Hydrocortisone in Severe Community Acquired Pneumonia

NEJM ARTICLE DATED 21/03/2023

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Aim and Objective

To determine whether the antiinflammatory and immunomodulatory effects of glucocorticoids decrease mortality among patients with severe community-acquired pneumonia

INTRODUCTION

- Community-acquired pneumonia still remains a major public health issue worldwide
- In the United States, more than 1.5 million adults are hospitalized for community-acquired pneumonia annually
- In high-income countries, the monthly rate of death among patients who are hospitalized with community-acquired pneumonia is approximately 10 to 12%

- Pneumonia may lead to intense pulmonary and systemic inflammation, which results in impaired gas exchange, sepsis and organ failure, and an increased risk of death
- Glucocorticoids have powerful antiinflammatory and immunomodulatory activities that mitigate the consequences of pneumonia
- This study was conducted to evaluate whether early treatment with hydrocortisone reduced mortality at 28 days among patients admitted to an intensive care unit (ICU) for severe community-acquired pneumonia.

- Eventhough the existing studies showed that glucocorticoids had positive effects in patients with community acquired pneumonia of varying severity; none of these trials showed a between-group difference regarding mortality.

Trial design

- A double-blind, randomized, controlled trial was conducted in 31 French centers by the members of the Clinical Research in Intensive Care and Sepsis–Trial Group for Global Evaluation and Research in Sepsis Network

Detailed inclusion criteria

- Age ≥ 18 years
- Patients affiliated to social security scheme
- Admission to a participating ICU or intermediate care unit
- Diagnosis of Community-Acquired Pneumonia (CAP) suggested by at least two of the following: cough, purulent sputum, chest pain, dyspnea
- Focal shadowing/infiltrate on chest X-ray or CT-scan
- Diagnosis of CAP during the 48 hours post-hospital admission
- Study drug infusion initiated no longer than 24 hours post first severity criterion

- Severity defined by at least one of the following:

1) Pneumonia Severity Index (PSI) > 130

2) Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more

3) Patient treated by high-flow oxygen therapy with a FiO_2 of 50% or more and a $PaO_2:FiO_2$ ratio lower than 300

4) Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO_2 is less than prespecified chart

- Principal non-inclusion criteria were a do-not intubate order, pneumonia caused by influenza and septic shock.

Randomization

- Randomization was centralized and performed electronically with the use of a Web-based response system
- Patients were randomly assigned in a 1:1 ratio to receive hydrocortisone or placebo according to a computer-generated random list prepared by a statistician who was uninvolved in the enrollment process

SAMPLE SIZE

- 800 Underwent randomization
- 401 Were assigned to receive hydrocortisone , 1 Died before receiving hydrocortisone - 400 Were included in the primary analysis
- 399 Were assigned to receive placebo,2 Withdrew consent - 395 Were included in the primary analysis

Intervention

- Patients received standard therapy for severe community-acquired pneumonia, including antibiotics and supportive care
- The choice of respiratory support was left to the discretion of the medical team
- In addition, within 24 hours after the onset of any severity criterion described above, patients in the hydrocortisone group received intravenous hydrocortisone administered continuously at a dose of 200 mg per day during the first 4 days
- On the fourth day, the medical team used predefined criteria to decide whether to administer hydrocortisone for a total of 8 or 14 days, depending on whether the patient’s condition had improved.

- Regardless of the duration of treatment, the dose of hydrocortisone was gradually tapered according to a prespecified plan
- In all cases, treatment was discontinued at the time of discharge from the ICU
- Patients in the control group received intravenous placebo (saline) according to the same regimen that was used in the hydrocortisone group.

Modulation of the duration and tapering of the treatment

Before the end of the fourth day, the clinician in charge decided on a short treatment regimen, if all of the following criteria were met:

1) patient breathing spontaneously

2) PaO2:FiO2 ratio greater than 200

3) Sequential Organ Failure Assessment (SOFA) score on day 4 less than or equal to SOFA score on day 1

4) high probability that the patient will be able to be discharged from the ICU by day 14

If all criteria are met,

The dose was reduced to 100 mg/d for two days

Then 50 mg/d for two more days.

If at least one of the criteria was absent,

Treatment was continued at 200 mg/d until the seventh day

Then decreased to 100 mg/d for four days

To 50 mg/d for the last three days.

Outcomes

- The primary outcome was death from any cause by day 28
- Secondary outcomes were,
    1) death from any cause by day 90
    2) the length of ICU stay
    3) ventilator free days by day 28
    4) vasopressor free days by day 28
    5) the change in the Pao2:Fio2 ratio by day 7

6) non-invasive ventilation or endotracheal intubation among patients who were not receiving any type of ventilation at baseline

7) endotracheal intubation among patients who were receiving noninvasive ventilation at baseline

RESULTS

- By day 28, death had occurred in 25 of 400 patients in the hydrocortisone group and in 47 of 395 patients in the placebo group

- By day 90, mortality was 9.3% in the hydrocortisone group and 14.7% in the placebo group

- Among 442 patients who had not received any mechanical ventilation at baseline, endotracheal intubation was performed in 18.0% in the hydrocortisone group and in 29.5% in the placebo group

- Among 618 patients who had received no invasive ventilation at baseline, the cumulative incidence of invasive mechanical ventilation before day 28 was 19.5% in the hydrocortisone group and 27.7% in the placebo group

- Among the 703 patients who had not received vasopressors at baseline, the cumulative incidence of vasopressor initiation was 15.3% in the hydrocortisone group and 25.0% in the placebo group

DISCUSSION

- The very short median time between admission to the ICU and the first administration of hydrocortisone or placebo in this trial (<15 hours) may have promoted an early effect.

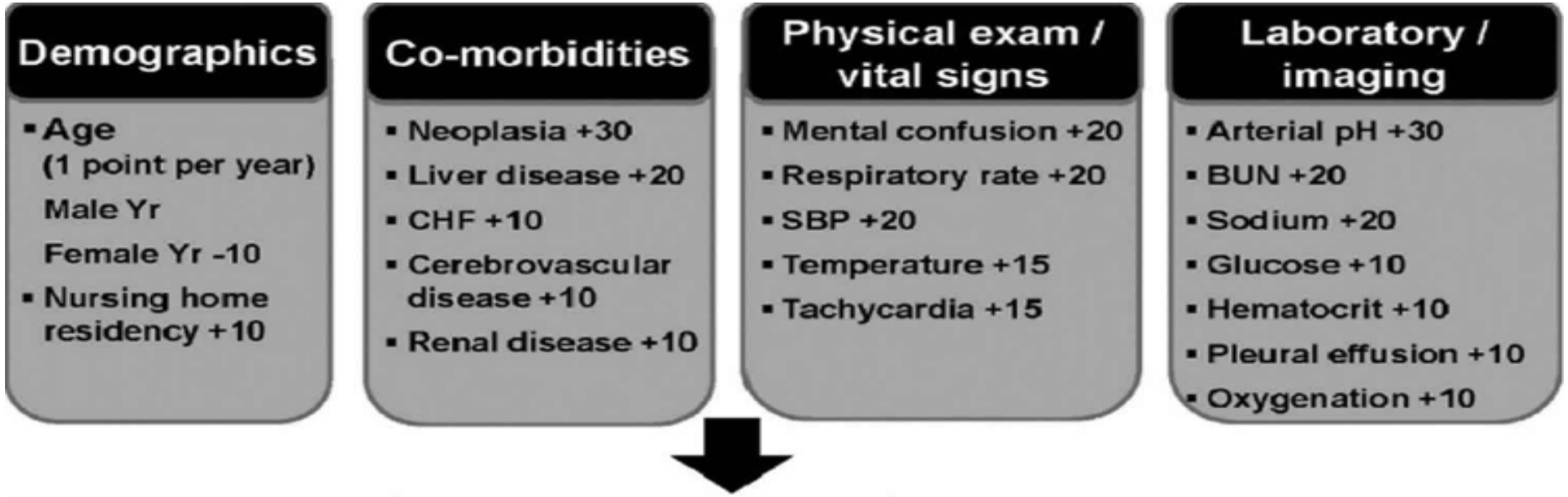
- The administration of hydrocortisone by continuous infusion and with tapering doses as compared with other potential regimens is not itself supported by a high level of evidence.

- Hydrocortisone was not associated with an increase in hospital-acquired infections or gastrointestinal bleeding.

- However, patients in the hydrocortisone group received higher doses of insulin during the first 7 days of treatment. An increased incidence of hyperglycemia, which is consistent with the pharmacodynamic effects of glucocorticoids, but this effect is transient.

- In this large, multicenter trial, early hydrocortisone therapy reduced the rate of death by day 28 among patients who had been admitted to the ICU for severe community-acquired pneumonia.

Pneumonia Severity Index



Risk class (Points)	Mortality (%)	Recommended site of care
I (<50)	0.1	Outpatient
II (51–70)	0.6	Outpatient
III (71–90)	2.8	Outpatient or brief inpatient
IV (91–130)	8.2	Inpatient
V (>130)	29.2	Inpatient

THANK YOU