ERJ Express. Published on May 30, 2007 as doi: 10.1183/09031936.00031007

The Need for Macrolides in Hospitalised Community-Acquired Pneumonia: Propensity Analysis

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Short title: Need for additional macrolides for pneumonia

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Abstract

Background: We compared beta-lactam-macrolide ('combination') therapy vs. beta-lactam alone ('monotherapy') for hospitalised community-acquired pneumonia, using propensity scores to adjust for the differences between patients.

Methods: Prospective multinational observational study. Baseline patient and infection characteristics were used to develop a propensity score for combination therapy. We matched patients by the propensity score (3 decimal point precision) and compared 30-day mortality and hospital stay. We used the propensity score as a covariate in a logistic model for mortality.

Results: Patients treated with monotherapy (N=169) were older (mean age 70.6±17.3 vs. 65.0±19.6 years) had a higher chronic diseases score and a different clinical presentation compared to patients given combination therapy (N=282). Unadjusted mortality was significantly higher with monotherapy (37/169, 22% vs. 21/282, 7%). Only 27 patients in the monotherapy group could be matched to 27 patients in the combination group using the propensity score. The mortality in these groups was identical, 3 (11%) demises each. The multivariable odds ratio for mortality associated with combination therapy, adjusted for the propensity score and the Pneumonia Severity Index, was 0.69, 95% CI 0.32-1.48.

Conclusions: The benefit of combination vs. monotherapy cannot be reliably assessed in observational studies, since the propensity to prescribe these regimens differs markedly.

Key words: community-acquired pneumonia; antibiotic treatment; macrolides; beta-lactams; combination; monotherapy; propensity score

Background

European and North-American guidelines generally recommend a combination of a beta-lactam drug plus a macrolide for patients admitted to the hospital because of community-acquired pneumonia. [1-5] Two main reasons underlie this recommendation. The first is to cover intra-cellular, 'atypical' pathogens that do not respond to beta-lactam drugs. Secondly, observational studies showed that the outcome of patients with community-acquired pneumonia [6-12] and with bacteremic pneumococcal pneumonia [13-16] was better if treated with a beta-lactam drug plus a macrolide compared with patients treated with a beta-lactam drug alone. All these studies, however, were non-randomized. In vitro studies did not show synergy between beta-lactams and macrolides. [17, 18]

Patients treated for atypical pathogens are probably a-priori different from patients treated with a beta-lactam drug alone. Physicians are likely to reflect in their choice of treatment common wisdom as to the presentation of 'atypical' pathogens, i.e. younger patients, lower fever and leukocyte count, non-productive cough, certain patterns of infiltrate on the chest radiography. Classical multi-variable techniques may not have been able to adjust adequately for the differences between the two groups of patients, and the observed differences in outcomes may have been due to these a-priori differences and not to higher efficacy of combination therapy.

We therefore addressed this question by analysing the outcomes of patients treated with a beta-lactam plus a macrolide vs. patients treated with a beta-lactam drug alone, using propensity analysis.

Methods

We included in the present analysis all patients with community-acquired pneumonia treated empirically with a combination of a beta-lactam plus a macrolide or with a beta-lactam antibiotic alone, participating in the TREAT study. [19, 20] Patients were enrolled as part of a two-phase study (observational and interventional) designed to evaluate the effectiveness of TREAT, a computerized decision support system for antibiotic treatment of common bacterial infections among inpatients (Clinical-Trials.gov Identifier: NCT00233376). Patients were admitted mainly to medical wards and the study was conducted in three university-affiliated primary and tertiary care hospitals in Israel, Germany and Italy. Data were collected between June to December 2002 in Israel and Germany, and between March and September 2003 in Italy (observational phase); and between May and November 2004 at all three sites (randomized controlled trial). Research ethics committees in the three sites approved study protocols.

Inclusion and exclusion criteria

Included in the TREAT study were patients fulfilling the systemic inflammation response syndrome diagnostic criteria [21]; patients with a focus of infection; patients with shock compatible with septic shock; patients with febrile neutropenia; patients prescribed antibiotics (not for prophylaxis); and patients from whom blood cultures were drawn. Excluded were HIV positive patients with a current (suspected or identified) opportunistic disease and/or AIDS defining illness currently or within the past 6 months; solid-organ or bone marrow transplant recipients; children <18 years; suspected travel infections or tuberculosis; and pregnant women.

Patients fulfilling inclusion criteria were prospectively identified by daily chart review. Within hours of admission we collected data on: demography (e.g. age, sex, place of infection acquisition); background conditions (e.g. diabetes mellitus, chronic obstructive pulmonary disease, malignancy, chronic heart failure, chronic and acute renal failure, acute coronary syndrome, immunodeficiency); predisposing conditions (e.g. recent surgery) and devices (e.g. urinary catheter, intravenous catheter); presence of chills, temperature, pulse rate, systolic and diastolic blood pressure; focal signs and symptoms (e.g. cough, vomiting, rash); all available routine laboratory data (e.g. blood count, creatinine, urea, electrolytes, liver function tests); and chest-radiography. At follow-up, 30 days after recruitment, we collected data on survival, final diagnosis, duration of hospital stay, fever days, duration of stay in the intensive care unit, treatment, adverse events and all microbiological results.

Definitions and outcomes

For the purpose of this study we defined community-acquired pneumonia as the presence of a new infiltrate on the admission chest x-ray in a patient fulfilling the TREAT inclusion criteria and symptoms/ signs compatible with lower respiratory tract infection. The final main diagnosis at discharge or death of all patients included in the present cohort was pneumonia or related diagnoses. We defined empirical treatment as the treatment given in the first two days following hospital admission. We assessed two main outcomes: mortality, defined as all-cause mortality at 30 days following hospital admission, and length of hospital stay.

Septic shock was defined as sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but

are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Functional capacity was measured on a scale of 0-3: with 0 indicating full functional capacity; 1 - limited; 2 – limited in daily life activities; 3 – bedridden. We used the Charlson score to account for the presence of underlying, chronic diseases. [22] We calculated the Pneumonia Severity Index (PSI) as predictor for mortality. [23]

Propensity analysis

To perform a propensity analysis we assessed the probability that a patient will be given combination vs. monotherapy using multivariate analysis. The model's predicted probability was used as the propensity score for each patient. We then matched patients given combination vs. monotherapy with similar propensity scores. This procedure provides two matched patient groups (combination vs. monotherapy) that permit comparison of outcomes as in a randomized trial (pseudo-randomization). [24] We used the propensity score in two ways to correct for baseline disparities between groups. First, we compared outcomes between the matched patient groups (univariate). Second, we conducted a multivariate analysis for mortality among all patients adjusting for the propensity score within the model. For this analysis, we excluded patients outside the mutual range of the propensity scores for patients given combination or monotherapy.

Statistical analysis

For univariate analysis, proportions were compared using a Fisher's exact test or chi-square test and continuous variables were compared using a Student's t test or Mann Whitney U test, as appropriate. Continuous variables values are reported as means $\pm$

standard deviation (SD). Univariate associations with a $p \leq 0.1$ were entered into the logistic regression analysis for the propensity score. We matched patients from the two groups according to their propensity scores using a pre-defined precision of 3 figures after the decimal point. If more than one match was found, the patient to be included was selected at random. Length of stay in the two groups was compared by the means of a General Linear Model (GLM), using the propensity score as a covariate. Model discrimination was assessed using the area under the receiver operating characteristics (ROC) curve with 95% confidence intervals (CI). Data analysis was performed using SPSS 11.5.

Results

Included in the TREAT study were 611 patients with community-acquired pneumonia, and we report on 451 patients (74%) given as empirical treatment a beta-lactam drug alone (n=169) or a beta-lactam plus a macrolide (n=282). Comparisons between the two groups as to the variables known at the time empirical treatment was decided upon are given in Table 1. Beta-lactam drugs prescribed in the two groups are shown in Table 2. The pathogen causing pneumonia was documented in 28 of 169 (17%) of patients given a beta-lactam drug and in 32 of 282 (11%) of patients given combination therapy, p=0.11. Legionella pneumonia was diagnosed in two patients receiving combination therapy. Blood cultures were positive in 10 of 169 patients (6%) vs. 13 of 282 (5%), respectively. Unadjusted 30-day mortality in the beta-lactam group was 22% (37 of 169), vs. 7% (21 of 282) in the beta-lactam plus macrolide group, univariate odds ratio (OR) for mortality with combination therapy 0.29 (95% CI 0.16-0.52), p=0.0001. There was no difference in the length of stay, mean of 8.5$\pm$8.8 vs. 8.8$\pm$8.4 days, respectively. Likewise, the mean length of stay was similar in the two groups when only patients alive on day 30 were included in the analysis.

Fourteen variables were included in the logistic regression analysis to develop the propensity score (Table 3). As expected, the propensity scores for the two groups differed markedly, 0.179$\pm$0.139 SD for patients given a beta-lactam alone vs. 0.074$\pm$0.103 for patients given combination therapy, p<0.0001. The propensity score was significantly higher for patients given a beta-lactam drug for each of the three study locations (data not shown). Only 27 patients in the beta-lactam group could be matched to (27) patients in the beta-lactam plus macrolide group using the propensity score with a precision of 3 figures after the decimal point. The mortality in these

groups was identical, 3 demises (11%) in each, p=1.0, OR 1.0, 95% CI 0.2-5.5. The length of stay in hospital in the two groups was similar.

The PSI score predicted mortality well within our cohort, AUC 0.78 (95% CI 0.72-0.84, p<0.001). We entered the treatment group as a co-variate to a logistic regression analysis for mortality with PSI. When patients outside the mutual range of the propensity scores for the two groups were excluded, 366 patients remained. Combination therapy remained significantly associated with lower mortality, OR 0.39, 95% CI 0.19-0.79 adjusted to PSI. However, when the propensity score (patients' predicted probability of being treated by combination vs. monotherapy) was entered to the model, treatment arm no longer remained significantly associated with mortality, OR 0.69, 95% CI 0.32-1.48. The PSI remained significantly associated with mortality in all models. Within this cohort, length of stay was not significantly different between groups (GLM model using the propensity score as a covariate).

We addressed the subgroup of the more severely ill patients in our cohort. Among all patients in PSI risk classes 4 or 5, all cause mortality was 27% (34/128) vs. 11% (19/170) for monotherapy vs. combination (p=0.001). In the propensity matched cohort the mortality for patients in the higher risk groups was 15% (3/20) vs. 16% (3/19), p=0.95.

Discussion

Patients given a beta-lactam alone for community-acquired pneumonia were markedly different in our cohort from patients given a combination of a beta-lactam plus a macrolide. They were older, chronic diseases were more common, and a higher percentage of patients had chronic obstructive lung disease. Pneumonia presentation was different, with septic shock, disturbed consciousness, and a lobar or bronchopneumonic infiltrates more common among patients given beta-lactam monotherapy. These differences were made evident in the markedly different propensity scores. The gross mortality rate in this group was higher.

These differences impeded a propensity-matched analysis. When we tried to match patients from the two groups using the propensity score with a pre-defined precision of 3 figures after the decimal point, only 27 patients in each group (12% of the cohort) could be matched. Among matched patients, mortality rates were identical. The difference in mortality between the two groups was non-significant when we used the propensity scores to adjust it in a logistic regression analysis. We found no differences in the length of stay.

Most observational studies have previously shown that the addition of a macrolide to beta-lactams is associated with reduced mortality among patients with community-acquired pneumonia. [6-16] Fewer studies showed no effect. [25-28] Some features of these studies are described in Table 4. Most studies were retrospective. Significant differences are noted between patients given combination vs. monotherapy in most studies. Outcome comparisons, however, were adjusted most commonly to risk factors for mortality, not identical to the risk factors for the treatment regimen.

Studies showing similar characteristics for patients given monotherapy and combination therapy, or adjusting for the differences observed between the groups, showed no differences in outcomes. [26-28] We believe that differences between study groups similar to those present in our cohort might have existed in former studies, and were not captured because the propensity for prescribing monotherapy vs. combination therapy was not investigated. These differences are not necessarily captured when using risk factors for mortality to correct the association between treatment and mortality. When the two groups are divergent, with large areas that do not overlap, classical methods for multivariate adjusting might not be adequate. [24]

We have previously conducted a systematic review and meta-analysis of randomized controlled trials assessing the effect of empirical therapy covering 'atypical' pathogens vs. empirical regimens including only beta-lactams. [29] We found no difference in all-cause mortality overall (23 trials, 4846 patients, relative risk 1.13, 95% CI 0.82-1.54) or in trials including a macrolide in the 'atypical' arm (5 trials, 1348 patients, relative risk 1.68, 95% CI 0.86-3.29, in favour of the beta-latam). However, a principal finding of this review was that the addition of a macrolide or a quinolone to a beta-lactam has never been assessed in a randomized controlled trial.

Our analysis is hampered by the small numbers of included patients. However, detailed data were prospectively and carefully collected using a uniform protocol in three hospitals in three countries. These data permitted a meticulous comparison between patients given monotherapy vs. those given combination therapy. The differences between the patient groups were remarkable in our cohort. Differences might have been subtler in previous studies (Table 4). We included patients admitted

from nursing homes, excluded from some definitions of community-acquired pneumonia. However, they consisted less than 7% of our cohort and were important to delineate the differences between patients given combination vs. monotherapy. We did not assess fluoroquinolones, currently among recommended regimens for hospitalised community acquired pneumonia, [5] since only few patients in our cohort received fluoroquinolones. We did not include patients hospitalised in intensive care unit, who may benefit preferentially from combination therapy. [11] However, among the more severely ill patients in PSI risk classes 4 or 5, the same trend was seen: higher mortality among all patients with monotherapy compared to combination therapy, but no difference among the few patients remaining in the propensity-matched cohort.

We conclude that patients given a beta-lactam alone for community acquired pneumonia are markedly different from patients given a combination of a beta-lactam plus a macrolide and that this difference precludes the use of observational studies to conclude on the advantage of one regimen over another. Excessive use of macrolides has consequences [30] and should be discouraged if it does not improve outcomes. A randomized controlled trial comparing a beta-lactam drug to a combination of the same beta-lactam plus a macrolide for community-acquired pneumonia is urgently needed.

Acknowledgments:

The TREAT project was funded by the EU 5th framework, Information Society Technologies, contract no.: IST-9999-11459, The funding source had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributions:

Conceived the project and basic concepts: Leonard Leibovici, Steen Andreassen

Built the interface, database and supporting software: Leif E. Kristensen, Karsten Falborg, Alina Zalounina, Anders D. Nielsen

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Mical Paul and Leonard Leibovici had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Comparisons between patients treated with a beta-lactam drug vs. patients given a beta-lactam drug plus a macrolide including variables known at the time empirical treatment was decided upon. Values are given as number of patients (percentages); and as mean and standard deviation for continuous variables.

Variable	**Beta-lactam alone** (N=169)	**Beta-lactam plus macrolide** (N=282)	**P value**
Age (years)	70.6±17.3	65.0±19.6	0.02
Nursing home residents	16 (9)	10 (4)	0.01
Limited in daily life activities or bed-ridden	65 (60)	43 (40)	0.0001
Charlson score	1.5±0.9	1.0±1.0	0.0001
PSI score	118.5±40.0	98.5±40.9	<0.001
Chronic obstructive lung disease	44 (26)	54 (19)	0.1
Smoking	30 (18)	71(25)	0.09
Previous antibiotic treatment	20 (12)	19 (7)	0.07
Duration of fever before admission (days)	2.8±4.6	2.1±2.5	0.1
Chills	15 (9)	54 (19)	0.003
Septic shock	9 (5)	4 (1)	0.02
Acute disturbed consciousness	36 (21)	20 (7)	0.0001
Pleuritic pain	18 (11)	59 (21)	0.005
Cough	64 (38)	184 (65)	0.0001

Infiltrate on chest x-ray: lobar or bronchopneumonia	79 (47)	90 (32)	0.001

Table 2: Beta-lactam drugs prescribed in the two groups.

Beta-lactam drug prescribed	**Beta -lactam alone** (N=169)	**Beta -lactam plus macrolide** (N=282)
Beta-lactam + beta-lactamase inhibitor	55 (33)	31 (11)
3rd generation cephalosporins	71 (42)	151 (54)
2nd generation cephalosporins	31 (18)	92 (33)
Penicillins	8 (5)	5 (2)
Carbapenems	4 (2)	3 (1)

Table 3: Logistic regression model for derivation of the propensity score. Dependent variable: combination vs. single beta-lactam treatment. Hosmer and Lemeshow test Chi^2=11.0, 8 degrees of freedom, p=0.2; area under the ROC curve 0.77, 95% confidence interval 0.72-0.82.

	Coefficient	**p**	**OR**	**95.0% C.I. for OR**	
Age*	-0.004	0.579	.996	0.981	1.011
Nursing home residents	-1.620	0.051	0.20	0.04	1.00
Limited in daily life activities or bed-ridden	-1.093	0.005	0.335	0.157	0.716
Charlson score*	0.067	0.392	1.070	0.917	1.247
Chronic obstructive lung disease	-0.898	0.006	0.407	0.215	0.772
Smoking	0.190	0.551	1.210	0.647	2.262
Previous antibiotic treatment	-0.687	0.086	.503	0.230	1.102
Duration of fever before admission*	-0.025	0.477	.975	0.909	1.045
Chills	0.378	0.321	1.459	0.692	3.077
Septic shock	-1.756	0.055	.173	0.029	1.036
Cough	0.700	0.006	2.014	1.223	3.316
Pleuritic pain	0.502	0.177	1.652	0.798	3.423
Acute disturbed consciousness	-0.462	0.252	0.630	0.286	1.388
Infiltrate on chest x-ray: lobar or broncho-pneumonia	0.407	0.109	1.502	0.913	2.472
Constant	0.669	0.270	1.953		

*Continuous variables: increment of 1 year for age; 1 point for Charlson score; 1 day for duration of febrile disease.

Table 4: Observational studies assessing beta-lactam-macrolide-combination therapy vs. beta-lactams alone among adult patients hospitalized with pneumonia

Study	**Study design**	**Patient characteristics**	**Baseline differences reported between patient groups**	**Adjustment variables for the comparison between treatments**	**Outcomes assessed**	**Results for the comparison of combination vs. monotherapy**
Aspa et al. [25]	Prospective	638 patients with CAP [1] due to *Streptococcus pneumoniae*	Lower PSI class with monotherapy, otherwise not reported	Risk factors for mortality	30-day survival	No significant difference
Baddour et al. [11]	Prospective	582 adults with pneumococcal bacteremia	Among severely ill patients, HIV and mechanical ventilation associated with	HIV and mechanical ventilation	14-day mortality	No significant difference overall; significantly higher among

			monotherapy [2]			severely ill patients
Burgess et al. [26]	Retrospective	213 adults with CAP and no organism specified	Combination patients younger, less severely ill.	Baseline differences between treatment groups	Length of stay mortality	No difference
Dudas et al. [9]	Prospective	2963 adults with an admission diagnosis of physician-presumed CAP	Not reported	Risk factors for mortality identified on univariate analysis	Length of hospital stay in-hospital mortality	Both significantly lower with combination among non-ICU patients
Dwyer et al. [27]	Retrospective analysis of prospectively collected	370 adults patients with bacteremic pneumococcal CAP	IVDU [3], liver disease, higher APACHE score and APS [4] associated	Risk factors for mortality, including the APS score	Mortality	No difference

	data		with combination; cardiac disease associated with monotherapy			
Garcia Vazquez et al. [12]	Retrospective analysis of prospectively collected data	1188 adults with CAP	PSI class IV associated with monotherapy; older age associated with combination	PSI	In-hospital mortality (after 24 hours)	Significantly lower with combination
Gleason et al. [6]	Retrospective	12,945 community- or long-term care facility dwelling patients ≥65 years with CAP	Monotherapy more common among patients admitted from long-term care facility; combinations more	Previously known risk factors for mortality	30-day mortality	Significantly lower with combination therapy or fluouroquinolone monotherapy

			common in lower PSI risk classes.			
Houck et al. [7]	Retrospective	10,069 patients ≥65 years from the community or nursing facilities with CAP	Combination more common in lower risk classes, other differences not reported	PSI and other risk factors for mortality	30-day mortality	Significantly lower with combination, or quinolone/ macrolide monotherapy. Yearly fluctuation
Loh et al. [28]	Prospective	141 adults with CAP	No significant differences in age and comorbidity scores	Unadjusted, stratified by severe pneumonia	In hospital mortality Length of Hospital stay	No difference

Martinez et al. [13]	Retrospective analysis of prospectively collected data	409 adults with bacteremic pneumococcal pneumonia	Monotherapy associated with fatal and non-fatal comorbidities; combination associated with shock and ICU [5] admission	Risk factors for mortality identified on univariate analysis	In hospital mortality	Lower with combination
Metersky et al. [10]	Retrospective	2,349 episodes of bacteremic pneumonia among adults admitted from home or a nursing facility	No atypical coverage associated with older age, admission from nursing home, higher PSI and longer time to antibiotic initiation	Risk factors for mortality	30-day mortality In-hospital mortality Hospital readmission	All significantly lower with macrolides, but not with quinolones or teteracyclines

Mufson et al. [15, 31]	Retrospective	328 adults and 45 children with bacteremic pneumococcal pneumonia	No significant differences observed	Unadjusted	In hospital mortality	Lower with combination
Stahl et al. [8]	Prospective	67 adults with CAP	Monotherapy associated with nursing home residence; no differences in age and PSI score	Adjusted for admission from nursing home	Length of hospital stay	Significantly shorter with combination
Waterer et al. [14]	Retrospective	225 adults with bacteremic pneumococcal CAP	Monotherapy associated with significantly higher APACHE and PSI	Risk factors for mortality	Mortality	Significantly lower with dual effective combination

			scores; chronic organ failure not significantly different			therapy
Weiss et al. [16]	Retrospective	95 adults with bacteremic pneumococcal CAP	Similar PSI score, otherwise not reported	Unadjusted	Mortality	Significantly lower with combination therapy

[1] CAP – community-acquired pneumonia

[2] – HIV – human immunodeficiency virus. Monotherapy in this study was not limited to beta-lactam alone

[3] IVDU – intravenous drug abuse

[4] APS – acute physiology score

[5] ICU – intensive care unit