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Research Article

Parenteral use of Fluoroquinolones Improves the Survival Outcome in Critical Non-HIV, Smear Positive Pulmonary Tuberculosis in Surin Hospital, Thailand: Propensity Score Matching Analysis

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Abstract

Introduction: Pulmonary tuberculosis (TB) is a severe disease spreading all over the world, with high mortality, particularly in patients who require ventilators. According to the World Health Organization (WHO), TB patients are suggested to be treated by concentrated drugs for 2 months and the other 4 months continuously because it can increase high rate of recovery from TB. However, high mortality is still found in patients with severe TB. For this reason, there are several suggestions that TB patients with high severity should receive parenteral drugs due to uncertain absorption of drugs, particularly TB drugs, in critical patients. Therefore, this research aimed to study the factors of enteral regimen and parenteral regimen on the difference in the risk of death.

Methodology: This is an observational study with the control group. The data of the patients with smear positive TB from 2013 to 2020 was collected. For the analysis of the new inpatients of this group in Surin Hospital, death was found. The 2 groups of the patients were compared by enteral regimen and parenteral regimen. Sixty day survival was evaluated. The data analysis included sex, age 70 years or over, underlying disease, and severity. The analysis was divided into 2 parts, before and after p-score matching. T-test was used for continuous numbers while Fisher's exact test and std. difference was used for clustered data. The statistic used to measure the difference in death was relative risk and hazard ratio, with 95% confidence interval. Cox regression analysis was used for statistical test.

Results: It was found that among all patients diagnosed from 2013 to 2020, 639 were with smear positive pulmonary TB. And when testing the receipt of regimens, it was found that the risk of death in the enteral regimen group increased (Risk ratio 0.817 times (95% confidence interval 0.50 - 1.33), p-value = 0.431; and with the risk of death (Hazard ratio = 1.44 times (95% confidence interval 0.78 - 2.65), p-value = 0.239 or 1.50times (95% confidence interval 0.83 - 2.71), stpm2 at degree of freedom = 3. No difference was found when comparing with the parenteral regimen group. However, when analyzing by matching patients with similar severity, 32 patients were obtained per group. And when testing the receipt of regimens, the risk was found in the enteral regimen group (Risk ratio 2.67 times (95% confidence interval 1.48 - 4.80), p-value < 0.001; and with the risk of death (Hazard ratio = 5.17 times (95% confidence interval 2.32 - 11.50), p-value < 0.001or 6.54 times (95% confidence interval 2.82 - 15.19). When comparing with the parenteral regimen group.

Conclusion: It can be concluded that parenteral regimen could help reduce 60day mortality in TB patients with high severity.

Keywords: *Pulmonary Tuberculosis; Anti-Tuberculosis Drug; Critical Care*

Introduction

Pulmonary tuberculosis (TB) has still been a public health problem at the national and international level despite the latest discovery of less new patients [1]. According to the World Health Organization (WHO), TB patients are suggested to be treated by concentrated drugs for 2 months and the other 4 months continuously because it can increase high rate of recovery from TB [2]. However, patients with high severity are found with the problem of enteral feeding. Patients with critical illness basically absorb drugs or even food less than usual, along with less ability of the digestive system [3-6]. Therefore, the basic principle for patients in ICU or with critical illness is that they should better receive parenteral regimen. According to literature review, it was found that therapeutic drug monitoring (TDM) in TB patients and with critical illness was conducted, and drugs were required for those in ICU. TDM of TB was found lower than the level of disinfection, particularly the key drug like rifampicin. Lower TDM affected clinical treatment in the sense that these patients had higher severity of TB [5], with worse symptoms. However, this test was conducted in a small number of patients due to the complex experiment.

However, mortality in TB patients is still high, particularly in older adult, with high severity. Mortalityin aging TB patients with severity, shock, and respiratory failure is usually very high in several countries, from 30% to 50% [7-12]. According to data collection from the patients in Surin hospital (2007 - 2017), mortality in those with high severity was 79%, which was very high in Surin hospital and higher than other countries. Mortality in Taiwan was 30% and 60% in Canada for intubated TB patients. Another key factor of their death is underlying disease, with the use of immunosuppressive. High mortality also occurs in young patients with weak immune system or immunodeficiency.

Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation remains high. Therefore, there are several suggestions that TB patients with high severity and in need of ventilators as well as care should receive parenteral regimen. That is because drug absorption, particularly TB drugs, in critical patients is not certain and may be lower than it should be. However, neither clear studies nor experiments have been conducted yet in TB patients requiring ventilators. Therefore, those suggestions are at the bottom level (Expert opinion).

Trials of TB drugs in critical patients have still been rarely found due to the number of patients or problems of regimens under a principle that various types of drugs are required to prevent drug resistance. That is because such resistance in TB drug resistance has become more severe. Therefore, it must be careful for the use of drugs. Practical drugs for parenteral use are fluoroquinolones [13-15]. Each physician has different ways of use. To clarify, some chooses enteral regimen (4 types of concentrated drugs) as they may think that it is sufficient; and may prefer to keep drugs in case of drug resistance. Some choose parenteral regimen to increase the chance of survival for their patients. Therefore, this research aimed to study the factors of enteral regimens and parenteral regimen on the difference in the risk of death in pulmonary TB patients.

Methodology

This is an observational study, with the control group. The data of patients with smear positive TB from 2013 to 2020 was collected. The researcher requested for the approval from the research ethic committee for data collection without access to personal data of the patients at all. For the analysis of the new inpatients with smear positive TB in Surin Hospital, death was found. The 2 groups of the patients were compared by enteral regimen and parenteral regimen. To evaluate the receipt of regimens, the patients under the exclusion criteria were those aged below 15 years, those died before diagnosis and treatment, and those died in the first 24 hours (Patients had died before they received drugs or before drug activation). Data of the inpatients at the hospital more once would be collected only at their first admission. Survival under critical phase was evaluated. Data analysis included general data, i.e., sex, age 70 years or over, underlying disease (diabetes, cirrhosis, and chronic renal failure at Phase 3 and over); severity, with or without respiratory failure (PaO2 < 60 mmHg or fingertip pulse < 90%, with ventilators); hypotension (Median of blood pressure < 65 mmHg all causes); acute renal failure (Increasing renal function during admission >1.0 ml/second); 60day death, another key factor. Data analysis was divided into 2 parts. Part 1 was general data analysis, with the comparison of the difference between both groups. T-test was used for continuous numbers while Fisher's

exact test and std. difference was used for clustered data, both before and after matching. The statistic used to measure the difference in death was relative risk and hazard ratio, with 95% confidence interval. Cox regression analysis was used for statistical test. Part 2 was p-score matching of both groups, with similar risk factors and severity at 1:1 ratio, i.e., sex, age, underlying disease, and severity (p-score matching analysis). Then, the data was analyzed and compared again. The indicator was death, with duration. It was planned that if Cox regression analysis failed for evaluation, further analysis would be based on stpm 2 at degree of freedom = 3 to predict death of each individual patient. The sample size was calculated by previous studies using the proportion of death in each group. Huge difference in death brought 18 patients per group, the expected sample size. However, matching of the sample size caused some lost samples due to randomization. Therefore, the samples were collected twofold just in case. After matching, power of sample size was calculated, from which 80% must be obtained. In case of no follow-up, the researcher would follow up from their patents to find out whether or not the patients were still alive. Available patents implied survival of the patients.

Results

For all patients diagnosed with TB from 2013 to 2020 in Surin, a provincial center hospital, 7314 times, there were 872 patients with smear positive pulmonary TB. The patients were admitted 1 - 5 times. Most of their second admission was caused bydrug allergy, totally 111 times (= 759 patients). According to the exclusion criteria, 5 patients aged below 15 years were excluded, along with 12 patients who had died before they were diagnosed and treated TB, and 52 patients died in 24 hours, totally 67 patients (8.8%) under exclusion; also, 53 patients (7.0%) with immunodeficiency or HIV disease, totally 15.8% of these patients were excluded. 639 patients were under the inclusion criteria. 601 of them received enteral regimen while 38 received parenteral regimen (Figure 1).

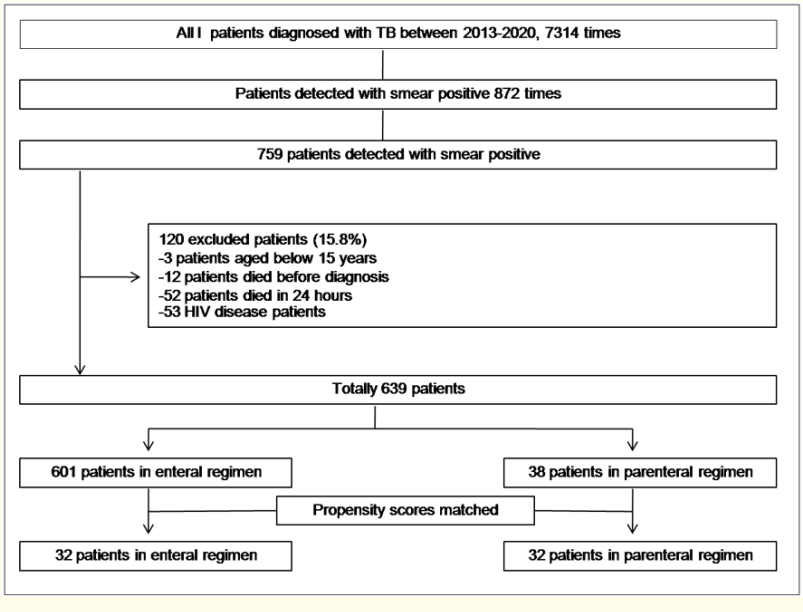

Figure 1: *Flow chart of patients through study.*

179 patients required ventilators. The youngest was 20 years old while the oldest was 93 years old. Totally 123 of them (68.72%) died while 56 (31.28%) survived. According to general data of the patients, male patients and those aged 70 years and over were found with very high severity of the disease. The factors affecting death were respiratory failure, hypotension, and chronic renal failure that increased the risk of death. The factors that did not affect their death were the underlying diseases, i.e., diabetes, cirrhosis, and acute renal failure. The details of all factors affecting their death are in table 1.

	Baseline				Propensity scores matched baseline			
Characteristics	**Parenteral regimen**	**Enteral regimen**	**P-value**	**Std. diff**	**Parenteral regimen**	**Enteral regimen**	**P-value**	**Std. diff**
Mean(SD) age	63.2(17.0)	60.2(15.8)	0.259	0.183	61.8(17.8)	64.1(16)	0.589	-0.136
Men	23(60.5)	380(63.2)	0.732	-0.055	21(65.6)	19(59.4)	0.797	0.127
Age>70yrs.	15(39.5)	174(29.1)	0.200	0.218	11(34.4)	14(43.8)	0.609	-0.190
DM	6(15.8)	83(15.0)	0.817	0.023	6(18.8)	6(18.8)	1.000	0.000
CKD	9(24.0)	3(0.5)	<0.001	0.749	3(0.1)	3(0.1)	1.000	0.000
Cirrhosis	2(5.3)	17(3.1)	0.347	0.109	2(0.6)	1(0.3)	1.000	0.146
ARF	36(94.7)	115(20.7)	<0.001	2.253	3(0.1)	3(0.1)	1.000	0.000
AKI	6(15.8)	58(9.7)	0.258	0.183	30(93.8)	30(93.8)	1.000	0.000
Shock	16(42.1)	83(15.0)	<0.001	0.625	14(43.8)	16(0.5)	0.802	-0.124
Mean(SD) Apache II score	18.5(7.37)	20.6(4.62)	0.539	0.342	20.6(4.6)	24(4.2)	0.412	0.126
Dead	12(31.6)	155(25.8)	0.448	0.128	9(28.1)	24(0.75)	<0.001	-1.045
M: male; DM: diabetes mellitus								
CKD: chronic kidney disease; ARF: acute respiratory failure								
AKI; acute kidney injury								
P-value by Fisher's exact test, t-test and Std. difference								

Table 1: *Baseline characteristics and propensity score matched baseline characteristics at inclusion. Values are numbers (percentages).*

Patient distribution by the severity before matching is in figure 2. And when testing the receipt of regimens, the risk was found in the enteral regimen group (Risk ratio 0.817 times (95% confidence interval 0.50 - 1.33), p-value = 0.431; and with the risk of death (Hazard ratio = 1.44 times (95% confidence interval 0.78 - 2.65), p-value = 0.239 or 1.50 times (95% confidence interval 0.83 - 2.71), stpm2 at degree of freedom = 3. No difference was found when comparing with the parenteral regimen group. The graph of survival rate is in figure 3.

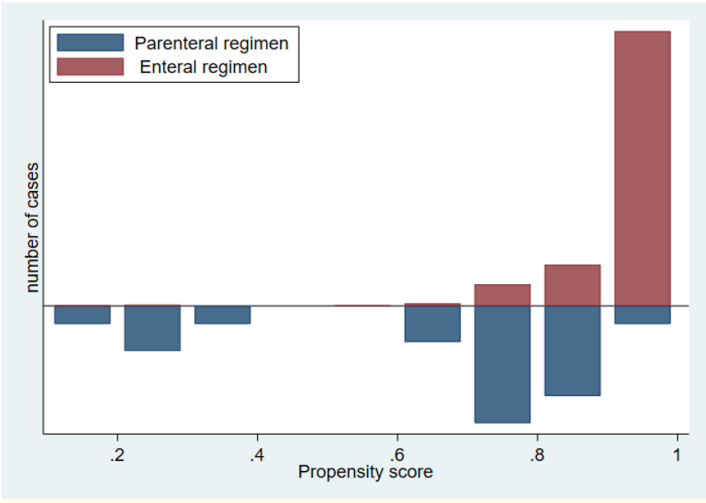

Figure 2: *Propensity score plot of the enteral regimen and parenteral regimen groups before p-score matching.*

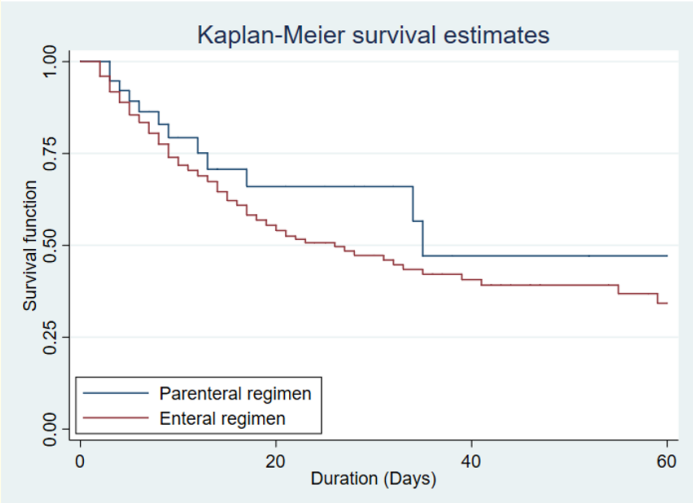

Figure 3: *Survival curves by the Kaplan-Meier method 60day survival curves of the enteral regimen and parenteral regimen groups before p-score matching.*

However, when analyzing by matching patients with similar severity, patient distribution by severity after matching is in figure 4. After matching by 1:1 ratio, 32 patients were obtained per group. And when testing the receipt of regimens, the risk was found in the enteral regimen group (Risk ratio 2.67 times (95% confidence interval 1.48 - 4.80), p-value < 0.001; and with the risk of death (Hazard ratio = 5.17 times (95% confidence interval 2.32 - 11.50), p-value < 0.001or 6.54 times (95% confidence interval 2.82 - 15.19). The graph of survival rate is in figure 5. Stpm2 at degree of freedom = 3. It was different when comparing with the parenteral regimen group. The graph of survival rate is in figure 6. Power of sample size = 97.94%.

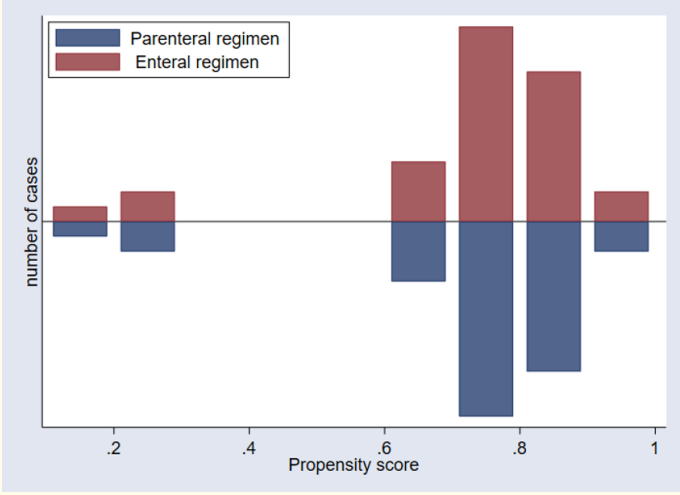

Figure 4: *Propensity score plot of the enteral regimen and parenteral regimen groups after p-score matching.*

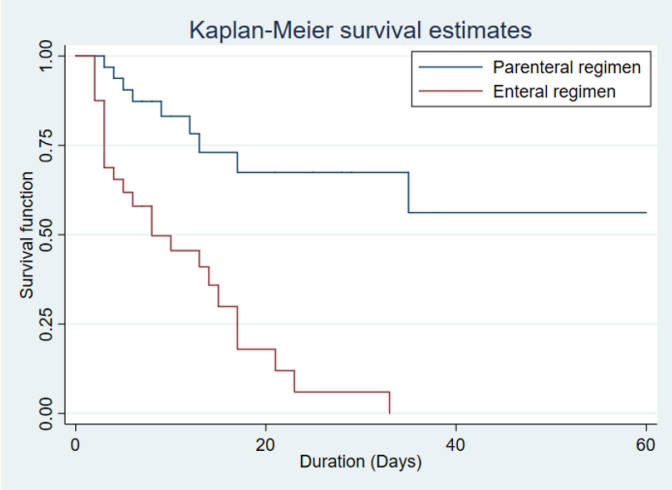

Figure 5: *Survival curves by the Kaplan-Meier method 60day survival curves of the enteral regimen and parenteral regimen groups after p-score matching analysis.*

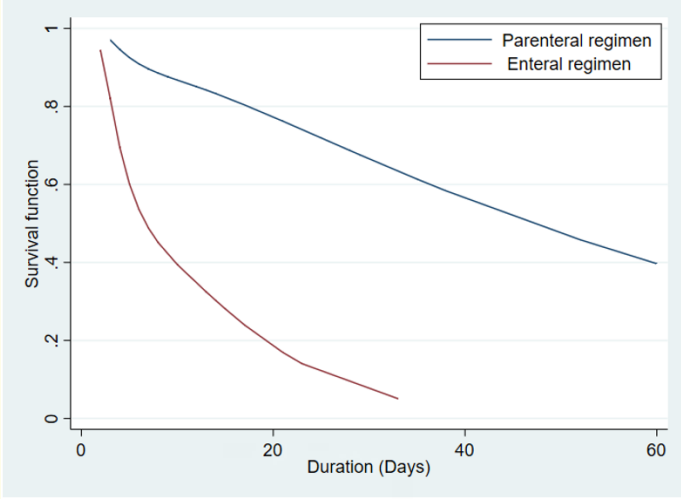

Figure 6: *Predicted survival curves by the Kaplan-Meier method 60day survival curves of the enteral regimen and parenteral regimen groups after p-score matching analysis.*

It was also found that the risk of death in the enteral regimen group was higher than the parenteral regimen group.

Discussion

It started from the observation of only 1 patient diagnosed with pneumonitis caused by a bacterium, with respiratory failure and a ventilator required. But because the patient was allergic to penicillin, ciprofloxacin was provided instead as a parenteral regimen. The

patient got better after the receipt of this single drug. However, the patient was diagnosed with smear positive pulmonary at that time. Because of his better symptoms, the same drug was provided without any change. Until no ventilator was required, 4 types of concentrated TB drugs were provided instead on the day the patient could eat. This was the researcher's first patient who survived from pulmonary TB with the ventilator required. And it was the starting point for long-term data collection. Parenteral regimen was usually a choice for critical patients. The oldest surviving patient was 93 years old. However, expert opinion was a suggestion at the bottom level. Patients can accidentally get better. For example, this patient might have good immune system or was under an initial phase of the disease, with the small amount of the bacterium or the one with high susceptibility of the drug. Therefore, according to the routine of physicians on daily patient care, routine-based research plans must be prepared. More various and larger number of patients must be collected before making more valuable conclusions.

For research on TB, Thailand can collect data from a large number of patients, particularly in Surin Province, because there a lot of TB patients all through the year. It is also one of the provinces with high mortality of TB patients when comparing with related international research papers that contain only a small number of patients. According to literature review, it was found that the factors of enteral regimen absorption are necessary but still contained only a small number of patients. Today, TB is still a key problematic infectious disease although it can be treated by regimens, dosage, and proper durations. Because this is an observational study, no exact type of drugs was specified for physicians. Some may choose parenteral regimen in patients with high severity while some may want to keep levofloxacin just in case of drug resistance. Because according to the review, it was found that the effects of drug resistance were different. Some research stated drug resistance was increased [16-20] while some pointed that it did not affect drug resistance [21-24]. Some physicians may feel comfortable to be able to diagnose and provide drugs in compliance with the standards. Adding more drugs can affect the risk of side effects or patients with renal failure or hepatitis. It can also cause more difficult drug management. These may finally result in high mortality. Countries with high mortality of TB may need more options for drug management, and may want to develop various capabilities of drugs [25-27]. Another limitation is that a number of patients receiving parenteral regimen are still small. Therefore, the results may not be reliable that much. Larger number of patients may be required for future research. One more limitation is about a day of starting the drugs/regimens. To clarify, it was found that some patients had died before they were diagnosed. Therefore, they did not receive any treatment. This research did not analyze the receipt of drugs, i.e., the date of receipt during admission, because it was all up to smear testing. Speed of drug receipt should affect survival ratel. Also, speed of diagnosis should affect efficient treatment as well.

For general data, it was found that the patients with high severity and with high mortality were male and older adults. Therefore, the data of this part can be useful for screening old patients as the main group. TB was rarely found in patients with diabetes, HIV, renal failure, or cirrhosis, possibly because these patients were regularly screened. Therefore, initial stage could be found. For the analysis results, no difference in death was found in both groups of the patients. However, patient distribution was totally different, implying that physicians still chose enteral regimen for general TB patients, but parenteral regimen for only those with high severity. Therefore, data analysis for evaluation must rely on statistical methods to adjust the similarity of severity between the two groups, like an experiment, for clearer treatment outcomes. Besides, due to huge different treatment outcomes, large number of the samples was not required. All patients in the research could be followed up, i.e., 32 patients per group, totally 64; 33 died while 31 survived. The 60day follow-up was completed, no missing. Observation of drug resistance should be continued, particularly the enteral regimen group.

Conclusion

When TB patients presented with high severity received parenteral regimen, 60day mortality would be reduced.

Conflict of Interest

An author declared there is no conflict of interest.

Bibliography

1. World Health Organization. Global tuberculosis report (2019).
2. Zumla A., *et al*. "Tuberculosis". *The New England Journal of Medicine* 368 (2013): 745-755.
3. Thompson JS. "The intestinal response to critical illness". *The American Journal of Gastroenterology* 90 (1995): 190-200.
4. Koegelenberg CF., *et al*. "The pharmacokinetics of enteral anti-TB drugs in patients requiring intensive care". *South African Medical Journal* 103 (2013): 394-398.
5. Kimberling ME., *et al*. "Low serum antimycobacterial drug levels in non-HIV-infected tuberculosis patients". *Chest* 113 (1998): 1178-1183.
6. Mer M Lipman. "Antibiotic administration in the critically ill-in need of intensive care!" *South African Medical Journal* 105 (2015): 357-359.
7. Alavi-Naini R., *et al*. "Factors associated with mortality in tuberculosis patients". *Journal of Research in Medical Sciences* 18.1 (2013): 52-55.
8. Sun J., *et al*. "A study of the prognostic factors associated with mortality in critically ill patients with tuberculous". *ZhonghuaJie He He Hu Xi ZaZhi* 34.1 (2011): 39-42.
9. Lee PL., *et al*. "Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation". *European Respiratory Journal* 22.1 (2003): 141-147.
10. Kim CW., *et al*. "Risk factors related with mortality in patient with pulmonary tuberculosis". *Tuberculosis and Respiratory Diseases* 73.1 (2012): 38-47.
11. Kethireddy S., *et al*. "Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Group (2013) Mycobacterium tuberculosis septic shock". *Chest* 144 (2013): 474-482.
12. Otu A., *et al*. "The critically ill patient with tuberculosis in intensive care: clinical presentations, management and infection control". *Journal of Critical Care* 45 (2018): 184-200.
13. Cremades R., *et al*. "Comparison of the bactericidal activity of various fluoroquinolones against Mycobacterium tuberculosis in an in vitro experimental model". *Journal of Antimicrobial Chemotherapy* 66 (2011): 2281-2283.
14. Yew WW., *et al*. "Outcome of patients with multi-drug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens". *Chest* 117 (2000): 744-751.
15. Ziganshina LE and Squire SB. "Fluoroquinolones for treating tuberculosis". *Cochrane Database of Systematic Reviews* 1 (2008): CD004795.
16. Dooley KE., *et al*. "Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis". *Clinical Infectious Diseases* 34 (2002): 1607-1112.
17. Wang JY., *et al*. "Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas". *Thorax* 61 (2006): 903-908.

18. Devasia RA., *et al*. "Fluoroquinolone resistance in Mycobacterium tuberculosis: the effect of duration and timing of fluoroquinolone exposure". *American Journal of Respiratory and Critical Care Medicine* 180 (2009): 365-370.

19. Long R., *et al*. "Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis". *Clinical Infectious Diseases* 48 (2009): 1354-1360.

20. Golub JE., *et al*. "Impact of empiric antibiotics and chest radiograph on delays in the diagnosis of tuberculosis". *The International Journal of Tuberculosis and Lung Disease* 9 (2005): 392-397.

21. Yoon YS., *et al*. "Impact of fluoroquinolones on the diagnosis of pulmonary tuberculosis initially treated as bacterial pneumonia". *The International Journal of Tuberculosis and Lung Disease* 9 (2005): 1215-1219.

22. Van den Boogaard J., *et al*. "Low rate of fluoroquinolone resistance in Mycobacterium tuberculosis isolates from northern Tanzania". *Journal of Antimicrobial Chemotherapy* 66 (2011): 1810-1814.

23. Park IN., *et al*. "Impact of short-term exposure to fluoroquinolones on ofloxacin resistance in HIV-negative patients with tuberculosis". *The International Journal of Tuberculosis and Lung Disease* 11 (2007): 319-324.

24. Wang JY., *et al*. "Fluoroquinolone resistance in Mycobacterium tuberculosis isolates: associated genetic mutations and relationship to antimicrobial exposure". *Journal of Antimicrobial Chemotherapy* 59 (2007): 860-865.

25. Tseng YT., *et al*. "Empirical use of fluoroquinolones improves the survival of critically ill patients with tuberculosis mimicking severe pneumonia". *Critical Care* 16 (2012): R207.

26. Boeree MJ., *et al*. "High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomized controlled trial". *The Lancet Infectious Diseases* 17 (2017): 39-49.

27. Choi R., *et al*. "Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations". *Annals of Laboratory Medicine* 37 (2017): 97-107.

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