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Original Article

Does Radiographic Evidence of Prior Pulmonary Tubercular Infection Influence the Choice of Empiric Antibiotics for Community-acquired Pneumonia in a Tuberculosis-endemic Area?

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BACKGROUND/PURPOSE: Recent medical literature suggests that use of fluoroquinolones (FQs) might be associated with the delayed diagnosis of pulmonary tuberculosis (TB). The purpose of this study was to assess the impact of radiographic evidence of prior pulmonary TB infection on empiric antibiotic choice in cases of community-acquired pneumonia (CAP), as well as the effect of antibiotic regimens on clinical outcome.

METHODS: A total of 280 patients with CAP between 1 May and 31 December 2007 were included in the study and their medical records were retrospectively reviewed. Patients were divided into two groups: those receiving FQs (FQ group) or those receiving β-lactam-based regimens (β-lactam group). Their demographic data, underlying diseases, clinical features, diseases severity and outcomes were compared.

RESULTS: Radiographic evidence of a previous pulmonary TB infection (odds ratio = 3.507, 95% confidence interval = 1.422–8.645; $p = 0.006$) was an independent factor associated with β-lactam-based regimens. Patients with a modified pneumonia severity index (mPSI) category V were more likely to receive FQ therapy (odds ratio = 2.53, 95% confidence interval = 1.140–5.615; $p = 0.022$). Of the patients with mPSI category V, the 14-day mortality rate of those in the β-lactam group was significantly lower than that of those in the FQ group (0% *vs.* 23%, respectively; $p = 0.044$).

CONCLUSION: Radiographic evidence of a previous pulmonary TB infection and a lower mPSI score increases the probability of the selection of a β-lactam-based regimen for the treatment of CAP.

KEYWORDS: β-lactam, community-acquired pneumonia, fluoroquinolone, tuberculosis

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Introduction

Community-acquired pneumonia (CAP) is a common infection associated with considerable morbidity, mortality and costs.[1–4] In contrast to other antibiotics used to treat CAP, fluoroquinolones (FQs) have excellent *in vitro* activity against *Mycobacterium tuberculosis*.[5,6] The empirical use of FQs in pulmonary tuberculosis (TB) patients who initially present with a clinical picture of CAP is associated with temporary improvement in pulmonary and systemic symptoms and signs.[7,8] However, these effects might also lead to delayed diagnosis of TB and prolonged infectivity, greater morbidity and mortality, and a prolonged period of spread of *M. tuberculosis* in the community.[7,8] In Taiwan, the annual incidence of TB has remained high, ranging from 62.7 per 100,000 population in 2000 to 63.2 per 100,000 population in 2007.[9] In a recent surveillance study in eight Asian countries, TB accounted for 3.0% (13/428) of CAP among those with a known microbiological etiology.[10] The issue of whether FQs should be the first-line antibiotics to treat CAP in TB-endemic areas is still controversial.[11,12] In an era of increasing awareness of TB infection and the announcement of judicious use of FQs, we conducted a study to evaluate whether any hint of a prior TB infection will influence the choice of empiric antibiotics for CAP treatment, and to compare the clinical outcomes of patients receiving different regimens.

Methods

Study design

The study was conducted at Taipei Veterans General Hospital, a 2,900-bed tertiary teaching medical center. This was a retrospective cohort study and included all patients hospitalized with a diagnosis of CAP between May 1 and December 31, 2007.

Inclusion criteria

Patients aged ≥ 18 years were eligible for the study if they had a diagnosis of pneumonia acquired in the community and had been admitted to hospital. These patients satisfied the definition of CAP suggested by the Infectious Disease Society of America:[13] (1) they had an acute illness (symptom onset within 10 days); (2) they had a new chest radiographic infiltrate confirmed by a radiologist; and (3) they had clinical signs suggestive of acute pneumonia, including either one major criterion [fever (aural temperature > 38 °C), hypothermia (aural temperature < 35 °C), cough or sputum production] or two minor criteria (dyspnea, pleuritic pain, clinical evidence of lung consolidation, or a leukocyte count > 10,000/μL or < 4,500/μL). For this study, patients must have received either a β-lactam-based regimen or "respiratory" FQs (moxifloxacin or levofloxacin) within the first 24 hours after presentation at the hospital and must have remained on therapy for at least 48 hours after admission.

Exclusion criteria

Patients were excluded if they: (1) died within the first 24 hours after presentation at the hospital; (2) had been resident in a long-term care facility for ≥ 14 days; (3) were hospitalized during the 90 days prior to admission; (4) had a human immunodeficiency virus (HIV) infection; (5) had primary or metastatic malignancy in the lung parenchyma; (6) had an absolute neutrophil count ≤ 1,000/μL; or (7) were receiving β-lactam plus FQs concomitantly.

Patient data

A structured data instrument collected the following data from the patients' medical records: demographic factors, medical history and comorbid diseases, physical examination, laboratory, image findings and antibiotic treatment. The presence of the following comorbid conditions was documented: diabetes mellitus, HIV infection, neoplastic disease, liver disease, heart failure, cerebrovascular and renal disease. The modified pneumonia severity index (mPSI)[14] scores were calculated based on the worst physiological score derived from physical and laboratory findings collected in our hospital within the first 24 hours. We did not include arterial pH < 7.35 in our mPSI calculation as blood gas analysis was not performed on all patients. Radiographic evidence of prior pulmonary TB infection was defined as fibronodular lesions, fibrocalcified lesions, or apical pleural thickening that was reported by radiologists.

Microbiology

To identify *M. tuberculosis* complex, specimens were cultured on Lowenstein-Jensen and Middlebrook 7H11 medium. Mycobacteria were identified using phenotypic

tests.[15] For bacterial pathogens other than mycobacteria, specimens collected within the first 48 hours of admission were cultured and identified using standard microbiological techniques.[16] *Legionella* was identified using the urinary antigen assay (Binax Inc., Portland, Maine, USA). A definite etiology was established by the recovery of a probable etiologic agent from an uncontaminated specimen (blood). A probable etiologic diagnosis was established by culture of a likely pulmonary pathogen in respiratory secretions (expectorated sputum or aspirate from an endotracheal tube).

Outcomes

The following clinical outcomes were noted: (1) respiratory failure with requirement for mechanical ventilation; (2) length of hospital stay ; (3) all available mycobacterial examinations within 180 days of hospital admission; (4) vital status 30 days after hospital admission (30-day mortality); and (5) vital status during hospital admission (in-hospital mortality). Outcomes were compared between treatment groups for the entire population and also between each mPSI class.

Data analysis

Qualitative variables were compared using the χ^2 or Fisher's exact tests, and quantitative variables were compared using Student's *t* test. Multivariate analyses were performed to determine the independent factors affecting the choice of antibiotic regimen. For all analyses, a p value < 0.05 was considered significant for two-tailed tests. The 30-day survival probability was derived using the Kaplan-Meier method. SPSS version 15.0 was used for all calculations (SPSS Inc., Chicago, IL, USA).

Results

A total of 551 patients were hospitalized with a diagnosis of pneumonia during the study period. However, 271 patients were excluded, including those who died within the first 24 hours after presentation at the hospital (3 patients), who had been resident in a long-term care facility (183 patients), who had been hospitalized in another hospital due to the same CAP episode (29 patients), who had had primary or metastatic malignancy in the lung parenchyma (53 patients), and those receiving concomitant β-lactam plus FQ therapy (3 patients). Of the 280 CAP patients who met the inclusion criteria, 227 received β-lactam-based therapy, and 53 received FQ monotherapy for at least 48 hours after admission (Table 1). A comparison of baseline clinical and laboratory characteristics between treatment groups is shown in Table 2. Univariate analysis showed that male gender and patients with a history of or radiographic evidence of a prior TB infection tended to receive β-lactam-based therapy. Patients with malignancy and more severe diseases tended to receive FQ-based regimens. Of the patients who had radiographic evidence of prior pulmonary TB ($n = 80$), most

Table 1. Empiric antibiotic regimens provided to patients[a]

Antibiotic regimens	*n* (%)
β-lactam-based therapy ($n = 227$)	
β-lactam alone	159 (70.04)
β-lactam/β-lactamase inhibitor	123 (54.19)
Cephamycins	8 (3.52)
Second generation cephalosporins	14 (6.17)
Third generation cephalosporins	10 (4.41)
Fourth generation cephalosporins	1 (0.44)
Carbapenem	3 (1.32)
β-lactam + aminoglycoside	12 (5.29)
β-lactam/β-lactamase inhibitor + aminoglycoside	11 (4.85)
Second generation cephalosporins + aminoglycoside	1 (0.44)
β-lactam + macrolide	52 (22.91)
β-lactam/β-lactamase inhibitor + macrolide	43 (18.94)
Cephamycins + macrolide	2 (0.88)
Second generation cephalosporins + macrolide	4 (1.76)
Third generation cephalosporins + macrolide	1 (0.44)
Fourth generation cephalosporins + macrolide	1 (0.44)
Carbapenem + macrolide	1 (0.44)
β-lactam + macrolide + aminoglycoside	2 (0.88)
β-lactam + minocycline	2 (0.88)
Fluoroquinolones-based therapy ($n = 53$)	
Moxifloxacin	37 (69.81)
Levofloxacin	16 (30.19)

[a]Data presented as *n* (%) of patients with each treatment group.

Table 2. Comparison of clinical characteristics between patients receiving empiric β-lactam-based versus fluoroquinolones therapy[a]

Characteristics	All patients			mPSI category V		
	β-lactam (*n*=227)	FQ (*n*=53)	*p*	β-lactam (*n*=22)	FQ (*n*=13)	*p*
Age (yr)	76.86±13.36	73.68±15.24	0.166	83.5±7.42	83.0±3.14	0.820
Sex, male	195 (85.9)	39 (73.6)	0.029	21 (95.5)	9 (69.2)	0.052
Underlying diseases						
Neoplastic diseases	21 (9.3)	10 (18.9)	0.045	5 (22.7)	6 (46.2)	0.258
Liver disease	5 (2.2)	0 (0)	0.276	1 (4.5)	0 (0)	1.000
Cerebrovascular disease	32 (14.1)	7 (13.2)	0.866	4 (18.2)	4 (30.8)	0.433
Congestive heart failure	26 (11.5)	5 (9.4)	0.673	5 (22.7)	3 (23.1)	1.000
Renal disease	26 (11.5)	8 (15.1)	0.465	8 (36.4)	4 (30.8)	1.000
History of prior TB	33 (14.5)	2 (3.8)	0.033	4 (18.2)	1 (7.7)	0.630
Physical findings						
Alerted mental status	8 (35)	4 (7.5)	0.250	6 (27.3)	3 (23.1)	1.000
Respiratory rate ≥30/min	22 (9.7)	5 (9.4)	0.954	7 (31.8)	5 (38.5)	0.726
Systolic blood pressure <90 mmHg	4 (1.8)	7 (13.2)	0.001	2 (9.1)	3 (23.1)	0.253
Body temperature <35°C or >40°C	3 (1.3)	0 (0)	1.000	0 (0)	0 (0)	–
Pulse rate ≥125 beats/min	16 (7.0)	2 (3.8)	0.540	3 (13.6)	1 (7.7)	1
Laboratory findings						
pH<7.35	11 (4.8)	5 (9.4)	0.196	1 (4.5)	2 (15.4)	0.541
BUN>30 mg/dL	22 (9.7)	5 (9.4)	0.954	16 (72.7)	9 (69.2)	1.000
Sodium<130 mmol/L	22 (9.7)	3 (5.7)	0.435	9 (40.9)	0 (0)	0.013
Glucose>250 mg/dL	19 (8.4)	10 (18.9)	0.024	9 (40.9)	5 (38.5)	0.886
Hematocrit<30%	23 (10.1)	13 (24.5)	0.005	8 (36.4)	6 (46.2)	0.568
PO_2<60 mmHg or oxygen saturation<90%	25 (11.0)	8 (15.1)	0.407	6 (27.3)	6 (46.2)	0.292
Albumin (g/dL)	3.06±0.52	2.98±0.59	0.447	2.59±0.54	2.88±0.64	0.227
CRP (mg/dL)	11.53±8.09	12.04±8.98	0.704	16.6±9.73	15.09±10.6	0.677
Radiographic findings						
Evidence of prior TB	73 (32.2)	7 (13.2)	0.006	6 (27.3)	2 (15.4)	0.680
Upper lung infiltrate						
Single lobe	13 (5.7)	1 (1.9)	0.481	0 (0)	0 (0)	–
Multi-lobes	53 (23.3)	16 (30.2)	0.298	9 (40.9)	6 (46.2)	0.762
Pleural effusion	43 (19.7)	8 (15.4)	0.472	7 (31.8)	2 (16.7)	0.339
mPSI score[b]	101.53±23.90	107.71±30.42	0.125	149.86±14.86	148.38±15.11	0.776
mPSI class						
I	11 (4.8)	5 (9.4)				
II	15 (6.6)	4 (7.5)				
III	68 (30.0)	9 (17.0)				
IV	111 (48.9)	22 (41.5)				
V	22 (9.7)	13 (24.5)	0.003			

[a]Data presented as *n* (%) or mean±standard deviation; [b]not include blood gas data. β-lactam=β-lactam-based therapy group; FQ=fluoroquinolones therapy group; TB=tuberculosis; BUN=blood urea nitrogen; CRP=C-reactive protein; mPSI=modified pneumonia severity index.

Table 3. Comparison of causative pathogens for patients receiving empiric β-lactam-based versus fluoroquinolones therapy[a]

Causative pathogen	β-lactam (n=227)	FQ (n=53)	p
Streptococcus pneumoniae	4 (1.76)	0 (0)	1.000
Haemophilus influenzae	1 (0.44)	0 (0)	1.000
Klebsiella pneumoniae	20 (8.81)	4 (7.55)	1.000
Staphylococcus aureus	7 (3.08)	4 (7.50)	0.229
Escherichia coli	3 (1.32)	1 (1.89)	0.570
Pseudomonas aeruginosa	10 (4.41)	0	0.217
Citrobacter diversus	0 (0)	1 (1.89)	0.189
Serratia sp.	1 (0.44)	0 (0)	1.000
Unidentified GNF-GNB	1 (0.44)	1 (1.89)	0.343
Mix pathogens	9 (3.96)	1 (1.89)	0.405
Mycobacterium tuberculosis	9 (3.96)	0 (0)	0.216
Total culture positive	65 (28.60)	12 (22.60)	0.494

[a]Data presented as n (%). β-lactam=β-lactam-based therapy group; FQ=fluoroquinolones therapy group; GNF-GNB=glucose non-fermenting Gram-negative bacilli.

of them received β-lactam-based therapy (90.1% *vs.* 9.9%). Other radiographic presentations including interstitial infiltration, alveolar infiltrate, and lobar infiltration of single or multi-upper lobes were not significantly different between treatment groups. There were also no significant differences in extra-pulmonary symptoms (including headache, dizziness, sore throat, myalgia, nausea, vomiting and diarrhea) between the two groups. Multivariate analysis showed that the proportion of patients with mPSI category V was significantly higher in the FQ group than in the β-lactam group (odds ratio=2.53, 95% confidence interval=1.140–5.615; p=0.022), but the proportion of patients with radiographic evidence of prior pulmonary TB infection was significantly higher in the β-lactam group (odds ratio=3.507, 95% confidence interval=1.422–8.645; p=0.006). Other characteristics including gender, neoplastic diseases, prior history of TB, anemia and hyperglycemia were not significantly different between the two treatment groups.

The etiologies of CAP are listed in Table 3. All except one were probable diagnoses. Only one definite etiology was documented (mixed *Escherichia coli* and *Edwardsiella tarda* bacteremia). There was no significant difference between the two treatment groups regarding the causative CAP pathogen. Nine patients were diagnosed with pulmonary *M. tuberculosis* infection, and they were all in β-lactam group. The mean interval between initial hospitalization and TB diagnosis was 44.3 days. The *Legionella* urinary antigen assay was performed in 24/280 patients, and the results were all negative.

Taking all patients into consideration, there was no difference in outcome between the two treatment groups (Table 4). The overall in-hospital mortality rate was 7.5% (21/280) and the in-hospital mortality rate in each mPSI group was 0% (category I, II and III), 7.5% (10/133, category IV), and 31.4% (11/35, category V). Comparisons of baseline clinical and laboratory characteristics between the treatment group with the most severe patient group (mPSI category V) are also shown in Table 2. The groups differed significantly only in the proportion of patients with hyponatremia (Sodium<130 mmol/L). A higher proportion of patients with hyponatremia received β-lactam-based therapy. However, no significant differences in length of hospital stay , 14-day mortality or in-hospital mortality were noted between mPSI category V patients either with or without hyponatremia (p>0.23). For patients with "severe CAP" (mPSI IV+V), there was no significant difference in clinical outcome, including 14-day mortality, in-hospital mortality, length of hospital stay and the use of mechanical ventilation between the two treatment groups. Of the patients with mPSI category V, the 14-day mortality rate was significantly lower for those

Table 4. Comparison of outcomes of patients receiving empiric β-lactam-based versus fluoroquinolones therapy[a]

	β-lactam	FQ	*p*
14-day mortality			
All patients	4/227 (1.8)	3/53 (5.7)	0.128
mPSI IV	4/111 (3.6)	0/22 (0)	1.000
mPSI V	0/22 (0)	3/13 (23.1)	0.044
mPSI IV+V	4/133 (3.0)	3/35 (8.6)	0.159
In-hospital mortality			
All patients	15/227 (6.6)	6/53 (11.3)	0.250
mPSI IV	9/111 (8.1)	1/22 (4.5)	1.000
mPSI V	6/22 (27.3)	5/13 (38.5)	0.708
mPSI IV+V	15/133 (11.3)	6/35 (17.14)	0.390
Mean length of stay (d)			
All patients	16.16	16.64	0.860
mPSI I	7.91	8.80	0.794
mPSI II	9.00	12.75	0.607
mPSI III	13.65	13.89	0.938
mPSI IV	17.30	14.68	0.324
mPSI V	27.23	26.08	0.909
mPSI IV+V	18.94	18.91	0.995
MV use within 24 hr			
All patients	14/227 (6.2)	6/53 (11.3)	0.232
mPSI IV	6/111 (5.4)	1/22 (4.5)	1.000
mPSI V	6/22 (27.3)	5/13 (38.5)	0.708
mPSI IV+V	12/133 (9.0)	6/35 (17.1)	0.216
MV use after 24 hr			
All patients	14/227 (6.2)	6/53 (11.3)	0.232
mPSI IV	11/111 (9.9)	3/22 (13.6)	0.702
mPSI V	2/22 (9.1)	2/13 (15.4)	0.618
mPSI IV+V	13/133 (9.8)	5/35 (14.3)	0.538

[a]Data presented as the number of positive cases/total number of cases in the group (%) or *n*. β-lactam = β-lactam-based therapy group; FQ = fluoroquinolones therapy group; mPSI = modified pneumonia severity index; MV = mechanical ventilation.

receiving β-lactam-based therapy than for those receiving FQ therapy (0% *vs.* 23%, respectively; $p = 0.044$). The 30-day survival curve is shown in the Figure. The *p* values for 14-day and 30-day survival between the groups were 0.019 and 0.197, respectively.

Discussion

There is evidence showing that empiric FQ use in pulmonary TB patients who initially present with a clinical picture of CAP is associated with delayed diagnosis and prolonged infectivity, greater morbidity and mortality and a prolonged period of spread of *M. tuberculosis* in the community.[7,8] Although our study cohort contains culture-positive TB patients rather than CAP patients, this report shows the importance of judicious use of FQs as empiric antibiotics for CAP in a TB-endemic area. The current Taiwanese guidelines on antimicrobial therapy for pneumonia in adults published by the Infectious Diseases Society of Taiwan recommend that newer FQs

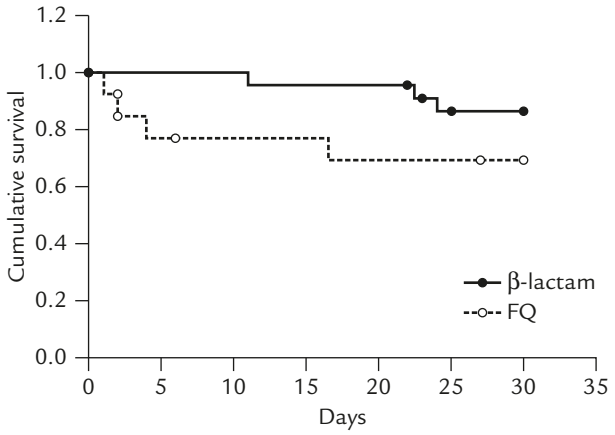

Figure. The 30-day survival curve in patients with modified pneumonia severity index category V. β-lactam = β-lactam-based therapy group; FQ = fluoroquinolones therapy group.

may be the drug-of-choice in the treatment of CAP, but emphasize that "when newer FQs are used, pulmonary TB should be considered and aggressive microbiological evaluation for *M. tuberculosis* should be performed".[17] This has affected the choice of antibiotics, as our results show that radiographic evidence of a prior TB infection increases the probability that a β-lactam-based regimen will be selected for the treatment of CAP, since reactivation of TB is the major source of TB infection in non-HIV-infected adult patients.[18,19] A history of prior TB infection is not an independent factor that influences the physician's prescription. Because some patients cannot provide enough (or correct) information, doctors still depend on radiographic findings to choose empiric antibiotics.

In this study, the proportion of patients with mPSI category V was significantly higher in the FQ therapy group than in the β-lactam-based therapy group. There are several possible reasons for this. First, FQs, but not β-lactams, are active against high level penicillin-resistant strains of *Streptococcus pneumoniae*.[20–22] Second, in Taiwan, FQs are available in intravenous form, but newer macrolides are available only in oral form for the treatment of atypical pathogens. Third, in some studies focusing on patients with *Legionella* pneumonia, the time-to-improvement of clinical symptoms, signs and laboratory examinations was shorter in those patients who received FQ therapy than patients who received macrolide therapy.[23,24] Fourth, the disease course and clinical picture of severe pneumonia tends to be more fulminate, which is more common in acute bacterial pneumonia than in TB infection.

Of the mPSI category V patients, there was only one clinical characteristic that showed a significant difference between the two treatment groups (increased hyponatremia in the β-lactam-based therapy group). However, the 14-day mortality was lower in the β-lactam-based therapy group. Despite a similar spectra of activity and favorable resistance patterns against CAP pathogens, emerging evidence suggests the superiority of combination therapy (β-lactam with macrolides) over FQ monotherapy for certain populations; particularly patients with severe CAP or bacteremic pneumococcal CAP.[25–34] The current Infectious Disease Society of America/American Thoracic Society guidelines on the management of CAP in adults recommends a β-lactam plus either azithromycin or an FQ in patients who are admitted to intensive care units.[21] The superiority of β-lactam-azithromycin combination therapy over FQ monotherapy for patients with severe CAP may be explained by many factors.[33] Macrolides have immunomodulatory properties that may contribute to the superiority of combination therapy.[35–37] Several studies have demonstrated that macrolides reduce the proinflammatory response to infectious stimuli, including many primary cytokines (such as interleukin-1, tumor necrosis factor-alpha, interleukin-6 and interleukin-8). Modulation of the immune response may improve patient outcomes by diminishing the proinflammatory complications of sepsis such as secondary organ dysfunction. Macrolides also reduce the adherence of pneumococci to respiratory epithelial cells.[38] In addition, the use of azithromycin and β-lactam, two agents with different mechanisms of action, may additively or synergistically enhance bacterial killing over that of single-agent therapy.[39,40]

There are some limitations in this study. Because of the retrospective nature of the investigation, the characteristics of the patients in the two treatment groups were not fully randomized. No aggressive survey of etiologic diagnoses led to an identifiable pathogen in most patients. A probable etiological diagnosis implicated that the identified organism might be a colonization or a contaminant. A small sample size also restricted the power of the study.

In conclusion, radiographic evidence of a prior pulmonary TB infection is the main factor that skews the choice of empiric antibiotics toward β-lactams for CAP. The proportion of patients with mPSI category V was higher in

the FQ therapy group. However, in patients with mPSI category V, the 14-day mortality rate was lower in the β-lactam group. In patients with severe CAP and with a risk of TB infection, β-lactam-based therapy is a safe and reliable choice of empirical treatment.

References

1. Gleason PP, Kapoor WN, Stone RA, Lave JR, Obrosky DS, Schulz R, et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *JAMA* 1997;278:32–9.
2. Whittle J, Lin CJ, Lave JR, Fine MJ, Delaney KM, Joyce DZ, et al. Relationship of provider characteristics to outcomes, process, and costs of care for community-acquired pneumonia. *Med Care* 1998;36:977–87.
3. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618–24.
4. Gilbert K, Gleason PP, Singer DE, Marrie TJ, Coley CM, Obrosky DS, et al. Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. *Am J Med* 1998;104:17–27.
5. Bozeman L, Burman W, Metchock B, Welch L, Weiner M. Fluoroquinolone susceptibility among Mycobacterium tuberculosis isolates from the United States and Canada. *Clin Infect Dis* 2005;40:386–91.
6. Yew WW, Piddock LJ, Li MS, Lyon D, Chan CY, Cheng AF. In-vitro activity of quinolones and macrolides against mycobacteria. *J Antimicrob Chemother* 1994;34:343–51.
7. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. *Clin Infect Dis* 2002;34:1607–12.
8. Wang JY, Hsueh PR, Jan IS, Lee LN, Liaw YS, Yang PC, et al. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. *Thorax* 2006;61:903–8.
9. Center for Disease Control. *Statistics of Communicable Diseases and Surveillance Report in Taiwan Area, 2007*. Taipei, Taiwan: *The Center*, 2008:141–54.
10. Song JH, Oh WS, Kang CI, Chung DR, Peck KR, Ko KS, et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. *Int J Antimicrob Agents* 2008;31:107–14.
11. Abiad H. Does the use of fluoroquinolones for the empiric treatment of pneumonia delay initiation of treatment of tuberculosis? *Clin Infect Dis* 2002;35:1572; author reply 1572–3.
12. Hsueh PR. Should fluoroquinolones be first-line antibiotics in the treatment of community-acquired pneumonia in areas with high incidence of tuberculosis? *J Microbiol Immunol Infect* 2007;40:386–7.
13. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis* 2000;31:347–82.
14. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243–50.
15. Tokars JI, Rudnick JR, Kroc K, Manangan L, Pugliese G, Huebner RE, et al. U.S. hospital mycobacteriology laboratories: status and comparison with state public health department laboratories. *J Clin Microbiol* 1996;34:680–5.
16. Thomson RB Jr, Miller JM. Specimen collection, transport, and processing: bacteriology. In: Murray PR, Baron EJ, Pfaller MA, Jorgensen JH, Yolken RH, eds. *Manual of Clinical Microbiology*, 8th edition. Washington DC: American Society for Microbiology Press, 2003:286–330.
17. Infectious Diseases Society of Taiwan, Taiwan Society of Pulmonary and Critical Medicine, Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines. Guidelines on antimicrobial therapy of pneumonia in adults in Taiwan, revised 2006. *J Microbiol Immunol Infect* 2007;40:279–83.
18. Cantwell MF, Snider DE Jr, Cauthen GM, Onorato IM. Epidemiology of tuberculosis in the United States, 1985 through 1992. *JAMA* 1994;272:535–9.
19. Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* 2005;293:2767–75.
20. Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group. *Arch Intern Med* 2000;160:1399–408.
21. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, 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;44Suppl 2:S27–72.
22. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37:1405–33.
23. Haranaga S, Tateyama M, Higa F, Miyagi K, Akamine M, Azuma M, et al. Intravenous ciprofloxacin versus erythromycin in the treatment of Legionella pneumonia. *Intern Med* 2007;46:353–7.
24. Sabria M, Pedro-Botet ML, Gomez J, Roig J, Vilaseca B, Sopena N, et al. Fluoroquinolones *vs.* macrolides in the treatment of Legionnaires disease. *Chest* 2005;128:1401–5.

25. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* 2004;170:440–4.
26. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 2003;123:1503–11.
27. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. *Ann Pharmacother* 2000;34:446–52.
28. Garcia Vazquez E, Mensa J, Martinez JA, Marcos MA, Puig J, Ortega M, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. *Eur J Clin Microbiol Infect Dis* 2005;24:190–5.
29. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. *Chest* 2001; 119:1420–6.
30. Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of beta-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. *Antimicrob Agents Chemother* 2007;51:3977–82.
31. Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2003;36:389–95.
32. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997. *Am J Med* 1999;107:34S–43S.
33. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med* 2001;161:1837–42.
34. Weiss K, Low DE, Cortes L, Beaupre A, Gauthier R, Gregoire P, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. *Can Respir J* 2004;11:589–93.
35. Ianaro A, Ialenti A, Maffia P, Sautebin L, Rombola L, Carnuccio R, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther* 2000;292:156–63.
36. Orman KL, English BK. Effects of antibiotic class on the macrophage inflammatory response to Streptococcus pneumoniae. *J Infect Dis* 2000;182:1561–5.
37. Parnham MJ. Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. *Curr Opin Infect Dis* 2005;18:125–31.
38. Lagrou K, Peetermans WE, Jorissen M, Verhaegen J, Van Damme J, Van Eldere J. Subinhibitory concentrations of erythromycin reduce pneumococcal adherence to respiratory epithelial cells in vitro. *J Antimicrob Chemother* 2000;46:717–23.
39. Deshpande LM, Jones RN. Antagonism between penicillin and erythromycin against Streptococcus pneumoniae: does it exist? *Diagn Microbiol Infect Dis* 2003;46:223–5.
40. Djurkovic S, Loeffler JM, Fischetti VA. Synergistic killing of Streptococcus pneumoniae with the bacteriophage lytic enzyme Cpl-1 and penicillin or gentamicin depends on the level of penicillin resistance. *Antimicrob Agents Chemother* 2005;49:1225–8.