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Predictors for individual patient antibiotic treatment effect in hospitalized community-acquired pneumonia patients

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Background: There is no consensus for the need of atypical coverage with macrolides or quinolones in moderate-severe CAP patients. Research has focused on predicting clinical outcome or causative pathogens, but was unsuccessful in predicting which individuals benefit from atypical coverage. Our objective was to identify clinical predictors of antibiotic treatment effects in non-ICU hospitalised CAP patients taking into account the heterogeneity of each individual.

Material/methods: We performed a post-hoc analysis of three prospective cohorts (two from the Netherlands (CAP-START and CAPiTA) and one from Spain (Bellvitge)) of CAP patients admitted to a non-intensive care unit (ICU) ward.

We included adults, hospitalised for at least 24 hours in a non-ICU ward and having received either beta-lactam monotherapy (BL), beta-lactam + macrolide (BLM), or fluoroquinolone-based (FQL) as

empiric antibiotic treatment. We selected a list of candidate clinical treatment effect predictors from previously published studies on CAP based on literature. Clinical outcomes 30-day mortality and length of hospital stay (LOS) were analyzed using mixed-effects logistic and linear regression models, respectively. Candidate clinical predictors were selected by a two-step approach. First, models were fitted for each candidate clinical predictor, including their interaction with empirical antibiotic choice (BL, BLM, or FQL) and adjusted for confounders. Next, the selected predictors, with interaction p-values <0.10, were analyzed in one regression model, adjusted for confounders. P-values were corrected for multiple testing (Figure 1).

Results: 8,562 patients were eligible. Empiric treatment was BL in 4,399 (51.4%), FQL in 3,373 (39.4%), and BLM in 790 (9.2%) patients. Older age (interaction OR 1.67, 95% CI 1.23 – 2.29, corrected p-value 0.034) and current smoking (interaction OR 2.36, 95% C.I. 1.34 – 4.17, corrected p-value 0.046) were associated with lower effectiveness of fluoroquinolone-based treatment on 30-day mortality. Older age was also associated with lower effectiveness of beta-lactam plus macrolide treatment on LOS (interaction effect ratio 1.13, 95% CI 1.08 – 1.18, p value < 0.0001).

Conclusions: Older age and smoke habit significantly modified the treatment effect of FQL based regimens compared to BL on 30-day mortality leading to lower effectiveness in older and smoker patients. However, as we cannot rule out bias on the direct effects of antibiotics, the same interaction effect could either mean benefit for one group, or harm for the other group. Considering this limitation, our results should be considered hypothesis generating and need to be confirmed in a randomized controlled trial designed to estimate these interaction effects.

Decision flowchart of candidate effect modifiers for 30-day mortality