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The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis

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ABSTRACT: **The present study compared β-lactam macrolide (''combination'') therapy *versus* β-lactam alone (''monotherapy'') for hospitalised community-acquired pneumonia, using propensity scores to adjust for the differences between patients.**

A prospective multinational observational study was carried out. Baseline patient and infection characteristics were used to develop a propensity score for combination therapy. Patients were matched by the propensity score (three decimal point precision) and compared with 30-day mortality and hospital stay. The propensity score was used as a covariate in a logistic model for mortality.

Patients treated with monotherapy (n=169) were older (mean±SD age 70.6±17.3 *versus* 65.0±19.6 yrs), had a higher chronic diseases score and a different clinical presentation compared with patients treated with combination therapy (n=282). Unadjusted mortality was significantly higher with monotherapy (37 (22%) out of 169 *versus* 21 (7%) out of 282). 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, with three (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% confidence interval 0.32–1.48).

The benefit of combination therapy *versus* monotherapy cannot be reliably assessed in observational studies, since the propensity to prescribe these regimens differs markedly.

KEYWORDS: **β-Lactams, combination, community-acquired pneumonia, macrolides, monotherapy, propensity score**

European and North-American guidelines generally recommend a combination of a β-lactam drug in combination with a macrolide for patients admitted to hospital due to community-acquired pneumonia (CAP) [1–5]. There are two main reasons that underlie this recommendation. The first is to cover intracellular, ''atypical'' pathogens that do not respond to β-lactam drugs. Secondly, observational studies have shown that the outcome of patients with CAP [6–12] and bacteremic pneumococcal pneumonia [13–16] was better if treated with a β-lactam drug in combination with a macrolide compared with patients treated with a β-lactam drug alone. However, all these studies were nonrandomised. *In vitro* studies did not show synergy between β-lactams and macrolides [17, 18].

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

Therefore, the present study addressed this question by analysing the outcomes of patients treated with a β-lactam in combination with a macrolide *versus* patients treated with a β-lactam alone, using propensity analysis.

METHODS

The present analysis included all CAP patients treated empirically with a combination of a

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β-lactam and a macrolide or with a β-lactam antibiotic alone, participating in the TREAT study [19, 20], a system for balancing antibiotic treatment against development of drug resistance. Patients were enrolled as part of a two-phase study (observational and interventional) designed to evaluate the effectiveness of TREAT, a computerised decision support system for antibiotic treatment of common bacterial infections among in-patients (Clinical-Trials.gov Identifier: NCT00233376). Patients were mainly admitted to medical wards and the study was conducted in three university-affiliated primary- and tertiary-care hospitals in Israel, Germany and Italy. During the observational phase, data were collected in Israel and Germany between June and December 2002, and in Italy between March and September 2003. The randomised controlled trial took place between May and November 2004 at all three sites. Research ethics committees in the three sites approved the study protocols.

Inclusion and exclusion criteria

The TREAT study included patients who: fulfilled the systemic inflammation response syndrome diagnostic criteria [21]; had a focus of infection; had shock compatible with septic shock; had febrile neutropenia; had been prescribed antibiotics (not for prophylaxis); and from whom blood cultures were drawn. The study excluded the following individuals: HIV-positive patients with a current (suspected or identified) opportunistic disease and/or AIDS-defining illness currently or within the previous 6 months; solid-organ or bone-marrow transplant recipients; patients <18 yrs of age; patients with suspected travel infections or tuberculosis; and pregnant females.

Patients fulfilling the inclusion criteria were prospectively identified by daily chart review. Within hours of admission data were collected on: demographics (*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, data were collected 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 the present study CAP was defined as the presence of a new infiltrate on the admission chest radiograph of a patient fulfilling the TREAT inclusion criteria and presenting with 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. Empirical treatment was defined as the treatment administered in the first 2 days following hospital admission. Two main outcomes were assessed: 1) mortality, defined as all-cause mortality at 30 days following hospital admission; and 2) 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: 0=full functional capacity; 1=limited functional capacity; 2=limited in daily life activities; and 3=bedridden. The Charlson score was used to account for the presence of underlying chronic diseases [22]. The authors calculated the Pneumonia Severity Index (PSI) as predictor for mortality [23].

Propensity analysis

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

Statistical analysis

For univariate analysis, proportions were compared using a Fisher's exact test or Chi-squared test and continuous variables were compared using an unpaired t-test or Mann–Whitney U-test, as appropriate. Continuous variable values are reported as mean±SD. Univariate associations with a p-value $\leqslant 0.1$ were entered into the logistic regression analysis for the propensity score. Patients from the two groups were matched according to their propensity scores using a pre-defined precision of three decimal points. 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 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 curve with 95% confidence intervals (CI).

RESULTS

In total, 611 patients with CAP were included in the TREAT study. The present study reports on 451 (74%) patients who received a β-lactam drug alone (n=169) or a β-lactam in combination with a macrolide (n=282) as empirical treatment. Comparisons between the two groups as to the variables known at the time empirical treatment was decided upon are given in table 1. The β-lactam drugs prescribed in the two groups are shown in table 2. The pathogen causing pneumonia was documented in 28 (17%) out of 169 patients receiving a β-lactam drug and in 32 (11%) out of 282 patients receiving combination therapy (p=0.11). *Legionella pneumonia* was diagnosed in two patients receiving combination therapy. Blood cultures were positive in 10 (6%) monotherapy *versus* 13 (5%) combination therapy patients. Unadjusted 30-day mor-

tality in the β-lactam group was 22% (n=37) *versus* 7% (n=21) in the β-lactam and macrolide group, univariate odds ratio (OR) for mortality with combination therapy was 0.29 (95% CI 0.16–0.52; p=0.0001). There was no difference in the mean±SD length of stay, 8.5±8.8 *versus* 8.8±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.

In total, 14 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±0.139 *versus* 0.074±0.103 for monotherapy *versus* combination therapy, respectively (p<0.0001). For each of the three study locations the propensity score was significantly higher for patients receiving a β-lactam drug (data not shown). Only 27 patients in the β-lactam group could be matched to 27 patients in the β-lactam and macrolide group using the propensity score with a precision of three decimal points. The mortality in these groups was identical, with three (11%) demises in each (OR (95% CI) 1.0 (0.2–5.5); p=1.0). The length of stay in hospital in the two groups was similar.

The PSI score predicted mortality well within the authors' cohort (area under curve 0.78; 95% CI 0.72–0.84; p<0.001). The treatment group was entered as a covariate 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 adjusted to PSI (OR 0.39, 95% CI 0.19–0.79). However, when the propensity score (patients' predicted probability of being treated by combination therapy *versus* monotherapy) was entered to the model, the 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).

The authors addressed the subgroup of the more severely ill patients in the cohort. Among all patients in PSI risk classes 4 or 5, all cause mortality was 34 (27%) out of 128 *versus* 19 (11%) out of 170 for monotherapy *versus* combination (p=0.001), respectively. In the propensity-matched cohort the mortality for patients in the higher risk groups was three (15%) out of 20 *versus* three (16%) out of 19 (p=0.95).

DISCUSSION

Patients who received a β-lactam alone for CAP were markedly different in the present study from those who received a combination of a β-lactam and a macrolide. The patients 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 lobar or bronchopneumonic infiltrates more common among patients receiving β-lactam monotherapy. These differences were evident in the markedly different propensity scores. The gross mortality rate in this group was higher.

These differences impeded a propensity-matched analysis. When the authors tried to match patients from the two groups using the propensity score with a pre-defined precision of three decimal points, 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 nonsignificant when the propensity scores were used to adjust it in a logistic regression analysis. No differences were found in the length of stay.

Most observational studies have previously shown that the addition of a macrolide to β-lactams is associated with reduced

TABLE 1 Comparison between patients treated with a β-lactam alone *versus* patients treated with a β-lactam and a macrolide including variables known at the time empirical treatment was decided

Variable	β-Lactam alone	β-Lactam and macrolide	p-value
Subjects n	169	282	
Age yrs	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 bedridden	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
COPD	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 radiograph: lobar or bronchopneumonia	79 (47)	90 (32)	0.001

Data are presented as n (%) or mean±SD, unless otherwise stated. PSI: Pneumonia Severity Index; COPD: chronic obstructive pulmonary disease.

TABLE 2 β-Lactam drugs prescribed in the two groups

β-Lactam drug prescribed	β-Lactam alone	β-Lactam and macrolide
Subjects n	169	282
β-Lactam and β-lactamase inhibitor	55 (33)	31 (11)
Third generation cephalosporins	71 (42)	151 (54)
Second generation cephalosporins	31 (18)	92 (33)
Penicillins	8 (5)	5 (2)
Carbapenems	4 (2)	3 (1)

Data are presented as n (%), unless otherwise stated.

mortality among patients with CAP [6–16]. Few studies showed no effect [25–28]. Some features of these studies are described in table 4; most studies were retrospective. Significant differences were noted between patients receiving combination therapy *versus* monotherapy in most studies. However, outcome comparisons were adjusted most commonly to risk factors for mortality, not identical to the risk factors for the treatment regimen. Studies that showed similar characteristics for patients receiving monotherapy and combination therapy, or adjusting for the differences observed between the groups, showed no differences in outcomes [26–28]. The authors believe that differences between study groups similar to those in the present cohort might have existed in former studies, and were not captured because the propensity for prescribing monotherapy *versus* 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].

A systematic review and meta-analysis of randomised controlled trials assessing the effect of empirical therapy covering atypical pathogens *versus* empirical regimens including only β-lactams has previously been carried out [30]. No difference was found in all-cause mortality overall (23 trials, 4,846 patients, relative risk 1.13, 95% CI 0.82–1.54) or in trials including a macrolide in the atypical arm (five trials, 1,348 patients, relative risk 1.68, 95% CI 0.86–3.29, in favour of the β-lactam). However, a principal finding of this review [30] was that the addition of a macrolide or a quinolone to a β-lactam has never been assessed in a randomised controlled trial.

The present analysis was hampered by the small numbers of patients included. However, detailed data were prospectively and carefully collected using a uniform protocol in three hospitals in three countries (Germany, Italy and Israel). These data permitted a meticulous comparison between patients receiving monotherapy *versus* combination therapy. The differences between the patient groups were remarkable in the cohort. Differences might have been subtler in previous studies (table 4). The current study included patients admitted from nursing homes, excluded from some definitions of CAP. However, these patients consisted of <7% of the cohort and were important to delineate the differences between patients receiving combination therapy *versus* monotherapy. The current authors did not assess fluoroquinolones, currently among the recommended regimens for hospitalised CAP [5], since only a few patients in the cohort received fluoroquinolones. Patients hospitalised in an intensive care unit, who may benefit preferentially from combination therapy, were also not included [11]. However, among the more severely ill patients in PSI risk classes 4 or 5, the same trend was seen: higher

TABLE 3 Logistic regression model for derivation of the propensity score

	Coefficient	p-value	OR (95% CI)
Age#	-0.004	0.579	0.996 (0.981–1.011)
Nursing home residents	-1.620	0.051	0.20 (0.04–1.00)
Limited in daily life activities or bedridden	-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	0.503 (0.230–1.102)
Duration of fever before admission#	-0.025	0.477	0.975 (0.909–1.045)
Chills	0.378	0.321	1.459 (0.692–3.077)
Septic shock	-1.756	0.055	0.173 (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 radiograph: lobar or bronchopneumonia	0.407	0.109	1.502 (0.913–2.472)
Constant	0.669	0.270	1.953

OR: odds ratio; CI: confidence interval. #: continuous variables, increment of 1 yr for age; 1 point for Charlson score; 1 day for duration of febrile disease. Dependent variable: combination *versus* single β-lactam treatment. Hosmer and Lemeshow Chi-squared test=11.0; 8 degrees of freedom; p=0.2. Area under the receiver operator curve 0.77; 95% CI 0.72–0.82.

TABLE 4 Observational studies assessing β-lactam macrolide combination therapy *versus* β-lactams alone among adult patients hospitalised with pneumonia

First author [Ref.]	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 *versus* monotherapy
ASPA [25]	Prospective	638 patients with CAP due to *Streptococcus pneumoniae*	Lower PSI class with monotherapy, otherwise not reported	Risk factors for mortality	30-day survival	No significant difference
BADDOUR [11]	Prospective	582 adults with pneumococcal bacteremia	Among severely ill patients, HIV and mechanical ventilation associated with monotherapy[#]	HIV and mechanical ventilation	14-day mortality	No significant difference overall; significantly higher among severely ill patients
BURGESS [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 [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 [27]	Retrospective analysis of prospectively collected data	370 adult patients with bacteremic pneumococcal CAP	IVDU, liver disease, higher APACHE score and APS associated with combination; cardiac disease associated with monotherapy	Risk factors for mortality, including the APS score	Mortality	No difference
GARCIA VAZQUEZ [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 h)	Significantly lower with combination
GLEASON [6]	Retrospective	12945 community- or long-term care facility dwelling patients ⩾65 yrs old with CAP	Monotherapy more common among patients admitted from long-term care facility; combinations more common in lower PSI risk classes	Previously known risk factors for mortality	30-day mortality	Significantly lower with combination therapy or fluouroquinolone monotherapy
HOUCK [7]	Retrospective	10069 patients ⩾65 yrs old 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 [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 [13]	Retrospective analysis of prospectively collected data	409 adults with bacteremic pneumococcal pneumonia	Monotherapy associated with fatal and nonfatal comorbidities; combination associated with shock and ICU admission	Risk factors for mortality identified on univariate analysis	In-hospital mortality	Lower with combination
METERSKY [10]	Retrospective	2349 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 [15, 29]	Retrospective	328 adults and 45 children with bacteremic pneumococcal pneumonia	No significant differences observed	Unadjusted	In-hospital mortality	Lower with combination
STAHL [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 [14]	Retrospective	225 adults with bacteremic pneumococcal CAP	Monotherapy associated with significantly higher APACHE and PSI scores; chronic organ failure not significantly different	Risk factors for mortality	Mortality	Significantly lower with dual effective combination therapy
WEISS [16]	Retrospective	95 adults with bacteremic pneumococcal CAP	Similar PSI score, otherwise not reported	Unadjusted	Mortality	Significantly lower with combination therapy

CAP: community-acquired pneumonia; PSI: Pneumonia Severity Index; ICU: intensive care unit; IVDU: intravenous drug abuse; APACHE: Acute Physiology and Chronic Health Evaluation; APS: acute physiology score. [#]: monotherapy in this study was not limited to β-lactam alone.

mortality among all patients with monotherapy compared with combination therapy, but no difference among the few patients remaining in the propensity-matched cohort.

It can be concluded that patients who receive a β-lactam alone for community-acquired pneumonia are markedly different from patients who receive a combination of a β-lactam and a macrolide. This difference precludes the use of observational studies to conclude on the advantage of one regimen over another. Excessive use of macrolides has consequences [31] and should be discouraged if the treatment does not improve the outcomes. A randomised controlled trial comparing a β-lactam drug with a combination of the same β-lactam and a macrolide for community-acquired pneumonia is urgently needed.

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Conceived the project and basic concepts: L. Leibovici (Rabin Medical Center, Beilinson Hospital, Tel-Aviv, Israel) and S. Andreassen (University Center for Model-based Medical Decision Support, Aalborg University, Aalborg, Denmark).

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M. Paul and L. 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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