

## Efficacy Of Anti-Tuberculosis Treatment Alone On Resolution Of Tuberculosis Pleural Effusions

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To determine the degree of resolution in pleural effusions treated with anti-tuberculosis treatment alone without thoracentesis, 62 eligible adult cases [mean age (SD), 46 (17) yrs; 77% male] of tuberculosis pleural effusions treated in two urban-based university teaching hospitals were retrospectively reviewed for changes in effusion size at 2, 6 and 12 months after initiation of treatment. The proportions of patients in whom resolution were complete, partial and unchanged were 64.5%, 27.4% and 8.1%. Effusions with size smaller than three tenth of hemithorax were at three-fold increased likelihood of complete resolution, compared with those with larger effusions [Odds ratio (95% CI): 3.295 (1.033 to 10.514);  $p=0.04$ ]. Consideration for thoracentesis is therefore still important in certain patients.

IeJSME 2007: 1 (2): 83-86

*Keywords: Tuberculosis, pleural effusions, chemotherapy, Malaysia*

While treatment of any pleural effusions involves treating the underlying disease, therapeutic thoracentesis may be necessary for rapid symptomatic relief and prevention of complications resulting from inadequate resolution such as pleural thickening, or from incomplete treatment that may result in empyema.<sup>1</sup> It has been estimated that up to 50% of TB pleural effusions develop pleural thickening<sup>2</sup>, and such development can cause restrictive lung impairment. Therapeutic thoracentesis is thought to reduce such incidence by facilitating a more complete drainage of effusion.<sup>3,4</sup>

A recent randomized study has cast doubts as to whether thoracentesis in addition to modern chemotherapy is necessary to treat TB pleural effusions.<sup>5</sup> To examine if chemotherapy alone in the context of TB pleural effusions could obviate the need for therapeutic thoracentesis in our Malaysian patients, we conducted a retrospective review of all cases notes of adult patients with TB pleural effusions treated by chemotherapy alone in our own chest clinics of two urban-based university teaching hospitals and evaluated the degree of the resolution of their effusions over time.

All medical case notes from chest clinics of Tuanku Jaafar Hospital (TJH), Seremban, and Port Dickson Hospital (PDH), Port Dickson, Negeri Sembilan, were retrospectively reviewed for eligibility. Included were adult patients with confirmed pulmonary TB with pleural effusion treated with standard anti-TB treatment regime (two months of rifampicin, isoniazid and pyrazinamide with or without ethambutol or streptomycin, followed by four months of rifampicin and isoniazid) as recommended by Ministry of Health, Malaysia, and were followed up for at least one year after commencement of treatment. Excluded were patients in whom TB diagnosis was unconfirmed, those with incomplete treatment or follow-up chest X-rays, and those whose medical records were incomplete. Data were collected using standard questionnaire form. The outcomes were changes in pleural effusion sizes at 2, 6 and 12 months after initiation of treatment, compared to baseline. The effusion sizes were defined according to tenths of a hemithorax by virtue of the maximum height occupied by the effusions. Median changes in pleural effusion sizes over time were analyzed with Kruskal-Wallis test. Correlation between initial size of pleural effusions and percentage resolution with treatment was assessed with Spearman rank correlation coefficient. Proportions of patients with various degrees of resolution of pleural effusion based on their initial sizes were assessed by Chi Square test and odds ratio calculated as appropriate. P values (two-tailed)  $< 0.05$  are considered significant. All statistical analysis was performed using SPSS<sup>TM</sup> Version 11.0 for Window and PrismGraph<sup>TM</sup> Version 3 for Window 95 and NT.

Sixty two patients were eligible for study. The patients' clinical and demographic characteristics are shown in Table 1. Except for two, all patients had unilateral pleural effusions. The degree of pleural effusion changes in these two patients was identical on both sides, and as such, their data are analyzed as any other patients with unilateral effusions.

The median sizes of pleural effusion of all patients were significantly reduced with treatment over time

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( $p < 0.0001$ ) and the percentage of resolution following treatment strongly correlated with the initial size of pleural effusions ( $r_s = 0.80$ ,  $p < 0.0001$ ) [Data not shown].

There were 40 (64.5%) patients with complete resolution, 17 (27.4%) with partial resolution, and 5 (8.1%) with persistent unchanged effusions. Complete resolution of pleural effusions occurred in proportionately more patients with smaller size effusions compared to those with larger ones (69% vs. 55%). Partial resolution however occurred in proportionately more patients with larger effusions (45% vs. 19%). Only in patients with small size pleural effusions (11%) had unchanged effusions. The differences were statistically significant ( $p = 0.47$ ; Figure 1). Pleural effusions with size  $<$  three tenth of hemithorax were at a three-fold increased likelihood of complete resolution, compared with those with  $\geq$  three tenth effusions [Odds ratio (95% CI): 3.295 (1.033 to 10.514);  $p = 0.04$ ]. When comparing patients with complete resolution of pleural effusions with those without (partial resolution or unchanged), there were no statistical significant associations in any of their documented patient demographics or clinical characteristics (Table 1).

We have shown that in the majority of patients, TB pleural effusions had significantly resolved by one year after anti-TB chemotherapy alone. The degree of resolution correlated with the initial effusion size but importantly, the complete resolution occurred more frequently in those with smaller effusions and its likelihood is three-fold higher in those with pleural effusions occupying less than three tenth of the hemithorax. Our study did not observe any other patients' clinical or demographic characteristics that could predict the complete resolution or its lack.

Our findings add to the existing evidence that have shown that anti-TB chemotherapy is effective in treating TB pleural effusions<sup>6</sup>. We have further explored the relationship between size of pleural effusion and its risk of incomplete resolution, providing another facet that has implication on the necessity of thoracentesis in larger effusions. Although our study has all the inherent weaknesses of a retrospective study, the outcome

measured is reliable as it is based on objective radiological findings. Despite this, caution should still be exercised with regards to the extent of the validity of our results. Firstly, we have deliberately excluded cases with effusions, presumably larger ones that had been treated with thoracentesis. We do not know the degree of resolution in these larger effusions with chemotherapy alone, and whether exclusion of such cases from our study would significantly bias our findings. Secondly, our sample size is probably inadequate to examine for possible factors associated with failure of complete resolution, particularly when the number of patients with end-stage renal, HIV, or chronic liver disease, is fewer than ten. Thirdly, without data on lung function, we do not know whether our patients with incomplete resolution had developed pleural thickening that were clinically relevant.

Nevertheless, the obvious implication of our study is that thoracentesis should still be considered in the treatment of TB pleural effusions, especially if they are large, in order to avoid the possibility of healing with pleural thickening and its risk of developing restrictive functional impairment. This rationale should be viewed with some skepticism in view of the evidence that thoracentesis does not necessarily prevent the development of residual pleural thickening.<sup>5,7</sup> Despite this, we believe our findings are still useful to help in practicing evidence-based medicine in Malaysia and that they provide preliminary benchmark data for further hypothesis testing in larger, prospective Malaysian studies.

#### Acknowledgement

The authors wish to thank the support of the Chest Clinics staff in Tuanku Jaafar Hospital, Seremban, and Port Dickson Hospital in the conduct of the study.

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**Table 1 : Patients’ Clinico-Demographic Characteristics Between Those With And Without Complete Resolution Of Tuberculosis Pleural Effusions**

VARIABLES	RESOLUTION OF PLEURAL EFFUSIONS			P**
	ENTIRE GROUP (N=62)	COMPLETE (N=40)	INCOMPLETE (N=22)	
Mean age (range)	46 (19-89)	46 (19-89)	46 (25-75)	0.884
Male	77.4	75.0	81.8	0.539
Mean (SD) weight, kg	48 (10)	45 (9)	51 (10)	0.146
Ethnicity				
<i>Malays</i>	43.5	45.0	40.9	–
<i>Chinese</i>	40.3	42.5	36.4	–
<i>Indians</i>	11.3	7.5	18.2	0.653
Known cigarette smokers	27.4	27.5	27.3	0.983
Comorbidity scoring*				
<i>Grade 1</i>	59.7	57.5	63.6	–
<i>Grade 2</i>	27.4	32.5	18.2	–
<i>Grade 3</i>	12.9	10.0	18.2	0.389
Presence of				
Chronic liver disease	3.2	2.5	4.5	0.663
End-stage renal disease	9.7	7.5	13.6	0.434
Diabetes mellitus	14.5	20.0	4.5	0.098
HIV positive	6.5	7.5	4.5	0.799
Mean days with symptoms (range)	11 (1-156)	6 (1-52)	17 (1-156)	0.143
Systemic symptoms of				
<i>Weight loss</i>	43.5	45.0	40.9	0.756
<i>Fever</i>	40.3	45.0	31.8	0.311

Values are in percentage unless otherwise specified.

SD = standard deviation.

\*Co-morbidity score 8: 1 = no important chronic illness; 2=moderate/severe disease of heart, lungs, GI tract; 3 = any cancer (except skin), end stage renal/liver disease.

\*\*Comparing between ‘complete’ and ‘incomplete’ group.

**FIGURE 1 : Proportion of patients with various degrees of resolution of tuberculosis pleural effusions (complete, partial or unchanged) based on whether they were small (less than three tenth of hemithorax) or large (three tenth or more) at the beginning of treatment.**

