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Original Article

Incidence and characteristics of antituberculosis drug-induced hepatotoxicity in children: a preliminary study

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Abstract

Background Antituberculosis drugs show good efficacy but have adverse effects including hepatotoxicity.

Objective To find the incidence and characteristics of antituberculosis hepatotoxicity in children during the first 2 weeks of therapy.

Methods A cohort study was performed in Cipto Mangunkusumo, Persahabatan, and Tangerang Hospitals from August 2008 toMarch 2009. The diagnosis of tuberculosis (TB) based on TB scoring system. Laboratory tests were performed including transaminase enzymes, bilirubin, γ-GT, albumin, ureum, and creatinine before and after 2 weeks of treatment. Patients were monitored during the first 2 weeks of therapy. Informed consent obtained from the parents.

Results Six of 81 subjects had hepatotoxicity reaction. Most of the patients were 1 to 5 years old (65%) and well nourished (50%). Extrapulmonary tuberculosis found in 67% of cases. Thirty-three percents of patients received four agents. Thirty-three percents of cases received 4 agents combined with other hepatotoxic drugs. Six subjects had hepatotoxicity (1 hepatitis, 2 mixed case, and 3 asymptomatic). Two of 50 children (4%) with pulmonary TB and 4 out of 31 (13%) children with extrapulmonary TB had hepatotoxicity reaction. Antituberculosis drug doses were similar between the hepatotoxicity group and control.

Conclusions Incidence of antituberculosis hepatotoxicity in the first 2 weeks of therapy was 7%, consisted of hepatitis (1 cases), mixed (2 cases), and asymptomatic (3 cases). There was no difference in sex as well as in nutritional state distribution found in cases with hepatotoxicity. **[Paediatr Indones. 2009;49:342-8]**.

Keyword*: antituberculosis, hepatotoxicity, incidence, characteristics*

Tuberculosis (TB) is a disease known for years. New cases of TB are increasing and most of them are in developing countries. Demographic data shows that tuberculosis in children is 5 to 6% from total tuberculosis cases.[1] In 1989, World Health Organization (WHO) predicted that every year there were 1.3 thousand new cases of TB in children and 450,000 cases under 15 years old died.

Antituberculosis drugs such as rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), and streptomycin give good efficacy but also many adverse effects.[1-2] Antituberculosis drug-induced hepatotoxicity is one of the adverse effects which causes increase of transaminases, bilirubin, icterus, anorexia, nausea, and vomiting.[1-3] WHO toxicity classification standards[4] categorize hepatotoxicity into mild hepatotoxicity if aspartat aminotransferase (AST) and/or alanin aminotransferase (ALT) increase 3 to 5 times from upper normal limits (121-200 U/L); moderate hepatotoxicity if transaminases increase 5 to 10 times from upper normal limits (201-400 U/L); severe hepatotoxicity if transaminases increase to >10 times from upper normal limits (>400 U/L).

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Study in Japan showed transient elevation of hepatocellular enzymes in 10% subjects with isoniazid and rifampicin and in 1 to 2 % subjects had to be stopped due to fulminant hepatitis.[5] Hepatotoxicity usually occurs in the first month of therapy and mostly happens in the first 2 weeks.[6,7] Concomitant therapy with isoniazid and rifampicin can cause hepatotoxicity in less than 10 day.[8] Chang et al[9] found that antituberculosis drug-induced hepatitis occured in 0.3 to 44.4 weeks mostly in 1.1 weeks. Mahmood K et al[10] found 19.76% hepatotoxicity due to antituberculosis. Most of the subjects (61%) suffered from hepatotoxiciy in 2 weeks after starting therapy with mild and moderate transaminases elevation. Schaberg et al[11] found that median interval of hepatotoxicity between antituberculosis drugs was not different, isoniazid was 16.5 (95% CI 7 to 47) days, rifampicin is 17.5 (95% CI 14 to 33) days, and pyrazinamide was 18.5 (95% CI 17 to 29) days.

Many studies investigated clinical parameters associated with susceptibility to hepatotoxicity due to antituberculosis drugs, but mainly in adult subjects.[4-5,12-18] In contrast, little is known about the risk factors of hepatotoxicity due to antituberculosis therapy in children.[5] Therefore it is a necessicity to identify incidence and characteristics of hepatotoxicity during antituberculosis therapy in children. This study intended to find the incidence and characteristics of antituberculosis drug induced-hepatotoxicity in children.

Methods

This was a cohort study carried out in Cipto Mangunkusumo, Persahabatan and Tangerang Hospitals from August 2008 to March 2009. The diagnosis of TB based on TB scoring system. Sample size was calculated using the formula for estimating single population proportion19 with $\alpha=0.05$, estimated prevalence of 30%, and accuracy of 10% revealing minimum sample size of 89 children. Subjects were selected from outpatient clinic and in-patient ward with inclusions criteria: age from 0 to 18 year old, diagnosed TB and received antituberculosis drugs. Children with chronic liver diseases, kidney diseases, chronic diarrhea, gastritis, metabolic diseases, HIV infection, history of familial liver diseases, low adherence to antituberculosis drugs therapy and disapproval of study were excluded.

Laboratory tests performed before and after 2 weeks of treatment to measure transaminase enzymes (AST, ALT), bilirubin, γ-GT (gamma-glutamyl transferase), albumin, ureum, and creatinin. Patients were monitored during the first 2 weeks of therapy. Patients were classified into those who received 3 antituberculosis agents consisted of isoniazid, rifampicin, and pyrazinamide and those who received 4 antituberculosis agents consisted of isoniazid, rifampicin, pyrazinamide and ethambutol/ streptomycin.

Hepatotoxicity was categorized into asymptomatic, hepatitis, cholestasis or mixed case (hepatitis-cholestasis).[20] Hepatitis was defined if there was transaminases elevation ≥ 5 times upper normal limit or ≥ 3 times upper normal limit with symptoms of icteric, anorexia, nausea, vomiting, fever, abdominal pain and hepatomegaly.[1,4] Cholestasis was defined if there was direct bilirubin elevation > 1 mg/dL for total bilirubin < 5 mg/dL or if total bilirubin > 5 mg/dL, direct bilirubin was > 20% of total bilirubin.21 Mixed case was defined if the patient had symptoms and signs of hepatitis and cholestasis.[4] Asymptomatic case was defined if the patient had transaminases elevation ≥ 3 and < 5 times upper normal limit without symptoms.[4] Informed consent was obtained from the parents. The study was approved by the Ethical Committee, Faculty of Medicine, University of Indonesia. Study results were processed using the SPSS version 15 program and presented in textual and tabular forms.

Results

During the study period there were 89 subjects collected. Three subjects did not fulfill the inclusion criteria. One patient died during two weeks therapy due to tuberculous meningitis. Four subjects were excluded due to poor adherence to antituberculosis therapy. At the end of the study period, only 81 subjects could be analyzed. Most of the subjects had pulmonary TB (62%) and 38% subjects had extrapulmonary TB. Fifty-four percents subjects with pulmonary TB were female, but male dominated in extrapulmonary TB cases with comparison of male : female was 2:1. Most of the subjects (55%) were 5 to

18 year old and 59% were malnourished. Most of the subjects (33%) were Sundanese, 20% Javanese, and the others (Batak, Betawi, other ethnic) were in small proportion. Majority of the subjects (77%) came from a low social economic status. **(Table 1)**

There were six from 81 subjects who suffered from hepatotoxocity, with equal number of male and female patients. There were 4/6 patients aged 1-5 years and 3/6 patients had good nutritional status **(Table 2)**. Clinical characteristics of these subjects in two weeks of monitoring are presented in **Table 3**.

Among the pulmonary TB subjects, there were 1 mixed case and 1 asymptomatic case, while among the extrapulmonary TB subjects there were 1 hepatitis, 1 mixed case, and 2 asymptomatic cases. There were 2 of 50 subjects (4%) with pulmonary TB and 4 of 31 subjects (13%)with extrapulmonary TB had hepatotoxicity. (Table 4) There was no difference in the antituberculosis drug dose between subjects with hepatotoxicity and those without. **(Table 5)**

No difference was found in sex nor in nutritional status distribution in subjects with hepatotoxicity but in those without hepatotoxicity male (52%) and malnourished (67%) were predominant. Both subjects with and without hepatotoxicity had normal albumin level (67% vs 84%). Most of hepatotoxicity subjects (4/6) had extrapulmonary TB and 64% subjects without hepatotoxicity had pulmonary TB. **(Table 6)**

Table 1. Demographic characteristics of subjects (n=81)

Characteristics	Pulmonary		Extrapulmonary	Total (%)	
	n	(%)	n		
Number	50	(62)	31	81	(100)
Sex					
Male	23	(46)	19	42	(52)
Female	27	(54)	12	39	(48)
Age (years)					
<1	6	(12)	1	7	(9)
1-5	17	(34)	12	29	(36)
5-18	27	(54)	18	45	(55)
Nutritional status					
Severe	4	(8)	1	5	(6)
Mild	35	(70)	13	48	(59)
Good	10	(20)	16	26	(32)
Overweight	1	(2)			
Ethnic/Race			1	2	(3)
Sundanese	15	(30)	12	27	(33)
Javanese	10	(20)	6	16	(20)
Betawi	8	(16)	4	12	(15)
Batak	6	(12)	1	7	(9)
Others**	4	(8)	5	9	(11)
Mixed***	7	(14)	3	10	(12)
Social-economic					
Low	35	(70)	27	62	(77)
Middle	15	(30)	4	19	(23)
High	0		0	0	

**Others = Bangka, Dayak, Madura, Menado, Melayu, Minahasa, Padang, Palembang. ***Mixed = Batak-Makasar, Betawi-Javanese, Betawi-Sundanese, Cirebon-Betawi, Javanese-Batak, Javanese-Betawi, Javanese-Palembang, Javanese-Sundanese, Sundanese-Flores

Table 2. Demographic characteristics in subjects with hepatotoxicity (n=6)

Characteristics	Hepatotoxicity
	n
Sex	
Male	3
Female	3
Age	
<1 years	1
1-5 years	4
5-18 years	1
Nutritional status	
Overweight	0
Good	3
Mild	1
Severe	2

Table 3. Clinical characteristics of patient with hepatotoxicity

Age	Sex	Symptoms	Disease extent	Therapy	Concomitant hep drugs	Hepatotoxicity
3 yr	M	Fever, vomiting, nausea, malaise	Meningeal TB	4 drugs	Phenytoin	Hepatitis
2 yr	M	Anorexia, nausea, vomiting	Spondilitis TB	4 drugs	Cotrimoxazole, paracetamol	Mixed
2 yr	F	Fever, malaise, anoreksia, icteric, hepatomegaly	Pulm TB	3 drugs	-	Mixed
4 yr	M	No symptoms	Meningeal TB	4 drugs	-	Asymptomatic
7 yr	F	No symptoms	Coxitis TB	4 drugs	-	Asymptomatic
10 mth	F	No symptoms	Pulm TB	3 drugs	Paracetamol	Asymptomatic

M= male, F= female, extra TB = extrapulmonary TB, Pulm TB= Pulmonary TB, yr= years, mth= month, d= days, hep drugs= others hepatotoxicity drugs

Table 4. Mean titer of transaminase, bilirubin, and γ-GT in subjects with hepatotoxicity and without hepatotoxicity

	With hepatotoxicity*		Without hepatotoxicity*	
	Before	Week II	Before	Week II
SGOT/AST (U/L)	63.33 (29.1)	220.16 (88.1)	52.10 (57.1)	41.20 (19.4)
SGPT/ALT (U/L)	40.33 (13.8)	220.66 (100.3)	33.10 (32.5)	28.89 (19.1)
Total bilirubin (mg/dL)	0.55 (0.3)	2.36 (0.3)	0.49 (0.3)	0.47 (0.2)
Direct bilirubin (mg/dL)	0.30 (0.2)	1.36 (2.2)	0.19 (0.2)	0.20 (0.2)
Indirect bilirubin (mg/dL)	0.25 (0.2)	0.99 (1.4)	0.30 (0.2)	0.26 (0.1)

* Mean (SD)

Table 5. Mean dose of antituberculous agents among subjects with hepatotoxicity and without hepatotoxicity

Agents	With hepatotoxicity (mg/kg/day) *	Without hepatotoxicity (mg/kg/day) *
INH	9.07 (2.2)	8.08 (2.2)
RMP	13.85 (2.7)	13.33 (6.9)
PZA	23.97 (4.1)	23.26 (7.2)
EMB	19.42 (3.8)	18.51 (5.6)

INH= isoniazid, RMP= rifampicin, PZA= pyrazinamide,

EMB= ethambutol

* Mean (SD)

Table 6. Charateristics subjects with and without hepatotoxicity

Variable	With hepatotoxicity n=6	Without hepatotoxicity n=75 (%)
Sex		
Male	3	39 (52)
Female	3	36 (48)
Age (years)		
0-5	5	31 (41)
5-18	1	44 (59)
Nutritional status		
Malnourished	3	50 (67)
Good	3	25 (33)
Albumin level		
Low	2	12 (16)
Normal	4	63 (84)
Diseases extent		
Extrapulmonary TB	4	27 (36)
Pulmonary TB	2	48 (64)
Therapy		
3 drugs	1	39 (52)
4 drugs	2	18 (24)
3 drugs + OH	1	11 (15)
4 drugs +OH	2	7 (9)

OH= other hepatotoxic drugs

Discussion

This was a preliminary study using cohort design due to ethical reason for not giving antituberculosis drug in normal children. Limitation of this study was no statistical analysis performed due to small subjects with hepatotoxicity. This study could not show which antituberculosis agents as the cause of hepatotoxicity because during the first 2 weeks of therapy, all subjects received 3 or 4 drugs.

Most of the subjects were male (52%) with age range of 5-18 years (55%). Regarding sex distribution, Tsagaropoulou-Stinga et al[22] and Ohkawa et al.[5] found that hepatotoxicity incidence was not correlated with sex.

In this study, most of the subjects with hepatotoxicity was 1 to 5 year old (67%). Ohkawa et al[5] found that all children with hepatotoxicity was under 5 years (mean age 2.3 ± 1.5 year old) and predominantly male (88%) compared to control only 45 % male. O'Brien et al[23] found that most of the subjects were from 1 to 4 years (49%). Tsagaropoulou-Stinga et al[22] found mean age of subjects was 4.5 years (4 months–14 years). Risk of complication increases in younger age (0 to 4 years old). [24]

Most of our subjects were malnourished (59%). Decrease of body weight may be due to TB infection. In this study, ethnicity of the subjects consisted of Sundanese, Javanese, Batak, Betawi and others. O'Brien et al[23] found TB infection in 48% black race and 40% white race. Most of our subjects came from low social economic status, where TB was still endemic.

Most of our subjects with hepatotoxicity had good nutritional status (50%). Study of Mahmood et al[10] found that most of the subjects with hepatotoxicity was malnourished (91%), Fernandez-Villar et al[4] found 28.6% malnourished children with hepatotoxicity, but Ohkawa et al[5] did not find malnourished subjects with hepatotoxicity. This condition maybe due to difference in population study.

In this study, there were 6 of 81 patients with hepatotoxicity, consisted of 3 asymptomatic, 1

hepatitis and 2 mixed cases. Ohkawa et al[5] found that 8 of 99 children with TB had hepatotoxicity. O'Brien et al[23] found 16 cases with hepatotoxicity of 874 children with TB. Tsagaropoulou-Stinga et al[22] found hepatotoxicity in 36 from 44 children with TB and 15 of them had hepatitis. This study was different from Tsagaropoulou-Stinga due to different drug dose given to the subjects. The dose given in the previous study was 15-20 mg/kg/day for isoniazid and 15 mg/kg/day for rifampicin. Ramachandran et al[25] found incidence of hepatitis in 50% patients with isoniazid dose 20 mg/kg/day and 20% cases with isoniazid dose of 12 mg/kg/day. Palusci et al[26] found hepatitis in 3.5% children given isoniazid. Meta analysis by Steele et al[27] showed that hepatitis was found in 6.9% children given isoniazid and rifampicin.

Symptoms in subjects with hepatotoxicity were fever, malaise, anorexia, nausea, vomiting, icterus, and hepatomegaly. Shakya et al[2] also found similar results. Black et al[14] found gastrointestinal manifestation in 55% cases and viral infection syndrome in 35% cases.

In this study, most of the subjects with hepatotoxicity was under 5 year old (83%) and 5 to 18 year old (17%). Meanwhile, most of the subjects without hepatotoxicity was from 5 to 18 year old (59%). A study in Japan showed that 8% of hepatotoxicity was under 5 year old.[5] Logistic regression analysis showed that age and pyrazinamide were significantly related to the risk of severe hepatotoxicity ($P<0.05$). Tsagaropoulou-Stinga et al[22] also found mean age of hepatitis after antituberculosis therapy was 4.5 years old (40%). O'Brien et al[23] did not find any correlation between age and hepatotoxicity.

Albumin level was normal in 67% subjects with hepatotoxicity and 84% subjects without hepatotoxicity. Ohkawa et al[5] found albumin levels were normal in control subjects (4.1 ± 0.3 g/dL) and subjects without hepatotoxicity (4.3 ± 0.4 g/dL). Mahmood et al[10] found that 27.1% patients with hepatotoxicity had albumin <3.5 g/dL. Patients with hypoalbuminemia had two times higher risks of having hepatotoxicity. In malnutrition, glutation store is depleted causing someone more vulnerable of having hepatotoxicity. Malnourished subjects also have slower drug metabolisms.[2]

In this study, most of the subjects with hepatotoxicity had extrapulmonary TB (67%), contrary to subjects without hepatotoxicity. Ohkawa et al[5] found that 4 of 8 patients with hepatotoxicity had extrapulmonary TB and showed significant relation ($P<0.05$). Shakya et al[2] found that the severity of the disease was the risk factor of having hepatotoxicity. O'Brien et al[23] found that extrapulmonary TB (milliary TB and meningitis TB) had risk of having hepatotoxicity 3 times higher than pulmonary diseases (6.9% vs 1.9%). Rahajoe et al[28] found hepatitis in 6 of 22 (27.3%) subjects of meningitis TB who received isoniazid, rifampicin, and streptomycin. In severe TB cases, there are micro lesions of tubercle in the liver. Liver damage in this case may be due to the tuberculin effect or tubercle product that is release in the liver after antituberculosis therapy. Hepatotoxicity in subjects with extrapulmonary TB maybe due to other concomitant hepatotoxic drugs.[29]

In this study, most of our subjects with hepatotoxicity received 4 antituberculosis drugs (33%) and 4 antituberculosis drugs with other concomitant hepatotoxic drugs (33%). Subjects without hepatotoxicity received 3 antituberculosis drugs (52%). Steele et al[27] found that incidence of hepatitis was 6.9% in children receiving isoniazid and rifampicin and 1.0% in 477 children receiving multiple isoniazid agents without rifampicin. Schaberg et al[11] found that other concomitant hepatotoxic drugs was not correlated significantly with severe adverse effect including hepatotoxicity from standard antituberculosis therapy ($P=0.80$; OR: 1.1, 95% CI 0.4 to 2.8). In this study, the cause of hepatotoxicity could not be determined whether due to antituberculosis agents or other concomitant hepatotoxic drugs. This was due to the small number of subjects receiving other concomitant hepatotoxic drugs, therefore statistical analysis could not be performed. Other concomitant hepatotoxic drugs that were given to the subjects with hepatotoxicity were acetaminophen, phenytoin, and cotrimoxazole. Acetaminophen can cause hepatocellular damage, while phenytoin and cotrimoxazole can cause mixed case.

In conclusion we found that the incidence of antituberculosis hepatotoxicity in the first 2 weeks of therapy was 7.4%. No difference in sex as well as in nutritional status distribution found in cases with hepatotoxicity.

References

1. Rahajoe NN, Basir DR, Makmuri, Kartasasmita CB. Pedoman nasional tuberkulosis anak. 2nd ed. Jakarta: UKK Respirologi PP IDAI, 2007; p.3-7, 47-59.
2. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother. 2004;38:1074-9.
3. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354:731-9.
4. Fernandez-Villar A, Sopena B, Fernandez-Villar J, Vazquez-Gallardo R, Ulloa F, Leiro V, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis. 2004;8:1499-1505.
5. Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, et al. Risk factors for antituberculosis chemotherapy-induced hepatotoxicity in Japanese pediatric subjects. Clin Pharmacol Ther. 2002;72:220-6.
6. Corrigan D, Paton J. Hepatic enzyme abnormalities in children on triple therapy for tuberculosis. Pediatr Pulmonol. 1999;27:37-42.
7. Durand F, Jebrak G, Pessayre D, Fournier M, Bernuau J. Hepatotoxicity of antitubercular treatments: rationale for monitoring liver status. Drug Saf. 1996;15:394-405.
8. Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, et al. Antituberculosis medication and the liver: dangers and recommendations in management. Eur Respir J. 1995;8:1384-8.
9. Chang KC, Leung CC, Yew WW, Tam CM. Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? Eur Respir J. 2007;29:347-51.
10. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B, Salkeen S. Hepatotoxicity with antituberculosis drugs: the risks factors. Pak J Med Sci. 2007;23:33-8.
11. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in subjects hospitalized for pulmonary tuberculosis. Eur Respir J. 1996;9:2026-30.
12. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, et al. Antituberculosis drug-induced hepatotoxicity. Am J Respir Crit Care Med. 1998; 157: 1871-6.
13. Dossing, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. [Abstract]. Tuber Lung Dis. 1996;77:335-40.
14. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. [Abstract]. Gastroenterol. 1975;69:289-302.
15. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risks factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax. 1996;51:132-6.
16. Singh J, Arora A, Garg PK, Thakur VS, Pande JN, Tandon RK. Antituberculosis treatment-induced hepatotoxicity: role of predictive factors. J Postgrad Med. 1995;71:359-62.
17. Smink F, Hoek v, Ringers J, Altena RV, Arend SM. Risk factors of acute hepatic failure during antituberculosis treatment: two cases and literature reviews. Neth J Med. 2006;64: 377-84.
18. Hwang SJ, Wu JC, Lee CN, Yen FS, Lu CL, Lin TP, et al. A prospective clinical study of isoniazid-rifampisin-pyrazinamide-induced liver injury in area endemic for hepatitis B. [Abstract]. J Gastroenterol Hepatol. 1997;12:87-91.
19. Madiyono B, Moeslichan S, Sastroasmoro S, Budiman I, Purwanto SH. Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. Dasar – dasar metodologi penelitian. 2nd ed. Jakarta: Sagung Seto, 2002; p. 259-286.
20. Oswari H. Penyakit hati akibat obat (PHAO) pada anak. Proceeding of 2nd Pediatric Gastroenterology National Congress; 2003 July 3-5; Bandung.
21. Oswari H. Kolestasis: atresia bilier dan sindrom hepatitis neonatal. In: Hadinegoro SR, Prawitasari T, Endyarni B, Kadim M, Sjakti HA, editors. Diagnosis dan tata laksana penyakit anak dengan gejala kuning. Proceeding of Continuing Medical Education, Department of Child Health, University of Indonesia; 2007 Nov 12-13; Jakarta. Jakarta: Department of Child Health, University of Indonesia, 2007; p. 42-54.
22. Tsagaropoulou-stinga H, Mataki-emmanouilidou T, Karida-kavalioti S, Manios S. Hepatotoxic reactions in children with severe tuberculosis treated with isoniazid-rifampin. Pediatr Infect Dis. 1985;4:270-3.
23. O'Brien RJ, Long MW, Cross FS, Lyle MA, Snider DE. Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. Pediatrics. 1983;72:491-9.
24. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children [homepage on internet]. c2006. Available from: http://www.who.int/child_adolescent_health/documents/htm_tb_2006_371/en/index.html
25. Ramachandran P. Chemotherapy of tuberculosis meningitis with isoniazid plus rifampicin-interim findings in a trial in children. Indian J Tuberc. 1979;27:54-7.
26. Palusci VJ, O'Hare D, Lawrence RM. Hepatotoxicity and transaminase measurement during isoniazid chemoprophilaxis in children. Pediatr Infect Dis J. 1995;14:144-8.

27. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest. 1991;99:465-71.
28. Rahajoe NN, Rahajoe N, Boediman I, Said M, Lazuardi S. The treatment of tuberculous meningitis in children with a combination of isoniazid, rifampisin and streptomycin-preliminary report. Tubercle. 1979;60:245-50.
29. Teleman MD, Chee CBE, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis. 2002;8:699-705.