Comparative Treatment Failure Rates of Respiratory Fluoroquinolones or β-Lactam + Macrolide Versus β-Lactam Alone in the Treatment for Community-Acquired Pneumonia in Adult Outpatients

Meng-Tse Gabriel Lee, PhD, Shih-Hao Lee, MA, Shy-Shin Chang, MD, PhD, Ya-Lan Chan, PhD, Laura Pang, JD, LLM, Sue-Ming Hsu, PhD, and Chien-Chang Lee, MD, ScD

Abstract: No comparative effectiveness study has been conducted for the following 3 antibiotics: respiratory uoroquinolone, β-lactam, and β-lactam + advanced macrolide. To gain insights into the real-world clinical effectiveness of these antibiotics for community-acquired pneumonia in adult outpatients, our study investigated the treatment failure rates in 2 million representative participants from the National Health Informatics Project (NHIP) of Taiwan.

A new-user cohort design was used to follow NHIP participants from January 2000 until December 2009. Treatment failure was defined by either one of the following events: a second antibiotic prescription, hospitalization due to CAP, an emergency department visit with a diagnosis of CAP, or 30-day nonaccident-related mortality. From 2006 to 2009, we identified 9256 newly diagnosed CAP outpatients, 1602 of whom were prescribed levofloxacin, 2100 were prescribed moxifloxacin, 5049 were prescribed β-lactam alone, and 505 were prescribed advanced macrolide + β-lactam. Compared with the β-lactam-based regimen, the propensity score-matched odds ratio for composite treatment failure was 0.81 (95% CI, 0.67–0.97) for moxifloxacin, 1.10 (95% CI, 0.90–1.35) for levofloxacin, and 0.95 (95% CI, 0.67–1.35) for macrolide + β-lactam.

Moxifloxacin was associated with lower treatment failure rates compared with β-lactam alone, or levofloxacin in Taiwanese CAP outpatients. However, due to inherent limitations in our claims database, more randomized controlled trials are required before coming to a conclusion on which antibiotic is more effective for Taiwanese CAP outpatients. More population-based comparative effectiveness studies are also encouraged and should be considered as an integral piece of evidence in local CAP treatment guidelines.

INTRODUCTION

Despite the wide availability of potent antimicrobial agents, community-acquired pneumonia (CAP) remains one of the leading causes for hospital admissions, and related mortality worldwide. In the United States (US), ~5 million adults are hospitalized annually because of CAP, and ~50,000 people die of CAP-related complications every year.1–3 In 2005, the 30-day all-cause mortality rate was estimated to be as high as 10%, and the 1-year all-cause mortality was as high as 28%.4 With the large number of incident CAP cases, it is not surprising that CAP leads to a huge socioeconomic burden. In fact, the cost to treat CAP patients in the US has been estimated to be more than $17 billion annually.5

CAP is commonly caused by several serotypes of bacteria, including Streptococcus pneumoniae, Haemophilus influenza, Gram-negative rods, and atypical organisms (Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella species), which can occur in isolation or together among CAP patients.6–8 To effectively target these possible broad spectrum of bacteria, the current Infectious Diseases Society of America (IDSA)’s treatment guidelines for CAP patients with comorbidities recommend using respiratory uoroquinolones (moxifloxacin, gemifloxacin, or levofloxacin) or β-lactams + advanced macrolides as the empirical antibiotic regimen.9 Several clinical trials and meta-analyses have suggested that respiratory fluoroquinolones, such as moxifloxacin, might have better CAP treatment success rates than β-lactam alone.10–18 However, the elderly are often underrepresented
in the clinical trials, and little is known about the comparative effectiveness of these regimens in real-world settings. To our knowledge, there have only been 2 closely related postmarket studies comparing the treatment failure rates of CAP outpatients who were prescribed respiratory fluoroquinolones, advanced macrolides, or β-lactam regimens alone.¹⁹,²⁰ Treatment failure for both studies were defined as a second antibiotic fill (either for the index drug or a new antibiotic) or a hospital/ER admission with a primary or secondary diagnosis of CAP. Using the US administrative claims database as their source population, both papers showed that levofloxacin had lower treatment failure rates than macrolides. However, due to differences in the local antibiotic resistance patterns, it is difficult to generalize these results outside the US. More importantly, a comparison has not been made using the guideline drug of either a fluoroquinolone or a combination of a β-lactam + an advanced macrolide. *Streptococcus pneumoniae* is becoming resistant (up to 70% resistant in countries like Taiwan, China, and Hong Kong) to either advanced macrolides or β-lactams alone, and a real-world comparison based on the combination of β-lactam + advanced macrolide would be much more useful.²¹,²²

As the information on the comparative effectiveness between respiratory fluoroquinolones, β-lactam alone, and advanced macrolides + β-lactam regimens is important for clinical decision making, we proposed to examine their treatment failure rates in adult outpatients. Subjects from this study were identified from the National Health Informatics Project (NHIP) of Taiwan.

### METHODS

#### Data Source

With approval from the institutional review board of National Taiwan University Hospital, we conducted an observational cohort study using the health insurance claims data from the National Health Informatics Project (NHIP), which was released by the Collaboration Center of Health Information Application (CCHIA) at the Department of Health in Executive Yuan. The NHIP contains a population of 2 million sampled from the ~24 million individuals who were enrolled in Taiwan’s National Health Insurance (NHI) in 2000. Taiwan’s NHI is a single-payer compulsory national health insurance with 99.9% of Taiwan’s population enrolled. A weighted stratified random sampling method was used to obtain the 2 million person sample. Sex was divided into 2 strata, age was divided into 20 strata (ie, 1 strata for every 5 years of age), and geographic location was divided into 6 strata. Thus, there were 240 (=2 × 20 × 6) strata, in which their respective weights were obtained from their relative proportion to the 24 million source cohort. Several studies have already shown that this database is appropriate for use in pharmacoepidemiologic research.²¹–²⁵

As this was an electronic database study using anonymous subjects, patient consent was not required. The anonymized and de-identified claims history includes patient demographics, outpatient and inpatient electronic claims records, individual diagnoses, operations, prescribed medications, and mortality. Detailed information is also available for the name of the prescribed drugs, route of administration, quantity, and number of days of supply. Due to the rich information available in the database, a person’s identity or the clinic/hospital in which the person was treated could still be identifiable. Thus, no statistics could be reported when the number of observations in any given tabulated cell was ≤5.

#### Study Cohort

The study cohort consisted of all subjects from the NHIP who were longitudinally followed from January 2000 to December 2009. We made slight modifications to published methods to improve the accuracy of identifying CAP outpatients from 1 January 2006 to 30 November 2009.¹⁹,²⁰ Seven inclusion criteria were used to identify new incident CAP outpatients from 1 January 2006 to 30 November 2009 (Fig. 1). First, patients diagnosed with CAP were identified by the ICD-9-CM codes of 481, 482.xx, 483.xx, 485, and 486. Each patient’s index date was defined as the first day of a CAP diagnosis. Second, patients were identified if they were between 18 and 120 years of age. Third, subjects had to have a chest x-ray on the index date. Fourth, subjects were prescribed with the study antibiotic (moxifloxacin, levofloxacin, azithromycin, clarithromycin, amoxicillin/clavulanate, ampicillin/sulbactam) for at least 3 days, and must not have received >1 prescription of pneumonia-related antibiotic on the index date. Fifth, to ensure that the index pneumonia episode was community-acquired rather than hospital-acquired, patients were excluded from the study sample if they experienced any hospitalization or emergency department (ED) within the 30 days before the index date. Sixth, existing CAP patients were excluded if they received a prescription for a study antibiotic within 180 days before the index date. Seventh, subjects had to be continuously enrolled in the NHI for the 365-day period before the index date and be followed for 30 days after the index date. The advanced macrolides included in this study were azithromycin and...
clarithromycin, and the β-lactams included in this study were amoxicillin/clavulinate and ampicillin/sublactam.

Primary Endpoints

The primary study outcome was evaluated as a composite outcome of 4 possible treatment failure events, within 8 to 30 days of the index date. The 4 events composed of a second antibiotic prescription, hospitalization due to CAP, an ED visit with a diagnosis of CAP, and 30-day non-accident-related mortality. Thirty-day non-accident-related mortality refers to 30-day all-cause mortality excluding any accident events.

Covariates

Our electronic database contains a large amount of information about the participants, and we wanted to include as many “confounders” in our adjustment models as possible so that the association between outcome and exposure would be unbiased. We identified 49 covariates for adjustment based on the literature review (S1 Table, http://links.lww.com/MD/A441). Most of the chronic comorbidity variables were collected from the initial assessment period (year 2000) to the index date. These variables included: demographic variables (age, gender, and geographic location); respiratory comorbidities; cardiovascular comorbidities; diabetes; alcohol/drug use; psychiatric disorders; and neurologic disorders. Utilization of healthcare facilities and the use of specific medications were assessed for a different time period from the chronic comorbidity variables. They were all assessed for a 1-year period before the index date. Utilization of healthcare facilities refers to the number of clinic visits, ED visits, and hospitalizations. The specific classes of medications included nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, systemic immunosuppressive agents and biologics, systemic corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), statins, and angiotensin-converting-enzyme (ACE) inhibitors. The proxy indicator for CAP severity was also assessed for a different time period, which is a total of 10 days before the index date. The proxy indicator for CAP severity was defined as the number of orders of CAP-related laboratory tests (smear/stain, blood cell count tests, blood cultures, blood gas analysis, and peak flow evaluation), imaging studies (computed tomography scan of chest/lung and similar), and procedures (intravenous infusion, any injections, and airway inhalation treatment and similar). The combined comorbidity score was used to quantify each individual’s burden of comorbidity. This score contains common comorbidities such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, neoplasms, and AIDS.

Data Analysis

Baseline characteristics are presented as frequencies and percentages for categorical variables, and as means and standard deviation for continuous variables. Multigroup categorical variable comparisons were conducted using chi-square tests, and multigroup comparisons of continuous variables were performed using 1-way analysis of variance (ANOVA) tests. We estimated the comparative risk of treatment failure by constructing logistic regression models to derive the odds ratio for patients receiving the study antibiotic, as compared with patients receiving β-lactam alone. We performed 3 types of analyses. The first analysis examined the crude effect estimates. The second analysis involved a traditional logistic regression model that used treatment failure as the main outcome variable (dependent variable), used antibiotic usage as the main exposure variable, and included all 49 covariates as the independent variables. The third analysis involved a propensity score (PS) analysis. In this study, the PS was the conditional probability of receiving the antibiotic regimens of interest as compared to a reference antibiotic for the index episode of CAP. The PS was derived from a logistic regression model that included all 49 potential predictors. We created 4 sets of PS (macrolide + β-lactam vs β-lactam, levofloxacin vs β-lactam, moxifloxacin vs β-lactam, and moxifloxacin vs levofloxacin) for each pair of antibiotic comparison. After deriving the PS, we performed PS matching by using a greedy matching algorithm without any trimming. We examined the distribution of the PS in the study population and checked the balance of each covariate across the 2 comparison groups using chi-square tests for categorical variables and the Mann–Whitney U tests for continuous variables. Subgroup analyses were performed in male patients or elderly patients >65 years of age. We also conducted sensitivity analyses comparing fluoroquinolones with β-lactam-based regimens using different outcomes. For all analyses, the results were considered to be significant when P < 0.05. Statistical analyses were conducted using SAS Version 9.3.

RESULTS

Participant Enrollment and Baseline Characteristics

Using the 2 million person source population, 7 criteria were used to identify new incident adult CAP outpatients using the antibiotic regimens of interests (Figure 1). After excluding non-CAP patients, underaged/overaged patients, patients without x-ray, patients without compatible antibiotics, hospital acquired pneumonia patients, existing CAP patients and drop-out patients, 9256 outpatients with CAP were identified. During the study period, β-lactam alone was the most common antibiotic regimen prescribed for patients with CAP (5049 persons; 54.5%), followed by moxifloxacin (2100 persons; 22.7%), levofloxacin (1602 persons; 17.3%), and macrolide + β-lactam (505 persons; 5.5%), respectively (Table 1). In our study, there were generally more males, but there were few differences in the gender distributions among the 4 antibiotic regimens. Patients prescribed β-lactam alone were older (mean age: 60.3 ± 19.9) than patients prescribed macrolide + β-lactam (mean age: 55.9 ± 20.5). Substantial differences were noted in the comorbidity score, prevalence of cerebrovascular diseases, prevalence of chronic obstructive pulmonary diseases, other respiratory diseases, laboratory tests or imaging studies received, and medication used. However, there were few differences in baseline characteristics upon propensity score (PS) matching (S2 Table, http://links.lww.com/MD/A441 and S3 Table, http://links.lww.com/MD/A441).

Composite Treatment Failure

Table 2 shows the treatment failure outcomes of the 4 antibiotic regimens. As the outcome definition becomes more stringent, we observed the number of treatment failures decreases. The 30-day non-accident-related mortality rate was <1.0% for all the 4 antibiotic regimens. Due to the possibility of identifying individual subjects from the rich demographic data, the Taiwanese Department of Health forbids reporting absolute mortality numbers if fewer than 5 cases are found.
| Specialty                                      | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | P Value |
|-----------------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------|
| Specialty                                     |       |       |       |       |       |       |       |       |       |         |
| Internal medicine                             | 1186  | 1370  | 117  | 2446  | 0.001  |
| Emergency medicine                            | 1186  | 1370  | 117  | 2446  | 0.001  |
| Others                                        | 1048  | 1174  | 137  | 2389  | 0.001  |
| Area                                          |       |       |       |       |       |       |       |       |       |         |
| Urban area                                    | 256   | 287   | 200  | 654   | 0.001  |
| Metro area                                    | 256   | 287   | 200  | 654   | 0.001  |
| Suburban area                                 | 256   | 287   | 200  | 654   | 0.001  |
| Countrywide area                              | 256   | 287   | 200  | 654   | 0.001  |
| Comorbidity score                             | 256   | 287   | 200  | 654   | 0.001  |
| Congestive heart failure                      | 256   | 287   | 200  | 654   | 0.001  |
| Myocardial infarction/acute coronary syndromes| 256   | 287   | 200  | 654   | 0.001  |
| Stroke or transient ischemic attack           | 256   | 287   | 200  | 654   | 0.001  |
| Periperal arterial disease                    | 256   | 287   | 200  | 654   | 0.001  |
| Angina                                        | 256   | 287   | 200  | 654   | 0.001  |
| Other ischemic heart disease                  | 256   | 287   | 200  | 654   | 0.001  |
| Cerebral atherosclerosis                      | 256   | 287   | 200  | 654   | 0.001  |
| Percutaneous coronary/ coronary artery bypass graft intervention | 256   | 287   | 200  | 654   | 0.001  |
| Chronic sinusitis                             | 256   | 287   | 200  | 654   | 0.001  |
| Chronic obstructive pulmonary disease          | 256   | 287   | 200  | 654   | 0.001  |
| Asthma                                        | 256   | 287   | 200  | 654   | 0.001  |
| Other diseases of the respiratory system       | 256   | 287   | 200  | 654   | 0.001  |
| Proxy indicators of severity                  | 256   | 287   | 200  | 654   | 0.001  |
| Intravenous infusion and any injections        | 256   | 287   | 200  | 654   | 0.001  |
| Airway inhalation treatment and similar        | 256   | 287   | 200  | 654   | 0.001  |
| Smeary/stain                                  | 256   | 287   | 200  | 654   | 0.001  |
| Computed tomography scan of chest/ lung and similar | 256   | 287   | 200  | 654   | 0.001  |
| Peak flow evaluation                          | 256   | 287   | 200  | 654   | 0.001  |
| Complete blood count (or component)           | 256   | 287   | 200  | 654   | 0.001  |
| and sedimentation rate testing                | 256   | 287   | 200  | 654   | 0.001  |
| Blood culture                                 | 256   | 287   | 200  | 654   | 0.001  |
| Blood gas analysis                            | 256   | 287   | 200  | 654   | 0.001  |
| NSAIDs                                        | 256   | 287   | 200  | 654   | 0.001  |
| Aspirin                                       | 256   | 287   | 200  | 654   | 0.001  |
| Systemic immunosuppressive agents and biologics| 256   | 287   | 200  | 654   | 0.001  |
| Systemic corticosteroids                      | 256   | 287   | 200  | 654   | 0.001  |
| DMARDs                                        | 256   | 287   | 200  | 654   | 0.001  |
| Statin                                        | 256   | 287   | 200  | 654   | 0.001  |
| ACE inhibitors                                | 256   | 287   | 200  | 654   | 0.001  |
| Diabetes Mellitus                             | 256   | 287   | 200  | 654   | 0.001  |
| Alcohol-related disease                       | 256   | 287   | 200  | 654   | 0.001  |
| Neurological disease                          | 256   | 287   | 200  | 654   | 0.001  |
| Psychiatric disease                           | 256   | 287   | 200  | 654   | 0.001  |
| Outpatient visits                             | 256   | 287   | 200  | 654   | 0.001  |
| Emergency department visits                   | 256   | 287   | 200  | 654   | 0.001  |
| The number of hospitalization                  | 256   | 287   | 200  | 654   | 0.001  |

ACE = angiotensin-converting-enzyme, DMARDs = disease-modifying anti-rheumatic drugs, NSAIDs = nonsteroidal anti-inflammatory drugs.
The composite treatment failure rate was 11% (231/2100) for moxifloxacin, 14.2% (228/1602) for levofloxacin, 13.8% (698/5049) for β-lactam alone, and 14.7% (74/505) for a combined macrolide + β-lactam regimen. In the multivariable binary logistic regression analysis, Figure 2 shows that moxifloxacin was associated with the lowest treatment failure rate by crude estimation, individual confounder adjusted estimation, and PS-matched effect estimation. Neither the macrolide + β-lactam regimen nor the levofloxacin therapy resulted in a significantly lower treatment failure rate, when compared with the use of β-lactam alone. Compared with levofloxacin, moxifloxacin was associated with a significantly lower treatment failure rate (PS-matched OR, 0.80, 95%CI, 0.65–0.99).

Sensitivity Analysis

In order to verify the robustness of the primary results, and examine the various effects of treatment failure definitions, we repeated the primary analyses using stricter outcome definitions within 3 to 30 days post-index date: ED visit or hospitalization, ED visit only, and hospitalization only. Using the outcome definitions defined as ED visit or hospitalization within 30 days of index date, we found similar results to the primary analyses (Table 2 and Table 3). The crude treatment failure rate was 4.2% (88/2100) for moxifloxacin, 6.0% (96/1602) for levofloxacin, 5.2% (265/5049) for β-lactam alone, and 3.6% (18/505) for the combined macrolide + β-lactam regimen (Table 2). For the multivariable binary logistic regression analysis, moxifloxacin was associated with the lowest treatment failure rate by crude estimation, individual confounder adjusted estimation, and PS-matched effect estimation. Neither the macrolide + β-lactam regimen nor the levofloxacin therapy resulted in a significantly lower treatment failure rate, when compared with the use of β-lactam alone. Compared with levofloxacin, moxifloxacin was associated with a significantly lower treatment failure rate (PS-matched OR, 0.80, 95%CI, 0.65–0.99).

### TABLE 2. Treatment Failure Outcomes in Users of Different Antibiotic Regimens

|                      | Composite (%) | ER or Hospitalization (%) | 30-Day Nonaccident Related Mortality (%) |
|----------------------|---------------|---------------------------|-----------------------------------------|
| Moxifloxacin         | 11% (231/2100)| 4.2% (88/2100)            | <0.24% (<5/2100)                        |
| Levofloxacin         | 14.2% (228/1602) | 6.0% (96/1602)         | <0.31% (<5/1602)                        |
| β-Lactams            | 13.8% (698/5049) | 5.2% (265/5049)          | 0.20% (10/5049)                         |
| Macrolide + β-lactams | 14.7% (74/505) | 3.6% (18/505)            | 0.99% (<5/505)                         |

*30-day nonaccident-related mortality refers to 30-day all-cause mortality excluding any accident events.

**FIGURE 2.** Forest plots comparing the composite treatment failure rates associated with different antibiotic regimens. Composite treatment failure was defined as a within 30 days outcome comprising of drug refill, change of medication, emergency department visit, and hospitalization.
was also associated with significantly lower crude treatment failure rates (OR, 0.69, 95%CI: 0.51–0.92) compared with levofloxacin treatment; however the association was not significant after PS matching (OR, 0.79, 95%CI: 0.56–1.09) (Table 3). Levofloxacin did not show significant differences in treatment failure rates compared with β-lactam alone. For treatment failure defined as an ED visit, there were no significant differences in treatment failure rates between the different antibiotic regimens (S4 Table, http://links.lww.com/MD/A441). Next, we used the strictest definition of treatment failure, which is CAP-related hospitalization within 30 days. In S5 Table, http://links.lww.com/MD/A441, we showed that moxifloxacin treatment was associated with significantly lower crude treatment failure rates than β-lactam alone (OR, 0.70, 95%CI: 0.53–0.92) or levofloxacin treatment (OR, 0.66, 95%CI: 0.47–0.93). However, the result became insignificant after PS matching.

**Subgroup Analysis for Treatment Failure Patients Defined as ED Visit or Hospitalization**

To investigate whether there was differential comparative effectiveness across different patient populations, we performed analyses on the predefined age and gender subgroups (Table 4). For the 3 comparison groups (moxifloxacin vs levofloxacin, moxifloxacin vs β-lactam alone, and macrolide+β-lactam vs β-lactam alone), there were no significant differences in the interaction term \( P < 0.05 \). However, for patients >65 years old, moxifloxacin was associated with significantly lower treatment failure rates compared to levofloxacin (OR, 0.69, 95%CI: 0.50–0.96) or β-lactam alone (OR, 0.65, 95%CI: 0.44–0.96).

**DISCUSSION**

In this analysis of a national representative dataset encompassing 9256 newly diagnosed patients with CAP, we found that moxifloxacin treatment was associated with the lowest risk for treatment failure after comprehensive adjustment with potential confounders. This trend was verified in the sensitivity analysis using different criteria to define treatment failure outcomes. In subgroup analyses, we found that the favorable effect of moxifloxacin versus either β-lactam or levofloxacin therapy was stronger among patients >65 years old. In addition, far fewer patients (3.2- to 10-fold fewer) were prescribed combination therapy compared with the other antibiotic regimens. As a result, meaningful head-to-head comparisons with other antibiotic regimens could not be conducted.

There are limited real-world clinical data on the comparative effectiveness of different antibiotic regimens for the treatment of CAP. To the best of our knowledge, only 1 population-based study has compared the treatment failure rates between

---

**TABLE 3.** Comparison of the Treatment Failure Rates Comprising of Emergency Department Visit or Hospitalization Within 30 days, Among the Four Antibiotic Regimens

| CAP Treatment Failure Defined as ED Visit or Hospitalization | Crude Estimate | Confounder Adjusted Effect Estimate | Propensity Score Matched Effect Estimate |
|-------------------------------------------------------------|----------------|------------------------------------|------------------------------------------|
| Macrolide + β-lactam vs β-Lactam                            | 0.67 (0.41–1.09) | 0.78 (0.46–1.27)                   | 0.59 (0.32–1.10)                         |
| Levofloxacin vs β-lactam                                   | 1.15 (0.91–1.46) | 1.03 (0.79–1.32)                   | 1.09 (0.80–1.47)                         |
| Moxifloxacin vs β-lactam                                   | 0.79 (0.62–1.01) | 0.86 (0.66–1.11)                   | 0.98 (0.73–1.31)                         |
| Moxifloxacin vs Levofloxacin                               | 0.69 (0.51–0.92) | 0.83 (0.60–1.14)                   | 0.79 (0.56–1.09)                         |

CAP = community-acquired pneumonia, ED = emergency department

“Refers to \( P < 0.05 \).

**TABLE 4.** Subgroup Analysis on Treatment Failure Rates Comprising of Both Emergency Department Visit and Hospitalization Within 30 Days

| Comparison of different antibiotic | Patient Subgroups | Propensity Score Adjusted OR (95% Confidence Interval) |
|-----------------------------------|-------------------|--------------------------------------------------------|
| Moxifloxacin vs Levofloxacin      | \( >65 \) years of age | 0.69 (0.50–0.96)*                                     |
|                                   | \( \leq 65 \) years of age | 1.27 (0.84–1.92)                                     |
|                                   | Male | 0.98 (0.72–1.32)                                     |
|                                   | Female | 0.68 (0.43–1.08)                                     |
| Moxifloxacin vs β-lactam          | \( >65 \) years of age | 0.65 (0.44–0.96)*                                     |
|                                   | \( \leq 65 \) years of age | 1.16 (0.68–1.96)                                     |
|                                   | Male | 0.85 (0.59–1.23)                                     |
|                                   | Female | 0.69 (0.39–1.21)                                     |
| Macrolide+β-lactam vs β-lactam    | \( >65 \) years of age | 0.85 (0.47–1.54)                                     |
|                                   | \( \leq 65 \) years of age | 0.64 (0.25–1.65)                                     |
|                                   | Male | 0.72 (0.37–1.39)                                     |
|                                   | Female | 0.94 (0.44–1.99)                                     |

*Refers to result that is significant.
different fluoroquinolone antibiotic regimens for outpatients diagnosed with CAP. Among a general cohort, the Hess group did not find significant differences in the treatment failure rates between moxifloxacin and levofloxacin. This finding starkly contrasts with our results, whereby we found that moxifloxacin therapy was associated with an ~20% reduction (PS-matched) in treatment failure rate compared to levofloxacin therapy.

There are several possible explanations for the observed difference with the Hess group. First, the resistance patterns of Streptococcus pneumoniae can vary in different countries, and our results are compatible with the S. pneumoniae resistance patterns in Taiwan. Streptococcus pneumoniae is the major CAP pathogen in Taiwan, found in ~26% of CAP patients. Recent surveys of Taiwanese hospital laboratories have shown higher resistance rates of S. pneumoniae to levofloxacin (6.5–6.8%) than moxifloxacin (1.7–3.2%). By contrast, a US survey reported that levofloxacin (98.8% susceptible) is potent against S. pneumoniae. Thus, the effectiveness of levofloxacin for CAP patients in Taiwan and the US may potentially differ. Second, the patient demographics are dramatically different in our study cohort and Hess’s study cohort. Our study cohort is made up of 98% Han Chinese, but the Hess cohort is made up of a mixture of Caucasian, African American, and Hispanic. Research suggests that different racial groups might have different incidence of pneumonia. In addition, patients in Hess’s study were on average ~4 to 5 years older, and the cohort included ~13% to 14% more female patients. Older patients may have a higher risk of CAP infection due to a higher risk of infection by Pseudomonas aeruginosa and Legionella pneumophila than younger patients. Likewise, gender can readily change the antibiotics susceptibility patterns of CAP pathogens. Finally, our group had a proxy measure to adjust/match patients with different CAP severities, which was not found in Hess’s study. Laboratory tests, imaging studies, and relevant procedures were used as indicators for CAP severity. Again, this might result into heterogeneity between our studies.

In addition to finding that levofloxacin has a higher treatment failure rate than moxifloxacin, we also found that levofloxacin did not have a significantly different treatment failure rate compared with β-lactam alone. This finding differs from various other published clinical trials and meta-analyses. We tend to ascribe this phenomenon to differences in local resistance patterns and differences in patient characteristics. As described earlier, S. pneumoniae has been observed to be more resistant to levofloxacin in Taiwan than in the US, so it is not surprising that different countries may have different treatment failure rates. In addition, our result is supported by 2 independent randomized controlled trials in France and Taiwan. The multicenter randomized controlled trial in France showed that there was no significant difference in clinical cure and bacteriologic response rates between levofloxacin and β-lactam alone. In another part of the world, a single hospital randomized controlled trial in Taiwan also found that there was no significant difference between the clinical response rate and the length of hospital stay between levofloxacin and β-lactam + advanced macrolides.

Using the claims data from the National Health Informatics Project of Taiwan, we were able to identify the treatment failure rates of nearly 10,000 new CAP patients prescribed with levofloxacin, moxifloxacin, and β-lactam therapy. However, this large population based-study has several limitations inherent in its design. Because this is an observational study, the results are subject to confounding bias. For example, based on the comorbidity profile of the population, patients with greater disease severity are more likely to be prescribed with fluoroquinolones, and healthy patients are more likely to be prescribed β-lactam alone. Thus, it would inappropriate to compare the treatment failure rate of fluoroquinolones and β-lactam alone without any adjustment. Unfortunately, a limitation in all claims database is that the standard pneumonia severity scoring systems such as PSI or CURB-65 are not available. To make a better comparison between patients, we included a proxy indicator of CAP severity in our PS score and use it for matching. Propensity score matching has been shown to address the sparse data problems and minimize the confounding bias by balancing the observable pretreatment characteristics between patients receiving 2 different treatments. However, despite the comprehensively matching on 49 covariates, we cannot exclude the possibility that there are uncontrolled variables, which may lead to residual confounding. Similar to most health insurance databases, our database does not record microbiological data. The lack of microbiologic data is a major limitation because we cannot know whether the most appropriate antibiotic was prescribed. For example, if there were a large number of patients with anaerobic pneumonia, moxifloxacin would be a more appropriate broad-spectrum antibiotic than levofloxacin. This is because moxifloxacin has better coverage of anaerobic bacteria as compared to levofloxacin.

In conclusion, the comparative effectiveness of different guideline-recommended empirical antibiotic regimens may be significantly different in the real-world practice. Moxifloxacin was associated with significantly lower treatment failure rates compared with β-lactam alone, or levofloxacin in Taiwanese CAP outpatients. However, due to limitations in observational research using claims database, more randomized controlled trials are required before coming to a conclusion on which antibiotic is more effective for Taiwanese CAP outpatients. Because there are often regional differences in antibiotic resistance, the results of this study also cannot be readily generalized to other countries. More population-based comparative effectiveness studies are encouraged and should be considered as an integral piece of evidence in local CAP treatment guidelines.

ACKNOWLEDGMENTS

We thank Mark Sculpher for proofreading our manuscript, the staff of the Core Labs, Department of Medical Research at the National Taiwan University Hospital for technical support and medical wisdom consulting group for technical assistance in statistical analysis.

REFERENCES

1. Colice GL, Morley MA, Asche C, et al. Treatment costs of community-acquired pneumonia in an employed population. Chest. 2004;125:2140–2145.
2. Niederman MS, McCombs JS, Unger AN, et al. The cost of treating community-acquired pneumonia. Clinical Ther. 1998;20:820–837.
3. Yu H, Rubin J, Dunning S, et al. Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. J Am Geriatr Soc. 2012;60:2137–2143.
4. Hoyert DL, Xu J. National Vital Statistics Reports. Deaths: Preliminary Data for 2012. 2011
5. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med. 2010;122:130–141.
6. Yen MY, Hu BS, Chen YS, et al. A prospective etiologic study of community-acquired pneumonia in Taiwan. J Formos Med Assoc. 2005;104:724–730.
7. Lauderdale T-L, Chang F-Y, Ben RJ, et al. Etiology of community-acquired pneumonia among adult patients requiring hospitalization in Taiwan. Respir Med. 2005;99:1079–1086.
8. Ruiz M, Ewig S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Resp Crit Care Med. 1999;160:397–405.
9. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–S72.
10. D’Ignazio J, Camere MA, Lewis DE, et al. Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2005;49:4035–4041.
11. Frank E, Liu J, Kinasewitz G, et al. A multicenter, open-label, randomized comparison of levofloxacin and azithromycin plus ceftriaxone in hospitalized adults with moderate to severe community-acquired pneumonia. Clin Ther. 2002;24:1292–1308.
12. Katz E, Larsen LS, Fogarty CM, et al. Safety and efficacy of sequential i.v. to p.o. moxifloxacin versus conventional combination therapies for the treatment of community-acquired pneumonia in patients requiring initial i.v. therapy. J Emerg Med. 2004;27:395–405.
13. Petitpretz P, Arvis P, Marel M, et al. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. Chest. 2001;119:185–195.
14. Portier H, Brambilla C, Garre M, et al. Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for non-severe community-acquired pneumonia in adults with risk factors. Eur J Microbiol Infect Dis. 2005;24:367–376.
15. Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Respir Med. 2004;98:697–707.
16. Welte T, Petermann W, Schurchmann D, et al. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis. 2005;41:1697–1705.
17. Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis. Ann Pharmacother. 2002;36:1938–1943.
18. Vardakas KZ, Siempos II, Grammatikos A, et al. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ. 2008;179:1269–1277.
19. Hess G, Hill JW, Raut MK, et al. Comparative antibiotic failure rates in the treatment of community-acquired pneumonia: results from a claims analysis. Adv Ther. 2010;27:743–755.
20. Ye X, Sikirica V, Schein JR, et al. Treatment failure rates and health care utilization and costs among patients with community-acquired pneumonia treated with levofloxacin or macrolides in an outpatient setting: a retrospective claims database analysis. Clin Ther. 2008;30:358–371.
21. Kim SH, Song JH, Chung DR, et al. Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. Antimicrob Agents Chemother. 2012;56:1418–1426.
22. Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother. 2003;52:229–246.
23. Chang CH, Lin JW, Wu LC, et al. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology. 2012;55:1462–1472.
24. Chen YJ, Wu CY, Shen JL, et al. Association between traditional systemic antipsoriatic drugs and tuberculosis risk in patients with psoriasis with or without psoriatic arthritis: results of a nationwide cohort study from Taiwan. J Am Acad Dermatol. 2013;69:25–33.
25. Lee MS, Lin YT, Chang YT, et al. The risk of developing non-melanoma skin cancer, lymphoma and melanoma in patients with psoriasis in Taiwan: a 10-year, population-based cohort study. Int J Dermatol. 2012;51:1454–1460.
26. Gagne JJ, Glynn RJ, Avorn J, et al. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64:749–759.
27. Tsai HY, Chen YH, Liao CH, et al. Trends in the antimicrobial susceptibilities and serotypes of Streptococcus pneumoniae: results from the Tigecycline In Vitro Surveillance in Taiwan (TIST) study, 2006–2010. Int J Antimicrob Agents. 2013;42:312–316.
28. Jones RN, Sader HS, Mendes RE, et al. Update on antimicrobial susceptibility trends among Streptococcus pneumoniae in the United States: report of ceftriaxone activity from the SENTRY Antimicrobial Surveillance Program (1998–2011). Diagn Microb Infect Dis. 2013;75:107–109.
29. Pfäffer MA, Farrell DJ, Sader HS, et al. Ceftriaxone Surveillance Program AWARE. (2008–2010): trends in resistance patterns among Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in the United States. Clin Infect Dis. 2012;55 (suppl 3):S187–S193.
30. Burton DC, Flannery B, Bennett NM, et al. Socioeconomic and racial/ethnic disparities in the incidence of bacteremic pneumonia among US adults. Am J Public Health. 2010;100:1904–1911.
31. Granoff DM, Basden M. Haemophilus influenzae infections in Fresno County, California: a prospective study of the effects of age, race, and contact with a case on incidence of disease. J Infect Dis. 1980;141:40–46.
32. Kaplan V, Angus DC, Griffin MF, et al. Hospitalized community-acquired pneumonia in the elderly: age and sex-related patterns of care and outcome in the United States. Am J Resp Crit Care Med. 2002;165:766–772.
33. Gutierrez F, Masia M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect. 2006;53:166–174.
34. Carbon C, Ariza H, Rabie WJ, et al. Comparative study of levofloxacin and amoxicillin/clavulanate in adults with mild-to-moderate community-acquired pneumonia. Clin Microbiol Infect. 1999;5:724–732.
35. Lin TY, Lin SM, Chen HC, et al. An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clari-thromycin for the treatment of hospitalized patients with community-acquired pneumonia. Chang Gung Medi J. 2007;30:321–332.