Back to the Future: Updated Guidelines for Evaluation and Management of Adrenal Insufficiency in the Critically Ill

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Disclosures

- No conflicts of interest to disclose

Objectives

1. Describe the pathophysiology of critical illness-related corticosteroid insufficiency (CIRCI)
2. Recommend appropriate diagnostic tests for CIRCI
3. Discuss the literature regarding corticosteroid use in various critical care conditions
4. Determine appropriate utilization of corticosteroids in the ICU

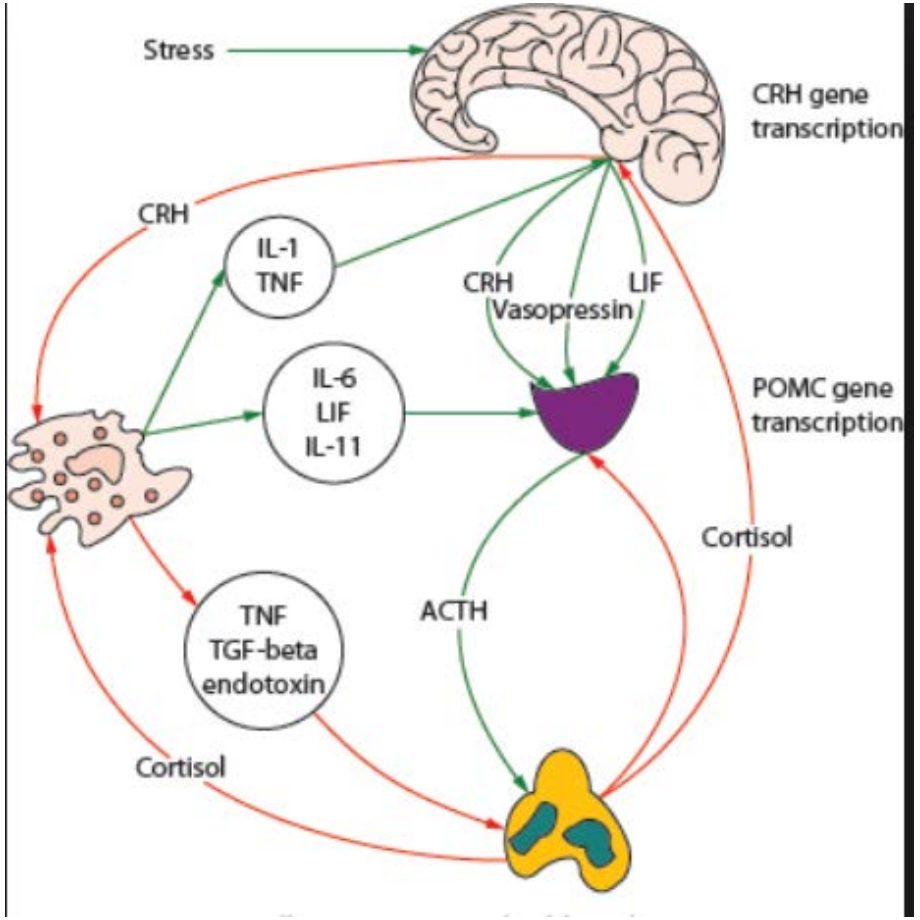
Pathophysiology

- Cortisol is essential for:
  - Gluconeogenesis
  - Anti-inflammatory effects on the immune system
  - Maintenance of vascular tone
  - Endothelial integrity
  - Increased sensitivity to catecholamines
  - Reduction in nitric oxide vasodilation
  - Modulation of angiotensinogen synthesis

- Increased cortisol production with severe infection, trauma, burns, illness, or surgery

Cooper MS *et al. NEJM.* 2003;348:727-34

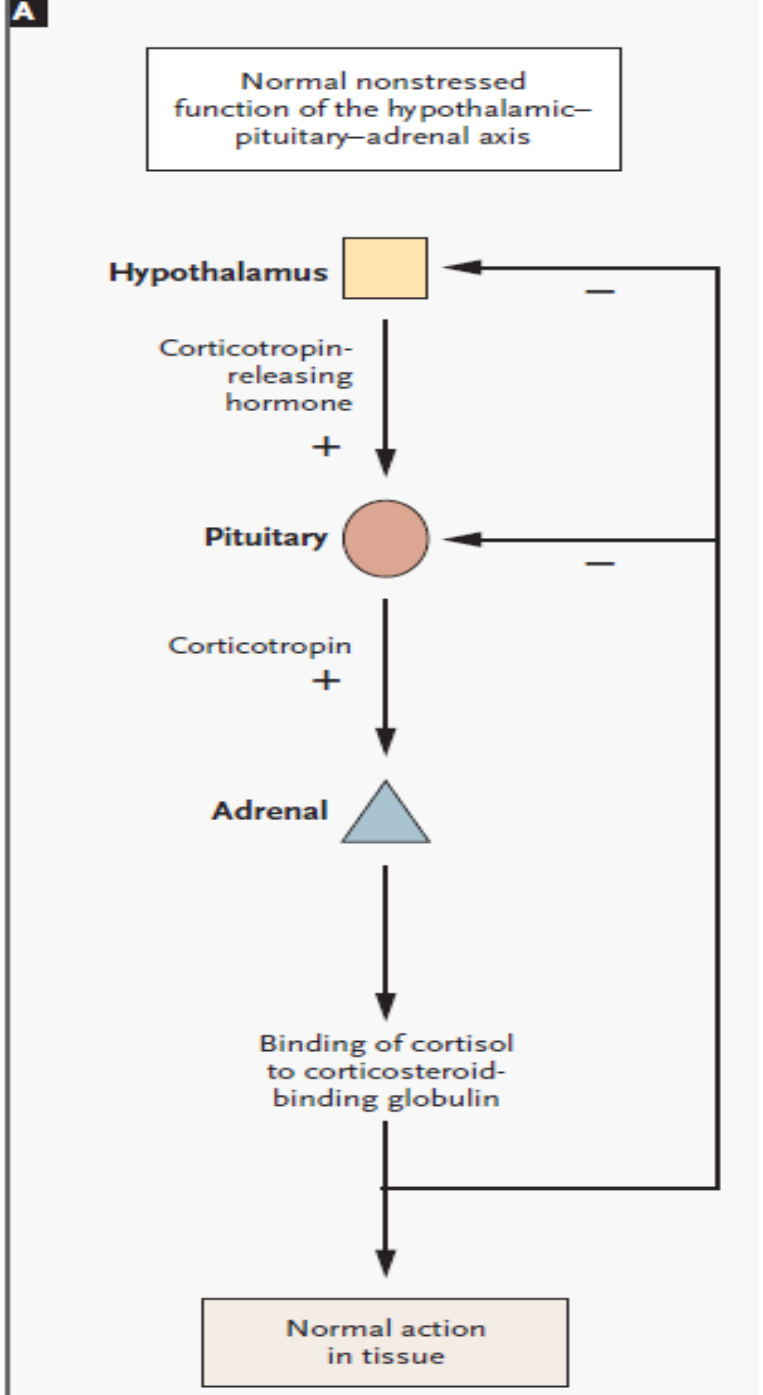
Pathophysiology



Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

- Inadequate corticosteroid activity for the severity of illness of a patient
- During severe illness, many factors can impair the normal corticosteroid response
- Adrenal cortisol synthesis can be impaired
  - High levels of inflammatory cytokines in patients with sepsis can directly inhibit cortisol synthesis
  - Decreased production of CRH, ACTH, and cortisol
- Increased systemic or tissue specific corticosteroid resistance
  - Excessive production of inflammatory cytokines during sepsis can lead to resistance

Cooper MS *et al. NEJM.* 2003;348:727-34



Cooper MS *et al. NEJM.* 2003;348:727-34

Consequences of CIRCI

- Exaggerated pro-inflammatory response and have relative corticosteroid insufficiency
  - Elevated levels of inflammation

- Decreased corticosteroid response leads to an increase in:
  - Morbidity
  - Mortality
  - ICU length of stay

Diagnosis

Diagnosis

1. Random cortisol level
   - A random cortisol level of less than 10 mcg/dL can be used to diagnose CIRCI

2. Cosyntropin stimulation test
   - A delta serum cortisol level of less than 9 mcg/dL following an IV dose of 250 mcg of cosyntropin can be used to diagnose CIRCI
     1. Obtain a baseline cortisol
     2. Give IV cosyntropin
     3. Obtain 30 minute cortisol
     4. Obtain 60 minute cortisol

Cosyntropin Stimulation Test

- Annane et al. completed a prospective cohort study looking at risk factors associated with 28 day mortality (n=189)
  - Factors associated with increased mortality
    - APACHE II score > 55
    - MAP < 60 mmHg
    - Arterial lactate > 2.8 mmol/L
    - PaO_2:FiO_2 < 160 mmHg
    - **Random cortisol level < 34 mcg/dL**
    - **Delta cortisol level < 9 mcg/dL**

Annane *et al. Am J Respir Crit Care Med.*2006;174:1319-1326

Adrenal Insufficiency During Septic Shock

- Marik et al. conducted a study that gave patients admitted to the MICU low dose (1 mcg) ACTH stimulation test followed by high dose (249 mcg) 60 minutes later (n=59)
  - Hydrocortisone 100mg IV q8h was started after the test
  - Steroids were discontinued if baseline cortisol was > 25 mcg/dL or delta cortisol > 18 mcg/dL
  - Steroid responsiveness: discontinuing norepinephrine for MAP > 65 mmHg within 24 hours of steroid use
- Results
  - Patients who were steroid responsive:
    - 95% had a cortisol < 25 mcg/ml
    - 54% had a diagnostic low dose ACTH test
    - 22% had a diagnostic high dose ACTH test

Marik PE *et al. Crit Care Med.* 2003;31 (1):141-145

Total vs. Free Cortisol Levels

- 90% of circulating cortisol is bound to protein (i.e. corticosteroid-binding globulin and albumin)
  - During critical illness elastase secreted from neutrophils at the site of inflammation cleave corticosteroid-binding globulin contributing to higher cortisol levels

- In a study looking at critically ill patients it was noted that patients had elevated glucocorticoid secretion that was not detectable when measuring serum cortisol but free cortisol was increased 7 to 10 fold

- Need to be careful interpreting total cortisol levels in patients with hypoproteinemia

Arafah *et al. J Clin Endocrinol Metab*. 2006;91(10):3725-45

Limitations of Tests

- Critically-ill patients have high baseline and cosyntropin stimulated cortisol levels
- Variable data on diagnostic values used in studies
  - Due to this the incidence of adrenal dysfunction ranges from 0 to 60%
- Diagnostic tests can over diagnosis the occurrence of adrenal insufficiency
  - ~40% of patients would not respond to consyntropin stimulation test and still recover from there illness without glucocorticoid therapy
- Reproducibility of the tests
  - ~50% of patients may have a positive cosyntropin test one day and a negative test the next
- Effects of hypoproteinemia

Arafah *et al. J Clin Endocrinol Metab*. 2006;91(10):3725-45

SCCM and ESICM Recommendations-2017

- No recommendation regarding whether to use delta cortisol or a random plasma cortisol for the diagnosis of CIRCI

- Suggest against using plasma free cortisol level rather than plasm total cortisol level for diagnosis
  - Conditional recommendation, very low quality of evidence
- Suggest that the high dose cosyntropin (250 mcg) rather than the low-dose (1 mcg) be used for diagnosis of CIRCI
  - Conditional recommendation, low quality of evidence
- Suggest the use of the ACTH stimulation test rather than the hemodynamic response to hydrocortisone for the diagnosis of CIRCI
  - Conditional recommendation, very low quality of evidence

Sepsis and Septic Shock

Sepsis and Septic Shock

- Sepsis
  - Life-threatening organ dysfunction caused by a dysregulated host response to infection
- Septic shock
  - Vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolemia
- Treatment
  - Antibiotics
  - Fluids
  - Vasopressors
  - Steroids

Role of Steroids in Septic Shock

- Glucocorticoids in sepsis play a beneficial role by:
  - Inhibiting of cytokine production
  - Preventing of migration of circulating inflammatory cells into tissues
  - Enhancing vasoactive tone
  - Increasing catecholamine responsiveness

Preventing Septic Shock

- The HYPRESS trial was conducted to compare hydrocortisone to placebo in the prevention of septic shock (n=353)
  - Hydrocortisone 200 mg IV as a continuous infusion followed by a taper

- Endpoints:
  - Development of septic shock within 14 days
  - Time until development of septic shock
  - ICU and hospital mortality
  - Need for mechanical ventilation
  - Need for renal replacement therapy

Keh D *et al. JAMA.* 2016;316 (17):1775-1785

Results

	Placebo (n=170)	Hydrocortisone (n=170)	p-value
Development of septic shock, n (%)	39 (22.9)	36 (21.2)	0.70
ICU mortality, n (%)	14 (8.1)	13 (7.6)	0.85
Hospital mortality, n (%)	22 (12.8)	23 (13.5)	0.86
Mechanical ventilation, n (%)	103 (59.9)	91 (53.2)	0.21
RRT, n (%)	21 (12.2)	21 (12.3)	0.98

Annane D *et al. JAMA*. 2002;288 (7):862-871

Results

- Cosyntropin stimulation test was performed on 206 patients in the HYPRESS trial
  - Diagnosed with CIRCI: 69/206 (33.5%)
  - Septic shock in placebo group
    - With CIRCI: 27%
    - Without CIRCI: 13.6%, p=0.09
  - There was no significant difference in any endpoint when comparing patients with or without CIRCI who received hydrocortisone or placebo

Annane D *et al. JAMA*. 2002;288 (7):862-871

SCCM and ESICM Recommendations-2017

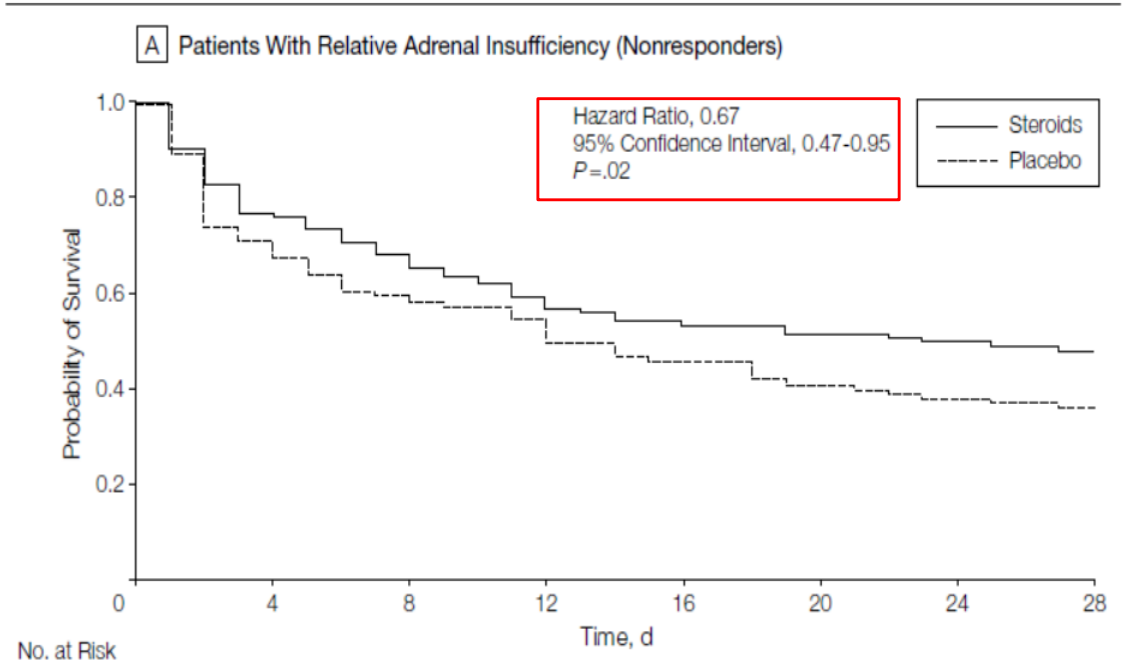
- Suggest against corticosteroid administration in adult patients with sepsis without shock
  - Conditional recommendation, moderate quality of evidence

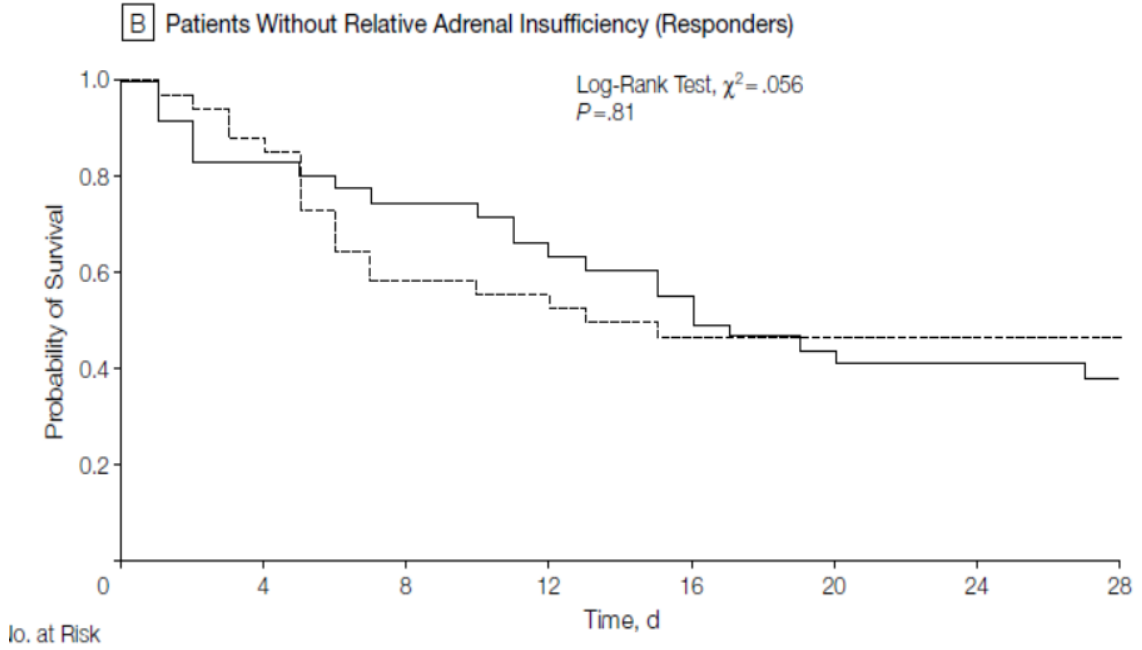
Low Dose Hydrocortisone and Fludrocortisone in Septic Shock

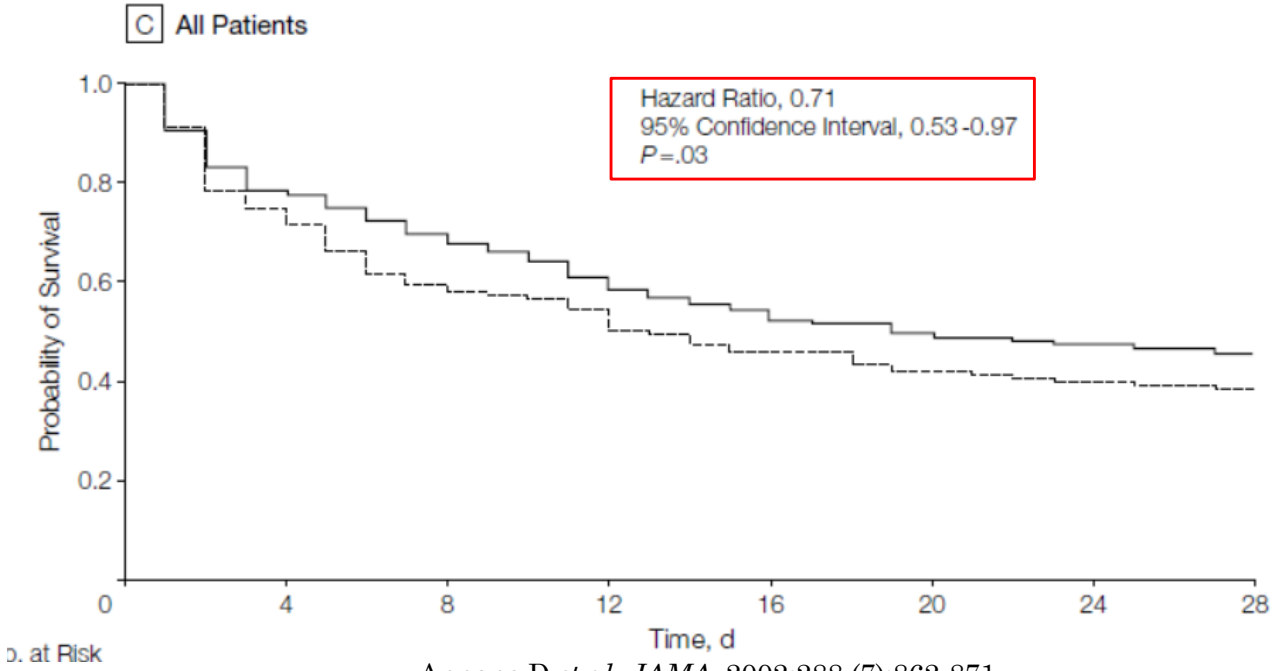
- Annane et al. completed a randomized, placebo controlled, double blinded study comparing the combination of hydrocortisone with fludrocortisone to placebo in patients with septic shock (n=299)
  - Hydrocortisone 50 mg IV q6h + Fludrocortisone 50 mcg PO daily
  - Treatment was continued for 7 days
  - All patients in the study received the cosyntropin stimulation test

- Endpoints
  - 28-day survival
  - ICU, hospital, and 1-year mortality
  - Time until vasopressor therapy withdrawal

Annane D *et al. JAMA*. 2002;288 (7):862-871







Annane D *et al. JAMA*. 2002;288 (7):862-871

	Non-responders		Responders		Total	
	Placebo (n=115)	Corticosteroids (n=114)	Placebo (n=34)	Corticosteroids (n=36)	Placebo (n=149)	Corticosteroids (n=150)
ICU mortality, n (%)	81 (70)	66 (58)*	20 (59)	24 (67)	101 (68)	90 (60)
Hospital mortality, n (%)	83 (72)	70 (61)*	20 (59)	25 (69)	103 (69)	95 (63)
1-year mortality, n (%)	88 (77)	77 (68)*	24 (71)	25 (69)	112 (75)	102 (68)
Time-to-vasopressor withdrawal, d	10	7*	7	9	9	7*

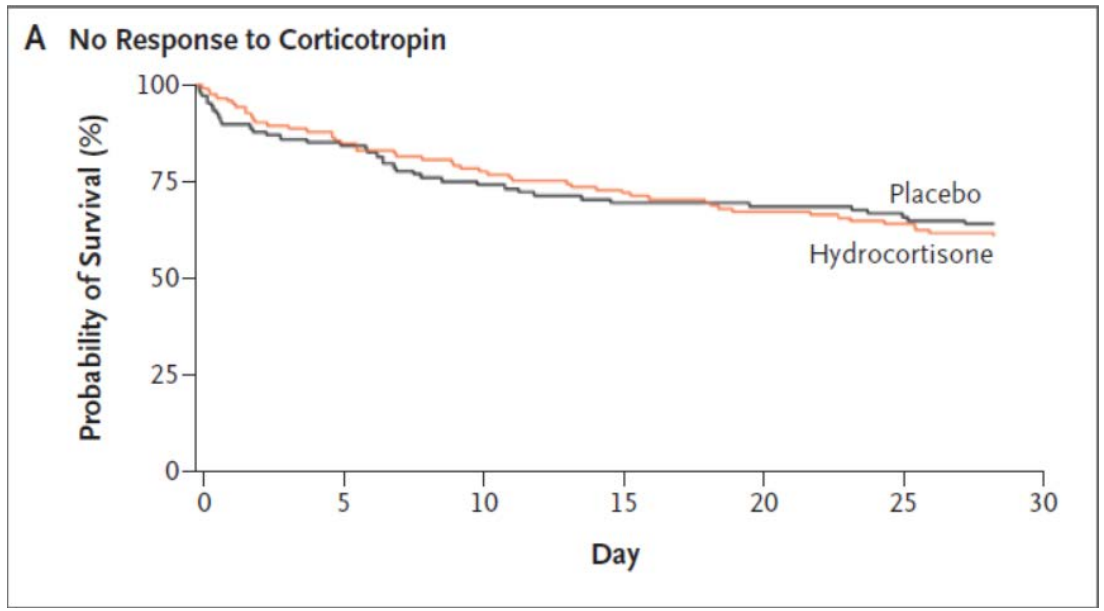
*p<0.05

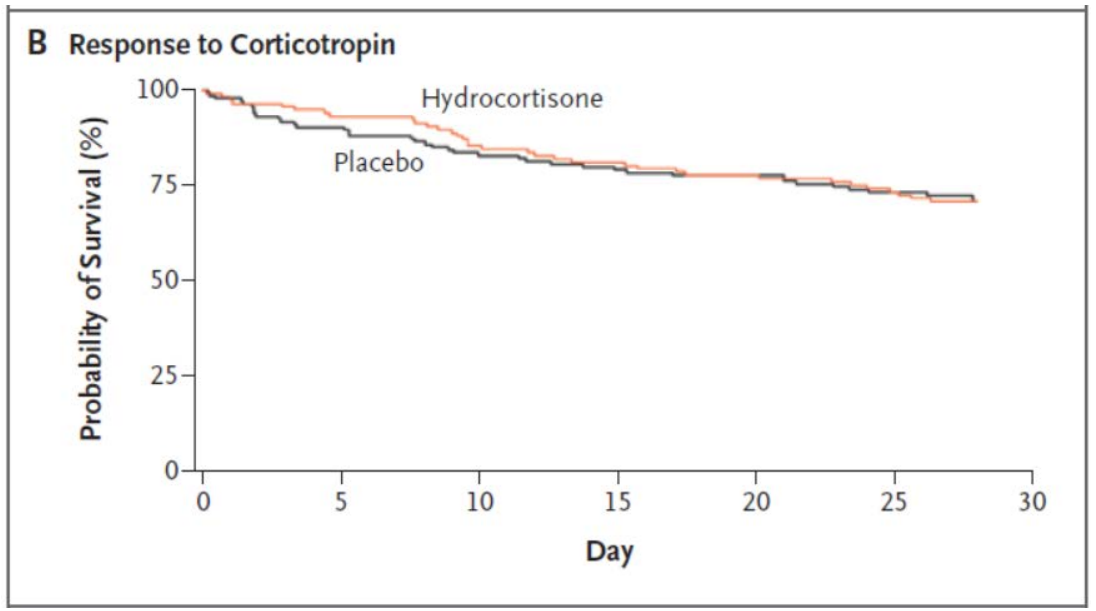
Annane D *et al. JAMA*. 2002;288 (7):862-871

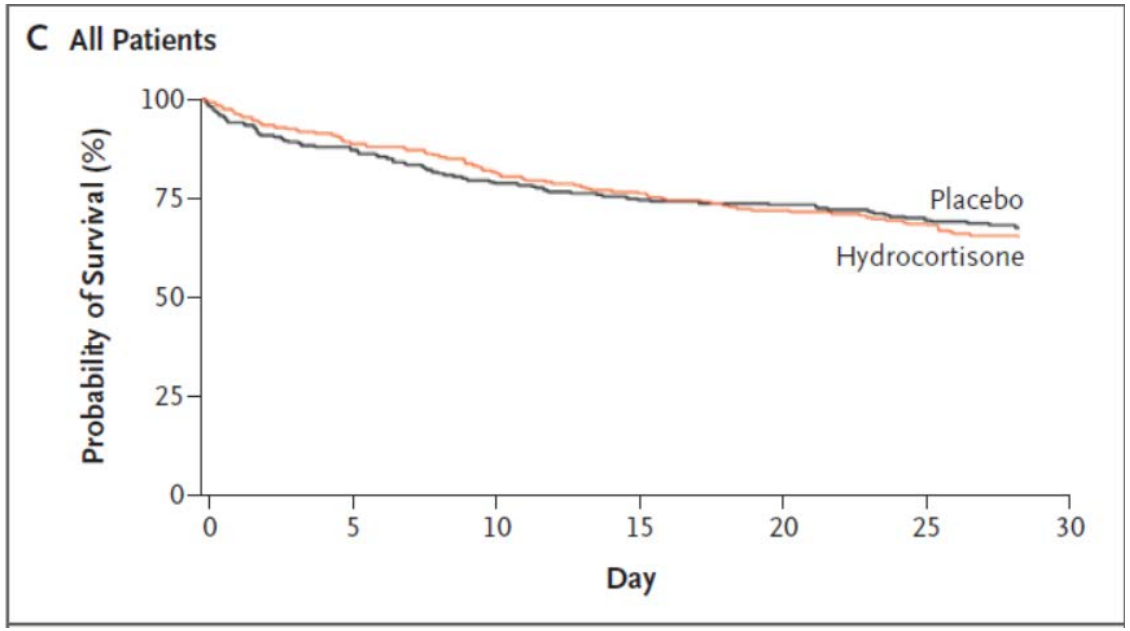
CORTICUS Trial

- Sprung et al. conducted a multicenter, randomized, double-blind, placebo-controlled trial comparing hydrocortisone to placebo in patients with septic shock (n=499)
  - Hydrocortisone 50mg IV q6h x 5 days, then tapered off for a total of 11 days of steroids
  - All patients underwent a cosyntropin stimulation test
- Endpoints
  - 28 day mortality
  - ICU, hospital, and 1-year mortality rates
  - Reversal of organ system failure
  - ICU and hospital LOS

Sprung CL *et al. NEJM,* 2008;358:111-24







Sprung CL *et al. NEJM,* 2008;358:111-24

	Non-responders		Responders		Total	
	Placebo (n=108)	Hydrocortisone (n=125)	Placebo (n=136)	Hydrocortisone (n=118)	Placebo (n=248)	Hydrocortisone (n=251)
ICU mortality, n (%)	44 (40.7)	58 (46.4)	45 (33.3)	41 (34.7)	89 (36)	102 (40.6)
Hospital mortality, n (%)	50 (46.3)	60 (48)	50 (37.6)	48 (40.7)	100 (40.8)	111 (44.2)
1-year mortality, n (%)	60 (57.1)	73 (58.9)	67 (53.2)	61 (55)	127 (54)	137 (56.6)
Time to shock reversal, d	6	3.9*	5.8	2.8*	5.8	3.3*

*$p < 0.05$

Sprung CL *et al. NEJM,* 2008;358:111-24

Comparing Trials

	Annane	CORTICUS
SAPS II (placebo/treatment)	57/60	49/50
Received etomidate	Excluded*	96
Control group mortality	61%	31.5%
Cosyntropin non-responders	77%	47%
Admission category: medical	60%	35%
Hospital acquired infection	16%	61%
Study powered	Yes	No

Corticosteroids for Treating Sepsis

- A meta-analysis was completed in 2015 that included 33 studies looking at the use of steroids in sepsis (n=4268)
- The analysis showed that corticosteroids resulted in:
  - Reduced 28 day mortality (RR=0.87, p=0.05)
  - Reduced ICU mortality (RR=0.82, p=0.04) and in-hospital mortality (RR=0.85, p=0.03)
  - Increased the proportion of shock reversal by day 7 (RR=1.31, p=0.0001)
  - Decreased survivors' length of stay in the ICU by 2.19 days
  - Had no effect on gastroduodenal bleeding (RR=1.24, p=0.15) or superinfections (RR=1.02, p=0.81)
  - Increased the risk of hyperglycemia (RR=1.26, p<0.00001)

Annane D *et al. Cochrane Database Syst Rev.* 2015;12

SCCM and ESICM Recommendations-2017

- Suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy
  - Conditional recommendation, low quality of evidence

- If using corticosteroids for septic shock, they suggest using long course and low dose (IV hydrocortisone < 400 mg/day for at least ≥ 3 days at full dose) rather than high dose and short course
  - Conditional recommendation, low quality of evidence

Acute Respiratory Distress Syndrome (ARDS)

Acute Respiratory Distress Syndrome (ARDS)

- Inflammatory injury to the lung that is characterized by acute hypoxemic respiratory failure
  - Early exudative phase followed by proliferative and fibrotic phase
- Diagnosis
  - Onset within 7 days of a defined event
  - Bilateral opacities on chest x-ray
  - Respiratory failure not fully explained by cardiac failure or fluid overload
- Classifications

	PaO_2:FiO_2 ratio	Mortality
Mild	200-300	27%
Moderate	100-200	32%
Severe	< 100	45%

Fanelli V *et al. J Thorac Dis.* 2013;5 (3):326-334

ARDS Treatment Options

- Protective mechanical ventilation
- Prone positioning
- High frequency oscillatory ventilation
- Extracorporeal membrane oxygenation
- Neuromuscular blocking agents
- Steroids

Fanelli V *et al. J Thorac Dis.* 2013;5 (3):326-334

Corticosteroids for Persistent ARDS

- ARDS net group conducted a multicenter randomized controlled trial to determine the efficacy and safety of corticosteroids in ARDS (n=180)
  - Methylprednisolone vs. placebo
    - 2 mg/kg x 1, followed by 0.5 mg/kg q6h for 14 days, followed by 0.5 mg/kg q12h for 7 days

- Endpoints
  - 60 day mortality
  - Ventilator free days
  - Days without organ failure
  - Infectious complications

Steinber KP *et al. NEJM.* 2006;354:1671-84

Results

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
60-Day mortality (%)	28.6	29.2	1.0
95% CI	20.8–38.6	20.8–39.4	
No. of ventilator-free days at day 28	6.8±8.5	11.2±9.4	<0.001
No. of organ-failure–free days			
Cardiovascular failure	17.9±10.2	20.7±8.9	0.04
Coagulation abnormalities	22.1±8.6	22.2±8.3	0.84
Hepatic failure	21.4±10.2	21.2±10.2	0.70
Renal failure	21.4±10.2	22.8±8.7	0.36
No. of ICU-free days at day 28	6.2±7.8	8.9±8.2	0.02
60-Day mortality according to time from ARDS onset			
7–13 Days (%)	36	27	0.26
No. of patients	66	66	
>14 Days (%)†	8	35	0.02
No. of patients	25	23	

Results

- Resuming ventilator assistance
  - Methylprednisolone: 20 patients
  - Placebo: 6 patients (p=0.008)
- Significant improvement in the PaO_2:FiO_2 with the use of methylprednisolone
- Significant decrease in plateau pressures with methylprednisolone
- No difference in the development of infection between the groups
- Conclusion
  - Methylprednisolone had no beneficial effect on survival and when initiated more than 2 weeks after onset of ARDS was associated with increased mortality

Steinber KP *et al. NEJM.* 2006;354:1671-84

Methylprednisolone in Early Severe ARDS

- A randomized controlled trial conducted by Meduri et al. looked at the use of methylprednisolone within the first 72 hours of ARDS (n=91)
  - All patients underwent a cosyntropin stimulation test
  - Methylprednisolone 1 mg/kg/day for 14 days followed by taper until day 28

- Endpoints
  - Improvement in lung injury score (LIS)
  - Improvement in PaO_2:FiO_2 ratio
  - Duration of mechanical ventilation
  - ICU length of stay
  - ICU mortality
  - Hospital mortality

Meduri GU *et al. CHEST.* 2007;131:954-963

Results

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Extubated or with ≥ 1-point reduction in LIS	44 (69.8)	10 (35.7)	1.96 (1.16–3.30)	0.002
Patients breathing without assistance	34 (54.0)	7 (25.0)	2.16 (1.09–4.26)	0.01
LIS† (mean ± SE)	2.14 ± 0.12	2.68 ± 0.14		0.004
Pao_2/Fio_2 ratio in ventilated patients (mean ± SE)	256 ± 19	179 ± 21		0.006
PEEP, cm H_2O	10.1 ± 4.6	12.9 ± 5.3		0.10
Mechanical ventilation-free days‡	2.2 ± 2.1	1.1 ± 1.9		0.02
MODS score†§	0.90 ± 1.1	1.9 ± 1.4		0.002
Patients with MODS score > 1	33 (54.1)	23 (85.2)	0.64 (0.48–0.84)	0.005
C-reactive protein level, mg/dL	2.9 ± 4.1	13.1 ± 6.8		< 0.0001
Cortisol level, μg/dL	5.7 ± 2.1	18.0 ± 1.6		< 0.0001
Patients with new infection‖	10 (15.9)	8 (28.6)	0.56 (0.25–1.26)	0.16
Patients with ventilator-associated pneumonia	4 (6.4)	6 (21.4)	0.30 (0.09–0.97)	0.06
Survivors	56 (88.9)	22 (78.6)	1.13 (0.92–1.40)	0.21
Patients with unresolving ARDS treated with open-label methylprednisolone at 2 mg/kg/d¶	5 (7.9)	10 (35.7)	0.22 (0.08–0.59)	0.002

Meduri GU *et al. CHEST.* 2007;131:954-963

Results

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Duration of mechanical ventilation, d†	5 (3–8)	9.5 (6–19.5)		0.002
Mechanical ventilation-free days to day 28‡	16.5 ± 10.1	8.7 ± 10.2		0.001
Length of ICU stay, d	7 (6–12)	14.5 (7–20.5)		0.007
Survivors of ICU admission	50 (79.4)	16 (57.4)	1.39 (0.98–1.96)	0.03
Length of hospital stay	13.0 (8–21)	20.5 (10.5–40.5)		0.09
Survivors of hospital admission	48 (76.2)	16 (57.1)	1.33 (0.94–1.89)	0.07

- Conclusion:
  - Glucocorticoid treatment induced down-regulation of systemic inflammation in ARDS resulting in an improvement in pulmonary dysfunction and reduction in duration of mechanical ventilation and ICU length of stay

Meduri GU *et al. CHEST.* 2007;131:954-963

Corticosteroids in Septic Shock with or without ARDS

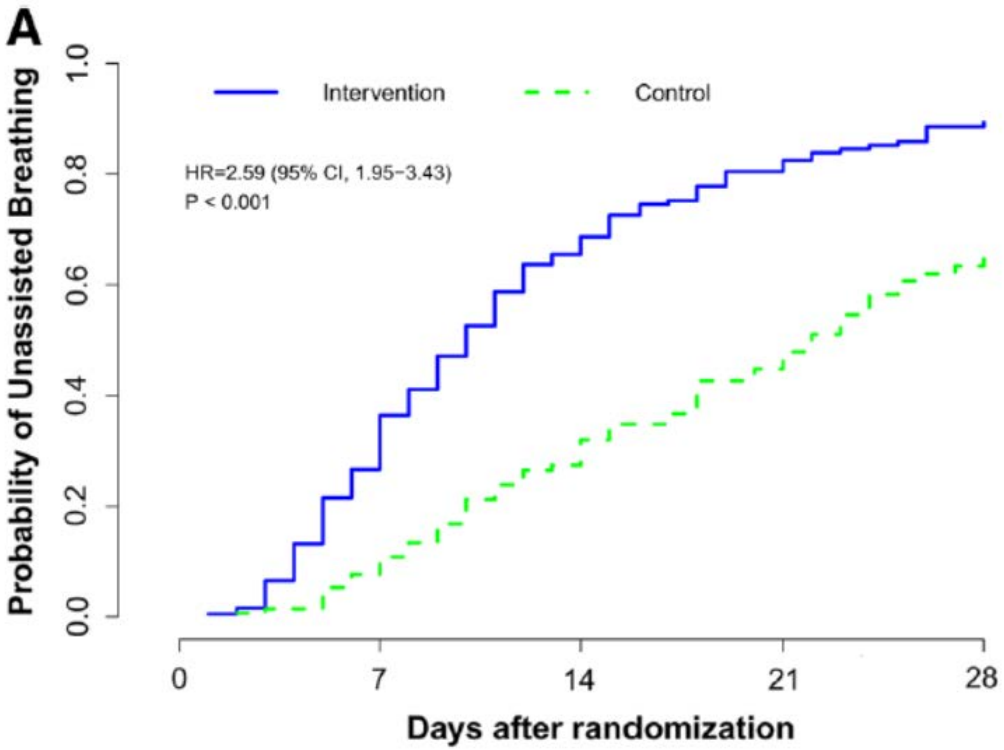
- Annane et al. conducted a post-hoc analysis of their previous study that compared hydrocortisone combined with fludrocortisone to placebo in patients with septic shock (n=177)
  - 177 of the initial 299 patients met the criteria for ARDS
- Endpoints
  - 28 day, ICU, and hospital mortality
  - Days alive and off the ventilator
  - Evolution of PaO_2:FiO_2
  - Circulating cytokine levels

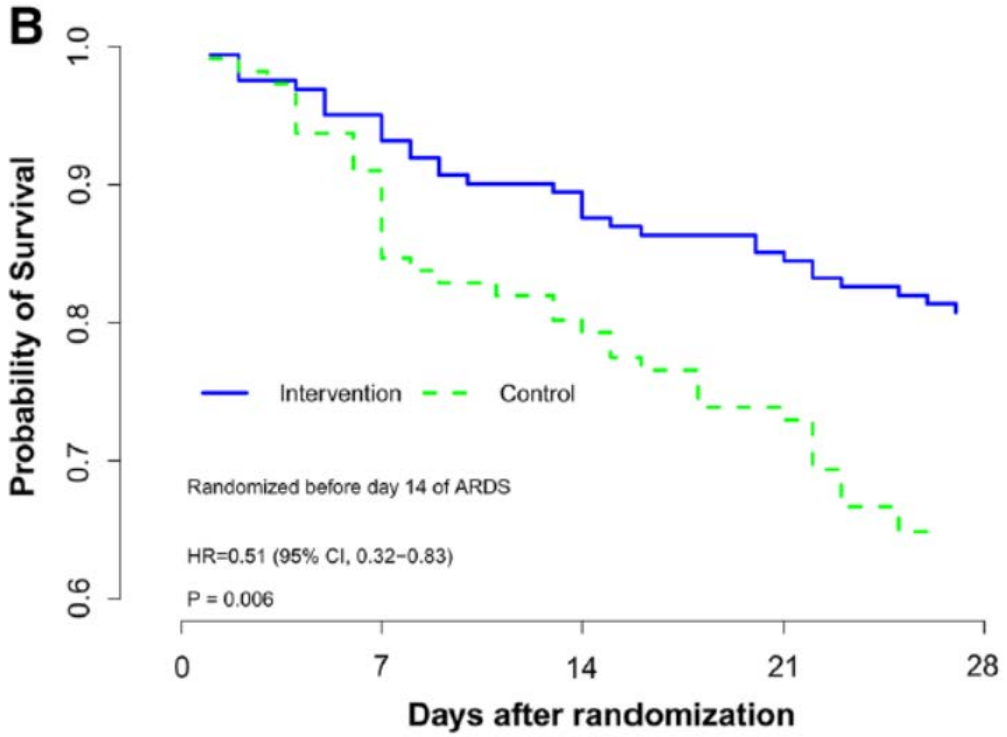
Annane D *et al. Crit Care Med* 2006;34 (1):22-30

Results for patients with ARDS

	Non-responders		Responders		Total	
	Placebo (n=67)	Corticosteroids (n=62)	Placebo (n=25)	Corticosteroids (n=23)	Placebo (n=92)	Corticosteroids (n=85)
28-day mortality, n (%)	50 (75)	33 (53)*	12 (48)	16 (70)	62 (67)	49 (58)
ICU mortality, n (%)	53 (79)	36 (58)*	14 (56)	17 (74)	67 (73)	53 (62)
Hospital mortality, n (%)	53 (79)	37 (60)*	14 (56)	17 (74)	67 (73)	54 (64)
Ventilator free days	2.6 ± 6.6	5.7 ± 8.6*	4.6 ± 7.6	2.8 ± 7.5	3.1 ± 6.9	4.9 ± 8.4
*p<0.05						

Annane D *et al. Crit Care Med* 2006;34 (1):22-30





Annane D *et al. Crit Care Med* 2006;34 (1):22-30

Results

- Cytokine levels
  - IL-6 plasma levels were significantly higher in non-responders
  - IL-6 levels decreased over 7 days in non-responders and values were significantly lower in the steroid group
- Conclusion
  - The use of hydrocortisone combined with fludrocortisone for 7 days improves 28-day, ICU, and hospital mortality as well as reducing duration of mechanical ventilation in patients with septic shock associated early ARDS who fail to respond to cosyntropin stimulation test

Annane D *et al. Crit Care Med* 2006;34 (1):22-30

Prolonged Glucocorticoid Treatment in Patients with ARDS

- Meduri et al. conducted an individual patient data analysis of four RCT's that used methylprednisolone for the treatment of ARDS (n=322)
  - Early vs. late initiation of steroids
  - Slow vs. rapid taper of steroids
- Endpoints
  - Time to successful removal of assisted breathing
  - Mechanical ventilation free days
  - ICU free days
  - Hospital mortality

Meduri GU *et al. Intensive Care Med.* 2016;42:829-840

Results

	Methylprednisolone (n=186)	Placebo (n=136)	p-value
Time until extubation, d	12.9 ± 13.4	23 ± 13.9	<0.001
MV free days	13.3 ± 11.8	7.6 ± 5.7	<0.001
Achieved extubation by day 28, n (%)	149 (80)	68 (50)	<0.001
ICU free days	10.8 ± 0.71	6.4 ± 6.4	<0.001
Hospital mortality	37 (20)	45 (33)	0.006
Mortality prior to extubation, n (%)	23 (12)	39 (29)	<0.001

Meduri GU *et al. Intensive Care Med.* 2016;42:829-840

Prolonged Glucocorticoid Treatment in Patients with ARDS

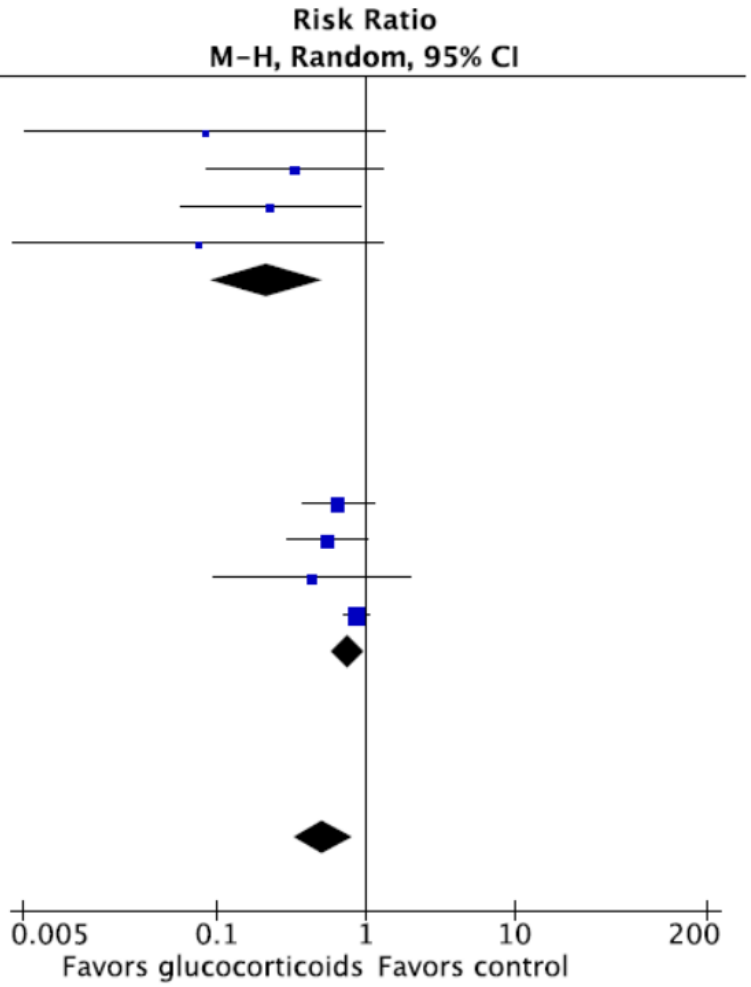
- Meduri et al. additionally completed a meta-analysis of the first four RCT's in addition to an additional four RCT's that used hydrocortisone for the treatment of ARDS (n=619)

- Glucocorticoid treatment was associated with:
  - Increase in mechanical ventilation free and ICU free days
  - Reduced risk of in-hospital mortality (29 vs. 45%, RR=0.56, p=0.009)
  - Reduced risk of mortality when randomized within 14 days (20 vs 48%, RR=0.52, p=0.006)
  - No increased risk of nosocomial infections

Meduri GU *et al. Intensive Care Med.* 2016;42:829-840

Results

Study or Subgroup	Glucocorticoids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Less than 60 patients						
Confalonieri, 2005 [11]	0	15	7	19	2.5%	0.08 [0.01, 1.35]
Liu, 2012 [14]	2	12	7	14	8.3%	0.33 [0.08, 1.31]
Meduri, 1998 [8]	2	14	5	8	8.1%	0.23 [0.06, 0.92]
Rezk, 2013 [7]	0	18	3	9	2.4%	0.08 [0.00, 1.32]
Subtotal (95% CI)		**59**		**50**	**21.3%**	**0.22 [0.09, 0.52]**
Total events	4		22			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.47$, df = 3 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 3.41 (P = 0.0006)						
1.1.2 More than 60 patients						
Annane, 2006 [12]	15	66	23	66	21.6%	0.65 [0.37, 1.13]
Meduri, 2007 [6]	15	63	12	28	20.2%	0.56 [0.30, 1.03]
Sabry, 2011 [13]	2	26	6	34	7.1%	0.44 [0.10, 1.99]
Steinberg, 2006 [9]	54	85	67	92	29.7%	0.87 [0.71, 1.07]
Subtotal (95% CI)		**240**		**220**	**78.7%**	**0.76 [0.59, 0.98]**
Total events	86		108			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.62$, df = 3 (P = 0.31); $I^2 = 17\%$						
Test for overall effect: Z = 2.11 (P = 0.03)						
Total (95% CI)		**299**		**270**	**100.0%**	**0.52 [0.33, 0.83]**
Total events	90		130			
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 15.64$, df = 7 (P = 0.03); $I^2 = 55\%$						
Test for overall effect: Z = 2.75 (P = 0.006)						
Test for subgroup differences: $Chi^2 = 7.23$, df = 1 (P = 0.007), $I^2 = 86.2\%$						



SCCM and ESICM Recommendations-2017

- Suggest the use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO_2:FiO_2 < 200 and within 14 days of onset)
  - Conditional recommendation, moderate quality of evidence

Methylprednisolone treatment of early severe ARDS and late unresolving ARDS

Early severe ARDS (PaO_2:FiO_2 < 200 on PEEP 5 cmH_20)

Time	Administration form	Dosage
Loading	Bolus over 30 min	1 mg/kg
Days 1 to 14* † ‡ ¶	Infusion at 10 cc/hour	1 mg/kg/day
Days 15 to 21* ‡ ¶	Infusion at 10 cc/hour	0.5 mg/kg/day
Days 22 to 25* ‡ ¶	Infusion at 10 cc/hour	0.25 mg/kg/day
Days 26 to 28* ‡ ¶	Infusion at 10 cc/hour	0.125 mg/kg/day

Unresolving ARDS = less than (a) 1-point reduction in lung injury score or (b) or 100 improvement of in PaO_2:FiO_2

- By day 7 of ARDS in patients not receiving methylprednisolone for early ARDS.
- By day 5-7 of ARDS in patients receiving methylprednisolone (above) for early ARDS.

Time	Administration form	Dosage
Loading	Bolus over 30 min	2 mg/kg
Days 1 to 14*† ‡ ¶	Infusion at 10 cc/hour	2 mg/kg/day
Days 15 to 21* ‡ ¶	Infusion at 10 cc/hour	1 mg/kg/day
Days 22 to 25* ‡ ¶	Infusion at 10 cc/hour	0.5 mg/kg/day
Days 26 to 28* ‡ ¶	Infusion at 10 cc/hour	0.25 mg/kg/day
Days 29 to 28* ‡ ¶	Bolus over 30 min	0.125 mg/kg/day

Comparing Guidelines

	SCCM/ESICM 2008	Surviving Sepsis 2016	SCCM/ESICM 2017
Diagnosis	Not recommended to perform ACTH stim test	No recommendation	ACTH stim test
Steroids in Sepsis	Septic shock not responsive to fluids or vasopressor therapy	Septic shock not responsive to fluids or vasopressor therapy	Septic shock not responsive to fluids or vasopressor therapy
Steroid Dose	50 mg q6h or 10 mg/h for at least 7 days	200 mg/day	<400 mg/day for > 3 days
Steroids in ARDS	Early severe ARDS within the first 14 days	No comment	Early moderate to severe ARDS

Conclusion

- Recommended to use ACTH stimulation test rather than the hemodynamic response to hydrocortisone for the diagnosis of CIRCI
- Corticosteroids should be used in patients with septic shock that is not responsive to fluid and moderate to high-vasopressor therapy
- A low dose and long duration of steroids are recommended if they are to be used in septic shock
- Corticosteroids can be used in patients with early moderate to severe ARDS

Back to the Future: Updated Guidelines for Evaluation and Management of Adrenal Insufficiency in the Critically Ill

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