Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial

Nicholas Heming et al. Lancet Respiratory Medicine, 2024

RESEARCH AIM

To investigate the effect of **hydrocortisone + fludrocortisone on 90-day mortality** among septic patients with and without **community-acquired pneumonia (CAP).**

BACKGROUND

Severity of CAP is often related to the intensity of inflammatory response.

The **CAPE COD** trial showed a **decreased 28-days mortality** in patients with CAP without shock receiving hydrocortisone[1].

The **APROCCHSS trial** revealed that hydrocortisone in combination with fludrocortisone **lowered 90-day mortality by 6%** in heterogenous ICU patients with septic shock[2].

This subgroup analysis of the APROCCHSS trial investigates the impact of hydrocortisone with fludrocortisone on a more **homogenous cohort of septic shock patients with or without CAP.**

METHODS

Design: A priori subgroup analysis of the phase 3 randomized APROCCHSS trial.

Population: Adult patients (>18 years of age) with septic shock

Intervention: Hydrocortisone 50 mg iv. every 6 h + fludrocortisone 50 µg via a nasogastric tube once daily.

Subgroups:
CAP vs. non-CAP, ARDS vs. non-ARDS

Primary outcome:
90-days all-cause mortality

Secondary outcomes: Mortality at ICU discharge, hospital discharge, and at 28- and 180-days. Organ support-, organ failure-, hospital- and ICU-free days.

Statistic: Interaction between subgroups were assessed with logistic regression for odds ratio (OR) and a generalized linear binomial model for risk difference.

RESULTS

1241 patients, from 34 centres in France were enrolled (September 2008 to June 2015): 562 with CAP, 648 without CAP, 31 without any classification.

90-day mortality:

Placebo	Treatment	OR (95%CI)	Placebo	Treatment	OR (95%CI)	p values mult. int.*	p values addit. int.**
With CAP (n=562)			**Without CAP (n=648)**				
143 /279 (51%)	109 /283 (39%)	0.60 (0.43-0.83)	157/329 (48%)	148/319 (46%)	0.95 (0.70-1.29)	0.046	0.046
With ARDS (n=648)			**Without ARDS (n=578)**				
186/328 (57%)	155/320 (48%)	0.72 (0.53-0.98)	115/288 (40%)	105/290 (36%)	0.85 (0.61-1.20)	0.045	0.042
With CAP, without ARDS (n=215)			**Without CAP, without ARDS(n=346)**				
43/106 (41%)	31/109 (28%)	0.58 (0.33-1.03)	68/174 (39%)	68/172 (40%)	1.02 (0.66-1.57)	0.124	0.130

*multiplicative interaction, ** additive interaction

Secondary endpoints:

Reduced mortality in septic CAP patients treated with hydrocortisone and fludrocortisone (OR with 95% CI) at:

- **Day 28:** 0.61 (0.43-0.87)
- **Day 180**: 0.59 (0.42-0.83)
- **ICU discharge:** 0.64 (0.46-0.90)
- **Hospital discharge:** 0.62 (0.44-0.87)

No significant differences between treatment and placebo group among patients with CAP for vasopressor-, organ failure-, ventilator-, ICU- and hospital-free days.

SIS COMMENTS

This post hoc analysis of the APROCCHSS trial[3] evaluated the effects of hydrocortisone + fludrocortisone in septic shock patients with and without CAP, highlighting their potentially beneficial impact on both short- and long-term survival. The differential effects on mortality in CAP vs non-CAP septic patients underscores the nuanced responses of different sepsis subpopulations to immunomodulatory treatments.

A dysregulated host response to infection has been increasingly appreciated as the pathophysiological hallmark of the syndrome, making its modulation an appealing therapeutic target. However, huge heterogeneity with regard to factors related to both the wide spectrum of pathogens and the individual host response makes this extremely challenging; many trials using unstratified patients with sepsis have been negative. Therefore, the Surviving Sepsis Campaign guidelines have been cautious to recommend corticosteroids primarily for treating refractory shock rather than as a broad anti-inflammatory treatment in the initial management of sepsis[4].

Recent studies, such as the CAPE COD trial[1], have focused on a more homogeneous entity of CAP, yielding much more promising results. The CAPE COD trial showed a 6% mortality reduction in 800 ICU-admitted CAP patients. These findings are in line with the results from COVID-19 mega-trials (RECOVERY). The biggest difference lies in the fact that those researchers have investigated a unique disease compared to the sepsis *syndrome.*

This post hoc analysis of the APROCCHSS trial now demonstrated that the beneficial effect of steroids in CAP holds true if the disease has progressed to septic shock. Obviously, the trial's design does not allow us to conclude whether the improvement is due to local anti-inflammatory effects on the side of the pneumonia or the disruption of systemic inflammatory processes, thereby reducing the risk of multiorgan failure in sepsis. Clarifying whether corticosteroids primarily preserve pulmonary function or act as a protective agent against systemic multiorgan failure could influence the consideration of steroid application in other sepsis subpopulations.

Further research is essential to address these questions and better understand the role of anti-inflammatory agents in sepsis management. Nonetheless, drawing from the evidence accumulated through this and prior studies, we believe that corticosteroids should be considered an essential part of the treatment regimen for critically ill patients with CAP.

1. Dequin et al. Hydrocortisone in Severe Community-Acquired Pneumonia. The New England Journal of Medicine, 2023.
2. Annane et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. The New England Journal of Medicine, 2018
3. Heming et al. Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial. The Lancet Respiratory Medicine, 2024.
4. Evans et al. Surviving Sepsis Campaign: International Guidelines for Man… …al Care Medicine, 2021