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Review

Does empirical treatment of community-acquired pneumonia with fluoroquinolones delay tuberculosis treatment and result in fluoroquinolone resistance in *Mycobacterium tuberculosis*? Controversies and solutions

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ABSTRACT

The role of fluoroquinolones (FQs) as empirical therapy for community-acquired pneumonia (CAP) remains controversial in countries with high tuberculosis (TB) endemicity owing to the possibility of delayed TB diagnosis and treatment and the emergence of FQ resistance in *Mycobacterium tuberculosis*. Although the rates of macrolide-resistant *Streptococcus pneumoniae* and amoxicillin/clavulanic acid-resistant *Haemophilus influenzae* have risen to alarming levels, the rates of respiratory FQ (RFQ) resistance amongst these isolates remain relatively low. It is reported that ca. 1–7% of CAP cases are re-diagnosed as pulmonary TB in Asian countries. A longer duration (≥7 days) of symptoms, a history of night sweats, lack of fever (>38 °C), infection involving the upper lobe, presence of cavitary infiltrates, opacity in the lower lung without the presence of air, low total white blood cell count and the presence of lymphopenia are predictive of pulmonary TB. Amongst patients with CAP who reside in TB-endemic countries who are suspected of having TB, imaging studies as well as aggressive microbiological investigations need to be performed early on. Previous exposure to a FQ for >10 days in patients with TB is associated with the emergence of FQ-resistant *M. tuberculosis* isolates. However, rates of *M. tuberculosis* isolates with FQ resistance are significantly higher amongst multidrug-resistant *M. tuberculosis* isolates than amongst susceptible isolates. Consequently, in Taiwan and also in other countries with TB endemicity, a short-course (5-day) regimen of a RFQ is still recommended for empirical therapy for CAP patients if the patient is at low risk for TB.

1. Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of death worldwide. The mortality rate has increased significantly over the past 10 years not only in Taiwan but also in other countries in the Asia-Pacific region [1–3]. The key causative pathogens of CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae* and atypical pathogens [1–3]. According to the antimicrobial treatment guidelines of the Infectious Diseases Society of America, the American Thoracic Society, the European Respiratory Society and the Infectious Diseases Society of Taiwan [1–3], the drugs of choice for CAP in outpatients are penicillin-related

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agents if urine cultures are positive for pneumococcal antigen, and macrolide- or tetracycline-related agents if urine cultures are negative for pathogens. However, the rate of penicillin, macrolide and tetracycline resistance amongst *S. pneumoniae* isolates is high in Taiwan [4]. The antibiotic options for inpatients with CAP are β-lactams or respiratory fluoroquinolones (RFQs) (levofloxacin, moxifloxacin and gemifloxacin). In the Intensive Care Unit (ICU), a β-lactam antibiotic combined with a macrolide or with a fluoroquinolone (FQ) is appropriate [1–3]. However, the increasing resistance of key pathogens to β-lactam antibiotics poses great challenges to physicians in Taiwan. RFQs can be used in the treatment of CAP in outpatients [5], inpatients and patients in the ICU. RFQs have been shown to have excellent activity against key causative pathogens of CAP as well as atypical pathogens; however, use of RFQs for empirical treatment of CAP might mask the diagnosis of tuberculosis (TB), leading to delayed treatment and FQ resistance amongst subsequently isolated *Mycobacterium tuberculosis* strains.

This article briefly reviews the common microbial causes of CAP, the resistance rates amongst key pathogens, and the proper administration of FQs in the treatment of CAP. The incidence of and mortality associated with TB and the status of multidrug-resistant *M. tuberculosis* (MDR-TB) in Taiwan are also described. In addition, we review the controversies surrounding the empirical use of FQs to treat patients with CAP, treatment options for patients with a delayed TB diagnosis, and the emergence of FQ resistance amongst *M. tuberculosis* isolates.

2. Community-acquired pneumonia

2.1. Aetiology of community-acquired pneumonia in Taiwan

Lauderdale et al. collected 168 isolates from 468 patients from December 2001 to April 2002 in Taiwan and found that the most common cause of CAP amongst adult patients in Taiwan was *S. pneumoniae* (24%), followed by atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*), *H. influenzae* and *Klebsiella pneumoniae* [6]. The aetiology of CAP was undetermined in ca. 40% of CAP cases [6,7]. *Staphylococcus aureus* was the causative pathogen in 2% of CAP cases, and the overall mortality rate of patients with CAP was 8.3% [6].

2.2. Antimicrobial susceptibility profiles amongst respiratory pathogens

Lin et al. found that amongst all *S. pneumoniae* strains that caused bacteraemia, only 29.2% were susceptible to penicillin, 15.1% to erythromycin, 18% to tetracycline and 33.7% to clindamycin [8]. However, 96.4% were susceptible to cefotaxime, 97.3% to levofloxacin and 98.4% to moxifloxacin. Amongst non-bacteraemic strains, only 23.8% were susceptible to penicillin, 5% to erythromycin, 30% to tetracycline and 30% to clindamycin. However, the rates of susceptibility amongst *S. pneumoniae* isolates to cefotaxime, levofloxacin and moxifloxacin were each 100% [8].

The rate of non-susceptibility of *S. pneumoniae* to levofloxacin in a medical centre in Taiwan was 1.2% in 2005, peaked at 4.2% in 2007 and then gradually decreased to 3% in 2010 [9]. For moxifloxacin, the non-susceptible rate was 1.3% in 2005, 4% in 2008 and then gradually decreased to 1% in 2009 and 2010. Hsieh et al. also showed that the prevalence of FQ-resistant *S. pneumoniae* isolates in Taiwan was low, even though FQs are widely used in that country [9]. Amongst the FQ-non-susceptible isolates in that study, serotype 9V (20%) was the most common, followed by 19F (6.8%), 23F (3.9%) and 14F (1.8%) [10]. These serotypes are all vaccine-type *S. pneumoniae*. Fig. 1 shows the proportion of levofloxacin resistance amongst

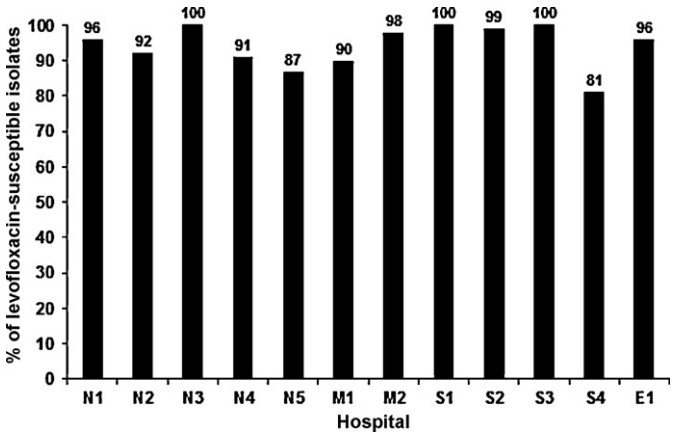

Fig. 1. Proportion of levofloxacin-susceptible *Streptococcus pneumoniae* isolates obtained from 12 major teaching hospitals in different parts of Taiwan, 2010. N1–N5, five hospitals in North Taiwan; M1–M2, two hospitals in central Taiwan; S1–S4, four hospitals in southern Taiwan; and E1, one hospital in eastern Taiwan.

S. pneumoniae isolated from 12 major teaching hospitals located in different parts of Taiwan in 2010. The majority (81–100%) of the *S. pneumoniae* isolates were susceptible to levofloxacin [9].

The susceptibility rate of *H. influenzae* to amoxicillin/clavulanic acid (AMC) decreased markedly from 95% in 2002 to 88% in 2009 in a medical centre in Taiwan [11]. AMC should be administered with caution to patients with CAP. In addition, Jean and Hsueh showed that the rate of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* strains in Taiwan was 26% [4]. Wang et al. found that the resistance rates to AMC, cefuroxime, cefaclor, ceftazidime, ceftriaxone and levofloxacin amongst *K. pneumoniae* isolates associated with community-acquired respiratory tract infection were all ≤10% [12]. Amongst 101 community-acquired meticillin-resistant *S. aureus* (CA-MRSA) isolated in a medical centre in Taiwan, 96% were susceptible to levofloxacin and moxifloxacin [13].

Regarding atypical pathogens in Taiwan, the rates of susceptibility to levofloxacin were reported to be 93.9% for *M. pneumoniae*, 85.7% for *C. pneumoniae* and 100% for *L. pneumophila* [14].

2.3. Role of respiratory fluoroquinolones in the treatment of community-acquired pneumonia

In Taiwan, patients with CAP who were previously healthy and have not used antibiotics in the 3 months prior to disease onset are normally given a macrolide or doxycycline as outpatient treatment [3]. However, the rates of non-susceptibility to penicillin and erythromycin amongst clinical isolates of *S. pneumoniae* have increased markedly in recent years [4]. Therefore, caution should be exercised before administering macrolides for CAP unless atypical pathogens are highly suspected. For patients with co-morbidities, a RFQ or a β-lactam antibiotic plus macrolide is suggested [3]. For inpatients with co-morbidities, especially in the ICU, a β-lactam antibiotic plus either azithromycin or a FQ is suggested [1–3]. For atypical pathogens, FQs are as effective as macrolides. The length of stay in hospital and the time to clinical stability favour the use of FQs [15]. Drago et al. showed that the combination of levofloxacin with ceftriaxone produced the highest rate of synergy (54%), mainly against macrolide-resistant isolates, whereas clarithromycin combined with AMC was shown to be antagonistic in 22% of isolates [16]. No antagonism was noted between FQ and β-lactam antibiotics [16]. The prevalence of levofloxacin-resistant *S. pneumoniae* increased markedly during the period 2001–2007 in Hong Kong, especially amongst the elderly [17]. The most common aetiology of levofloxacin resistance was suboptimal use of a FQ in which small