

Prevalence and Risk Factors of Antituberculosis Drug-induced Hepatitis in Malaysia

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Introduction

- Tuberculosis is one of the major diseases worldwide, affecting about one-third of the world's population.
- The introduction of antituberculosis drugs has improved tremendously the outcome of the disease.
- Isoniazid, rifampicin and pyrazinamide has been proven to be effective, but not without the side effects, particularly hepatotoxicity¹.

¹ Sharma *et al.* *Am J Respir Crit Care Med* 2002;166:916-9.

Introduction...

- The incidence of antituberculosis drug-induced hepatitis is higher in developing countries (8-39%)² than in developed countries (3-4%)³.
- Reported risk factors include
 - Older age⁴
 - Female sex⁴
 - Poor nutritional status⁵
 - High alcohol intake⁵
 - Hepatitis B carriage⁶
 - HIV infections⁷
 - Advanced tuberculosis⁸
 - Hepatitis C infection⁹

² Türктаş *et al. Tubercle Lung Dis* 1994;**75**:58-60.

³ Combs *et al. Ann Intern Med* 1990;**112**:397-406.

⁴ Døssing *et al. Tubercle Lung Dis* 1996;**77**:335-40.

⁵ Grönhagen-Riska *et al. Am Rev Respir Dis* 1978;**118**:461-6

⁶ Lee *et al. Chest* 2005;**127**:1304-11.

⁷ Ungo *et al. Am J Respir Crit Care Med* 1998;**157**:1871-6.

⁸ Pande *et al. Thorax* 1996;**51**:132-6.

⁹ Huang *et al. Hepatol* 2002;**35**:883-9.

Objectives

- To determine the prevalence of antituberculosis drug-induced hepatitis in a tertiary hospital in Malaysia.
- To determine the risk factors for the development of antituberculosis drug-induced hepatitis in a tertiary hospital in Malaysia.

Methodology

- Study Design: Retrospective, case-control study.
- Source Population: Tuberculosis patients treated and followed-up at the Chest Clinic, Hospital Universiti Sains Malaysia.
- Sample size: 236 tuberculosis patients to provide 95% confidence interval with 5% difference based on previous study².

² Türктаş *et al. Tubercle Lung Dis* 1994;75:58-60.

Methodology...

■ Inclusion Criteria⁷:

- Normal liver biochemistries prior to treatment.
- Patients received antituberculosis drugs (isoniazid, rifampicin or pyrazinamide) in standard doses at least 5 days prior to the development of hepatotoxicity.
- Elevation of liver enzymes while receiving antituberculosis treatment (ALT and/or AST \geq 120 IU/L, and/or elevated total bilirubin $>$ 25 μ mol/L).
- No other apparent cause for the elevation of liver enzymes.

⁷ Ungo *et al.* *Am J Respir Crit Care Med* 1998;157:1871-6.

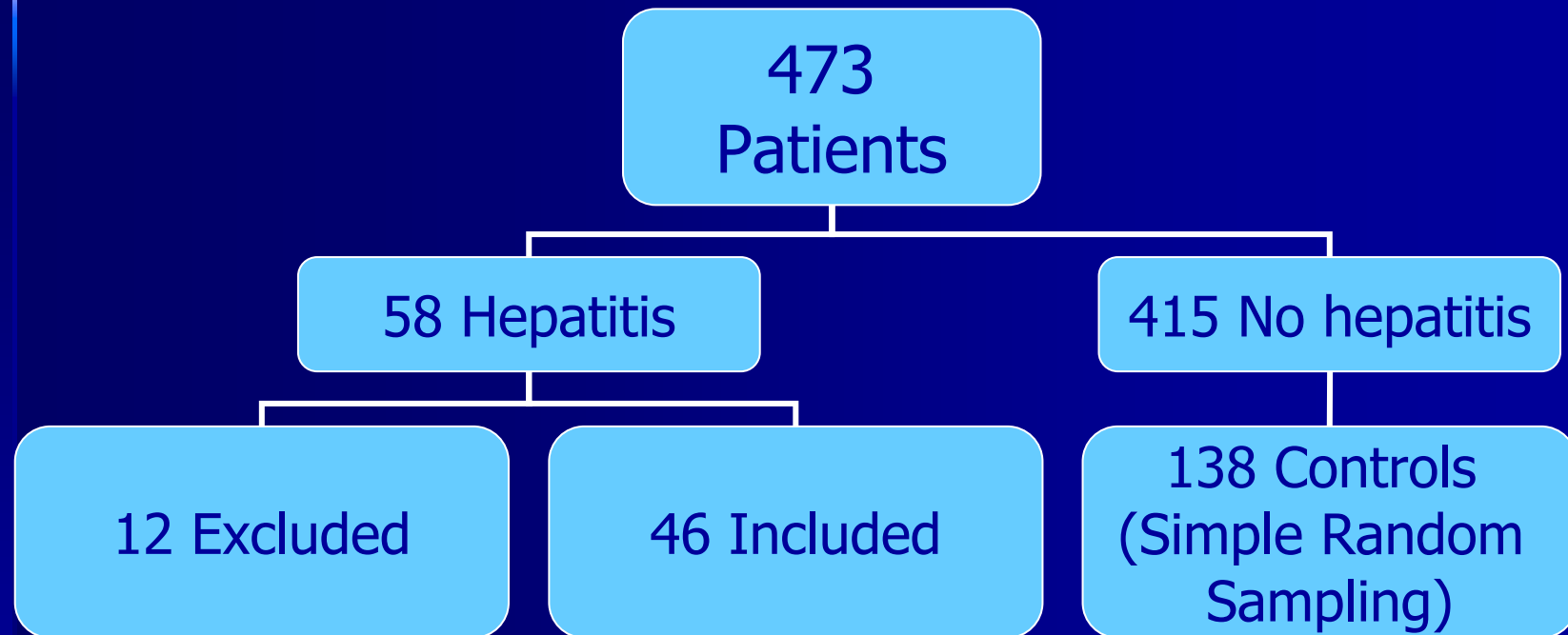
Methodology...

■ Exclusion Criteria⁷:

- Abnormal liver biochemistries prior to treatment.
- Patients who had serological evidence of acute infection with hepatitis B or C.
- Patients who had received higher doses of antituberculosis drugs than the recommended dosage based on body weight.
- Patients who had received other potential hepatotoxic medications at the same time of receiving antituberculosis drugs.

⁷ Ungo *et al.* *Am J Respir Crit Care Med* 1998;157:1871-6.

Methodology...



Results

- A total of 473 patients were registered at the Chest Clinic, HUSM for the 30-month study period (January 2003-June 2005).
- 58 patients had evidence of hepatitis; 46 patients eligible to be included in the study.
- 138 patients selected randomly by using Simple Random Sampling to be included in control group to make 1 case to 3 controls (1:3).

Baseline Variables of Cases and Controls

Variables	Cases (n=46) No. (%)	Controls (n=138) No. (%)	Total (n=184) No. (%)	df	p Value
Age > 35 years	32 (69.6)	97 (70.3)	129 (70.1)	1	0.926
Female sex	14 (30.4)	51 (37.0)	65 (35.3)	1	0.423
Hepatitis B Carrier	3 (6.5)	2 (1.5)	5 (2.7)	1	0.101
HIV Infection	9 (19.6)	8 (5.8)	17 (9.2)	1	0.005
Extrapulmonary Tuberculosis	24 (52.2)	42 (30.4)	66 (35.9)	1	0.008

Mean Baseline Characteristics and Liver Biochemistries of Cases and Controls

Characteristics	Cases (n=46) Mean (SD)	Controls (n=138) Mean (SD)	Mean Difference	p value
Age (years)	44.1 (15.4)	47.0 (17.8)	2.94	0.319
BMI (kg/m ²)	20.9 (2.7)	20.8 (2.1)	0.19	0.589
Albumin (g/L)	32.5 (6.6)	35.0 (6.5)	2.54	0.023
Globulin (g/L)	44.0 (6.4)	41.2 (7.4)	-2.78	0.025
ALT (IU/L)	26.7 (16.2)	24.5 (13.3)	-2.20	0.360
AST (IU/L)	31.5 (11.6)	28.8 (12.3)	-2.68	0.197
Bilirubin (μ mol/L)	7.5 (4.6)	7.0 (4.8)	-0.41	0.607

Significant Risk Factors after Binary Logistic Regression Analysis

Variables	OR	95% CI of OR		P	Percentage Correct (%)	Hosmer and Lemeshow Test
		Lower	Upper			χ^2 (p value)
Extrapulmonary TB +ve	2.33	1.16	4.67	0.017	76.6	6.368 (0.606)
Extrapulmonary TB -ve	1					
HIV +ve	3.54	1.25	10.05	0.018		
HIV -ve	1					
Constant	0.20			0.000		

Discussion

- The prevalence of antituberculosis drug-induced hepatitis was 9.7%.
- Comparable with those reported in developing and Asian countries (8-39%)^{2,10}.
- Probably one of the reasons was the higher prevalence of viral hepatitis in the developing countries.

² Türктаş *et al. Tubercle Lung Dis* 1994;**75**:58-60.

¹⁰ Parthasarathy *et al. Tubercle* 1986;**67**:99-108.

Discussion...

- Significant risk factors at univariate analysis:
 - HIV infection
 - Lower pretreatment serum albumin
 - Higher pretreatment serum globulin
 - Extrapulmonary tuberculosis.
- Significant risk factors by multivariate logistic regression analysis:
 - HIV infection ($p=0.018$)
 - Extrapulmonary tuberculosis ($p=0.017$)

Discussion...

- Lower level of serum albumin as a risk factor has been described^{1,11}.
- Why?
 - Degree of malnutrition or poor nutritional status.
 - Underlying HIV infection.

¹ Sharma *et al.* *Am J Respir Crit Care Med* 2002;166:916-9.

¹¹ Fauzi *et al.* *Med J Malaysia* 2004;59(1):72-7.

Discussion...

- HIV as a significant risk factor had been established in previous studies^{7,12}.
- Why?
 - Underlying viral replication or immunocompromised state
 - Co-infection of HIV with either hepatitis B virus or hepatitis C virus
 - Malnutrition/hypoalbuminaemia
 - Severe and advanced tuberculosis infection

⁷ Ungo *et al. Am J Respir Crit Care Med* 1998;157:1871-6.

¹² Ozick *et al. Am J Gastroenterol* 1995;90(11):1978-80.

Discussion...

- Extrapulmonary tuberculosis as a risk factor has not been reported in previous studies, beside in the paediatric age group patients¹³.
- Why?
 - Related to the severity and extend of the underlying disease.
 - Presence of HIV infection.
- Need further large-scale studies.

¹³ Ohkawa *et al. Clin Pharmacol Ther* 2002;72:220-6.

Conclusions

- The prevalence of antituberculosis drug-induced hepatitis was 9.7%, comparable to data from other developing countries.
- Significant risk factors at univariate analysis:
 - HIV infection
 - Lower pretreatment serum albumin
 - Higher pretreatment serum globulin
 - Extrapulmonary tuberculosis.

Conclusions...

- Significant risk factors by multivariate logistic regression analysis:
 - HIV infection
 - Extrapulmonary tuberculosis.

Thank You