At the end of treatment, all subjects were re-evaluated as to completion of medications without any interruptions or default; improvement of clinical signs and symptoms, conversion to sputum negative smears and stable Chest X-ray lesions.

Statistical Analysis. The two groups were compared with respect to Chest X-ray evaluation, AFB smear, clinical signs and symptoms, and completion of medication. Within groups comparison was analyzed by chi-square test, *McNemar* test. Likewise, chi-square test was used between group comparisons.

Results

During the period of July 2001 to May 2002, a total of 166 subjects were randomized. A total of 81 subjects for Group I (DOT) and 85 subjects for Group 2 (Conventional) were obtained. However, three patients were excluded in Group I (one patient diagnosed with MDRTB, one lost to follow up and one went into Acute Respiratory Failure secondary to COPD). Four patients were likewise excluded in Groups II (two lost to follow

Table II Demographic Characteristics

	DOT	Non DOT
Number of subjects included	78	81
Number of subjects excluded	3	4
Mean Age	64	61
Gender: Male	46	51 (p = 0.063)
Female	32	30 (p = 0.724)

Table III Sputum AFB Smear Positive (Within Group Comparison)

	Group I n=78	Group II n=81
Baseline	15	10
2nd month	0	0
p value	0.001	0.00
4th month	0	0
p value	0.001	0.001
6th month	0	0
p value	0.001	0.001

Table IV Sputum AFB Smear Positive (Between Group Comparison)

	Group I N=78		Group II n=81		p value
	No. of Cases	%	No. of Cases	%	
Baseline	15	19	10	13	0.329
2nd month	0	0	0	0	1.000
4th month	0	0	0	0	1.000
6th month	0	0	0	0	1.000

Table V Radiographic Evaluation of Unstable Lesions (Within Group Comparison)

	Group I n=78	Group II n=81
Baseline	78	81
6th month	0	2
p value	0.000	0.000

*In Grp II the two subjects who had unstable lesions were defaulters

Table VI Radiographic Evaluation of Unstable Lesions (Between Group Comparison)

	Group I n==78		Group II n=81		p value
	No. of cases	%	No. of cases	%	
Baseline	78	100	81	100	1.000
6th month	0	0	2	3	0.260

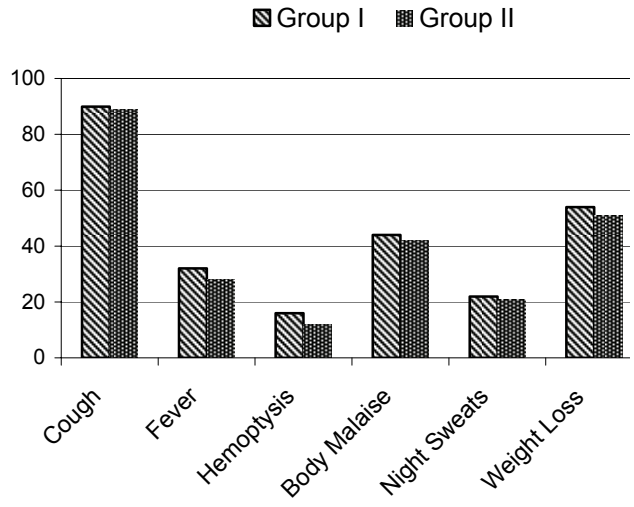

Figure 1. Baseline Distribution of Symptoms

up and two had liver disease). The demographic characteristics are summarized in *Table II*.

There was no significant difference between the two groups as regards to age and sex distribution with a p value of 0.063 and 0.724, respectively.

Sputum AFB smear was collected for three consecutive days according to WHO guidelines prior to treatment, then on the 2nd, 4th and 6th month.[5] *Table III* showed a significant conversion to negative smears in both groups whose subjects were noted to be initially sputum positive (p values of 0.002 on the 2nd, 4th and 6th month for both groups). Between Group Comparison (*Table IV*) showed no significant difference in sputum conversion between Groups I and II (p = 0.329 for baseline, p = 1.000 on 2nd, 4th, and 6th months).

Chest X-ray was evaluated in both groups prior to start of medications and 6 months after. Defaulters, subjects who had treatment interruptions for more than one month were likewise evaluated.

Both groups showed significant regression or stability of radiographic lesions (*Table V*), p value 0.000. Two of the three defaulters in Group II showed progression of radiographic lesions. However, when the two groups were compared, there was no significant difference, p = 0.260. (*Table VI*)

Table VII Signs and symptoms of patients

A.Cough					
month	Group 1		Group 2		p value
	No. of cases	%	No. of cases	%	
Baseline	70	90	72	89	1.000
2nd month	14	18	15	18	1.000
P value	0.000		0.000		
4th month	5	6	9	11	0.460
P value	0.000		0.000		
6th month	4	5	8	10	0.430
p value	0.000		0.000		
B. Fever					
month	Group 1		Group 2		p value
	No. of cases	%	No. of cases	%	
baseline	25	32	23	28	0.740
2nd month	4	5	3	3	0.960
P value	0.000		0.000		
4th month	0	0	1	1	1.000
P value	0.000		0.000		
6th month	0	0	0	0	1.000
P value	0.000		0.000		
C. Hemoptysis					
	Group 1		Group 2		p value
month	No. of cases	%	No. of cases	%	
baseline	9	16	10	12	1.000
2nd month	2	2	3	4	1.000
P value	0.391		0.015		
4th month	0	0	1	1	1.000
P value	0.000		0.004		
6th month	0	0	1	1	1.000
P value	0.000		0.004		

D. Body Malaise					
month	Group 1		Group 2		p value
	No. of Cases	%	No. of Cases	%	
baseline	34	44	34	42	0.963
2nd month	4	5	4	5	1.000
P value	0.000		0.000		
4th month	0	0	3	4	0.262
P value	0.000		0.000		
6th month	0	0	2	2	0.12859
P value	0.000		0.000		
E. Night Sweats					
month	Group 1		Group 2		p value
	No. of cases	%	No. of cases	%	
baseline	17	22	17	21	1.000
2nd month	2	3	3	3	1'.000
p value	0.003		0.001		
4th month	0	0	1	1	1.000
P value	0.001		0.000		
6th month	0	0	1	1	1.000
P value	0.000		0.000		
F. Weight Loss					
month	Group 1		Group 2		p value
	No. of cases	%	No. of cases	%	
baseline	42	54	41	51	0.804
2nd month	6	8	9	11	0.641
P value	0.000		0.000		
4th month	4	5	4	5	1. 000
p value	0.000		0.000		
6th month	0	0	2	2	0.494
P value	0.000		0.000		

Figure 1 shows baseline distribution of symptoms of both groups. Cough is the most common symptom followed by weight loss. The least common baseline symptom is hemoptysis. Other symptoms were likewise noted such as body malaise, fever, night sweats which comparatively had the same percentages in both groups.

Clinical signs and symptoms of both groups were listed and evaluated in Table 7. Between group comparisons were analyzed using McNemar test which showed no significant difference in the presenting signs and symptoms in both groups. However, within group analysis showed that there is a significant improvement and reduction of symptoms from the baseline to the 2nd, 4th, and 6th month follow-up in Groups I and II.

Group I (n=78) had 100% completion rate while Group II (n=84) had 96% completion rate. Group II had three defaulters who were not able to complete anti- TB medications. Group II had a 96% treatment completion, as compared to 100% in Group I. However, on statistical analysis, there was no significant difference between the two groups with a $p = 0.623$.

Discussion

The World Health Organization has reported that about half a million people die from tuberculosis each year.[4] Chaulk et al reported that there was a sudden incidence of tuberculosis surge from 1985 and a significant population of these cases are due to recent transmission of infection.[12] Treatment interruption or default is the major reason for resurgence and is the greatest public health challenge for tuberculosis control.[5] Block noted that in 1993 alone, twenty per cent(20%) of all patients treated for pulmonary tuberculosis did not complete therapy.[6]

The ability to predict adherence to and completion of treatment is unreliable. No demographic variable, occupation, level of income or level of education reliably and consistently predicts adherence to therapy.

To increase the probability of treatment completion, directly observed therapy has been recommended as the standard of care for pulmonary tuberculosis. The critical aim of treatment completion is to avoid the effects of non-adherence to therapy such as treatment failure rates, relapses and drug resistance. DOT prevents these problems because patients' consumption of medication is confirmed through observation whereby treatment is completed so that care is achieved.

The drawback of a strict DOT program would be taxing to both patient and health provider since frequent daily follow-ups is required. There are different DOT strategies designed to increase completion rates. The highest of which are those that used enablers and incentives, around 96.5%.[12] This study established a modified DOT program that was based on patient's convenience without using enablers or incentives.

Patient-convenience was the emphasis of the modified DOT program since the subjects were in the geriatric age. Supervisors were not health workers but family members of the patient. Management and treatment of any disease requires family support and involvement. Tuberculosis is one of them. A study by Kamoltratanakul, et al reported high completion rates in patients who were supervised by family members.[9]

The modified DOT program was then compared with the conventional management of treating pulmonary tuberculosis. The study evaluated 166 patients with active pulmonary tuberculosis. They were randomized into DOT vs conventional (self-administered) therapy and treatment outcomes were evaluated.

Both groups showed significant improvements with regards to Chest X-ray findings, negative sputum conversion, and post-treatment signs and symptoms.

Conversion to sputum negative smears was already noted on the second month of treatment. Cough and weight loss were noted to have significantly improved during the second to fourth months while the rest of the symptoms improved during the second month. A local study noted that the time of disappearance of symptoms from start of anti-tuberculosis treatment is 14-16 weeks for cough.[11] Comparing improvements in both groups showed no significant difference. This supports previous studies that treatment completion is a critical benchmark of cure.[8] Groups I and II subjects showed completion rates of 100% and 96%, respectively. Although Group II recorded three defaulters, there was no significant difference in completion rates between both groups. Since Group II subjects were likewise in their geriatric age, it was noted that they were handed and reminded about taking these medications by their care taker or family member. This was not required and emphasized to them during treatment. Medications were given for free which is a reason for high completion rate.

Review of several studies regarding DOT strategies showed that fully supervised DOT program with multiple incentives reported the highest completion rates. Chaulk et al[7] had a 90.2% completion rate while Pozsik[13] et al reported a 96.5% proportion completing therapy using incentives such as free medications, transportation fees, food, and books for patients.

Studies of DOT without enablers and incentives treatment completion rates ranged from 85-87%. Menzier et al noted an 82.6% proportion completing therapy in a modified DOT program. Non-supervised strategies were shown to have the lowest treatment completion rate ever reaching a rate of 41.9%.[6]

Relapse rates were also investigated by Alwood and revealed that self-administered treatment had a higher relapse rate ranging from 2.1 to 14%, as compared to DOT program of 0-11%.[10] Several studies have proven the importance of DOTS in completion rates for pulmonary tuberculosis especially in rural communities as compared to conventional therapy.[4] Although this study did not show significant difference between the two, it still puts emphasis on DOTS as part of tuberculosis management.

Conclusion

The World Health Organization recommends DOT program for tuberculosis treatment due to its documented efficacy in treatment completion and decrease in relapse rate.[4] The National Tuberculosis Control Program in the Philippines has placed emphasis on DOT during the intensive and maintenance phases.[5]

This study supports previous investigation that DOT is effective in treatment completion and cure rate in pulmonary tuberculosis patients. As was seen in the results, there was a significant improvement in clinical signs and symptoms, radiologic findings and sputum conversion to negative. It was however noted that in this institution, modified DOT and conventional (self-administered) treatment is comparable. Two plausible reasons are the free medications given and that the self-administered geriatric subjects were reminded about taking these medications. A wide population range would probably show a significant difference between the two since defaulters were noted in the conventional group.

The limitation of this study is that sputum AFB culture was not done due to financial constraints. Patients who were lost to follow up were excluded in the analysis, thus increasing results of completion rates. Lastly, geographic distribution of the patients was likewise not considered.

One of the most terrifying obstacles in fighting tuberculosis is the increase in multiple drug resistant-tuberculosis. Drug resistant strains of the disease are created when patients receive inconsistent, partial, incomplete treatment of anti-tuberculosis medications.

The World Tuberculosis Day Highlights commented that incomplete tuberculosis treatment is worse than no treatment at all. Reasons for incomplete tuberculosis treatment are attributed to inability to pay for the entire treatment and patient feels better so that they discontinue treatment.

Our recommendation is to establish and centralize a DOTS program in our institution to increase awareness and importance of this program to other clinicians and educate our patients on the impact of treatment completion. Lastly, we further recommend to follow- up our patients as to relapse and recurrence rates.

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A Randomized Trial Comparing Twice Weekly Clinic-Based Treatment and Daily Family Supervised Home Treatment in New Cases of Pulmonary Tuberculosis

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An open-label randomized controlled trial was undertaken to compare the acceptance and effectiveness of two methods of directly-observed treatment (DOT) clinic-based intermittent regimen and family-supervised daily treatment.

All patients aged more than 15 years seen at the Lung Center of the Philippines (LCP) Out-patient Department with a diagnosis of active Pulmonary Tuberculosis (PTB Class 3 by ATS Classification) without prior treatment were included in the study. Patients were randomly allocated to receive either intermittent treatment or daily treatment. All patients and their "treatment supervisors" received basic education on tuberculosis and an orientation on the mechanics of DOT prior to start of treatment. Patients in the intermittent group received $6H_2R_2Z_2E_2$ while those in the daily treatment group received 2HRZE/4HRE. Patients were monitored every month by symptoms, sputum smears and chest x-rays.

There were 92 patients included in the study, 46 in the Daily Regimen group and 46 in the Intermittent Regimen Group. Acceptance rate for the intermittent group was 100%. One patient allocated to the Daily Regimen declined treatment after randomization. Thus, acceptance rate was 98% in this group. The two groups were comparable in terms of baseline demographic data, clinical presentation, chest x-ray findings and sputum AFB smear positivity. Intention-to-treat analysis showed that the two groups showed no difference in terms of completion rate, compliance rate and cure rates. Completion rate was 69.6% for the daily regimen and 73.9% for the intermittent regimen. Compliance was 70% and 72% for the daily and intermittent regimens, respectively. The daily regimen had an over-all cure rate of 67.4% and the intermittent regimen, 71.9%. Among patients who completed their assigned regimen, the cure rate was nearly identical at 96.9% (31/32) in the daily regimen and 97.0% (33/34) in the intermittent regimen. There were four recorded deaths, with two coming from each study group. Two patients died due to severe TB disease. The other two deaths were not related to the treatment.

The Intermittent regimen showed a higher percentage of patients reporting any adverse event and hypersensitivity reactions but these were not statistically significant. However, the intermittent group showed a significantly higher incidence of nausea and vomiting while the daily regimen showed a significantly higher rate of joint pains.

The study concluded that the twice weekly hospital-based regimen and the daily home-based family-supervised regimen are comparable in terms of rates of completion, compliance and cure. The intermittent regimen is associated with a significantly higher incidence of nausea and vomiting while the daily regimen has a higher incidence of joint pains. *Phil. Journal of Chest Diseases Vol 12 No. 1 pp: 7-11*

Keywords: PTB, Therapy, DOT

Introduction

Patient compliance is considered a key factor in the success of treatment of tuberculosis. Ensuring adherence promotes early conversion of smear-positive cases which prevents further spread of the infection, as well as prevents the emergence of drug resistance.[1,2]

Directly-observed treatment (DOT) is a strategy to ensure patient compliance wherein a supervisor watches the patient swallowing the tablets. This ensures that a TB patient takes the right drugs, in the right doses, at the right intervals.[1,3] DOT can be carried out in a number of different ways, depending on the particular setting, facilities, resources and environment. This may be done in an in-patient setting or an out-patient setting. It may be administered by a health worker or by a trained and supervised community member. It may be given daily or intermittently, twice or thrice weekly.

Many patients with tuberculosis consult in out-patient clinics of secondary or tertiary hospitals for diagnosis and treatment. DOT treatment in this setting may be difficult because patients may find it inconvenient or expensive to go to the clinic twice or thrice a week to take their medications if they live far way from the health facility. However, Romulo and co-workers in 1997[4] have shown in a pilot study that clinic-

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based DOT with an intermittent treatment regimen is feasible in the urban Philippine setting with a high acceptance among TB patients and reasonable toxicity profile. They utilized a twice weekly regimen wherein patients were required to report to the clinic for the ingestion of all doses. This was compared with a non-DOT group wherein patients reported to clinic once a week for pick-up of medications. Completion rate was 63% for the DOT group and 61% in the non-DOT group. Based on this result, there doesn't seem to be an advantage for the twice weekly regimen under DOT in the clinic setting as compared to the usual home-based treatment. In the study of Romulo and co-workers treatment allocation was not randomized so that factors other than treatment regimen may have affected the results. Our present study aims to further test the hypothesis that use of the intermittent regimen under the DOT method results in higher completion rates among hospital-based patients using a randomized clinical trial design.

Methodology

Inclusion Criteria: All patients aged more than 15 years seen at the Lung Center of the Philippines (LCP) Out-patient Department with a diagnosis of active Pulmonary Tuberculosis (PTB Class III ATS Classification) without prior treatment were included in the study.

The diagnosis of PTB was made based on a positive AFB smear or chest x-ray findings suggestive of PTB such as apical or upper lung field infiltrates, cavitation or miliary pattern with typical clinical presentation such as cough > 2 weeks, hemoptysis, weight loss, afternoon fever and chest pain.

Since the program required frequent follow-up visits, the patient should be a resident of Metro-Manila and should be willing to sign a written contract to follow-up on a regular basis at the OPD.

Exclusion Criteria: Re-treatment cases, whether because of previous treatment failure or relapse, and documented multi-drug resistant (resistance to INH and rifampicin) tuberculosis were excluded. Also excluded were patients with on-going chemotherapy, known intolerance to any of the four anti- TB drugs, history of liver disease, current pregnancy or nursing and severe medical illness.

All patients meeting the criteria were randomly allocated to either of 2 methods of Directly-Observed Treatment (DOT) namely, daily home therapy supervised by a household member, or a hospital-based intermittent (twice weekly) regimen.

Daily Family-Supervised Home Therapy: All patients randomized in this group were required to designate a relative or household member to act as his/her "*treatment supervisor"* during the treatment period. The *supervisor* should be: a) a regular household member; b) at least an elementary graduate; c) able to understand instructions in both Filipino and English; d) willing to sign a contract to act as supervisor; and e) has a verifiable address or telephone number to facilitate follow-up.

If the designated *supervisor* met all requirements, he/she together with the patient, underwent a brief course of instructions on tuberculosis and TB treatment. The instructions were provided by a trained public health nurse using prepared teaching materials.

The instructions consisted of the following topics:

1 Brief review of the disease, including how the disease is contracted and spread

2 Basic principles of treatment

3 Monitoring of adverse effects/reactions

4 Signs of favorable response to treatment

5 Consequence of failure of treatment

6 Mechanics of the DOT program, including schedule of drug intake, schedule of pick- up of medications and follow-up visits.

Once instructions were completed, the treatment period was started. The regimen consisted of four drugs (2HRZE/4HRE), given once daily under the direct visual supervision of the designated household member. The drugs were provided by the Lung Center of the Philippines (LCP) for free and were picked up by the patient or his/her supervisor every week. The dosages of the drugs were as follows: Rifampicin, one 450 mg capsule; Isoniazid, one 300 mg tablet; Pyrazinamide, three 500 mg tablets; and Ethambutol, two 400 mg tablets. All drugs were taken in the morning after breakfast.

During the treatment period, the *supervisor* had the following duties and responsibilities:

1 Procure the drugs from the patient every week whenever the patient is unavailable;

2 Personally administer the drugs to the patient;

3 Keep a record of the date and time of drug administration;

4 Collect the blister-packs of consumed drugs and return them for counting

5 Accompany the patient during follow-up visits.

The *supervisor* was given free annual chest x-rays and consultations by LCP as incentive for his/her participation.

Hospital-based Intermittent (Twice Weekly) Regimen: All patients under this group, underwent the same pre-treatment training given to patients in the other group. After completion of the instructions, the treatment period was started. Patients were instructed to go to the DOT Clinic every Tuesday and Friday of the week to take their medications, which was observed directly by a physician or public health nurse in the clinic.

The regimen consisted of four drugs given for six months. The doses for the four drugs under the twice weekly regimen was as follows: Isoniazid, 15 mg/kg, maximum of 800 mg per day; Rifampicin, 10 mg/kg, maximum of 600 mg; Pyrazinamide, 50-70 mg/kg, maximum of 3.5 grams; and Ethambutol, 50 mg/kg, maximum of 2.4 grams. The pills were taken leisurely over one hour or less with water or any beverage.

If the patient could not meet a schedule, he was instructed to call the clinic by telephone to re-schedule drug intake to the following days. If the patient was not present during a scheduled follow-up and there was no notification by the patient, a clinic nurse contacted the patient either by phone, if available, or went to the patient's residence to administer the drugs and advise follow-up at the clinic for the next dose. If the patient regularly failed to take his medications at the clinic despite the frequent home visits or notification (at least four times in a month), the patient is considered non-compliant and unsuitable for the intermittent regimen, and hence dropped from the program. However, he was still prescribed the drugs for the standard short-course regimen (2HRZE/4HRE) and advised instead to follow-up at the regular OPD clinic.

Follow-up: All patients were required to follow-up with the DOT Clinic physician every month for 6 months for assessment of compliance recording of adverse drug events and evaluate clinical, bacteriologic and radiologic response to the treatment regimen.

Monitoring compliance: Compliance was assessed by clinic visits and pill count. Patients were classified as compliant during a visit if he/she consumed at least 80% of the prescribed drugs based on empty package wrappers and returned unconsumed pills. Patients were considered compliant for the whole treatment course if they consumed 80% of the total required number of pills and came to the clinic for at least four of the six scheduled visits.

Monitoring adverse effects and treatment response: Monitoring of adverse reactions consisted only of asking during the visit for particular symptoms like GI upset, jaundice, paresthesias and other neurological complaints. Laboratory examinations like liver function test, complete blood count and serum uric acid were requested if clinically indicated. Gastrointestinal complaints, if mild and tolerable, were managed by changing time of intake of drugs or giving antacids, H_2-blockers or antiemetics. Severe GI manifestations and jaundice were managed by stopping all medications and monitoring LFTs. Hypersensitivity reactions were treated with anti-histamines if mild, and by temporary cessation of medications and further observation. Arthralgia or frank arthritis due to hyperuricemia was treated with allopurinol, NSAIDs or by cessation of pyrazinamide, if indicated. Withdrawal from the program was done for severe adverse effects which required major adjustment of dosages or warranted prolonged cessation (> 2 weeks) of the regimen.

Clinical response was determined by the presence of local and constitutional signs and symptoms during the monthly visits. Chest x-rays were repeated at three months and at the end of treatment. Sputum microscopy was repeated at two, four and five months if the previous AFB smear was positive.

Withdrawal of patients: Patients were withdrawn from the DOT program if they: consistently failed to pick up their medications at the appointed schedule stopped medications on the advise of the physician for more than two weeks, transferred to other residence without notification refused to take medications or requested to withdraw for whatever reason.

Outcome Measures: The two regimens were assessed according to rate of acceptance, compliance, completion and cure.

Acceptance rate was assessed by computing the percentage of patients who agreed to follow their prescribed regimen among all the eligible subjects randomized to the group.

Completion rate was assessed as the percentage of patients completing the prescribed six-month regimen under the DOT program.

Compliance rate was the percentage of patients considered compliant by pill counts and follow-up visits.

Cure rate was the percentage of patients assessed as cured based on: a) clinical response (defervescence, weight gain, diminution of cough and phlegm or resolution of hemoptysis); b) regression of radiologic infiltrates; and c) sputum conversion, if initially positive.

Table I Baseline characteristics of included patients (%).

	Daily Regimen (n=45)	Intermittent Regimen (n=46)	*p* value
Age, yrs (mean + SE)	36.55 + 2.32	36.09 + 2.08	NS*
Sex (M:F)	28: 17:00	23:23:00	NS
Residence within QC	34 (76)	32 (70)	NS
Cavitary disease	24 (53)	31 (67)	NS
Bilateral disease	34 (76)	32 (70)	NS
Smear positive	30 (67)	23 (50)	NS
Cough	42 (93)	43 (93)	NS
Hemoptysis	20 (44)	19 (41)	NS
Weight loss	38 (84)	39 (85)	NS
Fever	33 (73)	33 (72)	NS
Chest pains	35 (78)	38 (83)	NS

NS = not significant

Table II Treatment Outcomes

OUTCOME	Daily Regimen (n=45)	Intermittent Regimen (n=46)	p value
Completed treatment	32 (71.1 %)	34 (73.9%)	
Withdrawn/lost	11 (24.4%)	10 (21.7%)	NS
Died	2 (4.40/0)	2 (4.3%)	
Good compliance	32 (71.1%)	33 (71.7%)	NS
Cure	31 (68.9%)	33 (71.7%)	
Treatment failure	1 (2.2%)	1 (2.2%)	NS
Unknown status	13 (28.95)	12 (26.1 %)	

NS = not significant

Statistical Analysis: Baseline demographic data, clinical presentation, chest x-ray findings and sputum positivity of all included subjects in the two groups were compared and analyzed by *t-test* or *chi square test*. Intention-to-treat analysis of rates of acceptability, completion, compliance and cure for all included subjects in the two groups were done using the *chi square test* to determine statistical significance. Efficacy analysis of the cure rates among patients completing treatment was also done. A $p < 0.05$ was considered significant.

Table III Adverse events

	Daily Regimen (n=45)	Intermittent Regimen (n=46)	p value
Any adverse event	22 (48.9%)	31 (67.4%)	NS
Pruritus	8 (17.8%)	14 (30.4%)	NS
Nausea	2 (4.4%)	10 (21.7%)	0.02
Vomiting	1 (2.2%)	9 (19.6%)	0.02
Dizziness	3 (6.7%)	9 (19.6%)	NS
Abdominal pain	4 (8.9%)	3 (6.5%)	NS
Drowsiness	2 (4.4%)	3 (6.5%)	NS
Joint pains	8 (17.8%)	2 (4.3%)	0.04

NS = not significant

Results

There were 92 patients included in the study, 46 in the Daily Regimen group and 46 in the Intermittent Regimen Group. Acceptance rate for the Intermittent group was 100%. One patient allocated to the Daily Regimen declined treatment. Thus, acceptance was 98% in this group.

Table I shows comparison of the baseline demographic data, clinical presentation, chest x-ray findings and sputum AFB smear positivity for the two study groups. The two groups were considered comparable.

Intention-to-treat analysis showed that the two groups showed no difference in terms of completion rate, compliance rate and cure rates. Completion rate was 69.6% for the daily regimen and 73.9% for the intermittent regimen. Compliance was 70% and 72% for the daily and intermittent regimens, respectively. The daily regimen had an over-all cure rate was 67.4% and the intermittent regimen, 71.9%. *Table II* shows the outcome of the treatments.

Among patients who completed their assigned regimen, the cure rate was nearly identical at 96.9% (31/32) in the daily regimen and 97.0% (33/34) in the intermittent regimen.

There were four recorded deaths, with two coming from each study group. Two patients, one from each group, were hospitalized at the Quezon Institute shortly after entry and died due to severe TB disease. The other two were doing well with their regimen when they died unexpectedly. One patient died in the Payatas garbage

dump accident and the other died of unknown cause. Both deaths were probably not related to the treatment.

Table III shows the incidence of adverse events recorded for each treatment regimen. The Intermittent regimen showed a higher percentage of patients reporting any adverse event and hypersensitivity reactions but these were not statistically significant. However, the intermittent group showed a significantly higher incidence of nausea and vomiting while the daily regimen showed a significantly higher rate of joint pains.

Discussion

The only proven way of ensuring adherence to the treatment regimen in tuberculosis is the directly-observed treatment (DOT) method. However, there is no single method of implementing DOT that is applicable for all situations. The way of ensuring direct observation of treatment depends on the setting, facilities, resources and environment. The Lung Center of the Philippines is a tertiary center for chest and lung diseases which receives referrals for TB not only from the nearby areas in Quezon City but also from more distant places within and outside of Metro Manila Area. The present study is aimed at determining which method of DOT works better in our setting: the intermittent clinic-based treatment or the daily family-supervised home-based treatment. The results show that the outcome between the two methods are the same in terms of rates of completion, completion and cure.

The completion rates in this study are slightly higher than those recorded by Romulo and coworkers.[4] The improved outcomes may be due to the components of the DOTS strategy adopted by LCP for its patients. These include the provision of free medications, use of treatment contracts, tracing of defaulters and use of treatment "supervisors" for those in the home-based regimen.

In terms of adverse events, the patients in the intermittent regimen had more complaints of any side effect, 67.4% versus 48.8% in the daily regimen, although this was not statistically significant. Hypersensitivity reactions (pruritus with or without rashes), nausea and vomiting are also more common with the intermittent group. The greater number of gastrointestinal complaints in the intermittent may be due to the ingestion of a large number of pills in this group. They particularly complained of the bitter taste of the pyrazinamide tablets. Joints pains were more frequently reported when administered daily, as would be expected. It is recommended that to reduce the incidence of hyperuricemia and arthralgia, regimens with intermittent administration should be prescribed.[2] While there was a high incidence of adverse events in this study, most of them were self-limiting and only required symptomatic treatment. However, it is possible that adverse events may have contributed to the decision of some of the patients to withdraw or drop-out.

The over-all cure rates of the two methods in this study were only around 70%, which falls short of suggested target of 85%.[1] Further efforts must be exerted to improve the completion rates and cure rates either by refining the selection criteria, improving tracing of defaulters or tailoring the treatment regimen to the patient's ability to comply.

Conclusion

The present study shows that in the Lung Center setting, the twice weekly hospital-based regimen and the daily home-based family-supervised regimen are comparable in terms of rates of completion, compliance and cure.

The intermittent regimen is associated with a significantly higher incidence of nausea and vomiting while the daily regimen has a higher incidence of joint pains.

Recommendations

Patients seen at the OPD clinic of the Lung Center of the Philippines should be offered DOT using either the intermittent or daily regimen and they should be allowed to select which regimen they prefer depending on their personal situation.

Patients may also be shifted to the other regimen if they encounter severe or troublesome adverse effects on their chosen regimen.

Methods to further improve completion rates should be adapted, including better methods for tracing of defaulters, modifying the selection criteria, and provision for incentives for completers and their family supervisors.

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Non-Compliance to Anti-Tuberculosis Regimen among Adult Patients with Tuberculosis at the University of Santo Tomas Hospital DOTS TB Clinic

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OBJECTIVES: To determine the prevalence and the risk factors for non-compliance to anti-tuberculosis regimen among adult patients with tuberculosis in the University of Santo Tomas Hospital DOTS TB clinic

DESIGN: Nested case control design

SETTING: DOTS TB Clinic of a private tertiary university hospital in Manila

PARTICIPANTS: Consecutive patients (N-217) enrolled in the TB Clinic from January 1997 to Dec 2000 were included in the study.

INTERVENTION / METHODOLOGY: All subjects enrolled in the DOTS project Charts of all subjects (DOTS and SAT patients) were reviewed for their personal data, demographic profile and epidemiological profile. Patients were classified into cases (non compliant patients) and control (compliant) based on the WHO criteria for compliance-being available for DOTS therapy 80% of the time or taking 80% of the prescribed medication. Risk factors to non compliance such as age, sex, employment status, distance of the home from the TB clinic, smoking history, alcoholism, any history of substance abuse, presence of co morbid illness, history of previous TB treatment, exposure to TB patients, occurrence of adverse drug reaction, present treatment strategy and regimen were compared in cases and control.

Data will be analyzed using *Intercooled Stata* ver 5.0 and odds' ratio for each specific risk factor was computed by constructing a 2 x 2 table for to quantitate the association between potential risk factors and the occurrence of noncompliance. Factors with associated with noncompliance with $p < 0.1$ in bivariate analysis will be included in a multivariate logistic regression model.

OUTCOME MEASURES: A. Primary Outcomes 1. Prevalence of non-compliance to anti-tuberculosis regimen in the USTH DOTS TB clinic 2. Demographic and Epidemiological Profile of all entries in the USTH DOTS TB clinic from January 1997 to December 2000. 3. Comparison of the demographic and epidemiological profile between compliant (control) and non-compliant patients (cases). 4. Risk factors to non-compliance

RESULTS This is a preliminary report on the prevalence of non-compliance and risk factors to the same. Of the 217 patients seen and started treatment for tuberculosis, 190 patients (87%) agreed to be included in the DOTS program. The remaining 27 (13%) underwent treatment with self-administered therapy (non-DOT or SAT). No attempt was made to match the two groups. Non compliance in the DOT group was lower, 15 (8%) compared to 9 (33%) in the non-DOT group. However, statistical analysis of the results showed the strategy of treatment (DOT vs non-DOT) had no effect on compliance; it was independent of compliance to treatment.

The demographic, socio-economic, and clinical profile of compliant vs noncompliant patients in the DOT and non-DOT group were compared and it was noted that specific variable that had a probable effect on compliance were male, area of residence more than the 5km radius of the USTH catchment area, (+) history of alcoholism, associated co morbidity, severe disease on chest radiograph and extra pulmonary TB. However, these results may be inconclusive because of the limited sample size.

It is the hope of the authors to come up with a full report and a bigger sample size. A predictive model for possible defaulters of outpatient DOT will be the subject of future studies. Comparison of the outcomes of patients who defaulted from treatment vs. those who complied with the prescribed regimen will also be the subject of future studies. *Phil Journal of Chest Diseases. Vol. 12 No. 1. pp: 12-16*

Keywords: DOTS, PTB, Anti-TB therapy

Introduction

Tuberculosis kills 2 million people each year. The global epidemic is growing and becoming more dangerous. The breakdown in health services, the spread of HIV/AIDS and the emergence of multidrug-resistant TB are contributing to the worsening impact of this disease.[13]

According to the World Health Organization (WHO), the Philippines is one of the 22 countries in the world, which account for 80% of the world's TB cases.

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Routine reporting systems consistently place tuberculosis among the top five causes of morbidity and mortality in the country. The rates for 1994· were 244.5 per 100,000 for morbidity and 39.81 per 100,000 for mortality. It is important to note that these figures, particularly morbidity, do not include the TB patients exclusively going to the private sector.[14]

Compliance can be defined as the extent to which patient's behavior coincides with medical advice.[1] No method used to assess compliance is applicable in all settings.[2]. Pill counting and measurement of drug levels in the urine are some of the more accurate ways of measuring drug compliance

Poor compliance may produce adverse effects on the quality of medical care and may waste resources. First, it interferes with therapeutic efforts by reducing the benefits of the preventive or curative services offered. Second, non-compliance may cause unnecessary diagnostic and treatment procedures, thus generating further costs. Third, poor compliance with treatment for infectious disease can increase the probability of the development of drug resistant strains and the possibility of infecting others. And because tuberculosis is a social disease, the last account is of special concern.

Table I Relative Risk of Selected Demographic and Epidemiologic Factors for Noncompliance with Outpatient DOT for TB, Denver Metro Tuberculosis Clinic, 1984-1994 [12]

FACTOR	% Non-compliant with Factor	% Non-compliant without Factor	RR (95% CI)	p Value
AGE> 42	26/140(19)	26/154(17)	1.1(0.7,1.8)	0.8
MALE	45/220(20)	7/74(9)	2.2(1.0,4.6)	0.03
ALCOHOLISM	38/115	14/179(8)	4.2(2.4, 7.4)	0.0001
HOMELESS	25/55 (45)	27/239 (11)	4.0 (2.5, 6.4)	0.0001
IV DRUG USE	2/19 (11)	50/275 (18)	0.6 (0.2, 2.2)	0.54
PRIOR THERAPY				
FOR ACTIVE TB	5/29(17)	47/265(18)	1.0(0.4,2.3)	1.0
TOXICITY FROM TX	6/35(17)	46/259(18)	1.0(0.4, 2.1)	1.0
HIV POSITIVE +	8/28(29)	44/265(17)	1.7 (0.9, 3.3)	0.12
DRUG RESISTANT				
ISOLATE*	7/47(15)	32/175(18)	1.0 (0.5,2.1)	1.0

+ Compared to patients having either a negative HIV serologic test result or whose HIV status was unknown

* Resistance to INH, Rifampicin, PZA, Streptomycin or EMB among the isolates from the 222 patients with a culture positive for *Mycobacterium tuberculosis* and results of susceptibility testing available

Noncompliance with self-administered multi-drug tuberculosis treatment regimens is common and is the most important cause of failure of initial therapy and relapse.[3-8]

Noncompliance may result in acquired drug resistance,[8] requiring more prolonged and expensive therapy that is less likely to be successful than the treatment of drug-susceptible tuberculosis.[9] In response to these findings, there is increasing emphasis on the use of directly observed therapy, in which a health worker observes the ingestion of each dose of anti-tuberculosis therapy. The adoption of DOT has been associated with reduced rates of treatment failure, relapse and drug resistance.[9]

The report from WHO's TB Programme said DOTS is the most cost-effective way to control TB in communities with a high incidence because it both cures the sick and protects the uninfected by interrupting the source of transmission of pulmonary TB contagious human beings.[13]

A DOTS programme in New York City has reduced TB by 21 % since 1992 and reduced the number of new drug-resistant TB cases by more than 25%. Just like New York, Tanzania - one of Africa's poorest countries - and China - the world's most populous nation - have registered impressive cure rates. And, just like New York, the secret of those isolated successes is DOTS.[13]

DOTS produces cure rates of up to 95 percent even in the poorest countries. DOTS prevent new infections by curing infectious patients. DOTS prevents the development of MDR-TB by ensuring the full course of treatment is followed.

A six-month supply of drugs for DOTS costs US $11 per patient in some parts of the world. The World Bank has ranked the DOTS strategy as one of the "most cost-effective of all health interventions."

Since DOTS was introduced on a global scale, millions of infectious patients have received effective DOTS treatment. In half of China, cure rates among new cases are 96%. In Peru, widespread use of DOTS for more than five years has led to the successful treatment of 91 percent of cases.[13]

Non-compliance with multidrug prolonged therapy required to cure tuberculosis is common[3-8] and results in treatment failure and relapse, sometimes with the acquisition of drug resistance.[9] Directly observed therapy markedly improves compliance with treatment regimens and decreases the rate of relapse and

Table II. Results of a Multivariate Logistic Regression Model for Non-compliance with Outpatient DOT[12]

Factor	Odds Ratio	95% CI	p Value
Male	1.3	(0.5, 3.3)	0.66
Alcoholism	3.0	(1.2, 7.5)	0.02
Homelessness	3.2	(1.5, 7.2)	0.004

development of drug resistance.[9] However, the use of directly observed therapy does not by itself ensure compliance with tuberculosis treatment.

In a study done in Denver by Dr. Sbarbaro and colleagues, noncompliance with DOT was common and was closely associated with alcoholism and homelessness. Noncompliance was associated with a 10-fold increase in the occurrence of poor outcomes from treatment and accounted for most treatment failures (*see Table I*).[12]

Despite the impressive gains in compliance associated with the use of DOT, noncompliance with DOT also occurs when patients fail to make themselves available for administration of drug therapy [12]. This study was done to assess the prevalence of non-compliance and risk factors to non-compliance in an outpatient DOTS clinic. Armed with these information, we may have better clinical outcomes and be able to maximize benefits of intermittent outpatient DOTS for tuberculosis.

We performed a retrospective study among adult patients with tuberculosis who were enrolled at the University of Santo Tomas TB clinic from 1997 to 2000 to be able to arrive at our conclusions.

The objectives of the study were to determine the present prevalence rate of noncompliance to DOTS regimen in an institutional setting and possible risk factors associated with noncompliance to anti TB regimen.

Methodology

Design: Nested Case Control Design

Setting: The TB clinic of a private tertiary university hospital in Manila

Study Population The study population included are patients enrolled in the UST TB clinic from January 1997 to December 2000 (N-217 patients).

Criteria for the Diagnosis of Tuberculosis Clinical Signs and Symptoms suggestive of Tuberculosis (chronic cough, fever, weight loss, anorexia, hemoptysis, etc), PLUS Typical radiographic lesions (minimal, moderately advanced or far advanced), OR AFB smear positive, and/or AFB culture positive

Patients enrolled in the DOTS program at the University of Santo Tomas TB Clinic underwent radiographic and sputum examination and were further classified on entry based on the WHO criteria [14] as:

New- A patient who has never had treatment for TB or who has taken anti-tuberculosis for less than 4 weeks

Relapse- A patient who has been declared cured from any form of TB in the past by a physician, after one full course of chemotherapy, and has become sputum smear-positive

Transfer In- A patient who was previously undergoing treatment either SAT or DOT from another institution

Treatment After Loss/interruption- a patient who interrupts treatment for two months or more, and returns to the health service with smear-positive (sometimes smear-negative but still with active TB as judged on clinical and radiological assessment).

Treatment Failure-A patient who, while on treatment, remained or became again smear-positive five months or later after commencing treatment. It is also a patient who was initially smear-negative before starting treatment and became smear-positive after the second month of treatment

Other- Not classified as any of the above

Interventions All patients seen and treated for tuberculosis (DOT or SAT/non DOT groups) were included in the study. The population was divided as to whether they were part of the DOT or non DOT group. Subjects were sub-classified as either control or cases. Cases were those patients who missed more than 20% of their scheduled clinic appointments or who were unable to take 80% of the total prescribed medication. Controls were those patients who were able to take 80% or more of the prescribed drug regimen and were available for their clinic appointments 80% of the time. The charts of all these patients were reviewed for their demographic, socio economic and clinical profiles. Comparison of the profile of the compliant and non-compliant patients was done and the relationship between risk variables and outcome variable was assessed.

0utcome Measures

A. Primary Outcomes 1. Prevalence of non-compliance to anti-tuberculosis regimen in the USTH DOTS TB clinic; 2. Demographic and Epidemiological Profile of all entries in the USTH DOTS TB clinic from January 1997 to December 2000. 3. Comparison of the demographic and epidemiological profile between

compliant (control) and non-compliant patients (cases).
4. Risk factors to non-compliance

Data Analysis Data were entered and analyzed using *Intercooled Stata version 5.0* and odds' ratio for each risk factor were computed by constructing a 2 x 2 table for each specific factor to quantitate the association between potential risk factors and the occurrence of noncompliance. Factors associated with noncompliance with a $p \leq 0.1$ in bivariate analysis were to be included in a multivariate logistic regression model.

Results

Two hundred seventeen cases of tuberculosis were started treatment at the UST TB Clinic from January 1997 to December 2000; all of these patients were invited to enroll in the DOTS program. One hundred ninety (87%) of these patients agreed to participate in the DOTS program, 27 (13%) patients underwent anti-tuberculosis treatment with self-administered therapy (SAT or non DOT). Demographic data, socio economic status and compliance rate between the two groups were compared. No attempt was made to match the patients between the two groups. Fifteen patients (8%) satisfied the criteria for non-compliance in the DOT group and nine (33%) for the non DOT group. Although in both instances, the TB clinic supplies the anti-tuberculosis medication for the patient, in the non DOT program, the patient is expected to return weekly to the clinic to pick up the free anti-TB medications and the patient is expected to take these medications daily as directed. The responsibility of taking the drugs and completing the treatment regimen therefore falls mainly on the patient. This is in contrast to the DOTS strategy wherein the TB clinic nurse is present to supervise all doses of anti-TB medications and is in charge of following up patients who may have missed some of their doses. This is probably the reason for the better compliance in the DOT group.[17]

The DOTS regimen followed by the UST TB clinic is a twice weekly, intermittent regimen using four drugs (HRZE) in the intensive phase of treatment. It follows the recommendation offered by the American Thoracic Society for the empiric treatment of tuberculosis.[15]

Of the 190 patients enrolled in the DOTS program, 117 (66.9%) lived within the UST catchment area, whereas for those patients under the SAT program 8 (44%) lived within the UST catchment area. Odds' ratio for this variable is 1.8. Distance from the DOT clinic may play a role in the compliance of a patient.

We also considered age, sex, civil status and employment as probable risk factors to non-compliance. In a study by Sbarbaro[12] and colleagues in the Denver Metro TB clinic, male sex, was associated with non-compliance to DOTS therapy in an outpatient setting (Odds' Ratio of 1.3,CI 0.5,3.3). However in a separate series done in 1996 by Caminero, et al[16] abandonment of treatment occurred more frequently in women aged less than 55 years. In our study, the preliminary report showed significant association between sex and compliance to treatment (OR 1.37). The civil status and employment status had no association to non-compliance to DOT regimen (OR 0.56 and 0.52, respectively).

Because homelessness, alcohol abuse/chronic alcoholism, extra pulmonary tuberculosis, abandonment of treatment in the past and poor adherence to treatment at the end of the 2nd month are often sited in literature as risk factors to non compliance (both in the series done by Sbarbaro, et al and Caminero, et al), we studied these factors in our patients in the TB clinic. Significant alcohol intake, presence of significant co morbidity, class (pulmonary or extra pulmonary) of tuberculosis (OR 1.8, 4.6. and 2.4, respectively) may be risk factors to non-compliance to outpatient DOT strategy.

We went further and looked into whether the severity of the disease based on the patients' symptoms, chest x-ray, AFB smear or MTB culture plays a significant role in identifying potential defaulters in the treatment. We found that severe disease (by chest radiography) is a risk factor to noncompliance. AFB (+) smears, however is a not a risk factor to noncompliance (OR 0.87) and may even be interpreted as a factor which may affect compliance.

Previous TB treatment, from our preliminary studies is not a risk factor to noncompliance (OR 0.45). However, presence of co morbid illness (OR 4.6) may be a significant risk factor to non-compliance.

Discussion

The aim of all antituberculosis programs is to increase the cure rate of patients Receiving treatment (18-20). Although achievements of this goal is hindered by Unfavorable socioeconomic and organizational conditions as in a developing nation like the Philippines, the implementation of appropriate controlled programmes based on short-term chemotherapy has proved successful in obtaining a high cure-rate amongst smear-positive patients.[21-22].

In order to increase the cure rate, it may be necessary to supervise the administration of all medications strictly[23] and to find low cost and effective regimens. It is often theorized that the primary reason for defaults in the treatment of patients with tuberculosis

in the Philippines is financial in nature. Patients cannot afford to buy the medicines; therefore, they would not be able to comply with the treatment. If this was the sole cause of non-compliance, the availability of free TB medicines in the different health centers should have solved our problems. But why is it that despite the availability of free drugs patients could still not comply with the treatment? We tried to look for factors, which could be predictors for defaulters.

The effect of socio-economic status on compliance should not be overlooked. Because the patient has to report to the clinic twice a week to ingest the medications, in a patient who is employed and supporting a family, the missed days from work could be a factor in compliance. On the other hand, because the head of the family should be well and be able to work productively, makes this person react more responsibly with regards to complying with the treatment. The results of our preliminary studies showed that male sex is a risk factor to non-compliance. This is because the Filipino family is still patriarchal, the head of the family is the father, who is the breadwinner and provides financial support for the family. The father would default from treatment because of the fear of missing days from work, which would mean less income to support the family.

Living outside of the five km area radius of the UST catchment area may be a significant factor to non-compliance. Revisions in the program, including encouraging people outside of the UST catchment area to enroll in an area nearing their residence would increase compliance to treatment. Furthermore, encouraging people with tuberculosis within the 5 km radius of the UST catchment area to enroll in the UST TB clinic can improve the services of the TB clinic and may help in decreasing the incidence of TB mortality and morbidity and reduce the incidence of MDR-TB in the area.

Presence of co morbid illness, severe disease and extra pulmonary TB are probable risk factors to noncompliance based on this preliminary study. Stressing to these patients the need to comply with the regimen by extensive lectures may improve compliance of these patients.

Non-compliance with therapy also has adverse consequences for the community - transmission of tuberculosis to contacts during periods of non-compliance. TB is not simply a disease of an individual person but a social disease because of its high infectivity. Therefore ways should be done to identify high-risk defaulters so that these persons can be monitored more closely. Management of non-compliance is the most important issue facing the DOT program.

Because this is only a preliminary report and we were limited by the small sample size (only 8% of the DOT group were non-compliant), we hope to come up with a predictive model for possible defaulters in treatment in the future. This could help the physician and health worker in monitoring patients.

And because most literature showed that most poor outcomes occurred among patients who defaulted from treatment, we also hope to compare the outcome of treatment between compliant and non-compliant patients in the succeeding studies in the future.

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Appendix 1 Comparison of the Demographic, Socio-economic and Clinical profile among DOTS Patients (Compliant and Non-compliant) and SAT Patients (Compliant and Non-compliant), UST TB Clinic, January 1997- December 2000, (n=217)

Variable	DOT Group Compliant (n=175)	DOT Group Non-compliant (n=15)	SAT Group Compliant (n=18)	SAT Group Non-compliant (n=9)
Age				
Arithmetic mean	38.8	41.6	34.5	39
Geometric mean	35.9	36.9	32.2	35
Harmonic mean	33.2	33.01	30.23	31.9
Sex				
Male	104 (59.4%)	10 (66.6%)	12 (66.6%)	6 (66.7%)
Female	71 (40.57%)	5 (33.3%)	6 (33.3%)	3 (33.3%)
Civil Status				
Single	50 (28.57%)	6 (40%)	7 (38.9%)	
Married	119 (68%)	8 (53.3%)	11 (61.1%)	4 (44.4%)
Widow/widower	6 (3.43%)	1 (6.7%)		4 (55.5%)
Employment Status				
Employed	139 (79.4%)	10 (66.7%)	16 (89%)	7 (78%)
Unemployed	36 (20.6%)	5 (33.3%)	2 (11%)	2 (22%)
Area				
Within UST catchment area	117 (66.9%)	8 (53.3%)	8 (44%)	6 (66.7%)
Outside UST catchment area	58 (33.1%)	7 (46.7%)	10 (55%)	3 (33.3%)
Smoking History				
Positive	66 (37.7%)	6 (40%)	10 (56%)	3 (33.3%)
Negative	109 (62.3%)	9 (60%)	8 (44%)	6 (66.7%)
Substance Abuse				
Negative	175 (100)	15 (100%)	18 (100%)	9 (100%)
Alcohol Intake				
Positive	48 (27.4%)	6 (40%)	7 (39%)	3 (33.3%)
Negative	127 (72.6%)	9 (60%)	11 (61%)	6 (66.7%)
Co-morbid Illness				
Positive	13 (7.4%)	4 (26.7%)	2 (11%)	
Negative	162 (92.6%)	11 (73.3%)	16 (89%)	9 (100%)
Previous TB Treatment				
Positive	78 (45%)	4 (26.7%)	10 (56%)	
Negative	97 (55%)	11 (73%)	8 (44%)	9 (100%)
Adverse Drug Reaction during Previous Treatment				
Not observed	97 (55%)	11 (73%)	8 (44%)	
Positive	2 (1.1%)			
Negative	76 (43.4%)	4 (26.7%)	10 (56%)	9 (100%)
Previous Treatment Compliance				
Not observed	97 (55%)	11 (73%)	8 (44%)	
Good	23 (13.1%)			3 (33.3%)
Poor	55 (31.4%)	4 (26.7%)	10 (56%)	6 (66.7%)
Previous Outcome				
Not observed	97 (55%)	11 (73%)	8 (44%)	
Good	23 (13.1%)		5 (27.8%)	
Poor	55 (31.4%)	4 (26.7%)	5 (27.8%)	9 (100%)
Exposure to TB Patients				
Positive	48 (27.4%)	5 (33.3%)	9 (50%)	3 (33.3%)
Negative	127 (72.6%)	10 (66.7%)	9 (50%)	6 (66.7%)
Chest x ray				
Minimal	63 (36%)	3 (20%)	6 (33%)	2 (22%)
Mod Advanced Disease	82 (47%)	8 (53%)	6 (33%)	4 (44%)
Far Advanced Disease	21 (12%)	2 (13.3%)	6 (33%)	2 (22%)
Normal	9 (5%)	2 (13.3%)		1 (11%)
AFB Smear				
Not observed		1 (6.7%)	1 (5.6%)	
Positive	87 (50%)	7 (46.7%)	9 (50%)	3 (33%)
Negative	88 (50%)	7 (46.7%)	8 (44%)	6 (67%)

Appendix 1 Comparison of the Demographic, Socio-economic and Clinical profile among DOTS Patients (Compliant and Non-compliant) and SAT Patients (Compliant and Non-compliant), UST TB Clinic, January 1997- December 2000, (n=217) (cont'd)

Variable	DOT Group Compliant (n=175)	DOT Group Non-compliant (n=15)	SAT Group Compliant (n=18)	SAT Group Non-compliant (n=9)
Symptoms				
Symptomatic	174 (99.4%)	15 (100)	18 (100%)	9 (100%)
Asymptomatic	1 (0.6%)			
Class				
Pulmonary	164 (94%)	13 (86.7%)	17 (94.1%)	8 (89%)
Extra-pulmonary	13 (6%)	2 (13.3%)	1 (5.6%)	1 (11%)
MTB Culture				
Not observed	149 (85%)	15 (100%)	17 (94.4%)	8 (89%)
Positive	19 (11%)		1 (5.6%)	1(11%)
Negative	7 (4%)			
Entry Category				
New Case	97 (55%)	11 (73%)	8 (44%)	
Relapse	23 (13.1%)	4 (26.7%)	1 (5.6%)	1 (11.1%)
TAI	54 (30%)		5 (27.8%)	6 (66.7%)
Failure	1 (0.57%)		4 (22%)	2 (22.2%)
Duration of Treatment				
3 months or less		14 (93%)		8 (89%)
3 – 6 months		1 (6.7%)		1 (11%)
6 – 9 months	173 (99%)		18 (100%)	
9 – 12 months	2 (1%)			
Adverse Drug Reaction				
Positive	1 (0.57%)			
Negative	174 (99.4%)	15 (100%)	18 (100%)	9 (100%)

Appendix 2 Odds Ratio of the Difference Risk Factors to Non-compliance, UST TB Clinic, January 1997 to December 2000

Variable	Odds Ratio
Male sex	1.37
Married	0.56
Employed	0.52
Area outside UST Catchment area	1.8
(+) Alcohol intake	1.8
Presence of co-morbid illness	4.6
Previous TB treatment	0.45
Adverse drug reaction	0
Previous treatment compliance	Not determined
Severe disease on chest x-ray	1.1
AFB +	0.87
Extra-pulmonary TB	2.4

Multiple Versus Single Drug Chemoprophylaxis In Patients Who are at High Risk to Develop Tuberculosis, A Meta-analysis Review

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Objectives: To compare the efficacy and adverse drug reactions of single TB drug versus multiple TB drug prophylaxis in patients who are at high risk for tuberculosis.
Design: Meta-analysis
Search strategy: Search in the Medline 1966 - 2002 using the search terms tuberculosis, Preventive therapy, chemoprophylaxis, and TB prophylaxis were done. Some of the full text versions of the studies were retrieved using the Ovid Search. Search in the Cochrane Controlled Trials Register was also done. In addition, search of the references of all retrieved articles were done to ensure that all completed trials had been identified.
Types of studies Randomized controlled trials were included.
Types of participants : Patients who are high risk to develop tuberculosis Types of interventions
Single drug using isoniazid as the control and multiple drug regimen using different combinations of INH, Rifampicin and PZA
Types of outcome measures The outcome measures were (1) frequency of active tuberculosis, and (2) occurrence of adverse drug reaction.
Main results A total of 4573 patients were extracted from the five trials to be evaluated for the first outcome of the review; the development of active tuberculosis, 2511 of which belong to multiple drug chemoprophylaxis arm, while 2062 belong to single drug chemoprophylaxis arm. Overall, the frequency of development of active tuberculosis was decrease in the multiple group than single drug group, 4.1 % and 5.2% respectively and the heterogeneity at 95% CI was not significant (p =0.66). Another outcome measure of this review was the adverse drug reactions. Only four trials were included in the evaluation. A total of 3760 patients were included in the analysis, 2068 in the multiple drug chemoprophylaxis arm and 1692 in the single drug chemoprophylaxis arm. The incidence of reactions was less in the multiple drug chemoprophylaxis than the single drug regimen, 14% and 17.5% respectively. This outcome was statistically significant at 95% CI with a p = 0.0093.
Conclusions: This review found that single and multiple drug regimens had the same efficacy in preventing the development of active tuberculosis. The therapeutic advantages of multiple regimen established are less adverse drug reactions and shorter duration treatment ,which is important in the adherence of patient to treatment .The above advantages are important not only on this subset of patients but also day to day clinical practice. *Phil Jour Chest Diseases. Vol 12 No. 1 pp: 19-23*

Keywords: TB prophylaxis, adverse effects, INH

Introduction

Daily isoniazid (INH) for 6 to 12 months is currently recommended for the prevention of tuberculosis among high risk patients especially the immuno-compromised.[1] Unfortunately INH is associated with definite hepatotoxicity and the duration of treatment is at least as long as that for the active tuberculosis it is intended to prevent. As has been pointed out, the approach to preventive therapy must be improved if it is to have an important impact on the tuberculosis problem. Furthermore, INH preventive therapy remains controversial for some populations. Because the previous standard 18-month course of chemotherapy for tuberculosis with three drug combination has been reduced to a 6 -month course by the combination of isoniazid with rifampicin and pyrazinamide; one wonders whether the addition of one or both of the last two in combination with INH might also shorten the duration of preventive therapy for tuberculosis. To

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address the issue of a novel preventive therapy, it is worth comparing and analyzing the results of well known prophylactic trials for tuberculosis.

Standard advice for many years has been to offer patients with inactive pulmonary TB a year of isoniazid preventive therapy. Clinical trials have demonstrated protection rates of 60% to 90%.[2-4] However, data from public health programs in recent years have shown completion rates of isoniazid preventive therapy to be only about 60%.[3] Most authorities believe that an equally safe and effective regimen of shorter duration would be completed by more patients and therefore would be of greater benefit to patients and to society. In 1994, the American Thoracic Society and the Center for Disease Control and Prevention (ATS-CDC) jointly recommended a regimen of 4 months of isoniazid and rifampin as acceptable chemotherapy for sputum smear and culture-negative TB.[5] That statement also suggests that 4 months of isoniazid and rifampin is an acceptable alternative to 12 months of isoniazid for patients with inactive pulmonary TB and those with silicosis, if the risk of isoniazid resistance is low. In 1990, in anticipation of the new ATS/CDC recommendations previously described, we undertook a preliminary evaluation of 4-months preventive therapy for immigrants who have arrived recently and were determined during their overseas visa application process to have inactive pulmonary TB ("Class II"). Because program data show rates of isoniazid resistance of 10 to 20% in cases of active TB from those populations, we chose a multiple-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for the full 4-mos duration of treatment. That regimen was chosen because of success with a 4-drug regimen in the treatment of culture-negative TB in similar populations in British Medical Research Council clinical trials, and lack of data on the efficacy of less intensive regimens for inactive TB in populations with a relatively high rate of isoniazid resistance.[3,5] Finally, we conducted a meta-analysis study of completion and toxicity of this new short-course preventive regimen for persons at risk of PTB, using a matched group of historical cases who have received the 9-months isoniazid preventive therapy regimen.

Methodology

Criteria for considering studies for this review

Types of studies. Only randomized controlled trials were included. The compared drug regimens were single vs multiple TB drug aimed at preventing tuberculosis. Trials were considered irrespective of setting or target group, and included all different drug regimens tested. Preventive Treatment Chemoprophylaxis was defined as tuberculosis chemotherapy given to people who have a particular risk of developing tuberculosis.

Types of participants: Patients who are high risk developing tuberculosis such as HIV seropositive patients, exposed patients to a person with active tuberculosis, recent PPD converter, diabetic patients, chronic steroid and immunosuppressant users and patients with fibrotic lung lesion other than TB fibrosis.

Types of interventions Single drug using isoniazid as the control and multiple drug regimen using different combinations of INH, rifampicin and PZA

Types of outcome measures. The outcome measures were (1) frequency of active tuberculosis, and (2) occurrence of adverse drug reaction.

Search strategy for identification of studies Search in the Medline 1966 - 2002 using the search terms tuberculosis, preventive therapy, chemoprophylaxis, and TB prophylaxis were done. Some of the full texts of the articles were retrieved in the OVID SEARCH. Search using the Cochrane Controlled Trials Register was also done. In addition, search of the references of all retrieved articles was done to ensure that all completed trials had been identified.

Method of Review

Data extraction. The decision as to which trials to include and which variables to use when more options were available for the same outcome were based on the methods section of the trials only. Details on diagnosis, drugs used, dose of the drugs, rules for use of the drug, length of the treatment, length of follow-up, randomization and blinding methods, number of randomized patients, number of patients excluded from analysis, number of patients who developed tuberculosis after the treatment were extracted by authors independently. Differences in the data extracted were resolved together.

Active tuberculosis was defined as either microbiologically (preferably by AFB culture) or histologically positive; or as a clinical syndrome consisting of typical symptoms; independently assessed chest x ray; and a documented response to treatment to anti TB drugs. Also, analyses of TB infection were considered according to the authors' own definitions.

Adverse drug reactions were defined as clinical signs and symptoms; or a new laboratory abnormality which occur during the trial period. Each study had different and common laboratory parameters but the

Table I. Characteristics of Included studies

Study	Methods	Participants	Interventions	Outcomes	Allocation concentration
Alfaro, et al	Allocation concealment: envelope Blinding: none	196 patients at high risk for tuberculosis as defined by CDC	Single INH 700-800 mg for 9 mos Multiple INH 300 mg + Rif 600 mg for 3 mos	Development of active PTB Adverse reaction to drug	B
Chan et al	Allocation concealment: envelope Blinding: Yes	493 patients with silicosis Negative for PTB	Single INH 300 mg for 6 mos or RIF 600 mg for 6 mos Multiple INH 300 mg + Rif 600 mg for 3 mos	Development of active PTB Adverse reaction to drug	A
Gordin, et al	Allocation concealment: not described Blinding: Yes	1583 HIV seropositive patients Negative PTB	Single INH 300 mg for 9 mos Multiple Rif 600 mg + PZA 20 mg/kg for 3 mos	Development of active PTB Adverse reaction to drug	B
Halsey, et al	Allocation concealment: envelope Blinding: Yes	784 seropositive HIV Negative for PTB	Single INH 600-800 mg for 9 mos Multiple Rif 450 mg + PZA 1.5 g for 3 mos.	Development of active PTB	A
Whalen et al	Allocation concealment: envelope Randomized by computer Blinding: Yes	2053 HIV seropositive patients (+) PPD No clinical PTB	Singl INH 600-800 mg for 6 mos Multiple INH 300 mg + Rif 600 mg for 3 months on 556 patients INH 300 mg + Rif 600 mg + PZA on 463 patients	Development of active PTB Adverse reaction to drug	A

Notes;

Number of drop outs and withdrawals were included in the statistical analysis

CDC defined high risk patient as close household contact with TB patients, PPD converter, presence of DM, malignancy, chronic use of steroids

reviewers considered only the parameters that were related to drugs as established.

Statistics

The outcomes were evaluated by the odds ratio. Since heterogeneity of the studies was expected because of various designs, diagnoses, drugs, doses, routes of administration and criteria for tuberculosis infection and adverse drug reaction, a random effects model was used. Ninety-five percent confidence intervals (95% CI) are likewise presented. All analyses were done using REVMAN 4.1.

Description of studies

Thirty two randomized clinical trials were identified using the Medline, Ovid and Cochrane databases. However, only 22 trials had clinical abstract, of which 14 had online and full text access. Five trials were eligible for the inclusion in this review because of similar and high methodological quality and outcome. The remaining nine trials were excluded because they did not meet the criteria in the objective of the review as well the critical appraisal of the article; some of the trials compared only isoniazid and placebo, three had different measured outcome while the other one was experimental trial in mice.

Results

The five trials included in the review had similar exclusion criteria which include the past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious inter-current illness. All treatment was self-administered and adherence was monitored variously through self reporting, attendance at scheduled clinic appointments. Follow up of the subjects generally ranged from an average of 24 to 60 months as specified in each trial. All were analyzed by intention to treat.

A total of 4573 patients were extracted from the five trials to be evaluated for the first outcome of the review; the development of active tuberculosis, 2511 of which belong to multiple drug chemoprophylaxis arm, while 2062 belong to single drug chemoprophylaxis arm. Overall, the frequency of development of active tuberculosis was decreased in the multiple group than single drug group, 4.1% and 5.2%, respectively. However the heterogeneity at 95% CI was not significant (p =0.66). Four of the five trials in this

outcome slightly favor the use of single drug chemoprophylaxis but it was reversed by the study of Gordin which favored multiple drugs at shorter duration of treatment because it had a greater number of participants.[10]

Another outcome measure of this review was the adverse drug reactions. The adverse drug reactions noted ranged from mild to severe as mentioned by each study. Only four trials were included in the evaluation because the remaining one which was done by Hasley et al did not include the above mentioned parameter. A total of 3760 patients were included in the analysis, 2068 in the multiple drug chemoprophylaxis arm and 1692 in the single drug chemoprophylaxis arm. The incidence of reactions was less in the multiple drug chemoprophylaxis than in the single drug regimen, 14% and 17.5% respectively. This outcome was statistically significant at 95% CI with a p value of 0.0093. Two of the trials favor single drug regimen while the other two favors multiple drug regimen but the individual weight of each trial was considered primarily in the statistical analysis.

Discussion

At present, all researches to date indicate that preventive treatment reduces the frequency of active tuberculosis in half of the patients at risk for tuberculosis. Protection against tuberculosis of patients at risk is greatest in the subset of patient infected with HIV sero-positive (approximately 90% reduction) both in the single and multiple drug regimen group. This result is comparable in the study of Wilkinson which compares the efficacy of INH prophylaxis with placebo and gives a prevention of greater than 70% protection on HIV seropositive patients.

In the other subset of patients who are at risk such as the recent PPD converter, diabetic patients, chronic steroid users, patients with silicosis as noted in the study of Alfaro and Chan[7,11] preventive treatment using single or multiple chemoprophylaxis will reduce the development of tuberculosis by more than 80% . The reduction rate was similar with the summary of evidences regarding chemoprophylaxis noted in the recent PCCP consensus.[6] Comparing efficacy between the two regimens, there is no statistically significant difference in the analysis.

Another issue settled by this review was the adverse reactions of the drug noted in both arm. In clinical practice this is more important to keep the patient compliant. It is not easy for the patient to take medicine for a longer period especially those drugs that have lot of interaction and reaction .The result of this review favor the use of multiple drug regimen over the single drug regimen. However, the heterogeneity of the four trials included was statistically significant which can affect the validity of the results of the mentioned outcome.

In patients who are HIV seropositive, 11% experienced adverse reactions and comparing the two regimens, they have similar results. Significant differences were noted in the subset of patients who are at high risk to develop tuberculosis but HIV seronegative. However the critical analyses of source articles were weak (grade B). The Average follow up in these trials was 24 to 60 months, and it is not possible to conclude that benefit persists beyond this time.

Reviewers' conclusions

Implications for practice

This review found that single and multiple drug regimens had the same efficacy in preventing the development of active tuberculosis. The therapeutic advantages of multiple regimen established are less adverse drug reactions and shorter duration of treatment,which is important in the adherence of patient to treatment .The above advantages are important not only on this subset of patient but also in day to day clinical practice.

Implications for research

Since therapeutic advantages of multiple drug chemoprophylaxis were suggested in the meta-analysis, a large, definitive, controlled trial of this multiple drug regimen should be performed on the other subset of the population at high risk for developing tuberculosis such as organ transplant patients and chronic user of immunosuppressant. Furthermore, the definite side effects of the therapy, which were not given in full detail in some of the included trials, could be addressed in future studies. The studies should also include parameters that allow cost-benefit analyses to be performed.

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Anti-TB Drug Resistance Pattern at the University of Santo Tomas Hospital from 1995-2000: The Impact of Changing but Declining Pattern

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Objective: To determine the prevalence rate and resistance pattern of anti-TB drugs and to illustrate the trend of resistant cases.
Design: A retrospective study of records of isolates of *Mycobacterium tuberculosis* with sensitivity results.
Setting: Section of Clinical Pathology, University of Santo Tomas Hospital
Participants: Ambulatory and hospitalized patients who submitted sputum and/or other specimens available for culture and sensitivity studies.
Intervention: Specimens submitted were cultured using BACTEC (Becton-Dickinson) method. Isolates were subjected to sensitivity studies to Rifampicin (R), Isoniazid (I), Ethambutol (E), and Streptomycin (S). Susceptibility results were recorded and resistance grouped singly or in combination.
Outcome Measures: Prevalence rate and pattern of resistance.
Results/Conclusion: A total of 1,266 cultures were isolated by radiometric method (BACTEC) from January 1995 to December 2000. 597 (47%) were isolated mostly in 1995 while only 88 (6.95%) were isolated in 1998. The overall resistance rate was 51.35%, majority of which were multiple drug resistance and was greatest in 1998, while single drug resistance was noted to be highest in 1999 and 2000. Among single drugs, resistance was greatest to Ethambutol at 7.97% followed by Streptomycin (6.2%), Isoniazid (5.6%) and Rifampicin (4.3%). When used singly or combined with other primary drugs, Isoniazid showed the highest resistance at 27.47% followed by Ethambutol (26.36%), Rifampicin (18.83%) and Streptomycin (18.42%). In cultures with resistance to combination of primary drugs, resistance to H-E (7.10%) was most frequent followed by H-R-E (3.5%), H-R (3.15%), and H-R-E-S (2.52%). Thus, Isoniazid and Ethambutol resistance confirms the growing concern of physicians. This fact will hamper our efforts to curb the disease. Overall resistance rate declined for the last 3 years, but may increase again unless we improve surveillance, act on the results and learn from the previous mistakes. *Phil Journal of Chest Diseases. Vol. 12 No. 1 pp: 24-28*

Keywords: TB resistance, TB culture, BACTEC

Introduction

Tuberculosis has been in existence for centuries. It, however, continues to be a major cause for global concern in spite of significant advancement in the science and technology concerned with its diagnosis and treatment. The Philippines has consistently been one of the 22 countries in the world, which accounts for 80% of the world's TB cases.[1] TB, likewise is always among the top 5 causes of morbidity and mortality in our country. It is estimated that 15 million Filipinos are infected, giving us the highest prevalence rate in the Western Pacific region (279/1000) as of 1992.[2] Based on the 1997 National Prevalence Survey, there are 213,600 cases of active tuberculosis nationwide. Moreover, there are 138 new cases of smear positive individuals per 100,000 population based on the Annual Risk of Tuberculosis. This is equivalent to a total of 103,118 new cases added to the existing pool of TB cases every year in the entire country.

During the past three decades, the prevalence of drug resistant organisms among patients with pulmonary tuberculosis in the United States and other countries has steadily risen to approximately 2-9%.[3] At present, the epidemic is made more serious by the increase of *multi-drug resistant (MDR)* strains of *Mycobacterium tuberculosis* (*M. tuberculosis* strains which show *in vitro* resistance to at least Isoniazid and Rifampicin, the two most potent anti-TB drugs, with or without associated

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resistance to other drugs).[4,5] In addition, *multiple drug resistant* TB, resistance to two or more first line drugs (H, R, S, Z, E) compounds this problem and has resulted in many slightly treatable, but often fatal disease.

From the microbiologic point of view, drug resistant tuberculosis is defined as the proportion of drug resistant mutants above which therapeutic success is less likely to occur, which is placed at 1%.[6] This means that if more than 1% of the test population of *M. tuberculosis* grew on a drug-containing medium, resistance to the drug has developed or is in advanced stage of development. This has been found most frequently in those with previous intake of anti-TB drugs for at least a month. Other factors are co-infection with the human immunodeficiency virus epidemic,[7] homelessness[8] that may lead to poor compliance and follow-up visits, residents in nursing homes and correctional facilities where transmission is greatly facilitated, immigration of previously infected people to low prevalence areas,[9,10] poor social conditions such as overcrowding and poor ventilation,[11] and deterioration in health care structure. Concomitant medical conditions such as alcoholism,[12] malignancy, substance abuse[13,10] and chronic lung disease are also associated with the disease, contributing to its increasing incidence. The problem therefore of multi-drug resistance of tuberculosis will be a major factor in the increase of the prevalence of difficult-to-treat TB contributing to the rise in morbidity and mortality from the disease. Needless to say, the anticipation and prompt detection of the occurrence of MDR- TB is of utmost importance so that an appropriate and adequate therapeutic intervention is rendered. This, in turn, will help decrease its prevalence and concomitantly, its morbidity and its mortality.

This study was therefore performed to determine the prevalence rate and resistance pattern of anti-TB drugs at the University of Santo Tomas Hospital from January 1995 to December 2000 and, to illustrate the trend of these resistant cases as was previously demonstrated during the past years.

Materials and Methods

A retrospective study was conducted of the records of all patients at the University of Santo Tomas Hospital from January 1995 until December 2000. This included all patients with specimens (respiratory system sputum, bronchial aspirates, endotracheal secretions, pleural fluid, pleura and lung tissues and extrapulmonary sources, fluids, secretions, tissues from other organs (e.g., synovial fluid, cerebrospinal fluid) submitted for TB culture and sensitivity. Thorough review of the results including sensitivity to Isoniazid (H), Rifampicin (R), Streptomycin (S) and Ethambutol (E) was done. The total number of isolates was counted and was classified as to which ones were susceptible and which ones were resistant to the assigned drugs. Prevalence rate was calculated and the pattern of resistance was analyzed.

Laboratory Method The BACTEC (Becton-Dickinson) method was used in the isolation and sensitivity of *Mycobacterium tuberculosis*. This study is a radiometric method that makes use of enriched Middlebrook 7H12 containing ^{14}C-labeled palmitic acid. The mycobacterial growth was determined by utilizing ^{14}C with the release of $^{14}C0_2$ by the multiplying bacteria and is detected in an ionic chamber with electronic detector in the BACTEC instrument bottle (see *Appendix).*

Statistical Analysis The yearly and total prevalence of single and multi-drug resistance to the most common drug combinations were determined by the number of resistance to such drugs divided by the total number of isolates with culture and sensitivity studies per year.

Results

A total of 1,266 cultures of mycobacterium were isolated by radiometric method (BACTEC) from January 1995 to December 2000. Five hundred ninety-seven (47%) were isolated mostly in 1995. In 1998, the least number was isolated with 88 (6.95%) only. Of these isolates, 88% (1114) were from pulmonary sources, 1014 of which were sputa. Of the remaining non-pulmonary sources, 3.5% each came from urine and colon tissue.

Sensitivity studies were performed in all isolates, and of these 48.65% were fully susceptible to the four anti-TB drugs. The overall resistance rate was 51.35% to either drug alone or in combination with an initial increasing trend from 1995 through 1997 followed by a subsequent decline from 1998 to 2000. Majority of these were multiple drug resistance which was noted to be greatest in 1998 (44.90%) whereas single drug resistance was noted to be greatest during the last two years (1999-2000). Note that the resistant cases out-numbered the susceptible ones until 1999 when there was an increase of susceptible over the resistant cases.

Among single drugs, resistance to Ethambutol alone was greatest at 7.97% followed by Streptomycin (6.2%), Isoniazid (5.6%), and Rifampicin (4.3%), in descending order of prevalence. Whether used singly or in combination with other drugs, Isoniazid showed the highest resistance at 27.47% followed by Ethambutol (26.36%), Rifampicin (18.83%) and Streptomycin

(18.42%) *(Table III)*. For the two or more drugs, resistance was highest with Isoniazid and Ethambutol (H-E) combination (7.10%) followed by two other H-E containing regimens; namely H-R-E (3.5%) and H-R-E-S (2.52%). R-E-S combinations showed the least resistance (0.94%).

With regard to the resistance pattern among the single drugs, Isoniazid demonstrated a rising trend until 1997 and began to decrease thereafter. Ethambutol showed an initial downward trend followed by an upward trend achieving the highest rate among the other three drugs in 1997. Rifampicin and Streptomycin exhibited the same pattern with peaks of resistance noted in 1998 and 1999, respectively. Overall, resistance rate of single drugs progressively declined towards the end of the study period.

The resistance involving Isoniazid and Ethambutol (H-E) showed a progressively upward course since 1995 followed by a sharp decline in 1999. It was also the most noted in 1997 and 1998. Surprisingly, there was no observed resistance in 2000. This was followed by the combination R-H which showed an alternating downward and upward trend. A similar trend was observed with R-E, although this was the combination with the least resistance.

Among the three-drug combinations, H-R-E showed the highest prevalence rate. The combination also demonstrated an alternating upward and downward trend with no reported resistance in 1999 and 2000. A similar trend was observed with H-R-S. The least resistance was noted with R-E-S combination.

A progressive rise in the resistance rate for the R-H-E-S combination was displayed, notably highest in 1998. There was a nil resistance in 1999 with minimal recurrence in 2000. It also ranked as the 3rd among the combined resistance patterns.

Thus, resistance among single or multiple drugs was consistently demonstrated with the H-E combination. In general, they illustrated an increasing trend only to decline during the last two years.

Lastly, it is of great importance and worthy of mention that 18 cases of Pyrazinamide resistance, in combination were recorded in 1995. None were noted for the rest of the years

Discussion

As previously mentioned, multiple drug resistance has been a global problem that has hampered the treatment of TB, and at the same time, altered its disease pattern. Yet, studies and surveillance in our setting have not been that vigilant and have been scarce. To achieve considerable reduction of TB cases in the future and avert increasing death due to the disease, the American Thoracic Society (ATS) recommended that high-risk groups be identified promptly, screened for infection and offered adequate treatment. Being one of the 22 countries accounting for the world's TB cases, the Philippines is a population with such risk. It remains a major health problem and 75 people die daily and 200,000 to 600,000 are spreading the disease and may be infecting 10 persons per year.[1] Hardly has there been a change in the TB state for the last 14 years and it is due to this sorry state that the directly observed treatment strategy (DOTS) was started in 1996 and expanded with the goal of being implemented all over the country. The adoption of DOTS has been associated with reduced rates of treatment failure, relapse and drug resistance. This is due to priority detection and cure of infectious smear positive patients, observation by a health worker that adequate dose is taken daily and proper monitoring during the treatment course through recording and reporting system to ensure cure of the patient.

The cumulative data regarding prevalence of drug resistance has begun to increase in the 1990's with studies concentrated mostly in the urban areas, especially in Metro Manila, with varying results, mostly pointing to significant resistance. Now the issue of knowing the rate and drug resistance pattern in the Philippines becomes even more urgent. Previous studies of susceptibility patterns of *Mycobacterium* isolates came from tertiary care hospitals and reported rates as high as 32% for MDR- TB.[14] Review of the local literature on studies done in these hospitals within Metro Manila proved that indeed increasing pattern of drug resistance was noted since 1988-1995. However, in 1995, a community-based surveillance conducted by Mendoza et al[15] showed that regional differences in the prevalence of multi-drug resistant tuberculosis occur and recommended that tuberculosis control efforts should be tailored according to the needs of each community. Ortega et al[16] completed a prevalence study from 1988 to 1991 among urban and poor rural communities within Metro Manila and nearby areas and found that total resistance to INH, Rifampicin and Ethambutol were 40%, 10% and 10%, respectively and there was none for Streptomycin. Luzano et al[17] obtained a seventy-one percent (71%) resistance rate in his study on the resistant pattern of tuberculosis at the Santo Tomas University Hospital. In contrast, our present study, which is just a continuation of the surveillance in the same institution, found an almost equal overall susceptibility and resistance rates of forty-eight (48.65%) and fifty-one (51.15%), respectively. Both studies found that single drug resistance had the highest rate. In comparison to previous studies, resistance to either one drug or in

combination noted Isoniazid to be highest at 27.56% followed by Ethambutol (26.46%), Rifampicin (18.95%) and Streptomycin (18.48%). This is a reduction in the prevalence compared with the previous report[17] but higher than another study done at the health center level.[18] A growing concern is confirmed by this report wherein Ethambutol resistance was the leading agent among single drug resistance followed by Streptomycin, Isoniazid and Rifampicin. This is a different bias from other studies conducted in tertiary hospitals, probably reflecting the rising resistance to the supplemental drugs. Physicians for a while were wary of the high Rifampicin resistance and resorted to Isoniazid and Ethambutol combination during the maintenance phase. The consequence of this may be the high prevalence of resistance of Isoniazid and Ethambutol-containing drugs, namely H-E and H-R-E combination as demonstrated in this study; R-E-S combination was noted to have the least. Based on these results, Ethambutol resistance has become a serious threat to the global fight against TB.

What becomes a potential problem of treatment failure and relapse is when both Isoniazid and Rifampicin, combined with Ethambutol, are no longer effective. Adding second-line drugs is expensive and full of adverse effects leading to noncompliance and acquired resistance requiring more prolonged therapy that is less likely to be successful than the treatment of drug-susceptible tuberculosis. Our study showed an alarming data of H-R-E resistance, although Rifampicin was consistently lowest at 28.6% and 18.95% when used singly or in combination. In his study in 1979 to 1980, Manalo et al, showed Streptomycin (48%) and Isoniazid (25%) to have the highest resistance rates, without resistance to Rifampicin, making it still an important agent that may augment the efficacy of other drugs.

Luzano likewise examined the trend of resistance of the different primary drugs and predicted that after 1994, the resistance to Isoniazid (H) alone, Isoniazid-Ethambutol (H-E) and Rifampicin-Isoniazid-Ethambutol combinations would increase, and that the rest would either decrease or remain stationary. Our present study demonstrated the same pattern of increased resistance for the above-mentioned drugs for the initial 2 to 3 years (1995-1997), only to decline thereafter. This may be the result of the successful campaign of the DOTS which has been consistently found to improve case holding and cure rates. Physicians' increased awareness and vigilance in curbing the TB problem may have similarly contributed to this phenomenon.

With these available data, resistance surveillance, preferably every 5 years, by further collection of figures on the prevalence of anti-TB drug resistance within the community must be undertaken. The data gathered from these studies should then be utilized in a manner to attain a significant reduction in the number of future resistant cases. Complete culture and sensitivity studies should be encouraged in all cases and data used to investigate correlation between resistance pattern of DOTS, although monetary considerations may hinder implementation of this plan. The data will help guide us in choosing a more appropriate initial therapy suited to the particular locality. The bases for future changes in the treatment regimens will be taken from these results.

Conclusion

Our study is limited only to the overall resistance rates and patterns obtained from cultures regardless of whether they are initial or acquired, primary or secondary. The consistent prevalence of single drug resistance over the various combinations, with changing pattern of Isoniazid predominance over the last five years, emphasizes the need for better treatment compliance. Likewise, the high prevalence Ethambutol resistance which has attained an almost unchanged status, remains a more serious threat considering its inclusion in the treatment especially where high resistance to Isoniazid is present. The misuse and abuse of physicians and health providers in treating this potentially curable disease and the reluctance of patients, not to mention the burden of high cost of medicines, have contributed to a state where resistance will be a deadly fact. Increase in resistant cases may again shoot up, unless we improve surveillance, act on the results and learn from the previous mistakes.

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APPENDIX

BACTEC (Becton-Dickinson) Method

The BACTEC (Becton-Dickinson) method is a radiometric method that makes use of enriched Middlebrook 7H12 containing l4C-labeled palmitic acid. The mycobacterial growth is determined by utilizing 14C with the release of 14 C02 by the multiplying bacteria and is detected in an ionic chamber with electronic detector in the BACTEC instrument bottle

Contaminated specimens like sputa are processed by digestion and decontamination using a mixture of sodium hydroxide, benzalkonium chloride, sodium lauryl sulfate and N-acetyl-L-cysteine (NALC). These alkaline agents serve primarily to eliminate non-mycobacterial organisms while the mucolytic serves to digest the mucus and to enhance the concentration step. Specimens considered normally sterile are not subjected to this procedure but are directly inoculated into the Middlebrook bottle.

After centrifugation at 3,000 x G for 15 minutes, 0.5 cc of sediment is inoculated into the BACTEC 12B vial where PANTA (polymyxin B, Azocillin, Nalidixic acid, Trimethoprim, Amphotericin B) are incorporated to destroy surviving non-mycobacterial contaminating organisms. The specimens are then incubated at 35 c. These vials are read using BACTEC model 460, daily for the first week and subsequently, every week for 40 days.

The radioactivity of 14 C02 released by multiplying mycobacteria in the vial is determined quantitatively with an electronic detector in terms of numbers on a scale from 0 to 999. These numbers are designated as the Growth Index (G.I). Acid fast bacilli (AFB) smears are done in those specimens with the reading of 50-100. If the smear showed positive result, p-nitro-a1pha-acetyl-amino-beta-hydroxypropiophenone (NAP) is added to differentiate Mycobacterium tuberculosis from Mycobacterium other than tuberculosis (MOTT).

After the latter step, another AFB smear is done to determine cord-like forming colonies which are a significant characteristic of *Mycobacterium tuberculosis*. The susceptibility tests to Isoniazid, Rifampicin, Ethambutol, and Streptomycin are done by radioactive liquid medium throughout the BACTEC instrument after identification of the organism.

Susceptibility Patterns for Drug Resistant *Mycobacterium tuberculosis* at Metropolitan Hospital

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Objective: To determine the prevalence, its susceptibility patterns and trend of drug resistant *Mycobacterium tuberculosis* in Metropolitan Hospital.
Background: The emergence of drug-resistant *Mycobacterium tuberculosis*, primary and acquired resistance has complicated tuberculosis treatment. It is the product of inadequate therapy; noncompliance with treatment, interrupted drug supplies, or inappropriate prescription.
Study Design: Retrospective, Descriptive Study
Setting: Metropolitan Hospital, Tertiary clinical care
Method: The drug susceptibility result of 199 positive cultures of *Mycobacterium tuberculosis* were retrospectively reviewed from January 1997 to July 2001. Excluded are patients diagnosed with pulmonary TB who are not confirmed microbiologically, positive cultures with no sensitivity tests and isolates with *Mycobacterium* other than tuberculosis.
Results: The overall drug resistance is 52.3 % (104 cultures). Of these cases, 24 (23.07%) were resistant to single drug and majority 80 (76.92%) were multiple drug resistant. Among the 104 resistant culture, resistance to isoniazid alone and in combination was the highest (91.34%). Resistance to Isoniazid and Rifampicin combination (69.23%) was the highest among the combined drugs. There is an increasing trend of resistance to four-drug and five-drug first line anti-TB regimen.
Conclusion: The results showed an increasing trend of resistance to four-drug and five-drug first line anti-TB regimen. This can be avoided by country-wide standardization of anti-tuberculosis regimen using Directly Observed Treatment Short Course (DOTS) strategy to ensure completion of treatment and cure for the majority of patients. *Phil. Journal of Chest Diseases. Vol. 12 No. 1 pp: 29-31*

Keywords, PTB, Therapy, DOT

Introduction

Modern chemotherapy, appropriately prescribed and administered, cures 98-99% of cases of previously untreated pulmonary tuberculosis. However treatment has to be continued with good quality drugs for as long as six months to ensure cure. Unfortunately, the very success of the drug treatment of tuberculosis has been the catalyst for the emergence of a new wave of drug resistance. The difficulties in ensuring treatment, especially in resource-poor countries, have resulted in an increasing incidence of tubercle bacteria resistant to the most effective drugs, so called "multi-drug resistant tuberculosis".[1] Inappropriate or inadequate anti-TB therapy serves as a major cause of acquired drug resistance, which may result in treatment failure and spread of drug resistant organisms to other persons.[2]

This study was therefore undertaken to determine the prevalence, as well as the susceptibility patterns and trend of drug resistant *Mycobacterium tuberculosis* in Metropolitan Hospital.

Methods

In this study, we reviewed the bacteriology records and included all cases of sputum culture positive pulmonary TB using *BACTEC*, reported in Metropolitan Hospital from January 1997 to July 2001. Patients with clinical diagnosis of TB that were not microbiologically confirmed, those with no sensitivity pattern testing and with an isolate of *Mycobacterium* other than tuberculosis (MOTT) were excluded.

Study Design: Retrospective, Descriptive study

Definition of terms:[9] Drug-resistant pulmonary tuberculosis. This is a case of tuberculosis excreting

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bacilli resistant to one or more anti-TB drugs. Multiple drug resistant/combined drug resistant tuberculosis.

Table I Multi-drug resistant tuberculosis

Pattern	Number	Percent
Fully Susceptible	95	47.9%
One Drug Resistance	24	12.6%
Isoniazid (INH)	16	8.0%
Rifampicin (RIF)	2	1.0%
Ethambutol (EMB)	3	1.5%
Streptomycin (STP)	1	0.5%
Pyrazinamide (PZA)	2	1.0%
Two Drug Resistance	36	18.0%
INH-RIF	30	15.0%
INH-PZA	2	1.0%
INH-EMB	1	0.5%
INH-STP	2	1.0%
PZA-STP	1	0.5%
Three Drug Resistance	25	12.56%
INH-RIF -EMB	1	0.5%
INH-RIF-PZA	12	6.0%
INH-RIF –STP	9	4.52%
INH-EMB-PZA	2	1.0%
INH-PZA-STP	1	0.5%
F our Drug Resistance	15	7.53%
INH-RIF-EMB-PZA	6	3.01%
INH-RIF-EMB-STP	1	0.5%
INH-RIF-PZA-STP	8	4.02%
Five Drug Resistance	4	2.0%
INH-RIF-EMB-PZA-STP	4	2.0%
TOTAL	199	100%

Infection by strain of *M. tuberculosis* resistant to two or more first line drugs (Isoniazid, Rifampicin, Streptomycin, Pyrazinamide, Ethambutol). Multi-drug resistant tuberculosis (MDR- TB). Infection by strain of *M. tuberculosis* which shows *in vitro* resistance to at least Isoniazid and Rifampicin, the two most potent anti-TB drugs, with or without resistance to the other drugs. Acquired drug resistance. Found in a patient who has received at least one month of prior anti-tuberculosis drug treatment. Primary drug resistance. Presence of resistant strains of *Mycobacterium tuberculosis* in a patient with no history of prior treatment for such.

Results

The drug susceptibility result of 199 cultures of *Mycobacterium tuberculosis* were retrospectively reviewed from January 1997 to July 2001. The overall drug resistance is 52.3% (104 cultures). Among the drug-resistant cultures, 81 (77.9%) were males and 23 (22.1%) were females, with a mean age of 46.37± 12.16 years. Of these cases, 24 (23.07%) were resistant to single drug and majority 80 (76.92%) were multiple drug resistant. Among the multiple drug resistant cases, 36 (34.61%) were of the two-drug combination, 25(24.03%) of the three-drug combination, 15 (14.42%) of the four-drug combination and four (3.84%) of the five-drug combination (*Table I*).

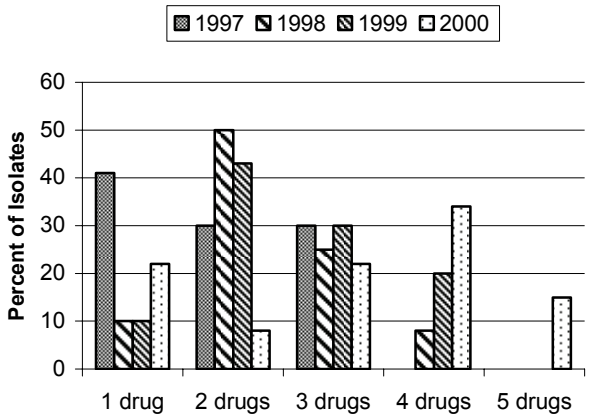

Figure 1 Pattern of Anti-TB Drug Resistance from 1997 to 2000

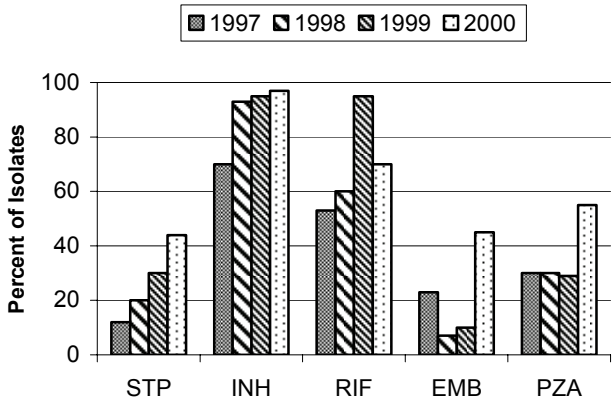

Figure 2 Patterns of Specific Anti-TB Drug Resistance from 1997 - 2000

Among the 104 resistant cultures, resistance to isoniazid alone and in combination was the highest (92.34%), followed by rifampicin (70.19%), PZA (36.51%), streptomycin (25.96%) and ethambutol (17.3%). Resistance to Isoniazid and Rifampicin with other drugs combined (68.26%) was the highest among the multiple drug resistant cases.

From 1997 to 2000, there was an increasing trend in resistance to the four-drug and five-drug combination (*Figure 1*). Among the anti-TB drugs INH, PZA, EMB, STP had an increasing pattern of resistance (*Figure 2*).

Discussion

Drug resistant tuberculosis was recognized shortly after the introduction of effective chemotherapy for the disease in the late 1940's.[3] Unfortunately, the very success of the drug treatment of tuberculosis have been the catalyst for the emergence of new wave of drug resistance. Patients have been allowed to take their medication at home completely unsupervised. The experience of the early single use of streptomycin taught us that taking one drug on its own for tuberculosis would lead to drug resistance. There is the danger that if the patient is sent home with three separate drugs, he or she might take a single drug at a time. In this way a combination of poor compliance and poor medical supervision may result to multi-drug resistance.[1]

Multi-drug resistant tuberculosis is defined as resistance to isoniazid and rifampicin whether there is resistance to other drugs or not.[8] The emergence of multidrug resistance appears to be multifactorial.[4-7] Identified factors include irregular administration of medications and monotherapy or both; previous anti-TB treatment; HIV-positive individuals; intravenous drug users; homeless and nosocomial transmission.

In Metropolitan hospital, 104 (52.3%) of 199 AFB culture positive specimens have either single, combined or multiple drug resistance. Although our population is limited only to patients who are suspected of having drug resistant tuberculosis, 28.84% of these patients have INH and Rifampicin resistance and 91.4% with other drug combination (including INH and RMP). INH alone has an 8% resistance of the total 199 specimen cultured. Comparing this data with the global incidence of drug resistant tuberculosis, INH resistance was estimated at 7.3% between 1994 and 1997.[3] Multi-drug resistance (MDR-TB) in our study accounts to about 35.6% (71/199) of the total specimen cultured, as compared to a study done by Granich et al in Mexico where resistance to multiple drug was at 22.4% and 51.5% to one drug respectively.[3] While local studies have shown a 32% MDR-TB coming from tertiary care referral hospital and 6.2% MDR rate for the National Capital Region utilizing health centers in the provinces during 1995-1996.[8] Tupasi in the 1997 National Prevalence Survey documented an MDR rate of 8.3% from 60 isolates of patients enrolled in a clinical trial run in seven sites in the Philippines.

The rise in the incidence of MDR tuberculosis is disturbing, since the case fatality rate for MDR is about 41% with treatment failure or relapse and approaches 50 to 90% among HIV-positive individuals.[9,10]

The most effective and important therapy is the directly observed administration of medication but it demands enormous resources. Awareness of the increasing prevalence of MDR-TB is important for both physicians and patients, so that the former can provide the optimum treatment regimen, and the latter should be advised to follow strictly the therapeutic program so that the projected increase of resistant cases will be minimized.[11] Finally, strengthening anti-tuberculous programs for prevention and control of tuberculosis and development of new diagnostic and therapeutic strategies for MDR-TB is essential.

In summary, 104 (52.3%) patients were reported having drug resistant tuberculosis, 80 (76.92%) cases are multi-drug resistant. Findings were found to be resistant most commonly to isoniazid followed by rifampicin. An increasing trend of resistance to four-drug and five drug first line anti- TB regimen may be explained by acquired resistance and it is presumed that these patients had previous history of treatment until proven otherwise.[2] Drug resistance can be avoided by widespread information dissemination, cooperation of government and non-government organization and implementation of countrywide standardization of anti-tuberculosis regimen using Directly Observed Treatment Short Course (DOTS) strategy to ensure completion of treatment and cure for the majority of patients.[8]

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Human Impact on the Perceptions and Knowledge to a Killer Disease "Pulmonary Tuberculosis" A Prospective Survey of the Metropolitan Hospital Patient

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Objective: To determine patient's perceptions and knowledge about pulmonary tuberculosis
Materials and Methods: Patients above 20 years of age with pulmonary tuberculosis seen at the Metropolitan Hospital in-patient and out-patient departments from August to October 2002 were included in the study. A Questionnaire was administered to the patients to elicit their knowledge on PTB
Results: Forty-four patients were included in the study with 19 male and 25 female patients. The mean age was 50 years. Seventy-seven percent agreed that tuberculosis was infectious. Cough was the most common symptom. Ninety percent said they would consult a doctor; 82% will take medication while 63% said they will stop the medication once they felt better. The most common side effect in taking the medication was orange urine (71%). Sixty eight percent discontinued the therapy once side effects were encountered even knowing the minimum duration of treatment.
Conclusion: Majority of the patients surveyed were knowledgeable about PTB, however a lack of awareness of developing MDR due to poor compliance or incomplete treatment set in the role of the physician to addressed this need. *Phil. Jour of Chest Diseases. Vol 12. No. 1 pp: 32-36*

Keywords: Pulmonary TB, TB treatment, Compliance

Introduction

Pulmonary Tuberculosis (PTB) is responsible for more than 3 million deaths each year and continues to be the leading infectious killer of adults and youth in the Western Pacific Region, with approximately 1000 people dying from the disease each day. The World Health Organization (WHO) has estimated that this figure will rise to more than 4 million by 2004. In fact, one in three people with PTB live in the Western Pacific Region. In response to the growing epidemic, the Regional Committee declared a tuberculosis crisis at its fiftieth meeting in September 1999 and in response, the Stop TB Special Project was established in February 2000. Its major goal is to reduce the prevalence and deaths due to PTB by 50% in 10 years.[1]

Seven high TB burden countries in the Region are all developing economies that suffer varying degrees of the same constraints. These countries are Cambodia, China, Lao People's Democratic Republic, Mongolia, Papua New Guinea, Philippines and Vietnam.

In the Philippines, PTB remains a major public health problem. In 2000, TB ranked sixth in the 10 leading causes of mortality and sixth in the 10 leading causes of morbidity. Our country ranks second to Cambodia in terms of new smear-positive TB notification rate, 99.7 per 100,000 population. The 1997 National Tuberculosis Prevalence Survey (NTPS) showed the annual risk of TB infection, showed an insignificant decline in 15 years from 2.5 % in 1982 to 2.3% in 1997. The survey also showed that 77% of TB patients are at their productive age of 15 to 54 years old, with the highest number in the 25-34 age group.[1]

Hence, this study aims to prevent and eradicate the progression of the killer disease "Pulmonary Tuberculosis" thru understanding the perception and knowledge of the patients toward PTB. This can help physicians assess the reason why more patients are suffering from the disease today than 20 years ago, despite tuberculosis being treatable since the 1950s.[1] Inadequate treatment fails to cure patients leaving them more infectious and worse due to the emergence of drug resistant strains of *Mycobacterium tuberculosis*, the causative organism of the disease.

Materials and Methods

Patients admitted or evaluated for pulmonary tuberculosis at Metropolitan Hospital as in-patient and

[1] Metropolitan Hospital

outpatients were included in the study. The inclusion criteria are 20 years of age or older, able to comprehend the written questionnaire, diagnosed to have PTB by symptomatology and any of the following: chest radiograph suggestive of PTB, positive sputum AFB stain and or culture, or currently taking anti-Koch's medications. The exclusion criteria are those diagnosed to have PTB but not on anti-Koch's medications or previously treated.

A survey form formulated as questionnaire (Appendix A), reviewed by a Pulmonologist were distributed to the patient to gather a consensus on the perception and knowledge about PTB.

Confidentiality was strictly observed on patients' responses.

Results

A total of 44 patients were included in the study with predominance of female participants (56.8%). The respondents' age ranged from 20-80 with a mean age of 50 years. Most of them are high school graduates

Table I. Demographic characteristics of patients included in the Survey

TOTAL	44
Gender	
Male	19 (43.2%)
Female	25 (56.8%)
Age	
20 – 30 years old	8 (18.2%)
31 – 40 years old	13 (29.5%)
41 – 50 years old	9 (20.5%)
51 – 60 years old	8 (18.2%)
61 – 70 years old	4 (9.0%)
71 – 80 years old	2 (4.6%)
Status	
Single	16 (36.3%)
Married	28 (63.7%)
Education	
Elementary undergraduate	3 (6.8%)
Elementary graduate	7 (15.9%)
High school undergraduate	9 (20.4%)
High school graduate	12 (27.3%)
College undergraduate	5 (11.4%)
College graduate	8 (18.2%)
Occupation	
None	4 (9.0%)
Clerks	3 (6.8%)
Driver	3 (6.8%)
Helper	4 (9.0%)
Housekeeper	7 (15.0%)
Laborer	5 (11.2%)
Midwife	2 (4.6%)
Nurse	1 (2.4%)
Painter	1 (2.4%)
Secretary	2 (4.6%)
Student	4 (9.0%)
Teacher	1 (2.4%)
Vendor	6 (13.5%)
Watch repairman	1 (2.4%)

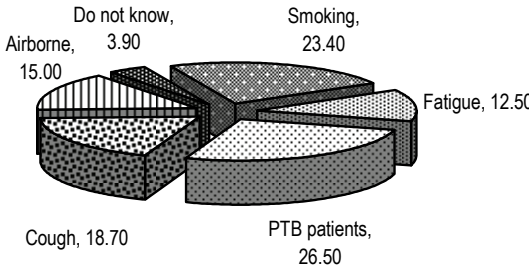

Figure 1. Knowledge of patients regarding the mode of PTB transmission (%)

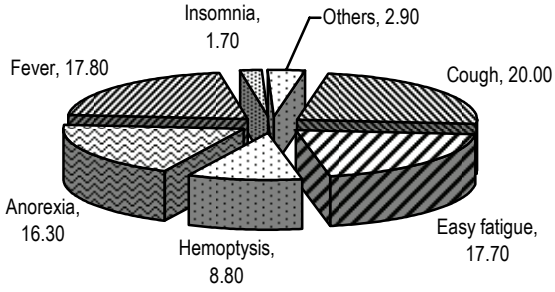

Figure 2. Knowledge of patients regarding the usual symptoms of PTB

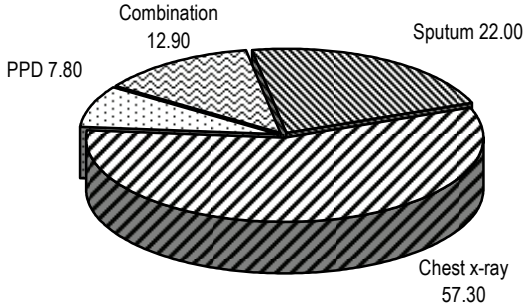

Figure 3. Knowledge of patients regarding how to diagnose PTB

(27%). Nine percent were unemployed. Of those employed, most were blue-collar workers (*Table 1*).

Majority (26.5%) of the respondents believed that the disease could arise from the exposure to a TB patient (*Figure 1*). Seventy-seven percent agreed that PTB was infectious and nine percent did not. The remaining respondents did not know the nature of the disease. (*Table II*)

Cough was the most common symptom associated with tuberculosis as reported by the respondents followed by fever and easy fatigability. Other symptoms

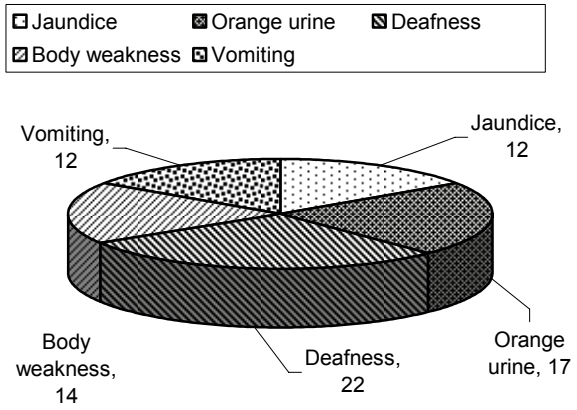

Figure 4 Complications Patients Experience while on Anti-TB medications

were anorexia, weight loss, back pain, hemoptysis and insomnia. (*Figure 2*).

Among those respondents who experienced symptoms, 90% would consult a doctor and nine percent would resort to oral hydration or cough preparation. Surprisingly, none of the respondents would do anything regarding their symptom. (*Table II*)

Most of the respondents had their disease diagnosed through radiographic findings (57.3%), sputum gram stain and culture (22.0%), PPD test (7.8%) and various combinations of diagnostic exams (12.9%) (*Figure 3*). Of those consulted, most will take the medication and only eighteen percent would not (*Table II*).

Sixty-three percent would discontinue anti-Koch's medications once they felt well. (*Table II*) Most common side effect experienced by the patients on anti-tuberculosis medication were orange-tinge urine (71.4%) followed by body weakness, deafness, vomiting and jaundice (*Figure 4*). When they experienced the side effect, 68% percent would discontinue the medications (*Table II*). When asked regarding the minimum duration of medical treatment of PTB, 72% answered six months (*Table II*).

Sixty-three percent would follow-up on their scheduled time. (*Table II*) When asked if PTB could recur after a complete treatment, 72.7% of the respondents answered "yes," while 15.9% answered "no" and 11.4% do not have any knowledge regarding its recurrence. (*Table II*) Eighty-one percent of the respondents would consult with other family members or relatives who have close contact with a doctor. (*Table II*)

Most of the respondents would consult a Pulmonologist (50%), followed by Internal Medicine specialists (31.8%), General Physicians (13.6%) and Surgeons (4.6%). (*Table II*) The doctor they consulted is stated to have explained the course of PTB well to them in about 72% of the cases. (*Figure 15*) Out of these 44 respondents, almost 91% trusted their doctor's management. (*Table II*)

Table II. Summary of patient answers (%)

Categories	Responses
Knowledge of patients regarding the infectiousness of PTB	
No	9.0
Yes	77.4
Do not know	13.6
Knowledge of patients regarding what to do with the symptoms	
Do nothing	0
Consult doctor	91
Take medicines	9
Knowledge of patients regarding taking the medications	
No	18.2
Yes	81.8
Knowledge of patients regarding compliance with Anti-TB medicines	
Yes	36.3
No	63.6
Perception of patients regarding the adverse reactions to anti-TB drugs	
Yes	31.8
No	68.2
Knowledge of patients to the duration of PTB treatment	
Doctor prescribed	27
2 months	0
6 months	73
Perceptions of patients how they will follow-up	
Monthly	36.4
Scheduled	54.5
When desired	9.1
Knowledge of patients regarding the possibility of recurrent PTB despite complete treatment	
Yes	73
No	16
Do not know	11
Perceptions of patients toward possible transmission to close contact	
Yes	81.8
No	9.1
Do not know	9.1
Perceptions of patients toward whom to consult	
Surgeon	4.6
Pulmonology	50
Internal medicine	31.8
General physician	4.6
Knowledge of PTB explained by doctors to patients	
Yes	72.7
No	27.3
Perceptions of patients toward the doctors	
Yes	90.1
No	9.1

Discussion

In the updates of health statistics in the year 2000, PTB remain to be the 6th most common cause of morbidity and mortality, with a rate of 165.7/100,000 population and 38.3/100,000 population respectively.[4]

According to Cantwell et al. a low income, crowded living conditions, unemployment and lower educational attainment account for much elevated risk for tuberculosis.[5] In the study populations, the perception and knowledge of the respondents regarding PTB agreed with the accepted medical knowledge. Majority considered it as infectious diseases (77%), which tell us that preventive measures are being practiced by people to prevent the disease.

Ninety percent of the respondents would seek consult with a doctor because they believe that they are the right person to see and most of the respondents are very eager to have an early recovery. Eighty-two percent would take the medication prescribed to them with good compliance.

Seventy-two percent of the respondents were aware of the minimum duration of medical treatment, but 63% would stop the medication once they felt well and 68% would discontinue the drugs once an adverse reaction is experienced. A problem may arise here. Inadequate treatment fails to cure the patients, even leaving them to be more infectious and worse - to the emergence of multiple drug resistance (MDR).

This is therefore the role of a physician. We must explain to our patients in great detail the risk of emerging resistance to treatment failure once an incomplete or poor compliance to therapy takes place. Since in the study group, majority (91%) of the respondents trusted their doctors.

Conclusion

Majority of the patients surveyed were knowledgeable about PTB. However lack of awareness regarding developing MDR from poor compliance or incomplete treatment should be especially addressed by the physician.

Directly Observed Therapy (DOT) as programmed by the WHO needs to be implemented to fight against tuberculosis and an understanding of the patient's perceptions and knowledge toward PTB may helps us reach the goal to eradicate the killer disease "PTB."

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APPENDIX

Name:
Sex:
Occupation:
Address:
Age:

Status:
Education:
Contact number:

1. Paano ba ninyo nakukuha ang sakit na tuberculosis? (How is PTB transmitted to a person)

- ☐ pagod
- ☐ usok
- ☐ ubo
- ☐ hangin
- ☐ hika
- ☐ nahawa sa may sakit na tuberculosis
- ☐ iba pa: _____

2. Ito ba ay nakakahawang sakit? (Is this communicable)

- ☐ oo
- ☐ Hindi

3. Ano ang mga pangkaraniwang sintomas ng tuberculosis? (What is/are the usual symptom of PTB)
- ☐ lagnat
- ☐ sakit ng katawan
- ☐ madaling mapagod
- ☐ iba pa: _____
- ☐ nangangayat
- ☐ walang ganang kumain
- ☐ ubo

4. Ano ang gagawin ninyo sa sintomas nararamdaman? (What would you do with the symptoms felt)
- ☐ hahayaan nalang
- ☐ magpapatingin sa mang-gagamot
- ☐ iinum ng gamut

Bakit? _____

5. Paano mo nalaman ang sakit ninyo? (How was your TB diagnosed)
- ☐ x-ray
- ☐ sputum OPPD
- ☐ combinasyon

6. Kung sakaling nagpatingin kayo, at binigyan kayo ng "5" gamut, iinumin ba ninyo ang mga ito, Bakit?
(If you seek consult and are given 5 medications, would you take it all, Why)
- ☐ oo
- ☐ Hindi

Bakit _____

7. Kung sakaling wala na kayong nararamdaman sintomas, ipagpapatuloy pa ba ninyo ang gamutan hanggang anim na buwan, Bakit?
(If there are no more symptoms, are you going to continue the medication for 6 months, Why)
- ☐ oo
- ☐ Hindi

Bakit _____

8. Ano ang mga komplikasyong napansin ninyo sa paginom ng gamot? (What are the side effects experienced during the therapy)
- ☐ wala
- ☐ nanghihina
- ☐ kulay orange-red ang ihi
- ☐ lumalabo ang paningin
- ☐ nandidilaw
- ☐ nagsusuka
- ☐ sumasakit ang tiyan
- ☐ nanghihina ang pandinig
- ☐ namamanhid
- ☐ nabibingi
- ☐ iba Pa: _____

9. kung sakaling may maramdaman kayong komplikasyon habang umiinom ng gamot, ipagpapatuloy pa ba ninyo ang gamutan, Bakit? Anong gagawin ninyo? (During your treatment, if you experienced side effect, are you going to continued the medication, Why and what would you do?)
- ☐ oo
- ☐ hindi

Bakit _____ Anong gagawin ninyo: _____

10. Hangang kailan niyo iinumin ang gamot para sa tuberkulosis, Bakit? (How long would you take the medication, Why)
- ☐ 1 months
- ☐ 2 months
- ☐ 3 months
- ☐ 4 months
- ☐ 5 months
- ☐ 6 months
- ☐ Iba Pa: _____

11. Paano kayo nagpapakonsulta sa doctor? (How will you have your follow-up treatment)
- ☐ tinatawagan
- ☐ bumabalik kada buwan
- ☐ bumabalik na lang kung gusto
- ☐ naaayon sa schedule ng doctor

12. Maari bang magkaroon ng tuberkulosis muli ang isang tao pagkatapos ng kumpletong gamutan? (Can PTB recur after a complete treatment?)
- ☐ oo
- ☐ Hindi

Bakit _____

13. Dapat bang magpatingin din ang ibang kasama sa bahay? (Is it important to seek consult other family members with close contact to you?)
- ☐ oo
- ☐ Hindi
- ☐ di alam

Bakit _____

14. Ano ang kurso ng inyong doctor? (What is the specialty of your doctor?)
- ☐ General physician
- ☐ Pulmonologist
- ☐ Internal medicine
- ☐ Surgeon

iba pa: _____

15. Nagpaliwanag ba ang doctor ninyo tungkol sa sakit na tuberkulosis? (Was the TB explained well by the doctors?)
- ☐ oo
- ☐ Hindi

Paano nila pinaliwanag: _____

16. Naniniwala ba kayo sa doktor ninyo tungo sa pang gagamot niya sa sakit ninyo tuberkulosis? (Do you trust your doctor's Treatment)
- ☐ oo
- ☐ di masabi
- ☐ Hindi

Non-Tuberculous Infection in Pulmonary Tuberculosis Patients

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Objectives: The study aims to determine the prevalence of community acquired, pneumonia in patients with pulmonary tuberculosis admitted at Quezon Institute from February to July 2002.
Setting: Quezon Institute
Methods: The population understudy comprised of 40 patients admitted at Quezon Institute with a diagnosis of pulmonary tuberculosis with concomitant bacterial pneumonia based on the NTP and Philippine Clinical Practice Guideline for CAP respectively. These patients were included in the study based on the inclusion and exclusion criteria that was made to determine who are eligible for the study. They were then subjected to CXR, sputum gram stain, sputum and blood culture and sensitivity. All patients were prescribed of empiric treatment based on how they were classified.
Results: Based on the data presented, patients with blood culture positive were about 12.5% and 52.5% comprised the sputum culture positive. About 62.5% comprised the patients with incomplete treatment and those who were not able to comply with the treatment regimen, whereas, only 37.5% had a complete treatment. The AFB smears were equally distributed, with 50% each for both AFB smear positive and negative. The mortality rate was 32.5% (13 patients), all of which had either incomplete or were no able to comply. Twenty-four patients (60%) were discharged improved and 3 went home against medical advice.
Conclusion: In summary, we believe that pneumonia can co-exist with pulmonary tuberculosis as shown by the data presented. *Phil Journal of Chest Diseases. Vol 12 No. 1 pp: 37-40*

Keywords: PTB, Diagnosis, Pneumonia

Introduction

Each year, 2 to 3 million cases of community acquired pneumonia account for 10 million physician visits, 500,000 hospitalizations and 45,000 deaths in the United States. Mortality rates ranges from less than 1% among outpatients and up to 30% for patients requiring hospitalizations.[1] A careful history and physical examination should be conducted to establish the clinical diagnosis of pneumonia. The initial approach to the patient with clinical diagnosis of community acquired pneumonia, should be directed towards identifying the etiologic pathogen, assessing the severity of infection and need for hospitalization, and instituting empirical treatment.[2]

Among common infections managed in the emergency department and ambulatory care clinic, few conditions have had treatment guidelines, antibiotic selection strategy or institutional change that revolved as rapidly as they have in community acquired pneumonia.[3] Unfortunately, no single set of guideline is applicable to every patient on practice environment, hence, clinical judgment must prevail.[3]

Majority of admitted patients at Quezon Institute are still pulmonary tuberculosis which comprise about 30-40% of total admissions and a number of these patients were diagnosed to have concomitant bacterial pneumonia.

The study was carried out to assess the patients admitted at Quezon Institute who were diagnosed as such. Do they really have pneumonia? Could it be a misdiagnosis? Should they be treated empirically for pneumonia? After all, the presentation and the signs and symptoms could still be a part of the pulmonary tuberculosis as a whole.

The study aims to determine the prevalence of community acquired pneumonia in a patient with pulmonary tuberculosis. It also aims to determine the compliance of patients to the prescribed treatment.

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Methodology

Between February and July 2002, 820 patients were admitted at Quezon Institute, and of these, 85 patients were diagnosed to have pulmonary tuberculosis with concomitant pneumonia. A follow up interview in the wards was made to determine who were eligible or who will be included in the study. The diagnosis of tuberculosis and community acquired pneumonia were based on the National Tuberculosis Program and the Philippine Clinical Practice Guideline for CAP, respectively.

Inclusion and exclusion criteria were set to produce the population under study:

Inclusion criteria are as follows: Patients diagnosed as PTB, CAP: acute onset of productive cough of less than two weeks, abnormal vital signs, abnormal chest findings, chest radiograph findings

Exclusion criteria are as follows: patients with prior history of treatment, presence of effusion, destroyed lung, consideration of bronchiectasis, and diagnosed CAP but with inappropriate empiric treatment.

Upon review of the patients' history and physical examination and applying the inclusion/exclusion criteria, 40 were eligible for the study. All these patients were subjected to chest x-ray, sputum gram staining, sputum culture and sensitivity, and blood culture and sensitivity.

All patients were prescribed empiric treatment based on how they were classified in accordance with the existing Philippine Clinical Practice Guidelines for Community Acquired Pneumonia.

Study Design: This is a prospective descriptive study of 40 patients admitted at Quezon Institute from February to July 2002 diagnosed as PTB with pneumonia.

Definition of Terms: NTP Classification of Pulmonary Tuberculosis Category I: New, pulmonary smear-positive; New, pulmonary smear-negative with extensive parenchymal involvement. Category II: Re-treatment cases, Relapse, Failure, Treatment after interruption. Category III: New, pulmonary smear-negative (other than category I).

Classification of Community Acquired Pneumonia: Minimal Risk (CAP I): age $\leq$ 65 years old, stable vital signs, no co-morbid condition; Low Risk (CAP II): age $\leq$ 65 years old, stable vital signs, stable co-morbid conditions; Moderate Risk (CAP III): regardless of age with anyone of the following: RR > 30 bpm, PR >125 bpm, T^o 35 or 40^{o}C, radiographic findings of bilateral or multilobar involvement, progression of lesion to 50% of initial findings within 24 hours, pleural effusion, abscess, suspected aspiration; High Risk (CAP IV): findings from CAP III plus any of the following: shock or signs of hypoperfusion, hypotension, altered mental state, urine output < 30 ml/hour, PO_2 < 60 mmHg or acute hypercapnea (PCO_2 > 50 mmHg)

Table I Demographic Characteristics of Patients

Age	Male		Female		Total	
	n	%	N	%	n	%
20 - 29	3	7.5	3	7.5	6	15.0
30 - 39	3	7.5	4	10.0	7	17.5
40 - 49	9	22.5	1	2.5	10	25.0
50 - 59	7	17.5	5	12.5	12	30.0
60 and above	4	10.0	1	2.5	5	12.5
Total	26	65.0	14	35.0	40	100.0

Table II Proportion of Patients Subjected to Blood Culture who Complied with the Prescribed Treatment Regimen

Results	Completed Tx		Incomplete Tx		Non-treated		Total	
	n	%	n	%	n	%	n	%
Blood CS (+)	2	5	2	5	1	2.5	5	12.5
Blood CS (-)	13	32.5	12	30	10	25.0	35	87.5
Total	15	37.5	14	35	11	27.5	40	100.0

Table III Proportion of Patients Subjected to Sputum Culture who Complied with the Prescribed Treatment Regimen

Results	Completed Tx		Incomplete Tx		Non-treated		Total	
	n	%	n	%	n	%	N	%
Sputum CS (+)	6	15	6	15	9	22.5	21	52.5
Sputum CS (-)	9	22.5	6	15	4	10.0	19	47.2
Total	15	37.5	12	30	13	40.0	40	100.0

Results

Incidence of Pneumonia. The study population consisted of 40 patients with a diagnosis of pulmonary tuberculosis with concomitant bacterial pneumonia. Of these patients, five (12.5%) were blood culture positive,

(three with *Pseudomonas*, two with *Staphylococcus*). The positive sputum cultures were noted in 52.5% (21) of patients without any similarity on growth recorded on the blood culture. Of the patients with positive sputum cultures, 81% conforms to the predominant microorganism seen in sputum gram stain. The results of sputum AFB smear were equally divided among the patients with 20 patients each for both AFB positive and negative findings.

This table shows that males are more affected than females comprising of 65% of the total study population. Likewise, it shows that most of the patients affected were those 40 years old and above with 22.5% of the male patient belonging to the 40 to 49 years old bracket while 12.5% of females belong to the 50 to 59 years of age group.

Of the 12.5% of patients who were blood culture positive, only 5% were able have a complete treatment regimen as compared to 32.5% of the blood culture negative patients.

These results show that 35% had incomplete treatment while 27.5% of patients were not able to take the prescribed medicines.

This table conveys us that of the 52.5% sputum culture positive, 15% of the patients completed the treatment and another 15% had an incomplete regimen while almost half of the patients with culture positive were not able to comply with the treatment. Of the 40 patients, 19% had sputum culture negative and most of them had a complete treatment.

As mentioned above, 81% of the sputum culture positive conforms with the predominant organisms found on sputum gram stain. Thirteen patients (32.5%) died from the study population. Of these mortalities, 2 patients had blood culture positive, however, 5 of the negative blood culture were found out to be sputum culture positive and likewise, the sputum culture conforms with the predominant findings of the gram stain. The rest of the mortalities (six patients) were negative for both blood and sputum culture findings. Of the two mortalities with positive blood culture, a 21 and a 31 year old male had *Pseudomonas* and *Staphylococcus* respectively. Both of these two mortalities were AFB negative and died with incomplete treatment. With regards to the patient who was blood culture negative but was sputum culture positive, one had *Klebsiella* and four had *Pseudomonas*. Of all the mortalities, five patients were without the benefit of the prescribed medicines while eight patients, died with incomplete treatment. About the AFB smear status, of the 13 patients who expired, six and seven patients were smear positive and negative, respectively.

Of the 40 patients included in the study, 24 were discharged apparently improved and 11 of them were sputum culture positive, and three had blood and sputum culture positive of different etiologies. Among these patients, 16 had a complete treatment, three had incomplete and irregular intake of medicines while five patients were not able to comply with the prescribed regimen. AFB smear are of equal distribution, with 12 patients each for both positive and negative smears.

Three patients went home against medical advice, all of whom had sputum culture positive which conforms the predominant gram stain findings (*Streptococcus*, *Klebsiella* and *Pseudomonas*). Two were patients without medications and one had an incomplete treatment. AFB smear positive were noted on two of three patients who went home against medical advice.

Discussion

Pneumonia is a lower respiratory tract infection presenting with an acute onset of within 24 hours to less than 2 weeks which when acquired in the community is referred to as community acquired pneumonia.[4] Community-acquired pneumonia remains a common and serious illness in spite of the availability of new antimicrobials and effective vaccines. In the US, pneumonia is the 6th leading cause of death and the number one cause of death from infectious disease.[5,6]

A patient with cough who has abnormal vital signs with at least one abnormal chest findings of diminished breath sounds, rhonchi, crackles or wheeze probably has pneumonia.[4] However, these clinical findings are not sufficiently accurate in diagnosing pneumonia. A chest radiographic examination showing new infiltrates is required to confirm the diagnosis. In this study, patients were included based on the inclusion and exclusion criteria to fit in the diagnosis of PTB with CAP.

The causes of pneumonia are difficult to established because of poor sensitivity of diagnostic test in non-invasive respiratory samples to identify the causative pathogens.[7] This study showed, that 87.5% of the patients were blood culture negative while 12.5% were blood culture positive which could be a true picture of all the patients who died in which growth from the blood culture was noted. Although the blood culture has a low sensitivity, a positive blood culture is specific and is considered the "gold standard" in the etiologic diagnosis of pneumonia.[4]

The value of gram staining of expectorated sputum is debated.[8,9] The IDSA recommend this relatively simple inexpensive procedure for guiding initial selection of antimicrobial therapy. The ATS however,

specify that gram staining should be used to guide interpretation of culture results and it cannot be used to focus initial empiric antibiotic therapy, but rather to broaden initial empiric antibiotic therapy to include organisms found in gram stain that are not covered by usual initial empiric therapy options.

With regards to sputum culture, they are neither sensitive nor specific. The most likely explanation for unreliable microbiological data is that the specimen did not provide rich in enough source of inflammatory material from lower respiratory.[10,11] This probably holds thru with our study, and probably some of those obtained from the sputum culture were just colonizers. Of the 40 patients in the study, 21 had sputum culture positive and of these twenty-one, 17 conforms to the predominant microorganisms identified in sputum gram stain. Eleven of these 17 patients were discharged improved, some of whom were non-compliant or had incomplete treatment while 6 patients died from the said group. Routine bacterial culture of sputum often demonstrate pathogenic organisms, but sensitivity and specificity are poor and should be correlated with the predominant organisms identified from the gram stain.[12]

Once a diagnosis of CAP was made, patients should receive their first dose of antibiotics within 8 hours after admission.[13] This study showed an overall mortality rate of 32.5% which could probably be attributed to some medical conditions present, presence of the pathogenic organisms, inability to comply with the prescribed medicines and probably the TB itself could be a factor.

Of the 32.5% mortality, 5% and 15% are blood culture and sputum culture positive respectively whereas 12.5% were both negative for blood and sputum culture. With regards to sputum bacteriology, several studies suggested that mortality associated with CAP in hospitalized patients is the same for those without an etiologic agent.[14,15]

Conclusion

In summary, we believe that pneumonia can co-exist with pulmonary tuberculosis as shown by the data presented.

Recommendations

The diagnosis of pneumonia is established by compatible clinical syndrome plus the recovery of probable etiologic agent; however, it is very difficult to establish the agent because of the poor sensitivity of diagnostic test in non-invasive respiratory samples to identify the causative pathogen.

The investigators wish to recommend a thorough history and physical examination which could perhaps increase the probability of the diagnosis.

Laboratory testing as a whole and technicians in particular play an important role in this endeavor. They should be continuously upgraded if necessary and continuous training done also if possible.

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Comparative Evaluation of Spot Sputum Specimen and Early Morning Sputum Specimen In the Diagnosis of Pulmonary Tuberculosis

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In countries where the prevalence of tuberculosis is high such as in the Philippines, sputum smear microscopy and culture for acid fast-bacilli plays a basic role in identifying and treating patients with pulmonary tuberculosis. The submission of three consecutive or separate early morning sputum specimens for AFB microscopy in suspected patients with PTB have been recommended and currently being practiced. The submission of spot specimens in this proposed alternative is more convenient and easier to comply on the part of the patients without compromising the number of examinations to be done. This can shorten the delay in the diagnosis of PTB thereby promoting immediate treatment. The aim of this study is to compare the AFB smear microscopy and - TB culture results between early morning and spot sputum specimens and to determine the sensitivity and specificity of both types of sputum specimens.

Among 195 new patients suspected of having pulmonary tuberculosis at the Lung Center of the Philippines, a total of 83 patients (42%) were culture positive for *Mycobacterium tuberculosis*. In this study, there was no significant difference in the yield of either smear and culture results between spot sputum specimens and early morning sputum specimens.

The results of this study suggest that the yield of the spot expectorated sputum specimen is comparable to the early morning sputum specimen. Increasing the sample size to 600 subjects is recommended to achieve its power. *Phil. Journal of Chest Diseases. Vol. 12 No. 1 pp: 41-45*

Keywords: PTB, Diagnosis, Sputum smear

Introduction

Tuberculosis (TB) is a great problem in most low-income countries. It kills more people than any other single agent. Ninety-five percent (95%) of TB cases and 98% of TB deaths are in developing countries. Seventy-five percent (75%) of these cases affect individuals in the productive age group (15 to 50 years).[1,2] Pulmonary tuberculosis is the most frequent form of the disease, occurring in over 80% of cases which maybe infectious.[1] The identification and cure of infectious cases, i.e., patients with smear positive pulmonary TB, is the most cost-effective public health measure to control TB.[2] In countries where the prevalence of pulmonary TB is high, such as in the Philippines, sputum smear microscopy for acid-fast bacilli plays a basic role.[1,3]

Sputum smear positivity for acid-fast bacilli remains as the most important diagnostic test in the evaluation of patients suspected of having active pulmonary tuberculosis,[1-12]

It is simple, economical and easy to perform. Approximately 10^4 organisms per milliliter of sputum are needed to yield a positive sputum smear result. It is in this light that sputum smear positivity is presumed to be an indicator of increased organism burden and infectivity, more so in patients with cavitary lesions. Studies have shown that the specificity of sputum smear microscopy for acid-fast bacilli is as high as 99.8% while sensitivity can be as low as 51.8%.[5-7]

For better case finding and eventual control of pulmonary tuberculosis, sensitivity of smears as well as cultures should be increased. Therefore, proper collection and handling of specimens is of utmost importance.[5] Sputum specimens for mycobacterial examination should be sent to the laboratory as soon as possible. If not, it is recommended that specimens be refrigerated and made sure that it is not exposed to direct sunlight to prevent bacterial contamination.[3]

The submission of three consecutive or separate early morning sputum specimens for AFB smear microscopy in patients suspected of having active pulmonary tuberculosis have been recommended and is currently being practiced.[5,8-9,12,13] It has been reported that examining multiple specimens (3 or more) increases the sensitivity of the AFB smear.[7-13] However, in situations when this scheme is not practical, the Department of Health recommends the submission of a spot specimen during the first consultation followed by a single early morning sputum specimen accompanied by

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another spot sputum specimen collected during the submission of the second specimen.[1,3-4]

The submission of spot specimens as a proposed alternative is more convenient on the part of patients as well as it ensures compliance on the submission of sputum specimens without compromising the number of examinations to be done. This likewise shortens the delay in the diagnosis, thereby promoting immediate treatment. Although it is expected that an early morning sputum specimen should yield higher positive AFB results than a spot sputum specimen because it is more concentrated, hence, with a higher bacterial load, a significant difference between these two types of specimens is still to be demonstrated.

Specifically, this study aims to compare AFB smear microscopy and TB culture results between early morning and spot sputum specimens using the McNemar Chi-square test. The sensitivity and specificity of both types of sputum specimens were likewise determined using the TB culture results as gold standard.

Methodology

Patient Population. This is a prospective cross-sectional study involving patients with suspected active pulmonary tuberculosis. Adults of both sexes who consulted at the Lung Center of the Philippines Out patient Department or admitted at the wards from September 2001 to September 2002 were included in this study. These patients have clinical signs and symptoms suggestive of pulmonary TB such as chronic cough, weight loss of more than 10% in a month, hemoptysis, blood-streaked sputum, and chest and/or back pain. Radiologic findings suggestive of pulmonary TB are also present such as diffuse reticulo-nodular infiltrates, haziness, cavitary or mass lesions, hilar or mediastinal lymphadenopathies and pleural effusion. Subjects must also be able to produce properly collected and adequate sputum samples (spontaneously expectorated or induced sputum specimens collected within 24 hours after oral hygiene and placed in a sterile wide-mouthed container with a volume of at least 5 ml.). Patients with previous diagnosis of pulmonary TB, previous intake of anti- TB medications or currently undergoing anti- TB therapy were excluded from this study. Pooled and unrefrigerated sputum specimens as well as sputum specimens directly exposed to sunlight were also excluded.

Sputum Collection. After clinical assessment, the subjects included in the study were instructed how to properly collect an early morning sputum specimen. Upon submission of the early morning sputum specimen, the subjects were again instructed to collect a spot sputum specimen to be paired with the previously submitted early morning sputum specimen. Both specimens were assessed in terms of volume and quality prior to processing.

Smear Preparation. Under a safety cabinet, the smears are made by using a sterile loop to transfer sufficient material taken from cheesy, necrotic or blood-tinged areas of the specimen directly on a clean glass slide and smeared evenly on an area approximately 1x2 cm. The smears are then air-dried and heat-fixed.

Ziehl-Neelsen Staining. After fixing, the slides were placed on a staining rack and flooded with *Ziehl-Neelsen* carbolfuchsin and heated slowly until steaming using a Bunsen burner. Steaming was maintained for 3 to 5 minutes using low or intermittent heat. After cooling, the stain was rinsed briefly with water and drained. Decolorization with 3% acid alcohol was done until color is drained from the slides and rinsed thoroughly with water. After which, counterstaining with methylene blue proceeded 30 seconds to 1 minute and rinsed with water. Slides were then allowed to air dry.

Direct Microscopy. Smears were examined under oil immersion objective (100x) of the microscope by a trained microscopist. A senior trained microscopist confirmed positive smears. Results were reported as follows: negative = no acid-fast bacilli found; 1+ = 1-9 per 10 fields; 3+ = 1-9 per field; 4+ = more than 10 per field.

Mycobacterial Culture. Approximately 5 to 10 ml. of the sputum specimen were transferred to a 50-ml screw cap conical tube and an equal volume of NaOH-nALC digestant mixture was added. The mixture was homogenized using a vortex mixer for 15 to 20 seconds until it is well mixed and allowed to stand at room temperature for 15 minutes with periodic swirling. Caution is observed not to have this digestion time exceed 20 minutes since "over treatment" of the specimen results in fewer viable organism yield for culture. Enough phosphate buffer pH 6.8 (KH_2P0_4 and Na_2HP0_4) was added and the tube was inverted to mix solutions and to stop digestion process as well as to reduce the specific gravity which aids in the sedimentation of the bacilli during centrifugation. Centrifugation was done at 3000xG for 15 to 20 minutes. After centrifugation, the supernatant was decanted and the sediments were re-suspended in 1 to 2 ml of phosphate buffer.

Prior to inoculation, the 12B (*Middlebrook* 7H12B culture medium) vials were tested on the *BACTEC 460* TB system instrument to eliminate vials with high background readings and to establish a CO_2 enriched atmosphere in the vial.

Table I Comparison of Smear Results Between Single Early Morning Sputum Specimen (SEM) and Spot Sputum Specimen

	AFB (+)	AFB (-)	Total
SEM	45 (23%)	150	195
SPOT	39 (20%)	156	195

Table II Comparison of Culture Results Between Single Early Morning Sputum Specimen (SEM) and Spot Sputum Specimen

	Culture (+)	Culture (-)	Total
SEM	78 (40%)	117	195
SPOT	75 (38%)	120	195

Addition of 0.1 ml of *PANTA* to each vial of 12 B media was done to reduce contamination prior to inoculation. Using a tuberculin syringe, 0.5 ml of the specimen was inoculated in each 12B medium vial. After inoculation, the rubber septum of each vial was cleansed with 70% alcohol. Vials were incubated at $37^oC \pm 1^oC$. Growth index (GI) was read twice for the first 2 weeks and once from the third to the sixth week of incubation.

The result of each *BACTEC* test is a GI number. The GI is a measure of the $^{14}C0_2$ aspirated from the test vial. GI numbers below 10 are representative of negative cultures.

A G1 of 10 or more is considered "presumptive positive". The AFB smear stained with the *Ziehl-Neelsen* method is important for the confirmation of presence of Mycobacteria. Once AFB is observed on the smear made from a positive vial, the specimen may be reported as culture positive for AFB (identification pending). Negative cultures were reported after six weeks of incubation. A sudden increase in GI or the presence of turbidity may indicate contamination. This is confirmed by making a smear and subculturing on a blood agar plate.

Mycobacterial Identification When the 12B vial shows a GI of 10 or more, it is tested daily until it reaches a GI of 50 to 100. After which a smear is made and stained with *ZiehlNeelsen* stained and examined for the presence of serpentine cords and clumps that is characteristic of *M. tuberculosis*. Using a tuberculin syringe, 1 ml of culture was aseptically transferred to a NAP vial. The top of the NAP vial and the control (original culture) were swabbed with 70% alcohol. Vials were tested on the *BACTEC 460TB* system to purge 5-10% CO_2 and the reading is disregarded. Incubation at $37°C \pm 1°C$ is done and tested daily for the next two to six weeks. Daily GI of the NAP and control vials are recorded. The isolate is identified as TB complex if there is a decreased GI after inoculation or a slight but no significant increase in the first two days and there is a decrease or no increase in GI. *Mycobacteria* other than tuberculosis (MOTT) are identified if the daily GI reading increases to over 400 within four days; or if there is a slight decrease or no increase in the first one to three days after inoculation followed by two consecutive daily significant increases following day two.

Results

There were 195 patients included in the study. Most of the subjects were male (67%) with a mean age of 40 years. Only 2 out of the 250 subjects were in-patients while the rest (193) were out-patients. The most common presenting symptoms are chronic cough (90%) followed by fever(45%) and back pain(39%).

Majority of the radiologic findings were infiltrates (apical, basilar and reticulo- nodular) (37%) followed by cavitary lesions and fibrosis.

Table I shows AFB smear results of both spot and early morning sputum specimens. Smear results were positive in 23 % of early morning sputum specimens and is slightly higher than the 20% positive results obtained from the spot sputum specimens.

The corresponding culture results of both specimens are illustrated in *Table II*. This table shows 40% of the early morning sputum specimens yielded positive culture results in comparison with the 38% positive yield from the spot sputum specimens.

Table III illustrates the agreement of smear results between the early morning and spot sputum specimens. Out of the 45 smear positive sputum samples, 36 gave concordantly positive results for both early morning and spot sputum specimens while the remaining nine gave positive results only in the early morning specimens which were not detected by the spot specimens. Smear negative sputum samples totaled 150. Out of these samples, 147 gave negative results for both types of specimens while three spot sputum specimens tested positive but was negative in the early morning specimens. *McNemar* Chi-square test was used for statistical analysis. The exact *McNemar* significance probability was computed at 0.1460 with a 44% power.

Table III Comparison of Smear Results Between Single Early Morning Sputum Specimen and Spot Sputum Specimen

	SPOT (+)	SPOT (-)	TOTAL
SEM (+)	36	9	45
SEM (-)	3	147	150
TOTAL	39	156	195

Exact McNemar Significance Probability = 0.1460 (44% power)

Table IV Comparison of Culture Results Between Single Early Morning Sputum Specimen (SEM) and Spot Sputum Specimen

	SPOT (+)	SPOT (-)	TOTAL
SEM (+)	70	8	78
SEM (-)	4	113	117
TOTAL	74	121	195

Exact McNemar Significance Probability = 0.3877 (22% power)

Table V Comparison of Smear and Culture Results of Single Early Morning Sputum Specimens

	Culture (+)	Culture (-)	Total
Smear (+)	43	2	45
Smear (-)	40	110	150
Total	83	112	195

Sensitivity: 51.8% (Confidence Interval = 40.7% - 62.8%)
Specificity: 98.2% (Confidence Interval = 93.1 % - 99.7%)
Positive Predictive Value: 95.6%
Negative Predictive Value: 73.3%
Overall Accuracy: (43 + 110)/(195) = 78%

Table VI Comparison of Smear and Culture Results of Spot Sputum Specimens

	Culture (+)	Culture (-)	Total
Smear (+)	39	0	39
Smear (-)	44	112	156
Total	83	112	195

Sensitivity: 47% (Confidence Interval = 36.1 - 58.2)
Specificity: 100% (Confidence Interval = 96.8 - 99.9)
Positive Predictive Value: 100%
Negative Predictive Value: 71.8%.
Overall Accuracy: (39 + 112)/(195) = 77.4%

Table IV shows the agreement of culture results between the spot and the early morning sputum specimens. A total of 78 sputum specimens were culture positive - 70 samples were concordantly positive in both types of specimens while the remaining eight samples were positive only in the early morning specimens but negative in the spot specimens. *McNemar* Chi-square test was likewise used in the statistical analysis with the computed exact *McNemar* significance probability at 0.3877 with a power of 22%.

Tables V and VI shows a tabulation of the smear and culture results for early morning and spot sputum specimens, respectively. Based on these results, the specificity and sensitivity with corresponding confidence interval, negative predictive value, positive predictive value and overall accuracy for each type of specimen were computed. The specificity of the spot sputum specimen is 100%, which is slightly higher than that of the early morning sputum specimen. Sensitivity of the early morning sputum specimen, however, is slightly higher at 51.8% compared to the 47% obtained for the spot sputum specimen. Positive predictive value is higher for the spot sputum specimen (100%) compared to the early morning sputum specimen (95.6%). Negative predictive value, on the other hand, is slightly higher in early morning sputum specimen (73.3%) than the spot sputum specimen (71.8%). Likewise, the overall accuracy was also slightly higher in the early morning sputum specimen (78%) compared to the spot - sputum specimen (77.4%).

Discussion

Pulmonary tuberculosis is a highly infectious disease. Infectiousness is an important feature of a case because the identification of infectious cases leads to reduction and if possible, elimination of infection. The presumptive diagnosis of active disease is based on the demonstration of acid-fast bacilli by microscopy with definitive diagnosis by subsequent culture of *Mycobacterium tuberculosis*. In this study, the extent of pulmonary tuberculosis, as evidenced by chest x-ray findings and presenting signs and symptoms, as well as the volume and type of sputum specimen collected correlates with smear-positivity and subsequently culture-positivity. Higher frequencies of smear-positive cases are seen in advanced pulmonary tuberculosis, especially in cavitary disease. The submission of at least 5 ml of sputum in this study further increases the yield of AFB smears and cultures.

Single early morning sputum specimen has been the standard specimen submitted for AFB smear examination because it is concentrated and therefore has a higher bacterial load. In this study, the single early morning sputum specimen yielded slightly higher smear and culture positivity results compared to that of the spot sputum specimen, attesting to its more concentrated

nature. However, when subjected to statistical analysis, no significant difference was noted between the single early morning sputum specimen and the spot sputum specimen in terms of smear and culture positivity. Therefore, spot sputum specimens may be submitted along with single early morning sputum specimens in a proposed alternative scheme instead of submitting three consecutive early morning sputum specimens as previously practiced. This study likewise determined the specificity of the two types of specimen, which showed the spot sputum specimen to be more specific than the single early morning sputum specimen.

Based on this finding, submission of spot sputum specimen for AFB smear examination maybe used as a screening procedure in the initial evaluation of patients suspected of pulmonary tuberculosis for it can help rule out negative cases. Sensitivity for both types of specimen was likewise determined which showed the single early morning sputum specimen to have slightly higher sensitivity than the spot sputum specimen. In this sense, submission of a single early morning sputum specimen will yield higher culture positive results.

Conclusion

In conclusion, there is no significant difference in the smear and culture results between spot sputum specimens and early morning sputum specimens. The specificity of spot sputum specimens in this study is higher (100%) than the single early morning sputum specimen (98.2%). Sensitivity, on the other hand, is higher in the single early morning sputum specimen (51.8%) than the spot sputum specimen (47%).

Recommendations

1. In this study, spot expectorated sputum specimen may be used for smear and culture in patients suspected of having pulmonary tuberculosis since no significant difference was noted when early morning expectorated specimen was used.

2. It is recommended that the sample size of this study be increased to 600 subjects to achieve its power.

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Health Seeking Behavior among Filipinos with Symptoms of Tuberculosis

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Setting: Out-Patient-Department Quezon Institute
Objective: To determine factors that influences the health seeking behavior of Filipino patients with symptoms of PTB and to analyze their implication for TB control.
Study Design and Method: Subjects seen at Out-Patient-Department of Quezon Institute aged 18 years old and above with symptoms of tuberculosis were given pre-tested questionnaires. A total of 125 subjects were included.
Results: Demographic characteristics of respondents were male, aged 25-36 years old, unemployed and residing in Metro Manila. Perceived causes of tuberculosis were to be caused by smoking and sweat drying 113 (90%) and 103 (80%) respectively. Most symptoms were cough of 2 weeks duration and chest/back pains 109 (87%) and 99 (79%) respectively. Most of the respondents sought consult with a health practitioner before intake of medications at 100 (80%). However financial difficulties deter consult and intake of medications.
Conclusion: The health seeking behavior of Filipino patient with symptoms of tuberculosis are appropriate as most of the respondents sought consult first to a hospital and that they took their medications after the consult. Symptoms of the patient influence their health seeking behavior. Identified factors who will probably not take action regarding their symptoms were male respondents who are between the age of 36-55 years old, unemployed and whose residence is within Metro Manila. *Phil. Journal of Chest Diseases. Vol. 12 No. 1 pp: 46-50*

Keywords: Tuberculosis, Health seeking behavior, Diagnosis

Introduction

Tuberculosis is a reportable disease; it is a disease of overcrowding and poverty. The problem of Tuberculosis is substantial in the Urban settlements, and was appreciably worse than that in general urban population.

A study conducted by WHO from year 1980-1997, the total number of cases reported on tuberculosis in the Western Pacific Region (including the Philippines), was 834,573 during 1997 alone (as reported by 29 countries). The reported smear positive cases reported was 375,809 in 1997 alone.

According to WHO, the Philippines is one of the 22 countries in the world which account for 80% of the world TB cases.

In the study Health seeking and perceived causes of tuberculosis among patients in Manila, conducted by Christian Auer, Jesus Sarol Jr., Marcell Tanner and Mitchell Weiss, a total of 319 smear positive TB patients were interviewed. Twenty-nine percent of the respondents had gone first to a health center after onset of TB related symptoms; 53% had initially consulted a private doctor; 13% had gone first to a hospital, and 3% first to a traditional healer. Among those patients who had used the health center before falling sick with TB, 45% went to the health center first after initial symptoms of TB, compared with only 19% of those who had not yet used the health center when they fell sick with TB.

The health seeking delay after symptom onset was relatively short. Sixty-four percent of the respondents said they went to a health facility within one month. Only two factors were found to be significantly related to increased health seeking delay: feeling ostracized due to TB and having a marital partner. The main perceived factors contributing to delay were: considering the symptoms harmless, and high cost of medical care.

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Table I Demographic Characterisitcs of Patients (n=125)

Characteristics	Number	Percentage (%)
Age		
16-25	20	16
26-35	34	27
36-45	27	21
46-55	27	21
56-65	15	12
66-75	2	1.6
Sex		
Male	86	68
Female	39	31
Occupation		
Professional	8	6
Skilled workers	37	29
Unemployed	80	64
Residence		
Metro Manila	87	69
Provinces	38	30
Religion		
Roman Catholic	98	78
Iglesia ni Cristo	10	8
Islam	4	3
Protestant	7	5
Seventh Day Adventist	0	0
Jehovahs Witness	0	0
Others	6	4
Marital Status		
Single, never been married	33	26
Single, living with friend	6	4
Married	65	52
Separated, living alone	6	4
Widowed	5	4
Widowed, live-in	10	8
Degree Earned		
No educational attainment	3	2
Elementary	32	25
High School	18	14
College	23	18
Post Graduate	1	1
Vocational	8	6
Home companions		
Living with parents	33	26
Living with brothers/sisters	34	27
Living with relatives	40	32
Living with nephew/niece	11	8

Most TB patients used other health providers and partly spent considerable amounts of money before approaching the health center. Perceived causes of TB do not seem to contribute to delayed health seeking.

The cardinal signs and symptoms of tuberculosis include cough of 2 weeks duration or more, hemoptysis of any duration, chest or back pains and fever of 1 month or more. A person with any of these signs and symptoms is considered to have tuberculosis.

As part of the 1997 nationwide Tuberculosis prevalence survey, individuals 20 years or older were interviewed to determine whether they have experienced any of these cardinal signs and symptoms of Tuberculosis.

Action-taking was influenced by the symptoms reported by the patient. More symptomatic than asymptomatic subjects presented for the subsidized radiographic screening offered during the survey. This shows that those with TB symptoms were more likely to use health services provided they were free and conveniently located.

Perception and belief have been reported to influence health seeking behavior. Delays in health seeking were due to the perception that the symptoms were considered harmless and the cost of medical care was high.

Self medication among subjects was frequent.

The choice of whom to consult is generally based on satisfaction, trust and confidence, which appears to be greater for private care givers compared to public health centers. Private practitioners were consulted more frequently than public health centers by those with TB symptoms.

This study was undertaken to determine factors that influence the health seeking behavior of Filipino patients with symptoms of PTB. We also wanted to determine the factors that deter the health seeking behavior of Filipino patients with symptoms of PTB. The factors that influence the health seeking behavior of Filipino patients with symptoms of PTB will also be described. And lastly, their implication for TB control will be analyzed

Methodology

Study Population and Sample size: This descriptive study was undertaken in a hospital-based population from September 1, 2001 to September 30, 2002. Subjects were surveyed at the Out-Patient-Department of Quezon Institute in Quezon City. Subjects who were 20 years old and above were eligible for interview. A total of 125 subjects were surveyed. The study subjects were Filipino Patients seen at the Outpatient Department with symptoms and diagnosis of PTB.

Inclusion criteria were the following: Filipino patients seen at the Out-Patient-Department of Quezon Institute; patients with cough with more than 2 weeks duration; hemoptysis at any given time; fever of more than 2 weeks duration; and patients who are 18 years and above

Data collection: Individual surveys were undertaken utilizing a pre-tested questionnaire. Subjects were encouraged to volunteer for information regarding their

Table II Knowledge about Tuberculosis

KNOWLEDGE	NUMBER	PERCENT
CAUSES OF TB		
smoking	113	90
pagkatuyo ng pawis sa likod	101	80
bacteria	75	60
unsanitary surroundings	76	60
alcoholism	69	55
overwork	81	64
hereditary	70	56
SYMPTOMS OF TUBERCULOSIS		
cough more than 2 weeks	109	87
fever	93	74
chest/back pains	99	79
bloody sputum	86	68
weight loss	97	77
dyspnea	79	63

Table III Attitudes towards Tuberculosis (n=125)

ATTITUDES	NUMBER	PERCENT
How did you acquire TB		
got infected to a person with TB	100	80
inherited TB	59	47
poor health	89	71
many vices	76	60
What should you have done when you felt symptoms of TB		
seek consult with a doctor	118	94
seek consult with albularyo	4	3
seek consult to health center	73	58
What should you do to avoid TB		
avoid smoking	115	92
avoid "matuyo ang pawis sa likod"	109	87
clean the surroundings	95	76
avoid alcohol beverage drink	78	62
avoid overwork	87	69
avoid people with TB	111	88
Type of doctor		
Private MD, specialist	102	81
Private MD, non-specialist	83	66
Private MD. young physician	27	21
Private MD, old experienced physician	104	83
MD in health center	100	80
MD in government hospital	108	86

Table IV. Practices towards tuberculosis (n=125)

PRACTICES	NUMBER	PERCENT
What were your symptoms when you got TB		
cough more than 2 weeks	105	84
fever	95	76
chest/back pain	102	81
cough with blood	81	64
What did you do when you got the symptoms of TB		
took medication without consultation	22	17
seek consult to a doctor before taking medicines	100	80
seek consult with a health worker	52	41
went to an albularyo	4	3
didn't do anything	10	8
Reasons not to consult a physician		
The doctor is far	24	19
Health center is far	19	15
No companion to seek consult	31	24
No money	115	92
Reasons wherein medication were not continued		
no money	116	92
no one will give the medicines	30	24
drugstore is far	21	16

Table V Correlation between demographics and intake of medications

	No money	No companion to buy Medicines	Location of pharmacy Inaccessible
Male	67	11	8
Female	34	12	12
Professional/ skilled worker	29	9	5
Unemployed	67	19	15
Age			
16-35	37	4	7
36-55	73	10	6
55 and above	23	6	6
Residence			
Metro Manila	72	11	11
Provinces	19	9	9

general data and symptoms. Every 4th patient seen at the Out-Patient-Department with symptoms of pulmonary tuberculosis, whether male or female was given the questionnaire.

Sample size: Sample size is 125 patients computed on the basis of the following assumption 99% confidence level, prevalence rate of 50% and worst acceptability of 60%.

Results

A total of 125 persons were surveyed from the Out-Patient-Department of Quezon Institute Hospital aged 18 years old and above. *Table I* shows the demographic characteristics of the subjects. 68% were males and 31% were females. Most of the subjects were from age 26-35 years old which comprises 27% of the total population. Sixty four percent were unemployed and most are living in Metro Manila which comprises about 69%. Most of

Table VI Correlation between demographics and consultation to health practitioner

	No money	No companion to buy Medicines	Location of pharmacy Inaccessible
Male	71	21	25
Female	29	22	17
Professional/ skilled worker	28	11	15
Unemployed	70	30	30
Age			
16-35	40	13	16
36-55	41	6	17
55 and above	19	7	17
Residence			
Metro Manila	71	24	24
Provinces	29	14	18

Table VII Correlation between demographics and type of doctor seen

	Specialist	Non specialist	Young MD	Old MD
Male	70	44	29	72
Female	35	26	10	34
Professional/ skilled worker	32	13	7	30
Unemployed	71	59	44	77
Age				
16-35	40	18	10	42
36-55	41	32	14	45
55 and above	18	10	5	19
Residence				
Metro Manila	78	49	23	76
Provinces	23	20	9	29

Table VIII Correlation between demographics and action-taking

	Took medications without consult	Took medications after consult	Did not do anything at all
Male	19	36	4
Female	16	22	12
Professional/ skilled workers	2	5	0
Unemployed	34	20	19
Age			
16-35	22	9	4
36-55	11	18	4
55 above	26	37	10
Residence			
Metro Manila	49	37	21
Province	17	17	12

them are married and 25% finished only primary level of education.

Table II shows the knowledge of the subjects concerning Tuberculosis. Smoking and letting the sweat dry in their back were described as the most common causes of tuberculosis, comprising about 90% and 80% respectively. Only 60% know that the cause of tuberculosis is bacterial in nature. The most reported symptom of tuberculosis is cough of more than 2 weeks duration.

Table III shows the attitudes of subjects concerning tuberculosis. Eighty percent of the respondents know that they got infected of tuberculosis through a person infected with the disease. Ninety four percent went to a doctor when they felt symptoms of tuberculosis.

Most of the respondents chose to go to a government hospital to seek consult which comprises about 86%.

Table IV shows the practices of subjects towards tuberculosis. Most of the respondents actually sought consult first before taking any medications for their symptoms which contributed 80%. Only 17% took medications without consultation.

Financial difficulties are still the most common reason for health seeking delay and delay in intake of medications.

Table V shows the demographic characteristics of the subject in relation to the reason for delay in intake of medications. Financial problem is the most common reason for the delay in intake of medications. These are more common among male respondents who are between the age of 36-55 years old, unemployed and whose residence is within Metro Manila.

These were also the same profile of respondents noted for health seeking delay as shown in *Table VI* and *VII* correlating demographic characteristics and consultation to heath practitioner.

Table VIII shows the profile of the respondents and their action-taking regarding their symptom. A male who is unemployed who belong to older age group and residing in Metro Manila will take his medications without prior consult. However, a typical female who is unemployed and belong to an older age group whose residence is in Metro manila will take no action regarding their symptom.

Discussion

In the Philippines, tuberculosis remains prevalent with the recent report from Health seeking behavior among Filipinos with symptoms of tuberculosis by T.E Tupasi et al showed that the prevalence of the bacillary disease was 39/1000 population. The WHO Western Pacific Region reported an annual case of 834,573 and a

total of 375,809 smear positive in the year 1997 alone. The Philippines is one of the 22 countries which account for 80% of the world TB cases.

We have surveyed 125 patients seen at the Out-Patient-Department of Quezon Institute from September 2001 to September 2002. Demographic profile, knowledge, attitudes and practice were investigated regarding to symptoms of tuberculosis.

In the study health seeking and perceived causes of tuberculosis by Christian Auer in Malabon area, more individuals considered tuberculosis to be caused by smoking and sweat drying. These causes were also perceived by our subjects and lesser number of individuals considered tuberculosis to be caused by bacteria. Persons with tuberculosis believe that vice and hard-work were also the reason for tuberculosis infection.

In the report on a National Tuberculosis Prevalence Survey in the Republic of the Philippines by the National Institute of Tuberculosis, reasons for not taking action in regards to their symptom is that the symptom is harmless, either had no money and no time to seek consult. We have identified that the primary reason for not seeking consult or not taking medicine is that the respondents are financially constrained. These are more common among male respondents who are between the age of 36-55 years old, unemployed and whose residence is within Metro Manila. Personal health is not regarded as a priority in poor communities where people are struggling to survive.

Self medication as reported from Health seeking behavior of Filipino with symptoms of tuberculosis by T.E Tupasi et al was frequent. However in our survey, more subjects sought consult first to a health practitioner before intake of medication. Residents from Metro Manila either male or female who are elderly and unemployed were among the respondents.

We have found out that action -taking was influenced by the symptoms reported by the patient. Ninety four percent of the respondents actually sought consult to a health practitioner.

Respondents also prefer to seek consult to old physicians and who are specialist compared to young physicians and non-specialist. This is probably based on trust and confidence of the care givers. Most of the patients also prefer to seek consult to a government hospital, this is because the consultation is free of charge and medicines are affordable. We found out that most of the respondents consulted first to a hospital than to private practitioners.

Conclusion

The health seeking behavior of Filipino patients with symptoms of tuberculosis are appropriate as most of the respondents sought consult first to a hospital and that they took their medications after the consult. This will somehow decrease a large pool of patients identified from previous studies who took no action and self medicated which have probably led to untreated patients with a high level of transmission of the disease.

Identified risk factors to determine who will probably not take action regarding their symptoms were male respondents who are between the age of 36-55 years old, unemployed and whose residence is within Metro Manila. In this regard, it is advisable to take more time for discussion regarding the seriousness of their disease.

Symptoms of the patient influence their health seeking behavior. It was reported from studies that more symptomatic patients were more likely to use health services.

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The Relationship of AFB Sputum Smear with Chest X-ray and PTB Symptoms in patients Admitted at Manila Doctors Hospital

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Tuberculosis, particularly pulmonary tuberculosis remains a big problem in the Philippines. Our country continues to be one of 22 countries that have 80% of the global TB burden according to the WHO. According to the Philippine TB consensus, case finding by AFB sputum examination is the most important component in addressing this problem. However, it is common practice especially in large medical centers such as the Manila Doctors Hospital to rely on radiologic findings todiagnose PTB. Therefore, this study will examine the relationship of AFB smear results and clinical (symptomatology) and radiological findings.

Patients suspected with pulmonary tuberculosis that were admitted to the Manila Doctors Hospital from January to June 2001, age 18 years old and above, were asked to submit sputum specimen for AFB smear. Chest x-rays were also done on admission. There were a total of 48 patients who submitted their sputum for AFB smear. Positive AFB smear was shown in three (6.25%) cases and negative AFB smear in 45 (93.75) of cases. Of the 75% with PTB by chest x-ray, only three subjects yielded positive for AFB smear. All subjects who showed normal or other findings in Chest x-ray (25%) yielded negative AFB smear. Three of the symptomatic patients (91.6%) yielded positive for AFB smear while none of the asymptomatic patients (8.3%) yielded positive for AFB smear. Using the chi square test, it was concluded that there is no relationship between AFB smear result and chest x- ray finding, as well as the AFB smear result and the presence of symptoms. A positive chest x-ray for PTB and the presence of symptoms will not necessarily yield a positive AFB smear. *Phil. Journal of Chest Diseases. Vol. 12 No. 1 pp: 51-53*

Keywords: PTB, Diagnosis, AFB smear

Introduction

Tuberculosis caused by bacteria belonging to the *Mycobacterium tuberculosis* complex is one of the oldest diseases known to affect humans. It usually affects the lungs although other organs are also involved. Mycobacteria belong to the family *Mycobacteriaceae* and order *Actinomycetales*. The complex includes *M. tuberculosis*, *M. bovis*, *M. africanum* and *M. microti*. *M. tuberculosis* is the most important and most frequent.[5]

M. tuberculosis is a rod-shaped, non-spore forming aerobic bacterium. The bacilli cannot be decolorized by acid alcohol thus classified as acid-fast bacilli (AFB). The organism's high content of mycolic acid, long chain fatty acid and cell wall lipids make it acid fast.[5]

The Philippines is one of the 22 countries that accounts for 80% of the world's TB cases as reported by the World Health Organization (WHO). TB is one of the top five causes of morbidity and mortality.[6]

It is essential to diagnose TB early to avoid emergence of resistance cases and disease complications. High index of suspicion is the key to the diagnosis of TB. Signs and symptoms such as chronic productive cough, fever, weight loss, night sweats, hemoptysis are characteristics of PTB. There are also different ways to diagnose and screen patients with PTB: PPD or tuberculin skin test, chest x-ray, microscopic examination of sputum for acid fast bacilli (AFB), and sputum TB culture.

The 1997 National Prevalence Survey showed that there are 213,600 cases of tuberculosis nation-wide. Based on the Annual Risk of Tuberculous Infections (ARTI), there are 138 new cases of smear positive individuals per 100,000 population.[5]

According to the Philippine TB consensus, sputum examination for acid fast bacilli (AFB) or direct microscopy is the most important diagnostic test to request for a patient clinically suspected to have PTB. In the clinics sputum smears for AFB bacilli are less commonly requested than Chest x-rays. It is accepted however, that a chest radiograph can only suggest the possibility of PTB. Definitive diagnosis is established

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by test for acid fast bacilli (AFB) in sputum specimens. Studies showed that sputum AFB has high specificity at 97.5-99 8% but low sensitivity (51.8-53.1%). It is estimated that a positive test result required the presence of at least 104 bacilli per ml of specimen. In the clinics, a positive test result for a specific patient warrants a presumptive diagnosis of active PTB. While a chest radiograph is a common aid in the diagnosis of PTB, it has 80% sensitivity with 26% specificity.

It is a common practice in most institutions, including the Manila Doctors Hospital that clinicians rely on chest radiography examination alone for the diagnosis of pulmonary tuberculosis and can firmly be established by bacteriologic examination from secretions of the infected host.

This study will evaluate the relationship between: 1) sputum AFB and radiographic findings (chest xray), and 2) sputum AFB and the presence or absence of symptoms

Table I Frequency Distribution of AFB smear

	AFB1	AFB2	AFB3
Positive	3 (6.25%)	3 (6.25%)	3 (6.25%)
Negative	45 (93.75%)	45 (93.75%)	45 (93.75%)

Table II Chest x-ray Findings

Reading	Frequency (%)
Normal	5 (10.14%)
PTB both upper lobes	19 (39.58%)
PTB right upper lobe	11 (22.92%)
PTB left upper lobe	4 (8.33%)
PTB with cavitations	2 (4.16%)
Other	7 (14.52%)

Table III Distribution of Patients according to Symptoms

Symptom	Frequency (%)
Asymptomatic	4 (8.33%)
Cough	42 (87.5%)
Fever	24 (50%)
Anorexia	9 (18.75%)
Weight Loss	14 (29.17%)
Hemoptysis	8 (16.67%)
Sputum production	10 (20.83%)

Table IV Relationship of AFB smear and Chest x-ray Findings

Xray Findings	AFB (+)	AFB (-)	Total
PTB	3	33	36 (75%)
No PTB	0	12	12 (25%)

Table V Relationship of AFB smear and Symptoms

Symptoms	AFB (+)	AFB (-)	Total
Asymptomatic	0	4	4 (8.3%)
Symptomatic	3	41	44 (91.66%)

Materials and Methods

This study was conducted at the Manila Doctors Hospital. Patients suspected with pulmonary tuberculosis who were admitted from January to June 2001, age 18 years old and above, were asked to submit sputum specimen for AFB smear. Chest x-rays were done on admission.

Subjects, may or may not have symptoms such as cough, fever, weight loss, etc. Patients who are intubated, those with previous history of pulmonary tuberculosis and those who were treated for PTB were excluded in the study.

The result of AFB smear, all done at Manila Doctors Hospital laboratory were reviewed, as well as the medical charts of each patient to determine the initial chest x-ray findings and the presence or absence of symptoms.

Sputum AFB smears were categorized as positive for *M. tuberculosis* or negative. A positive AFB smear was considered as active PTB.

Initial chest x-ray readings were classified as PTB both upper lobes, PTB left upper lobe, PTB right upper lobe, PTB with cavitations, normal and others (pneumonia, effusion, congestion)

The data gathered were tabulated and percentage distribution were done.

Results

There were a total of 48 patients who submitted their sputum for AFB smear. Positive AFB smear was shown in three (6.25%) cases and negative AFB smear in 45 (93. 75) of cases.

Chest radiography reading revealed tuberculosis in 75% (36) of cases, while 25%[12] showed either normal or other x-ray findings. When classified further, five (10.41%) have normal findings, 19 (39.52%) have PTB both upper lobes, 11 (22.92%) have PTB

Right upper lobe, four (8.33%) have PTB left upper lobe, two (4.16%) have PTB with cavitations and seven (14.58%) have other findings like pneumonia or congestion.

Of the 48 patients, 4 (8.33%) were asymptomatic and 44 (91.66%) were symptomatic. Symptoms were cough 42 (87.5%), fever 24 (50%), Anorexia nine

(18.75%), weight loss 14 (29.17%), hemoptysis eight (16.67%) and sputum production 10 (20.83%).

Of the 75% with PTB by chest x-ray, only three subjects yielded positive for AFB smear. All subjects who showed normal or other findings in Chest x-ray (25%) yielded negative AFB smear.

Three of the symptomatic patients (91.6%) yielded positive for AFB smear while none of the asymptomatic patients (8.3%) yielded positive for AFB smear.

Discussion

In areas where PTB is endemic, a positive sputum AFB smear is frequently regarded as almost diagnostic of pulmonary tuberculosis. The main problem is when the AFB smear is negative[10]. It has been shown in this study that sputum AFB smear has a low yield in diagnosing PTB. It may be due to its low sensitivity as stated earlier. Several factors might have contributed to this, poor sputum collection, improper handling of specimen, timing of collection etc.[3] Thus, it is essential that patients must be made aware of the importance of sputum quality. Proper education and instruction to patients and well trained personnel with quality assurance policies are vital in PTB diagnosis by AFB smear.

Counter checking slides with discordant results is crucial for accurate assessment.[9] Although chest radiography showed a good amount of readings showing PTB, its sole use cannot be relied upon. In other studies, some revealed that there is a wide variety of variance in appreciation of signs of pulmonary TB in chest radiograph which borders on the subjectivity of the radiologist.[2]

A high index of suspicion, along with signs and symptoms of PTB are also essential in the diagnosis of PTB. In this study, all AFB positive specimens came from patients who are symptomatic. The most common among the symptoms are cough, fever and weight loss.

A positive AFB smear is important in diagnosing active PTB along with the support of radiographic findings and presence of symptoms. However, due to its low sensitivity, its yield is also low. Thus, sputum TB culture is helpful and is actually the gold standard in diagnosis. However, it is not available in our institution and results take time.

Therefore, using the chi square, it can be concluded that there is no relationship between AFB smear result and chest x- ray finding, as well as the AFB smear result and the presence of symptoms. A positive chest x-ray for PTB and the presence of symptoms will not necessarily yield a positive AFB smear.

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Polymerase Chain Reaction for the Diagnosis of Pulmonary Tuberculosis - A Meta-analysis

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Background: Tuberculosis remains an enormous global burden with new cases totaling to an estimated 7.96 million in a year. The need for rapid diagnosis of this infectious disease is imperative that with recent advances in technology, gene amplification technique of Polymerase Chain Reaction (PCR) assay has found its use.

Objectives: To determine the accuracy of polymerase chain reaction (PCR) assay in the rapid diagnosis of pulmonary tuberculosis

Search strategy: A computerized literature search was done in MEDLINE and EMBASE databases from 1985 to 2002, using Medical Subject Heading (MeSH) "polymerase chain reaction" AND "tuberculosis, pulmonary" AND "cohort" OR "case-control" OR "single-blind" OR double-blind", with further links to the reference lists of selected studies. Limits used were English language and adult patients above 19 years old. Available full-text journals were downloaded while other articles were hand-searched and photocopied.

Selection criteria: All cohort and case-control studies were included if DNA amplification was done on sputum alone or sputum and other respiratory specimens with comparison to *Mycobacterium tuberculosis* (MTB) culture. Nine studies met the inclusion criteria.

Data collection & analysis: Data were extracted by one investigator but were examined by two reviewers for adherence to inclusion criteria. Disagreements were resolved by a third reviewer.

Main results: Five studies were included in the review involving 1,235 patients with reported sensitivities for PCR range from 68% to 100% and specificities range of 87% to 100%. In all studies, likelihood ratio for positive result was greater than 1 while the likelihood ratio for negative result was less than one.

Reviewers' conclusions: The use of PCR assay in the diagnosis of tuberculosis is limited to symptomatic patients. Confirmation by a positive smear and/ or culture is warranted for PCR to be accurate. Further studies are recommended that would use adequate reference standard tests and standardized methods for the performance of PCR. And finally, evaluation of specimens should be done by persons blinded to both the clinical status and to the results of the diagnostic tests. *Phil. Journal of Chest Diseases. Vol. 12 No. 1 pp: 54-57*

Keywords: PTB, Polymerase chain reaction, diagnosis

Introduction

Tuberculosis is an infectious disease and early detection is needed to control it with treatment of infected individuals and identification of exposed individuals. Culture is the "gold standard" for the diagnosis of pulmonary tuberculosis but a minimum of 2 weeks is required. The most rapid method of detecting mycobacteria in samples is direct microscopy, but it lacks sensitivity and specificity, thereby prompting a need for another rapid diagnostic test.

Polymerase chain reaction (PCR) is a gene amplification technique that was developed in 1985[9] and since then has found widespread use. As a diagnostic test for pulmonary tuberculosis, PCR allows the exponential amplification of target DNA or RNA molecules which are then detected and identified. If the diagnostic accuracy of PCR is acceptable, then the clinician has one more armamentarium for the fight against tuberculosis.

This study was therefore undertaken to determine the accuracy of polymerase chain reaction (PCR) assay in the rapid diagnosis of pulmonary tuberculosis

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Table I Results of Literature Search

Classification	Studies, n
Potentially eligible studies	9
Excluded Studies	
Inadequate data to calculate sensitivity	2
PCR not done in sputum	2
PCR not done on all specimen	1

Methodology

Criteria for considering studies for this review

Types of studies. All cohort and case-control studies.

Types of participants. Adult patients 19 years old and above with a clinical diagnosis of PTB.

Types of interventions. PCR assay was compared with sputum AFB smear and with the reference standard of culture method.

Types of outcome measures. The sensitivity, specificity, negative predictive value NPV, positive predictive value PPV, and likelihood ratio were determined.

Search strategy for identification of studies

A computerized literature search was done in MEDLINE and EMBASE databases from 1985 to 2002, using Medical Subject Heading (MeSH) "polymerase chain reaction" AND "tuberculosis, pulmonary" AND "cohort" OR "case-control" OR "single-blind" OR "double-blind", with further links to the reference lists of selected studies. Available full-text journals were downloaded while other articles were hand-searched and photocopied.

Methods of the review

Data were extracted by one investigator but were examined by two reviewers for adherence to inclusion criteria. Disagreements were resolved by a third reviewer.

Table II Description of Studies

STUDY ID	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOME
1 Cohen RA	prospective single-blind cohort	US 85 patients	Clinical Diagnosis sputum AFB sm, Culture & PCR	PCR Sensitivity = 74% Specificity = 93% PPV = 83% NPV = 88% LR for (+) result = 3 LR for (-) result = 0.278 Confidence Intervals
2 D' Amato, RF	cohort	US 372 patients	Clinical Diagnosis sputum AFB sm, Culture & PCR	PCR Sensitivity = 82% Specificity = 98% PPV = 66% NPV = 99% LR for (+) result = 41 LR for (-) result=0.3876 Confidence Intervals
3 Cartuyvels	cohort	Belgium 536 patients	sputum AFB sm, Culture & PCR, Clinical Diagnosis	PCR Sensitivity = 68% Specificity = 97% PPV = 51% NPV = 98% LR for (+) result = 26 LR for (-) result = 0.328 Confidence Intervals
4 Querol JM	cohort	Spain 242 patients	Clinical Diagnosis sputum AFB sm, Culture & PCR	PCR Sensitivity = 100% Specificity = 87% PPV = 82% NPV = 100% LR for (+) result = 1 LR for (-) result = 0.01 Confidence Intervals

Results

Nine studies were initially considered for meta-analysis; however, two studies investigated only smear negative patients and two studies used respiratory specimen but not sputum. Five studies were finally included in the review involving 1,235 patients with reported sensitivities for PCR ranging from 68% to 100% and specificities range of 87% to 100%. In all studies, likelihood ratio for positive result was greater than 1 while the likelihood ratio for negative result was less than one. Characteristics of included studies are shown in *Table II* while the methodologic quality score is shown in *Table III*.

Discussion

This systematic review examined published studies that have reported the use of PCR for the rapid diagnosis of pulmonary tuberculosis. It showed the limitations of PCR as a diagnostic test due to the low sensitivity but high specificity seen in three studies1-3. In comparison with MTB culture, the specificity range for PCR of 93% to 100% enabled it to discriminate patients without tuberculosis by a negative result. However, sensitivity range for PCR of 57% to 74% results to its decreased ability in detecting presence of tuberculosis.

In the study of Querol et al, PCR was positive in ten non-treated patients with negative culture. The discordance between the two methods may be due to the differences in their sensitivity since culture by LJ medium detects only Mycobacteria greater than 100 per ml while PCR could identify 42 colony forming units of Mycobacteria in a specimen.[10] Furthermore, culture allows growth of viable bacteria while PCR can also be positive even with nonviable bacteria due to treatment. False positive results can be obtained with PCR so that US FDA indicates its use only in AFB smear positive respiratory tract specimens from patients who (1) have not been on anti-tuberculosis medication for seven or more days; or (2) have not been treated for tuberculosis within the last twelve months.[6] Other causes of false positives could be cross-contamination of samples during sample preparation.

False negatives can occur, prompting a low sensitivity of PCR, due to the decontamination procedures done for the samples with loss of the Mycobacteria colony forming units.

AFB smear is comparable to PCR in sensitivity and specificity. Two studies[1,3] used PCR in smear negative patients and found PCR sensitivity being decreased further to 46-53% while specificity remained at 93-97%. Therefore, when AFB smear is negative and PCR is negative, tuberculosis is very unlikely. When AFB smear and PCR are both positive, the diagnosis of tuberculosis is considered established. However, when disparity occurs between these two tests, repeat testing should be done.[6] American Thoracic Society (A TS) recommends that direct amplification test (DAT) PCR should be performed in conjunction with microscopy and culture and not instead of culture. As with any diagnostic test, clinical setting should be considered.

The clinical usefulness of a diagnostic test is determined by the accuracy with which it recognizes its target disease and the measurement of accuracy used in this review is the likelihood ratio.[7] This is defined as the ratio of the probability of a particular test result in

Table III Methodological Quality of Included Studies

STUDY ID	Blinding	Spectrum of pts	Use of Reference Standard	PCR test Quality	Reference test Quality	Score
1 Cohen	1	2	2	2	2	0.9
2 D'Amato	0	1	2	2	2	0.7
3 Cartuyvels	0	2	2	2	2	0.8
4 Querol	0	2	2	2	1	0.7

Blinding
Two points were given if the PCR assay and the reference test were done with the investigator blinded to all other tests and clinical information; one point if either PCR or the reference test but not both was done with the investigator blinded; zero point is no blinding or that blinding was not described.

Spectrum of Patients
Two points were given if the study population had adequate spectrum of patients and that assembly of cohort was described in detail to permit another investigator to do the same; one point if inadequate spectrum of patients or assembly methods were incompletely described; zero point if assembly methods of the spectrum of patients were not described or the results of the PCR were used to determine which participants received the reference test (selection bias).

Application of Reference Test
Two points were given if reference test (gold standard test) was used in all diseased and nondiseased group; one point if all participants received a reference test but did not consistently received the same test; zero point if the reference test was not used in all participants.

PCR test quality
Two points were given if PCR assay was described in detail to permit replication, one point if incomplete description of method and zero point if PCR assay was not described.

Reference test quality
Two points were given if reference test (MTB culture) was described in detail to permit replication, one point if incomplete description of method and zero point if reference test was not described

people with disease to the probability of the same test result in people without disease.[8] An LR of 1 denotes that the post test probability is exactly the same as the pretest probability and the diagnostic test used did not help the clinician. An LR of greater than 1, as seen in the use of PCR for positive result, means that PCR is helpful in the diagnosis of pulmonary tuberculosis when it is positive. However, an LR less than 1 shows that when the PCR is negative, it is not helpful to the clinician in increasing the post test probability of the patient having tuberculosis.

Conclusion

The use of PCR assay in the diagnosis of tuberculosis is limited to symptomatic patients. Confirmation by a positive smear and/or culture is warranted for PCR to be accurate. Further studies are recommended that would use adequate reference standard tests and standardized methods for the performance of PCR. And finally, evaluation of specimens should be done by persons blinded to both the clinical status and to the results of the diagnostic tests.

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Tuberculin Skin Test as a Screening Tool for TB Infection among Health Care Workers in a Tertiary Hospital

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Background: The Philippines is one of the 22 countries in the world which account for 80% of the world's TB cases. Approximately 15 million Filipinos are infected.
Objectives: To evaluate if tuberculin skin testing is still considered a valuable screening tool for monitoring TB infection among health care workers in a tertiary care hospital.
Design: Prospective purposive
Setting: Manila Doctors Hospital April - June 2002.
Methodology: A total of 147 patients participated in the study. Information on age, sex, history of PTB, family history, previous BCG and chest x ray results were extracted by interview. All patients were examined for presence of BCG scar. Tuberculin skin testing was done on each participant with results read after 48-72 hours. Induration of < 8mm was non-reactive or negative and > 8 mm was considered reactive or positive. Chest x-ray (PA-APL) was requested for those who were positive. Chi-square tests were done to determine if symptoms, previous history of PTB and history of BCG were significantly associated with tuberculin skin test result. Pearson correlation test was done to determine if age and years of service were significantly correlated with induration.
Results and Conclusion: The overall reactor rate was 53% with reactor rates between sexes being found to be significantly different (x^2 =5.094, $p < 0.05$). There was no significant association between the history of exposure to Mantoux test ($x^2 = 0.89$, $p > 0.05$). Presence of BCG scar was not significantly related to reactivity rate ($x^2 = 0.39$, $p > 0.05$). There was a low correlation between age and the size of induration (r = 0.204, r = 0.201, respectively). With these data, tuberculin skin test may still be considered an indispensable diagnostic tool for screening populations especially among health care workers who belong to the high risk group. *Phil Journal Chest Diseases. Vol. 12 No. 1 pp: 58-62*

Keywords: PTB, Diagnosis, Tuberculin skin test

Introduction

The 1998 World Health Organization Global Tuberculosis report has cited the PhiLippines as one of the 22 countries in the world which account for 80% of the world's TB cases.[1] It has been estimated that in 1989 1.3 million cases of TB occurred in the world and that approximately 450,000 deaths occurred.[1]

In the Philippines, 75 Filipinos die of tuberculosis each day approximately 200,000 to 600,000 Filipinos are spreading the disease and infecting 10 other individuals annually. Approximately 15 million Filipinos or 20% of the total population are infected with tuberculosis and there has been little change in the state of TB problem for the past 14 years.[1] The reason why TB remained uncontrolled in the Philippines are due to inadequate case findings, poor case holding and deficient TB program.[1]

With these data, the present report describes the utility of a simple and universally accepted method of immunologic examination, the tuberculin skin test or the Mantoux test.

The tuberculin skin test is currently the only widely used method for identifying infection with *M. tuberculosis* in persons who do not have the disease. The tuberculin skin test has been advocated as an important aspect of tuberculosis screening and surveillance in a given community, determining the prevalence of infection and identifying those who need prevention therapy.[3]

In western countries, health care workers or hospital staff routinely undergo tuberculin screening tests as recommended by the American Thoracic Society and Center for Disease Control.[4] There has been no published local reports among tertiary hospitals as to the prevalence of the TB infection among their employees.

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This paper evaluates whether the tuberculin skin test or Mantoux test should be performed and included as part of the annual examination for our health care workers as screening of tuberculosis infection.

Methodology

Subjects: Manila Doctors Hospital is a 300 bed capacity tertiary care hospital located at United Nation Avenue, Manila. The hospital presently has 339 full time staff nurses and 124 nursing aides. The Hospital presently hires 80 new full time nurses annually.

This is prospective purposive study of 147 health workers comprising of 125 nurses and 22 nursing aides tested from April to June 2002.

Data Collection: The data from the subjects tested included age, sex, history of tuberculosis, family history of exposure to tuberculosis, previous BCG vaccination, latest chest xray result. Arms and back were inspected for scar $\geq$ 4 mm or any sign of inoculation consistent with a previous BCG vaccination.

Tuberculin Testing: The 2 TU Purified Protein Derivative (PPD) was obtained from *Pedia Aid* Pharmaceutical firm. Disposable single dose plastic syringes with 26 gauge needle were used exclusively. Skin was cleansed with an alcohol swab. The freshly prepared 0.1 ml of PPD was injected intracutaneously into the volar surface of the forearm at the juncture of the upper third and lower two thirds, needle bevel upwards, to produce a discrete pale elevation of the skin at least six to ten millimeters in diameter.

Table I Relationship of Mantoux Test among males and females

Sex	Reactors	Non-reactors	Total
Males	22	9	31
Females	56	60	116
Total	78	69	147

x^2 =5.094
x^2 critical = 3.84

Table II Association of Mantoux Test reactivity to family history of tuberculosis

Reactivity	(+) History	(-)History	Total
Positive	1	0	1
Negative	77	69	146
Total	78	69	147

x^2 = 0.89
x^2 critical = 3.84

Table III Association of Mantoux Test reactivity and history of previous BCG vaccination

BCG Scar	(+) Reactivity	(-) Reactivity	Total
(+) Scar	62	48	110
(-) Scar	16	21	37
Total	78	69	147

x^2 = 0.39
x^2 critical = 3.84

The results were read after 48 to 72 hours, the time when the induration was most evident. The basis of the reading was the presence of induration (not the erythema). The size of the induration was determined by palpation, the border was encircled with a pen, and the average of the two perpendicular diameters measured with a provided ruler and was recorded in millimeters. The induration of 1-7 millimeters was recorded as non-reactive or negative and reactions $\geq$ 8 millimeters were considered positive or reactors. A chest x-ray PA and apicolordotic view was requested for those subjects who were identified as reactors (positive) and was compared to their baseline Chest-x-ray.

Statistical Analysis: A. Relationship of Tuberculin skin test (induration) among variables such as age and years of service to Manila Doctors Hospital was done using Pearson coefficient correlation. B. Comparison of the study population according to sex, previous history of TB infection, history of BCG vaccination was done using chi-square test with a p value < 0.05 as a level of significance.

Results

A total of 147 subjects were tested. Nurses comprised 85.7 % of the total population (n=126) and the rest were nursing aides. Females comprised 78.9% (n=116) and males 21.1% (n=31) with an age range of 21-59 years and a mean age of 27.74. Majority of the subjects belonged to 26-30 years old age group (47.61%, n = 70) followed by 20-25 years old age group (35.37%, n = 52) (*Figure 1*). There were five areas wherein the subjects under study population were assigned; 74.15% (n = 109) came from the wards/floors (new and old bldg.), 12.9% (n = 19) from ICU, 4.09% (n = 6) from the ER, 4.40% (n = 5) from Hemodialysis and 5.44% (n = 8) from NICU (*Figure 2*).

Upon history and review of data, two subjects (1.36%) acknowledged a previous history of TB disease and were treated accordingly; they are presently asymptomatic. Two other subjects had history of chronic cough, weight loss, decreased appetite and have been taking on and off mucolytics for the past eight months. All of the subjects had baseline chest x-ray (PA-view) during their annual physical examination November 1999. Review of films of all the subjects revealed that out of the 147 films, only one film resulted with a pulmonary nodule at the upper lobe suggestive of an old PTB, the rest of the subjects were read as

essentially normal findings by three radiology consultants.

One hundred ten of the study population (78.23%) had previously received BCG vaccination as evidenced by the presence of scar. All of the 147 subjects were available for interpretation 48-72 hours after administering the PPD test.

Results of the Mantoux test ranged from: a.) non-reactive - induration of 1-7 mm; b.) reactive - induration $\geq$ 8 mm.

The over-all reactor rate was 53% (n=78), 46.9% (n = 69) were non-reactors. More than half of the population 58.57% (n = 41) belonged to 26 - 30 age group. Of the non-reactors 47.8 % belonged to 20 - 25 age group.

There is a significant difference in the reactor rates between men and women ($x^2 = 5.094$, $p < 0.05$) (*Table I*). No significant association was seen when the Mantoux results was correlated with the history of exposure to TB ($x^2 = 0.88$, $p < 0.05$) (*Table II*). Notably the presence of BCG scar was not significantly associated with the Mantoux test reactivity ($x^2 = 0.38$, $p < 0.05$) (*Table III*).

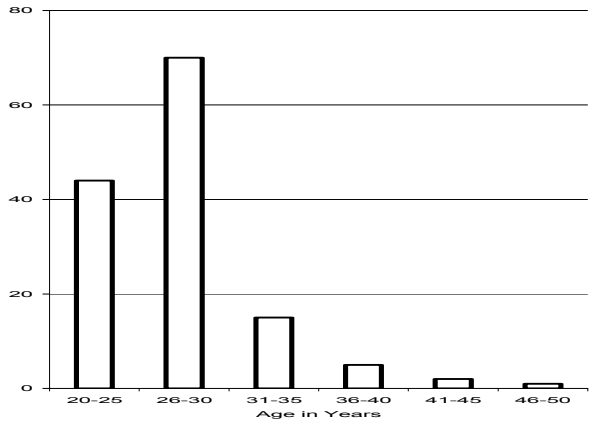

Figure 1 Age distribution of 147 subjects tested for Mantoux Test

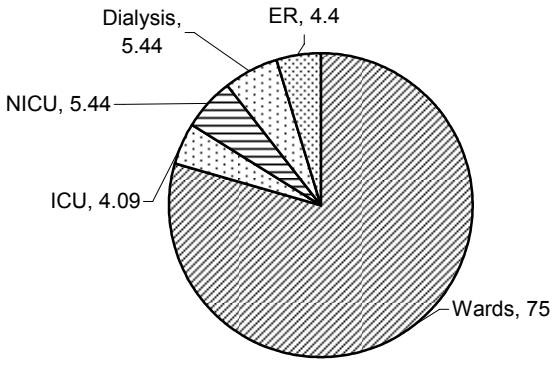

Figure 2 Distribution of subjects according to areas assigned

Table IV High prevalence groups. ATS Criteria[2]

Persons born in countries with high prevalence of TB
Groups with poor access to health care
Persons who live or spend their time in facilities such as hospitals, nursing homes, correctional institutions, drug treatment centers
Persons who inject drugs

Table V Factors causing False-negative skin tests

Reasons related to the tuberculin used for testing
Improper dilution or diluent
Chemical denaturation
Improper storage
Reasons related to person tested
Anergy (suppression of delayed hypersensitivity such as infection, neoplastic diseases, sarcoidosis, on immunosuppressive therapy
Warning of tuberculin sensitivity

All subjects with a positive tuberculin skin test ($\geq$ 8 mm.) were requested to have chest x-ray with an apicolordotic view. The chest x-ray films of the two out of these 78 reactors were read as PTB of undetermined activity.

There is a low correlation between age and in the size of the induration (r = 0.204) as well as years of service and the size of induration (r = 0.201).

Discussion

Over the years, diagnostic skin tests have played a significant role in the practice of medicine. Clinicians have become increasingly aware of the practical significance and the use of simple immunologic tools in the diagnosis of infectious diseases. The diagnosis of pulmonary tuberculosis becomes definitive once *Mycobacterium* bacteria are isolated by culture. However in view of the costs of culture and prevailing limited technical facilities, sputum culture of TB is not recommended as part of the routine screening for PTB. The tuberculin skin tests is instead primarily used in the detection of asymptomatic, infected individuals. It is based on the fact that infection with TB produces a delayed type of hypersensitivity response mediated by T lymphocytes. Cellular infiltration by T cells in combination with other recruited inflammatory cells results in maximal induration at 48 - 72 hours after inoculation with intra-dermal antigen. Reactivity to this

test separates the infected individual from the exposed without infection.[3] When only few are infected, the initial tuberculin testing used in place of radiographic screening can lead to important reductions in expense.

In our study, induration of the PPD tests was read by a single observer, intra-observer variability was decreased by using the palpation and ball point pen method. According to the study of Moira and Anderson et al[4] screening of hospital employees for TB infection should be done regularly as recommended by the American Thoracic Society and Center for Disease Control.

This is due to the recent consensus that these individuals belong to the "high prevalence groups" and have a likelihood of being infected with *M. tuberculosis* without other risk factors. (see *Table IV*). Thus, the purpose of this paper is to initially screen the hospital staff for a probable hospital acquired Tuberculosis.[2-5]

It has been shown that persons who have been in close contact with individuals with infectious tuberculosis (in hospital setting) then has a 25 to 50 % chance of being infected.[1]

In this study, a relatively high positive reaction rate 53% was observed, this may be reflective of the general demographic characteristics of the group, most reactors belonged to 26-30 age group (58.57%), assigned in wards. This is due to a larger sample size coming from the wards as compared to other mentioned areas. However, there is a common occupational trait that might confer increased risk of infection in this group. Procedures such as suctioning and assisting in intubation promotes droplet formation, daily contact with tuberculosis-suspect patients (airborne spread) poses a high risk of acquiring the infection.

Our results showed that there is an association of the reactivity among males and females, (*Table I*) this may be due to the female preponderance of the study group. In the National TB consensus statement positive reactivity rates among males are higher and rates of TB infection increases with age with the highest prevalence among the reproductive age group. In a previous study of Reichman and O'day[6] they concluded that there is an increased probability of tuberculosis infection as age increases. This was not a trend seen in this study, wherein there is a low correlation of reactivity rates as age increases.

Several possibilities may also explain the differences between the observed and expected results of the tuberculin skin tests. There can be several reasons why a negative response may occur in a person with a tuberculosis infection (see *Table V*). The problems related to technique and to reading has been obviated by a thorough training of a single person doing the tests.

Reasons related to tuberculin used for testing are not applicable because of the exclusive use of 5 TU stabilized PPD. Inoculation with a previous Bacillus Calmette -Guerin (BCG) can be the cause of a significant tuberculin test. The tuberculin reaction produced by the BCG vaccine cannot be distinguished from that due to *Mycobacterium tuberculosis* infection.[3] However, a significant reaction to tuberculin skin test would usually represent a true tuberculous infection. The results of the BCG vaccination campaigns carried out by the National Tuberculosis Committee[5] showed that there was a significant difference in the size of tuberculin reaction of those with old BCG scars and those without any scars. Analysis of the present data however failed to show a significant difference between the size of tuberculin reactivity and the presence of a BCG scar. Several reasons for not assuming that a large reaction to tuberculin is due to BCG: [3] 1) tuberculin test reactivity caused by BCG is usually < 10 mm^2) tuberculin sensitivity tends to wane with over the years, resulting in an apparent non-significant reaction. The years of service of the present study population however has a low correlation to their reactivity rates. Nonetheless, this may not be conclusive because the whole staff was not tested for PPD.

In any given population, the likelihood that a positive tuberculin test represents a true infection is influenced by the prevalence of the TB disease.

According to the recent National Prevalence Survey,[1] the overall prevalence of the tuberculin sensitive (induration > 8 mm to 2 TU) was 63%. This 63% positive tuberculin reaction can be applied to the whole adult population, which translates to 14.8 million or 21.6 % infected Filipinos.

Our study population which belongs to the high risks group can be classified as Class V (ATS Criteria). Upon testing for PPD it can be then subdivided to:

Class I: 46.9% (n = 69) of our study population had history of exposure, but a negative reaction to tuberculin skin test. If there has been significant exposure within 3 months, a follow-up skin test should be performed on this group of health care workers. An increase in reaction size of $\geq$ 10 mm within a period of two years should be considered skin test conversion indicative of a recent infection of *M. tuberculosis*. If the results from the second test will be positive, the individual is considered to be previously infected, however if the result is still negative, it is considered uninfected.

Class II: 53.06% (n=78) Persons in this class have a positive reaction (≥ 8 mm induration), a positive history of exposure, no clinical, nor radiographic evidence of active tuberculosis. A follow-up chest x-ray (Apicolordotic view) was requested for this group of subjects. Review of history revealed two subjects were having symptoms of chronic cough (for the last 6 months), loss of appetite and non-purposeful weight loss. The chest x-ray of these two subjects turned out to have alveolar infiltrates at the apical lung field and official radiographic results revealed PTB of undetermined activity, which was not seen from their baseline film.

Class III: 2.5% (n = 2) of the initial positive reactors were classified to be with clinically active tuberculosis. The presence of an exposure to TB, (+) tuberculin skin test, (+) clinical symptoms, and radiographic evidence eventually make them Class III. Presently they are being treated with appropriate anti-Koch's medications.

In our local setting where there is an increasing incidence of PTB, a good diagnostic test that is rapid, simple with a high sensitivity and specificity is recommended. Tuberculin skin test remains a key diagnostic and screening tool for the detection of a tuberculous infection, reducing the necessity for a routine radiographic screening which only has 68-75% sensitivity.[1,2]

Since the results yielded two subjects with a TB disease, the risk of occupationally acquired tuberculosis should be the main concern and the cornerstone of determining the effectiveness of the infectious control team in our institution.

Limitation of the Study

Due to limited resources a two step tuberculin skin test was not done to the study population.

Conclusion

This study attempted to evaluate tuberculin skin test as a valuable screening tool among health care workers in Manila Doctors Hospital, and to ascertain the association of age, sex, previous family history of tuberculosis, and previous BCG vaccination. The results of the study revealed a relatively high reaction rate of 53%. There was significant difference between male and female population in terms of reactivity. The presence or absence of family history of exposure to TB did not associate well with a prominent tuberculin test result and neither did a previous BCG vaccination.

Out of the 53% reactors (n = 78), 2.5% (n=2) were identified as having a clinically active tuberculosis which is probably occupationally-acquired.

With this data, tuberculin skin test is still considered to be an indispensable diagnostic tool for screening of populations, especially those belonging to the high risk groups.

Recommendations

Since this paper is only pilot study at the Manila Doctors Hospital, a second tuberculin skin testing should be done among health care workers. In this procedure, persons with an initial negative PPD skin test should undergo a second tuberculin test within a period of two years. An increase in reaction size of 10 mm or more is considered a skin test conversion indicative of a recent infection with *M. tuberculosis*.

All hospital employees should undergo a two -step tuberculin screening test included in their annual examination as recommended by American Thoracic Society and the Center for Disease Control, which allows detection of new skin test converters who might require preventive therapy regardless of age.

For the new MDH hospital, it should have a facility, that has a TB isolation room wherein laminar air flow or non-recirculated air would be made available to prevent airborne spread of infection. A specialized face mask known as disposable particulate respirators[9] should be provided to all health care workers who are in frequent contact with patients highly suspected with TB disease.

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Short Report

Sensitivity and Specificity of AFB Smear at Manila Doctors Hospital

ANDREW GONZALES, MD, CAMILO C. ROA, JR., MD, FPCCP[1]

This study was done to determine the sensitivity and specificity of acid fast bacilli (AFB) smear performed at Manila Doctors Hospital (MDH). All adult patients suspected of having pulmonary tuberculosis admitted from November 1, 2000 to May 31, 2001 who had sequential AFB smears done at MDH were included. A total of 35 patients suspected to have PTB were admitted during the prescribed dates. Of these 35 patients only 24 (68.6%) were able to comply with treatment. Smears performed at MDH have a specificity of 50 to 56% and a sensitivity of 66 to 80%. This is quite different from more specialized centers, e.g., at the nearby Philippine General Hospital, but it is deemed acceptable since results are release within 24 hours. *Phil. Journal Chest Diseases. Vol. 12 No. 1 pp: 63-64*

Keywords: PTB, Diagnosis, AFB smear

Introduction

Cultures of respiratory specimen are frequently scrutinized for *Mycobacterium tuberculosis* (MTB) to identify the cause of a pulmonary pathology, as well as to demonstrate the efficacy of a given therapy and to determine when a patient undergoing treatment is no longer contagious. Unfortunately, even when using the most modern methods, the results of culture examination are only available after 7 to 12 days in the case of a positive result, whereas a negative result is only reliable after 8 to 12 weeks.[1] Presently the most important criteria for establishing a presumptive diagnosis of tuberculosis are the AFB smear and a case definition.[2,3]

Methods

All adult patients suspected of having pulmonary tuberculosis, based on the Philippine Consensus[2], admitted from November 1, 2000 to May 31, 2001 who had sequential AFB smears done at MDH and pooled specimen for AFB smear and MTB culture done at the Philippine General Hospital (PGH). They should be able to complete treatment.

Results

A total of 35 patients suspected to have PTB were admitted during the prescribed dates. Of these 35 patients only 24 (68.6%) were able to comply with treatment. There were 14 females and 10 males. The youngest subject was 19 years old while the oldest was 68 years old with a mean age of 48 for the study population.

The AFB smears performed at MDH had a sensitivity of 80%, specificity of 56%, PPV of 0.75, a NPV of 0.62, a LR + of 1.80 and a LR - of 0.36. Those performed at PGH had a sensitivity of 67%, specificity of 67%, PPV of 0.77, a NPV of 0.54, a LR + of 2.0 and a LR - of 0.50 with a 95% CI.

When compared to clinical response the AFB smears performed at MDH had a sensitivity of 66%, specificity of 50%, PPV of 0.97, a NPV of 0.06, a LR + of 1.32 and a LR – of 0.68. Those performed at PGH had a sensitivity of 54%, specificity of 50%, PPV of 0.96 a NPV of 0.04, a LR + of 1.08 and a LR - of 0.04 with a 95% CI

Discussion

The main objective of this study is to validate the accuracy of AFB smears performed at MDH. Because of the proximity and of its practicality specimen for MTB culture, of patients seen at MDH, have been sent to PGH since it has an established facility. Sputum microscopy for AFB is easy and relatively cheap to perform. Studies throughout the years have established at 97.5 to 99.8% specificity for AFB smears however its sensitivity is low at 51.1 to 53.1%.2 Smears performed at MDH have a specificity of 50 to 56% and a sensitivity of 66 to 80%. Although the specificity is not close to the established specificity of 97.5% the sensitivity of examinations done at MDH are more than at par with the established sensitivity of 51.1%. Sensitivity and

[1] Manila Doctors Hospital

Table I AFB Smear and Culture

AFB Smear	Culture	
	(+)	(-)
MDH (+)	12	4
MDH (-)	3	5
PGH (+)	10	3
PGH (-)	5	6

Table II AFB Smear and Clinical Response

AFB Smear	Clinical Response	
	(+)	(-)
MOH (+)	16	0
MDH (-)	8	0
PGH (+)	13	0
PGH (-)	11	0

specificity of this test is also comparable to those done at PGH, which has a specialized unit for this. Given these reasons the test has an acceptable reliability specially since results are released within the 24 hours and it is results are comparable to those done in a larger more specialized laboratory.

Still the importance of requesting an AFB smear with adequately collected specimen should be highlighted because it is the most important diagnostic test to request for patient clinically suspected to have PTB.[2,3] But this importance is only truly significant if the AFB smear is performed in a reliable facility[4].

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