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EDITORIAL

Corticosteroids for severe community-acquired pneumonia: a story without an ending

Bram Rochwerg[1,2*]

Regardless of pathogen, lower respiratory tract infection is associated with profound host response leading to altered permeability of the alveolar capillary membrane due to complex systemic and pulmonary inflammatory/immune responses [1–3]. As such, various immune modulators, including corticosteroids, have been evaluated as potential treatment options in patients with severe community-acquired pneumonia (CAP). A previous systematic review and meta-analysis included 13 randomized controlled trials (RCTs) and found that corticosteroids possibly reduced mortality, need for invasive mechanical ventilation and progression to acute respiratory distress syndrome (ARDS) [4] in patients hospitalized with CAP. Included trials investigated a range of corticosteroid doses, agents, and lengths of treatment. However, none of these factors demonstrated evidence of credible subgroup effects. The same review found an increase in hyperglycemia with corticosteroids with no increase in other adverse events including gastrointestinal hemorrhage, neuropsychiatric complications or re-hospitalization. Based on this evidence, as part of the 2017 SCCM/ESICM Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency in Critically Ill Patients, we made a conditional recommendation to use corticosteroids in patients hospitalized with CAP. The American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) took a different approach, and due to concerns with quality of RCT data, variations in how severe CAP was defined among studies, and inconsistency in findings between different meta-analyses addressing the topic, recommended against corticosteroid treatment in CAP except in high-risk patients (asthma, chronic obstructive pulmonary disease (COPD) and sepsis) until more high-quality data were available [5]. Unsurprisingly, given this evidence base and heterogeneity in guidance, clinical practice when it comes to corticosteroids for severe CAP remains highly variable. One other consideration, understanding the shared pathophysiology related to dysfunctional host response, and over-activation of the inflammatory cascade, is whether recent positive findings from RCTs evaluating corticosteroids in patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID-19), or those from ARDS trials [6], are generalizable to bacterial CAP [7].

It is in this context that Meduri and colleagues have published the ESCAPe RCT in *Intensive Care Medicine* evaluating low dose methylprednisolone in critically ill patients with severe community-acquired pneumonia [8]. As part of this trial, adult patients admitted to an intensive care unit (ICU) presenting with a clinical diagnosis of severe CAP (one major or three minor modified ATS/IDSA criteria for severe pneumonia), who were within 72–96 h of hospital presentation, were randomized to receive methylprednisolone or placebo for 20 days following a decremental dosing schedule. The primary outcome was 60-day mortality. However, a range of secondary outcomes including need for life support, adverse effects, long-term mortality and quality of life were reported. The study was originally powered to detect a 7% absolute reduction in 60-day mortality assuming a baseline risk of 28% with a plan to randomize 1420 participants over 5 years. Due to low recruitment, study enrollment was halted early, after 586 patients had

*Correspondence: rochwerg@mcmaster.ca
[1] Department of Medicine, McMaster University, 1200 Main St W, Hamilton, ON, Canada
Full author information is available at the end of the article

been enrolled. Of these 586 patients, 33% were receiving mechanical ventilation at the time of randomization. Results of the study demonstrated no difference in 60-day mortality with corticosteroids (adjusted odds ratio 0.90, 95% CI 0.57 to 1.40). Similarly, there were no differences in use of life-support modalities, length of stay, quality of life, long-term outcomes or adverse events.

Meduri and colleagues should be congratulated for publishing this high-quality study that addresses a crucial research question using such a rigorous design. Investigators minimized bias using a placebo control, carefully assessed adverse events, and examined long-term outcomes including mortality and quality of life, both generally accepted as critically important to patients and decision-making. Despite a hypothesis that corticosteroids would be beneficial in this population, no effect was seen. Could this have been due to insufficient sample size and under-powering? ESCAPe randomized less than 50% of their planned sample size, and baseline risk among the control group was much less than anticipated (18% actual vs. 28% anticipated), so this remains an important consideration and may lower the overall certainty of study findings due to imprecision [9]. As with other syndromes, CAP includes a heterogeneous population with varying pathogens, host factors and severity of illness. Is it possible that corticosteroids have a heterogenous effect across these subgroups and benefit in one subpopulation is masked by harm in other subpopulations? Although no subgroup effects were demonstrated in ESCAPe, these analyses also likely suffer from under-powering or perhaps focus on the wrong variables of interest. Future RCTs may benefit from prognostic enrichment [10], an attempt to select subgroups of patients most likely to benefit from corticosteroid therapy to maximize the opportunity to demonstrate positive findings, if they do exist.

Are the results of the ESCAPe trial generalizable to other contexts? Although the study was completed with a high degree of scientific rigor (internal validity), there are potential issues with generalizability (external validity) worth further discussion when applying these findings to critically ill patients worldwide. Patients in the trial were enrolled exclusively from hospitals in the United States, a high-income country, and therefore applicability to low- and middle-income countries which may have different etiologies of CAP and different risk profiles for reactivation of latent infections with corticosteroid therapy (e.g., tuberculosis, mucormycosis [11]) is uncertain. Enrollment for ESCAPe took over 4 years and the trial was ultimately halted due to recruitment issues. It is possible that some patients met eligibility criteria but, for whatever reason, were not enrolled and this may impact generalizability of results at the population level. Of note, those who were enrolled in ESCAPe were mostly elderly (mean age 69), white (81%) and male (96%).

As the title of this editorial suggests, the story of corticosteroids in patients with severe CAP is not over. ESCAPe provides an important contribution and adds to the hesitancy in using corticosteroids in all-comers hospitalized with severe CAP. However, further large-scale RCTs are required before strong recommendations addressing this intervention are possible. Perhaps, selection of specific subgroups of patients is the optimal approach, or optimizing the treatment protocol considering molecule, duration, and dose or titrating corticosteroids to serum biomarker levels. In the meantime, this remains yet another area of clinical uncertainty that will likely continue to see a high degree of variability in practice based on individual risk profile, values and preferences and shared decision-making.

Author details
[1] Department of Medicine, McMaster University, 1200 Main St W, Hamilton, ON, Canada. [2] Department of Health Research Methods, Evidence and Impact, McMaster University, 1200 Main St W, Hamilton, ON, Canada.

Declarations

Conflicts of interest
BR was methodologist for the 2017 SCCM/ESICM Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency in Critically Ill Patients. No other conflicts of interest.

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