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Correspondence

From severity-guided to C-reactive protein–guided corticosteroid treatment

Jim M. Smit[1,2,3,*], Jesse H. Krijthe[2], Melanie Lloyd[4], Antoni Torres[5], Pierre-François Dequin[6], Philip A. van der Zee[3,7]

[1]Data Science Group, Institute for Computing and Information Sciences, Radboud University, Nijmegen, The Netherlands
[2]Pattern Recognition and Bioinformatics Group, Delft University of Technology, Delft, The Netherlands
[3]Department of Intensive Care, Erasmus MC–University Medical Center Rotterdam, Rotterdam, The Netherlands
[4]Centre for Medicine Use and Safety, Monash University, Melbourne, VIC, Australia
[5]School of Medicine, Institut d'Investigacions August Pi I Sunyer (IDIBAPS) Ciberes, University of Barcelona, Barcelona, Spain
[6]Medecine intensive reanimation, CHRU Hôpitaux de Tours, Hospital Bretonneau, Tours, France
[7]Department of Pulmonary Medicine, Erasmus MC–University Medical Center Rotterdam, Rotterdam, The Netherlands
*Corresponding author: Jim M. Smit, Data Science Group, Institute for Computing and Information Sciences, Radboud University, Mercator 1 Building, Toernooiveld 212, 6525 EC Nijmegen, The Netherlands (Jim.m.smit@outlook.com).

To the Editor:

We commend the authors for their updated American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guideline,[1] which also discusses adjuvant treatment with corticosteroids in hospitalized patients with community-acquired pneumonia (CAP). However, we have concerns regarding their recommendation against systemic corticosteroids in nonsevere CAP and in favor of corticosteroids in severe CAP (based on the ATS/IDSA severe CAP criteria), as it appears to overlook recent evidence and methodological limitations.

Recent trials on severe CAP show mixed results.[2-4] The CAPE-COD trial[3] found a significant mortality benefit from corticosteroids, which seems to drive the current guideline. However, this finding is contradicted by both the ESCAPe[2] and REMAP-CAP[4] trials, which found no benefit. Since 2 out of 3 recent severe CAP trials showed no positive effect of corticosteroids, it raises the question whether corticosteroids benefit all patients with severe CAP. Given that the REMAP-CAP trial was published after the current guideline's meta-analysis, its future inclusion will likely weaken the current perceived benefit across severe CAP trials.

As acknowledged by the authors, an aggregate meta-analysis is limited in its ability to identify specific patient subgroups that would benefit most from corticosteroids (ie, heterogeneity of treatment effect [HTE]). Individual patient data meta-analyses (IPDMAs), such as our recent one,[5] covering 8 randomized controlled trials, overcome this limitation. We examined HTE through a multivariate approach, considering demographics, clinical parameters, laboratory values, and comorbidities. We found no HTE for various CAP severity criteria (ie, Pneumonia Severity Index, CURB-65, initial intensive care unit admission, or invasive mechanical ventilation). In contrast, HTE across baseline C-reactive protein (CRP) levels was externally validated in unseen trials, showing clear 30-day mortality reduction starting around CRP values of ≥200 mg/L. While the authors acknowledge our findings regarding baseline CRP, it remains unclear why they chose a severity-based recommendation over a more specific CRP-based approach.

The authors mention that they eagerly await new evidence on patient subphenotypes to improve treatment precision. According to the European Society of Intensive Care Medicine definition,[6] patients with elevated baseline CRP already constitute a subphenotype, as our data-driven, multivariate model identified this group and the HTE was reproduced in different populations. This suggests that the subphenotype they await may already be available.

We agree with the authors' caution against using corticosteroids in CAP patients with influenza. While they base this on observational studies, our IPDMA[5] (based on patients with randomized treatment, including 6% with influenza) also suggests a nonsignificant trend toward harm, regardless of baseline CRP. We advocate further investigation, for instance with new data from the REMAP-CAP trial.[4]

We support the authors' call for future research into inflammatory markers, optimal corticosteroid type, dosing and timing, and nonmortality outcomes. Our IPDMA[5] also touched on these areas, suggesting a potential benefit for early treatment (within 24 hours) and a significant overall increase in hospital readmissions with corticosteroid use. Additionally, we stress the need for future trials to standardize the collection of inflammatory markers like cytokines, as inconsistent measurement techniques could seriously limit the comparability of these data.[5]

In conclusion, we agree that adjuvant treatment with corticosteroids should be considered for a subgroup of patients with CAP. However, we believe the evidence for survival benefit in patients with elevated baseline CRP is currently stronger than the evidence supporting severity-guided therapy. Further validation in newly available clinical data, like REMAP-CAP,[4] could further strengthen the yet robust evidence for CRP-driven HTE and may confirm other potential sources of HTE, such as etiology and treatment timing.

Author contributions

Study concept and design: J.M.S. Critical revision of the manuscript for important intellectual content: All authors.

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Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material.

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