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Evaluation of severity score guided approaches to macrolide use in community-acquired pneumonia

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ABSTRACT

Background: International guidelines including those in UK, Japan, Australia and South Africa recommend avoidance of macrolide use in patients with low-severity community acquired pneumonia (CAP). We hypothesized that severity scores would be poor predictors of atypical pneumonia and response to macrolide therapy and thus be inadequate tools for guiding antibiotic prescribing.

Methods: A secondary analysis of four independent prospective CAP datasets was conducted. The predictive value of CURB65 and PSI for clinically important groups of causative pathogens was evaluated. The effect of macrolide use according to risk class was assessed by multivariable analysis.

Results: 3,297 patients were included in the study. The predictive value of CURB65 and PSI for atypical pathogens was poor(AUC value of 0.37 and 0.42 respectively). There were no significant differences between effect of macrolide use on mortality in patients with mild, moderate and severe CAP according to either CURB65(interaction testing severe vs mild disease OR=0.74(0.29–1.89)) or PSI(interaction testing severe vs mild disease OR=3.4(0.055–2.10)), indicating that severity scores are not significant modifiers of response to macrolide therapy.

Conclusion: Severity scores do not accurately predict response to macrolide therapy in CAP suggesting that current guidance to use these tools for empirical antibiotic choices may not be justified.

INTRODUCTION

Community acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide and accounts for a large proportion of antibiotic prescribing in primary and secondary care.[1] The empirical antibiotic choice is a crucial early management decision for patients presenting with CAP in view of the fact that microbial aetiology is usually unknown at presentation. International guidelines recommend varying approaches to empirical prescribing with most countries advocating treatment based on site of care, with the assumption that site of care depends on disease severity.[2-4] The most commonly used CAP severity scores, CURB65 and the Pneumonia severity Index (PSI), were developed and validated specifically for prediction of 30-day mortality.[5-7] However, these scores are increasingly being extrapolated to aid other clinical decisions including antibiotic prescribing choice.[8]

The British Thoracic Society (BTS) / National Institute for Health and Care Excellence (NICE) and other international guidelines including those in Australia, Japan and South Africa recommend a specific approach using the CURB65 score to guide antibiotic choices.[9-12] These recommendations are based on the assumption that low severity CAP (CURB65 score 0-1) may be safely treated with oral amoxicillin monotherapy with broader spectrum cover (including coverage of atypical pathogens with inclusion of macrolides) reserved for moderate (CURB65 score 2) or severe (CURB65 score 3-5) disease. This recommended approach is dependent on the assumption that atypical coverage with a macrolide is unnecessary in patients with CURB65 scores of 0-1 because they are at low risk adverse outcome and therefore coverage of atypical pathogens with macrolide therapy is not essential. These recommendations were based on expert opinions due to a lack of existing studies to draw guidance from.

Recently published clinical trials have reported no additional benefit associated with addition of macrolides to beta lactam as initial empirical CAP therapy[13, 14], although one trial[13] did demonstrate benefit in a sub-group who had microbiologically confirmed atypical infection. This study also showed no difference in outcome when macrolides were prescribed in low CURB65 score patients versus higher scores[13]. These data provide justification for a formal evaluation of the ability of CURB65 to accurately predict the presence of atypical infection and response to macrolide therapy to determine whether a severity score guided antibiotic approach is appropriate.

The issue of judicious use of macrolide therapy remains extremely important clinically. Macrolides are known to be potent inducers of antibiotic resistance[15] and are associated with important adverse effects including *Clostridium difficile* associated infections[16] and potentially cardiotoxicity[17]. Therefore, use of these drugs must be rigorously justified. Despite CURB65 guided therapy being advocated by the BTS/NICE, a previous UK nationwide audit showed that 51% of patients with low severity CAP according to CURB65 received broad-spectrum cover with beta lactam plus macrolide therapy [18]. This apparent failure of clinicians to adopt the recommended approach further justifies an examination of whether it is appropriate.

The aim of our study was to determine the value of the severity score-based approaches for guidance of antibiotic therapy in patients hospitalized with CAP. We hypothesized that CURB65 and PSI would be poor predictors of the presence of atypical pathogens and would also be poorly predictive of response to macrolide therapy and thus be inadequate tools for guiding appropriate prescription of macrolides in CAP.

METHODS

Study populations

This was a secondary analysis of four large prospective observational datasets: the Edinburgh Pneumonia Study (Edinburgh, UK; 2005-2010), the Milan Pneumonia Study (Policlinico Hospital, Milan, Italy; 2008-2010), the FAILCAP dataset (an Italian multicenter study; 2009-2012), and the Barcelona pneumonia cohort (Barcelona, Spain; 2008-2012). All four studies enrolled consecutive and unselected adult patients hospitalized with radiographically confirmed CAP. Details for each study have been previously published. [19-22] Inclusion and exclusion criteria for the four studies are detailed in the online supplementary methods.

Data collection

In all four cohorts, demographic variables, baseline admission observations, standard blood tests (full blood count, urea and electrolytes, liver function tests, albumin and C-reactive protein) and initial therapies including antibiotics were measured and recorded on hospital admission. Patients were risk-assessed on admission using the CURB65 score[5] and the PSI[6]. In the Barcelona cohort, only PSI could be calculated.

Microbiological Evaluation

Microbiological testing was conducted according to BTS recommendations in the Edinburgh cohort[9], according to European Respiratory Society recommendations in the Milan, FAILCAP and Barcelona cohorts[23]. Admitting clinicians were responsible for decisions regarding microbiological testing. Sputum and blood cultures were recommended within 24 hours of hospital admission. Urinary antigen testing was

performed for *Legionella pneumophila* in all three cohorts and for *Streptococcus pneumoniae* in the Milan cohort only. Pleural puncture, tracheobronchial aspirates, and bronchoalveolar lavage fluid, when available, were also collected and cultured. Identification of microorganisms and susceptibility testing were performed according to standard methods. Identification of atypical pathogens by PCR was carried out in all four cohorts and atypical serology was carried out only in the Milan and FAILCAP cohorts. The online supplementary information gives detailed information regarding atypical testing. Multidrug resistant pathogens were defined as previously described[20].

Statistical analyses

All data was analyzed and processed on SPSS version 21.0 for windows (SPSS Inc., Chicago, Ill). Descriptive statistics of demographic and clinical variables are expressed as median (interquartile range) (IQR) unless otherwise stated. The area under the receiver operator characteristic curve (AUC) was used to assess predictive tests.

Multivariable logistic regression was used to test the effect on antibiotic therapies on 30-day mortality after adjustment for relevant confounders (all variables included in PSI except altered mental status, urea, respiratory rate, blood pressure and age in the case of CURB65 and multilobar radiographic changes and presence of severe sepsis on admission in the case of PSI). To test if severity scores were a modifier of the effect of antibiotics on mortality, odds ratios for mortality between the mild, moderate and severe severity groups were compared using interaction testing as described by Altman et al[24]. For all analyses a two tailed p value <0.05 was considered statistically significant.

RESULTS

There were 790 patients from the Edinburgh pneumonia study, 935 patients from the Milan cohort, 667 patients from the Barcelona pneumonia study and 905 patients from the FAILCAP cohort included in the study, giving a total overall combined cohort of 3,297 patients. Table 1 shows baseline characteristics of the three cohorts separately and the overall combined cohort. Table 2 shows frequency of identified pathogens in each cohort separately and in the combined cohort.

Table 1: Baseline characteristics of individual cohorts and overall combined dataset					
	Edinburgh Pneumonia study	**Milan cohort**	**Barcelona cohort**	**FAILCAP**	**Combined cohort**
Number	790	935	667	905	3297
Male	392 (49.6%)	504 (54.0%)	264 (39.6%)	531 (58.7%)	1691 (51.3%)
Age (median (IQR))	66 (51-77)	79 (69-86)	66 (50-81)	76 (65-84)	74 (59-83)
Comorbidities					
COPD	201(25.4%)	270 (28.9%)	90 (13.5%)	255 (28.2%)	816 (24.7%)
Diabetes	77 (9.7%)	140 (15.0%)	123 (18.4%)	187 (20.7%)	527 (16.0%)
Cerebrovascular	83 (10.5%)	190 (20.3%)	16 (2.4%)	195 (21.5%)	484 (14.7%)
Chronic renal failure	51 (6.5%)	147 (15.7%)	n/a	76 (8.4%)	274(10.4%)
Liver disease	37 (4.7%)	53 (5.7%)	49(7.3%)	48 (5.3%)	177 (5.4%)
Cardiac failure	144(18.2%)	264(28.2%)	67 (10.0%)	178(19.7%)	653 (19.8%)
Physical findings					
SBP<90mmHg or DBP < 60mmHg	234 (29.6%)	180 (19.3%)	110 (16.5%)	117 (12.9%)	641 (19.5%)
Pulse rate (median (IQR))	100 (90-120)	95 (82-110)	98 (84-110)	96(82-110)	100 (84-110)
Altered mental status	127 (16.1%)	255 (27.3%)	109 (16.3%)	129 (14.3%)	620 (18.8%)
Respiratory rate $\geq$30	298(37.7%)	195 (20.9%)	116 (17.4%)	156 (17.2%)	765 (23.2%)
Laboratory tests					
Urea (mg/dL)	4.0(2.3-5.3)	4.8(3.3 – 7.3)	n/a	3.7(2.0-5.7)	4.2 (2.7–6.2)
Sodium (mEq/L)	137(134-139)	137(134-140)	136(133-139)	136(133-140)	137(133-39)
Glucose>125	30 (3.8%)	383 (40.9%)	314 (47.1%)	397 (43.9%)	1124(34.1%)
pH<7.35	149 (18.9%)	80 (8.6%)	42 (6.3%)	56 (6.2%)	279 (11.1%)
Severity & Outcomes					
In hospital mortality	72 (9.1%)	152(16.3%)	46 (6.9%)	81 (9.0%)	351(10.6%)
Length of hospital stay	5 (3-12)	12 (8-18)	7 (4-10)	9 (7-13)	9 (5-14)
CURB65>2	274 (34.7%)	352 (37.6%)	n/a	319 (35.2%)	908(36.0%)
PSI>3	392 (49.6%)	711 (76.0%)	258 (38.7%)	692 (76.5%)	2053(62.3%)

Antibiotic usage Macrolide Use Atypical coverage	553 (70.0%) 571 (72.4%)	396 (42.4%) 684 (73.2%)	170 (25.5%) 602 (90.3%)	434 (48.0%) 765 (84.5%)	1553(47.1%) 2622(79.6%)

Table 2: Pathogen frequency in individual cohorts and combined dataset

	Edinburgh cohort (n=790)	**Milan cohort (n=935)**	**Barcelona cohort (n=667)**	**FAILCAP (n=905)**	**Combined cohort (n=3297)**
n (% of patients with positive pathogen identified)	224 (28.3%)	170 (18.2%)	181 (27.1%)	145 (16.0%)	720 (21.8%)
S. pneumoniae	107 (47.8%)	63 (37.1%)	123 (68.0%)	54 (37.2%)	347 (48.2%)
H. influenzae	22 (9.8%)	6 (3.5%)	5 (2.7%)	3 (2.1%)	36 (5.0%)
M. pneumoniae	13 (5.8%)	5 (2.9%)	3 (1.7%)	8 (5.5%)	29 (4.0%)
L. pneumophila	8 (3.6%)	26 (15.3%)	12 (6.6%)	19 (13.1%)	65 (9.0%)
MSSA	18 (8.0%)	21 (12.4%)	1 (0.5%	8 (5.5%)	48 (6.7%)
MRSA	2 (0.9%)	16 (9.4%)	10 (5.5%)	12 (8.3%)	40 (5.6%)
Klebsiella pneumoniae	10 (4.5%)	13 (7.6%)	3 (1.7%)	2 (1.4%)	28 (3.9%)
C. pneumoniae	1 (0.4%)	4 (2.4%)	0 (0%)	2 (1.4%)	7 (1.0%)
All atypicals Combined	22 (9.8%)	35 (20.6%)	15 (8.3%)	29 (20.0%)	101 (14.0%)
Gram negative *Enterobacteriaceae*	15 (6.7%)	30 (17.6%)	10 (5.5%)	13 (9.0%)	68 (9.4%)
P. aeruginosa	2 (0.9%)	12 (7.1%)	13 (7.2%)	7 (4.8%)	34 (4.7%)
MDR pathogens combined	7 (3.1%)	58(34.1%)	12 (6.6%)	18 (12.4%)	95 (13.2%)

Frequency of Pathogens according to CURB65 or PSI risk class

Table 3 shows frequency of pathogens in severe *versus* non-severe risk classes, according to CURB65 with risk ratios showing comparison of frequencies between severe and non-severe classes. The frequency of *M. pneumoniae* and all atypical pathogens combined was significantly higher in patients with non-severe disease according to either CURB65 or PSI. The frequency of *L. pneumophila* was significantly higher in patients with non-severe disease according to CURB65. The frequency of Gram-negative *Enterobacteriaceae* was significantly higher in patients with severe disease compared to those with non-severe disease, according to either CURB65 or PSI. MSSA was significantly more frequent in patients with severe disease according to CURB65 or PSI while MRSA and MDR pathogens combined were significantly more frequent in patients with severe disease according to PSI. The frequency of pathogens according to CURB65 and PSI in each of the individual cohorts is shown in eTables 1 and 2 (online supplementary information).

Table 3: Pathogen frequency according to admission severity class

CURB65	**n**	**Mild 0-1**	**Moderate 2**	**Severe ≥ 3**	**Risk ratio Severe vs mild/moderate**	**Risk ratio Moderate/severe *vs.* mild**
N	539	155	157	227		
S. pneumoniae	224	57 (36.3%)	70 (44.6%)	97 (42.7%)	1.05 (0.85 – 1.28)	1.18 (0.93-1.50)
H. influenzae	31	16 (10.3%)	6 (3.8%)	9 (4.0%)	1.01 (0.48 – 2.12)	**0.38 (0.19 – 0.75)**
M. pneumoniae	31	19 (12.3%)	6 (3.8%)	6 (2.6%)	**0.33 (0.14 – 0.79)**	**0.26 (0.13 – 0.51)**
L. pneumophila	48	15 (9.7%)	20 (22.4%)	13 (5.7%)	**0.51 (0.28 – 0.94)**	0.89 (0.50-1.59)
MSSA	47	10 (6.5%)	7 (4.5%)	30 (13.2%)	**2.42 (1.37 – 4.29)**	1.49 (0.77-2.93)
MRSA	30	3 (1.9%)	13 (8.3%)	14 (6.2%)	1.20 (0.60 - 2.41)	**3.63 (1.12 – 11.80)**
C. pneumoniae	7	3 (1.9%)	3 (1.9%)	1 (0.4%)	0.23 (0.03 – 1.89)	0.54 (0.12 – 2.38)
All atypicals Combined	86	37 (23.8%)	29 (18.5%)	20 (8.8%)	**0.42 (0.26 – 0.67)**	**0.53 (0.36-0.78)**
Gram negative *enterobacteriaceae*	58	6 (3.9%)	15 (9.6%)	37 (16.3%)	**2.42 (1.46 – 4.03)**	**3.50 (1.54-7.98)**
P. aeruginosa	21	4 (2.6%)	5 (3.2%)	12 (5.3%)	1.83 (0.79 – 4.28)	1.72 (0.50-5.02)
MDR pathogens combined	83	16 (10.3%)	27 (17.2%)	40 (17.6%)	1.28 (0.86 – 1.90)	**7.73 (4.80 – 12.44)**

PSI		**Mild (1-2)**	**Moderate (3)**	**Severe (4-5)**		
N	720	162	119	439		
S. pneumoniae	347	77 (47.5%)	64 (53.8%)	206 (46.9%)	0.93 (0.80 – 1.09)	1.01 (0.85-1.22)
H. influenzae	36	12 (7.4%)	10 (8.4%)	14 (3.2%)	**0.41 (0.21 – 0.78)**	0.58 (0.30 – 1.14)
M. pneumoniae	24	16 (9.9%)	2 (1.7%)	6 (1.4%)	**0.21 (0.09-0.53)**	**0.14 (0.063 – 0.33)**
L. pneumophila	70	17 (10.5%)	11 (9.2%)	42 (9.6%)	0.96 (0.61 – 1.51)	0.91 (0.54 – 1.52)
MSSA	48	8 (4.9%)	3 (2.5%)	37 (8.4%)	**2.15 (1.12 – 4.15)**	1.45 (0.69-3.04)
MRSA	40	5 (3.1%)	4 (3.4%)	31 (7.1%)	**2.20 (1.07 – 4.56)**	2.03 (081 – 5.10)
C. pneumoniae	7	3 (1.9%)	1 (0.8%)	3 (0.7%)	0.48 (0.11-2.13)	0.39 (0.09 – 1.71)
All atypicals Combined	101	36 (22.2%)	14 (11.8%)	51 (11.6%)	**0.65 (0.45 – 0.94)**	**0.52 (0.36 – 0.76)**
Gram negatives enterobacteriaceae	68	6 (3.7%)	7 (5.9%)	55 (12.5%)	**2.71 (1.51 – 4.86)**	**3.0 (1.32 – 6.81)**
Pseudomonas	34	1 (0.6%)	7 (5.9%)	26 (5.9%)	2.08 (0.96 – 4.53)	**9.58 (1.32-69.51)**
MDR pathogens	**95**	8 (4.9%)	9 (7.6%)	78 (17.8%)	**2.94 (1.78-4.86)**	**3.17 (1.57 – 6.40)**

Predictive value of severity scores for determining causative pathogens in CAP

The predictive value of severity scores CURB65 and PSI, for clinically relevant groups of pathogens was evaluated. Table 3 shows AUC for prediction of atypical bacteria, methicillin-sensitive *Staphylococcus aureus* and MRSA, Gram-negative enterobacteriaceae, *Pseudomonas aeruginosa* and MDR pathogens. Both severity scores performed poorly for prediction of all pathogen groups with AUC values consistently less than 0.7 (the minimum threshold regarded as being a clinically useful test). The AUC value for prediction of atypical bacteria was <0.5 for either CURB65 or PSI indicating that use of these scores provides misleading information.

Table 4: Predictive value of severity scores for clinically important groups of pathogens in CAP

	Atypical Bacteria	**Gram negative *Enterobactericeae***	**MSSA**	**MRSA**	**Pseudomonas**	**All MDR Pathogens**
CURB65	0.37 (0.31-0.43)	0.65 (0.58-0.72)	0.61 (0.52-0.69)	0.57 (0.48-0.67)	0.58 (0.46-0.71)	0.56 (0.49-0.62)
PSI	0.42 (0.35-0.48)	0.61 (0.55-0.68)	0.58 (0.50-0.66)	0.69 (0.50-0.67)	0.60 (0.52-0.69)	0.63 (0.57-0.68)

Macrolide use and mortality according to admission severity score in CAP

The effect of macrolide use on mortality, stratified according to admission severity score is shown in table 5. Although macrolide use was significantly associated with reduced mortality in severe disease but not moderate or mild disease according to CURB65, severity criteria were not modifiers of the benefit of macrolide use as there were no significant differences between the effect of macrolide use on mortality when comparing patients with mild, moderate or severe disease according to CURB65 by interaction testing (see table 6). Similar observations were seen for PSI except for severe *versus* moderate disease, where there was a significantly greater effect on mortality seen in the moderate severity group. These findings indicate that existing severity scores are not significant modifiers of response to macrolide use.

Table 5: Association between macrolide use and mortality stratified according to severity

	CURB65	**Pneumonia Severity index**
Mild		
- Unadjusted	0.47 (0.21 – 1.06)	0.57 (0.45 - 0.73)
- Adjusted	0.51 (0.21 – 1.21)	0.44 (0.31 – 0.61)
Moderate		
- Unadjusted	0.66 (0.43-1.02)	0.47 (0.35-0.64)
- Adjusted	0.60 (0.36-1.01)	0.35 (0.24-0.53)
Severe		
- Unadjusted	0.67 (0.53-0.86)	0.62 (0.53-0.72)
- Adjusted	0.69 (0.49 – 0.97)	0.52 (0.42-0.64)

Table 6: Interaction testing of different severity classes according to either CURB65 or PSI for effect of macrolide use on mortality

Macrolide use	**Ratio of Relative risk**	**Z score**	**95% CI**
Severe vs. mild			
CURB65	0.74	-0.63	0.29 – 1.89
PSI	0.34	-1.16	0.055 – 2.10
Moderate vs. mild			
CURB65	0.85	-0.31	0.30 – 2.35
PSI	0.80	-0.86	0.47 – 1.34
Severe vs. Moderate			
CURB65	1.15	0.38	0.55 – 2.39
PSI	0.61	-2.06	0.29 - 0.98

Interaction testing performed as previously described by Altman *et al*. **{** ADDIN EN.CITE <EndNote><Cite><Author>Altman</Author><Year>2003</Year><RecNum>1774</RecNum><DisplayText>[24]</DisplayText><record><rec-number>1774</rec-number><foreign-keys><key app="EN" db-id="tdsf559xypaws2epadyxrpab5rr9dz2ee0vd" timestamp="1468535188">1774</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Altman, D. G.</author><author>Bland, J. M.</author></authors></contributors><auth-address>Cancer Research UK Medical Statistics Group, Centre for Statistics in Medicine, Institute for Health Sciences, Oxford OX3 7LF. doug.altman@cancer.org.uk</auth-address><titles><title>Interaction revisited: the difference between two estimates</title><secondary-title>BMJ</secondary-title></titles><periodical><full-title>BMJ</full-title></periodical><pages>219</pages><volume>326</volume><number>7382</number><keywords><keyword>Analysis of Variance</keyword><keyword>Confidence Intervals</keyword><keyword>*Statistics as Topic</keyword></keywords><dates><year>2003</year><pub-dates><date>Jan 25</date></pub-dates></dates><isbn>1756-1833 (Electronic)
0959-535X (Linking)</isbn><accession-num>12543843</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/12543843</url></related-urls></urls><custom2>PMC1125071</custom2></record></Cite></EndNote>**}** Relative risk ratio <1 = lesser relative benefit for first group stated; Relative risk ratio >1 = greater benefit for first group

stated.

Macrolide use in subgroups with confirmed atypical pathogens and non-atypical pathogens.

There were 101 patients with confirmed atypical pathogens in the combined cohort. Of these patients, 57 received macrolide therapy. In the sub-group with confirmed atypical pathogens the unadjusted effect of macrolide use (either monotherapy or in combination) showed no significant effect on mortality (OR 0.48 (0.21-1.05)) but this became significant after adjustment for admission severity according to PSI (OR 0.36 (0.13-0.99)).

In the sub-group with only evidence of typical pathogens, macrolide use (either monotherapy or in combination) was also significantly associated with reduced mortality (OR = 0.60 (0.43-0.84)) an effect that remained significant after adjustment for admission severity (OR 0.47 (0.30 – 0.74).

Sensitivity analysis excluding patients in whom atypical pathogens were solely diagnosed by serological tests alone.

Since previous studies have demonstrated that serology for *C.pneumoniae* and *M.pneumoniae* (with the exception of IgM antibody) is not accurate for diagnosis of atypical pneumonia [25, 26], we performed a sensitivity analysis where atypical pneumonia cases identified by serology alone were excluded (only present in the Barcelona cohort and thus only relevant for analysis of PSI). A consistent effect was observed in this sub-group with the frequency of atypical pathogens combined being significantly higher in patients with non-severe disease versus severe disease according to PSI (risk ratio 0.51 (0.35-0.75)). The AUC for prediction of atypical bacteria for PSI, after exclusion of cases diagnosed by serology alone was 0.39 (0.32 – 0.46).

DISCUSSION

Our study in a large international cohort comprising four independent European datasets demonstrates that international guidance from UK, Japan, Australia and South Africa to use admission severity scoring for empirical antibiotic prescribing in CAP, specifically to determine the use of macrolides, is unjustified. This conclusion is based on our finding that severity scores such as CURB65 and PSI are not predictors of response to macrolide therapy and also do not accurately predict the presence of atypical pathogens.

We show that severity scores such as CURB65 and PSI are poor predictors of microbial aetiology with AUC values consistently below 0.7, the minimum threshold above which predictive scores can be deemed to be clinically useful.[27] In particular, with regard to atypical pathogens, we show that severity is not a reliable predictor of their presence. Strikingly, in our study, CURB65 had an AUC of 0.37 for prediction of atypical microorganisms, indicating that atypical pathogens were actually more frequent in the low severity classes of CURB65 and that a coin-toss (giving an AUC of 0.5) would be more predictive of atypical pathogens. The more detailed score PSI had a similarly low AUC value of 0.42.

The current approach advocated by UK, Japanese, Australian and South African pneumonia guidelines is based on the premise that narrow spectrum therapy (with lack of atypical cover) is adequate for patients with low severity disease with broader spectrum therapy including coverage of atypical pathogens and *S. aureus* being reserved for patients in higher severity classes. These guidelines recommend that macrolide therapy should be omitted from patients with low admission severity CAP (CURB65 score of 0-1). Given our findings that atypical pathogens occur frequently in this group, this approach would be expected to lead to inadequate coverage of atypical bacteria in a considerable proportion of patients. These concerns are reinforced by previous studies which have also evaluated microbial aetiology according to severity of CAP and have similarly shown that atypical pathogens are more frequent in lower severity classes.[28-30] Expert opinion has previously raised concerns over inadequate coverage of atypical microorganisms in hospitalised patients with low severity disease, as recommended by

such strategies.[31] A counter-argument to this theory would be that inadequate pathogen coverage in such patients with milder disease is less likely to be harmful and may simply require a treatment alteration. However, in a study focusing on *Legionella* pneumonia by Von Baum *et al*, 37.5% of patients who died within 6 months received antibiotics that did not initially cover atypical microorganisms after initially presenting with mild pneumonia[32]. Therefore, this would suggest that withholding macrolide therapy may not be appropriate for all patients with mild pneumonia based exclusively on severity scores.

Regardless of whether or not severity scores can accurately predict microbial aetiology, it may be argued that the benefits of macrolide therapy are not solely related to anti-bacterial activity but may also be related to the widely reported anti-inflammatory effects of these drugs[33]. Previous studies have shown that even in patients with confirmed non-atypical (pneumococcal) infection, addition of macrolide therapy has beneficial effects[34, 35]. Although some observational studies have historically reported a benefit associated with macrolide use in CAP[36], two recent randomized controlled trials have disproved this and shown no additional benefit associated with addition of macrolide to beta lactam empirical therapy in hospitalized patients with CAP[13, 14]. Despite these reported findings, specific sub-groups of patients that derive benefit from macrolides may still exist. A severity score guided approach would still be justifiable if severity scores could be shown to accurately predict macrolide treatment response with minimal beneficial effect in patients with low CURB65 scores. However, the findings of our study also contradict this assertion because we found no significant differences between the effect of macrolide use on mortality when comparing patients with mild, moderate or severe disease according to CURB65 by interaction testing, thereby demonstrating that severity criteria are not modifiers of the benefit of macrolide use. A previous study by Rodrigo et al evaluated 30-day mortality in patients treated with combined beta lactam/macrolide versus beta lactam therapy alone and concluded that combination therapy was associated with lower inpatient mortality specifically in patients with moderate and severe CAP according to CURB65 but not in low severity CAP[37]. However, the authors did not apply interaction testing to their data and this would have shown a result consistent with our finding that there is no

difference in the effect of macrolide use on mortality in mild versus severe pneumonia according to CURB65.

Our findings mirror those in the trial reported by Garin *et al*[13] which showed no significant benefit of combination therapy for achieving the primary outcome of reaching clinical stability at day 7, although it should be noted that patients with positive urinary antigen for *Legionella* were excluded from this study and their inclusion may have led to demonstration of a greater effect. However, although macrolide use was shown to confer greater benefit in the group with severe disease according to PSI *versus* those with low PSI scores, there was no difference in outcomes when stratifying the cohort according to CURB65[13]. Combined with our findings, these data argue strongly against the use of CURB65 as a tool for guiding use of macrolides in clinical practice and suggest reconsideration of the current international guidance.

The aforementioned study by Garin *et al* also reported that the macrolide use increased achievement of clinical stability at day 7 in patients with confirmed atypical infection but not in those non-atypical infection[13], suggesting that presence of atypical pathogens is an important factor in determining macrolide responses. Given our finding that atypical pathogens occur most frequently in patients with CURB65 scores, it seems counterintuitive to deny these patients macrolide therapy. It should be noted that our study found a beneficial effect of macrolide use on mortality in both patients with atypical and non-atypical infection. The apparent discordance with the Garin *et al* study may be explained by presence of inter-cohort variability in atypical testing conducted in the cohorts included in our study. There was a 2-fold increase in the frequency of atypical pathogens seen in the Milan and FAILCAP cohorts, based in Italy, most likely reflecting the increased use of atypical serology testing employed at these centres. Therefore, it may be possible that some patients in our combined cohort may have been misclassified as having no atypical infection due to lack of appropriate testing. This may account for the differences between our observational study and those of the randomized controlled trial by Garin *et al*[13], in which standardized microbiological testing was adopted.

Macrolide use in CAP has been a subject of growing interest and judicious use of these therapies is strongly advocated due to emerging concerns regarding complications associated with over-use such as *C. difficile* related infections and development of antibiotic-resistant strains[15, 16, 38]. Severity-score guided approaches are commendable in that they are geared towards limiting macrolide over-use and thus minimizing such risks. However, the data from our study would argue that using CURB65 as a method for deciding which patients should receive macrolide therapy is unjustified. Despite CURB65 guided therapy being clearly advocated by the BTS/NICE guidance, a previous nationwide audit of CAP management in the UK reported poor uptake of these recommendations[18]. Over 50% of patients with low CURB65 scores were empirically prescribed combination beta lactam/macrolide therapy in contradiction to the recommended approach of targeting such therapy at patients with severe disease only. Studies are now required to determine the specific sub-groups of patients with CAP that derive clinical benefit from use of macrolides to further inform practice and future guidance.

Despite the fact that PSI and CURB65 were shown to be poor predictors of microbial aetiology in our study, there were statistically significant associations observed between the severity scores evaluated and the presence of Gram-negative *Enterobacteriaceae*, *S. aureus*, and MDR pathogens. This would emphasise and support international guideline recommendations to provide Gram-negative and *Staphylococcal* coverage to patients with a high severity of illness.[9] To date, only one study has evaluated a CURB65-guided antibiotic therapy strategy in a clinical setting[39]. This was a study that compared antibiotic prescribing and outcomes before and after implementation of this strategy in a tertiary centre. The post intervention group had a significant reduction in broad-spectrum antibiotic prescribing, without any corresponding effect on mortality. Although macrolide use did reduce post intervention, it still remained high, even in patients with low severity disease. Although this study suggested that a CURB65 guided antibiotic approach was a safe strategy in a hospitalised cohort, there has been no other independent validation of these findings and it is also important to note that this was a before and after evaluation rather than a carefully matched randomised controlled trial.

The current study is not designed to answer the question of whether empirical macrolide therapy is effective in CAP. This is a question that can only be answered by large randomized controlled trials. Rather, our study was designed to evaluate whether the evidence supports using a severity scoring system to decide which patients should receive a macrolide. Our study demonstrates that CURB65 does not predict populations with different levels of macrolide response. Alternative severity scores, such as the Japanese respiratory guidelines, which have been evaluated for prediction of *Mycoplasma* pneumonia[40], might perform more effectively than CURB65 at guiding appropriate macrolide therapy but further studies are needed.

Our study should not be interpreted as a call to treat all hospitalised CAP patients with macrolides, but rather to remove an imperfect scoring system from this decision making process, and to focus exclusively on the balance between the existing evidence for macrolide treatment and the risks of macrolide treatment, such as antimicrobial resistance and drug related adverse effects. This balance may be different in different patients, or in different healthcare environments.

The strengths of this study are the prospective collection of data and the demonstration of the validity of our findings in four independent cohorts from Northern and Southern Europe with different empirical antibiotic prescribing practices, microbiological testing regimes and healthcare systems. This suggests that our data are robust and likely to be applicable to similar healthcare settings internationally. Nevertheless, limitations of the analysis must also be acknowledged. The rate of positive microbiology was low, although this is similar to other cohorts reported internationally and reflect the limitations of the currently available microbiological tests for CAP. Additionally, in all four cohorts, microbiological testing was left to the discretion of the admitting physician but carried out in accordance with international guidelines. As stated previously, we cannot exclude the occurrence of false negative results where a micro-organism was unidentified due to lack of appropriate testing. Future studies using a more systematic approach to atypical testing in all patients regardless of admission severity would provide clarity. It should also be noted that our study considers only hospitalised patients and further research is needed to determine the value of severity scores for guidance of antibiotic choices in patients treated in the community.

In conclusion, our study demonstrates that severity scores cannot be used to accurately identify subgroups of patients with CAP with different macrolide responses. Further evidence of impact is required before severity score guided regimes can be recommended for empirical antibiotic prescribing in CAP.

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