ORIGINAL ARTICLE

Macrolide use in the treatment of critically ill patients with pneumonia: Incidence, correlates, timing and outcomes

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BACKGROUND: Macrolide antibiotics are commonly used to treat pneumonia despite increasing antimicrobial resistance. Evidence suggests that macrolides may also decrease mortality in severe sepsis via immunomodulatory properties.

OBJECTIVE: To evaluate the incidence, correlates, timing and mortality associated with macrolide-based treatment.

METHODS: A population-based cohort of critically ill adults with pneumonia at five intensive care units in Edmonton, Alberta, was prospectively followed over two years. Data collected included disease severity (Acute Physiology and Chronic Health Evaluation [APACHE] II score), pneumonia severity (Pneumonia Severity Index score), comorbidities, antibiotic treatments at presentation and time to effective antibiotic. The independent association between macrolide-based treatment and 30-day all-cause mortality was examined using multivariable Cox regression. A secondary exploratory analysis examined time to effective antimicrobial therapy.

RESULTS: The cohort included 328 patients with a mean Pneumonia Severity Index score of 116 and a mean APACHE II score of 17; 84% required invasive mechanical ventilation. Ninety-one (28%) patients received macrolide-based treatments, with no significant correlates of treatment except nursing home residence (15% versus 30% for nonresidents [P=0.02]). Overall mortality was 54 of 328 (16%) at 30 days: 14 of 91 (15%) among patients treated with macrolides versus 40 of 237 (17%) for nonmacrolides (adjusted HR 0.93 [95% CI 0.50 to 1.74]; P=0.8). Patients who received effective antibiotics within 4 h of presentation were less likely to die than those whose treatment was delayed (14% versus 17%; adjusted HR 0.50 [95% CI 0.27 to 0.94]; P=0.03).

CONCLUSIONS: Macrolide-based treatment was not associated with lower 30-day mortality among critically ill patients with pneumonia, although receipt of effective antibiotic within 4 h was strongly predictive of survival. Based on these results, timely effective treatment may be more important than choice of antibiotics.

Key Words: *Critical care; Intensive care; Lung; Macrolides; Mortality; Pneumonia*

L'utilisation des macrolides pour le traitement des patients atteints d'une grave pneumonie : l'incidence, les corrélats, les délais et les issues

HISTORIQUE : Les macrolides sont souvent utilisés pour soigner la pneumonie, malgré une résistance croissante aux antimicrobiens. Selon les données probantes, les macrolides réduiraient également la mortalité en cas de septicémie sévère, en raison de ses propriétés immunomodulatoires.

OBJECTIF : Évaluer l'incidence, les corrélats, les délais et la mortalité associés à un traitement fondé sur les macrolides.

MÉTHODOLOGIE : Pendant deux ans, les chercheurs ont procédé au suivi rétrospectif d'une cohorte en population d'adultes atteints d'une grave pneumonie, hospitalisés dans cinq unités de soins intensifs d'Edmonton, en Alberta. Ils ont colligé la gravité de la maladie (indice APACHE II d'évaluation de la physiologie aiguë et de la santé chronique), la gravité de la pneumonie (indice de gravité de la pneumonie), les comorbidités, les traitements antibiotiques à la présentation et le délai avant la prise efficace d'antibiotiques. Ils ont examiné l'association indépendante entre le traitement aux macrolides et le décès au bout de 30 jours toutes causes confondues au moyen de la régression de Cox multivariable. Ils ont utilisé une analyse exploratoire secondaire pour examiner le délai avant un traitement antimicrobien efficace.

RÉSULTATS : La cohorte se composait de 328 patients dont l'indice moyen de gravité de la pneumonie se situait à 116 et l'indice APACHE II moyen à 17; 84 % d'entre eux ont eu besoin d'une ventilation mécanique. Quatre-vingt-onze patients (28 %) ont reçu des traitements aux macrolides, sans corrélats significatifs du traitement à part le fait d'habiter dans un centre d'hébergement et de soins de longue durée (15 % par rapport à 30 % pour les non-résidents [P=0,02]). La mortalité globale correspondait à 54 cas sur 328 patients (16 %) au bout de 30 jours, soit 14 des 91 patients (15 %) traités aux macrolides par rapport à 40 des 237 (17 %) n'en ayant pas pris (RR rajusté de 0,93 [95 % IC 0,50 à 1,74]; P=0,8). Les patients qui prenaient des antibiotiques efficaces dans les quatre heures suivant leur présentation étaient moins susceptibles de mourir que ceux dont le traitement était retardé (14 % par rapport à 17 %; RR rajusté 0,50 [95 % IC 0,27 à 0,94]; P=0,03).

CONCLUSIONS : Le traitement aux macrolides ne s'associait pas à une réduction du taux de mortalité au bout de 30 jours chez les patients atteints d'une grave pneumonie, mais la prise d'antibiotiques efficaces dans les quatre heures était fortement prédictive de la survie. D'après ces résultats, l'administration rapide d'un traitement efficace serait plus importante que le choix d'antibiotique.

Community-acquired pneumonia (CAP) is the leading cause of infectious death, with up to 22% of patients hospitalized for pneumonia requiring intensive care unit (ICU)-level care (1-3) and 18% to 56% dying during hospitalization (4-6). Guidelines recommend a macrolide or respiratory fluoroquinolone combined with a beta-lactam in critically ill patients with CAP to ensure coverage of typical pathogens, such as *Streptococcus pneumoniae*, and atypical pathogens such as *Mycoplasma*, *Legionella* and *Chlamydophila* species (7-10).

There have been increasing reports of *S pneumoniae* macrolide resistance averaging 8% in Canada, 27% in the United States and

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approaching 35% in Asia (11-13). However, macrolides continue to demonstrate treatment efficacy in patients with macrolide-resistant *S pneumoniae* (13), potentially due to their immunomodulatory properties (14). Indeed, studies have shown that macrolides downregulate leukocyte adhesion and inhibit the production of inflammatory cytokines, thereby minimizing excessive inflammatory responses (14,15).

Macrolides also improve outcomes in chronic pulmonary inflammatory conditions such as chronic obstructive pulmonary disease (16), diffuse panbronchiolitis and bronchiectasis (17). More recent studies have demonstrated a mortality benefit with macrolide-based acute treatment – specifically in the treatment of severe pneumonia – compared with nonmacrolide-based therapies (18-21). However, except for Rodriguez et al (21), these studies have been limited by relatively small, critically ill cohorts and/or suboptimal risk adjustment.

Therefore, the objective of our prospective study was to determine the incidence, correlates, timing and mortality-related outcomes of macrolide-based treatment in critically ill patients with pneumonia. We hypothesized that macrolide-based treatment would be associated with decreased 30-day mortality.

METHODS

The Edmonton pneumonia study from which this population was drawn has been fully described elsewhere (22-25). In brief, the present population-based prospective cohort study enrolled all adult patients with CAP admitted in the Edmonton (Alberta) region from 2000 to 2002. Only patients with severe pneumonia who were admitted directly to the ICU were included in the present analysis. The Health Ethics Research Board at the University of Alberta granted study approval (#6584).

Pneumonia was defined as an acute lower respiratory tract infection characterized by two or more of the following: cough, pleuritic chest pain, dyspnea, temperature >38°C, crackles or bronchial breathing on auscultation, plus radiographic evidence of pneumonia. Exclusion criteria were pregnancy/lactation, aspiration pneumonia, hospitalization within the previous 30 days, immunosuppression, pulmonary tuberculosis, cystic fibrosis and advanced HIV infection. Nursing-home patients were not excluded at the time of enrollment because health care-associated pneumonia was not yet considered to be a pneumonia subtype.

Although hospitalized patients were treated according to a validated clinical pathway (26), patients admitted directly to the ICU were treated at the discretion of the attending intensivist(s). Trained research nurses collected clinical data prospectively using standardized abstraction forms including age, sex, comorbidities, nursing home residence, functional limitation (needing a walker/cane/wheelchair to mobilize or being completely bedridden), Pneumonia Severity Index (PSI) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores, need for invasive mechanical ventilation, presence of shock (defined as a systolic blood pressure <90 mmHg at the time of ICU admission), microbiology and the type/timing of antimicrobial treatment.

A microbiological cause for CAP was assigned if any of the following conditions were met: endotracheal aspirate or sputum sample of acceptable quality (>25 polymorphonuclear cells and <10 epithelial cells per high-power field) with growth of a bacterial pathogen; bronchoscopic respiratory sample with significant isolation ($>10^4$ colony-forming units/mL) of a respiratory pathogen; positive pleural fluid culture; or positive blood culture for a bacterial pathogen in the absence of extrapulmonary infection. Polymicrobial CAP was defined as CAP in which two or more pathogens were isolated. A patient was considered to have CAP of unknown etiology if the respiratory specimen had no growth or identified mixed oropharyngeal flora, coagulase-negative staphylococci, enterococcus species or yeast. Respiratory virus and atypical bacterial infection testing was not routinely performed.

The independent variable of interest was macrolide-based antimicrobial treatment, defined as receiving at least one dose of any macrolide within 24 h of presentation. This 'intent-to-treat' framework was chosen to ensure validity of the analytical approach and to reflect real-world practice and outcomes. Post hoc, a variable referred to as 'effective antibiotic treatment' was defined, which was based on information available over the entire course of illness. Antibiotic therapy was defined as 'effective' if patients received antibiotic(s) to which their identified pathogen(s) were susceptible or that were guideline-concordant therapy if no pathogen(s) were identified. Guideline-concordant regimens at the time were similar to current recommendations (10).

The primary outcome of interest was all-cause mortality at 30 days. In-hospital mortality was identified prospectively. De-identified linkages to provincial databases using unique personal health numbers were performed to obtain vital statistics for patients discharged to the community. These linkages and the databases used have great fidelity and validity, as previously described (23,26,27).

Statistical analysis

Characteristics for subjects in each antibiotic group were compared using *t* tests or Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. An intent-to-treat framework analogous to a randomized trial was undertaken, adjusting models for the characteristics available at the time of presentation.

To examine the relationship between macrolide exposure and mortality, Kaplan-Meier survival curves were constructed and the log-rank test performed. Multivariable Cox regression models were used to assess the impact of macrolide-based treatment on 30-day mortality. Age, sex and macrolide-based treatment were forced into all models. Variables of clinical significance identified to be significantly associated with increased mortality ($P<0.1$) on univariate analyses, or that confounded (changed beta coefficient >10%), were entered into the model. To avoid overadjusting for age and to dissociate acute from chronic disease, we calculated acute and chronic component PSI scores as previously described (5,25). All first-order interaction terms were checked – none achieved statistical significance. There were no violations of proportional hazards using time covariate interaction terms. Results are presented as adjusted HRs (aHRs) and 95% CIs. All statistical tests were two-sided; $P<0.05$ was considered to be statistically significant.

Several sensitivity analyses were conducted with respect to 30-day mortality. First, the APACHE II score was used for risk adjustment instead of the PSI. Second, nursing home patients were excluded because current definitions consider these patients to have health care-associated pneumonia. Third, to avoid confounding based on aggressiveness of care, patients with living wills were excluded. Fourth, only patients with confirmed microbial etiologies were examined. Fifth, patients with severe disease (PSI class V and APACHE II >25) were examined. Finally, only patients with shock were included. In addition, microbiologically confirmed cases were compared with cases with no microbial etiology, adjusting for all variables in the main model.

Finally, in a secondary analysis, the timely delivery of 'effective' antibiotic therapy was examined. Time to effective therapy was examined as a continuous variable; however, given its non-normal distribution, it was dichotomized by median split (<4 h or ≥4 h). In addition, this cut-off has previously been used as a quality measure in differentiating between timely and delayed CAP treatment (10,28). Forty-two patients who did not have timing data (received first doses in peripheral hospitals [n=36] or did not receive any effective therapy [n=6]) were excluded. For this analysis, information that was not available to intensivists at the time of presentation was considered, eg, for methicillin-resistant *Staphylococcus aureus* CAP, the timing of effective antibiotic treatment would be based on when anti-methicillin-resistant *S aureus* therapy was started. Complications of prognostic value that developed during hospitalization (eg, acute kidney injury requiring renal replacement therapy) were also adjusted for in the model. Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc, USA).

RESULTS

A total of 3415 patients were admitted with CAP, of whom 351 (10%)

TABLE 1
Baseline characteristics of entire cohort and according to macrolide exposure

Variables	All patients, n=328 (100%)	Macrolide exposure No, n=237 (72%)	Macrolide exposure Yes, n=91 (28%)	P*
Age, years, mean ± SD	61±18	62±18	60±17	0.31
Male sex	192 (55)	141 (59)	51 (56)	0.57
Functional limitation†	139 (42)	100 (42)	39 (43)	0.99
Comorbidities				
Cerebrovascular disease	30 (9)	22 (9)	8 (9)	0.89
Coronary artery disease	28 (9)	22 (9)	6 (7)	0.44
Congestive heart failure	81 (25)	61 (26)	20 (22)	0.48
Malignancy	32 (10)	22 (9)	10 (11)	0.64
Chronic liver disease	25 (8)	17 (7)	8 (9)	0.62
Chronic kidney disease	54 (16)	39 (16)	15 (16)	0.99
Diabetes mellitus	56 (17)	38 (16)	18 (20)	0.42
Nursing home residence	53 (16)	45 (19)	8 (9)	**0.02**
Living will	39 (12)	33 (14)	6 (7)	0.07
Current smoker	105 (32)	70 (30)	35 (38)	0.12
PSI, mean ± SD	116±37	116±37	115±37	0.73
PSI class IV or V	240 (73)	177 (75)	62 (69)	0.32
APACHE II score, mean ± SD	17±7	17±7	18±80	0.54

*Data presented as n (%) unless otherwise indicated. Bolded values indicate statistical significance. *χ^2 test used in all analyses; †Missing indicator variable used (n=74 missing). APACHE Acute Physiology and Chronic Health Evaluation; PSI Pneumonia Severity Index*

were admitted to the ICU within 24 h of presentation. Of these, 23 were excluded because of missing data, leaving 328 patients in the final study sample. Baseline characteristics for patients with missing data were virtually identical compared with those without missing data (data not shown).

Baseline characteristics

The mean (± SD) age was 61±18 years; 55% were male and 16% were admitted from nursing homes (Table 1). With respect to pneumonia severity, the mean PSI score was 116±37, with 73% of patients belonging to PSI class IV or V. The mean APACHE II score was 17±7; 27 (8%) of patients had shock, 274 (84%) required invasive ventilation and 122 (37%) were treated with systemic glucocorticoids (Table 2). Glucocorticoid therapy was prescribed at the discretion of the attending physician and included methylprednisolone or prednisone (72%), hydrocortisone (26%) and dexamethasone (2%), with durations of therapy exceeding five days in 63% of patients.

Microbiology

Microbiological diagnoses were made in 156 (48%) patients. *S pneumoniae* was the most commonly isolated pathogen (59 (18%); only five isolates were macrolide-resistant), followed by *S aureus* (46 [14%]; only one was methicillin-resistant) (Table 2).

Antibiotic treatments

Ninety-one (28%) patients received macrolide-based treatment (all received combination therapy, 84 [92%] with a third-generation cephalosporin). Fifty-five (17%) received a full course of macrolide therapy (defined as five days of azithromycin, or at least seven days of clarithromycin or erythromycin) and 36 (11%) patients received a partial course. Of the 237 (72%) patients who received nonmacrolide-based therapies, 169 (52%) received a fluoroquinolone-based regimen.

Patient characteristics, stratified according to macrolide-based treatment, are presented in Table 1. Baseline characteristics between groups were virtually identical except those from nursing homes were less likely to be treated with macrolides than the rest of the cohort (15% versus 30% for those from the community; P=0.02).

TABLE 2
Clinical course and microbial etiology for all critically ill patients with pneumonia and according to macrolide exposure

Variables	All patients, n=328 (100%)	Macrolide exposure No, n=237 (72%)	Macrolide exposure Yes, n=91 (28%)	P*
Bacteremia	44 (13)	33 (14)	11 (12)	0.66
Shock at presentation	27 (8)	23 (10)	4 (4)	0.12
Invasive mechanical ventilation	274 (84)	197 (83)	77 (85)	0.74
Systemic glucocorticoid therapy	122 (37)	91 (38)	31 (34)	0.47
Microbial etiology				
Streptococcus pneumoniae	59 (18)	39 (16)	20 (22)	0.24
Macrolide-susceptible	29 (9)	21 (9)	8 (9)	0.98
Macrolide-resistant	5 (2)	4 (2)	1 (1)	0.70
No macrolide susceptibilities†	25 (8)	14 (6)	11 (12)	0.06
Streptococcus pyogenes	6 (2)	4 (2)	2 (2)	0.76
Staphylococcus aureus	46 (14)	35 (15)	11 (12)	0.53
Methicillin-sensitive	45 (14)	34 (14)	11 (12)	0.59
Methicillin-resistant	1 (0.3)	1 (0.4)	0 (0)	0.53
Moraxella catarrhalis	6 (2)	4 (2)	2 (2)	0.76
Haemophilus influenzae	33 (10)	25 (11)	8 (9)	0.64
Enterobacteriacae	22 (7)	20 (8)	2 (2)	**0.04**
Pseudomonas aeruginosa	6 (2)	5 (2)	1 (1)	0.54
Other bacteria	18 (6)	15 (6)	3 (3)	0.28
Polymicrobial	26 (8)	22 (9)	4 (4)	0.14
Unknown etiology	172 (52)	122 (51)	50 (55)	0.57

*Data presented as n (%) unless otherwise indicated. Bolded values indicate statistical significance. *χ^2 or Fisher's exact (when cell counts <5) tests used; †Penicillin-susceptible with no further antimicrobial susceptibilities performed*

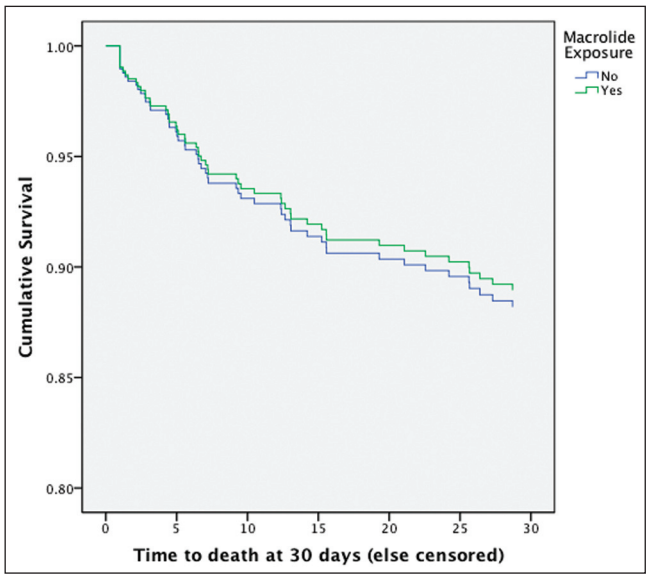

Figure 1) *Adjusted Kaplan-Meier survival curve for critically ill patients with pneumonia, stratified according to macrolide use*

Macrolide-based treatments and 30-day mortality

The overall mortality of the entire cohort was 54 of 328 (16%) at 30 days. The mortality rate was 14 of 91 (15%) at 30 days among individuals who received macrolides and 40 of 237 (17%) among individuals not treated with macrolides (log-rank P=0.76; Figure 1). The results of the univariate analyses are presented in Table 3. On multivariable analysis (Table 4), macrolide-based treatment was not independently associated with 30-day mortality (aHR 0.93 [95% CI 0.50 to 1.74]; P=0.8). The median hospital length of stay was 14 days (interquartile range eight to 27 days).

TABLE 3
Univariate analyses of 30-day mortality in critically ill patients with pneumonia

Variable	30-day mortality			
	Alive, n=274 (84%)	Deceased, n=54 (16%)	P*	cHR (95% CI)†
Baseline demographics				
Age, years, mean ± SD	60±17	69±17	**0.001**	**1.35 (1.13–1.62)**
Male sex	156 (57)	36 (67)	0.18	1.45 (0.82–2.55)
Nursing home residence	40 (15)	13 (24)	0.08	1.67 (0.90–3.11)
PSI, mean ± SD	112±36	134±34	**<0.001**	**1.02 (1.01–1.02)**
PSI class IV or V	190 (69)	50 (93)	**0.004**	**4.93 (1.78–13.6)**
APACHE II score, mean ± SD	16±7	20±9	**0.01**	**1.06 (1.02–1.09)**
Invasive mechanical ventilation	225 (82)	49 (91)	0.11	1.92 (0.77–4.82)
Shock at presentation	18 (7)	9 (17)	**0.01**	**2.43 (1.19–4.97)**
Bacteremia	32 (12)	12 (22)	**0.04**	**1.90 (1.00–3.61)**
Living will	23 (8)	16 (30)	**<0.001**	**3.70 (2.06–6.63)**
Functional limitation‡	95 (42)	10 (34)	**<0.001**	**2.58 (1.76–3.78)**
Cerebrovascular disease	23 (8)	7 (13)	0.3	1.58 (0.72–3.50)
Coronary artery disease	23 (8)	5 (9)	0.8	1.09 (0.43–2.73)
Congestive heart failure	65 (24)	16 (30)	0.4	1.31 (0.73–2.35)
Malignancy	26 (9)	6 (11)	0.7	1.17 (0.50–2.73)
Chronic liver disease	23 (8)	2 (4)	0.2	0.45 (0.11–1.85)
Chronic kidney disease	44 (16)	10 (19)	0.7	1.15 (0.58–2.28)
Diabetes mellitus	41 (15)	15 (28)	**0.02**	**1.96 (1.08–3.56)**
Microbial etiology				
Staphylococcus aureus	32 (12)	14 (26)	**0.006**	**2.88 (1.53–5.44)**
Antimicrobial therapy				
Macrolide	77 (28)	14 (26)	0.74	0.91 (0.49–1.67)
Respiratory fluoroquinolone	168 (61)	39 (72)	0.13	1.54 (0.85–2.79)

*Data presented as n (%) unless otherwise indicated. Bolded values indicate statistical significance. *χ^2 or Fisher's exact (when cell counts <5) tests used; †Single-variable Cox regression model; ‡Missing indicator variable used (n=74 missing). APACHE Acute Physiology and Chronic Health Evaluation; cHR Crude hazard ratio; PSI Pneumonia Severity Index*

TABLE 4
Results of multivariable regression examining macrolide exposure as a correlate of 30-day mortality in critically ill patients with pneumonia

Variable	30-day mortality	
	aHR (95% CI)	P*
Macrolide exposure	0.93 (0.50–1.74)	0.8
Age (per decade)	**1.29 (1.06–1.56)**	**0.01**
Male sex	1.28 (0.72–2.27)	0.4
Functional limitation	1.85 (0.76–4.52)	0.18
Living will	**3.07 (1.64–5.73)**	**0.001**
Acute PSI (per 10 points)*	**1.10 (1.01–1.21)**	**0.05**
Chronic PSI (per 10 points)†	0.94 (0.74–1.14)	0.4
Invasive mechanical ventilation	2.14 (0.82–5.58)	0.1
Shock at presentation	1.48 (0.61–3.56)	0.4
Bacteremia	1.23 (0.59–1.54)	0.6

*Bolded values indicate statistical significance. *Multivariable Cox regression model; †Component Pneumonia Severity Index (PSI) scores calculated as follows: acute PSI – physical examination, laboratory and radiographic findings; chronic PSI – nursing home status, coexisting illnesses. aHR Adjusted HR*

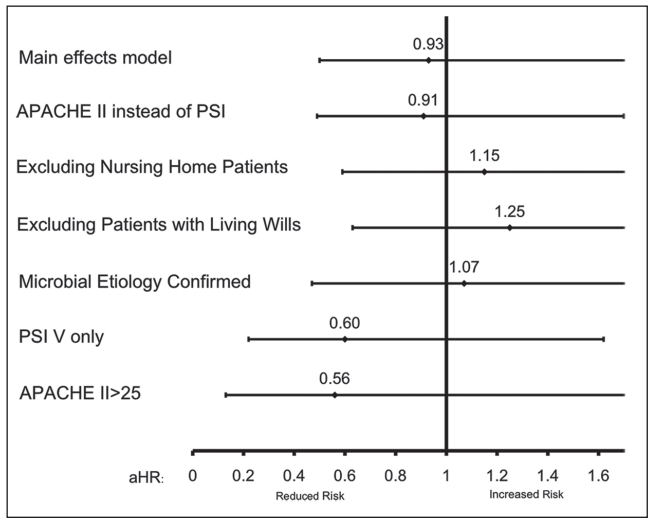

Figure 2) *Sensitivity analyses. aHR Adjusted HR; APACHE Acute Physiology and Chronic Health Evaluation; PSI Pneumonia Severity Index*

Sensitivity and exploratory analyses

Although the point estimates varied across analyses, there were no statistically significant associations between macrolide-based treatment and mortality in any of the sensitivity analyses (P value range 0.3 to 0.9; Figure 2). In patients with shock, macrolide use was not associated with mortality compared with those without shock (33% versus 15% mortality; aHR 1.41 [95% CI 0.01 to 153]; P=0.9); however, given the low prevalence of shock (n=27) it is difficuly to draw any conclusions. In addition, there was no difference in 30-day mortality when microbiologically confirmed cases were compared with cases with no etiology (aHR 1.15 [95% CI 0.62 to 2.11]; P=0.7).

Mortality in patients who received effective therapy (n=286) appeared to be lower compared with patients that did not have timing data or received ineffective therapy (n=42) but this was only a trend (aHR 0.48 [95% CI 0.23 to 1.01; P=0.05]). Time to effective antibiotics, however, yielded different results. In patients who received effective therapy, the mean time to therapy was 9±16 h (median time 4 h; interquartile range 2 h to 8 h). A total of 170 (52%) received therapy within 4 h, 116 (35%) between 4 h and 12 h, six (2%) between 12 h and 24 h and 36 (11%) at >24 h postadmission. In analyses adjusted for age, sex, PSI, acute kidney injury and *S aureus* etiology, timely antibiotic treatment was independently associated with lower 30-day

mortality: 24 of 170 (14%) within 4 h versus 20 of 116 (17%) if delayed (aHR 0.50 [95% CI 0.27 to 0.94]; P=0.03). Additionally, to ensure early deaths were not influencing results, patients who died within 24 h were excluded, with no change in effect measure or significance (aHR 0.48 [95% CI 0.25 to 0.92]; P=0.03).

DISCUSSION

In our cohort of patients requiring ICU admission for severe CAP, the overall mortality rate was 16% at 30 days with no observed mortality benefit in patients treated with macrolides compared with nonmacrolides (P=0.8). This represents one of the largest, clinically risk-adjusted, prospective studies to date examining macrolide-based treatment in critically ill patients with pneumonia.

Our findings, however, are discrepant from previous studies. (18-21) In a study by Martin-Loeches et al (19), combination therapy with macrolides was associated with reduced mortality compared with fluoroquinolone-based combination therapies in ventilated CAP patients (aHR 0.48 [95% CI 0.23 to 0.97]; P=0.04) However, broad-spectrum beta-lactam therapy (piperacillin/tazobactam or a carbapenem) was used in combination with fluoroquinolones in 46% of patients compared with 7% in the macrolide group, suggesting that the fluoroquinolone group was at higher risk of multidrug-resistant pathogens and treatment failure (29).

Similarly, Restrepo et al (20) demonstrated decreased 30-day mortality in CAP patients with severe sepsis treated with macrolide-based combination therapies compared with nonmacrolides (aHR 0.3 [95% CI 0.2 to 0.7]; P=0.001) and, specifically, in patients with macrolide-resistant pathogens (aHR 0.1 [95% CI 0.02 to 0.5]; P=0.005). However, the macrolide cohort had higher rates of guideline-concordant antibiotic therapy and less severe sepsis. Both of the above studies were, therefore, at risk of confounding by indication.

In a large study of bacteremic pneumococcal pneumonia, Baddour et al (18) observed decreased mortality in those treated with macrolide combination therapies versus monotherapy (14.3% versus 23.1%, P=0.007). However, only 94 critically ill patients were included, 14 of whom received beta-lactam/macrolide therapy. The remainder received varying combination therapies, similarly demonstrating a mortality reduction, thereby failing to show any unique benefit offered by macrolides.

Lastly, Rodriguez et al (21) demonstrated a 28-day adjusted survival advantage in 529 critically ill CAP patients treated with combination therapy. When specifically comparing beta-lactam/macrolide combinations to monotherapy in 183 patients with shock, a survival advantage was similarly observed; however, other combination therapies (specifically beta-lactam/fluoroquinolone) were similarly associated with improved outcomes, negating a macrolide-specific advantage.

So, above reasons aside, why else might our results be discrepant from previously published studies? First, perhaps the anti-inflammatory properties of macrolides are only beneficial in patients with shock and/or high disease severity – those with a robust systemic inflammatory response. Although we did not observe a mortality reduction with macrolide-based therapies in our sensitivity analyses of patients with severe disease (those with septic shock, mechanical ventilation or higher risk scores) the point estimates suggest that a benefit may exist. A much larger study would be required to specifically examine these 'sicker' ICU cohorts. Second, perhaps the literature in this field is hindered by publication bias – with similar 'negative' studies never reaching publication. In addition, although studies have demonstrated potential immunomodulatory benefits to macrolide therapy in the setting of low-grade chronic inflammation (16,17), these putative benefits may be clinically insignificant in acute illness. In addition, potential antagonism between macrolides and beta-lactams may offset a benefit if one exists (30) – as has been described when macrolides are administered before beta-lactams (31).

Our findings related to mortality reduction with timely administration of effective antibiotics support the premise that rapid and effective antibiotic administration is essential to high-quality care, particularly in critically ill patients (28,32-35). Of course, the present study involved a post hoc analysis and was, therefore, biased toward demonstrating a benefit. However, given that we defined a single, clinically relevant time point (4 h) – and avoided multiple comparisons – we believe our statistical result is not only valid but can be used as hypothesis-generating in future studies. In addition, the prospective nature of our data mitigates the issue of post hoc analysis.

Despite some strengths, we recognize several limitations to our study. First, although the sample size was large, only 91 patients received macrolides and there were only 54 total deaths. Thus, the study may be underpowered to detect minor differences between groups; however, this is unlikely to be a clinically relevant difference. Furthermore, our study is larger than most of the previous reports that were able to find a macrolide effect. Indeed, our study is one of the largest severe CAP cohorts to date. Second, we did not collect complete data on respiratory virus or atypical bacterial infections, identifying a microbial etiology in only 48% of cases. This, however, is not dissimilar compared with other CAP studies, even with specialized testing (36,37). In addition, patients with viral pneumonia also exhibit inflammatory (cytokine) responses, and when we prospectively analyzed this in Alberta in a different study, there were no features that could distinguish viral from bacterial pneumonia (38). Therefore, we believe any immunomodulatory benefits conferred by macrolides should not be limited to patients with bacterial infection. Third, the person-time accrued, although large compared with previous studies, limited the number of sensitivity analyses we were able to perform. Finally, some would question the time since the collection of our data; however, we strongly believe it is still generalizable because pneumonia epidemiology, treatment, guidelines and outcomes have remained stable over the past 10 years (39). Pneumococcus remains the most common cause of CAP. As well, no major changes in care in this patient population have occurred.

CONCLUSIONS

In the present study, empirical macrolide-based treatment for patients with severe pneumonia requiring ICU admission was not associated with decreased 30-day mortality compared with other antibiotic regimens. Given the limitations of observational data, we suggest that a randomized trial is needed to further explore this relevant and controversial area. In the meantime, our findings suggest that perhaps less emphasis be placed on the theoretical immunomodulatory advantages derived from macrolides and more attention devoted to the rapid delivery of effective antimicrobial treatments.

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