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# Enteral Anti-Tuberculosis Drugs Regimen Contributes to Mortality in Critical Patients with Smear Positive Pulmonary Tuberculosis

**Sueyanyongsiri P[1*], Sueyanyongsiri S[2] and Sumpansirikul N[3]**

[1]*Department of Internal Medicine, Surin hospital, Affiliated Institutes of Suranaree University of Technology, Thailand.*

[2]*Department of Community Nursing Group, Surin hospital, Affiliated Institutes of Suranaree University of Technology, Thailand.*

[3]*Medical student in Department of Internal Medicine, Suranaree University of Technology, Thailand.*

**[*]Correspondence:**
Sueyanyongsiri P, Department of Internal Medicine, Surin Hospital, Affiliated Institutes of Suranaree University of Technology, Thailand.

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## ABSTRACT

*In severe pulmonary tuberculosis that requiring ventilation and critical care should have uncertain enteral absorption. This study aimed to evaluate the impact of enteral anti-tuberculosis regimen used on the survival of patients with smear positive pulmonary tuberculosis requiring mechanical ventilation. Patients aged >15 years with critical smear positive pulmonary tuberculosis were divided into enteral and parenteral antituberculosis drugs regimen groups based on the type of anti-tuberculosis used. Those patients who died or discharged within 24 hours of hospitalization were excluded. The primary endpoint was 40-day survival. In 5844 patients of tuberculosis from 2013 to 2018 have 675 patients identified that smear positive pulmonary tuberculosis, 657 were in enteral drugs group and 18 were in the parenteral fluoroquinolones group, 140 patients die and 535 patients survived. The two groups had statistically significant difference in acute respiratory failure and shock. There had no statistically significant difference between two groups in mortality by univariable risk ratio regression analysis. In generally parenteral regimens are increase mortality rate, but after adjusted all variable factors by multivariable risk ratio regression analysis, there had statistically significant difference between two groups in mortality (risk ratio=1.80; 95%confidence interval=1.25 to 2.58; P=0.001). The medial survival was 8 and 34 days in enteral and parenteral groups, significant difference in log rank test (P<0.002). Enteral anti-tuberculosis regimen may contribute to survival of smear positive pulmonary tuberculosis requiring mechanical ventilator.*

## Keywords

Critical care, acute respiratory failure, Mortality, Pulmonary tuberculosis.

## Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease (including 0.3 million among people with HIV).Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis is curable and preventable. TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected. Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries [1]. The risk of active TB is also greater in persons suffering from other conditions that impair the immune system. TB occurs in every part of the world. In 2017, the largest number of new TB cases occurred in the South-East Asia and Western Pacific regions, with 62% of new cases, followed by the African region, with 25% of new cases. In 2017, 87% of new TB cases occurred in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. In Thailand, the mortality from tuberculosis remains high and exceeds 9.2% at Surin province in 2017.

Tuberculosis (TB) remains a nationwide and worldwide public health concern [1,2] and high mortality rate especially in patients who need ventilator [3]. Although treatment regimens as suggested by the World Health Organization (WHO) result in survival rates

of 95% under trial conditions [4], but in the severe patients also have high mortality rate more than 30-50% [5-8], in particularly patients who need ventilator and have acute respiratory failure. Patients admitted with multiple organ failure may have uncertain enteral absorption, hepatic and renal dysfunction. Sub therapeutic levels of anti-tuberculosis drugs have been associated with a slow clinical response, treatment failure and drug resistance [9-11]. Other recommendations, in severe pulmonary tuberculosis that need ventilation and critical care should select parenteral drugs more than enteral drugs due to probably have poor absorption, as well as in patients who have hypotension or acute kidney injury [12,13]. In fact, the recommendations are not also a consensus because these are not any big clinical trial research to support. As a consequence, in this paper will study about three associated risk factors to mortality in smear positive pulmonary tuberculosis. First is about host, second is the severity of the disease, and the last one is the route of drug regimens, parenteral or enteral drugs regimen, that patients are treated.

## Methodology

### Subjects

A five years retrospective cohort study was conducted at Surin hospital, a secondary-care referral center in Thailand. The database of diagnosis records was searched to identify TB patients from January 2013 to December 2018. The inclusion criteria were age 15 years, smear positive. The identified patients were divided into two groups. Patients who received parenteral fluoroquinolones therapy (ciprofloxacin or levofloxacin) and those who received enteral anti-tuberculosis drugs were enrolled. And the most important factor is the route of regimen that patients are treated is associated to mortality rate. Patients who die or discarded within first 24 hour it's mean they have not given drugs or drugs are not effective were be rule out. If patients admit more than one times all the administration was rule in.

### Methods

All of the general data and medical records for the enrolled patients were reviewed. Patients who had diabetes, acquired immunodeficiency syndrome (HIV disease), chronic kidney disease, cirrhosis or age more than 60 years were defined as immunocompromised host. The clinical endpoint to study is the death in hospital compare with the 40-days survival. In patients who have given drugs, subgroup analysis should be planed to evaluate. The potential factors included gender, age> 60 years, diabetes, HIV disease, chronic kidney disease, cirrhosis, acute respiratory failure, hypotension, acute kidney injury and multiple organ failure. Acute respiratory failure was defined as hypoxic failure, in arterial blood gas: $PaO_2$<60 mmHg and need mechanical ventrilator.

### Statistical analysis

The general data were compared between the group of patients who died and the group who survived during hospitalization. Fisher's exact tests were used to compare categorical variables. All of the values were expressed as percentage of the group for categorical variables. The data were compared between the group of enteral and parenteral drugs group regimen during hospitalization. The Risk ratio regression analysis was used. Significance testing by Fisher's exact test and time-to-event curves were generated by the Kaplan-Meier method and compared using the log-rank test. All factors associated with survival were further analyse with the Cox-proportional hazards regression analysis was performed to identify prognostic factors for 40-day survival after admission. Two-sided P<0.05 was considered significant. All statistical analyses were performed using STATA 14 software.

## Results

In 5844 patients of tuberculosis from 2013 to 2018 have 675 patients identified that smear positive pulmonary tuberculosis, 657 were in enteral drugs group (ED) and 18 were in the parenteral fluoroquinolones group (PD), 140 patients died and 535 patients survived.

### Demographic characteristics

Table 1 is the list of the demographic characteristics of the patients. The difference between the survivors and those that died was statistically significant in HIV disease, ARF, AKI and shock. Males outnumbered females, Male 63.6%, age more than 60 (49.2%) no difference in survivors. The details about clinical risk factor for mortality are show in table 1. Of the 93 patients who were excluded, 32 (4.3%) were died in 24 hours and 61(8.1%) were came home within 24 hours. Based on the clinical risk of dead in the ED and PD groups (Table 2), there were statistically significant difference in acute respiratory failure and shock. More patients in the PD group had acute respiratory failure than in the ED group (83.3% vs. 22.8%, P<0.001) and had shock than ED group (38.8%vs.15.7%, P=0.017).

### Factors predicting in-hospital mortality

Four factors were found to be associated with in-hospital mortality in the univariate analysis (Table 3). A trend of higher mortality rate among patients with ARF (P<0.001), AKI (P<0.001), shock (P<0.001) and HIV disease (P=0.021). There had no statistically significant difference between two drugs regimen groups in mortality by univariable risk ratio regression analysis. In generally parenteral regimens are increased mortality rate (Table 3), but after adjusted all variable factors by multivariable risk ratio regression analysis, there had statistically significant difference between two groups in mortality (risk ratio=1.80; 95%confidence interval=1.25 to 2.58; P=0.001). If treated by enteral regimens the mortality rate increase 1.80 times (Table 4).

**Table 1:** Clinical characteristics of patients in survival and death groups.

| Variable | Survival | % | Death | % | P-value |
|---|---|---|---|---|---|
| M | 337 | 63.0 | 92 | 65.7 | 0.622 |
| Age>60yrs. | 256 | 47.9 | 76 | 54.3 | 0.185 |
| HIV | 35 | 6.5 | 18 | 12.9 | 0.020 |
| DM | 74 | 13.8 | 13 | 9.3 | 0.201 |
| CKD | 40 | 7.5 | 16 | 11.4 | 0.167 |
| Cirrhosis | 10 | 1.9 | 6 | 4.3 | 0.230 |

| | | | | | |
|---|---|---|---|---|---|
| ARF | 51 | 9.5 | 114 | 81.4 | <0.001 |
| AKI | 23 | 4.3 | 28 | 20.0 | <0.001 |
| Shock | 36 | 6.7 | 74 | 52.9 | <0.001 |
| Parenteral | 12 | 2.24 | 6 | 4.29 | |
| Enteral | 523 | 97.76 | 134 | 95.71 | 0.233 |

M: Male; HIV: Human Immunodeficiency Virus Infection; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; ARF: Acute Respiratory Failure; AKI: Acute Kidney Injury; CI: Confidence Interval.
P-value by Fisher's exact test.

**Table 2:** Clinical characteristics of patients in the ED and PD groups.

| Variable | Parenteral | % | Enteral | % | P-value |
|---|---|---|---|---|---|
| Total | 18 | 100 | 657 | 100 | |
| M | 14 | 77.78 | 415 | 63.17 | 0.320 |
| Age>60yrs. | 10 | 55.56 | 322 | 49.01 | 0.638 |
| HIV | 0 | | 53 | 8.07 | 0.386 |
| DM | 2 | 11.11 | 85 | 12.94 | 0.999 |
| CKD | 1 | 5.56 | 55 | 8.37 | 0.999 |
| Cirrhosis | 0 | | 16 | 2.44 | 0.999 |
| ARF | 15 | 83.33 | 150 | 22.83 | <0.001 |
| AKI | 1 | 5.56 | 50 | 7.61 | 0.999 |
| Shock | 7 | 38.89 | 103 | 15.68 | 0.017 |

M: Male; HIV: Human Immunodeficiency Virus infection; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; ARF: Acute Respiratory Failure; AKI; Acute Kidney Injury; CI: Confidence Interval.
P-value by Fisher's exact test

**Table 3:** Univariable analysis of factors potentially associated with mortality in patients with smear positive pulmonary tuberculosis.

| Univariable | Risk ratio | Std. Err. | 95%CI | | P-value |
|---|---|---|---|---|---|
| Enteral drugs | 0.61 | 0.50 | 0.31 | 1.20 | 0.233 |
| Gender | 1.10 | 0.20 | 0.80 | 1.50 | 0.622 |
| Age>60 | 1.23 | 0.20 | 0.91 | 1.65 | 0.185 |
| HIV | 1.73 | 0.40 | 1.15 | 2.60 | 0.021 |
| DM | 0.69 | 0.21 | 0.41 | 1.17 | 0.201 |
| CKD | 1.43 | 0.30 | 0.92 | 2.22 | 0.167 |
| Cirrhosis | 1.30 | 0.82 | 0.82 | 2.06 | 0.305 |
| ARF | 13.55 | 2.26 | 9.19 | 19.98 | <0.001 |
| AKI | 3.06 | 0.58 | 2.27 | 4.13 | <0.001 |
| Shock | 5.76 | 0.76 | 4.43 | 7.48 | <0.001 |

M: Male; HIV: Human Immunodeficiency Virus infection; CKD: Chronic Kidney Disease; ARF: Acute Respiratory Failure; DM: Diabetes Mellitus; AKI; Acute Kidney Injury; CI; Confidence Interval.
P-value by risk ratio regression model.

**Table 4:** Multivariable analysis of factors potentially associated with mortality in patients with smear positive pulmonary tuberculosis by risk ratio regression model.

| Multivariable | Risk ratio | Std. Err. | 95%CI | | P-value |
|---|---|---|---|---|---|
| Enteral drugs | 1.80 | 0.33 | 1.25 | 2.58 | 0.001 |
| Gender | 0.95 | 0.06 | 0.84 | 1.08 | 0.415 |
| Age>60 | 0.99 | 0.07 | 0.86 | 1.14 | 0.908 |
| HIV | 1.15 | 0.12 | 0.94 | 1.41 | 0.179 |
| DM | 0.98 | 0.10 | 0.80 | 1.21 | 0.875 |
| CKD | 1.32 | 0.12 | 1.10 | 1.59 | 0.003 |
| Cirrhosis | 1.00 | 0.06 | 0.90 | 1.11 | 0.989 |
| ARF | 9.50 | 2.05 | 6.22 | 14.49 | <0.001 |
| AKI | 1.18 | 0.09 | 1.02 | 1.38 | 0.028 |
| Shock | 1.63 | 0.11 | 1.43 | 1.86 | <0.001 |

M: Male; HIV: Human Immunodeficiency Virus infection; CKD: Chronic Kidney Disease; ARF: Acute Respiratory Failure; DM: Diabetes Mellitus; AKI: Acute Kidney Injury; CI; confidence Interval.
P-value by risk ratio regression model.

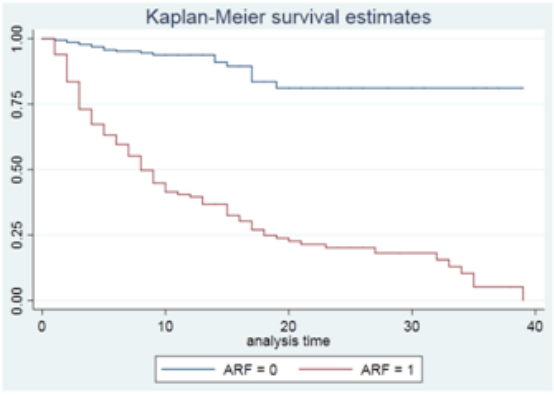
The highest mortality risk ratio is acute respiratory failure. The survival patterns of patients in acute respiratory failure and no need ventilator are shown in Figure1. The medial survival was 8 and 34 days in ED and PD group, significant in log rank test (P=0.002). By multivariable Cox's regression analysis, enteral drugs used regimen (hazards ratio=3.61; 95%confidence interval=1.45 to 9.01; P=0.006) was associated with 40 days survival (Table 5). The Kaplan-Meier survival curve of patients in acute respiratory failure between ED and PD group are shown in Figure 2.

**Table 5:** Multivariable analysis of factors potentially associated with mortality in patients with smear positive pulmonary tuberculosis requiring mechanical ventilator by Cox's regression model.

| Multivariable | Hazard ratio | Std. Err. | 95%CI | | P-value |
|---|---|---|---|---|---|
| Enteral drugs | 3.61 | 1.68 | 1.45 | 9.01 | 0.006 |
| Gender | 0.94 | 0.19 | 0.62 | 1.41 | 0.749 |
| Age>60 | 0.85 | 0.19 | 0.55 | 1.32 | 0.480 |
| HIV | 1.08 | 0.38 | 0.54 | 2.15 | 0.836 |
| DM | 1.54 | 0.54 | 0.77 | 3.05 | 0.219 |
| CKD | 0.97 | 0.32 | 0.51 | 1.84 | 0.927 |
| AKI | 1.09 | 0.28 | 0.65 | 1.82 | 0.743 |
| Cirrhosis | 0.83 | 0.17 | 0.56 | 1.24 | 0.367 |
| Shock | 1.39 | 0.27 | 0.94 | 2.04 | 0.097 |

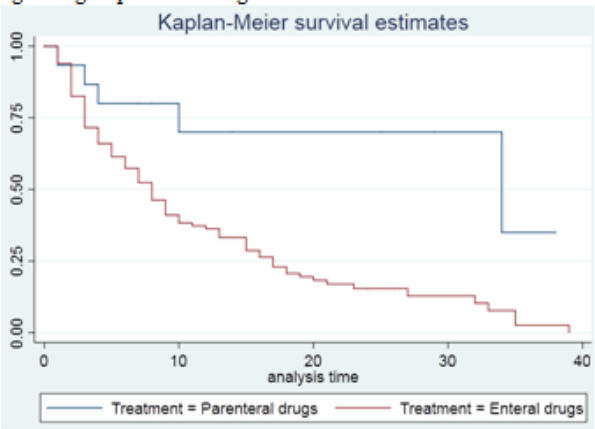
M: Male; HIV: Human Immunodeficiency Virus infection; CKD: Chronic Kidney Disease; ARF: Acute Respiratory Failure; DM: Diabetes Mellitus; AKI: Acute Kidney Injury; CI: Confidence Interval.
P-value by risk ratio regression model.

Figure1. Survival curves by the Kaplan-Meier method 40 day survival curves for patients in ARF and no ARF groups.




ARF: acute respiratory failure; 0: no acute respiratory failure; 1: with acute respiratory failure

Figure2. Kaplan-Meier 40 day survival curves for acute respiratory failure patients in enteral and parenteral drugs regimen groups and the log-rank test.




## Discussion of the Findings

Mycobacterial tuberculosis one of the leading cause of death associated with acute respiratory failure, shock and multiple organ failure. The mortality of tuberculosis associated critical illness remain high, 30-50%. In the present study, 69.1% (114 from 165) were not survived from acute respiratory failure. The finding of a high mortality is higher than previous study. Before adjusting for potential confounding effects, four factors contributing to in-hospital mortality were identified, acute respiratory failure, acute kidney injury, shock and HIV disease. In univariable regression study, patients infected with human immunodeficiency virus (HIV) have statistically significant difference in mortality (risk ratio=1.73; 95%confidence interval=1.15 to 2.60; P=0.021).

After adjusting confounding effects, three factors contributing to in-hospital mortality were identified, acute respiratory failure, shock and treatment regimens. In generally parenteral regimens are increase mortality rate, but in acute respiratory failure if treat by enteral regimens the mortality rate increase 1.80 times. However, fluoroquinolones is nephrotoxic drugs, only one critically case used under hemodialysis. Though HIV infection was not an exclusion criterion in this study, none of the parenteral regimen patients were HIV-positive. HIV patients, 18 from 53 (12.9%) were dead, which is not enough for HIV to become a significant causal factor of mortality.

WHO recommends an intensive treatment regimen (isoniazid+ rifampicin+ethambutal+pyrazinamide) for 2 months followed by a continuation regimen (isoniazid+rifampicin) for 4-7 months. Fluoroquinolones have excellent *in vitro* and *in vivo* bactericidal activity against Mycobacterial tuberculosis [14-16]. Empirical use of fluoroquinolones has raised delays in the initiation of appropriate anti-tuberculosis drugs, an increase in drug resistance [17-20]. Some other studies do not corroborate these findings [21-23]. This is a retrospective cohort study, most of physicians follow WHO recommendation. But in severe cases, some physicians add parenteral fluoroquinolones. In enteral drugs group, the 8 days mortality rate was 50%, with nearly all deaths occurring within the first 2 weeks of hospital admission. In contrast parenteral group, the 34 days mortality rate in the study was 50%, which is to become a significant causal factor of difference in mortality.

Acute respiratory failure was a strong independent factor contributing to in-hospital death. These findings were similar to other studies discussing predictors of in-hospital death or shortterm prognosis for patients with pulmonary tuberculosis. By multivariable Cox's regression analysis, enteral drugs used regimen (hazards ratio=3.61; 95% confidence interval=1.45 to 9.01; P=0.006) was associated with 40 days survival. It is possible that physicians were prone to favour the parenteral regimens, particularly for patients with immunodeficiency, old ages and multiple organ failure. Another possible reason was that those patients may have uncertain enteral absorption, hepatic and renal dysfunction. Low absorption had been associated with a slow clinical response, treatment failure and drug resistance, and death was a consequence of sub therapeutic levels of anti-tuberculosis drugs. In the present study, patients with ARF had higher mortality rates than those without. The finding was similar to other studies examining critically ill patients with active pulmonary TB and acute respiratory failure. The higher number of organ failures reflects the propensity of uncontrolled, untreated infection to cause multiple organ dysfunction. However, there are few parenteral drugs for Mycobacterial tuberculosis. Fluoroquinolones can improve the survival of smear positive pulmonary tuberculosis requiring mechanical ventrilator. If patients have hepatic and renal dysfunction, it's very difficult for the physician to use medicine. Recommendations for special condition should be review to improve the survivors.

This study has several limitations. For example, timely treatment was not collected data that are important missing data. The decision of choosing drugs regimen therapy in one important fact of physician adjustment. Small sample in parenteral group remain low power of sample size (0.30). In acute respiratory failure subgroup, 3 were excluded in parenteral group. However, there is enough sample size (0.87) to explain the effect.

## Conclusion

In pulmonary tuberculosis requiring mechanical ventilator have high mortality rate same as other studies. HIV disease is one of affect to increase mortality rate, but acute respiratory failure is the most impact of mortality. According to tuberculosis guidelines if treated by parenteral regimens have more mortality rate than enteral regimens. But in critically ill patients, enteral anti-tuberculosis regimen may contribute to survival of smear positive pulmonary tuberculosis requiring mechanical ventilator.

## Recommendation

In practice is to prefer parenteral drugs regimen in smear positive pulmonary tuberculosis requiring mechanical ventrilator during 8-14 days of admission.

## References

1. http://www.who.int/tb/publications/global_report/en/
2. http://www.searo.who.int/tb/documents/annual_tb_

repot_2017/en/
3. Otu A, Hashmi M, Mukhtar AM, et al. The critically ill patient with tuberculosis in intensive care: clinical presentations, management and infection control. J Crit Care. 2018; 45: 184-196.
4. Zumla A, Raviglione M, Hafner R, et al. Tuberculosis. N Engl J Med. 2013; 368: 745-755.
5. Alavi-Naini R, Moghtaderi A, Metanat M, et al. Factors associated with mortality in tuberculosis patients. J Res Med Sci. 2013; 18: 52-55.
6. Kim CW, Kim S-H, Lee SN, et al. Risk factors related with mortality in patient with pulmonary tuberculosis. Tuberculosis and Respiratory Diseases. 2012; 73: 38-47.
7. Sun J, Fang K, Ren DH, et al. A study of the prognostic factors associated with mortality in critically ill patients with tuberculous. ZhonghuaJie He He Hu Xi ZaZhi. 2011; 34: 39-42.
8. Lee PL, Jerng JS, Chang YL, et al. Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation. EurRespir J. 2003; 22: 141-147.
9. Koegelenberg CF, Nortje A, Lalla U, et al. The pharmacokinetics of enteral anti-TB drugs in patients requiring intensive care. S Afr Med J. 2013; 103: 394-398.
10. Kimberling ME, Phillips P, Patterson P, et al. Low serum antimycobacterial drug levels in non-HIV-infected tuberculosis patients. Chest. 1998; 113: 1178-1183.
11. Thompson JS. The intestinal response to critical illness. Am J Gastroenterol. 1995; 90: 190-200.
12. Kethireddy S, Light RB, Mirzanejad Y, et al. Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Group. Mycobacterium tuberculosis septic shock. Chest. 2013; 144: 474-482.
13. Mer M, Lipman. Antibiotic administration in the critically ill—in need of intensive care! S Afr Med J. 2015; 105: 357-359.
14. Cremades R, Rodriquez JC, Garcia-Pachón E, et al. Comparison of the bactericidal activity of various fluoroquinolones against Mycobacterium tuberculosis in an in vitro experimental model. J Antimicrob Chemother. 2011; 66: 2281-2283.
15. Yew WW, Chan CK, Chau CH, et al. Outcome of patients with multi-drug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000; 117: 744-751.
16. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev. 2008; 1: CD004795.
17. Dooley KE, Golub J, Goes FS, et al. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. Clin Infect Dis. 2002; 34: 1607-1612.
18. Wang JY, Hsueh PR, Jan IS, et al. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. Thorax. 2006; 61: 903-908.
19. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis: the effect of duration and timing of fluoroquinolone exposure. Am J Respir Crit Care Med. 2009; 180: 365-370.
20. Long R, Chong H, Hoeppner V, et al. Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis. Clin Infect Dis. 2009; 48: 1354-1360.
21. Golub JE, Bur S, Cronin WA, et al. Impact of empiric antibiotics and chest radiograph on delays in the diagnosis of tuberculosis. Int J Tuberc Lung Dis. 2005; 9: 392-397.
22. Yoon YS, Lee HJ, Yoon HI, et al. Impact of fluoroquinolones on the diagnosis of pulmonary tuberculosis initially treated as bacterial pneumonia. Int J Tuberc Lung Dis. 2005; 9: 1215-1219.
23. van den Boogaard J, Semvua HH, van Ingen J, et al. Low rate of fluoroquinolone resistance in Mycobacterium tuberculosis isolates from northern Tanzania. J Antimicrob Chemother. 2011; 66: 1810-1814.
24. Park IN, Hong SB, Oh YM, et al. Impact of short-term exposure to fluoroquinolones on ofloxacin resistance in HIV-negative patients with tuberculosis. Int J Tuberc Lung Dis. 2007; 11: 319-324.
25. Wang JY, Lee LN, Lai HC, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis isolates: associated genetic mutations and relationship to antimicrobial exposure. J Antimicrob Chemother. 2007; 59: 860-865.
26. Tseng YT, Chuang YC, Shu CC, et al. Empirical use of fluoroquinolones improves the survival of critically ill patients with tuberculosis mimicking severe pneumonia. Crit Care. 2012; 16: R207.
27. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomized controlled trial. Lancet Infect Dis. 2017; 17: 39-49.
28. Choi R, Jeong BH, Koh WJ, et al. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. Ann Lab Med. 2017; 37: 97-107.