Corticosteroids for Sepsis:

Rationale and Critical Appraisal of the Literature

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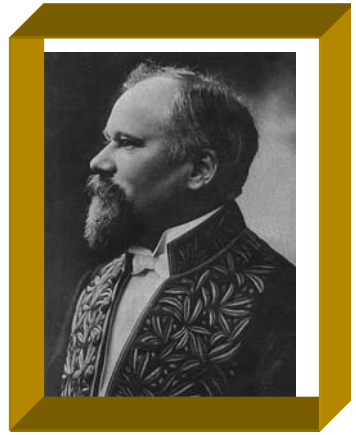


Background

- Systemic inflammation is the **hallmark** of sepsis or ARDS
- Corticosteroids **modulate the immune response** to sepsis through genomic and non-genomic effects
- Cytokines suppress cortisol production or access to tissues, **inducing corticosteroids insufficiency** in almost half of septic shock

Regulation of Inflammation

Two TFs are central to the regulation of inflammation

Stimulatory

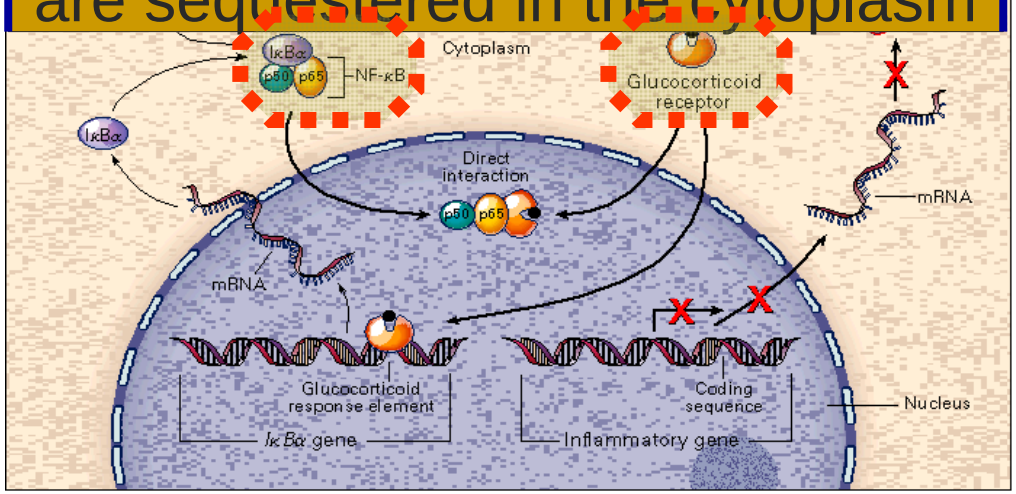
Nuclear Factor-κB

Inhibitory

Glucocorticoid Receptor α

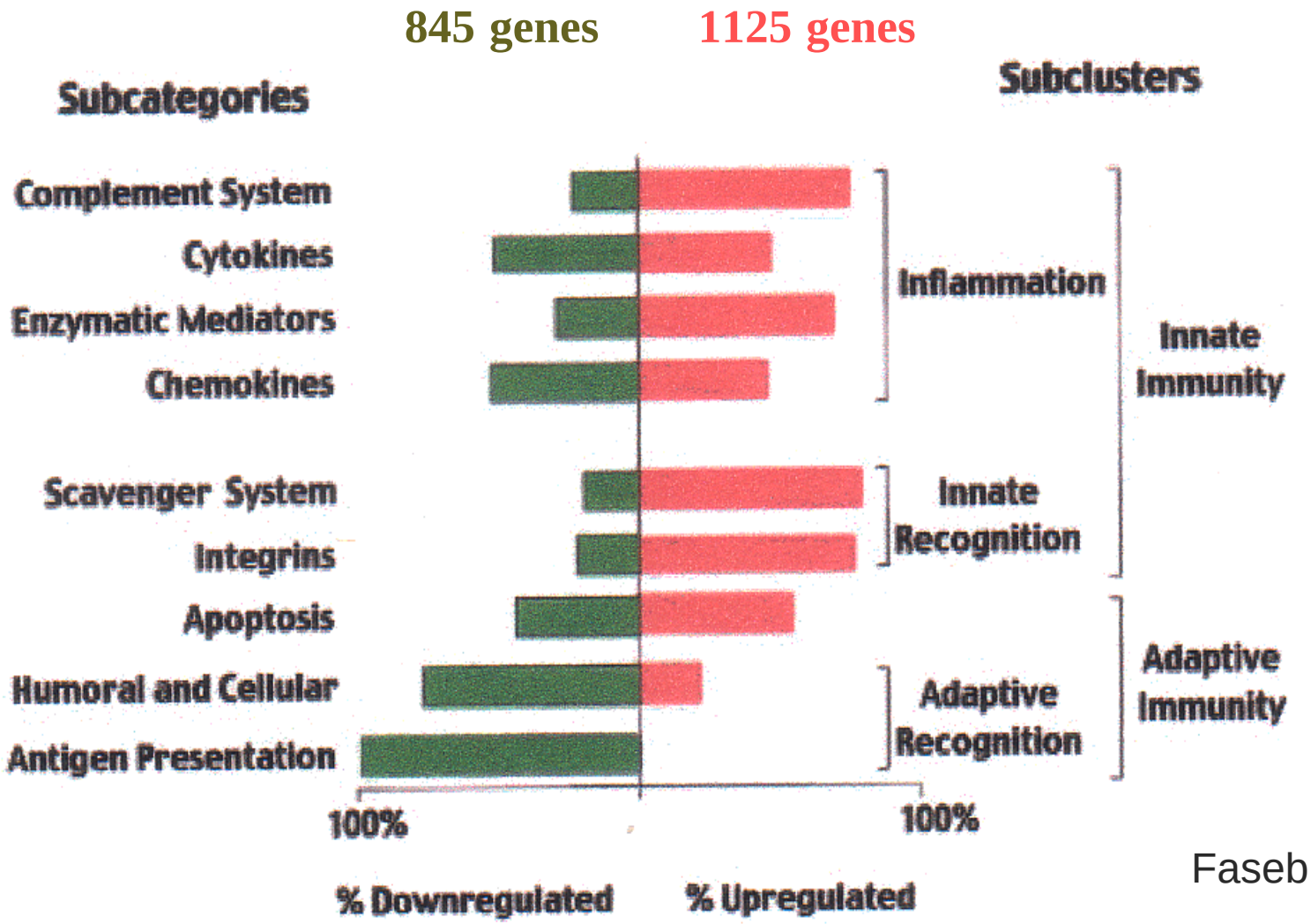
Found in all cells

In unstimulated cells, NF-κB & GRα are sequestered in the cytoplasm



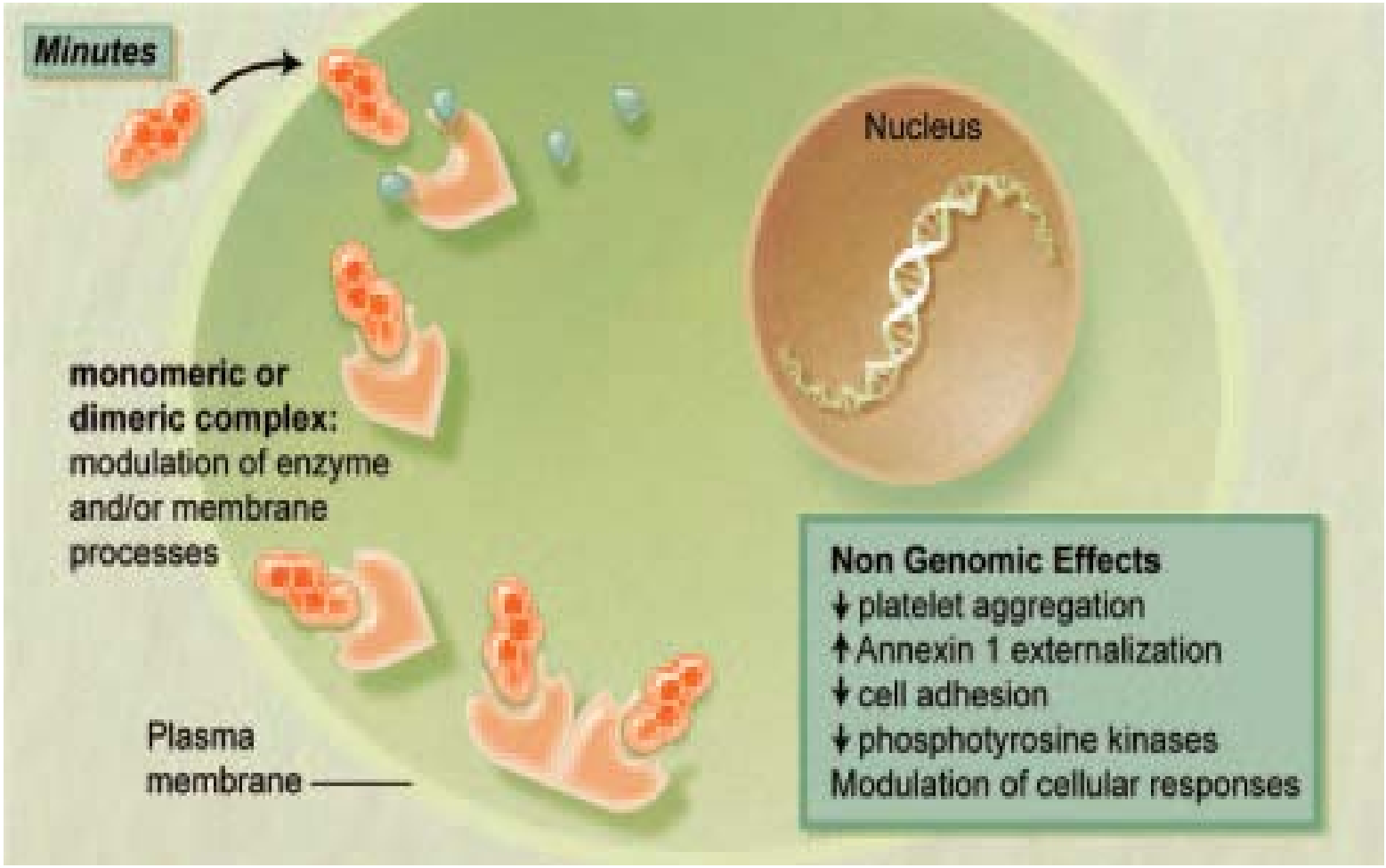
Barnes and Karin. NEJM 1997; 336: 1066.

Reprogrammation rather than suppression!



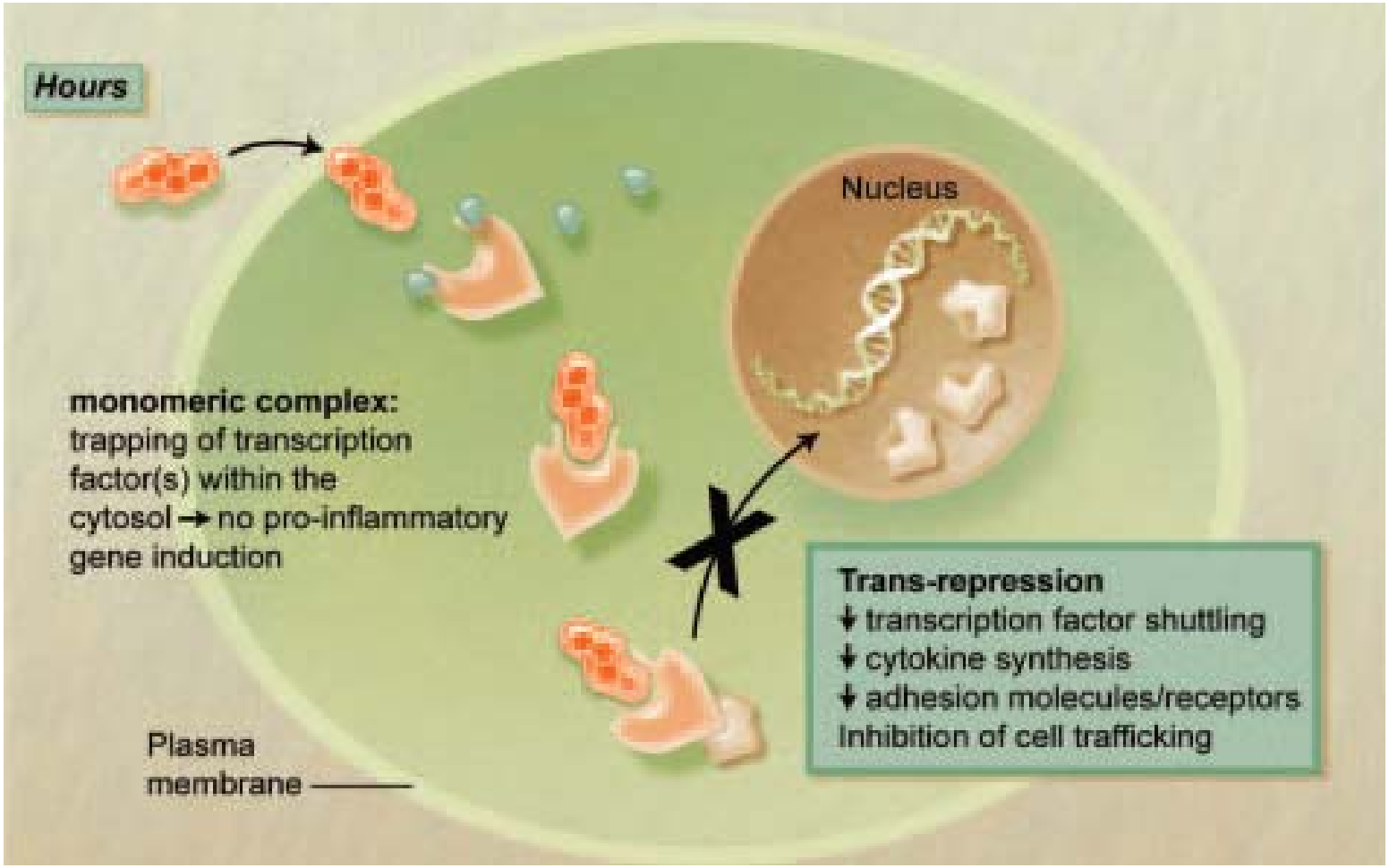
Faseb, 2002

Within minutes!



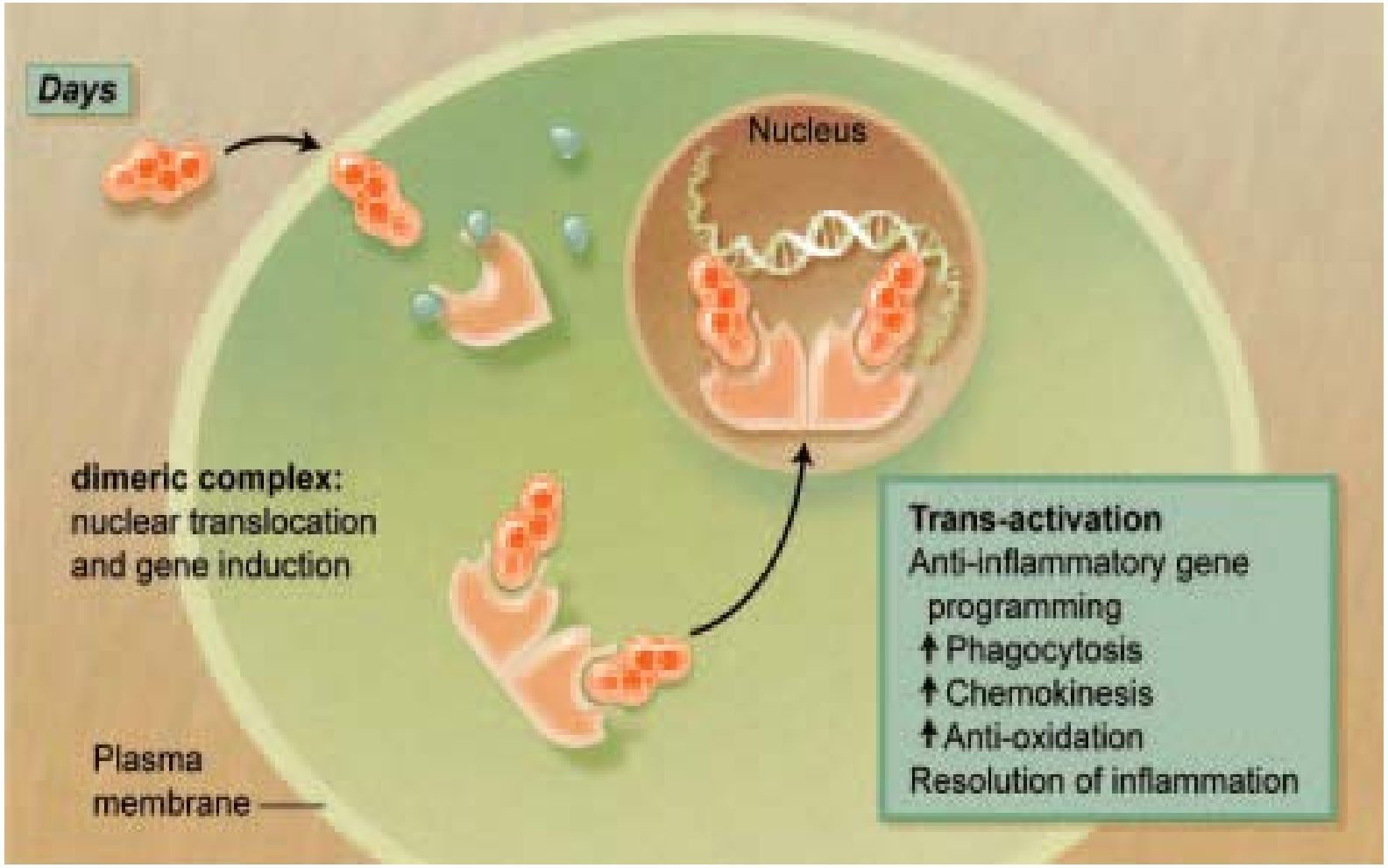
Perreti, Blood 2007

Within hours!



Perreti, Blood 2007

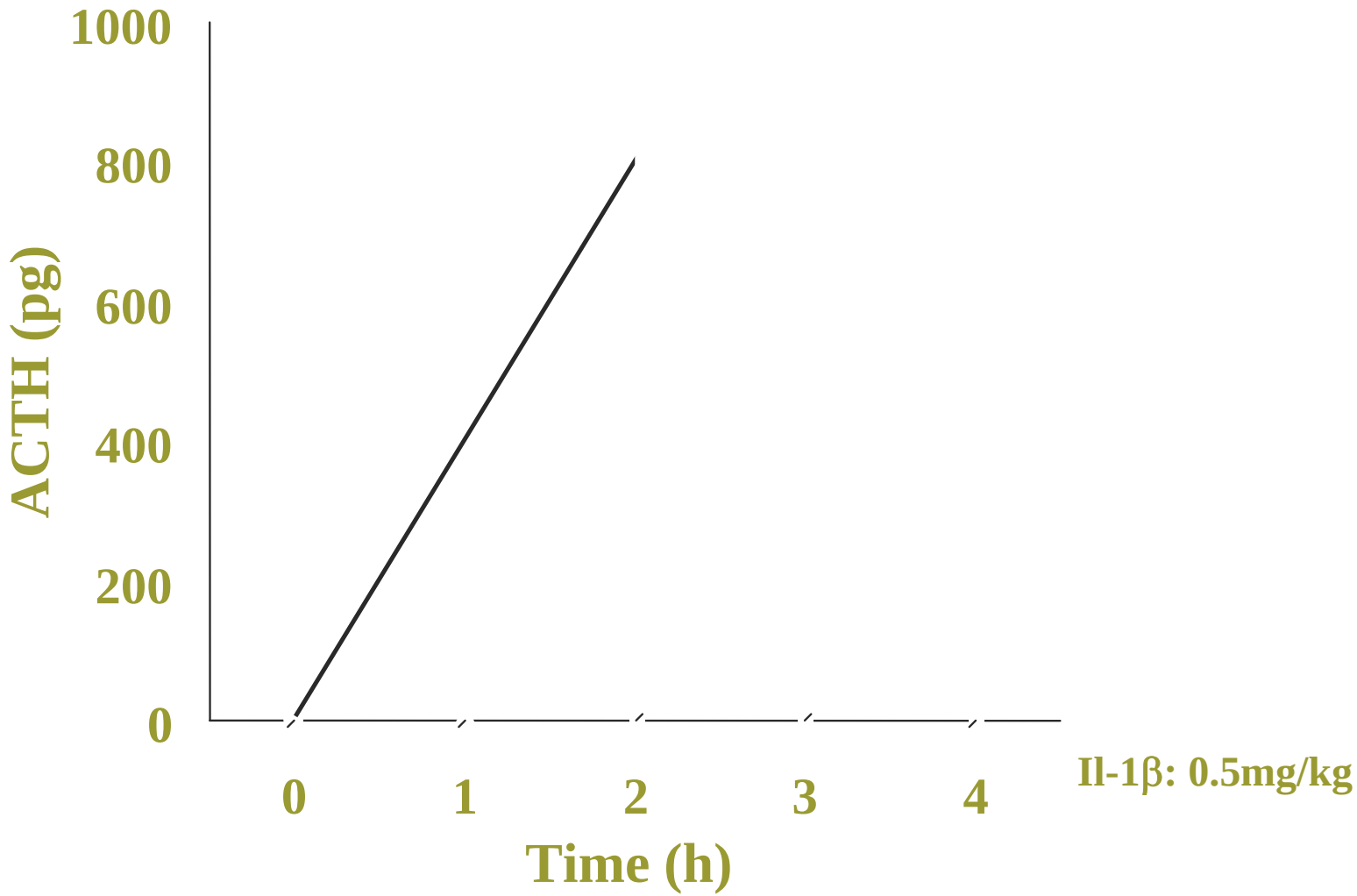
Within days



Perreti, Blood 2007

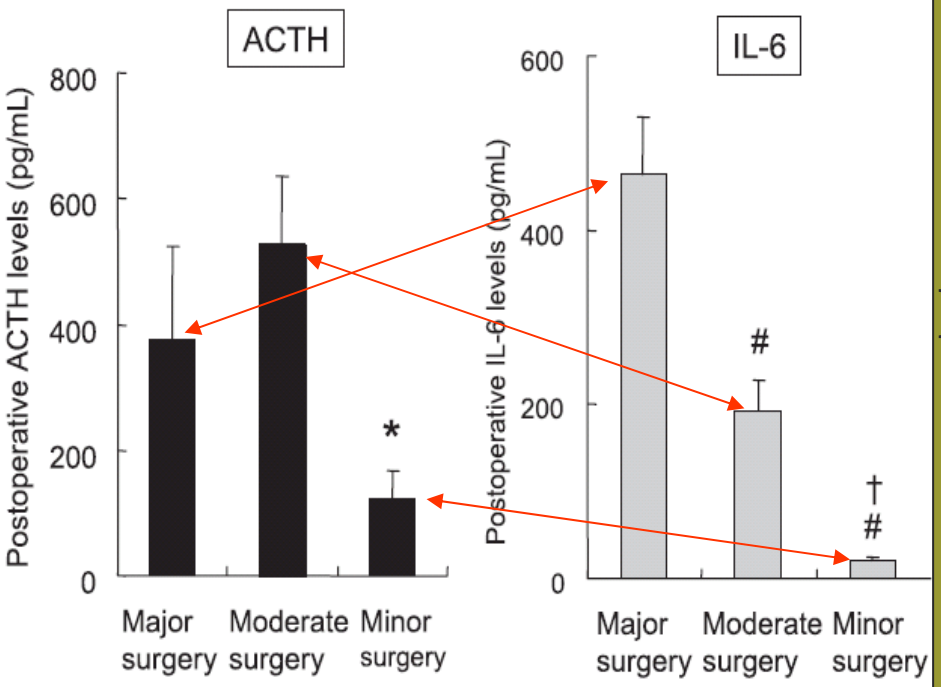
Evidence for an Inappropriate Activation of the HPA axis

Effects of sustained cytokines activation



Surgical Trauma-Induced Adrenal Insufficiency is Associated with Postoperative Inflammatory Responses

Postoperative Inflammatory Responses and Adrenal Insufficiency



Minor surgery: ACTH/IL-6 >1

Moderate surgery ACTH/IL-6 >1

Major surgery ACTH/IL-6 <1

Kashiwabara et al, J Nippon Med Sch 2007

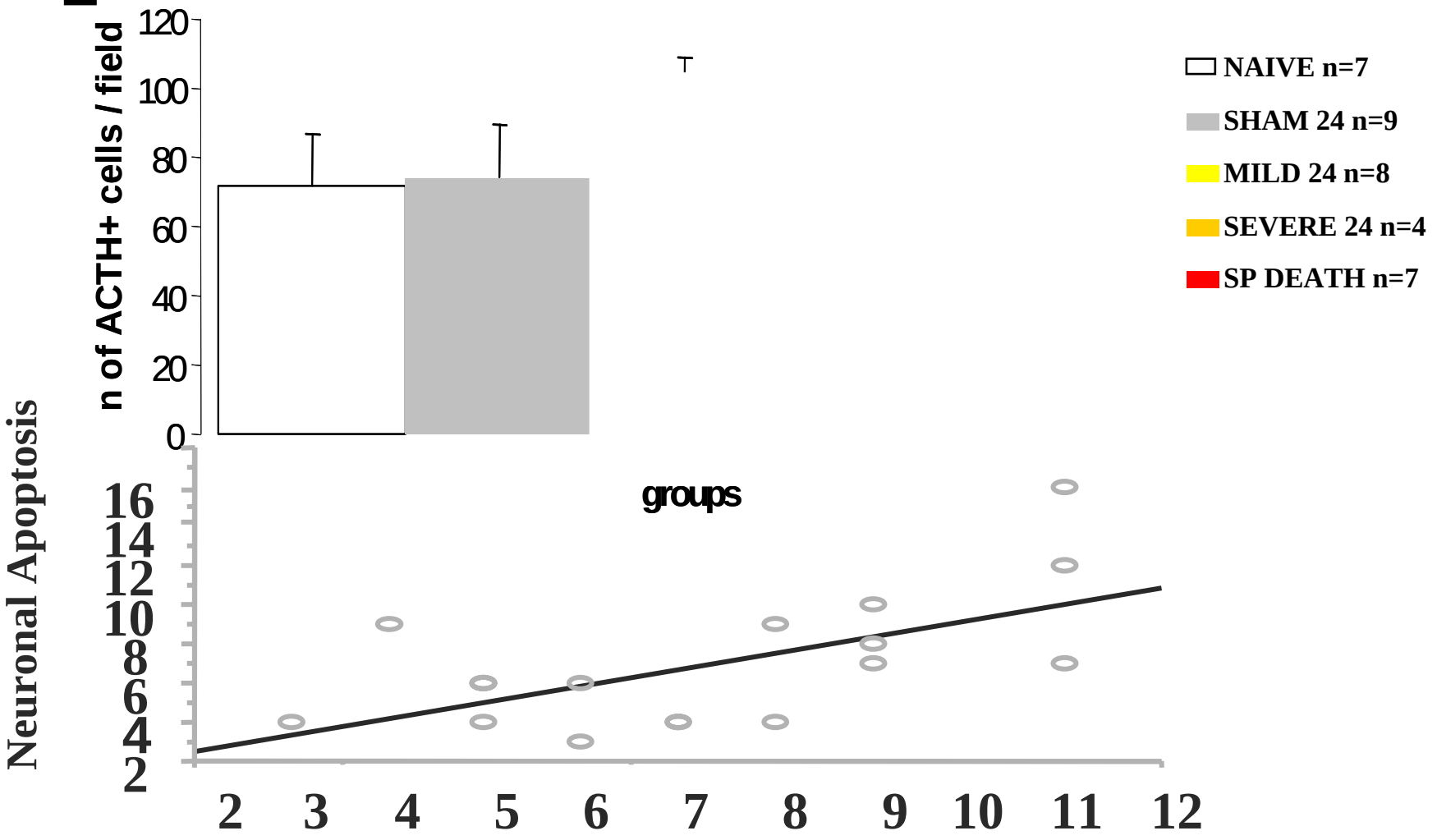
NO plays a major role

FIG. 4. Brightfield photomicrograph illustrating a representative sample of the effect of LPS (100 μg/kg, iv) on PVN citrulline-immunoreactive cells. Immunocytochemistry for citrulline was performed in vehicle and at varying intervals after LPS treatment. Magnification, ×160.

[Citrulline] (iNOS product)

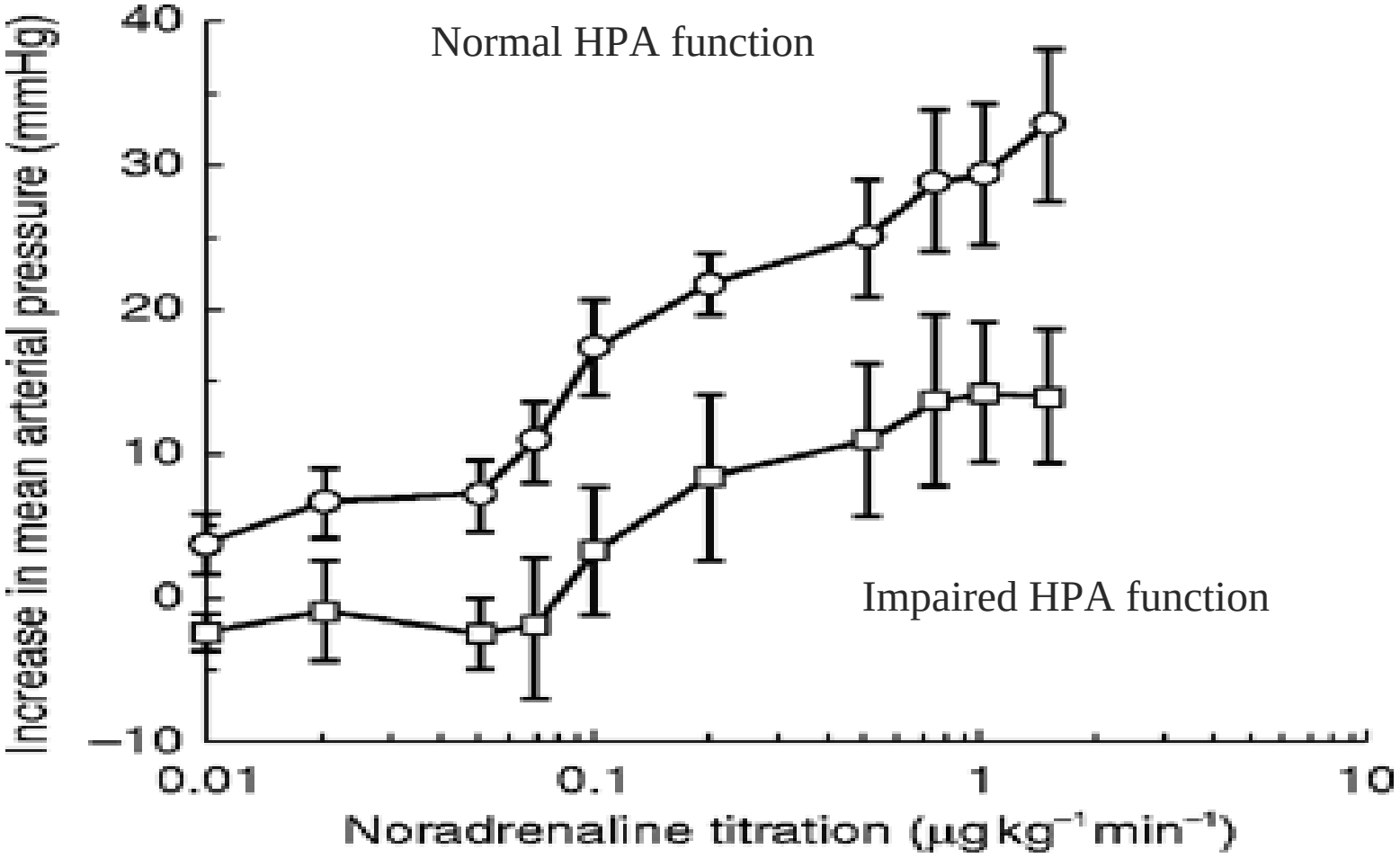
Li et al Cir Res 2003

NO plays a major role



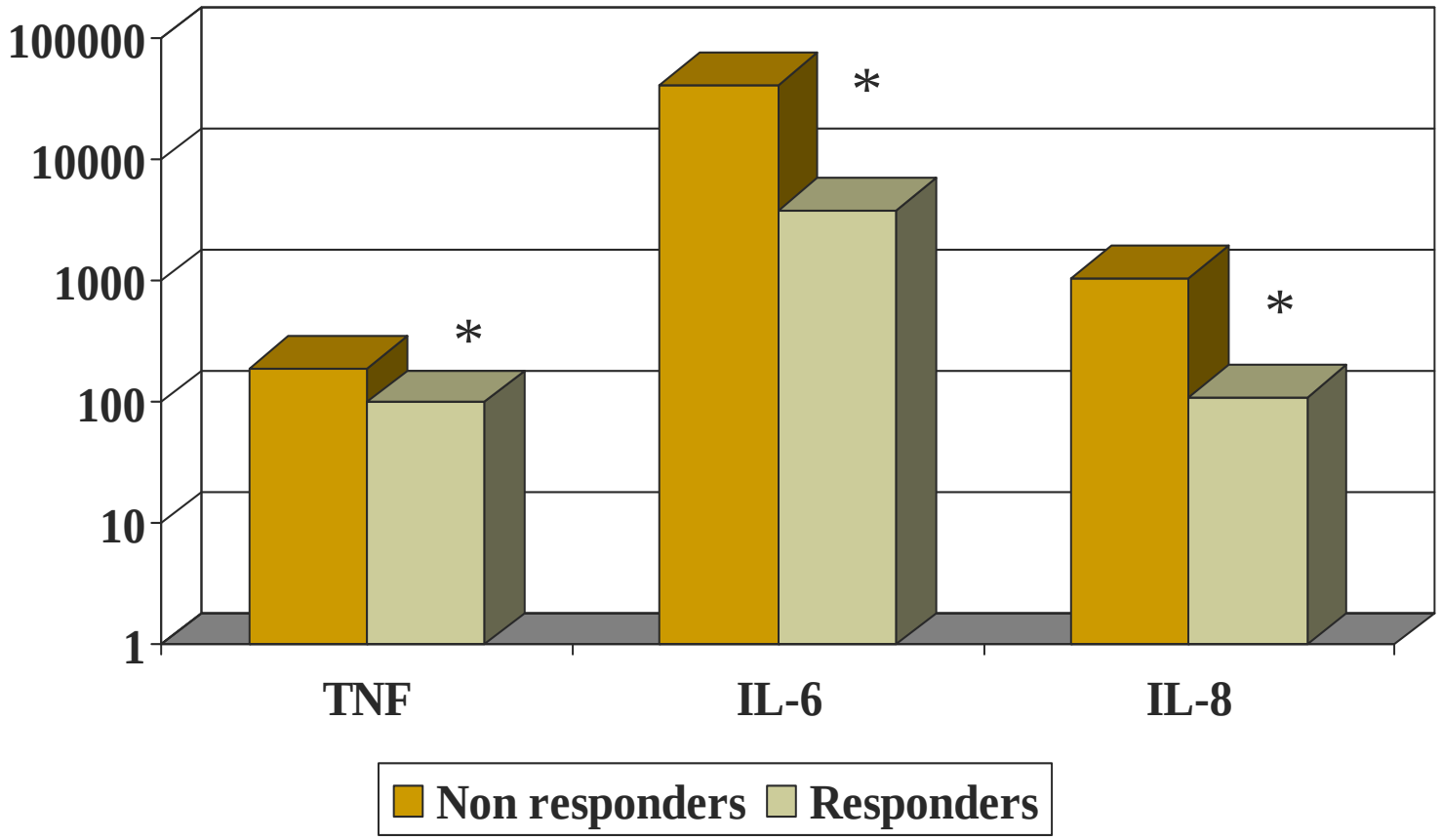
Sonneville Brain Pathol 2010 & Sharshar Lancet 2003

Clinical consequences of the impaired HPA axis



Annane, Br J Clin Pharmacol, 1998

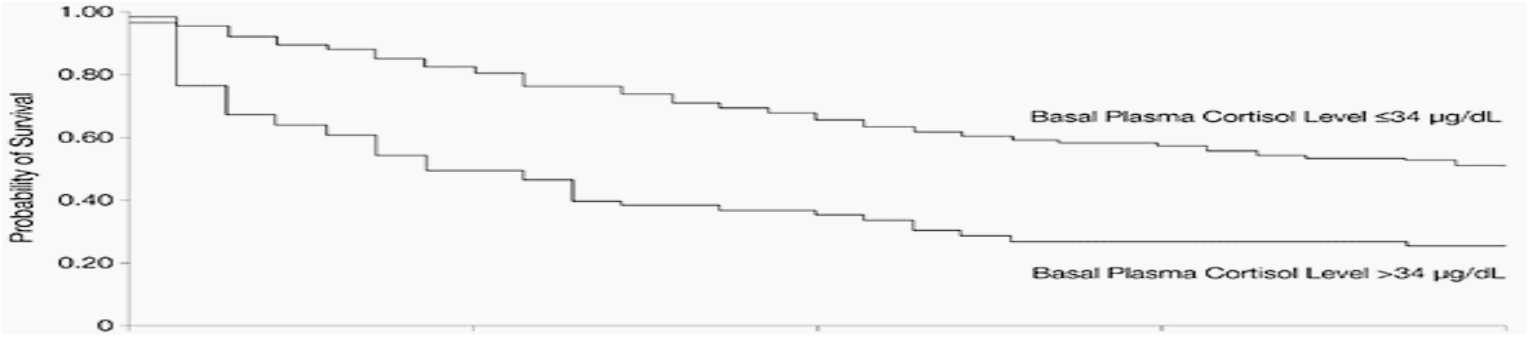
Clinical consequences of the impaired HPA axis



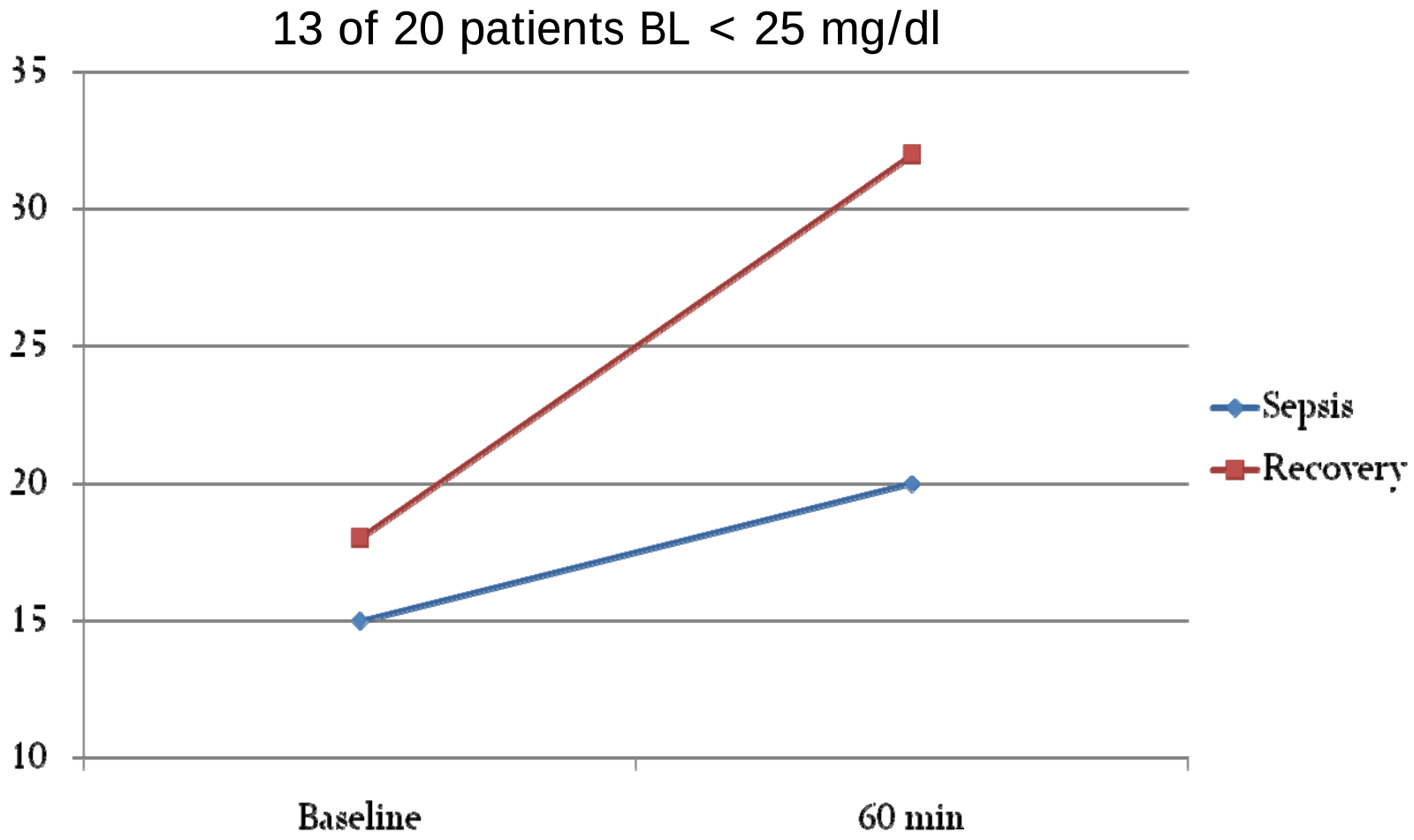
Annane, CCM 2006

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

Annane, *JAMA* 2000



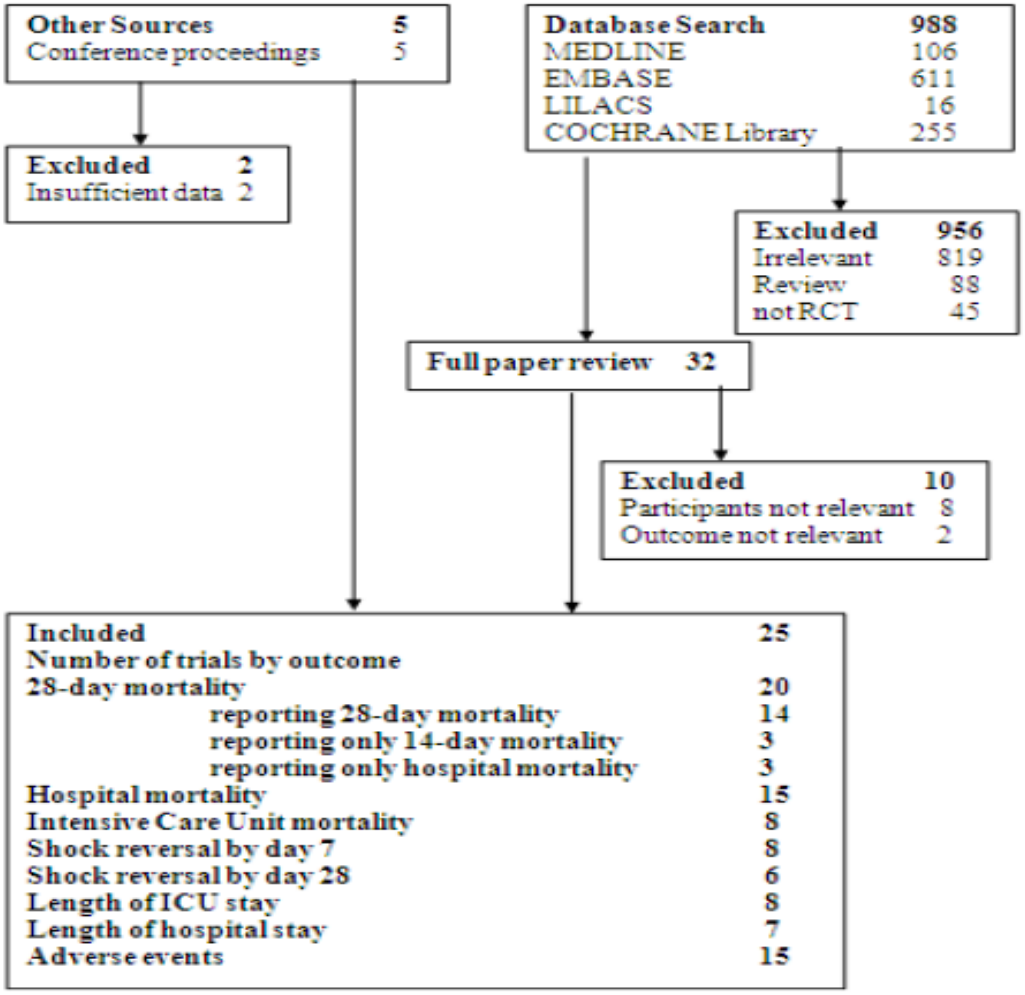
Survivors will recover a normal HPA axis!



Briegel, Intensive Care Med 1996;22:894

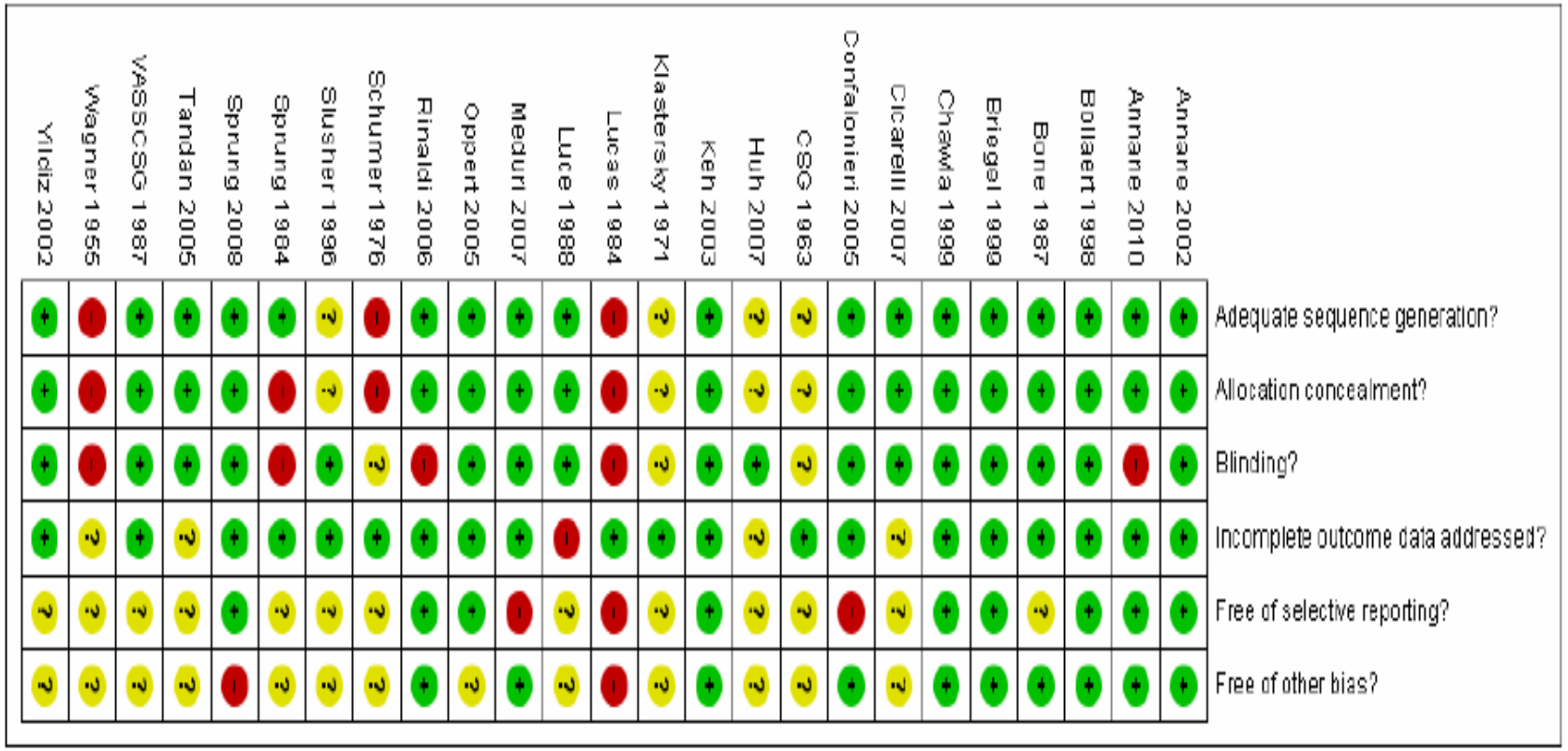
Critical Analysis of the Literature

Results of the literature search



Annane, JAMA 2009 &CDSR 2010

Methodological Quality of Trials

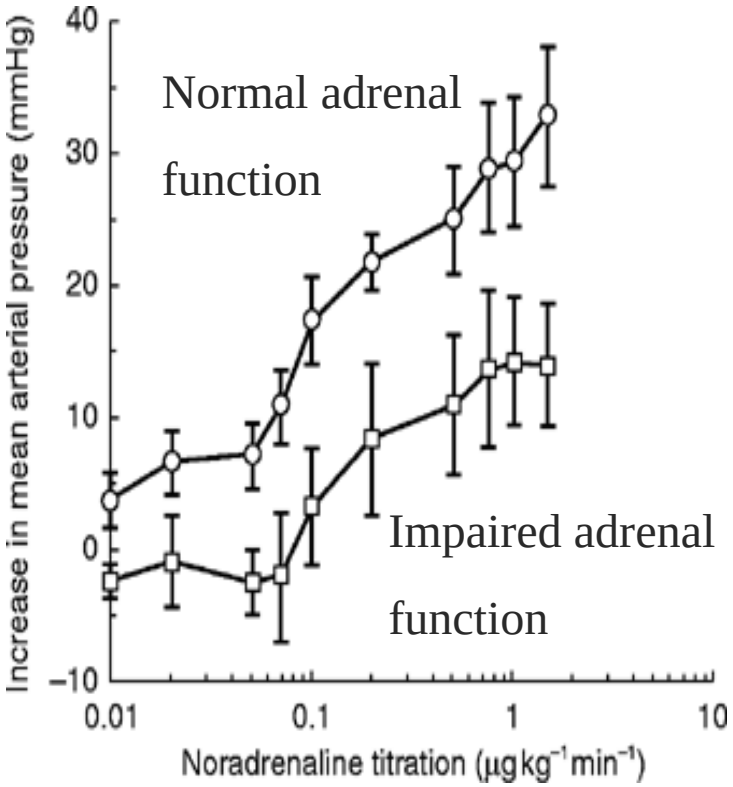


Annane, JAMA 2009 &CDSR 2010

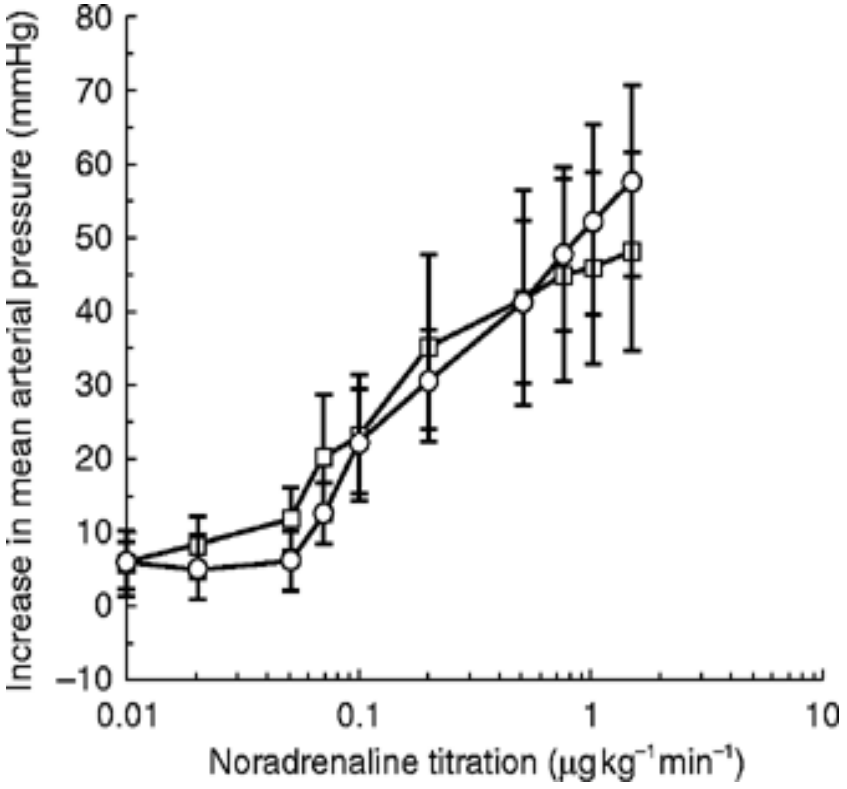
Glucocorticoids Restore Cardiovascular Homeostasis

Hydrocortisone Restores the Responsiveness to Vasopressors

Before HC

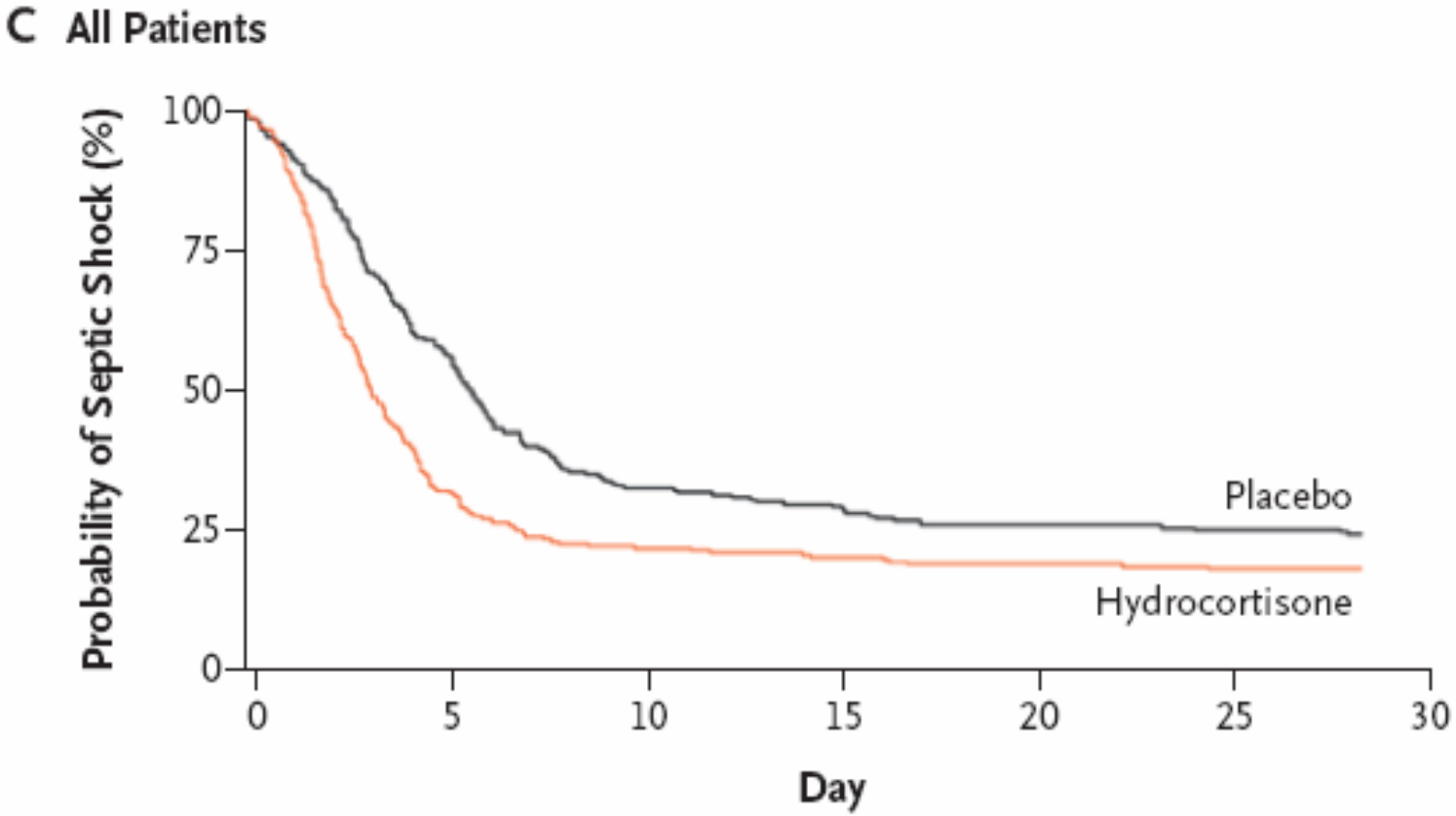


After HC



Annane, British Journal of Clinical Pharmacology, 1

Hydrocortisone reduces the time on vasopressors



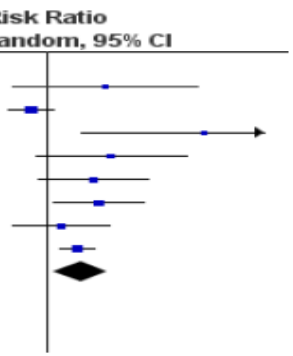
Sprung, NEJM 2008

Hydrocortisone normalizes the cardiovascular function

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.8.1 Shock reversal at day 7							
Sprung 1984	25	43	6	16	6.3%	1.55 [0.78, 3.06]	1984
Bone 1987	85	130	83	114	20.2%	0.90 [0.76, 1.06]	1987
Bollaert 1998	15	22	4	19	4.0%	3.24 [1.30, 8.10]	1998
Chawla 1999	16	23	9	21	8.3%	1.62 [0.92, 2.85]	1999
Briegel 1999	17	20	12	20	12.1%	1.42 [0.95, 2.12]	1999
Annane 2002	60	151	40	149	14.4%	1.48 [1.06, 2.06]	2002
Oppert 2005	14	18	16	23	13.2%	1.12 [0.78, 1.61]	2005
Sprung 2008	186	251	145	248	21.5%	1.27 [1.12, 1.44]	2008
Subtotal (95% CI)		**658**		**610**	**100.0%**	**1.29 [1.06, 1.58]**	
Total events	418		315				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 21.48$, df = 7 (P = 0.003); $I^2 = 67\%$

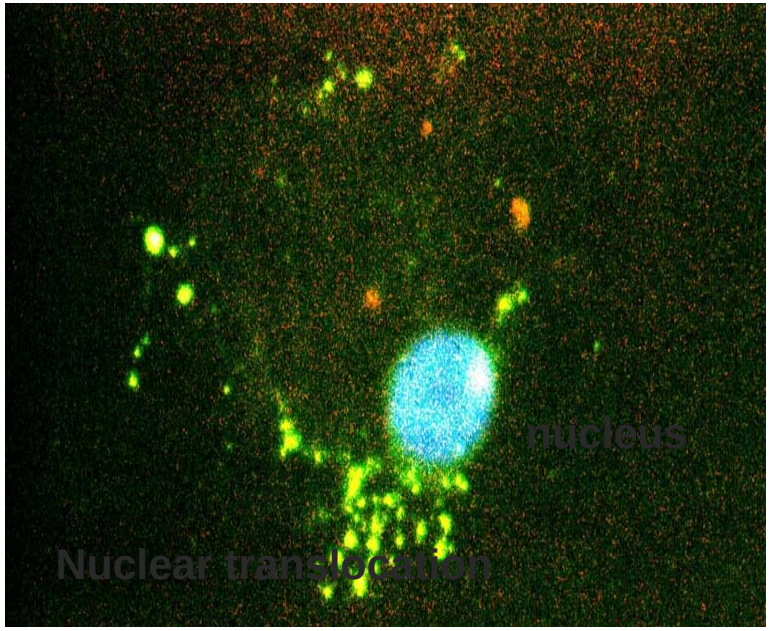
Test for overall effect: Z = 2.51 (P = 0.01)



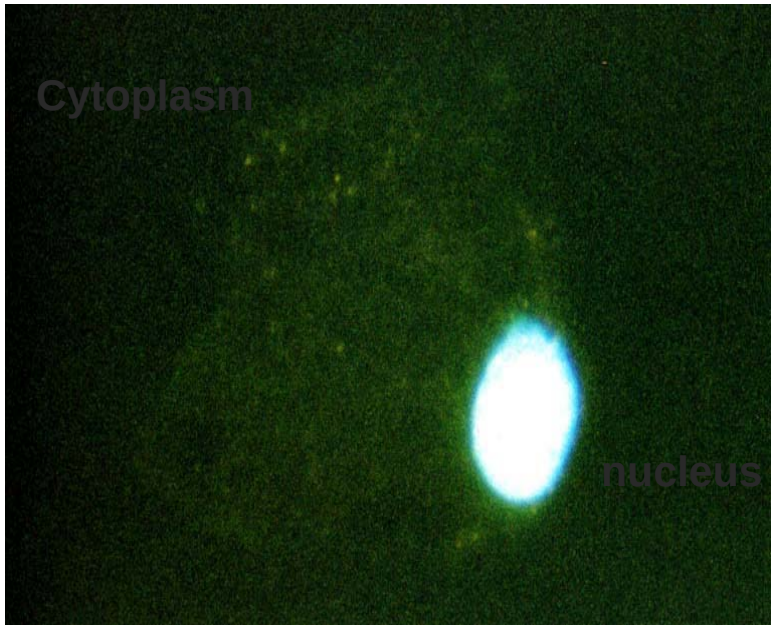
Annane JAMA 2009 & CDSR 2010

Glucocorticoids Restore Immune Homeostasis

Corticosteroids inhibited NF-kB Activation



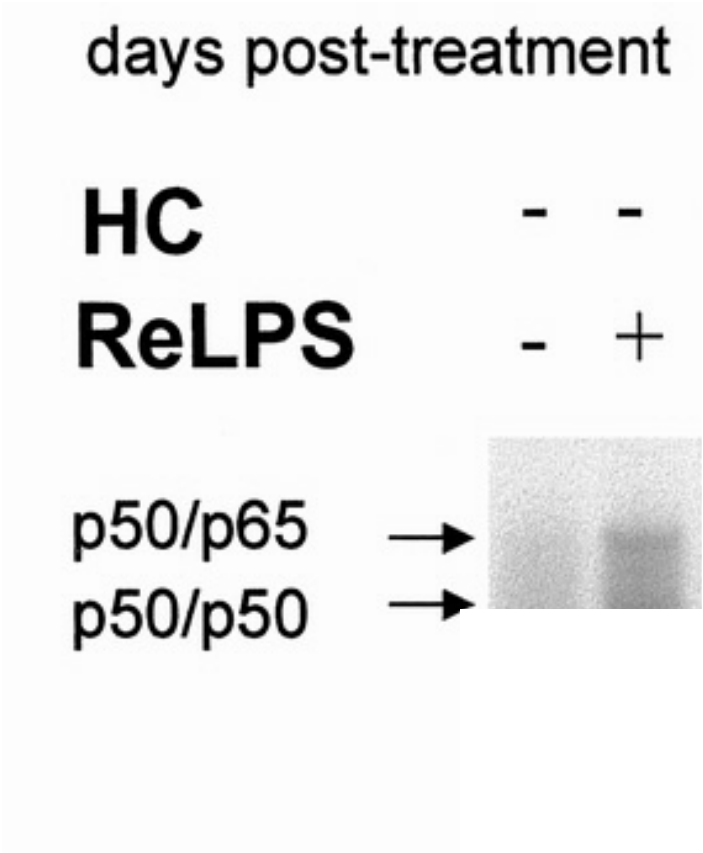
Before steroids



After 10 days of steroids

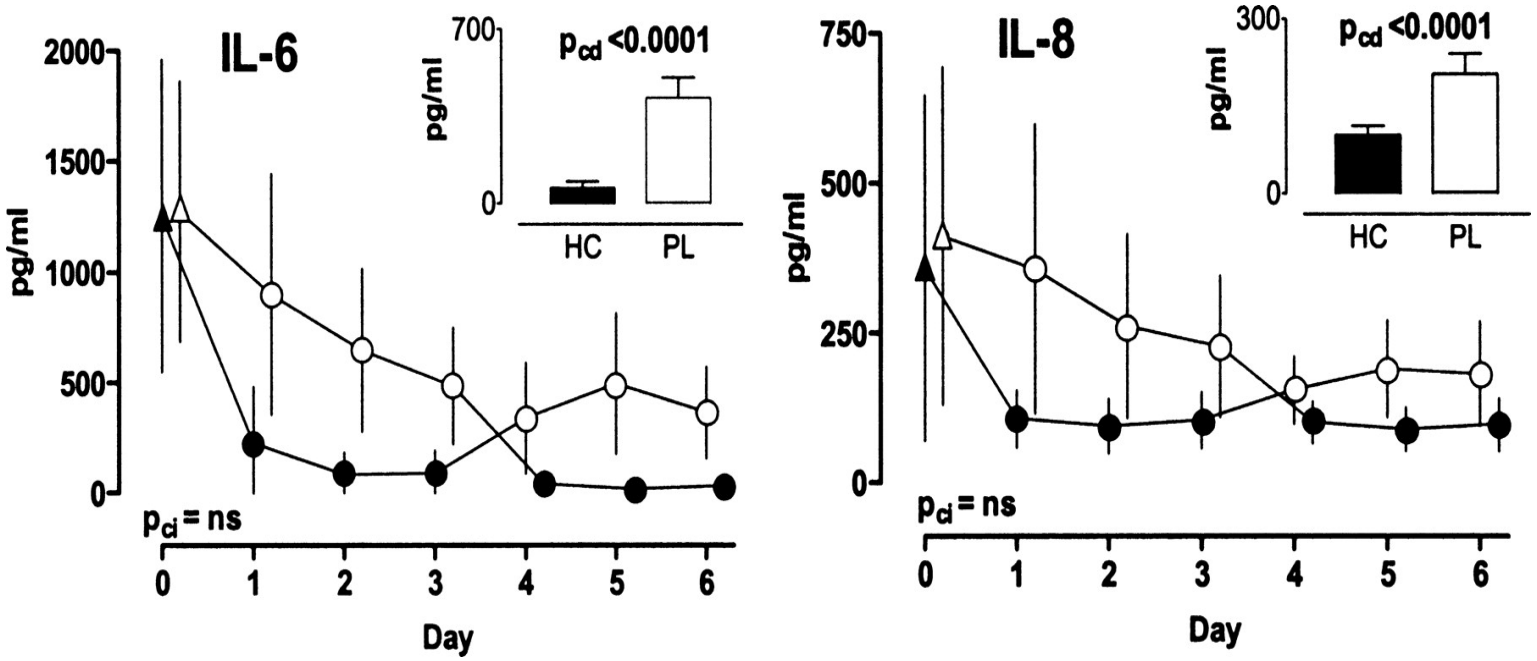
NF-κB staining with FITC-Ab

Corticosteroids inhibited NF-kB Activation



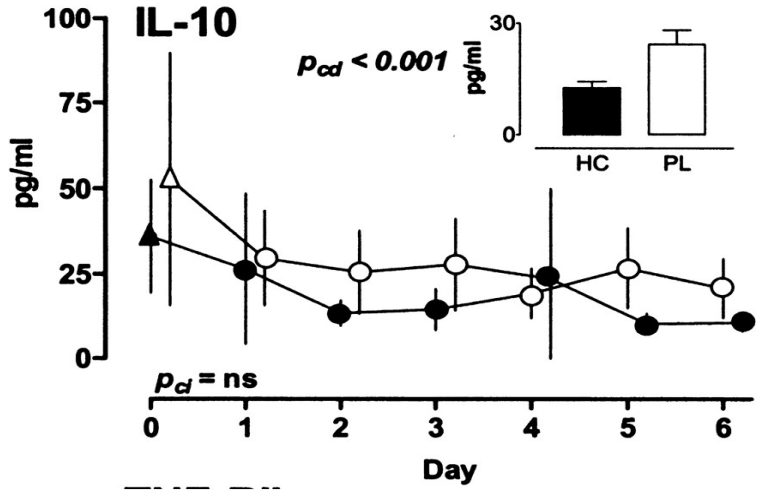
Crit Care Med 2001; 29:1074

Corticosteroids decreased circulating levels of all pro-inflammatory cytokines



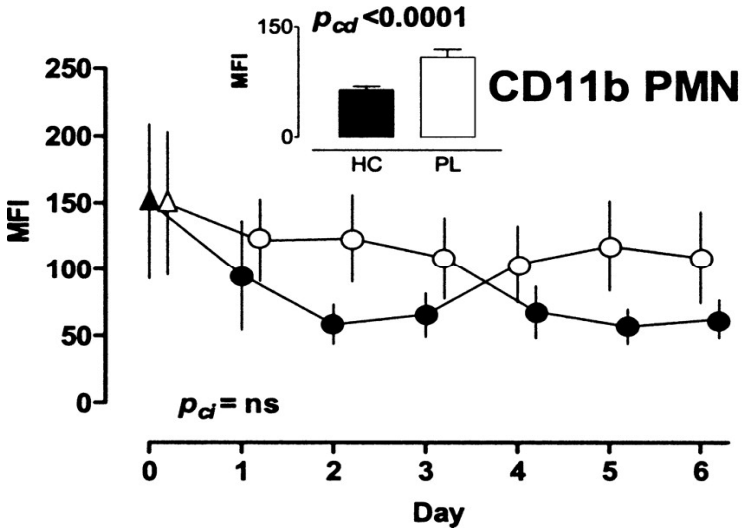
Didier Keh, AJRCCM 2003

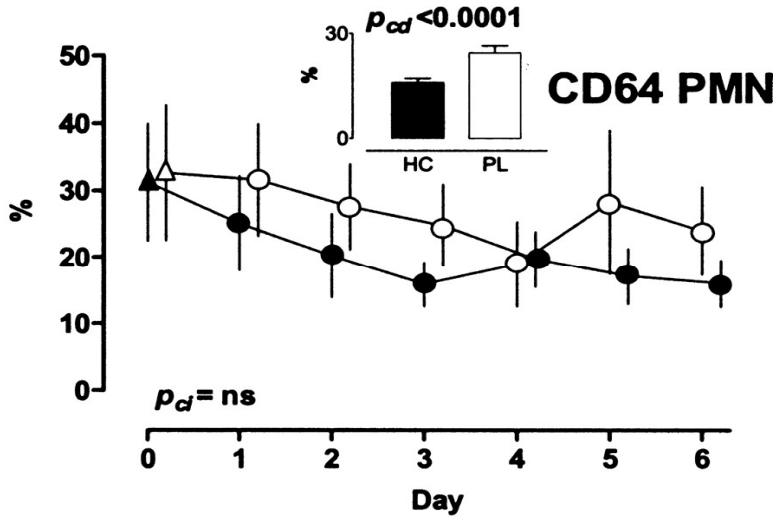
Corticosteroids decreased circulating levels of most of anti-inflammatory cytokines

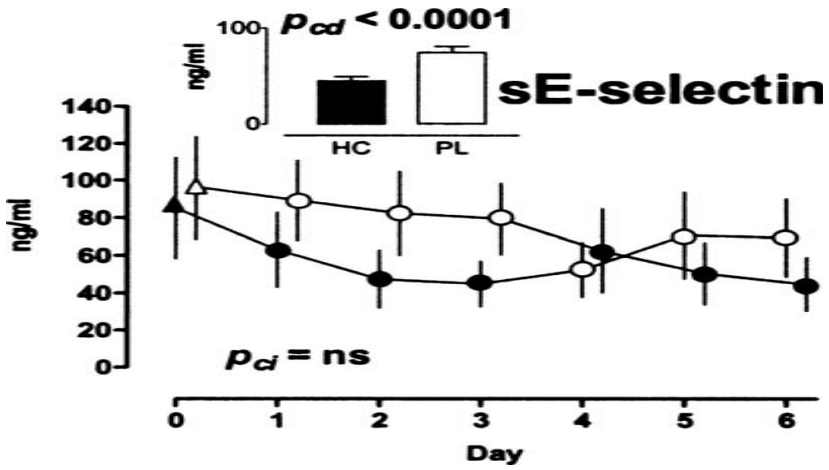


Didier Keh, AJRCCM 2003

Corticosteroids attenuated the endothelial activation







Keh, AJRCCM 2003

Glucocorticoids Restore Organs Function

Corticosteroids reduced the number and intensity of organ dysfunctions

	HC (n=251)	Placebo (n=248)	P
0	10.6 ± 3.4	10.6 ± 3.2	NS
1	10.4 ± 3.7	10.7 ± 3.6	NS
2	10.2 ± 3.8	10.3 ± 3.7	NS
3	8.7 ± 4.4	9.7 ± 4.0	0.01
4	7.8 ± 4.2	9.9 ± 4.4	0.03
5	6.9 ± 4.4	8.4 ± 4.6	0.006
6	6.4 ± 4.3	7.7 ± 5.0	0.004
7	6.1 ± 4.4	7.1 ± 4.8	0.03

Moreno, Intensive Care Medicine 2011

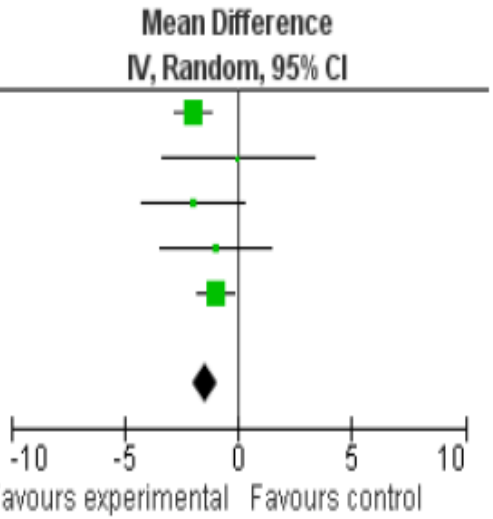
Corticosteroids reduced the number and intensity of organ dysfunctions

1.9 SOFA score at day-7

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2002	7.5	3	151	9.5	4	149	43.7%	-2.00 [-2.80, -1.20]
Cicarelli 2007	9	4	15	9	5	14	2.7%	0.00 [-3.31, 3.31]
Oppert 2005	6	4	23	8	4	25	5.8%	-2.00 [-4.27, 0.27]
Rinaldi 2006	1	4	20	2	4	20	4.8%	-1.00 [-3.48, 1.48]
Sprung 2008	6.1	4.4	251	7.1	4.8	248	43.0%	-1.00 [-1.81, -0.19]
Total (95% CI)			**460**			**456**	**100.0%**	**-1.47 [-2.01, -0.92]**

Heterogeneity: Tau² = 0.01; Chi² = 4.09, df = 4 (P = 0.39); I² = 2%

Test for overall effect: Z = 5.27 (P < 0.00001)

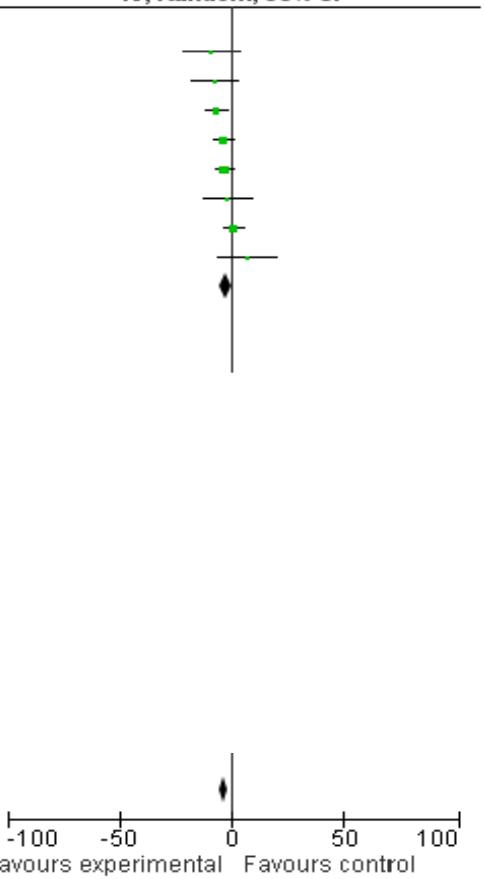


Annane JAMA 2009 & CDSR 2010

Corticosteroids reduced ICU length of stay

1.10 Length of ICU stay

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 For all patients								
Briegel 1999	29	16	20	38	24	20	1.6%	-9.00 [-21.64, 3.64]
Meduri 2007	7	14	42	14.5	21	19	2.5%	-7.50 [-17.85, 2.85]
Confalonieri 2005	7.2	7.1	23	14.2	9.8	23	10.8%	-7.00 [-11.95, -2.05]
Annane 2002	22	24	151	25.5	18	149	11.5%	-3.50 [-8.30, 1.30]
Chawla 1999	7.4	6.2	23	10.7	7.6	21	15.5%	-3.30 [-7.42, 0.82]
Rinaldi 2006	19	21	26	21	19	26	2.2%	-2.00 [-12.89, 8.89]
Sprung 2008	19	31	251	18	17	248	13.7%	1.00 [-3.38, 5.38]
Bollaert 1998	26	24	22	19	18	19	1.6%	7.00 [-5.89, 19.89]
Subtotal (95% CI)			**558**			**525**	**59.4%**	**-3.11 [-5.79, -0.43]**
Heterogeneity: Tau² = 3.90; Chi² = 9.72, df = 7 (P = 0.21); I² = 28%								
Test for overall effect: Z = 2.27 (P = 0.02)								
Total (95% CI)			**889**			**816**	**100.0%**	**-3.62 [-5.24, -2.00]**
Heterogeneity: Tau² = 0.00; Chi² = 13.26, df = 15 (P = 0.58); I² = 0%								
Test for overall effect: Z = 4.37 (P < 0.0001)								

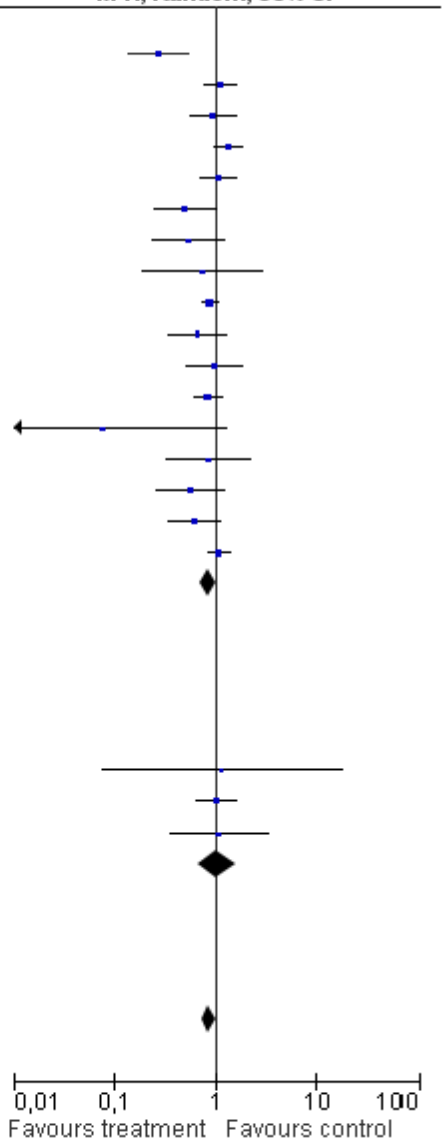


Annane JAMA 2009 & CDSR 2010

Glucocorticoids Save Life

1.1 28-day all-cause mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Randomized controlled trials							
Schumer 1976	9	86	33	86	3.9%	0.27 [0.14, 0.53]	1976
Sprung 1984	33	43	11	16	7.9%	1.12 [0.77, 1.61]	1984
VASSCSG 1987	23	112	24	111	5.6%	0.95 [0.57, 1.58]	1987
Bone 1987	65	191	48	190	9.0%	1.35 [0.98, 1.84]	1987
Luce 1988	22	38	20	37	7.3%	1.07 [0.72, 1.60]	1988
Bollaert 1998	7	22	12	19	3.6%	0.50 [0.25, 1.02]	1998
Chawla 1999	6	23	10	21	2.9%	0.55 [0.24, 1.25]	1999
Briegel 1999	3	20	4	20	1.2%	0.75 [0.19, 2.93]	1999
Annane 2002	82	151	91	149	11.7%	0.89 [0.73, 1.08]	2002
Yildiz 2002	8	20	12	20	4.1%	0.67 [0.35, 1.27]	2002
Oppert 2005	10	23	11	25	4.1%	0.99 [0.52, 1.88]	2005
Tandan 2005	11	14	13	14	9.1%	0.85 [0.62, 1.15]	2005
Confalonieri 2005	0	23	6	23	0.3%	0.08 [0.00, 1.29]	2005
Rinaldi 2006	6	26	7	26	2.3%	0.86 [0.33, 2.21]	2006
Meduri 2007	10	42	8	19	3.3%	0.57 [0.27, 1.20]	2007
Cicarelli 2007	7	14	12	15	4.8%	0.63 [0.35, 1.12]	2007
Sprung 2008	86	251	78	248	10.4%	1.09 [0.85, 1.40]	2008
Subtotal (95% CI)		**1099**		**1039**	**91.5%**	**0.84 [0.71, 1.00]**	
Total events	388		400				
Heterogeneity: Tau² = 0.06; Chi² = 33.82, df = 16 (P = 0.006); I² = 53%							
Test for overall effect: Z = 1.96 (P = 0.05)							
1.1.2 Quasi randomized controlled trials							
Wagner 1955	1	52	1	61	0.3%	1.17 [0.08, 18.30]	1955
Klastersky 1971	22	46	18	39	6.4%	1.04 [0.66, 1.63]	1971
Lucas 1984	5	23	5	25	1.7%	1.09 [0.36, 3.27]	1984
Subtotal (95% CI)		**121**		**125**	**8.5%**	**1.05 [0.69, 1.58]**	
Total events	28		24				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.21 (P = 0.83)							
Total (95% CI)		**1220**		**1164**	**100.0%**	**0.87 [0.74, 1.01]**	
Total events	416		424				
Heterogeneity: Tau² = 0.04; Chi² = 34.18, df = 19 (P = 0.02); I² = 44%							
Test for overall effect: Z = 1.81 (P = 0.07)							



Annane JAMA 2009 & CDSR 2010

1.3 28-day all-cause mortality by subgroups based on treatment dose/duration

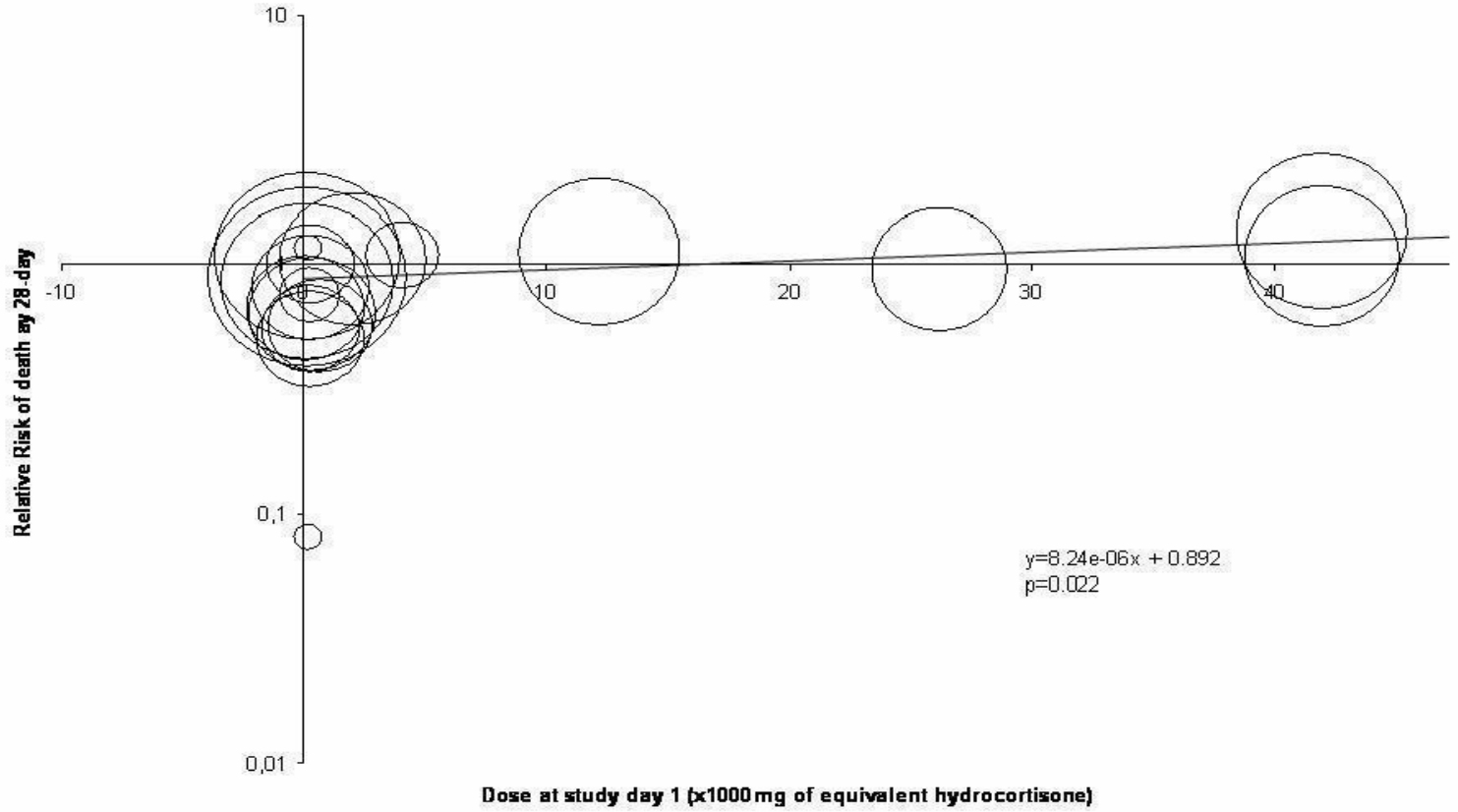
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.3.1 Long course of low dose corticosteroids							
Bollaert 1998	7	22	12	19	4.2%	0.50 [0.25, 1.02]	1998
Chawla 1999	6	23	10	21	3.1%	0.55 [0.24, 1.25]	1999
Briegel 1999	3	20	4	20	1.2%	0.75 [0.19, 2.93]	1999
Annane 2002	82	151	91	149	30.0%	0.89 [0.73, 1.08]	2002
Yildiz 2002	8	20	12	20	4.9%	0.67 [0.35, 1.27]	2002
Confalonieri 2005	0	23	6	23	0.3%	0.08 [0.00, 1.29]	2005
Tandan 2005	11	14	13	14	16.8%	0.85 [0.62, 1.15]	2005
Oppert 2005	10	23	11	25	5.0%	0.99 [0.52, 1.88]	2005
Rinaldi 2006	6	26	7	26	2.4%	0.86 [0.33, 2.21]	2006
Meduri 2007	10	42	8	19	3.7%	0.57 [0.27, 1.20]	2007
Cicarelli 2007	7	14	12	15	6.0%	0.63 [0.35, 1.12]	2007
Sprung 2008	86	251	78	248	22.4%	1.09 [0.85, 1.40]	2008
Subtotal (95% CI)		**629**		**599**	**100.0%**	**0.84 [0.72, 0.97]**	
Total events	236		264				

Heterogeneity: Tau² = 0.01; Chi² = 12.89, df = 11 (P = 0.30); I² = 15%

Test for overall effect: Z = 2.31 (P = 0.02)

Annane JAMA 2009 & CDSR 2010

Corticosteroids dose: the lower the better



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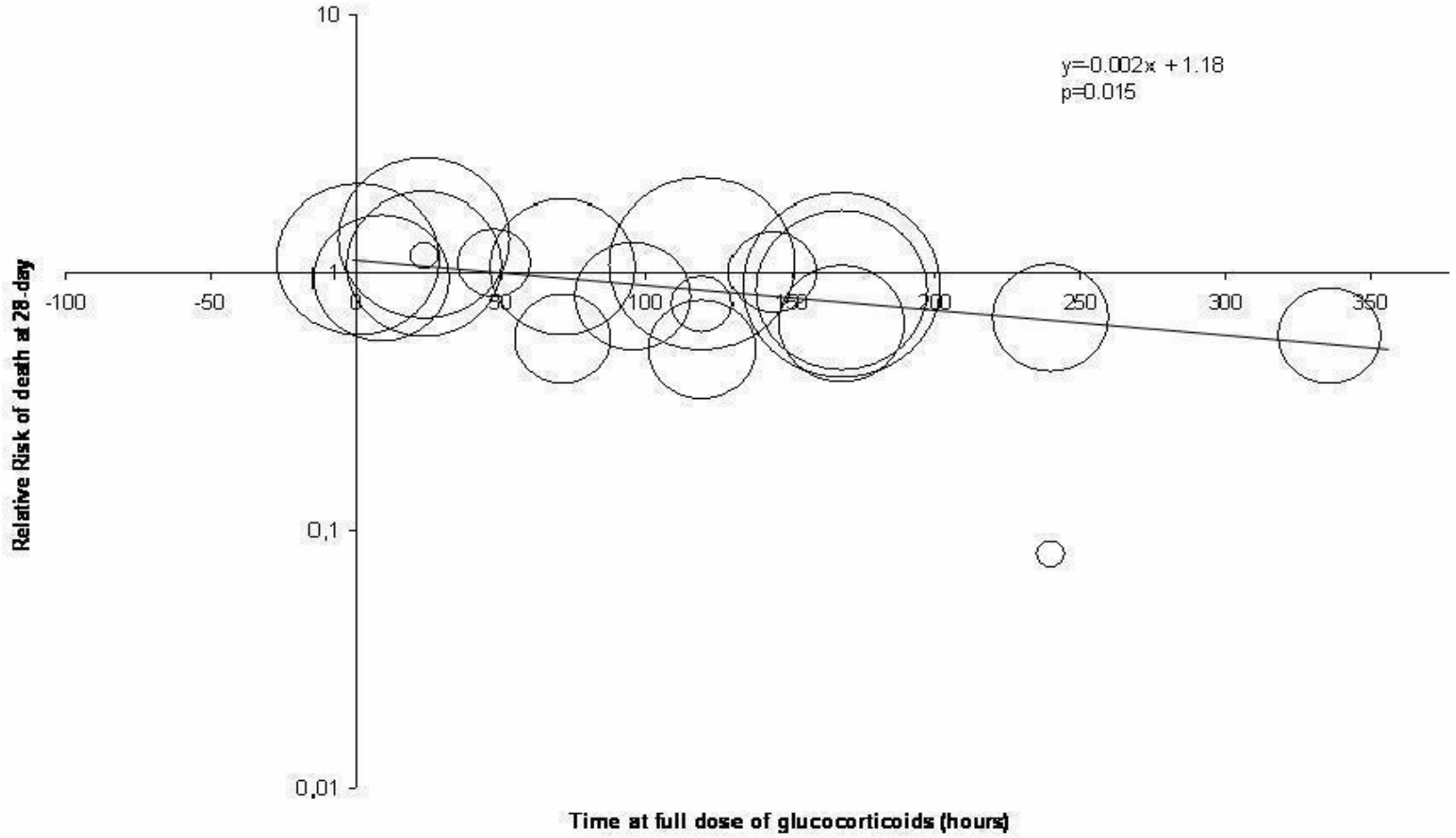
Corticosteroids duration: the longer the better



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Glucocorticoids Tolerance

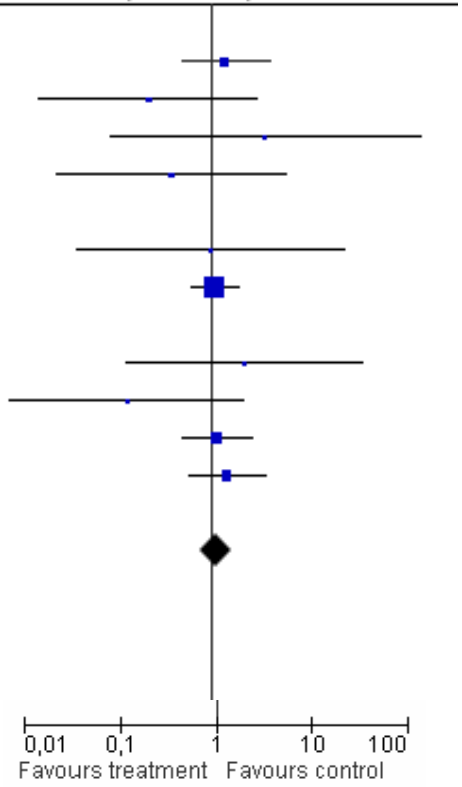
Corticosteroids and risk of stress ulcer

1.12 Number of patients with adverse events

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Gastroduodenal bleeding						
Annane 2002	11	151	8	149	12.8%	1.36 [0.56, 3.28]
Bollaert 1998	1	22	3	19	2.1%	0.29 [0.03, 2.54]
Briegel 1999	1	20	0	20	1.0%	3.00 [0.13, 69.52]
Chawla 1999	1	23	2	21	1.8%	0.46 [0.04, 4.68]
Cicarelli 2007	0	14	0	15		Not estimable
Confalonieri 2005	1	23	1	23	1.4%	1.00 [0.07, 15.04]
Luce 1988	18	37	16	36	41.1%	1.09 [0.67, 1.79]
Meduri 2007	0	42	0	19		Not estimable
Schumer 1976	2	86	1	86	1.8%	2.00 [0.18, 21.65]
Sprung 1984	1	43	2	16	1.8%	0.19 [0.02, 1.91]
Sprung 2008	15	234	13	232	19.2%	1.14 [0.56, 2.35]
VASSCSG 1987	14	112	10	111	16.9%	1.39 [0.64, 2.99]
Yildiz 2002	0	20	0	20		Not estimable
Subtotal (95% CI)		**827**		**767**	**100.0%**	**1.12 [0.81, 1.53]**
Total events	65		56			

Heterogeneity: Tau² = 0.00; Chi² = 5.45, df = 9 (P = 0.79); I² = 0%

Test for overall effect: Z = 0.68 (P = 0.50)



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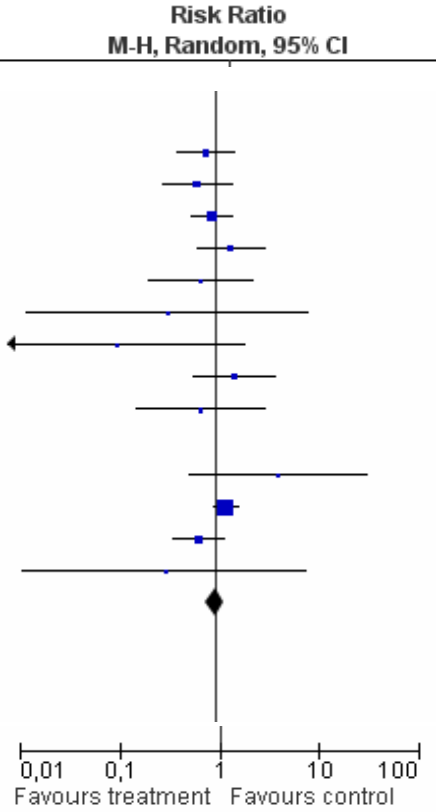
Corticosteroids and risk of superinfection

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.2 Superinfections						
Annane 2002	15	151	18	149	9.4%	0.82 [0.43, 1.57]
Bollaert 1998	7	22	9	19	6.8%	0.67 [0.31, 1.46]
Bone 1987	29	152	30	147	17.2%	0.93 [0.59, 1.48]
Briegel 1999	10	20	7	20	7.4%	1.43 [0.68, 3.00]
Chawla 1999	4	23	5	21	3.1%	0.73 [0.23, 2.36]
Cicarelli 2007	0	14	1	15	0.4%	0.36 [0.02, 8.07]
Confalonieri 2005	0	23	4	23	0.5%	0.11 [0.01, 1.95]
Klastersky 1971	11	46	6	39	5.1%	1.55 [0.63, 3.82]
Luce 1988	3	37	4	36	2.1%	0.73 [0.18, 3.03]
Schumer 1976	0	86	0	86		Not estimable
Sprung 1984	11	43	1	16	1.1%	4.09 [0.57, 29.20]
Sprung 2008	78	234	61	232	35.0%	1.27 [0.96, 1.68]
VASSCSG 1987	16	112	23	111	11.4%	0.69 [0.39, 1.23]
Yildiz 2002	0	20	1	20	0.4%	0.33 [0.01, 7.72]
Subtotal (95% CI)		**983**		**934**	**100.0%**	**1.01 [0.82, 1.25]**
Total events	184		170			

Heterogeneity: Tau² = 0.01; Chi² = 13.02, df = 12 (P = 0.37); I² = 8%

Test for overall effect: Z = 0.10 (P = 0.92)



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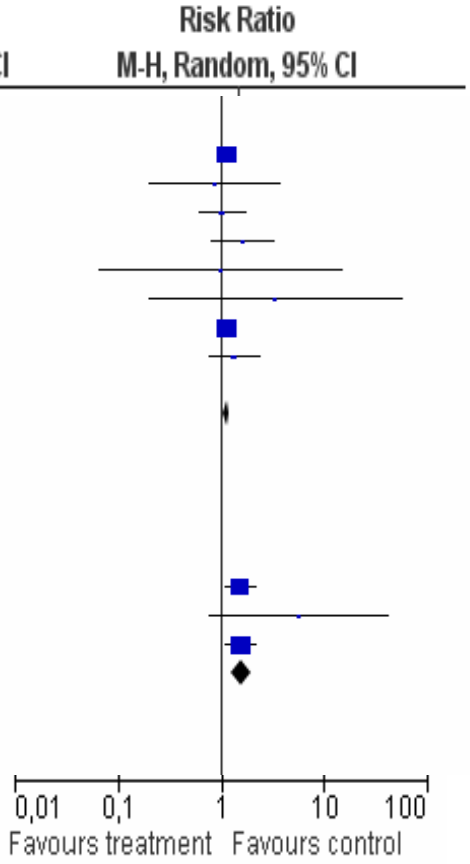
Corticosteroids and risk of metabolic complications

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.3 Hyperglycaemia						
Annane 2002	130	150	111	149	45.0%	1.16 [1.04, 1.30]
Bollaert 1998	3	22	3	19	0.3%	0.86 [0.20, 3.79]
Luce 1988	16	37	15	36	2.0%	1.04 [0.61, 1.77]
Meduri 2007	22	42	6	19	1.1%	1.66 [0.81, 3.41]
Schumer 1976	1	86	1	86	0.1%	1.00 [0.06, 15.73]
Sprung 1984	4	43	0	16	0.1%	3.48 [0.20, 61.18]
Sprung 2008	186	234	161	232	49.7%	1.15 [1.03, 1.28]
VASSCSG 1987	23	111	17	112	1.8%	1.37 [0.77, 2.41]
Yildiz 2002	0	20	0	20		Not estimable
Subtotal (95% CI)		**745**		**689**	**100.0%**	**1.16 [1.07, 1.25]**
Total events	385		314			
Heterogeneity: Tau² = 0.00; Chi² = 2.30, df = 7 (P = 0.94); I² = 0%						
Test for overall effect: Z = 3.83 (P = 0.0001)						
1.12.4 Hypernatremia						
Annane 2002	54	150	34	149	45.9%	1.58 [1.10, 2.27]
Briegel 1999	6	20	1	20	1.5%	6.00 [0.79, 45.42]
Sprung 2008	67	234	42	232	52.6%	1.58 [1.13, 2.22]
Subtotal (95% CI)		**404**		**401**	**100.0%**	**1.61 [1.26, 2.06]**
Total events	127		77			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 3.79 (P = 0.0002)						



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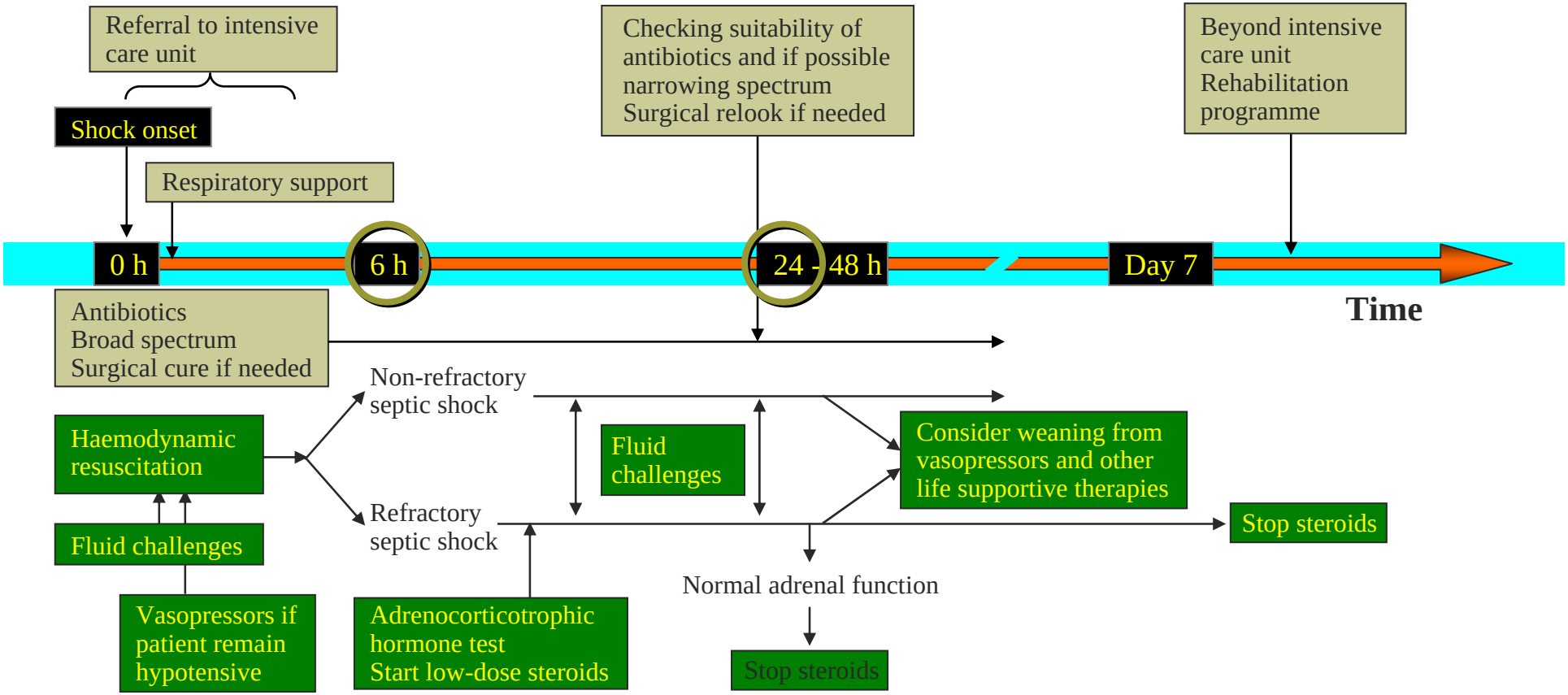
When I use Corticosteroids?



(1) Annane D. et al. Lancet 2005

Surviving Sepsis Campaign

Surviving Sepsis Campaign

Guidelines for Management of Severe Sepsis/Septic Shock

2012

Tentative draft

Corticosteroids

1. We suggest that a minimum of five day course of continuous infusion of intravenous hydrocortisone (200-300 mg daily and no higher) be used only in adult septic shock patients who require persistent high dose of vasopressors to keep adequate blood pressure despite adequate fluid resuscitation (Grade 2C).
2. We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B).
3. We suggest that patients with septic shock receive hydrocortisone rather than other steroids (Grade 2B). Further we recommend that hydrocortisone alone be used instead of hydrocortisone plus fludrocortisone (Grade 1B).

Corticosteroids

4. We suggest that clinicians taper the patient from steroid therapy when vasopressors are no longer required (Grade 2D).
5. We recommend that corticosteroids not be administered for of the purpose of treating severe sepsis in the absence of shock (Grade 1C).