Eur J Gen Med 2017;14(1):1-4
ISSN:1304-3889 eISSN:1304-3897
DOI: 10.29333/ejgm/81870

***Original Article***

# *Risk factors for hepatotoxicity in patients hospitalized for tuberculosis*

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***ABSTRACT***
**Introduction:** Combination therapy with four drugs (isoniazid, rifampicin, pyrazinamid and ethambutol) is the treatment of choice in tuberculosis but hepatotoxicity due to these drugs is an important medical concern. Therefore identification of patient groups with increased risk for antituberculosis therapy induced hepatotoxicity is crucial.
**Objective:** To assess the rate of hepototoxicity due to antituberculosis drugs and to determine factors associated with hepatotoxicity in hospitalized tuberculosis patients.
**Methods:** This retrospective cohort study included hospitalized patients with the diagnosis of tuberculosis during a ten year period. Only patients with microbiological (culture positive) or histopathological (presence of granulomatous reaction with caseification necrosis in the tissue) evidence of tuberculosis infection were included. Incidence of hepatotoxicity and the association of hepatotoxicity with known and unknown risk factors were investigated.
**Results:** Sixty four patients (33 female-31 male; median age 48.0 years) were included into the study. Most of the patients had extrapulmonary tuberculosis (n=49). Antituberculosis therapy was started with four drugs in all patients and 7 patients developed hepatotoxicity. Age, gender, previous tuberculosis history, extent of tuberculosis, positive hepatitis B virus serology, diabetes mellitus and chronic renal insufficiency were not related with the development of hepatotoxicity. The presence of rheumatologic disease and chronic corticosteroid use was associated with increased risk of hepatotoxicity ($p<0.01$ and $p=0.01$, respectively).
**Conclusion:** In this study we found that patients with rheumatologic diseases and patients on chronic corticosteroid treatment had increased risk for hepatotoxicity during antituberculosis therapy. These patients should be closely monitored for hepatotoxicity especially during the initial treatment phase.

**Keywords:** tuberculosis, drug, side effect

## INTRODUCTION

Mycobacterium tuberculosis (*M. tuberculosis)* infection is still a major health problem throughout the world. Nine million people develop active disease attributable to *M. tuberculosis* infection annually, and one third of the world's population, approximately 2 billion people, are thought to be latently infected with *M. tuberculosis* (1). Isoniazid, rifampicin, ethambutol pyrazinamide and streptomycin are first line antituberculosis drugs and are commonly used in combination. Hepatotoxicity is one of the major drawbacks of the combination therapy which is observed approximately in 5 to 33% of patients (2). Isoniazid and pyraziamide are hepatotoxic agents by themselves and rifampicin, a potent enzyme inducer, may enhance isoniazid induced hepatotoxicity (2). Antituberculosis therapy induced hepatotoxicity can range from asymptomatic increase in liver enzymes to severe hepatic failure requiring liver transplantation. Moderate to severe hepatotoxicity may lead to discontinuation of therapy, which may cause treatment failure, relapse or drug resistance. Identification of patient groups who are at an increased risk for antituberculosis therapy induced hepatotoxicity is important as hepatoxicity causes additional burden on morbidity and mortality of tuberculosis infection. Previously reported risk factors for hepatotoxicity are older age, female gender, malnutrition, low albumin level, chronic alcohol abuse, pre-existent liver disease, human immunodeficiency virus (HIV) infection and the presence of genetic factors such as slow N-acetyltransferase activity, cytocrome P450 2E1 homozygosity and glutathione S-transferase homozygosity (3). In this study our aim was to determine additional risk factors that might predispose antituberculosis drug induced hepatoxicity in hospitalized patients.

## MATERIAL AND METHODS

### Patients

The study was conducted in a tertiary reference center and was approved by local ethics committee. We retrospectively identified patients with a diagnosis of tuberculosis over a period of ten years (August 1997-November 2007) from a prospectively collected database to which all patients with tuberculosis are recorded. Only patients with microbiological (culture positivity) or histopathological (presence of granulomatous reaction with caseification necrosis in the tissue) evidence of tuberculosis infection were included into the study. Patients with a diagnosis of tuberculosis solely done by clinical judgement, pre-existing liver disease, and positive serology for HIV were excluded from the study. Demographic, clinical and laboratory characteristics were collected from hospital records. Laboratory values for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total and direct bilirubin before and during treatment were recorded. Patients were stratified into two groups according to presence or absence of hepatotoxicity after the initiation of antituberculosis treatment. Antituberculosis therapy related hepatotoxicity was defined as normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of antituberculosis drugs and the presence of at least one of the following criteria during use of antituberculosis therapy: i.) elevation of ALT and/or AST >3 times the upper limit of normal in the presence of

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*Received: 19 Apr 2016, Accepted: 06 Jun 2016*

**Table 1:** *Demographic and clinical characteristics of study population (n=64)*

| | |
|---|---|
| Age (years) | 48.0 (36.3-61.8) |
| Female | 33 (51.6) |
| Localization of tuberculosis infection | |
| *Pulmonary* | 15 (23.4) |
| *Extrapulmonary* | 49 (76.6) |
| Tuberculosis diagnosis | |
| *Microbiological* | 15 (23.4) |
| *Histopathological* | 34 (53.1) |
| *Microbiological and histopathological* | 15 (23.4) |
| Previous tuberculosis history | 9 (14.1) |
| Chronic corticosteroid use | 6 (9.4) |
| Symptoms on admission | |
| *Fever* | 39 (60.9) |
| *Cough* | 36 (56.3) |
| *Fatigue* | 32 (50.0) |
| *Night sweating* | 29 (45.3) |
| *Anorexia-weight loss* | 28 (43.8) |
| *Sputum production* | 20 (31.3) |
| *Hemoptysis* | 9 (14.1) |
| Comorbidities | |
| *Chronic renal failure* | 11 (17.2) |
| *Diabetes mellitus* | 8 (12.5) |
| *Heart failure* | 5 (7.8) |
| *Malignancy* | 5 (7.8) |
| *Rheumatologic disease* | 3 (4.7) |
| *Hepatitis B virus (+) serology* | 4 (6.3) |
| *Other* | 4 (6.3) |
| Baseline laboratory values | |
| *White cell count (x10$^6$/µl)* | 8.0 (6.5-10.8) |
| *Erythrocyte sedimentation rate (mm/hour)* | 73 (36-107) |
| *Alanine aminotransferase (U/l)* | 22.0 (11.0-31.0) |
| *Aspartate aminotransferase (U/l)* | 23.0 (16.0-35.0) |
| *Total bilirubin (mg/dl)* | 0.5 (0.4-0.7) |
| *Gamma glutamyltranspeptidase (U/l)* | 38.0 (16.8-67.0) |
| *Alkaline phosphatase (U/l)* | 181.5(100.8-285.0) |
| Hepatotoxicity | 7 (10.9) |
| Time to hepatotoxicity (days) | 12.0 (11.0-33.0) |
| Time from diagnosis to hospital discharge (days) | 16.0 (7.0-36.0) |
| Length of hospitalization (days) | 23.0 (11.3-34.0) |

*n: number, µl: microliter, U/l: units per liter, mm/hour: millimeter per hour, m/dl: milligram per deciliter.*

**Table 2:** *Transaminase (U/l) and bilirubin (mg/dl) levels*

| | Patients with hepatotoxicity n=7 | Patients without hepatotoxicity n=57 |
|---|---|---|
| $ALT_0$ | 20.0 (17.0-59.0) | 22.0 (10.2-26.5) |
| $ALT_1$ | 108.0 (72.0-345.0) | 20.0 (14.5-33.0) |
| $AST_0$ | 36.0 (19.0-38.0) | 21.0 (16.0-33.0) |
| $AST_1$ | 80.5 (34.0-185.0) | 25.0 (19.0-37.0) |
| Total $bilirubin_0$ | 0.5 (0.4-0.7) | 0.5 (0.4-0.7) |
| Total $bilirubin_1$ | 0.6 (0.6-4.4) | 0.4 (0.3-0.8) |

$ALT_0$, $AST_0$, Total $bilirubin_0$: Levels at the beginning of the therapy
$ALT_1$, $AST_1$, Total $bilirubin_1$: Level at the end of the first month of the therapy

**Table 3:** *Distribution of transaminase index in patients with hepatotoxicity (n=7)*

| Transaminase index | n |
|---|---|
| 1-5 | 3 |
| 6-10 | 2 |
| >10 | 2 |

**Table 4:** *Possible risk factors for antituberculosis therapy induced hepatotoxicity on bivariate analysis*

| | Hepatotoxicity | | P value |
|---|---|---|---|
| | No (n=57) | Yes (n=7) | |
| Age | 48.0 (36.5-61.0) | 54.0 (31.0-74.0) | 0.53 |
| Female | 29 (50.9) | 4 (57.1) | 1.00 |
| Localization of tuberculosis infection | | | |
| *Pulmonary* | 13 (22.8) | 2 (28.6) | 0.06 |
| *Extrapulmonary* | 44 (77.2) | 5 (71.4) | |
| Previous tuberculosis history | 9 (15.8) | 0 | 0.30 |
| Chronic corticosteroid use | 3 (5.3) | 3 (42.9) | 0.01 |
| Chronic renal insufficiency | 11 (19.3) | 0 | 0.37 |
| Diabetes mellitus | 6(10.5) | 2 (28.6) | 0.36 |
| Heart failure | 4 (7.0) | 1(14.3) | 0.71 |
| Malignancy | 5 (8.8) | 0 | 0,62 |
| Hepatitis B virus (+) serology | 4 (7.0) | 0 | 0.58 |
| Rheumatologic disease | 0 | 3 (42.9) | <0.01 |
| Time from diagnosis to hospital discharge (days) | 14.0 (7.0-30.5) | 47.0 (43.0-49.0) | 0.02 |
| Length of hospitalization | 16.0 (9.5-32.5) | 37.0 (26.0-56.0) | 0.02 |

n= number, Categorical variables are expressed as number (%) and continuous variables are expressed as median (interquartile range). A p value of <0.05 was considered significant

hepatotoxicity symptoms (anorexia, nausea-vomitting, jaundice); ii.) elevation of ALT and/or AST >5 times the upper limit of normal irrespective of clinical findings associated with hepatotoxicity; or iii.) elevation of bilirubin level to at least 2mg/dL (2). Transaminase index (highest transaminase level/pretreatment transaminase level) for the first month was calculated in patients who developed hepatotoxicity (4, 5).

### Antituberculosis Drug Regimen

The usual treatment was initiated according to national tuberculosis program in all patients (6). Patients received first line antituberculosis drugs and doses were as follows: isoniazid 5mg/kg/day with a maximum dose of 300mg/day, rifampicin 10mg/kg/day with a maximum dose of 600mg/day, ethambutol 15mg/kg/day with a maximum dose of 1500mg/day and pyrazinamide 25-30mg/kg/day with a maximum dose of 2000mg/day. Initial treatment was the combination of these 4 drugs for two months followed by isoniazid and rifampicin combination for 4 to 10 months according to extent of the disease. All patients also received prophylactic vitamin B6 (pyridoxine) during treatment phase.

### Statistical Analysis

All numerical variables are expressed as mean±standart deviation (SD) or median (inter-quartile range, IQR). Continuous variables were compared by Mann-Whitney U test and categorical variables were compared by Chi-square test. A two-tailed p value of ≤0.05 was considered significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 14.0.

## RESULTS

We identified a total of 156 hospitalized patients that fulfilled the inclusion criteria. Ninety-two patients were excluded as they were discharged just after treatment or lost to follow-up. The remaining 64 hospitalized patients comprised the study population. The demographic and clinical characteristics of patients are summarized in Table 1. Four patients had positive hepatitis B serology. None of the patients had positive serology for hepatitis C or history of chronic alcohol abuse. After antituberculosis therapy, one patient had erythematous skin rash but this resolved during treatment. No patient had any ototoxic or neurotoxic side effect.

Antituberculosis drug induced hepatotoxicity was detected in seven patients (10.9%) within a median of 12.0 (IQR: 11.0-33.0) days after initiation of therapy. Levels of transaminases in the beginning and in the first month of therapy is presented in Table 2 and the distribution of transaminase index is presented in Table 3. Bivariate analysis showed presence of rheumatologic disease and chronic corticosteroid use to be associated with development of hepatotoxicity (p<0.01 and p=0.01, respectively; Table 4). The types of rheumatologic diseases were rheumatoid arthritis (n=2) and sarcoidosis (n=1). The disease was active in both rheumatoid arthritis patients and they were receiving tumor necrosis factor (TNF) blocker therapy in addition to other disease modifying agents (one patient receiving infliximab-methylprednisolone and the other receiving etanercept-methylprednisolone-sulfasalazine-leflunomide-auranofin therapy). None of the patients with rheumatoid arthritis were on isoniazid prophylaxis. As sarcoidosis can be misdiagnosed in tuberculosis cases, medical records of the patient with sarcoidosis were reviewed in detail which showed that the diagnosis of sarcoidosis was confirmed pathologically from mediastinal lymph nodes that were obtained with open thoracotomy 6 years prior to diagnosis of tuberculosis. Out of 64 patients, 6 were on chronic corticosteroid treatment for different causes (three for rheumotologic diseases, one for suspected sarcoidosis, one for adrenal insufficiency and one for glomerulonephritis); three of these patients developed hepatotoxicity.

The duration of hospitalization, as expected, was significantly longer in patients with hepatotoxicity (Table 4). All patients were reintroduced to antituberculosis therapy after

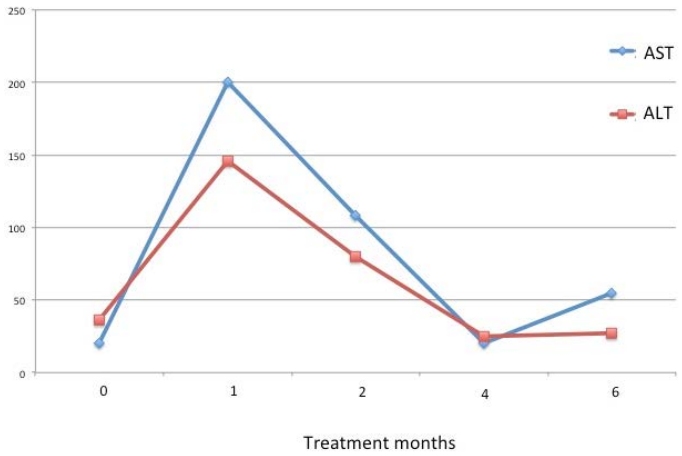


**Figure 1:** *Changes in transaminase levels throughout treatment period in patients with hepatotoxicity (n=7)*

liver enzymes levels returned to normal levels. In two patients hepatotoxicity recurred and antituberculosis drug regimen was changed according to national guidelines. Patients transaminase levels for the first six months of therapy is presented in Figure 1.

## DISCUSSION

Combination therapy with antituberculosis drugs is proven to be a very effective treatment modality for active tuberculosis infection. However, combination of these drugs may cause serious side effects, including hepatotoxicity. Severe hepatotoxicity is a major concern in therapeutic effectiveness as it may lead to interruption of therapy. Other important issues related with hepatotoxicity are the need for alternative drug regimens, increased length of hospitalization and cost. Because of these reasons, patient groups at increased risk for antituberculosis drug induced hepatotoxicity should be identified.

In the present study, we found the presence of rheumatologic disease and chronic corticosteroid use to be associated with antituberculosis therapy related hepatotoxicity. All of these patients' liver function tests were within normal range at the beginning of antituberculosis therapy and two rheumatoid arthritis patients were on therapy with TNF blockers. Patients with active rheumatologic disease are usually on disease modifying and/or TNF blocker treatment and liver injury has been documented with this treatment modality (7, 8). Adding a second group of hepatotoxic drug regimen, such as antituberculosis therapy, may increase the risk. Vanhoof et al reported higher hepatotoxicity rate due to isoniazid treatment in rheumatoid arthritis patients (9). The proposed reason for increased hepatotoxicity was interference between isoniazid and disease modifying agents (such as methotraxate and sulfasalazine). A study reported by Haroon et al showed higher hepatotoxicity rate in isoniazid chemoprophylaxis for latent tuberculosis infection in patients treated with TNF blockers; 22% of the patients developed hepatotoxicity with the incident being severe in 13% (10). Bray et al also reported high hepatotoxicity rates with isoniazid and rifampicin in patients receiving TNF blocker therapy (11). Hanta et al also reported that 8% of patients treated with TNF blocker had hepatotoxicity with izoniazid. (12). On the other hand, another study reported that prophylactic treatment only with isoniazid for latent tuberculosis in rheumatoid artritis patients was safe (13). Our findings, together with other reports in the literature, suggest that patients receiving therapy with multiple disease modifying drugs may have increased risk of hepatotoxicity during combination antituberculosis therapy. As there is no specific suggestion for this patient group, we think that assesment of hepatotoxicity should be carried out routinely.

We have also found an association between chronic corticosteroid use and antituberculosis therapy related hepatotoxicity. High dose corticosteroid use is known to be related with liver injury (14). Although low doses of corticosteroids are considered to be safe, chronic administration may be associated with steatosis or steatohepatitis (15,16). Our findings suggest that in such patients, the risk of hepatotoxicity may be increased with the addition of antituberculosis drug therapy.

The incidence of antituberculosis therapy related hepatotoxicity in our study is similar to previous reports (2-28%) in the literature (17). Incidence of hepatotoxicity was between 2.4-11.3 % in Turkish population (5, 18-21). The high variance for hepatotoxicity among studies may be attributed to different patient groups as genetic factors play an important role in the development of hepatotoxicity. A meta-analysis study showed N-acetyl transferase 2 homozygous variant genotype, cytochrome p450 2E1 wild genotype and glutathione S-transferase homozygous null type as risk factors for antituberculosis therapy related hepatotoxicity (22). Another reason for high variance in the incidence might be the use of different definitions for hepatotoxicity; some studies define hepatotoxicity as any increase in liver function tests whereas others only accept hepatotoxicity when there is need for treatment discontinuation.

Older age and female gender were previously shown to be related to antituberculosis therapy related hepatotoxicity; however we were unable to show such an association in our study (23-26). Older patients may be more vulnerable to hepatotoxic reactions due to changes in drug metabolism and clearence, but the data is inconsistent in the literature regarding the relationship between age and hepatotoxicity (2, 27). Some studies also showed increased risk hepatotoxicity in females most of which were whether not statistically significant or treatment limiting (25, 27, 28).

Comorbidities are important for the hepototoxicity development. A study performed in Turkey (n=1443) evaluated the association between comorbidities and hepatoxicity however they didn't find an increased risk (29).

The highest risk period for hepatotoxicity is generally between second and third week of therapy (21). In this study we followed all patients during this high-risk period and hepatoxicity was seen with a median of 12 days after initiation of therapy. Ateş et al reported that the first two weeks were the most critical time for the development of hepatoxicity (30).

Some limitations of our study merit consideration. First, due to the retrospective design of the study and inclusion of only hospitalized patients, selection bias is inevitable and the results are not attrituble to other patient populations. Second the present study was done in a tertiary reference center and we think that most of these hospitalized patients were relatively complicated extrapulmonary tuberculosis cases. Although hepatotoxicity was expected to be higher in these patients, we found a similar antituberculosis therapy related hepatotoxicity rate. We also think that this is one of the strengths of our study as this study gives important information regarding a relatively less studied patient cohort. Another important strength is that the study was restricted to patients in whom the diagnosis of tuberculosis was established by gold standard methods.

In conclusion, antituberculosis therapy with four drugs is very effective in the treatment of tuberculosis, but it should be kept in mind that combination of possibly hepatotoxic drugs may cause liver damage. Our findings show presence of rheumatologic disease and chronic corticosteroid use as risk factors for hepatotoxicity during tuberculosis treatment in

hospitalized patients. Therefore we think that these patients should be closely monitored for hepatotoxicity especially during initial treatment phase.

**REFERENCES**


1. World Health Organization. Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009. Geneva, Switzerland: World Health Organization; 2009. Available at http://www.who.int/tb/publications/global_report/2009/pdf.
2. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935-52.
3. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology. 2006; 11(6):699-707.
4. Brande PV, Steenberg WV, Vervoort G, Demedts M. Aging and hepatotoxicity of isoniazid and rifampin in pulmonary tuberculosis. Am J Respir Crit Care Med. 1995;152:1705-8.
5. Uzun K, Ozbay B, Gulsun A, Zehir I. Tüberküloz tedavisi sırasında karaciğer fonksiyon testleri. T Klin J Med Sci. 1999;19:137-40.
6. T. C. Sağlık Bakanlığı Verem Savaşı Daire Başkanlığı. Türkiye'de tüberkülozun kontrolü için başvuru kitabı. Ankara, 2003 (www.verem.org.tr).
7. Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol. 2011;7:139-50.
8. Curtis JR, Beukelman T, Onofrei A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis. 2010;69:43-7.
9. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazineand anti-tumour necrosis alpha inhibitors. Ann Rheum Dis. 2003;62:1241-2.
10. Haroon M, Martin U, Devlin J. High incidence of intolerance to tuberculosis chemoprophylaxis. Rheumatol Int. 2010 Jul 24 (epub ahead print).
11. Bray M, Poulin C, Dougados M, Gossec L. Frequency and tolerance of antituberculosis treatment according to national guidelines for prevention of risk of tuberculosis due to tumor necrosis factor blocker treatment. Joint Bone Spine. 2010;77:135-41.
12. Hanta I, Ozbek S, Kuleci S, Sert M, Kocabas A. Isoniazid intervention for latent tuberculosis among 86 patients with rheumatologic disease administered with anti-TNF alpha. Clin Rheumatol. 2007;26:1867-70.
13. Mor A, Bingham CO III, Kishimoto M, et al. Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated inpatients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis. 2008;67(4):462–5.
14. Gutkowski K, Chwist A, Hartleb M. Liver injury induced by high-dose methylprednisolone therapy: a case report and brief review of the literature. Hepat Mon. 2011;11:656-61.
15. Stravitz RT, Sanjay AJ. Drug induced steatohepatitis. Clin Liver Dis. 2003;7:435-51
16. Dourakis SP, SavastianosVA, Kaliopi P. Acute severe steatohepatitis related to prednisolone therapy. Am J Gastroenterol. 2002;97:1074-5.
17. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23:192-202.
18. Gülbay BE, Gürkan OU, Yıldız OA, et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med. 2006;100:1834-42.
19. Kıter G, Coşkunol İ, Alptekin S, Aydın M, Arslaniray S. Tüberküloz tedavisi alan hastalarımızda karaciğer toksisitesi araştırması: 5 yıllık retrospektif değerlendirme. Tüberküloz ve Toraks Dergisi. 2000;48:20-5.
20. Ceylan E. Bingöl Verem Savaş Dispanseri'nde tüberküloz tedavisine bağlı toksik hepatit sıklığı. Toraks Dergisi. 2005;6:132-6.
21. Yurdakul AS, Çalışır HC, Taci N, Çelik N, Öğretensoy M. Tüberküloz tedavisi sırasında gelişen hepatotoksisite. Türk Toraks Dergisi. 2003;4:16-20.
22. Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. Int J Tuberc Lung Dis. 2008;12:994-1002.
23. Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis. 2002;6:699-705.
24. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996 Oct;9(10):2026-30.
25. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax. 1996;51:132-6.
26. Dossing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis. 1996;77:335-340.
27. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother. 2004;38:1074-79.
28. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167:1472-1477.
29. Babalık A, Arda H, Bakırcı N, et al. Management of and risk factors related to hepatotoxicity during tuberculosis treatment. Tuberk Toraks. 2012;60:136-44.
30. Ateş G, Yıldız T, Akyıldız L. Tüberküloz tedavisi sırasında hepatotoksisite. Dicle Tıp Dergisi. 2008;35:1:5-9.


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