Mortality reduction in severe community-acquired pneumonia: key findings from a large randomized controlled trial and their clinical implications

Ovidiu Vornicu[1,2], Emily Perriens[3], Sydney Blackman[3], Elina Smoos[4], Christophe Al Sammour[4], Ilann Oueslati[4], Alexis Philippot[4], David Vidal Bankier[4], Charbel Haddad[4], Maha Bendoumou[4], Tom François[4], Isabelle Michaux[1], Anne-Sophie Dincq[1,2], Patrick Evrard[1], Pierre Bulpa[1], Patrick M. Honore[1]^

[1]ICU, CHU UCL Godinne Namur, UCL Louvain Medical School, Yvoir, Belgium; [2]ICU and Anesthesiology Departments, CHU UCL Godinne Namur, UCL Louvain Medical School, Yvoir, Belgium; [3]ULB University Centre Hospitalier Universitaire Brugmann, Brussels, Belgium; [4]ULB University, Brussels, Belgium

Correspondence to: Prof. Patrick M. Honore, MD, PhD, FCCM. ICU, CHU UCL Godinne Namur, UCL Louvain Medical School, Campus Godinne, Avenue G Thérasse 1, 5530 Yvoir, Belgium. Email: patrick.honore@chuuclnamur.uclouvain.be.

Comment on: Dequin PF, Meziani F, Quenot JP, *et al.* Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med 2023;388:1931-41.

Keywords: Severe community-acquired pneumonia (severe CAP); septic shock excluded; hydrocortisone; 28 days mortality; implications for clinicians

Submitted Jun 22, 2023. Accepted for publication Aug 07, 2023. Published online Aug 18, 2023.
doi: 10.21037/atm-23-1719
View this article at: https://dx.doi.org/10.21037/atm-23-1719

Introduction

The use of steroids, particularly hydrocortisone, in the treatment of community-acquired pneumonia (CAP) remains a topic of debate and is generally not recommended as part of standard treatment guidelines. It is advised against initiating steroid therapy during the early stages of the disease. However, Dequin *et al.* conducted a study in which they administered it at an early stage of severe non-shocked CAP, when ventilatory support is necessary, whether through invasive or non-invasive methods (1). Ventilatory support (invasive or non-invasive) in this context involves applying a positive end expiratory pressure (PEEP) of at least 5 cmH_2O or delivering oxygen via a high flow nasal cannula or a non-rebreathing mask, with a partial pressure of arterial oxygen to the inspired fraction of oxygen (PaO_2:FiO_2) ratio of less than 300 (1). In their phase III study, they randomized those non-shocked CAP patients to receive 200 mg of hydrocortisone, the equivalent of 6 mg of dexamethasone, for 4 to 8 days depending on the patient's clinical response (1,2) versus placebo. The obtained results were unexpected; intensive care unit (ICU) patients with severe non-shocked CAP who received hydrocortisone not only exhibited a lower incidence of endotracheal intubation and vasopressor initiation within 28 days, but also demonstrated a lower average mortality rate compared to those who received placebo. This positive impact on 28-day mortality is mainly observed in elderly women who were not mechanically ventilated (1). While this discovery brings positive implications for patients, it does raise new questions that warrant further exploration.

Study population

The study population was highly selected as it included patients with severe CAP who required invasive or/and non-invasive ventilatory support (1) and who were not in septic shock. The respiratory support included either a

^ ORCID: 0000-0002-6697-4890.

mechanical ventilation with a PEEP of at least 5 cmH_2O, or high flow nasal cannula or non-rebreathing mask, both with a PaO_2:FiO_2 ratio less than 300 (1). Additionally, half of the patients were categorized into group V on the Pulmonary Severity Index, which is associated with the highest mortality rate (1). Immuno-compromised patients, as well as patients suffering from influenza, COVID-19, tuberculosis, and fungal infections were all excluded; as well as septic shock patients (1,3). The presence of acute respiratory distress syndrome (ARDS) was not a criterion for either inclusion or exclusion from the study. To our opinion, this highly selected population represents a strength and weakness of this study: a strength as it analyzes a very homogenous population of ICU CAP patients, a weakness as it does not represent the majority of our ICU CAP patients, who are most often in septic shock.

Rationale for the use of steroids in severe CAP?

Pneumonia is the most common cause of infection-related mortality and is still one of the leading causes of death worldwide, regardless of gross national income (4,5). Despite significant advances in new antibiotics and supportive care, mortality related to CAP remains high (14.7 per 100,000 according to the Centers for Disease Control and Prevention) (5). Given that in severe cases of CAP, the cytokine storm and excessive inflammatory response are similar to that observed in SARS-CoV2, the use of corticosteroids to modulate the immune response in COVID-19 raises the question of whether corticosteroids may also have a beneficial role as adjunctive therapy in mitigating the inflammatory response in severe CAP (6). In a post-hoc analysis done on 51 patients recruited in two separate randomized controlled trials (RCTs), Nawab *et al.*, explored the effects of corticosteroid treatment and duration in patients with severe CAP and compared the use of methylprednisolone and hydrocortisone (6). They found that patients with ARDS received methylprednisolone (1 mg/kg/day) for more than 21 days, while those without ARDS received hydrocortisone (240 mg/day) for an average of 7 days (6). Baseline characteristics were similar between the two groups, except for a higher proportion of patients requiring mechanical ventilation in the steroid group (97% *vs.* 78%; P=0.05) (6). By day 7, the glucocorticoid treatment group showed significant improvements in C-reactive protein (CRP) levels, extubation rates (64% *vs.* 28%; P=0.02), and multiple organ dysfunction syndrome (MODS) scores (0.66±1 *vs.* 1.4±1; P=0.05), and a non-significant change in mortality (7% *vs.* 22%; P=0.17) (6). The extubation rate was similar in the methylprednisolone and hydrocortisone groups (61% *vs.* 67%). After discontinuation of hydrocortisone treatment, 7 patients (44%) experienced rebound systemic inflammation, characterized by a three- to five-fold increase in CRP (6), with 3 patients showing worsening MODS and 3 requiring re-intubation (6). To the contrary, continuation of methylprednisolone treatment was associated with a sustained anti-inflammatory effect without re-exacerbation of respiratory failure (6). They emphasized the importance of tapering corticosteroid (methylprednisolone or hydrocortisone) treatment to avoid adverse effects (6).

In the study conducted by Dequin *et al.*, hydrocortisone treatment was tapered, prompting further exploration into the mechanisms by which hydrocortisone alleviates severe CAP, beyond its anti-inflammatory effects (1,6).

Rationale of using hydrocortisone: mineralo- or gluco-corticoid effects?

The choice of hydrocortisone over other corticosteroids in this study lacks explanation (1). A recent meta-analysis conducted a subgroup analysis on the efficacy of different corticosteroids as adjunct therapy for severe CAP, revealing that methylprednisolone reduced total mortality, whereas hydrocortisone did not (7). These contrasting results further contribute to the confusion surrounding the authors' decision to use hydrocortisone (1,7).

From our perspective, the most logical rationale for hydrocortisone use in severe CAP comes from a small trial conducted by Confalonieri *et al.*, led by Meduri (8). This trial involved 24 patients who were randomly assigned to receive either a hydrocortisone 200 mg bolus followed by 10 mg/h for 7 days or placebo, with a gradual tapering of hydrocortisone (8). By day 8, compared to the placebo group, patients treated with hydrocortisone demonstrated significant improvements in oxygenation, chest radiographic score, and a reduction in delayed septic shock, hospital length of stay, and mortality (including those in the ICU) (8). This study is the first to report a decrease in secondary septic shock through hydrocortisone administration (8). However, it is important to note that this trial was too small to draw meaningful conclusions regarding mortality (8). Additionally, measuring the effects of hydrocortisone on mortality was not the primary objective, and septic shock was neither an inclusion nor an exclusion criterion (8).

In terms of the justification for employing hydrocortisone, Jalloul *et al.* (9) aimed to compare the studies conducted by Confalonieri *et al.* and Annane *et al.* (8,10). In Annane *et al.*'s large RCT, patients with adrenal insufficiency, indicated by a non-response to the corticotropin test (a cortisol rise of more that 9 g/dL after administration of 250 micrograms of corticotropin), showed a higher likelihood of benefitting from cortisol supplementation, resulting in 1-month survival rates of 37% *vs.* 47% (P<0.02) (10). However, corticosteroid treatment had no effect in patients who reacted properly to the corticotropin test (10). While Confalonieri *et al.* mentioned the study done by Annane *et al.*, they did not emphasize the potential beneficial mineralocorticoid effects on shock patients (8,10). The benefits of corticosteroid replacement in septic patients without shock and adrenal insufficiency remain uncertain. Future studies on the role of corticosteroids in the treatment of severe CAP should include an assessment of adrenal reserve to provide more conclusive recommendations (10). Notably, the study conducted by Dequin *et al.* did not assess full functional adrenal function as they assess baseline cortisone which was similar in both groups, possibly because shock was not an inclusion criterion (1).

Meduri *et al.* conducted a double-blind placebo-controlled RCT to investigate the effects of a 21-day methylprednisolone treatment (40 mg methylprednisolone for 7 days, 20 mg for 7 days, 12 mg for 7 days) on 584 patients with severe CAP (11). The study found no significant differences in 60-day mortality between the methylprednisolone and placebo groups [16% *vs.* 18%; adjusted odds ratio (OR) 0.9; 95% confidence interval (CI): 0.57–1.4] (11). However, it is worth noting that the trial was stopped early due to recruitment difficulties and lack of statistical power to detect the expected differences between the groups (11). Despite the underpowered nature of the study, it was observed that methylprednisolone did not affect mortality (11).

Additionally, the guidelines by Martin-Loeches recommend the use of corticosteroids in patients with severe CAP and shock based on a meta-analysis (12). However, the Dequin *et al.* study, published after the guidelines, do not follow their recommendation by showing a potential beneficial effect in patients without shock as they were looking at a very different population somewhat a "NICHE" (1).

A separate study discovered a strong correlation between cortisol, dehydroepiandrosterone sulfate (DHEAS), and their ratios with the severity of CAP, with DHEA and cortisol serving as predictors of mortality (13). This suggests that not only cortisol levels, but also overall adrenal function and the potential shift from DHEAS to cortisol production within the adrenal glands play important roles in the outcome and survival of severe CAP (13). Serum cortisol, as an indicator of stress, reflects the activation of the hypothalamopituitary-adrenal (HPA) axis and the severity of illness, with cortisol levels gradually increasing as the disease severity worsens (13). By administering corticosteroids, which can modulate the HPA axis and influence cortisol production, it is possible to potentially mitigate the severity of CAP and improve patient outcomes, even in the absence of septic shock. Therefore, the study supports the consideration of corticosteroid therapy in patients without shock as means to address CAP severity and potentially enhance treatment effectiveness. Based on this rationale, it is unfortunate that Dequin *et al.* did only measure basal cortisol which was identical between both group and did not use dynamic testing like a corticotropin test as a marker of CAP severity requiring hydrocortisone, considering the strong association between cortisol, dynamic assessment of adrenal function, and disease outcome (1,13).

The RECOVERY study showed the beneficial effects of corticosteroids in respiratory illness needing respiratory support. The choice of 200 mg of hydrocortisone in the study by Dequin *et al.* is equivalent to 6 mg of dexamethasone, which demonstrated positive outcomes in reducing mortality in severe COVID-19 ARDS patients in this study (14). Furthermore, the RECOVERY study's insights also suggest that investigating the mineralocorticoid effects of methylprednisolone, as mentioned earlier, could be a valuable avenue for future research (14). Nevertheless, the Dequin study was finished prior to the start of RECOVERY and therefore, Dequin study was not taking any inspirations from RECOVERY.

In conclusion, the rationale for using hydrocortisone in Dequin *et al.*'s study on severe CAP lacks a clear explanation (1). Previous studies have shown conflicting results regarding the efficacy of different corticosteroids in reducing mortality in CAP patients (15,16). However, Confalonieri *et al.* demonstrated significant improvements with hydrocortisone treatment (8). The study by Annane *et al.* highlighted the potential benefits of cortisol supplementation in patients with adrenal insufficiency, while the study by Meduri *et al.* found no significant differences in mortality (15,16). The guidelines by Martin-Loeches recommend corticosteroid use in severe CAP with shock, but Dequin *et al.*'s study a different

population of severe CAP (1,7). The study from Mueller emphasized the correlation between cortisol, adrenal function, and CAP severity and mortality but Dequin *et al.* made no connections to this study (1,13). Exploring the mineralocorticoid effects is suggested for future research (17,18). The RECOVERY study demonstrated the effectiveness of corticosteroids in respiratory illnesses, which did not influence the choice of hydrocortisone dose in Dequin *et al.*'s study as the Dequin's study was terminated anterior to the start of RECOIVERY (14). Overall, these findings support considering corticosteroid therapy to address CAP severity and improve outcomes, even without septic shock but there is not much support to justify the choice of hydrocortisone in this study excepted the "NICHE" effect like in the recovery study (1,14).

Hemodynamic stability between groups

At the time of inclusion, administration of vasopressors was not allowed. The percentage of patients receiving vasopressors at baseline was similar in the hydrocortisone and control groups, with no statistical difference (10.2% and 12.9%, respectively) (1). However, among patients not initially on vasopressors, initiation of vasopressor therapy by day 28 was lower in the hydrocortisone group compared to the control group (1) and attributed by the authors to the effects of positive pressure ventilation and/or sedative drugs. This suggests that hydrocortisone may have played a role in preventing the need for vasopressors, although further research is needed to explore this effect (1). The variation in mortality rates observed could potentially be explained by differences in the requirement for vasopressors and in the fluid balance. Nevertheless, Dequin *et al.* did not mention the fluid balance in any groups (1), it is worth noting that excluding septic shock patients from the study is different from current guidelines by Martin-Loeches *et al.* that recommend corticosteroid use in severe CAP in shock but the Dequin's study is looking at a different population probably a "NICHE" (1,3). CAP is a common cause of septic shock, and a recent RCT found that up to 46% of patients with septic shock had CAP (16). Nonetheless, in the RECOVERY study no single mention was made about the need of vasopressors (14). Therefore, the exclusion of patients with septic shock in the Dequin study, which accounted for approximately 20% of patients, must be highlighted as it omits a significant proportion of patients with severe CAP who could potentially benefit from hydrocortisone treatment (1). It is possible that the authors excluded patients with septic shock to avoid administering hydrocortisone in the control group and to focus on the corticosteroid effects of hydrocortisone in non-shock patients (1). Obviously, the Dequin *et al.*'s study was finished prior to the start of RECOVERY and therefore, they could not take any inspiration from it to build their trial (1,14).

Implications for bedside clinicians

As already alluded to, the recent large multi-center RCT on the use of methylprednisolone in severe CAP showed no significant impact on 60-day mortality, but the study was prematurely stopped and inconclusive (11). In contrast, Dequin *et al.*'s large double-blind RCT demonstrated a significant reduction in 28-day mortality and no significant adverse effects with hydrocortisone in severe CAP patients without septic shock (1). The aforementioned conflicting results point toward the absence of strong evidence to recommend routine corticosteroid administration in all severe CAP cases, particularly in viral pneumonias excluding SARS-CoV-2 due to the inhibition of viral clearance and the masking of a worsening infection (3). The guidelines by Martin-Loeches specify that the presence of septic shock in severe CAP is a mandatory condition to administer steroids, which was not the population studied by Dequin *et al.* (1,12,19). The divergence in recommendations reflects the challenge of reconciling different patient populations. Notably, previous guidelines by some of the same authors (Póvoa *et al.*) acknowledged the recommendation of corticosteroids in Pneumocystis jiroveci pneumonia in HIV-infected patients but contraindicated their use in cases of Influenza (19). Therefore, except for SARS-CoV2, the available evidence does not support the widespread use of corticosteroids as adjunctive therapy in other forms of CAP (12). Further studies are needed to identify specific subgroups of severe CAP that could benefit from corticosteroids (20). However, in a later editorial, the same authors deny that the study by Dequin *et al.* provides sufficient evidence to support the routine use of hydrocortisone in severe CAP without septic shock (19).

Conclusions

In conclusion, corticosteroids have shown potential benefits improving outcomes and survival in severe CAP. They can modulate the inflammatory response, enhance oxygenation, reduce the risk of delayed septic shock, and potentially shorten hospital stays. However,

the rationale for using hydrocortisone in Dequin *et al.*'s study for severe CAP remains disputable, particularly due to the exclusion of septic shock, which limits insights into the mineralocorticoid effects of hydrocortisone and understanding the mechanism by which 28-day mortality was significantly reduced. The equivalence of 200 mg of hydrocortisone to 6 mg of dexamethasone used in COVID ARDS provides some understanding regarding the relative corticosteroid potency of hydrocortisone, but further clinical evaluation is necessary to fully determine specific anti-inflammatory properties and optimal use in different clinical settings. However, the study's lack of acknowledgement of the pathophysiological background and its limitations raises concerns about drawing definitive conclusions.

Therefore, based on the available evidence, it is currently challenging to issue a clear recommendation regarding the routine administration of corticosteroids in all severe CAP patients. Further research, including a confirmatory study that addresses the limitations and explores the underlying pathophysiology is necessary to make an informed decision. Future studies should also consider the role of dynamic adrenal function assessment, including cortisol measurement and corticotropin test, to better understand the relationship between corticosteroid therapy, disease severity, and patient outcomes. Only with a more comprehensive understanding can we establish evidence-based guidelines for the use of corticosteroids in severe CAP without shock.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1719/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med 2023;388:1931-41.
2. Taher A, Lashkari M, Keramat F, et al. Comparison of the efficacy of equivalent doses of dexamethasone, methylprednisolone, and hydrocortisone for treatment of COVID-19-related acute respiratory distress syndrome: a prospective three-arm randomized clinical trial. Wien Med Wochenschr 2023;173:140-51.
3. Martin-Loeches I, Torres A. Corticosteroids for CAP, influenza and COVID-19: when, how and benefits or harm? Eur Respir Rev 2021;30:200346.
4. Kegler SR, Baldwin GT, Rudd RA, et al. Increases in United States life expectancy through reductions in injury-related death. Popul Health Metr 2017;15:32.
5. Centers for Disease Control and Prevention. Pneumonia. Available online: www.cdc.gov/nchs/fastats/pneumonia.htm
6. Nawab QU, Golden E, Confalonieri M, et al. Corticosteroid treatment in severe community-acquired pneumonia: duration of treatment affects control of systemic inflammation and clinical improvement. Intensive Care Med 2011;37:1553-4.
7. Huang J, Guo J, Li H, et al. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e14636.
8. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171:242-8.
9. Jalloul A. Hydrocortisone infusion for severe community-acquired pneumonia: the role of relative adrenal insufficiency. Am J Respir Crit Care Med 2005;172:781; author reply 782-3.
10. Annane D, Renault A, Brun-Buisson C, et al.

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378:809-18.
11. Meduri GU, Shih MC, Bridges L, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med 2022;48:1009-23.
12. Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med 2023;49:615-32.
13. Mueller C, Blum CA, Trummler M, et al. Association of adrenal function and disease severity in community-acquired pneumonia. PLoS One 2014;9:e99518. doi: 10.1371/journal.pone.0099518. Erratum in: PLoS One 2014;9:e102637.
14. RECOVERY Collaborative Group; Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704.
15. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131:954-63.
16. Meduri G, Golden E, Umberger R. Randomized clinical trial evaluating the effects of low-dose prolonged hydrocortisone infusion on resolution of MODS in severe sepsis. Chest 2009;136:45S-h1-45S-h2.
17. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
18. Nishimura H, Yoshikawa T, Kobayashi N, et al. Effects of methylprednisolone on hemodynamics and beta-adrenergic receptor signaling in rabbits with acute left ventricular failure. Heart Vessels 1997;12:84-91.
19. Póvoa P, Nseir S, Salluh J. Severe community-acquired pneumonia: in search of the guiding star. Intensive Care Med 2023;49:656-8.
20. Póvoa P, Coelho L, Salluh J. When should we use corticosteroids in severe community-acquired pneumonia? Curr Opin Infect Dis 2021;34:169-74.

Cite this article as: Vornicu O, Perriens E, Blackman S, Smoos E, Al Sammour C, Oueslati I, Philippot A, Bankier DV, Haddad C, Bendoumou M, François T, Michaux I, Dincq AS, Evrard P, Bulpa P, Honore PM. Mortality reduction in severe community-acquired pneumonia: key findings from a large randomized controlled trial and their clinical implications. Ann Transl Med 2023;11(11):395. doi: 10.21037/atm-23-1719

