

How to Diagnose and Treat Critical Illness-Related Corticosteroid Insufficiency (CIRCI)?

Wan-Chu Hung, DVM, MS, DACVECC

whung@ufl.edu

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Outline



Definition



Pathophysiology



Diagnosis



Management

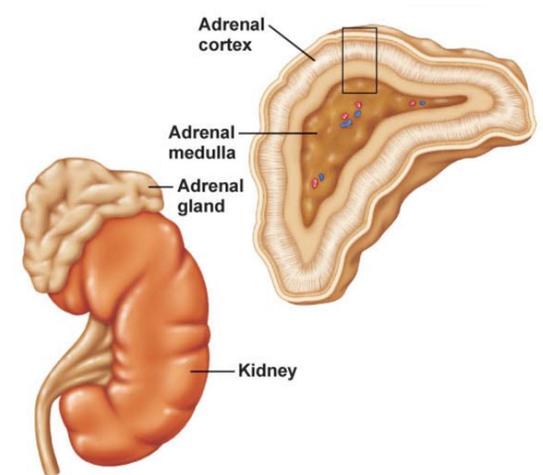
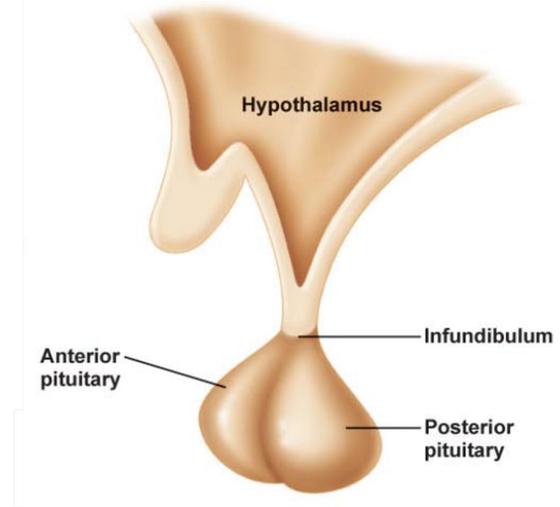
Definition

- **First described in Annane D, et al. *JAMA*. 2000**
 - Relative adrenal insufficiency
- **Marik PE, et al. *Crit Care Med*. 2008**
 - Critical illness-related corticosteroid insufficiency (CIRCI)

Definition

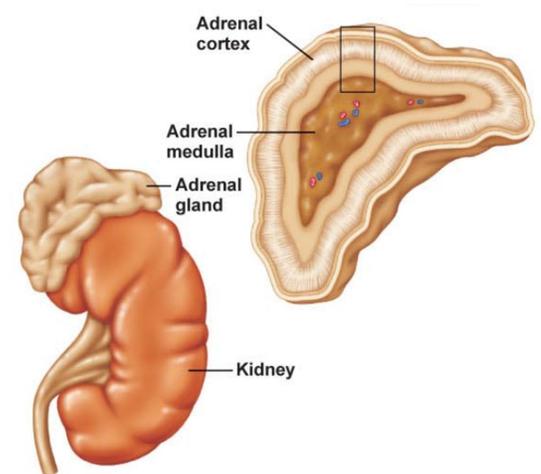
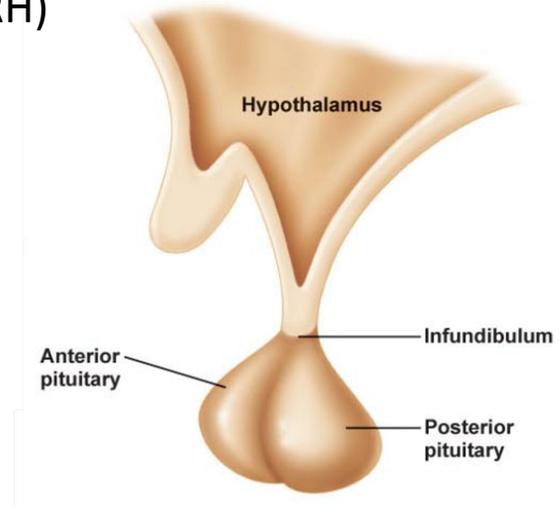
- **Inadequate cellular corticosteroid activity relative to the severity of the patient's critical illness**
 - Dysregulated systemic inflammation (usually exaggerated) due to abnormal intracellular glucocorticoid-mediated anti-inflammatory response

Hypothalamic–Pituitary–Adrenal Axis



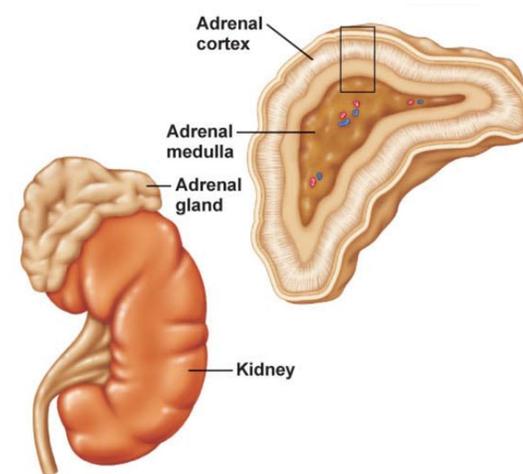
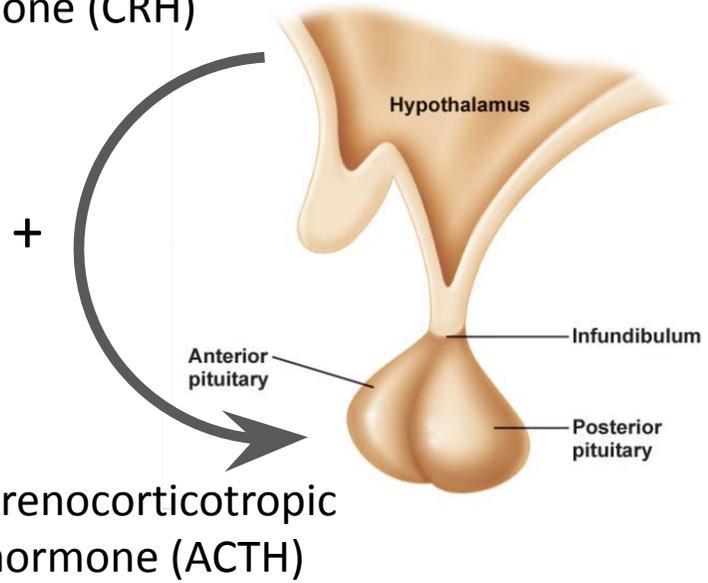
Hypothalamic–Pituitary–Adrenal Axis

Corticotropin-releasing hormone (CRH)



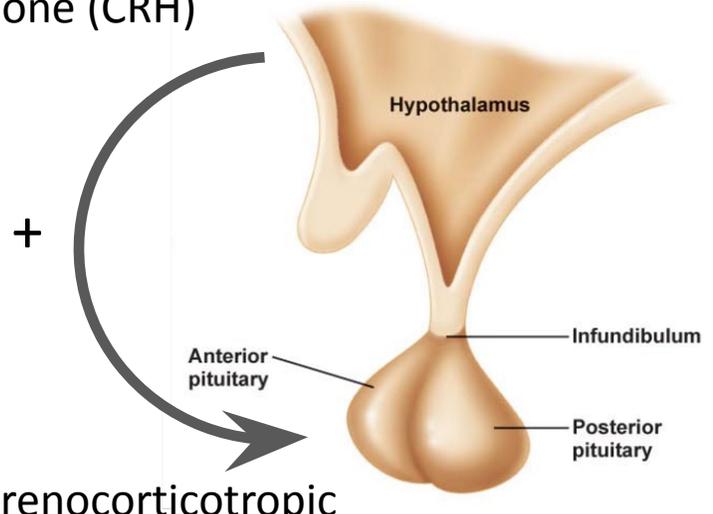
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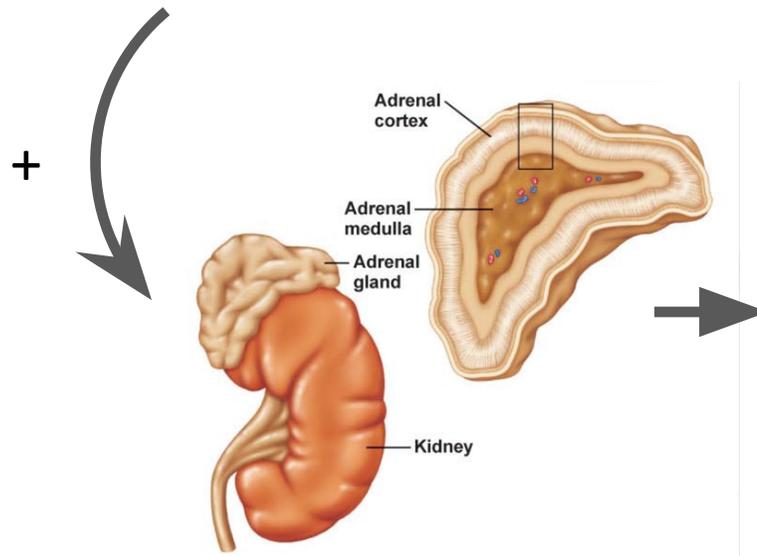


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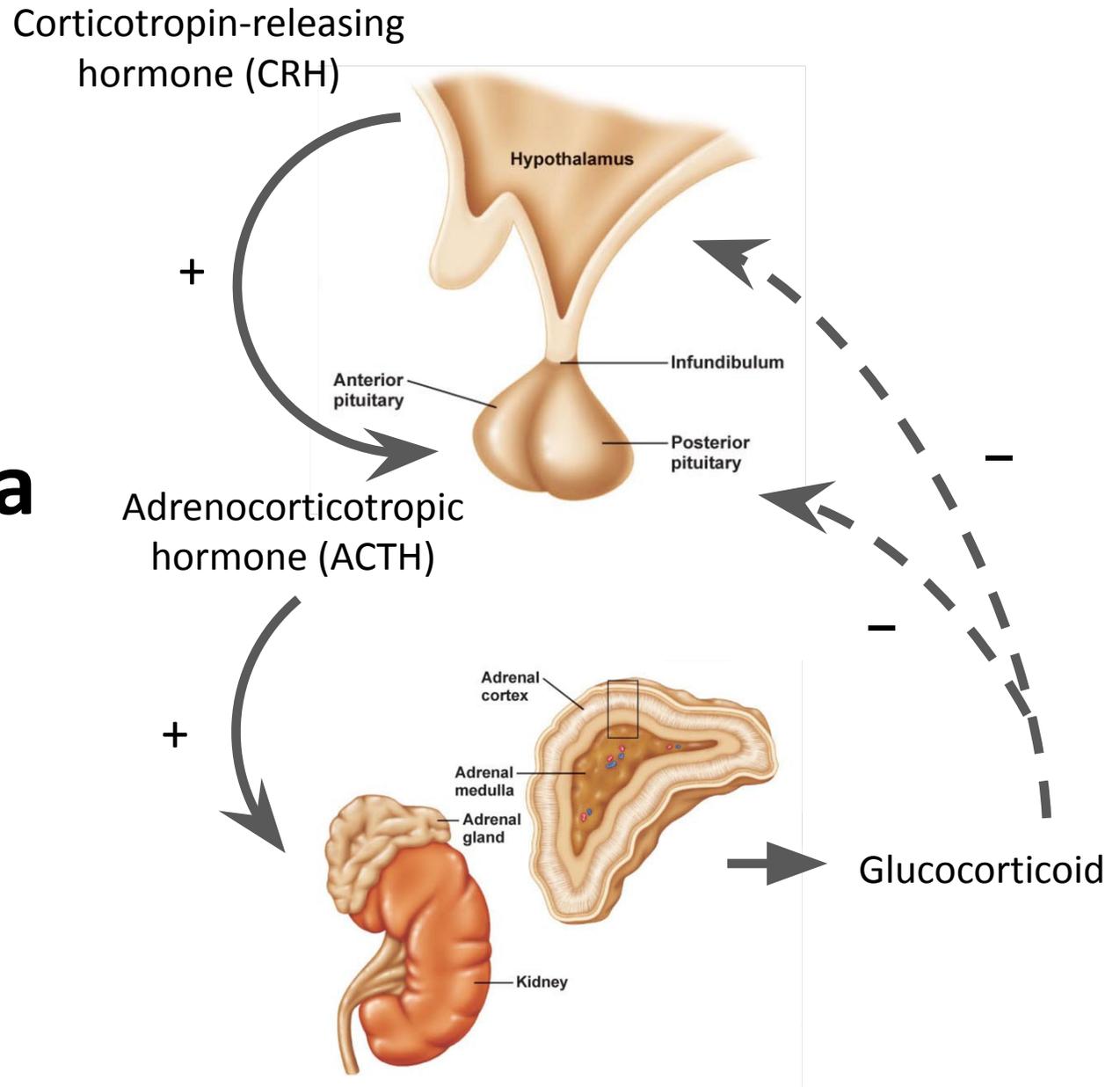


Adrenocorticotrophic hormone (ACTH)



Glucocorticoid

Hypothalamic–Pituitary–Adrenal Axis



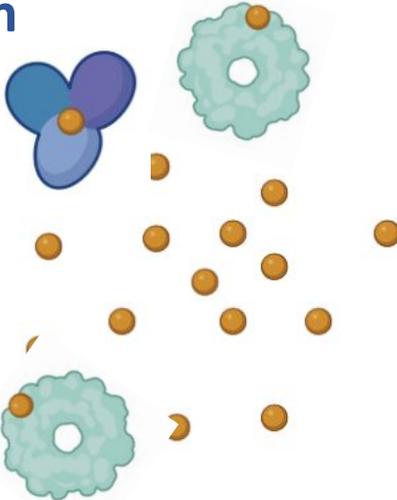
Endogenous Glucocorticoids

- **Cortisol (95 % of the glucocorticoid activity)**
- Corticosterone (4% of the glucocorticoid activity)
- Deoxycorticosterone

Circulating Cortisol

Circulation

Albumin



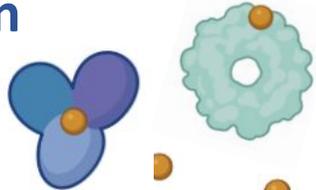
Free
Cortisol

Corticosteroid-binding
globulin (CBG)

Circulating Cortisol

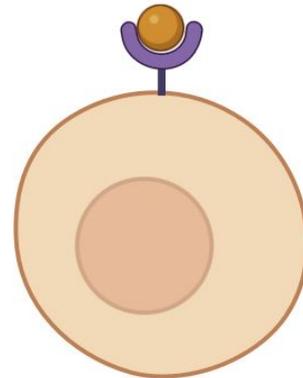
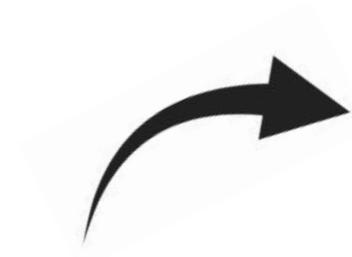
Circulation

Albumin



Corticosteroid-binding
globulin (CBG)

Cortisol

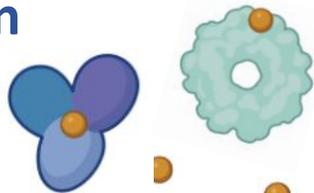


Target cell with glucocorticoid
receptors (GR)

Circulating Cortisol

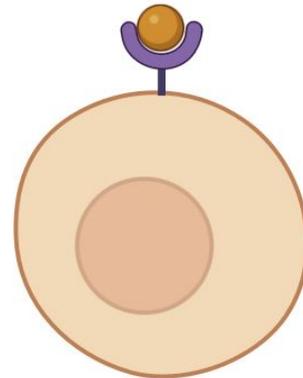
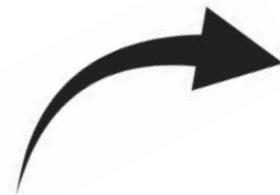
Circulation

Albumin



Cortisol

Corticosteroid-binding
globulin (CBG)



Target cell with glucocorticoid
receptors (GR)



Modify cellular function by
influencing multiple transcription
and translation pathways

Functions of Glucocorticoids

- Under normal conditions, cortisol follows a circadian rhythm to regulate physiological functions
- During illness or injury, the HPA axis upregulates cortisol production
→ prevent organ failure or shock, combat infections, support tissue healing



Functions of Glucocorticoids

Stimulates
gluconeogenesis

Reduces
intracellular protein
store (except liver)

Mobilizes fatty
acids

Prevents & Slows
down inflammation

Maintains the
gastric mucosal
barrier

Maintains vascular
tone & permeability

Inhibits the release
of ADH

Pathophysiology of CIRCI

Dysfunction of the HPA axis

Alterations in glucocorticoid production

Modifications in glucocorticoid metabolism

Changes in cortisol protein binding

Impaired target tissue responses

Conditions Associated with CIRCI

- Sepsis and septic shock
- Acute respiratory distress syndrome (ARDS)
- Severe trauma
- Burns
- Severe pneumonia
- Major surgeries

Diagnosis of CIRCI

- Challenging
- Clinical findings
 - **Pressor-resistant hypotension**
 - Cardiovascular, neurological or respiratory abnormalities

Diagnosis of CIRCI

- **Human medicine**

- Resting plasma cortisol level $<10 \mu\text{g/dL}$
- Change in baseline cortisol level $<9 \mu\text{g/dL}$ 60 minutes after cosyntropin (250 μg) administration

Diagnosis of CIRCI

- **Human medicine**

- Resting plasma cortisol level $<10 \mu\text{g/dL}$
- Change in baseline cortisol level $<9 \mu\text{g/dL}$ 60 minutes after cosyntropin (250 μg) administration

~~Plasma free cortisol levels
Low-dose (1- μg) ACTH stimulation tests
Corticotropin levels~~

Diagnosis of CIRCI

- **Human medicine**

- Differences in consensus among various guidelines
 - 2021 Surviving Sepsis Guidelines - No laboratory testing is required before initiating corticosteroid therapy

Diagnosis of CIRCI

- **Veterinary medicine**
 - No established consensus
 - Change in baseline cortisol level $<3 \mu\text{g/dL}$

Management

Corticosteroid

Recommendations in Human Medicine

- **Septic shock**
 - **SCCM & ESICM CIRCI Guideline (2017)**
 - Hydrocortisone should be considered in adult patients with septic shock that is unresponsive to fluids and moderate- to high-dose vasopressor therapy (e.g., norepinephrine >0.1 $\mu\text{g}/\text{kg}/\text{min}$ or equivalent)
 - Dose: <400 mg/day; administered at full dose for at least 3 days

Recommendations in Human Medicine

- **Septic shock**
 - **Surviving Sepsis Campaign guidelines (2021)**
 - Corticosteroid should be considered when vasopressor support with norepinephrine or epinephrine CRI $\geq 0.25 \mu\text{g}/\text{kg}/\text{min}$ is required for ≥ 4 hours
 - Dose: 200 mg/day; either divided into 4 doses IV q6h or CRI

Recommendations in Human Medicine

- **Septic shock**
 - **CCM Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia (2024)**
 - Similar to Surviving Sepsis Campaign guidelines

Recommendations in Human Medicine

- **Acute respiratory distress syndrome (ARDS)**
 - **SCCM & ESICM CIRCI Guideline (2017)**
 - Corticosteroid is recommended in early moderate to severe ARDS (PaO₂/FiO₂ <200)
 - Methylprednisolone is recommended - superior lung tissue penetration, longer residence time
 - Dose: gradual taper over 13 days
 - Early (up to day 7 of onset): 1 mg/kg/day
 - Late (after day 6 of onset): 2 mg/kg/day

Recommendations in Human Medicine

- **Acute respiratory distress syndrome (ARDS)**
 - **CCM Focus Updates: Guidelines on Use of Corticosteroids in Sepsis, ARDS, and CAP (2024)**
 - Refer to the proceedings

Recommendations in Human Medicine

- **Community-acquired pneumonia (CAP)**
 - **SCCM & ESICM CIRCI Guideline (2017)**
 - Corticosteroid should be considered in hospitalized adult patients with CAP
 - Dose: duration of 5–7 days at a daily dose of <400 mg IV hydrocortisone or its equivalent

Recommendations in Human Medicine

- **Community-acquired pneumonia (CAP)**
 - **CCM Focus Updates: Guidelines on Use of Corticosteroids in Sepsis, ARDS, and CAP (2024)**
 - Corticosteroid should be considered only in patients with severe pneumonia (e.g. septic shock requiring vasopressor therapy or mechanical ventilation)
 - Dose: refer to the proceedings

Recommendations in Human Medicine

- **Major Trauma**
 - **SCCM & ESICM CIRCI Guideline (2017)**
 - Corticosteroid is NOT recommended

What about mineralocorticoid?

- **APROCCHSS trial (2018 NEJM)**
 - Hydrocortisone plus Fludrocortisone for Adults with Septic Shock
 - Multicenter, randomized, placebo-controlled trial
 - Hydrocortisone 50mg IV q6h + Fludrocortisone 50 mcg PO q24h for 7 d
 - 1241 patients
 - Significant reduction in 90-day mortality in intervention compared to control group

What about mineralocorticoid?

- **Fludrocortisone Dose Response Relationship in Septic Shock - FluDReSS trial**
 - Just completing recruitment

Currently there is no recommendation made for mineralocorticoid administration in CIRCI.

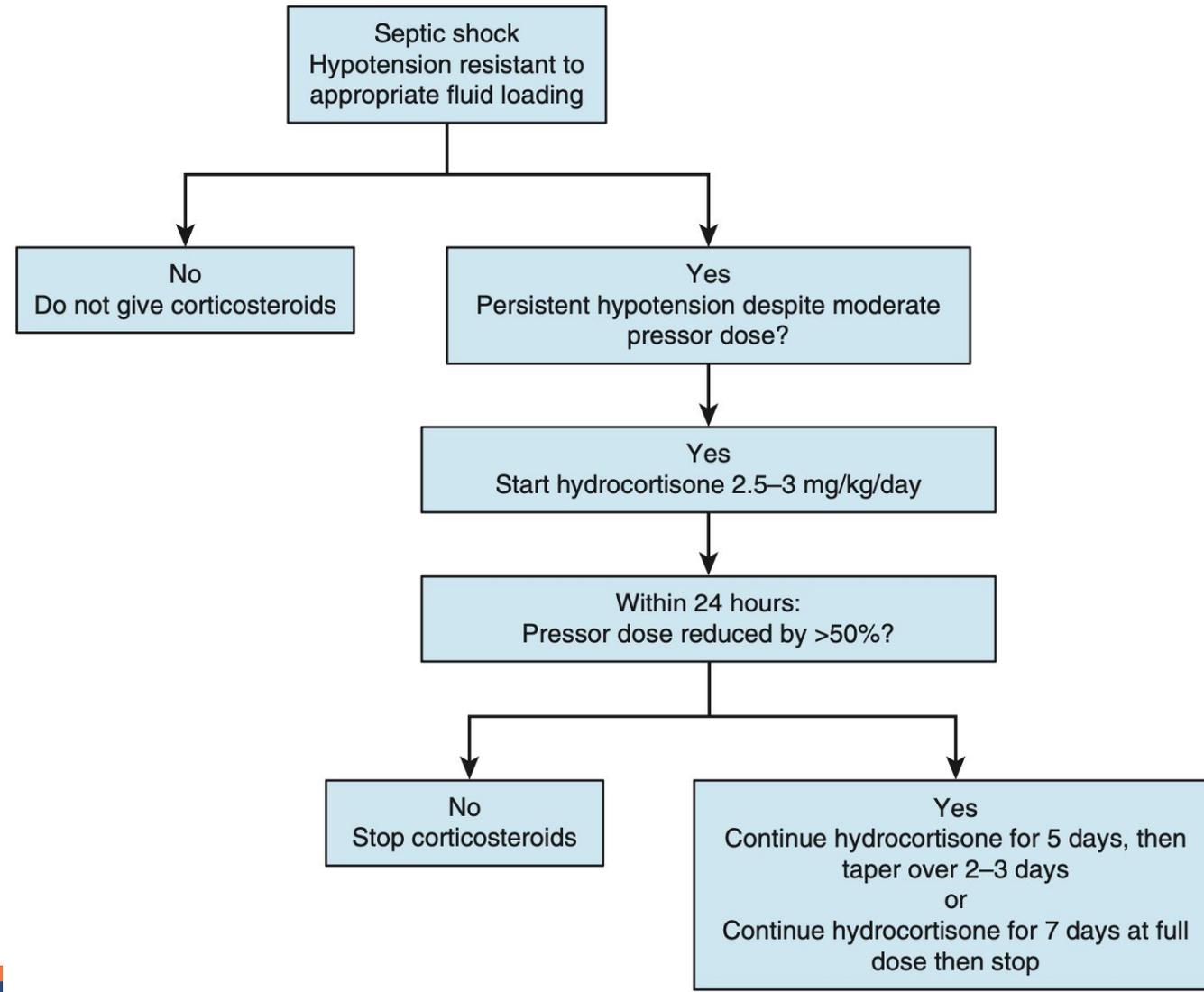
Recommendations in Veterinary Medicine

- Few available studies
- Dog
 - Peyton JL, et al. (2009)
 - Hydrocortisone 0.5 mg/kg IV q6h for 4 days, then 0.5 mg/kg IV q8h for 3 days, and further tapered to q12h on day 8 before discontinuation
 - Summers AM, et al. (2021)
 - loading dose 1 mg/kg IV bolus followed by a CRI of 0.08 mg/kg/h

Recommendations in Veterinary Medicine

- Cat
 - Durkan S, et al. (2007)
 - Dexamethasone 0.08 mg/kg IV q24h for 7 days, later transitioned to prednisone (0.2 mg/kg PO q12h) tapering over two weeks
 - Pisano SRR, et al. (2017)
 - Hydrocortisone 1 mg/kg IV followed by CRI 0.16 mg/kg/h, then tapered by 50% q48h over 5 days prior to discontinuation

Recommendations in Veterinary Medicine



Different Corticosteroids

Short-acting

↓

Long-acting

| | Relative GC & anti-inflammatory potency | Relative MC potency | Equivalent pharmacologic dose (mg) |
|---------------------------|-----------------------------------------|---------------------|------------------------------------|
| Cortisol | 1 | 1 | 20 |
| Hydrocortisone | 1 | 0.8 | 20 |
| Cortisone | 0.8 | 0.8 | 25 |
| Prednisone | 4 | 1 | 5 |
| Prednisolone | 4 | 1 | 5 |
| Methylprednisolone | 5 | 0 | 4 |
| Dexamethasone | 30 | 0 | 0.75 |
| Betamethasone | 30 | 0 | 0.6 |

Different Corticosteroids

- Gardiner D, Harris B. *J Vet Emerg Crit Care (San Antonio)*. 2025.
 - Retrospective study
 - 60 septic dog with vasopressor-resistant hypotension
 - 26 dogs received DxSP (0.002-0.39 mg/kg IV, variable frequency), 34 did not
 - No significant differences in time to vasopressor discontinuation or survival to discharge

Side Effects of Corticosteroids in CIRCI

- Sparse research in both human and veterinary medicine
- Hyperglycemia is the most common one
- No evidence suggests an increased risk of GI bleeding or secondary infections

Take Home Messages

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Take Home Messages

- CIRCI is associated with a range of diseases and critical conditions.
- The pathophysiology of CIRCI is complex and multifactorial.
- Identifying CIRCI in patients remains a diagnostic challenge.
- Corticosteroid therapy serves as the primary treatment for CIRCI.
- Further research is needed to improve diagnosis and management strategies.



Thank you!

Definitions

February 23, 2000

A 3-Level Prognostic Classification in Septic Shock Based on Cortisol Levels and Cortisol Response to Corticotropin

Djillali Annane, MD, PhD; Véronique Sébille, PhD; Gilles Troché, MD; [et al](#)

» [Author Affiliations](#)

JAMA. 2000;283(8):1038-1045. doi:10.1001/jama.283.8.1038

Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine

Marik, Paul E. MD, FCCM; Pastores, Stephen M. MD, FCCM; Annane, Djillali MD; Meduri, G Umberto MD; Sprung, Charles L. MD, FCCM; Arlt, Wiebke MD; Keh, Didier MD; Briegel, Josef MD; Beishuizen, Albertus MD; Dimopoulou, Ioanna MD; Tsagarakis, Stylianos MD, PhD; Singer, Mervyn MD; Chrousos, George P. MD; Zaloga, Gary MD, FCCM; Bokhari, Faran MD, FACS; Vogeser, Michael MD

[Author Information](#) ☺

Critical Care Medicine 36(6):p 1937-1949, June 2008. | DOI: 10.1097/CCM.0b013e31817603ba

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Pathophysiology of CIRCI

**Dysfunction of the
HPA axis**

**Alterations in
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**Modifications in
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**Changes in cortisol
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**Impaired target
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