Comparing Hydrocortisone and Prednisolone for Community Acquired Pneumonia (CAP)

– The *MineraloCAP Trial*

Sponsor

Jens-Ulrik Jensen, Professor of Respiratory Medicine, Senior Consultant &

Department of Medicine, Section of Respiratory Medicine

Herlev & Gentofte Hospital

Department of Clinical Medicine, University of Copenhagen

Principal investigator

Pradeesh Sivapalan, Associate professor, Consultant

Department of Medicine, Section of Respiratory Medicine

Herlev & Gentofte Hospital

Department of Clinical Medicine, University of Copenhagen

Trial sites and primary investigators:

Nordsjællands Hospital Hillerød og Frederikssund: Site Investigator, Jon Gitz Holler, ledende overlæge, Lunge og infektionsmedicinsk afdeling.

Bispebjerg og Frederiksberg: Site investigtator, Theis Skovsgaard Itenov, Afdelingslæge, forskningslektor, Anæstesiologisk afdeling.

Herlev og Gentofte Hospital: Site investigtator, Professor Jens-Ulrik Jensen, Medicinsk afdeling.

Amager, Glostrup og Hvidovre Hospital: Site investigator ,Vibeke Gottlieb, Ledende overlæge, lungemedicinsk afdeling.

Background

Community acquired pneumonia (CAP) is a leading cause of morbidity and mortality world-wide [1]. In Denmark, CAP is responsible for 48,000 hospital admissions annually [2]. The inflammatory response in CAP can progress to sepsis and organ failure, complications that may be mitigated by the anti-inflammatory effects of corticosteroids. Previous studies and multiple meta-analyses have demonstrated the efficacy and safety of corticosteroids in treating CAP of varying severity. The beneficial effects on mortality and morbidity appear most pronounced in severe CAP cases [3], [4], [5], [6]. The largest randomized controlled trial to date, published in 2023, showed a reduction in mortality from hydrocortisone treatment in patients admitted to the intensive care unit (ICU) with CAP [7]. Corticosteroid treatment in CAP has been endorsed by some professional societies [8], while many still reserve it for patients with shock [9], [10]. The Danish Society of Respiratory Medicine, in collaboration with the Danish Society for Clinical Microbiology and Infectious Diseases, currently recommends routine use of corticosteroids in patients with severe CAP without preference for a specific type of corticosteroid [11].

Rationale

The choice of corticosteroid has varied in previous studies (hydrocortisone, methylprednisolone, prednisolone and dexamethasone have been used), as well as the dose. A meta-analysis found a greater beneficial effect on mortality from hydrocortisone, compared to other corticosteroids [5], although this has never been studied in a head-to-head prospective trial. Further, the data that drive this seemingly pronounced difference in effect on mortality and hospital length of stay almost entirely arises from one study of hydrocortisone in patients with CAP admitted to the intensive care unit, and only few events (more deaths in the placebo-group than the hydrocortisone group) drive the difference in the RCT and consequently in the meta-analysis.

The most frequently investigated corticosteroids are hydrocortisone and methylprednisolone. Both have glucocorticoid effects, but there is a substantial difference in mineralocorticoid affinity with methylprednisolone having minimal affinity [12]. This difference could drive differences in patient important outcomes, since electrolyte as well as fluid shifts are commonly observed in patients with CAP.

Pneumonia is a frequent cause of hospital admissions and even small differences in effectiveness resulting from choice of correct corticosteroid could impact significantly on population-level mortality, morbidity and health-care costs (via hospital length of stay).

We propose a large cluster-randomized controlled trial to compare the effectiveness of hydrocortisone versus prednisolone in community-acquired pneumonia admitted to hospital. The study aims to determine whether the dual glucocorticoid-mineralocorticoid profile of hydrocortisone offer superior clinical outcomes compared to the predominantly glucocorticoid profile of prednisolone.

Aim

The goal of the study is to determine the optimal treatment by comparing the effects and side effects of the two steroid medications. If the hypothesis is proven, the study will help improve recovery, reduce hospitalization stay and mortality, and minimize side effects for the benefit of future patients. The advantage of this trial design is that it includes all-comers, including older and more severely ill patients, who are often not represented in traditional randomized trials.

Hypothesis

We hypothesize that hydrocortisone is superior to methylprednisolone with regards to survival, with no difference in adverse effects (infection, hyperglycemia / need for insulin) when comparing the two types of corticosteroids.

Patients

Participants will be recruited from hospitals in the Capital Region of Denmark based on a relevant ICD-10 diagnoses (CAP). All patients approached within 24 hours of admission are candidates to be included in the study. Generally, all patients will be included in the study unless they choose to opt out. For further details, please refer to the section on Research Ethics below.

Inclusion criteria:

- Age > 18 years
- Diagnosis of severe CAP for who the physician in charge decides for corticosteroid therapy for severe CAP*.

Exclusion criteria:

- Admitted >24 h
- Pregnant or breastfeeding women
- Active tuberculosis or fungal infection
- Pneumonia caused by influenza
- Intolerance to either study drug

*The treating physician assesses that systemic corticosteroid therapy would be indicated for the management of severe CAP, regardless of the patient's participation in the trial.

Intervention

Patients will be cluster randomized with an intended 1:1 ratio of either:

- Hydrocortisone
    - Dose: 200 mg intravenously once daily, can be changed to 50 mg x 4 daily orally if appropriate
    - Duration: 5 days
    - ATC-code: H02AB09
- Methylprednisolone
    - Dose: 40 mg intravenously once daily; can be changed to Prednisolone 50 mg orally if appropriate
    - Duration: 5 days
    - ATC code: H02AB06

Both medicinal products are authorized medications in Denmark that are being used in accordance with their marketing authorization in this case. Doses can be reduced if deemed appropriate by the treating physician, e.g., due to low body weight.

Methods

Participant inclusion and consent

Written information about the ongoing trial will be available to the patients participating.

Generally, all patients will be included in the study unless they choose to opt out. For further details, please refer to the "section on Research Ethics" below.

Recruitment and randomization

Patients will be recruited from emergency departments and acute medical wards at hospitals in the Capital Region of Denmark (Region Hovedstaden). See the list of hospitals on page 1. All patients with a diagnosis of CAP will be eligible for screening and will be included if they fulfill inclusion criteria (and none of the exclusion criteria).

Patients will be allocated to either hydrocortisone or prednisolone using the randomization module in Sundhedsplatformen (EPIC) as part of treatment for CAP. A generic module in Sundhedsplatformen will be developed that can randomize at cluster levels directly from the system. The clusters in this study are time frames of 1 hour, meaning that every hour the recommended choice of corticosteroid will change. This randomization system has already been

developed for the ongoing trial “Cluster-randomized trial of low molecular weight heparins - Directly through EPIC”. (EU-CT number: 2022-502402-32-00).

Clinicians and other health care providers will be unblinded to the allocated treatments. Statisticians analyzing outcomes will be blinded to treatments (just allocated Treatment A and B).

Adherence to the allocated treatment will be ensured through dispensing the medication during the hospital stay. In case of discharge from the hospital, they will be guided by health care personnel in continuing the treatment for the allocated duration. The medication is prescribed in the electronic patient record, and the nurse records the administration of the medication every day to ensure that adherence is maintained.

Storage and handling of investigational medicinal products

The medications used in the trial (hydrocortisone and prednisolone) are existing corticosteroid drugs that are approved and in use in Denmark. They will be readily available at the sites of the trial where they are stored according to national regulations.

The detailed plan continues with information on the participant timeline, follow-up visits, data collection, and handling of collected data. The section also includes information on the statistical analysis plan, endpoints, and the analysis population.

Assessments

All blood samples collected at baseline, Day 3, and Day 7 (if the patient remains hospitalized) are obtained strictly as part of routine clinical care and standard treatment protocols for patients with community-acquired pneumonia. No additional blood samples or analyses are performed beyond those clinically indicated and required for optimal patient management.

Follow-up visits

There are no scheduled follow-up visits. All subsequent information will be retrieved from registers.

Participation in the trial is not expected to lead to requirement of altered subsequent treatment or additional care for study participants after the trial that differs from what is normally expected for this medical condition.

Data collection

Our studies rely on comprehensive datasets managed by the Sundhedsdatastyrelsen, which includes a central registry of clinic allocations. All data required for this study will be gathered and meticulously analyzed within our research facilities. A dedicated project will be officially registered

in our system. Through our access to the Central Person Register, The National Patient Register, and the National Prescription Register, we have ready access to all the essential data needed for our research.

Data will be collected after the completion of the trial. The information to be extracted includes demographic data, medication data, alcohol, smoking status and tobacco use, blood samples, clinical parameters, treatments, complications, and outcome data necessary for evaluation of the study's primary and secondary endpoints. We confirm that no additional data beyond those described in the protocol will be collected.

The collected data will be treated confidentially and only by staff that associated with the study. It will be handled in accordance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act. Data will be encrypted, stored on online servers and protected by the Data Protection Authority.

Outcomes

Primary outcome:

- All-cause mortality (30 days)

Secondary outcomes:

- All-cause mortality (time frame: 90 days)
- All-cause infections (time frame: 90 days)
- Need for vasopressor treatment (time frame: 30 days)
- Need for mechanical ventilation (time frame: 30 days)
- Admission to ICU (time frame: 30 days)
- Daily amount of insulin administered to the patient by day 7 or discharge from hospital (time frame: 7 days)
- Gastrointestinal bleeding (time frame: 30 days)
- Blood glucose levels at day 3 and day 7

Statistical analysis

Power calculation:

The study is powered on efficacy of the 2 corticosteroid regimens.

14-day mortality is estimated at 10% for admitted adults in the Capital Region.

We anticipate a 25% reduction in mortality, significance Level (α) 0.05, and a power (1-β) of 80%, 2,004 patients are needed in each group, 4,008 in total. We will aim for recruiting 4,200 patients into study 1

Outcome analyses:

Statistical analyses of outcomes will follow the principles for statistical analysis and interpretation of medical randomized controlled trials. A separate statistical analysis plan (SAP) will be made in cooperation with experienced statisticians and bioinformaticians.

Statistical analysis of the primary outcome will involve time-to-event analysis using Kaplan-Meier survival curves and the log-rank test to compare the two treatment groups. Cox proportional hazards regression will be used to estimate the hazard ratios and adjust for potential confounders.

Data will be analyzed using ITT principles and main analyses will also be involve modified ITT analysis (started but not completed) and per protocol analysis (completed all intervention). When applying the ITT principle, all randomized patients will be analyzed in the groups to which they were originally allocated, regardless of treatment adherence or protocol violation.
Patients who withdrew consent for the use of their data will not be included in any analysis. Only the fact that they were enrolled into the trial and withdrew consent, and the original study group to which they were allocated, will be reported.
A secondary analysis of the primary efficacy outcome will use a per protocol (PP) population.

Statistical analysis will be carried out using SAS (Statistical Analysis System, version 9.4).

Safety

Safety outcomes will be assessed throughout the study. It will include the occurrence of serious adverse events and reactions (SAEs and SARs) and adverse events and reactions (AEs and ARs). The frequency and severity of SAEs, SARs, AEs and ARs will be evaluated and compared between the two groups. Any safety concerns will be reported to the relevant regulatory authorities. Definitions and procedures for managing safety issues are the usual for RCTs.

Investigators and study sites

The principal investigator (PI) of this trial is Associate professor, Pradeesh Sivapalan, MD, PhD, affiliated with the Department of Medicine, Herlev and Gentofte Hospital, Denmark. The PI will be responsible for the overall coordination of the trial, day-to-day management, data integrity, and communication with collaborators and relevant authorities.

The sponsor of the trial is Professor Jens-Ulrik Stæhr Jensen at the Department of Medicine, Herlev and Gentofte Hospital. Professor Jensen has taken the initiative for this clinical trial and holds overall responsibility for its conduct and compliance with Good Clinical Practice (GCP) and

applicable regulatory requirements. Two senior investigators will support the trial with their scientific and clinical expertise: Professor Jens-Ulrik Stæhr Jensen, as described above, and Professor Jørgen Vestbo, Professor of Respiratory Medicine at the University of Manchester and Consultant at the North West Lung Centre, Manchester University NHS Foundation Trust. Both senior investigators are internationally recognized experts in the field of respiratory medicine. Their roles include scientific input to the protocol design, interpretation of results, and contribution to the dissemination of findings.

The current initiative will operate under COMET, a research network focused on improving the treatment of medical emergency patients and is represented by leading researchers and senior consultants from the major medical emergency departments in the Capital Region.The study will recruit participants from 4 major emergency departments in the Capital Region of Denmark (Region Hovedstaden). These sites have been carefully selected to ensure adequate patient flow and representativeness for patients hospitalized with community-acquired pneumonia.

Participant Compensation and Insurance

All participants in this study are covered by the Danish Patient Compensation Association (Patienterstatningen). This ensures that participants are entitled to compensation in the event of any harm directly caused by their participation in the trial. Information regarding this coverage is also clearly stated in the participant information sheet.

Budget

Set-up of algorithms in Sundhedsplatformen (EPIC)	932,000 DKK
Project coordinator (2 years, 0.6 FTE experienced study nurse or equivalent Health care professional	640,000 DKK
PhD student (1 year, 2 years co-financed by institution)	669,330 DKK
Publication fees for major outcome manuscripts	80,000 DKK
Two investigators presenting at 2 international conferences (US and Europe)	80,000 DKK
Administrative assistant (2 years, 0.2 FTE)	87,300 DKK
Total	2,488,630 DKK

Publication of results

Results from the trial, whether positive, negative, or inconclusive, will be submitted for publishing in international peer-reviewed scientific journals. The trial will be registered on clinicaltrials.gov.

Research ethical statement

The study uses existing, approved medicinal products to evaluate and contribute to determining optimal treatment strategies for community acquired pneumonia.

The study is reported to the Regional Data Protection Agency ("Videncenter for Dataanmeldelser") for the Capital Region of Denmark. The trial has been submitted for approval to the Danish National Committee on Health Research Ethics (De Videnskabsetiske Medicinske Komiteer, VMK). All relevant ethical approvals will be obtained prior to trial initiation.

The study will comply with the Danish Act on Research Ethics Review of Health Research Projects, and will be conducted in compliance with the protocol, the Regulation (EU) No 536/2014 and with the principles of good clinical practice (GCP).

Simpelt consent procedure

Due to the acute and life-threatening nature of severe community-acquired pneumonia (CAP), many patients eligible for inclusion are critically ill upon admission, often presenting with severe respiratory distress or impaired consciousness. As a result, obtaining written informed consent prior to randomisation is not feasible.

In accordance with Sections 3–5 of the Danish Committee Act (Komitéloven), a waiver of informed consent is justified based on the following conditions:

- The study intervention (systemic corticosteroids) represents an adjunctive therapy already considered in standard care for patients with severe CAP.
- Both treatments have well-known efficacy and safety profiles, including established short- and long-term adverse event profiles, with available management options for potential side effects.
- The additional risk to participants is minimal compared to standard treatment practices.
- Requiring informed consent prior to treatment would lead to delays in the initiation of potentially beneficial therapy, which could negatively affect patient outcomes.

Information to patients is provided through a simplified consent process based on written information included in this document. Patients are informed that participation is voluntary and that they can decline participation without any impact on their standard treatment. If patients do not wish to participate, they can indicate this by signing the last page of the information document. Informed consent will only be obtained from patients deemed competent by the investigator or treating physician.

Patients who consent to participate can withdraw their consent at any time. Additionally, one month after discharge, patients will receive a letter via their secure digital mailbox (e-Boks) providing an opportunity to withdraw consent for use of their data.

If a patient or their legal representative objects to participation or withdraws consent, this is immediately documented, and no further data will be collected for the study from that individual. Previously collected data will only be used if the patient has not explicitly withdrawn consent for its use. The research team continuously monitors and updates the study database to ensure that no further data collection occurs for individuals who have opted out or withdrawn.

The protocol ensures adequate protection of patient rights and confidentiality, and patients or their legal representatives will be informed about the study and their participation as soon as possible after inclusion. This approach aligns with ethical guidelines for emergency research involving patients who are temporarily unable to provide informed consent due to the severity of their condition.

Study Funding and Financial Commitment The study is already partially funded by the Department of Respiratory Medicine, Herlev and Gentofte Hospital, and additional grant applications have been submitted to several major national funding bodies.

If full external funding is not obtained, Copenhagen Respiratory Research – led by Professor Jens-Ulrik Jensen, Chief Director at the Department of Medicine, Herlev and Gentofte Hospital – will guarantee that the study can proceed as planned, as internal funds have already been allocated for this purpose. The study will not commence without a documented plan and a formal guarantee of full financial coverage.

All funders, along with awarded amounts (both lump sums and per-participant payments), will be listed in the protocol and study synopsis once funding agreements are finalized.

All financial support for the study will be managed by the Department of Respiratory Medicine at Herlev and Gentofte Hospital. No funds will be paid directly to the individual investigators. All grants and external funding will be deposited into a dedicated project-specific research account and administered in accordance with the financial and research governance policies of the hospital and the Capital Region of Denmark. The trial period extends from the inclusion of the first patient in November 2025 and is expected to be completed by December 2028. We will have access to your personal data throughout this period and until September 2040, at which point all data will be deleted

Conflict of interest

None of the investigators, including the sponsor Professor Jens-Ulrik Jensen, have any financial ties to the study's current or potential funders, or to any commercial entities with an interest in the trial. There are no stock holdings, consultancy agreements, advisory board roles, honoraria, or other financial relationships that could create a conflict of interest. Any future financial support will be managed in full compliance with the Capital Region of Denmark's policies on research integrity and conflict of interest.

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