Hydrocortisone for Severe Community-Acquired Pneumonia

Key Article: *Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in severe community-acquired pneumonia. N Engl J Med. Published online March 21, 2023. Presented at the 2023 International Symposium on Intensive Care and Emergency Medicine.*

Background

- Over 1.5 million adults are hospitalized for CAP annually, which is one of the top 10 causes of death in the US.
- Patients requiring mechanical ventilation have a particularly high mortality, which can reach up to 30% in severe cases.
- In addition to the primary infection, patients can also experience a severe inflammatory response leading to impaired lung function, gas exchange, and multiorgan failure which is why glucocorticoids have been so heavily considered as an important therapy to reduce mortality.
- To date, there are 7 RCTs have found positive non-mortality effects of steroids in severe CAP, but only one Italian trial reduced mortality (Confalonieri et al., AJRCCM 2005).
- We know steroids in Pneumonia is a controversial topic, so much so that the current ATS/ISDA guidelines recommend against steroids in severe CAP, but ESICM & SCCM guidelines favor their use.

Recent Literature

- Confalonieri (2005): 10 days of hydrocortisone reduced mortality in severe CAP in a 46 patient RCT
- Fernandez-Serrano (2011): Methylprednisolone improved resolution of hypoxia, but no difference in mortality in a 56 patient RCT
- Torres (2015): 5 days of methylprednisolone decreased incidence of progression to shock, need for invasive mechanical ventilation, or death within 72 hours of treatment in a 120 patient RCT.
- DEXA-ARDS (2020): 10 days of dexamethasone therapy decreased mortality in Non-COVID ARDS – in a 277 patient RCT

Objective:

- To evaluate whether hydrocortisone administration reduced mortality at 28 days among patients admitted to an intensive care unit (ICU) for severe community-acquired pneumonia.

Methods

- Double-blind, Randomized, controlled superiority trial of hydrocortisone versus placebo
- Location: 31 French centers between October 2015 – March 2020 (Stopped enrollment at COVID-19 outbreak)
- Patients
  - General Inclusion Criteria
    - Adults aged $\geq$ 18 years old
    - Diagnosis of pneumonia with clinical and radiographic criteria

        - Severe pneumonia defined by requiring 1 or 4 criteria:
            - Mechanical Ventilation (invasive or noninvasive)
            - HFNC with a FiO2 $\geq$ 50% and PaO2:FiO2 ratio < 300
            - Non-rebreather mask with PaO2:FiO2 ratio < 300
            - Pneumonia severity index (PSI) > 130
        - Able to be randomized/receive allocated treatment within 24h of onset of severity criteria
    - Excluded patients with:
        - Do not intubate orders
        - Pneumonia caused by influenza (BUT They did include non-flu viral PNA)
        - Septic shock
- Trial Procedures
    - All patients received usual care for pneumonia (antibiotics, provider determined respiratory support)
    - Randomized 1:1 to either control or intervention
        - **Control Group:** received a blinded injection of placebo (saline) according to the same regimen used in the hydrocortisone group
        - **Hydrocortisone Group:** Received hydrocortisone treatment where dose/duration was *determined on Day 4* by predefined discontinuation criteria
            - **Short duration group (8 days):** 200mg x 4 days + taper (100mg x 2 days, 50mg x 2 days)
            - **Long duration group (14 days):** 200mg x 7 days + taper (100mg x 4 days, 50mg x 3 days)
            - Criteria used to determine hydrocortisone duration (8 vs. 14 days)
                - Spontaneously breathing patients
                - PaO2:FiO2 > 200
                - Day 4 SOFA score $\leq$ Day 1 SOFA
                - High probability that patient will be able to be discharged from ICU by day 14.
- Primary outcome: Survival with favorable neurologic outcome (CPC score of 1 or 2) at 30 days
- Secondary Outcomes:
    - **Clinical outcomes:** 90d mortality, patients not progressing to mechanical ventilation, 28d incidence of endotracheal intubation initiation, 28d incidence of vasopressor initiation
    - **Adverse Events:** 28d incidence of hospital acquired infection, VAP, blood stream infection, GI Bleed, insulin requirements for hyperglycemia, weight change through hospital day 7.
- Sample size:
    - Power calculation: **1146 patients needed** to provide 80% power to detect a 25% relative risk reduction in mortality from a baseline of 27%
    - 800 patients enrolled before COVID, then trial paused; after COVID, the DSMB met July 2021 and recommended discontinuation of enrollment at planned second interim analysis because:
        - 1. They felt an additional 400 patients unlikely to change outcome to a negative trial
        - 2. As a result, they thought It would be unethical to continue to give placebo
        - 3. The prolonged suspension due to COVID-19 would adversely affect trial enrollment

Results

- Enrolled a total of 800 patients were randomized, 795 were included in final analysis
    - 400 received hydrocortisone

    - 395 received placebo
    - 5 patients excluded (FYI: 1 patient died, 2 withdrew, 2 were unknowingly prisoners)
- Demographics were well matched, as expected
    - Mean Age was 67 years old
    - ~ 70% male
    - Comorbidities (COPD, Diabetes, immunosuppression), Pneumonia Severity Index, and vasopressor requirements were similar
    - Most patients (>80%) had a PSI score of 4 or 5 (highest)
    - Pathogen detected in about 45% of patients, a majority were S. Pneumoniae (22%), and < 10% nonbacterial causes (viral, fungal pneumonias)
    - Respiratory support:
        - HFNC: 42%
        - NIV: 22%
        - Invasive MV: ~ 22%
        - NRB: 14%
- Primary Outcome: Hydrocortisone treatment decreased Death at 28d
    - **Hydrocortisone: 6.2% (95% CI: 3.9 – 8.5)**
    - Placebo: 11.9% (95% CI: 8.7 – 15.1)
    - ***P-value: 0.006***
- Secondary Outcomes
    - **No differences** in secondary clinical outcomes
    - **Adverse events:** higher cumulative insulin requirement in the hydrocortisone group
- Pre-defined subgroups that may benefit from hydrocortisone (worth warning that these are really small numbers, so could be due to random chance)
    - Patients not requiring mechanical ventilation
    - Women
    - High PSI score > 130
    - Age > 65

Limitations Identified by the Authors

- The observed mortality was much lower in the control group (11.9%) than expected (27%), indicating a lower severity of illness

Other limitations worth discussing or questions this trial did not answer:

- Significant under-enrollment (800 enrolled out of 1200 planned). This could have affected the trial outcome (Fragility index of 6)
- What steroid to use? Hydrocortisone vs. dexamethasone (COVID19, ARDS trials had (+) outcomes with different steroid), does it matter? Does it matter how the glucocorticoid is administered (infusion vs. intermittent dosing)?
- Septic shock patients were not enrolled since hydrocortisone is often used for refractory hypotension