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

## *An Analysis of a Nationally Representative Claims Database*

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**Abstract:** No comparative effectiveness study has been conducted for the following 3 antibiotics: respiratory uoroquinolone,  $\beta$ -lactam, and  $\beta$ -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  $\beta$ -lactam alone, and 505 were prescribed advanced macrolide +  $\beta$ -lactam. Compared with the  $\beta$ -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 +  $\beta$ -lactam.

Moxifloxacin was associated with lower treatment failure rates compared with  $\beta$ -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.

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**Abbreviations:** CAP = community-acquired pneumonia, OR = odds ratio, PS = propensity score.

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## 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.<sup>1–4</sup> 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%.<sup>5</sup> 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.<sup>5</sup>

CAP is commonly caused by several serotypes of bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, Gram-negative rods, and atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species), which can occur in isolation or together among CAP patients.<sup>6–8</sup> 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  $\beta$ -lactams + advanced macrolides as the empirical antibiotic regimen.<sup>9</sup> Several clinical trials and meta-analyses have suggested that respiratory fluoroquinolones, such as moxifloxacin, might have better CAP treatment success rates than  $\beta$ -lactam alone.<sup>10–18</sup> 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 postmarketing studies comparing the treatment failure rates of CAP outpatients who were prescribed respiratory fluoroquinolones, advanced macrolides, or  $\beta$ -lactam regimens alone.<sup>19,20</sup> 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  $\beta$ -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  $\beta$ -lactams alone, and a real-world comparison based on the combination of  $\beta$ -lactam + advanced macrolide would be much more useful.<sup>21,22</sup>

As the information on the comparative effectiveness between respiratory fluoroquinolones,  $\beta$ -lactam alone, and advanced macrolides +  $\beta$ -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

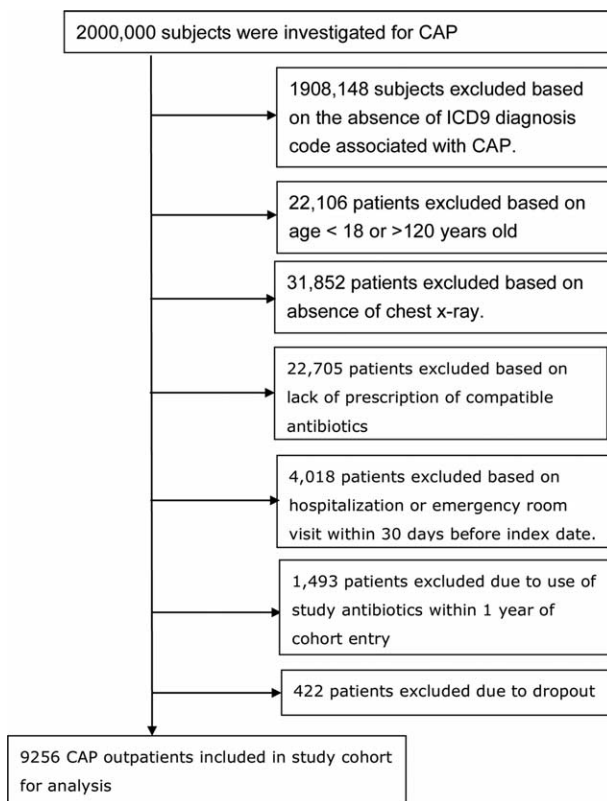
### Data Source

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 ( $=2 \times 20 \times 6$ ) 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.<sup>23–25</sup>

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  $\leq 5$ .

### 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.<sup>19,20</sup> 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



**FIGURE 1.** Assembling of study cohort. Seven criteria were used to identify new incident CAP outpatients from 1 January 2006 to 30 November 2009. CAP = community-acquired pneumonia.

clarithromycin, and the  $\beta$ -lactams included in this study were amoxicillin/clavulanate and ampicillin/sulbactam.

### 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 nonaccident-related mortality. Thirty-day nonaccident-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.<sup>26</sup> 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  $\beta$ -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 +  $\beta$ -lactam vs  $\beta$ -lactam, levofloxacin vs  $\beta$ -lactam, moxifloxacin vs  $\beta$ -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  $\beta$ -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,  $\beta$ -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 +  $\beta$ -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  $\beta$ -lactam alone were older (mean age:  $60.3 \pm 19.9$ ) than patients prescribed macrolide +  $\beta$ -lactam (mean age:  $55.9 \pm 20.5$ ). 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 nonaccident-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.

**TABLE 1.** Participant Enrollment and Baseline Characteristics

	Levofloxacin (N = 1602, 17.3%)	Moxifloxacin (N = 2100, 22.7%)	Macrolide + $\beta$ -Lactam (N = 505, 5.5%)	$\beta$ -Lactam (N = 5049, 54.5%)	P Value
Gender male (%)	915 (57.1)	1195 (56.9)	287 (56.8)	2988 (59.2)	0.23
Age	59.5 $\pm$ 20.9	57.8 $\pm$ 20.1	55.9 $\pm$ 20.5	60.3 $\pm$ 19.9	<0.0001
Year					
2006	355 (22.2)	453 (21.6)	83 (16.4)	953 (18.9)	<0.0001
2007	399 (24.9)	517 (24.6)	123 (24.4)	1124 (22.3)	
2008	439 (27.4)	560 (26.7)	134 (26.5)	1414 (28.0)	
2009	409 (25.5)	570 (27.1)	165 (32.7)	1558 (30.9)	
Specialty					
Internal medicine	711 (44.4)	820 (39.1)	202 (40.0)	2499 (49.5)	<0.0001
Emergency medicine	723 (45.1)	1025 (48.8)	242 (47.9)	1782 (35.3)	
Others	168 (10.5)	255 (12.1)	61 (12.1)	768 (15.2)	
Area					
Urban area	462 (28.8)	653 (31.1)	185 (36.6)	1382 (27.4)	<0.0001
Metro area	462 (28.8)	626 (29.8)	141 (27.9)	1451 (28.7)	
Suburban area	262 (16.4)	372 (17.7)	99 (19.6)	825 (16.3)	
Countryside area	416 (26.0)	449 (21.4)	80 (15.8)	1391 (27.6)	
Comorbidity score	2.3 $\pm$ 2.5	2.0 $\pm$ 2.3	1.7 $\pm$ 2.0	2.2 $\pm$ 2.4	<0.0001
Congestive heart failure	293 (18.3)	362 (17.2)	74 (14.6)	896 (17.8)	0.28
Myocardial infarction/acute coronary syndromes	57 (3.6)	88 (4.2)	16 (3.2)	182 (3.6)	0.56
Stroke or transient ischemic attack	252 (15.7)	248 (11.8)	43 (8.5)	766 (15.2)	<0.0001
Peripheral arterial disease	83 (5.2)	84 (4.0)	19 (3.8)	244 (4.83)	0.23
Angina	212 (13.2)	255 (12.1)	61 (12.1)	653 (12.9)	0.71
Other ischemic heart disease	469 (29.3)	573 (27.3)	137 (27.1)	1509 (29.9)	0.12
Cerebral atherosclerosis	60 (3.8)	86 (4.1)	15 (2.9)	179 (3.6)	0.57
Percutaneous coronary/coronary artery bypass graft intervention	11 (0.7)	15 (0.7)	3 (0.6)	37 (0.7)	0.98
Chronic sinusitis	122 (7.6)	154 (7.3)	42 (8.3)	371 (7.4)	0.87
Chronic obstructive pulmonary disease	890 (55.6)	1102 (52.5)	260 (51.5)	2924 (57.9)	<0.0001
Asthma	459 (28.7)	559 (26.6)	124 (24.6)	1454 (28.8)	0.08
Other diseases of the respiratory system	272 (16.9)	279 (13.3)	49 (9.7)	697 (13.8)	<0.0001
Proxy indicators of severity	2.6 $\pm$ 2.1	2.4 $\pm$ 2.0	2.9 $\pm$ 1.9	2.4 $\pm$ 2.1	<0.0001
Intravenous infusion and any injections	879 (54.9)	1064 (50.7)	292 (57.8)	2253 (44.6)	<0.0001
Airway inhalation treatment and similar	485 (30.3)	578 (27.5)	163 (32.3)	1344 (26.6)	0.004
Smear/stain	413 (25.8)	464 (22.1)	180 (35.6)	1444 (28.6)	<0.0001
Computed tomography scan of chest/ lung and similar	185 (11.6)	208 (9.9)	60 (11.9)	551 (10.9)	0.34
Peak flow evaluation	22 (1.4)	39 (1.9)	9 (1.8)	95 (1.9)	0.59
Complete blood count (or component) and sedimentation rate testing	1134 (70.8)	1461 (69.6)	406 (80.4)	3090 (61.2)	<0.0001
Blood culture	677 (42.3)	915 (43.6)	261 (51.7)	1836 (36.4)	<0.0001
Blood gas analysis	362 (22.6)	361 (17.2)	108 (21.4)	886 (17.6)	<0.0001
NSAIDs	1218 (76.0)	1706 (81.2)	419 (82.9)	3973 (78.7)	0.0002
Aspirin	273 (17.0)	246 (11.7)	59 (11.7)	638 (12.6)	<0.0001
Systemic immunosuppressive agents and biologics	13 (0.8)	17 (0.8)	6 (1.2)	39 (0.8)	0.80
Systemic corticosteroids	669 (41.8)	848 (40.4)	188 (37.2)	2011 (39.8)	0.29
DMARDs	24 (1.5)	35 (1.7)	8 (1.6)	66 (1.3)	0.68
Statin	141 (8.8)	186 (8.9)	52 (10.3)	485 (9.6)	0.55
ACE inhibitors	210 (13.1)	262 (12.5)	50 (9.9)	647 (12.8)	0.27
Diabetes Mellitus	441 (27.5)	561 (26.7)	126 (24.95)	1481 (29.3)	0.03
Alcohol-related disease	4 (0.3)	5 (0.2)	37 (7.2)	16 (0.3)	0.9
Neurological disease	32 (2.0)	30 (1.4)	9 (1.8)	109 (2.2)	0.24
Psychiatric disease	130 (8.1)	163 (7.8)	36 (7.1)	416 (8.2)	0.78
Outpatient visits	149.3 $\pm$ 120	142.8 $\pm$ 122.4	133.6 $\pm$ 110.9	148.9 $\pm$ 122.8	0.005
Emergency department visits	2.1 $\pm$ 3.8	1.8 $\pm$ 3.3	1.3 $\pm$ 2.2	1.9 $\pm$ 3.9	0.0005
The number of hospitalization	2.5 $\pm$ 3.7	2.2 $\pm$ 3.8	1.8 $\pm$ 3.7	2.3 $\pm$ 3.8	0.0002

ACE = angiotensin-converting-enzyme, DMARDs = disease-modifying anti-rheumatic drugs, NSAIDs = nonsteroidal anti-inflammatory drugs.



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

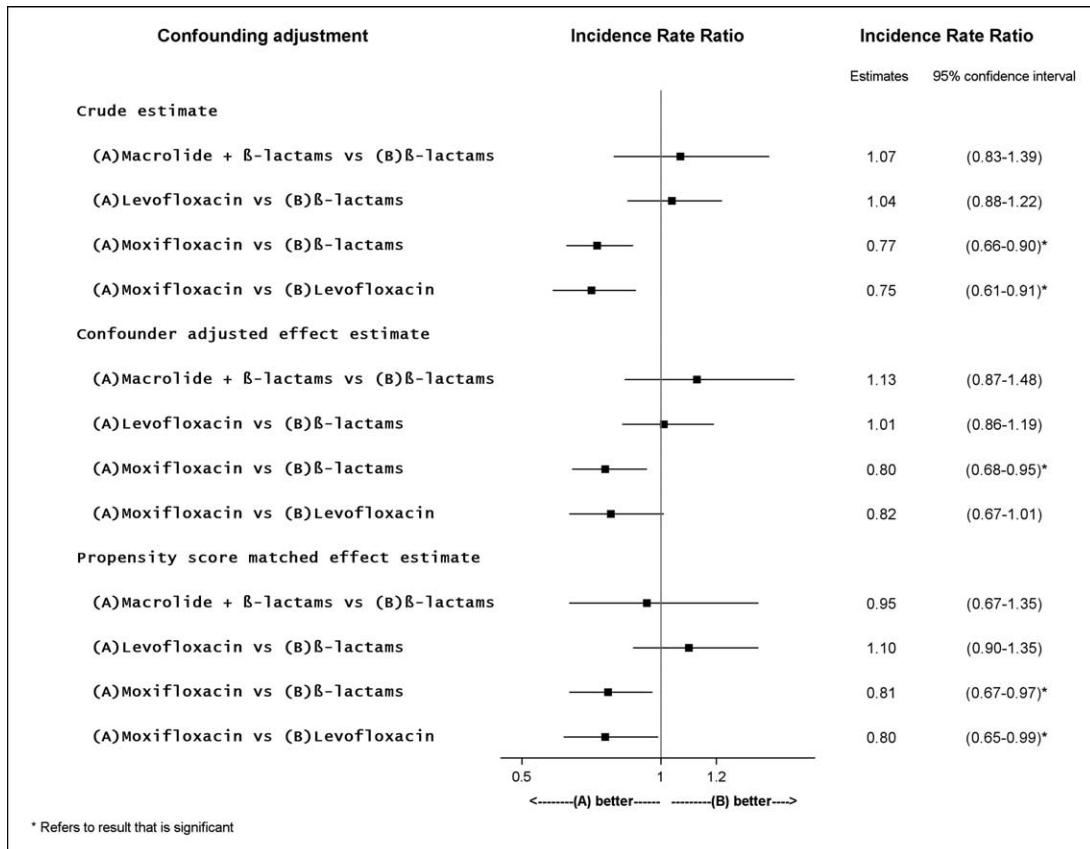
	Composite (%)	ER or Hospitalization (%)	30-Day Nonaccident Related Mortality (%)*
Moxifloxacin	11% (231/2100)	4.2% (88/2100)	<0.24% (<5/2100)
Levofloxacin	14.2% (228/1602)	6.0% (96/1602)	<0.31% (<5/1602)
β-Lactams	13.8% (698/5049)	5.2% (265/5049)	0.20% (10/5049)
Macrolide + β-lactams	14.7% (74/505)	3.6%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

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

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 results in a significantly lower treatment failure rates, 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 postindex 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



**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.

**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 + $\beta$ -lactam vs $\beta$ -Lactam	0.67 (0.41–1.09)	0.78 (0.46–1.27)	0.59 (0.32–1.10)
Levofloxacin vs $\beta$ -lactam	1.15 (0.91–1.46)	1.03 (0.79–1.32)	1.09 (0.80–1.47)
Moxifloxacin vs $\beta$ -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  $P < 0.05$ .

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  $\beta$ -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  $\beta$ -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  $\beta$ -lactam alone, and macrolide+ $\beta$ -lactam vs

$\beta$ -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  $\beta$ -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  $\beta$ -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 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 $\beta$ -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+ $\beta$ -lactam vs $\beta$ -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.<sup>19</sup> Among a general cohort, the Hess group did not find significant differences in the treatment failure rates between moxifloxacin and levofloxacin.<sup>19</sup> 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.<sup>6</sup> 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%).<sup>21,27</sup> By contrast, a US survey reported that levofloxacin (98.8% susceptible) is potent against *S. pneumoniae*.<sup>28,29</sup> 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.<sup>30,31</sup> 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.<sup>8,32,33</sup> Likewise, gender can readily change the antibiotics susceptibility patterns of CAP pathogens.<sup>33</sup> 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  $\beta$ -lactam alone. This finding differs from various other published clinical trials and meta-analyses.<sup>10–18</sup> 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 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  $\beta$ -lactam alone.<sup>34</sup> 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  $\beta$ -lactam + advanced macrolides.<sup>35</sup>

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  $\beta$ -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  $\beta$ -lactam alone. Thus, it would inappropriate to compare the treatment failure rate of fluoroquinolones and  $\beta$ -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  $\beta$ -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.

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