Corticosteroids in Sepsis

Introduction

1. Sepsis is a systemic inflammatory response (SIRS) with associated organ dysfunction as a result of an infection.
2. Sepsis is defined as ≥2 of the criteria:
    a. Temperature >38 ºC or <36 ºC
    b. Heart rate of >90 bpm
    c. Respiratory rate of >20 breaths/minute or pCO2 of <32 mmHg
    d. WBC >12,000 cells/mL or <4000 cells/mL
3. Initial management of sepsis includes:
    a. Intravenous fluids (LR/NS) 30 mL/kg (based on total body weight) administered within the first 3 hours.
    b. Empiric antibiotic therapy based on the common bacteria and site of infection initiated within the first hour.
4. Per the Surviving Sepsis guidelines, IV hydrocortisone is recommended for patients at least 4 hours after initiation of norepinephrine/epinephrine ≥0.25 mcg/kg/min to maintain a MAP of ≥65 mmHg.

Pharmacology

	Hydrocortisone	Methylprednisolone	Fludrocortisone
Dose	IV: 50 mg Q6H or 100 mg Q8H x 5-7 days	IV (succinate): 40 to 125 mg/day (maximum of 1 to 2 mg/kg/day)	PO (in addition to another glucocorticoid): 0.05 mg/day x 7 days
Administration	IV: over ≥30 seconds	IV: over several minutes or over 15 to 60 minutes as an infusion	Administer by NG tube
PK/PD	-Onset of action (IV): 1 hour -T ½ elimination (IV): 2 +/- 0.3 hours	-Onset of action (IV): 1 hour -T ½ elimination (IV): 0.25 +/- 0.1 hour	-Onset of action (PO): 1-2 hours -T ½ elimination (PO): ~3.5 hours
Mechanism of Action	-Anti-inflammatory (decreased synthesis and release of inflammatory mediators) -Immunosuppressive (decreased response to hypersensitivity reactions) -Antiproliferative: vasoconstriction and decreased permeability of WBC to the injury	-Same mechanism of action as hydrocortisone with a 4-5x greater potency	- Mineralocorticoid activity > hydrocortisone or methylprednisolone
Adverse Effects	-Cardiovascular: increased blood pressure -Endocrine: fluid retention, hyperglycemia, weight gain -Gastrointestinal: increased appetite -Psychiatric: altered behavior	-Similar adverse effects as hydrocortisone	-Higher risk of fluid retention, hypertension, and decreased electrolyte concentrations
Drug Interactions and warnings	**-Warnings:** adrenal suppression, immunosuppression (higher doses for increased duration of therapy), psychiatric changes **-Drug Interactions:** antacids (separate by 2 hours), live vaccinations, DDAVP (risk of hyponatremia), succinylcholine	**-Warnings:** adrenal suppression, acute hepatitis (rare) **-Drug Interactions:** similar to hydrocortisone and fludrocortisone	**-Warnings:** patients with underlying hepatic dysfunction, myasthenia gravis, systemic sclerosis, or thyroid disease **-Drug Interactions:** similar to hydrocortisone and methylprednisolone
Compatibility	**Drug in Solution:** None tested	**Drug in Solution:** -Compatible: D5W- ½ NS, NS -Incompatible: D5W, D5NS, LR	N/A

Overview of Evidence

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Author, year	Design/ sample size	Intervention & Comparison	Outcome
French Trial Annane D, 2002.	RCT (n = 300)	hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50-micro g tablet once daily) (n = 151) or matching placebos (n = 149) for 7 days.	7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.
Teng-Jen Yu, 2009.	RCT (n = 40)	Hydrocortisone 50 mg IV Q6H or methylprednisolone 20 mg Q12H x 7 days	**-Higher survival rates with hydrocortisone vs methylprednisolone**
VANISH Gordan, 2016	RCT (n = 1400)	Vasopressin vs. norepinephrine plus hydrocortisone vs. placebo	No significant difference in mortality at 28 days, but vasopressin plus hydrocortisone was associated with faster reversal of shock and reduced need for renal replacement therapy
Gibbison B, 2017.	Systematic review & meta-analysis (n = 33 clinical trials)	Systemic treatment with any corticosteroids	**-Decreased septic shock reversal with methylprednisolone vs hydrocortisone** -Increased 28-day mortality with methylprednisolone vs dexamethasone -Decreased risk of superinfections with methylprednisolone -Decreased ICU mortality and LOS with methylprednisolone
CORTICUS Sprung, 2018	RCT, (n=499)	Hydrocortisone 50 mg every 6 hours vs. placebo	The study found no significant difference between the two groups in 28-day mortality, but hydrocortisone was associated with a higher rate of shock reversal and a lower rate of progression to multiple organ dysfunction syndrome.
HYPRESS Key, 2018	RCT (n = 380)	Infusion of hydrocortisone 200 mg daily for five days followed by tapering until day 11 vs placebo	The study found no significant difference between the two groups in the primary outcome of time alive and free of vasopressor support by day 7 The study also found no significant difference between the two groups in secondary outcomes such as mortality at 28 days, ICU-free days, and hospital-free days
ADRENAL Venkatesh B, 2018.	RCT (n = 3800)	Hydrocortisone 200 mg IV daily	-No difference in 28 or 90-day mortality with hydrocortisone **-Decreased time to resolution of septic shock and discharge from the ICU with hydrocortisone** -Decreased number of patients received a blood transfusion with hydrocortisone -Higher number of adverse events with hydrocortisone
APROCCHHSAnnane D, 2018.	RCT (n = 1280)	-Hydrocortisone 50 mg IV Q6H + fludrocortisone 50 mcg PO daily in AM x 7 days -Drotrecogin alfa -Combination therapy of the three medications	**-Decreased 90-day mortality with hydrocortisone + fludrocortisone** -Decreased mortality with hydrocortisone + fludrocortisone at ICU and hospital discharge -Decreased time to discontinue vasopressor therapy and mechanical ventilation and achieve a SOFA score of <6 with hydrocortisone + fludrocortisone

Conclusions

- Per the Surviving Sepsis guidelines, hydrocortisone is recommended first-line for the treatment of septic shock in patients that are refractory to fluid (volume) resuscitation.
- Hydrocortisone portrayed greater efficacy in clinical trials than methylprednisolone.
- There are no clinical trials for the comparison of hydrocortisone monotherapy versus hydrocortisone + fludrocortisone; however, it is hypothesized that hydrocortisone provides sufficient mineralocorticoid activity as monotherapy without the increased risks of adverse effects with the addition of fludrocortisone.
    - Necessary to avoid fludrocortisone in specific patient populations (i.e. congestive heart failure, hepatic and renal disease, etc.)

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