C-reactive protein-guided treatment in pneumonia

Charting a personalised approach – Authors' reply

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C-reactive protein-guided treatment in pneumonia: charting a personalised approach

Authors' reply

We appreciate the opportunity to further clarify our findings in response to the insightful comments from Shota Yamamoto and colleagues and Luis Felipe Reyes and Ignacio Martin-Loeches[1] regarding our recent community-acquired pneumonia (CAP) study.[2]

Yamamoto and colleagues highlight the importance of considering the risks of multiple testing and multicollinearity. We agree and explicitly took steps to mitigate these risks: following Lu Tian and colleagues'[3] recommendation, we pre-registered[4] our model and used the two most recent trials[5,6] as an independent test cohort, confirming statistically significant and clinically relevant heterogeneity of treatment effect in this external validation. Regarding multicollinearity, the variance inflation factor for C-reactive protein (CRP), at only 1·25 in the training cohort and 1·20 across all eight trials, suggest CRP is unlikely to be a proxy for another observed variable. Although we cannot rule out that multicollinearity or other factors obscure additional predictors of treatment benefit, we showed that CRP's predictiveness for treatment response is externally validated.

Yamamoto and colleagues also mention the importance of considering outcomes other than 30-day mortality to get a more comprehensive picture of treatment effects, which was addressed in our analysis with the inclusion of multiple secondary outcomes, including intubation and 90-day mortality, both trending toward greater benefit for patients with high baseline CRP—aligning with our primary outcome findings.

While the significant reduction in 30-day mortality for patients with high CRP is a key benefit and our study revealed no increase in superinfections or gastrointestinal bleeding, the observed increase in readmissions and hyperglycaemia rates in patients treated with corticosteroids (regardless of baseline CRP) leads us to share Yamamoto and colleagues' concern about an important trade-off with potential short-term and long-term implications, warranting further investigation beyond the 30-day timeframe.

Reyes and Martin-Loeches[1] raise concerns that using CRP might be premature for guiding clinical practice and advocate for a phenotype-based approach incorporating multiple biomarkers. We support further research into additional inflammatory markers (eg, cytokines), but our multivariate approach, using nearly all currently available randomised controlled trial data provides evidence only for a CRP-based method. CRP measurement is widely available, routinely used, and therefore an accessible and evidence-supported tool to guide corticosteroid therapy.

Of note, Reyes and Martin-Loeches do support corticosteroid use in severe CAP, aligning with the latest Society of Critical Care Medicine (SCCM) guidelines.[7] However, severity classifications vary across guidelines, with SCCM[7] and the European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Latin American Thoracic Association[8] using different criteria. Furthermore, in our analysis, we did not observe a greater relative treatment benefit in severe versus non-severe CAP, regardless of the severity definition used (ie, pneumonia severity index,[9] CURB-65,[10] initial intensive care unit admission, or initial invasive mechanical ventilation), challenging the current severity-based approach.

Reyes and Martin-Loeches suggest that many of the included trials lacked data on aetiology or baseline inflammation. However, we obtained aetiological data for seven (87·5%) of eight trials and had access to inflammatory markers (ie, CRP and white blood-cell counts) for all included trials. Our analyses on aetiology (based on patients with randomised treatment, including 11% of viral cases and 6% with influenza) suggest a non-significant trend toward harm in patients with viral CAP, including influenza, regardless of baseline CRP. Hence, we agree caution is warranted in these cases and advocate further investigation. Additionally, we encourage research on the potential benefits of response-adaptive corticosteroid regimens,[6] early treatment initiation, and hydrocortisone usage (rather than other corticosteroids).

In conclusion, our analysis provides clear evidence that baseline CRP is a strong predictor of corticosteroid response, while severity-based classifications do not show the same treatment effect differentiation. We believe updates to the guidelines should reflect this.

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