# PHYSICIANS' PRACTICES REGARDING MANAGEMENT OF ANTITUBERCULOSIS DRUG-INDUCED HEPATOTOXICITY

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**Abstract.** To investigate the practices of physicians regarding the diagnosis and management of antituberculosis drug-induced hepatotoxicity (ATH), a cross sectional descriptive survey using a self-administered questionnaire with multiple choice questions was conducted among physicians who treated adult tuberculosis (TB) patients at 74 public hospitals in southern Thailand. Of the 272 questionnaires mailed, 204 (75%) were returned. Sixty-two physicians (31.0%) said they used alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin concurrently to diagnose ATH. Only 9.0% of physicians adhered to the American Thoracic Society (ATS) guidelines of using either an ALT or AST level. Nearly all physicians (96.6%) withheld suspected antituberculosis (anti-TB) drugs in their management of ATH patients. While waiting for normalization of liver enzyme, the alternative combination regimen of ethambutol, ofloxacin, and streptomycin (EOS) was used by most physicians (99/197). Of the 197 physicians who withheld anti-TB drugs, 175 (88.8%) decided to reintroduce them. Among these, 169 (96.6%) used a sequential rechallenge method (16.6% prescribed a full dosage, 71.4% prescribed an increasing dosage) and 1 (0.6%) used a simultaneous rechallenge method. Isoniazid was prescribed as the first drug for rechallenge in 77.5% of physicians. Only 6.5% of physicians complied with the ATS guidelines by prescribing rifampicin as the first agent. The reported practices of physicians in the diagnosis and management of ATH noticeably diverged from ATS guidelines. However, alternative regimen selection and rechallenge method complied with ATS guidelines.

**Keywords:** antituberculous drug, hepatotoxicity, manangement, physician compliance

## INTRODUCTION

Tuberculosis (TB) is a significant public health problem both in developed and developing countries (WHO, 2010). It is a curable disease with treatment usually consisting of at least four first-line antituberculosis (anti-TB) drugs, including isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (WHO, 2009). These drugs are safe, fairly well tolerated and have usually minor side effects, such as nausea/vomiting and peripheral neuropathy (Gülbay *et al*, 2006; Marra

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*et al*, 2007). Anti-tuberculosis drug induced hepatotoxicity (ATH) has been reported in 3-14% of patients (Teleman *et al*, 2002; Gülbay *et al*, 2006; Marra *et al*, 2007), often resulting in discontinuation of some or all anti-TB drugs.

The management of ATH during TB treatment is difficult because at least four anti-TB drugs are used concurrently. Moreover, three anti-TB drugs, namely isoniazid, rifampicin and pyrazinamide, have been reported as potentially hepatotoxic agents (Yee *et al*, 2003). There have been several guidelines on the management of ATH (BTS, 1998; Saukkonen *et al*, 2006). The content of these guidelines differs slightly and most are not evidenced based but rely on experts opinions. This makes them difficult for physicians to follow. Improper management of ATH patients may lead to fatal hepatitis, treatment failure or drug resistance.

There have been no reports about the reported practices of physicians in the management of ATH, such as diagnosis, initial management, selection of alternative regimens or methods of reintroducting anti-TB drugs. This study aimed to identify these practices and evaluate physician compliance with the American Thoracic Society (ATS) 2006 guidelines (Saukkonen *et al*, 2006).

## MATERIALS AND METHODS

### Ethical considerations

The study protocol was approved by the Ethical Review Committee for Research in Human Subjects of the Ministry of Public Health, Thailand.

### Study design, setting and subjects

This cross sectional descriptive survey was carried out in seven provinces in southern Thailand. This area has 74 public hospitals under the management of the Ministry of Public Health. A list of the 894 physicians working in this area was obtained from a database kept by the Ministry of Public Health (MOPH, 2011). From this database, 622 physicians who did not treat adult TB patients were excluded and 272 physicians were included in this survey.

### Study instruments

A self-administered questionnaire was created by the principal investigator. Its contents were derived from various sources, including guidelines (BTS, 1998; Saukkonen *et al*, 2006), review articles (Tostmann *et al*, 2008) and opinions from TB experts. Then, it was face-validated by three physicians: a pulmonologist, an infectious disease specialist and a TB specialist. The questionnaire was then used in a pilot study of 30 physicians and modified according to the results.

Variables included in this 4-page questionnaire were 1) physician characteristics: age, sex, specialty, practice setting, special TB training course and time interval since completing the highest level of education; 2) the physician's practices regarding the diagnosis of ATH (3 questions); and 3) the physician's practices regarding the management of ATH, including initial management (1 question), alternative regimen selected (2 questions) and method for reintroduction of anti-TB drugs (5 questions). The questions were close-ended, multiple choice. The ATS 2006 guidelines for managing ATH (Saukkonen *et al*, 2006) were used as the standard for evaluating physician compliance.

### Data collection

From March to June 2010, questionnaires were mailed to the selected study physicians. Non-respondents were sent

a repeat mail after two and four weeks if they had not yet returned their questionnaire. Anonymous replies were ensured by means of an enclosed business reply envelope. Questionnaires with more than three-fourths of the questions answered were used for analysis.

**Statistical analysis**

Statistical analyses were carried out using the R-program, version 2.0.1 (R Development Core team, 2004). Descriptive statistics were used. Categorical variables, such as physician sex, specialty, practice setting and type of practice were expressed as frequencies and percentages. Continuous variables, such as physician age and time interval since completing their highest education level were expressed as means and standard deviations.

## RESULTS

**Characteristics of physicians**

A total of 272 questionnaires were mailed and the response rate was 75.0% (204/272). There were no significant differences between respondents and non-respondents in terms of age, sex, practice setting or specialty. Characteristics of the respondents are shown in Table 1. Of the 204 respondents, 54.4% were male. The mean age was 32.5 years (SD 7.7, range 24-56 years). Most (83.3%) worked at community hospitals. A total of 156 (76.5%) were general practitioners and 33 (16.2%) were internal medicine physicians. Eighty (39.2%) had attended TB training courses. The mean time from completing the highest education level was 6.5 years (SD 6.2, range 1-27 years).

**Physicians' practices regarding the diagnosis of anti-tuberculosis drug-induced hepatotoxicity**

The patient data used by physicians to diagnose ATH are shown in Table 2. Of 204 physicians, 98.0% said they considered the patient's clinical presentation and laboratory data; 1.0% considered only the clinical presentation, and 1.0% did not answer this question. Of the 200 physicians who reported they used laboratory data to diagnose ATH, 31.0% used a combination of alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level and bilirubin level. Forty-three (21.5%) used ALT and AST levels and 18 (9.0%) used either an ALT or an AST level. The symptoms considered by 202 physicians to diagnose ATH were jaundice (99.5%), nausea/vomiting (90.6%), fatigue (80.2%), anorexia (77.2%), abdominal pain (60.9%) and other symptoms (3.5%), such as fever and dark urine.

Table 3 shows the laboratory data used by physicians to diagnose ATH. For patients with hepatitis symptoms; sixty point five percent of physicians reported using a transaminase level greater than 3 times the upper limit of normal (ULN) to diagnose ATH, 6.5% used a value greater than 5 times the ULN and 22.0% used other criteria. For patients without hepatitis symptoms, 45.5% of physicians reported using a transaminase level of greater than 5 times the ULN and 26.5% used a value greater than 3 times the ULN to diagnose ATH. Sixty-one percent of physicians complied with ATS guidelines by not using a bilirubin level to diagnose ATH.

**Physicians' practices regarding management of ATH**

**Initial management of ATH (*N*=204).** A total of 197 (96.6%) physicians withheld anti-TB drugs until liver enzymes returned to normal. Two physicians continued treatment with a reduced dosage of all anti-TB drugs and one physician continued treatment at a reduced dosage

Table 1
Characteristics of physicians (*N*=204).

| Characteristics | Statistic values |
|---|---|
| Gender, *n* (%) | |
| Male | 111 (54.4) |
| Female | 90 (44.1) |
| Unknown | 3 (1.5) |
| Age (year) | |
| Mean (SD; range) | 32.5 (7.7; 24-56) |
| Practice site, *n* (%) | |
| Community hospital | 171 (83.8) |
| General hospital | 18 (8.8) |
| Regional hospital | 15 (7.4) |
| Specialty, *n* (%) | |
| General practice | 156 (76.5) |
| Internal medicine | 33 (16.2) |
| Others | 15 (7.3 ) |
| Attendance of special TB training courses, *n* (%) | 80 (39.2) |
| Time since completing highest education level, years | |
| Mean (SD; range) | 6.5 (6.2; 1-27) |

Table 2
Physician practices regarding diagnosis of antituberculosis drug-induced hepatotoxicity.

| Physician practices | Number (%) |
|---|---|
| Patient data used for diagnosis (*N*=204) | |
| Laboratory and clinical data | 200 (98.0) |
| Clinical data only | 2 (1.0) |
| Unknown | 2 (1.0) |
| Patient laboratory data used for diagnosis (*N*=200) | |
| AST and ALT and bilirubin | 62 (31.0) |
| AST and ALT | 43 (21.5) |
| AST and ALT and ALP | 28 (14.0) |
| AST or ALT [a] | 18 (9.0) |
| AST or ALT or bilirubin or ALP | 10 (5.0) |
| AST only | 10 (5.0) |
| AST or ALT or bilirubin | 5 (2.5) |
| ALT only | 2 (1.0) |
| Others | 22 (11.0) |

[a] Practices that complied with American Thoracic Society 2006 guidelines.
ALT, alanine aminotransferase; AST, aspartate aminotransferase
ALP, alkaline phosphatase

Table 3
Laboratory criteria used by physicians to diagnose antituberculosis drug-induced hepatotoxicity (*N*=200).

| Criteria | Number of physicians (%) | |
|---|---|---|
| | Patient with hepatitis symptoms | Patient without hepatitis symptoms |
| Transaminase level | | |
| > 3 times ULN | 121 (60.5) [a] | 53 (26.5) |
| > 5 times ULN | 13 (6.5) | 91 (45.5) [a] |
| Others | 44 (22.0) | 15 (7.5) |
| Do not use | 14 (7.0) | 14 (7.0) |
| Unknown | 8 (4.0) | 27 (13.5) |
| Bilirubin level regardless of hepatitis symptoms | | |
| >2 times ULN | 18 (9.0) | |
| >3 times ULN | 17 (8.5) | |
| >5 times ULN | 14 (7.0) | |
| >1 times ULN | 7 (3.5) | |
| >1.5 times ULN | 1 (0.5) | |
| Do not use | 122 (61.0) [a] | |
| Unknown | 21 (10.5) | |

ULN, upper limit of normal; [a] Practices that complied with American Thoracic Society 2006 guidelines.

of some of the suspected anti-TB drugs. Four physicians (2.0%) did not answer this question.

**Selection of alternative regimens (*N*=197).** Table 4 shows the regimens used by physicians to manage ATH while waiting for normalization of liver enzymes. Of the 197 physicians who withheld suspected anti-TB drugs, 157 (79.7%) selected the same regimen regardless of the results of the patient's sputum test or extra-pulmonary disease, while 40 (20.3%) based their treatment on sputum results. Of the 157 who ignored the sputum results, 42 (26.8%) prescribed no alternative regimen, while 24 of the 40 (60.0%) physicians who based their treatment on sputum results prescribed no alternative regimen. The drugs used for the alternative regimens were isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, and ofloxacin. These regimens were prescribed as a combination of two or three drugs. The regimen of ethambutol, ofloxacin, and streptomycin (EOS) was used by most physicians (99/197). Two physicians prescribed pyrazinamide, a drug reported as a being highly hepatotoxic.

**Reintroduction of anti-tuberculosis drugs** (Table 5)**.** Of the 197 physicians who said that they would withhold suspected anti-TB drugs, 175 (88.8%) stated that they would re-prescribe them. Of the 175 physicians who decided to rechallenge with first-line anti-TB drugs, 63 (36.0%) reintroduced a drug combination which excluded pyrazinamide, 169 (96.6%) used a sequential rechallenge method (16.6% with a full dosage, 71.4% with an increasing dosage), and one used a simultaneous

Table 4
Physician practices regarding selection of alternative regimens (*N*=197).

| Physician practices | Number of physicians (%) | | |
|---|---|---|---|
| | Same for all patients (*n*=157) | Dependent on type of TB patient (*n*=40) | |
| | | Smear-positive TB | Smear-negative TB/ extra-pulmonary TB |
| Prescribed no alternative regimen | 42 (26.8) | 1 (2.5) | 23 (57.5) |
| Prescribed alternative regimens | | | |
| E, O, S | 75 (47.8) | 22 (55.0) | 2 (5.0) |
| E, O | 4 (2.5) | 2 (5.0) | 1 (2.5) |
| E, S | 4 (2.5) | 2 (5.0) | 0 (0.0) |
| H, S | 4 (2.5) | 0 (0.0) | 0 (0.0) |
| O, S | 3 (1.9) | 1 (2.5) | 0 (0.0) |
| H, R, E | 0 (0.0) | 0 (0.0) | 2 (5.0) |
| R, Z, E | 2 (1.3) | 0 (0.0) | 0 (0.0) |
| Others | 17 (10.8) | 6 (15.0) | 4 (10.0) |
| Unknown | 6 (3.9) | 6 (15.0) | 8 (20.0) |

H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin; O, ofloxacin

Table 5
Physician practices regarding rechallenge of anti-tuberculosis drugs.

| Physician practices | Number (%) |
|---|---|
| Considered anti-TB drug rechallenge (*N*=197) | |
| Yes | 175 (88.8) |
| No | 18 (9.1) |
| Unknown | 4 (2.1) |
| Pyrazinamide rechallenge (*N*=175) | |
| Yes, for all patients | 38 (21.7) |
| Yes, for some patients | 56 (32.0) |
| No | 63 (36.0) |
| Unknown | 18 (10.3) |
| Methods used for rechallenge (*N*=175) | |
| Sequential rechallenge [a] | 169 (96.6) |
| Full dose | 29 (16.6) |
| Increasing dose | 125 (71.4) |
| Unknown | 15 (8.6) |
| Simultaneous rechallenge | 1 (0.6) |
| Unknown | 5 (2.8) |
| If sequential rechallenge, the first drug prescribed (*N*=169) | |
| Isoniazid | 131 (77.5) |
| Rifampicin [a] | 11 (6.5) |
| Pyrazinamide | 1 (0.6) |
| Unknown | 26 (15.4) |

[a] Practice that complied with American Thoracic Society 2006 guidelines.

rechallenge method. Of the 169 physicians who used a sequential rechallenge method, 131 (77.5%) prescribed isoniazid as the first agent for reintroduction. Only 11 physicians (6.5%) used rifampicin as their first drug. Pyrazinamide was used as the first anti-TB drug by one physician.

## DISCUSSION

The diagnostic criteria for ATH given by the ATS (Saukkonen *et al*, 2006) are a serum transaminase level: 1) greater than three times the ULN with jaundice and/or hepatitis symptoms; or 2) greater than five times the ULN regardless of hepatitis symptoms. The present study shows few physicians followed ATS guidelines by checking only an ALT or AST level. When diagnosing ATH, most physicians checked ALT, AST and bilirubin levels concomitantly, although a bilirubin level was not mentioned in the guidelines. This may be due to the fact many previous reports included the bilirubin level as part of the criteria to diagnose ATH (Tahaoglu *et al*, 2001; Agal *et al*, 2005; Sharma *et al*, 2010).

The standard regimen for tuberculosis treatment consists of at least three potentially hepatotoxic drugs, including isoniazid, rifampicin and pyrazinamide. A toxic metabolite of isoniazid, namely hydrazine, is accountable for liver cell damage (Tafazoli *et al*, 2008) resulting in an increase in transaminase levels. Rifampicin, a potent inducer of the hepatic CYP450 system, increases the formation of isoniazid toxic metabolites (Sarma *et al*, 1986). Therefore, the concomitant usage of isoniazid and rifampicin increases the risk of hepatotoxicty. Rifampicin may inhibit the re-uptake of bilirubin resulting in elevated bilirubin levels (McColl *et al*, 1987). Patients treated with standard anti-TB regimens, may have different abnormal liver function test results, such as an elevation in a transaminase level alone, a bilirubin level alone or both (Agal *et al*, 2005; Mankhatiham *et al*, 2011). For this reason, the bilirubin level should be considered in ATH diagnosis (BTS, 1998). Guidelines for the diagnosis and management of ATH should include how to manage a patient with an abnormal bilirubin level.

About half of physicians followed ATS guidelines regarding the diagnosis of ATH using a transaminase level greater than 3 times the ULN for patients with symptoms of hepatitis and greater than 5 times the ULN for patients without symptoms (Saukkonen *et al*, 2006). However, nearly one-third of physicians reported using other levels. If physicians used a lower transaminase level than that recommended by the ATS, patients may be incorrectly diagnosed with having ATH resulting in unnecessary discontinuation of their treatment. Physicians who use a higher transaminase level than that recommended by the ATS could have a deleyed diagnosis of ATH, putting the patient at risk for more severe hepatotoxicity, including fuminant hepatitis (Makhlouf *et al*, 2008). Although more than half of physicians adhered to the ATH guidelines by ignoring bilirubin when diagnosing their patients, some physicians reported using levels recommended in other published studies (Tahaoğlu *et al*, 2001; Agal *et al*, 2005; Sharma *et al*, 2010).

Potentially hepatotoxic drugs such as isoniazid, rifampicin and pyrazinamide should be discontinued without delay when a patient is suspected of having ATH until liver enzymes have returned to normal values (BTS, 1998; Saukkonen *et al*, 2006). The present study showed most physicians followed this recommendation. Three physicians continued with

the drugs at a reduced dose. This practice may be useful in cases using high doses of anti-TB drugs. Grades 1 and 2 ATH are more common among patients using higher doses (13 mg/kg) of rifampicin than the standard doses (10 mg/kg) (Ruslami *et al*, 2007). ATH occurred in patients with a higher dose of isoniazid (1,000 mg/day) and did not reoccur when rechallenged with a normal dose (Danielides *et al*, 1983).

While waiting for normalization of liver enzymes, alternative anti-TB drugs with a low risk of inducing hepatotoxicity should be prescribed. This study showed the decision of most physicians in this area was not based on the severity of patient disease (smear positive *versus* smear negative or extra-pulmonary TB); one-third did not prescribe any regimen. When suspected ATH, anti-TB drugs should be discontinued and replaced with 3 less hepatotoxic anti-TB drug (BTS, 1998; Saukkonen *et al*, 2006), such as ethambutol and streptomycin (BTS, 1998). Many studies have confirmed the safety of alternative regimens, including fluoroquinolones for both TB patients with underlying hepatic disease and TB patients with ATH (Saigal *et al*, 2001; Szklo *et al*, 2007; Ho *et al*, 2009). In this study, the three-drug regimen of ethambutol, streptomycin and ofloxacin was prescribed by nearly half the physicians. Potentially hepatotoxic drugs, such as pyrazinamide, rifampicin and isoniazid, were selected as alternative anti-TB drugs by a few physicians in this study.

The ATS 2006 guidelines (Saukkonen *et al*, 2006) suggest first-line anti-TB drugs withheld should only be reintroduced when the ALT level returns to less than twice the ULN. In this study, nearly all the physicians followed this suggestion.

A drug rechallenge is defined as the readministration of a drug suspected to be a possible cause of an adverse reaction which was previously administered and then discontinued. Although drug rechallenge following drug-induced liver injury may lead to serious or fatal liver toxicity, first-line anti-TB drugs, such as isoniazid, rifampicin and pyrazinamide, are crucial for treating tuberculosis patients. Second-line anti-TB regimens, such as fluoroquinolones, entail longer treatment durations and may produce more treatment failures (Moadebi *et al*, 2007). About one-third of physicians in this study did not rechallenge with pyrazinamide. This may be due to its high hepatotoxicity, with incidences of ATH reported at 0.30-0.52 per 100 person-months (Yee *et al*, 2003). Regimens which exclude pyrazinamide during rechallenge have been shown to be safe with no known reports of patients experiencing recurrent hepatotoxicity (Tahaoğlu *et al*, 2001).

In this study nearly all physicians used the sequential rechallenge method instead of the simultaneous method. The sequential rechallenge method is recommended by ATS because it can more readily identify the causative agent. Rates of recurrent hepatotoxicity have been shown to be no different between the two methods (Sharma *et al*, 2010). Sequential rechallenge with full dosage or increasing dosage yielded similar rates of recurrent hepatotoxicity (Sharma *et al*, 2010). Most physicians in this study preferred to use the rechallenge with increasing doses. This may be due to the fact that hepatic adaptation may occur with gradually increasing doses (Danielides *et al*, 1983).

Rifampicin is recommended by the ATS as the first agent to reintroduce, a recommendation supported by one study which found, compared to isoniazid alone, rifampicin had a lower incidence

of hepatotoxicity (1.1% *versus* 1.6%) (Steele *et al*, 1991). Seventy-seven point five percent of physicians in this study rechallenged with isoniazid first, while only 6.5% rechallenged with rifampicin first. It is likely these physicians followed the guidelines of the British Thoracic Society (BTS, 1998) or the Thailand National Tuberculosis Control Program Guidelines (MOPH, 2008), both of which recommend the use of isoniazid as the first agent to reintroduce.

To our knowledge, this is the first study describing the reported practices of physicians on the management of ATH in Thailand. All aspects of ATH management are reported: diagnosis, initial management, selection of alternative regimens and rechallenge methods. Although the simulated client method (SCM) and standardized patient (SP) method have both been used by many studies as the gold standard for measuring physician practices (Dresselhaus *et al*, 2000), there are a limited range of symptoms and syndromes that can be simulated on physical examination. Therefore, in this study, it was difficult for the patient to present as a hepatotoxic patient and it was unethical to use a real patient. Chart abstraction, another method used to assess the physician practices, is known to have a high rate of incomplete information.

A limitation of this study was the self-administered questionnaires used to measure physician practices. Poor recall, lack of relevant experiences, and "observation bias" toward "socially desirable" behavior have been reported as problems associated with this method (Ross-Degnan *et al*, 1996; Dresselhaus *et al*, 2000). The large number of questions used in the questionnaire resulted in a non-response rate of 15% for some questions. This may have resulted in a misinterpretation of physician practices.

In conclusion, the reported practices of physicians in the diagnosis and management of ATH noticeably diverged from ATS guidelines. However, some practices, such as alternative regimen selection and rechallenge method complied with the guidelines. A special training course focused on the diagnosis and management of patients with ATH should be provided for physicians in this area. ATS guidelines should be discussed, including details about the importance of bilirubin level in ATH diagnosis, the optimal doses for anti-TB drugs and the preferred drug of first choice for anti-TB drug rechallenge.

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