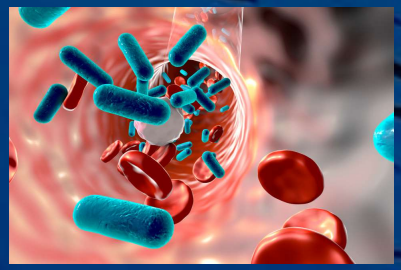

Adjunctive Hydrocortisone Therapy for Adults with Septic Shock: Is The Evidence Conclusive?

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- Chelsea and Westminster Hospital for sponsoring my ICU course
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Outline of Presentation

- Define sepsis
- Current treatment
- How adjunctive glucocorticoids work
- Side Effects
- Literature Review
- Findings
- Limitations of studies
- Recommendations

Sepsis Definitions

- Surviving Sepsis Campaign (2016) defines sepsis as:
- " A life-threatening organ dysfunction caused by a dysregulated host response to an infection"
- "Occurs when an infection is complicated by organ failures which is defined by a sequential organ failure assessment score (SOFA) score ≥2"
- Septic Shock is a "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality"

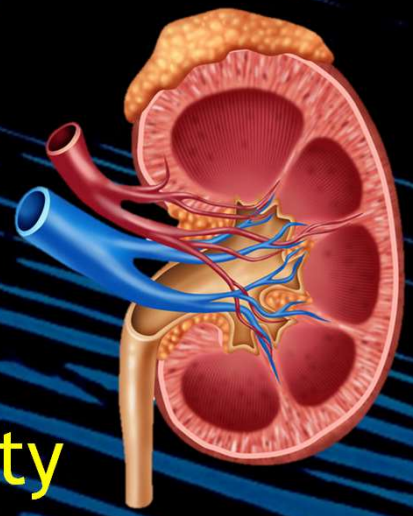
Surviving Sepsis Campaign Recommendations

1. Empirical antibiotics, fluid resuscitation and vasopressors
2. SSC (2016) recommends:
   - IV hydrocortisone 200mg/day for patients with refractory hypotension despite adequate fluid resuscitation and vasopressor therapy
   - Corticosteroids may be indicated with patients with a history of steroid therapy or adrenal dysfunction
3. Contraindications:
   - Patients who respond to fluid resuscitation and vasopressor therapy
   - In septic patients to prevent septic shock

Current Guidelines

1. Surviving Sepsis Campaign (2016) graded these as ‘weak recommendations’ based on ‘low quality of evidence’
2. NICE (2016) sepsis guidelines make no specific recommendation for the use of glucocorticoids in the management of sepsis

How adjunctive glucocorticoids work



- Hormones produced by the adrenal cortex
- Maintain vascular tone and cardiac contractility
- Cortisol deficiency intensifies the clinical effects of hypovolaemia
- Under stress, the adrenal gland and thyroid may be unable to sustain hormone production
- An adjunctive therapy in septic shock e.g. hydrocortisone to elevate the circulating level of hormones

Side Effects

- Immunosuppression
- Hyperglycaemia
- Tissue integrity problems
- Delayed wound healing
- Steroid induced psychosis
- Peptic Ulceration

Systematic Literature Search

- 374 papers
- Exclusion criteria applied
- 4 papers identified
- 4 placebo controlled, double blinded, randomised control trials

Study	Country	Population	Units
Keh *et al.*, (2016)	Germany	353	34
Lv *et al.*,(2017)	China	118	1
Venkatesh *et al.*, (2018)	Australia,UK, New Zealand, Denmark and Saudi Arabia	3686	69
Annane *et al.*, (2018)	France	1241	34

Studies findings

- Papers evaluating different outcomes
- One key outcome in common: mortality
- 3 out of 4 papers found that mortality was not reduced up to 28,90 and 180 days (continuous IV infusions)

Annane *et al.* (2018)

- Annane *et al.*, (2018) had different results
- Placebo group was 12% more likely to die at 90 days
- Administered IV hydrocortisone 50mg boluses 6hrly plus 50mcg fludrocortisone via NG
- Mortality reduced at ICU discharge, hospital discharge and at 180 days.
- Hydrocortisone plus fludrocortisone group had more vasopressor free days to day 28 and organ failure free days to day 28

Criticism of Annane *et al.* (2018)

- Trial suspended twice
- First time for 7 months (Xigris)
- Second time (3 months from the data & safety board)
- Guidelines superceded (SSC 2008)

Baseline Adrenal Function Tests

- Baseline adrenal function tests were conducted in some studies
- No difference in patient outcomes for patients who tested positive for adrenal deficiency compared to those who didn't
- SSC (2016) random cortisol levels may only be useful for patients with absolute adrenal deficiency

Other Key Outcomes of the 4 Studies

Ventilator Free Days	Length of stay in ICU or Hospital	Resolution of Shock
3 out of 4 studies found no significant difference between groups in ventilator free days (Annane *et al.*, *2018*;Keh *et al.*, 2018;Vankatesh *et al.*, 2018)	2 out of the 4 studies found no significant difference in length of stay in ICU or hospital (Keh *et al.*, *2018*; Lv *et al.*, 2017)	Vankatesh *et al.*, (2018) found the hydrocortisone group had a shorter time to resolution of shock and discharge from ICU

GRADE tool

Study	Placebo controlled, double blinded randomised control trial (limit bias)	Large Number of Participants	Intention to treat analysis	Flow Diagram
Keh *et al.*, (2016)	✓	✓	✓	✓
Venkatesh *et al.*, (2018)	✓	✓	✗	✗
Lv *et al.*,(2017)	✓	✗	✗	✓
Annane *et al.*, (2018)	✓	✓	✗	✗

GRADE tool Miscellaneous Strengths

Study	Strengths
Keh *et al.*, (2016) Grade: 3/4	<5% loss at follow up
Venkatesh *et al.*, (2018) Grade: 3/4	69 sites in 5 countries (Increases external validity) Hydrocortisone administered via continuous IV infusion (mimics more natural physiologic response/reduces incidence of hyperglycaemia)
Lv *et al.*,(2017) Grade:2/4	Patients treated as per SSC guidelines (SSC 2012) First study in which hydrocortisone and placebo commenced simultaneously with vasopressors (able to exclude time delay of therapy in reducing mortality) Hydrocortisone given via continuous IV infusion
Annane *et al.*, (2018) Grade: 2/4	Non experimental interventions were harmonised across centres according to SSC (2008)

GRADE tool Limitations of Studies

Study	Limitations
Keh *et al.*, (2016) Grade: 3/4	Downgraded for imprecision: 380 patients were required to detect an absolute difference of 15% with a P-value of .05 and a power of 0.8. However sample size reduced statistical power of study. Former severe sepsis/ septic shock definition used, which has now been superseded.
Venkatesh *et al.*, (2018) Grade: 3/4	Downgraded for inconsistency as other aspects of patient care were at the discretion of treating clinicians. Therefore potential risk for performance bias.
Lv *et al.*,(2017) Grade:2/4	Sample size, single centre reduces statistical power and generalisability. Differences between heterogeneity of patients (SOFA score)
Annane *et al.*, (2018) Grade: 2/4	Downgraded for risk of reporting bias. Paper did not discuss own limitations. Suspended twice Downgraded for impression due to sample size (97% of original sample size obtained)

Conclusion

- Research suggests hydrocortisone alone does not reduce patient mortality
- However Annane *et al.*, (2018) found that 90 day mortality was reduced with patients who received hydrocortisone plus fludrocortisone
- Additionally vasopressor free days up to day 28 were significantly lower in the hydrocortisone plus fludrocortisone group compared to the placebo.
- Further research required
- Limitation of current research: variance in administration of steroids and terminology of sepsis and septic shock

Thank you