



Guideline adherence and macrolides reduced mortality in outpatients with pneumonia

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Summary

Background: For outpatients with pneumonia, guidelines recommend empiric antibiotics and some suggest macrolides are preferred agents. We hypothesized that both guideline-concordant antibiotics and macrolides would be associated with reduced mortality.

Methods: All outpatients with pneumonia assessed at 7 Emergency Departments in Edmonton, Alberta, Canada were enrolled in a population-based registry that included clinical-radiographic data, Pneumonia Severity Index (PSI) and treatments. Guideline-concordant regimens included macrolides and respiratory fluoroquinolones; other regimens were “discordant”. Main outcome was 30-day all-cause mortality.

Results: The study included 2973 outpatients; mean age 51 years, 47% female, most had mild pneumonia (73% PSI Class I–II). Over 30-days, 38 (1%) patients died, 228 (8%) were hospitalized, and 253 (9%) reached the endpoint of death or hospitalization. Most (2845 [96%]) patients received guideline-concordant antibiotics. Compared to patients receiving discordant antibiotics, those receiving guideline-concordant antibiotics were less likely to die within 30-days (8 [6%] versus 30 [1%], adjusted OR 0.23, 95% CI 0.09–0.59, $p = 0.002$). Within the guideline-concordant subgroup, compared to the 947 (33%) patients treated with fluoroquinolones, those receiving macrolides [1847 (64%)] were less likely to die (25 [3%] versus 4 [0.2%], adjusted OR 0.28, 95% CI 0.09–0.86, $p = 0.03$).

Conclusions: In outpatients with pneumonia, treatment with guideline-concordant antibiotics and macrolides were both associated with mortality reduction.

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Community acquired pneumonia (CAP), combined with influenza, is the eighth leading cause of death in developed nations.^{1,2} In 2006, in the US alone, there were 4.2 million ambulatory care visits for pneumonia with direct costs of almost \$9 billion annually.^{2–4} Although 80% of the treatment for CAP is provided in the outpatient setting,^{5,6} most of the published research has only studied hospitalized patients.

The most commonly identified bacterial etiologies for pneumonia in the outpatient setting are similar to inpatients, and include “typical” organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* and “atypical” organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella spp.*⁷ Unfortunately, available diagnostic studies only identify the causative organism in about half of cases.⁷ Therefore, empiric treatment is needed and most treatment guidelines acknowledge this premise.⁸ The recommended treatment regimens are based upon the likely etiologic agents, expected susceptibilities, and expert opinion. Recent studies of hospitalized patients with pneumonia report that use of guideline-concordant antibiotics reduce morbidity and mortality.^{9–12} In addition, several recent lines of evidence indicate that regimens containing macrolides lead to improved outcomes.^{13–17}

Therefore, we undertook a population-based cohort study of more than 3000 outpatients with pneumonia. We hypothesized that guideline-concordant antibiotics in general, and macrolide antibiotics in particular, would be associated with reduced 30-day all-cause mortality in outpatients with pneumonia.

Methods

Subjects and setting

We conducted a population-based prospective cohort study of all adult outpatients with community acquired pneumonia (CAP) seen at seven Emergency Departments (EDs) in Edmonton, Alberta, Canada. Patients were enrolled from 2000 to 2002 and followed until 2007. The sites included two tertiary care hospitals, two hospitals that provided secondary and tertiary care, two community hospitals and one free-standing ED.

CAP was defined as two or more symptoms or signs (cough, productive or nonproductive; pleuritic chest pain; shortness of breath; temperature $> 38^{\circ}\text{C}$; and crackles, or bronchial breathing on auscultation) plus radiographic evidence of pneumonia as interpreted by the treating physician. All CAP patients in the cohort were managed according to a validated clinical pathway that outlined recommendations for triage (based on the Pneumonia Severity Index [PSI]), investigations and guideline-concordant antibiotics. Any patient with a PSI score >90 (Class IV or V) or any patient that the ED physician thought required hospital admission was referred to an inpatient physician. All others were treated as outpatients and discharged home. Excluded from the pathway (and thus, our study) were immunosuppressed patients, defined as patients who were using 10 mg per day of prednisone for 1 month, or who were using other immunosuppressive agents, or who had human immunodeficiency virus with a CD4 cell count $< 250/\mu\text{L}$. As well, excluded were those who had been

hospitalized within the previous 10–14 days, were pregnant, or had tuberculosis or cystic fibrosis. The study was approved by the Health Ethics Review Board of the University of Alberta (Edmonton, Alberta, Canada; approval #Pro00004999).

Data collected

Trained research nurses collected sociodemographic variables, clinical characteristics (e.g., premorbid functional status, smoking status), laboratory tests and chest radiograph reports for all patients. The PSI was calculated at point of care as part of the pathway. The PSI is a summary measure of the severity of pneumonia-specific illness at presentation and it is based on three demographic variables (age, sex, nursing home residence), five co-morbidities (cancer, chronic kidney disease [CKD], heart failure, liver disease, stroke), five physical findings (confusion, tachypnea, tachycardia, hypotension, fever or hypothermia), and seven laboratory tests (acidosis, elevated BUN, hyponatremia, hyperglycemia, anemia; hypoxemia, pleural effusion on chest radiograph). The PSI score (continuous variable) is an exhaustively validated summary measure of 20 independent prognostic variables for patients with pneumonia and it is designed to predict 30-day all-cause mortality.

Antibiotic regimens

Pre-printed prescriptions with suggested antibiotic options were provided to all ED physicians as part of the clinical pathway, although there were no mandatory choices. The antibiotics recommended were 10-days of any one of the following: doxycycline 200 mg po \times 1 then 100 mg po BID, levofloxacin 500 mg po daily, azithromycin 500 mg po \times 1 then 250 mg po daily, clarithromycin 500 mg po BID or erythromycin 500 mg po QID. For the purposes of our study, a regimen needed to contain *at least one* of the antibiotics on the pre-printed prescription to be considered “guideline-concordant”. The guideline-concordant antibiotic choices were based on the 2000 IDSA CAP guidelines¹⁸ and closely correspond with 2003 and 2007 guidelines (all emphasizing coverage of “atypical” organisms such as *C. pneumoniae*, *M. pneumoniae* and *Legionella spp.*).^{8,19} Within the concordant antibiotic choices, we examined differences between the macrolides and the respiratory fluoroquinolones. Any regimen that did not have doxycycline, a respiratory fluoroquinolone, or a macrolide was considered “guideline-discordant”. Because “over-treatment” might be considered guideline-discordant by some, we undertook a sensitivity analysis wherein we excluded the 16 patients that received non-recommended combination regimens irrespective of whether or not atypical coverage was provided.

Outcomes

The primary outcome was 30-day all-cause mortality. In addition, we examined the composite endpoint of 30-day mortality or hospitalization. These outcomes were ascertained using multiple linked and well-validated provincial administrative databases.²⁰ The rate of successful linkage

between population-based clinical registries and our provincial administrative databases generally exceeds 95%.²⁰

Statistical analysis

The baseline characteristics of patients receiving guideline-concordant versus discordant antibiotics were compared using a χ^2 or Students' *t*-test, as appropriate. Multivariable logistic regression was used to determine the independent association between receipt of guideline-concordant antibiotics and 30-day mortality. We forced use of guideline-concordant antibiotics (dichotomous variable representing the independent exposure of interest), the PSI (continuous summary measure of pneumonia severity calculated using 20 variables: age, sex, nursing home status, 5 co-morbidities, 5 physical signs, and 7 laboratory findings) and chest radiograph confirmation of pneumonia into all models. We did not separately adjust for older age, sex, and nursing home residence again because the PSI already controls for these variables and because we wanted to avoid unnecessary overfitting of models; with only 38 "events" we could only adjust for 3–4 variables before overfitting might arise. We refer to our final models as "age, sex, and clinical-radiographic severity of illness at presentation" adjusted. We then considered other variables based on clinical importance, univariate *p*-values < 0.1 or when a variable confounded (a confounder was identified by a greater than 10% change in beta-coefficient) the association between use of guideline-concordant antibiotics and outcomes, irrespective of statistical significance. We tested all first order interaction terms, but none achieved statistical significance and none were included. As a measure of

model "fit" we calculated the c-statistics (akin to the ROC or area under the curve).

We then restricted analyses to only those patients who had received guideline-concordant antibiotics. We excluded doxycycline users as well as those who had received any combination therapy, as these regimens made up less than 3% of the guideline-concordant antibiotic regimens. We compared respiratory fluoroquinolone with macrolide monotherapy and undertook identical analyses to those already described to determine the independent association between macrolide monotherapy and outcomes.

We carried out 12 sensitivity analyses, 6 for the guideline concordance studies and then repeated the same 6 analyses for the macrolide versus quinolone studies. First, we used an alternate approach to control for pneumonia severity. Rather than use the PSI score, we created models that directly adjusted for age, sex, nursing home status, all 17 of the other variables included in the PSI, chest radiograph confirmation and then included guideline-concordant antibiotic use.

Second, using standard methods,²³ we conducted a propensity (to receive guideline-concordant antibiotics or macrolides) score adjusted analysis of outcomes rather than the traditional multivariable logistic regression models used for our main analyses. The propensity score is intended to control for the possibility of physician selection bias (i.e., forms of confounding by indication or channeling) and other unmeasured confounders.²³ The variables included in the propensity score were all variables presented in Table 1 as well as number of medications, site of care, and a term for age-squared that helped improve model fit as assessed by the c-statistic.²³

Table 1 Characteristics of 2973 outpatients with pneumonia according to the use of guideline-concordant antibiotics.

Characteristics	Guideline-concordant antibiotics, <i>n</i> = 2845 No. (%)	Guideline-discordant antibiotics, <i>n</i> = 128 No. (%)	<i>P</i> value
Age in years, Mean (SD)	51.4 (20.0)	52.5 (22.0)	0.54
Age > 65	804 (28)	46 (36)	0.06
Female	1132 (47)	61 (48)	0.85
Nursing home resident	116 (4)	14 (11)	<0.001
Current Smoker	570 (20)	18 (14)	0.10
Impaired Mobility	140 (5)	17 (13)	<0.001
<i>Co-morbidities</i>			
Cancer	149 (5)	10 (8)	0.20
COPD	235 (8)	16 (13)	0.10
Heart Failure	104 (4)	7 (5)	0.29
Diabetes Mellitus	199 (7)	12 (9)	0.30
Liver Disease	25 (1)	2 (2)	0.43
Chronic Kidney Disease	58 (2)	8 (6)	0.002
<i>Pneumonia Severity Index</i>			
Mean (SD) Score	54.5 (28.5)	63.1 (35.3)	0.001
Class I	448 (16)	13 (10)	0.002
Class II	1654 (58)	61 (48)	
Class III	408 (14)	29 (23)	
Class IV	290 (10)	21 (16)	
Class V	45 (2)	4 (3)	
Chest Radiograph Confirmed Pneumonia	1512 (53)	71 (55)	0.61

Third, we re-ran the main analyses after excluding 1390 patients with chest radiographs interpreted as normal by radiologists post-discharge, as some experts still contend that one cannot have pneumonia without radiographic abnormalities on plain films.^{21,22} Fourth, we re-ran analyses after excluding 725 patients at high risk of multi-drug resistant (MDR) organisms because of nursing home residence, impaired functional status, or already treated with antibiotics before presentation. As mentioned, patients recently discharged from hospital were already excluded. Fifth, we removed 16 patients who were over-treated from guideline-concordant group and re-ran analyses.

Last, we re-examined outcomes among all 2779 patients that survived to 30-days and followed them until 1-year after their episode of pneumonia (i.e., a post-convalescent analysis). Because it is somewhat implausible that short-term exposure to guideline-concordant antibiotics would affect outcomes so long after the acute episode of illness has passed, a statistically significant benefit attributable to antibiotic exposure still present at 1-year would suggest residual and possibly refractory confounding. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA.)

Results

Patient characteristics

Overall, almost 7000 consecutive adult patients were triaged and treated according to the validated clinical pathway for pneumonia. Of these patients, 3344 were discharged home from the ED and potentially eligible for inclusion. We excluded 237 (8%) patients who could not be linked to provincial administrative databases and 134 (3%) patients without any antibiotic data, leaving a final sample size of 2973 outpatients. The mean age was 51 (SD 20) years, 47% were female, and 73% had "mild" pneumonia (PSI Class I–II; see Table 1). Only 16 (<1%) patients left the ED against medical advice. Within 30-days, 38 (1%) patients had died, 228 (8%) were admitted to hospital, and 253 (9%) reached the composite endpoint of death or hospitalization.

Site-level clinical pathway adherence

In terms of overall measures of adherence to the clinical pathway, 100% of patients had a chest radiograph, 96% received guideline-concordant antibiotics, 94% had oxygen saturation measured and 88% of those discharged home had PSI Class I–III pneumonia. Overall use of guideline-concordant antibiotics across the seven sites was very high (96%). There was minimal variation across the sites, with rates of guideline-concordant antibiotic use ranging from 94 to 98% ($p = 0.11$).

Guideline-concordant versus discordant antibiotic use

Most ($n = 2845$, 96%) patients received guideline-concordant antibiotics. Only 16 (<1%) of these patients might be considered to have received "discordant" regimens on the basis of over-treatment with non-

recommended combination regimens (Table 1). Those who received guideline-concordant antibiotics were younger, less likely to be from a nursing home or have impaired mobility, and had less severe pneumonia (Table 1). Overall, respiratory fluoroquinolones ($n = 947$, 34%) and macrolides ($n = 1832$, 66%) were the most commonly used regimens (Table 2). Patients receiving guideline-concordant therapy were less likely to die within 30-days (8[6%] v. 30[1%] with discordant antibiotics, $p < 0.001$ for difference, see Fig. 1). The independent association between receipt of guideline-concordant antibiotics and mortality persisted in multivariable analyses that controlled for age, sex, and clinical-radiographic severity of illness at presentation (adjusted OR 0.23; 95% CI 0.09–0.59; $p = 0.002$; c-statistic = 0.90). There was also a non-significant reduction in the combined endpoint of 30-day death or hospitalization with guideline-concordant antibiotic use (20 [16%] versus 233 [8%]), age, sex, and clinical-radiographic severity of illness at presentation adjusted OR 0.64; 95% CI 0.37–1.09; $p = 0.10$; c-statistic = 0.76 and see Fig. 1).

In terms of sensitivity analyses, regardless of how severity of pneumonia was modeled, use of propensity scores (c-statistic for propensity model = 0.70), or exclusion of 3 pre-defined subgroups of patients, the main results of our analyses with respect to 30-day all-cause mortality were essentially unaltered although some results achieved only borderline statistical significance (Fig. 2). Conversely, in the post-convalescent analysis among 2935 30-day survivors, guideline-concordant antibiotics were not associated with reduced 1-year mortality (adjusted OR 0.75, 95% CI 0.37–1.54, $p = 0.43$).

Macrolide versus respiratory fluoroquinolone use

Within the guideline-concordant subgroup of 2845 patients, there were 1832 (66%) macrolide users and 947 (33%) respiratory fluoroquinolone users. Their characteristics,

Table 2 The number and proportion of guideline-concordant versus discordant antimicrobial regimens used for outpatients with pneumonia.

Antimicrobial Regimens	Patients, No. (%)
<i>Guideline-Concordant (n = 2845)</i>	
Macrolides	1832 (64)
Azithromycin	1292 (45)
Clarithromycin	518 (18)
Erythromycin	22 (1)
Quinolones	947 (33)
Levofloxacin	915 (32)
Moxifloxacin	28 (1)
Gatifloxacin	4 (0.1)
Doxycycline	26 (1)
Macrolide + Beta-lactam	24 (1)
Other Combinations	16 (1)
<i>Guideline-Discordant (n = 128)</i>	
Cephalosporins	55 (43)
Amoxicillin or Amoxicillin-Clavulanate	35 (27)
Ciprofloxacin	13 (10)
Trimethoprim-Sulfamethoxazole	8 (6)
Other Combinations	17 (13)

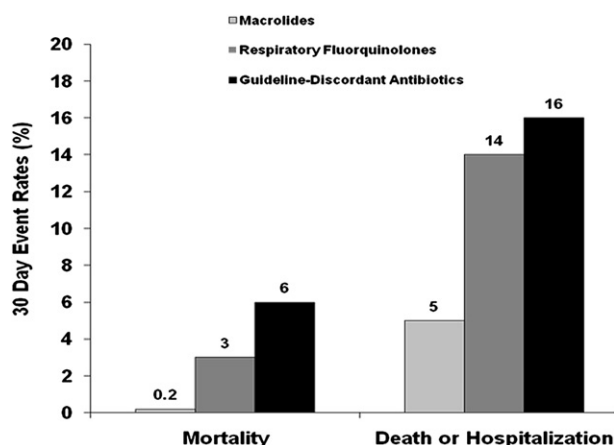


Figure 1 30-Day outcomes for outpatients with pneumonia who received guideline-concordant (either macrolide or respiratory fluoroquinolone based) versus guideline-discordant antibiotic regimens.

stratified by antibiotic regimen, are presented in Table 3. Compared to fluoroquinolone users, the patients treated with macrolides were younger, healthier, and had less severe pneumonia (Table 3). In terms of 30-day mortality, 4 of 1832 (0.2%) macrolide users died versus 25 of 947 (3%) fluoroquinolone users (age, sex, and clinical-radiographic severity of illness adjusted OR 0.28; 95% CI 0.09–0.86; $p = 0.030$; c-statistic = 0.89 and see Fig. 1). There was also a statistically significant reduction for the composite endpoint of death or hospitalization within 30-days: 90 (5%) with macrolides versus 137 (14%) for fluoroquinolones (age, sex, and clinical-radiographic severity of illness adjusted OR 0.61; 95% CI 0.45–0.84; $p = 0.003$; c-statistic = 0.80).

In terms of sensitivity analyses, regardless of how severity of pneumonia was modeled, use of propensity scores (c-statistic for model = 0.78), or exclusion of 2 pre-defined subgroups of patients, the main results of our analyses with respect to 30-day all-cause mortality were similar (Fig. 3). Conversely, in the final post-convalescent analysis among the 2749 30-day survivors who had been exposed to guideline-concordant antibiotics, macrolide use itself was not associated with reduced 1-year mortality (adjusted OR 0.70, 95% CI 0.47–1.04, p -value = 0.08).

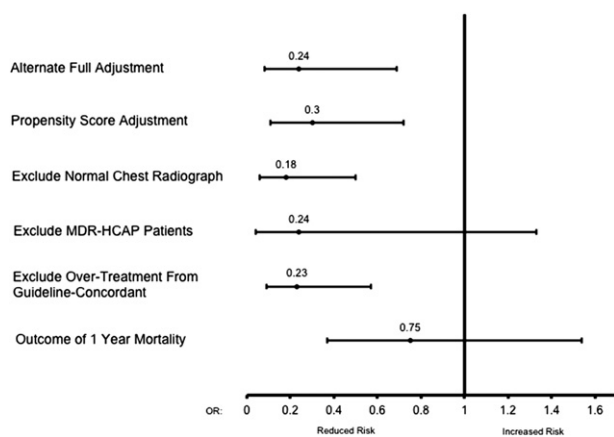


Figure 2 Six sensitivity analyses with respect to guideline-concordant antibiotic treatments and 30-day mortality.

Discussion

In a population-based cohort of almost 3000 outpatients with pneumonia managed according to a validated clinical pathway, we found high rates (96%) of guideline-concordant antibiotic treatment could be achieved with little variation across 7 sites. Furthermore, guideline-concordant antibiotic use was associated with a significant 77% adjusted relative reduction in 30-day all-cause mortality. Within the guideline-concordant subgroup, we also found that those who used macrolides had a 72% adjusted relative reduction in 30-day mortality when compared to those treated with fluoroquinolones.

To our knowledge, this is the largest prospective study investigating the impact of guideline-concordant antibiotic use in outpatients with pneumonia, as well as the first to report a clinical benefit with either guideline concordance or macrolide use. Previous studies in outpatients with pneumonia were either relatively small, retrospective, or had limited clinical data for multivariable adjustment.^{5,24,25} Gleason et al. prospectively looked at 864 outpatients and found that antibiotic treatments concordant with the 1993 ATS guidelines did not improve outcomes, perhaps because these guidelines did not recommend routine coverage for atypical organisms.²⁴

In contrast to outpatient studies, the mortality benefits we observed with guideline-concordant antibiotic use are similar to the results of several studies in hospitalized patients with more severe pneumonia.^{9–12} These investigators have usually interpreted their findings as evidence that atypical coverage leads to better outcomes.^{9,12} Given that at least 20–30% of patients with pneumonia have infections with atypical organisms, perhaps this is unsurprising.^{7,26}

More surprising, perhaps, is that the patients exposed to macrolides had significantly lower 30-day mortality than those exposed to respiratory fluoroquinolones. While this phenomenon has been consistently documented with observational studies of hospitalized patients,^{15–17} it has not previously been reported for outpatients. Furthermore, in a systematic review of six active-comparator randomized trials of antibiotic treatment in 1857 very low risk outpatients with pneumonia, macrolide related mortality benefits were not demonstrable.²⁷ However, there were no reported deaths in these six trials compared with the 38 deaths in our cohort of 2973 patients. Our study is larger than all the published trials together and it might simply be that the trial subjects studied were at such low risk of mortality that a benefit could not be appreciated.

If our results are not a result of chance, bias, or confounding, the most likely mechanistic explanation rests on the macrolide-specific immunomodulatory effects that have been previously reported.²⁸ These effects are believed to be mediated by several properties of macrolides that have been observed, in-vitro and in-vivo, and include: decreases in pro-inflammatory cytokines (TNF- α , IL-1, IL-6, IL-8 and IFN- γ), increases in anti-inflammatory cytokines, and decreases in neutrophil chemotaxis, leukocyte adhesion, and oxidative metabolism.²⁹ Although the evidence is more limited, in fact the fluoroquinolones also modulate the immune system and have been demonstrated to reduce pro-inflammatory cytokine levels and inhibit

Table 3 Characteristics of 2779 outpatients with pneumonia who received guideline-concordant antibiotics stratified by antibiotic treatment.

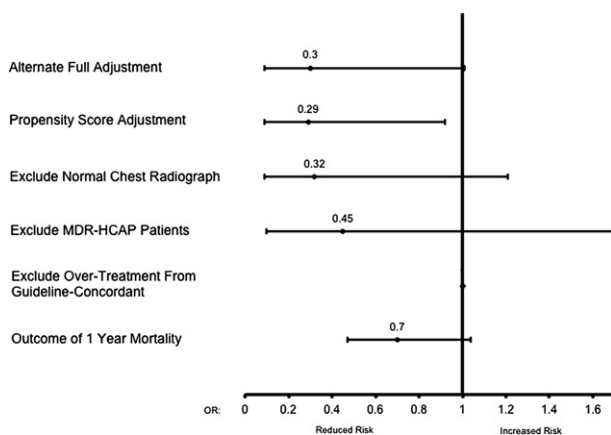
Characteristics	Macrolide-Based Regimens <i>n</i> = 1832, No. (%)	Respiratory Fluoroquinolones <i>n</i> = 947, No. (%)	<i>P</i> Value
Age in years, Mean (SD)	46.1 (17.9)	61.9 (19.7)	<0.001
Age > 65	314 (17)	470 (50)	<0.001
Female	871 (48)	427 (45)	0.22
Nursing home resident	17 (1)	97 (10)	<0.001
Current Smoker	151 (16)	405 (22)	<0.001
Impaired Mobility	34 (2)	101 (11)	<0.001
<i>Co-morbidities</i>			
Cancer	55 (3)	90 (10)	<0.001
COPD	58 (3)	171 (18)	<0.001
Heart Failure	23 (1)	78 (8)	<0.001
Diabetes Mellitus	83 (5)	112 (12)	<0.001
Liver Disease	17 (1)	8 (1)	0.83
Chronic Kidney Disease	18 (1)	39 (4)	<0.001
<i>Pneumonia Severity</i>			
Mean (SD) Score	46.0 (22.6)	71.3 (31.4)	<0.001
Class I	363 (20)	78 (8)	<0.001
Class II	1209 (66)	404 (43)	
Class III	181 (10)	217 (23)	
Class IV	76 (4)	207 (22)	
Class V	3 (0.2)	41 (4)	
Chest Radiograph Confirmed Pneumonia	528 (56)	948 (52)	0.04

secretion of TNF- α , IL-6 and IL-8.³⁰ Although we cannot examine the degree and balance of immunomodulation that might be present, it might be interesting to speculate that the non-microbial effects of both antibiotic classes are among the reasons that the guideline-concordant patients (99% exposed to macrolide or fluoroquinolone) had such good outcomes.^{28–30}

Despite the strengths of this study, we acknowledge at least five limitations. First, it was not a randomized trial and “confounding by indication” could explain our results. This is of course the major limitation of any observation study and not restricted to our work. Second, we do not know why treating physicians chose a particular antibiotic regimen or

elected to be guideline-discordant. Third, we also do not know (other than for those few discharged against medical advice) why certain groups of patients were discharged home when guidelines suggested hospital admission. For example, 360 (12%) of our study patients had severe or very severe pneumonia (PSI Class IV or V) and were still treated as outpatients. Some of this could relate to very clinically well-looking older patients as the PSI is driven heavily by age, but it is also possible this is the reason our mortality and re-admission rates might seem high. Fourth, we did not have any post-discharge microbiologic data and do not know the proportion of patients who may have had an atypical bacterial infection or macrolide-resistant *S. pneumoniae*. Fifth, some might be concerned about the generalizability of our findings given the cohort was enrolled between 2000 and 2002 and our definitions of guideline-concordant treatments were based on older guidelines.

In conclusion, in a large prospective population-based study of outpatients with pneumonia, receipt of guideline-concordant antibiotics was associated with a significant 77% reduction in 30-day mortality while those treated with macrolides had the lowest mortality of all. Consistent with work done in hospitalized patients^{9–12} our study suggests that treatment with guideline-concordant antibiotics that cover atypical infections and macrolide-based regimens are associated with better outcomes for outpatients with pneumonia.

**Figure 3** Five sensitivity analyses with respect to macrolide antibiotic treatment and 30-day mortality.

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Conflict of interest statement

We declare that we have no conflicts of interest with respect to this study. The funding agencies had no role in the design, conduct, completion, or submission of the article. The corresponding author (SRM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' contribution

SRM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors participated in study conception, design, interpretation, critical revisions, and approved the final manuscript. LA drafted the initial manuscript. JMS and DTE undertook analyses. SRM will act as guarantor and corresponding author. SRM, DTE, TJM obtained funding and supervised the study. All authors have seen and approve the final version.

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