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Review

Community-acquired pneumonia and tuberculosis: differential diagnosis and the use of fluoroquinolones

Ronald F. Grossman [a,*], Po-Ren Hsueh [b], Stephen H. Gillespie [c], Francesco Blasi [d]

[a] University of Toronto, 2300 Eglinton Ave West, Suite 201, Mississauga, Ontario, L5M 2V8, Canada
[b] Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[c] School of Medicine, University of St Andrews, St Andrews, Fife, UK
[d] Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Cà Granda Milano, Milan, Italy

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SUMMARY

The respiratory fluoroquinolones moxifloxacin, gemifloxacin, and high-dose levofloxacin are recommended in guidelines for effective empirical antimicrobial therapy of community-acquired pneumonia (CAP). The use of these antibiotics for this indication in areas with a high prevalence of tuberculosis (TB) has been questioned due to the perception that they contribute both to delays in the diagnosis of pulmonary TB and to the emergence of fluoroquinolone-resistant strains of *Mycobacterium tuberculosis*. In this review, we consider some of the important questions regarding the potential use of fluoroquinolones for the treatment of CAP where the burden of TB is high. The evidence suggests that the use of fluoroquinolones as recommended for 5–10 days as empirical treatment for CAP, according to current clinical management guidelines, is appropriate even in TB-endemic regions. It is critical to quickly exclude *M. tuberculosis* as a cause of CAP using the most rapid relevant diagnostic investigations in the management of all patients with CAP.

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1. Introduction

The respiratory fluoroquinolones moxifloxacin, gemifloxacin, and levofloxacin (at a daily dose of 750 mg) are recommended for empirical antimicrobial therapy of community-acquired pneumonia (CAP).[1,2] Despite their proven worth in CAP, it has been suggested that fluoroquinolone use should be restricted to the management of tuberculosis (TB), even though there have been few well-controlled clinical studies of their use in TB-endemic parts of the world.[3–6] More specifically, some authors have proposed that newer fluoroquinolones should not be used in areas of TB endemicity, given the potential to mask active TB and the threat of an emerging epidemic of fluoroquinolone- and extensively drug-resistant (XDR) TB.[7,8]

In this review, we examine the role of respiratory fluoroquinolones in the treatment of both TB and CAP and consider how these agents should be used in the context of both infections.

2. Fluoroquinolone treatment in the management of CAP

CAP may be caused by a wide variety of pathogens, but a limited number of agents are responsible for most cases. Recent data have confirmed *Streptococcus pneumoniae* to be the most common pathogen isolated from patients with CAP.[1,2] Other bacterial causes include non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*, generally in patients with underlying bronchopulmonary disease, *Staphylococcus aureus*, especially during an influenza outbreak, and so-called 'atypical' organisms, such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella* species, and respiratory viruses.[1,9]

There is good pharmacological and clinical evidence to support the use of respiratory fluoroquinolones in CAP. Their favourable pharmacokinetic and pharmacodynamic profiles result in good penetration of respiratory tissues; the administration of a single 400-mg oral dose of moxifloxacin, for example, achieves higher concentrations in alveolar macrophages (56.7 μg/ml) and

* Corresponding author. Tel.: +1 905 828 5168; fax: +1 905 828 0113.
E-mail address: RGrossman@cvh.on.ca (R.F. Grossman).

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epithelial lining fluid (20.7 μg/ml) than in serum (3.2 μg/ml).[10] The broad antibacterial activity of respiratory fluoroquinolones provides excellent coverage of the major CAP-causing pathogens, including penicillin- and macrolide-resistant *S. pneumoniae*.[11] Dosing is once daily and the availability of oral and intravenous formulations of moxifloxacin and levofloxacin allows delivery of effective therapy to a wide range of patients, including the critically ill.[2] Ineffective initial therapy of CAP is the most significant prognostic and single intervention-related factor linked to mortality.[12] A meta-analysis of 15 clinical trials showed that pneumonia was cured or improved in significantly more patients treated with fluoroquinolones than those treated with macrolide ± beta-lactam antibiotics.[13] Moxifloxacin monotherapy, for example, has been shown to be superior to amoxicillin–clavulanic acid ± clarithromycin in terms of clinical cure and bacteriological success in the treatment of patients hospitalized with CAP.[14] Fluoroquinolones were also more effective than macrolides ± beta-lactams for patients with severe pneumonia, those who were hospitalized and those who required intravenous therapy.[13]

Fluoroquinolones are generally recommended in different management guidelines for use in CAP, i.e., pneumonia in immunocompetent subjects arising outside of the hospital. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) consensus guidelines, for example, recommend monotherapy with a respiratory fluoroquinolone for patients with CAP admitted to general medical wards, or a combination of a beta-lactam and a respiratory fluoroquinolone for patients admitted to intensive care units (ICUs) and who do not have risk factors for methicillin-resistant *S. aureus* or *Pseudomonas spp.*[1] The European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend a fluoroquinolone as: (1) first-line monotherapy for hospitalized (non-ICU) patients with CAP; (2) monotherapy or in combination with a non-antipseudomonal cephalosporin for patients with severe CAP in the ICU or intermediate care; and (3) second-choice agent for the treatment of CAP in outpatients.[2] In the treatment of patients hospitalized with CAP with guideline-concordant antibiotic regimens, fluoroquinolone monotherapy is as effective as macrolide/beta-lactam combinations.[15] Importantly, non-adherence to CAP treatment guidelines is a significant risk factor for treatment failure and mortality.[16]

An assessment of existing national guidelines for the treatment of lower respiratory tract infections (LRTIs) and/or CAP in Europe was recently conducted by questionnaire sent to ERS national delegates.[17] The survey revealed that 18 of 24 responding delegates had national or regional guidelines for the management of CAP, and of those, seven guidelines included recommendations on the differential diagnosis, treatment, and management of TB. Seven responders also confirmed that their guidelines included recommendations on the use of fluoroquinolones in CAP and the risk of selecting fluoroquinolone-resistant *M. tuberculosis* in misdiagnosed patients. In several countries in Europe with low TB incidence, opportunities for physicians to investigate a TB patient are relatively rare and so there is a risk that TB is not considered as a potential diagnosis when a patient with an LRTI presents for consultation. Revision of national and regional guidelines for the management of LRTIs and/or CAP is therefore warranted, specifically to describe the need to consider the differential diagnosis of TB and highlight the potential risk of fostering fluoroquinolone resistance in TB patients who are misdiagnosed and do not receive appropriate therapy.

3. Diagnosis of CAP

Data from clinical studies illustrate that the differential diagnosis of TB from bacterial pneumonia is not straightforward. In Asian countries, 1–7% of cases presenting as CAP were re-diagnosed as pulmonary TB.[18] Most of these patients were over 65 years of age with various comorbidities.[18] In contrast, studies in Africa have identified *M. tuberculosis* as the cause of pneumonia in approximately 30% of HIV-infected patients,[19,20] indicating a shift in the aetiology of pneumonia in severely ill patients immunocompromised with advanced HIV.

In the absence of a diagnostic 'gold standard', the diagnosis of CAP is based on demonstration of a new infiltrate on chest radiograph or other imaging technique in the presence of recently acquired respiratory signs and symptoms. Chest radiography of patients with cough and fever lasting 2–3 days due to bacterial pneumonia reveals an airspace infiltrate, in clear contrast to the cavitating lung lesions seen in patients with a history of cough for 3 months or longer accompanied by weight loss, which are typical of TB. Clinical findings do not, however, reliably predict radiologically confirmed pneumonia,[21] as features of TB may sometimes be quite similar to those of CAP among patients who experience symptoms at the early stage. In addition, the etiology cannot be simply differentiated clinically or radiologically and is undefined in approximately 50% of patients.

The presence of HIV influences the presentation of pulmonary infections and so complicates the diagnosis of CAP and TB, particularly in areas of high TB prevalence. In HIV-positive patients, lung characteristics identified by chest X-ray or computed tomography imaging together with clinical course (acute vs. chronic onset) can be helpful in suggesting the etiology. This has enabled an algorithm approach to the evaluation of hospitalized HIV-seropositive patients with suspected CAP to be recommended.[22]

4. Fluoroquinolone treatment for TB

Fluoroquinolones have considerable potential to treat TB due to their favourable pharmacokinetics and activity against the target pathogen. Later-generation fluoroquinolones including gatifloxacin, levofloxacin (750 mg/day), moxifloxacin (maximum 400 mg/day), and even ofloxacin, are suggested by the World Health Organization (WHO) as second-line anti-TB agents.[23] However, none is licensed for use in the treatment of drug-susceptible TB, and these should only be used for the treatment of multidrug-resistant TB (MDR-TB),[24] or when toxicity curtails the use of standard anti-TB therapy. Earlier fluoroquinolones (sparfloxacin and ciprofloxacin) have also been evaluated in some clinical trials, but are not generally considered effective as second-line agents. Ciprofloxacin should not be used.[25] While some small studies have indicated the efficacy of fluoroquinolones in TB,[3–6] no large-scale controlled clinical trial has been completed. In addition, these drugs are intended and approved for short-term use and safety data are lacking for their long-term use.

Moxifloxacin 400 mg is currently being tested in two phase III multicentre international clinical trials: the Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive Tuberculosis (REMoxTB) study and the International Multicentre Controlled Clinical Trial to Evaluate High Dose Rifapentine and a Quinolone in the Treatment of Pulmonary Tuberculosis (RIFAQUIN). Both studies are investigating the possibility of shortening chemotherapy from 6 to 4 months, which is expected to substantially improve treatment completion rates and adherence. In the REMoxTB study, one group is given 6 months of standard treatment, a second group receives moxifloxacin substituted for ethambutol as part of a 4-month regimen, and a third group receives moxifloxacin substituted for isoniazid as part of a 4-month regimen.[26,27] In the now completed RIFAQUIN study,[28] three drug combination regimens were compared. The 6-month control standard regimen contained rifampin, isoniazid, ethambutol, and

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