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Impact of fluoroquinolone treatment on delay of tuberculosis diagnosis: A systematic review and meta-analysis

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ABSTRACT

Background: Fluoroquinolones are among the most commonly used antibiotics for the treatment of respiratory infections. Because fluoroquinolones show bactericidal activity against *Mycobacterium tuberculosis*, there is concern that their use can delay the diagnosis of tuberculosis. We conducted a systematic review and meta-analysis to assess whether empiric treatment with fluoroquinolones delays the diagnosis and treatment of tuberculosis in patients with respiratory tract infections.

Objectives: The primary objective was to assess the delay in days in the diagnosis and treatment of tuberculosis, among patients who received quinolones, compared to those who received non-fluoroquinolone antibiotics.

Methods: We included studies of adult patients treated with fluoroquinolones prior to a confirmed diagnosis of tuberculosis. We performed a literature search of 7 databases (including PubMed, Embase and Cochrane Library) with no language restrictions. We calculated an unweighted mean of estimate of difference in delay across all studies. For the studies for which the estimate was available as a mean with standard deviation, a weighted average using a random effects meta-analysis model was estimated.

Results: A total of 3983 citations were identified from the literature search; of these, 17 articles were selected for full-text review. A total of 10 studies were retained for the synthesis. These included 7 retrospective cohort studies and 3 case-control studies. Only one of these studies was from a high TB burden country, South Africa. The most commonly used fluoroquinolones were levofloxacin, gemifloxacin and moxifloxacin. The unweighted average of difference in delay between the fluoroquinolone group and non-fluoroquinolone group was 12.9 days (95% CI 6.1–19.7). When these differences were pooled using a random effects model, the weighted estimate was 10.9 days (95% CI 4.2–17.6). When stratified by acid-fast smear status, the delay was consistently greater in the smear-negative group.

Conclusion: Although results are variable, the use of fluoroquinolones in patients with respiratory infections seems to delay the diagnosis of TB by nearly two weeks. Consistent with the International Standards for TB Care, their use should be avoided when tuberculosis is suspected.

1. Introduction

Fluoroquinolones are among the most widely used antibiotics [1] and they are commonly used for the treatment of respiratory tract infections. Because fluoroquinolones show bactericidal activity against Mycobacterium tuberculosis complex, there is concern that their use can delay the diagnosis of tuberculosis. The literature on this topic has yielded variable results regarding this association. The International Standards for TB Care recommend against the use of fluoroquinolones in adults with suspected tuberculosis [2]; however, these recommendations may not be followed consistently, as shown in recent simulated patient studies from India [3,4]. Moreover, both the IDSA/ATS as well as the European guidelines for the treatment of community-acquired pneumonia include respiratory fluoroquinolones (moxifloxacin, gemifloxacin or levofloxacin) as a first-line treatment option for patient with co-morbidities [5, 6]. A previous meta-analysis on the topic was published in 2011 [7];

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Table 1
Study quality assessment of the ten studies included in the systematic review.

Main author, publication year (reference)	Patient sampling			Definition of delay*			Definition of confirmation of TB diagnosis		Dealing with confounding	
	Consecutive or random (low risk of bias)	Not consecutive or random (high risk of bias)	Not described (no description)	Clearly stated delay definition (low risk of bias)	Stated but delay definition unclear (high risk of bias)	No definition (no description)	Clearly stated method of Dx of TB (low risk of bias)	No definition (no description)	Potential confounders identified and adjusted for (low risk of bias)	Potential confounders not identified, or identified but not adjusted for (high risk of bias)
Rush 2016 [11]	All cases included			Clearly stated			Culture or PCR			Confounders identified but not adjusted for
Wang 2015 [12]	All cases included			Clearly stated				50–60% by culture or NAAT; rest by ICD code		Confounders identified but not adjusted for
Kim 2013 [13]			Not described	Clearly stated			Culture			Confounders identified but not adjusted for
Wang 2011 [14]	All cases included			Clearly stated			Culture			Confounders identified but not adjusted for
Jeon 2011 [15]			Not described	Clearly stated			Culture			Confounders identified but not adjusted for
Wang 2006 [16]	All cases included			Clearly stated			Culture		Yes, adjusted for smear status	
Sierros 2006 [17]	All cases included; some cases later excluded re: availability of medical records or results			Clearly stated			Culture		Yes, adjusted for smear status	
Golub 2005 [18]			All cases eligible but sampling strategy not described	Clearly stated			Culture			Confounders identified but not adjusted for
Yoon 2005 [19]			Not described	Clearly stated			Culture			Confounders identified but not adjusted for
Dooley 2002 [20]	All cases included			Clearly stated			Culture		Yes, adjusted for smear status	

* The definition of delay varied between the studies: time of sputum collection to initiation of anti-TB medications: 2 studies; presentation to initiation of anti-TB medications: 5 studies; time of initiation of antibiotics to initiation of anti-TB medications: 2 studies; time of sputum collection to culture growth: 1 study

since then, new studies have been published, warranting an updated systematic review.

2. Methods

We conducted a systematic review and meta-analysis to assess whether empiric treatment with fluoroquinolones delays the diagnosis and treatment of tuberculosis in patients with lower respiratory tract infections.

The primary objective was to assess the delay in days in the diagnosis and treatment of tuberculosis, among patients who received fluoroquinolones, compared to those who were treated with non-fluoroquinolone antibiotics. We aimed to limit selection bias by restricting the comparison to patients who had received non-fluoroquinolone antibiotics only instead of patients who had not received any antibiotics. This was done to ensure comparability of both groups as patients may be subject to differential prescribing patterns and medical investigation procedures depending on their pre-test probability of tuberculo-sis as determined by their treating physician.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8] for the planning and execution of this study. With the assistance of a medical librarian (GG), we performed a literature search of seven databases (PubMed, Embase, CINAHL, Cochrane Library, Web of Science, Biosis and Global health) with no language restrictions through to