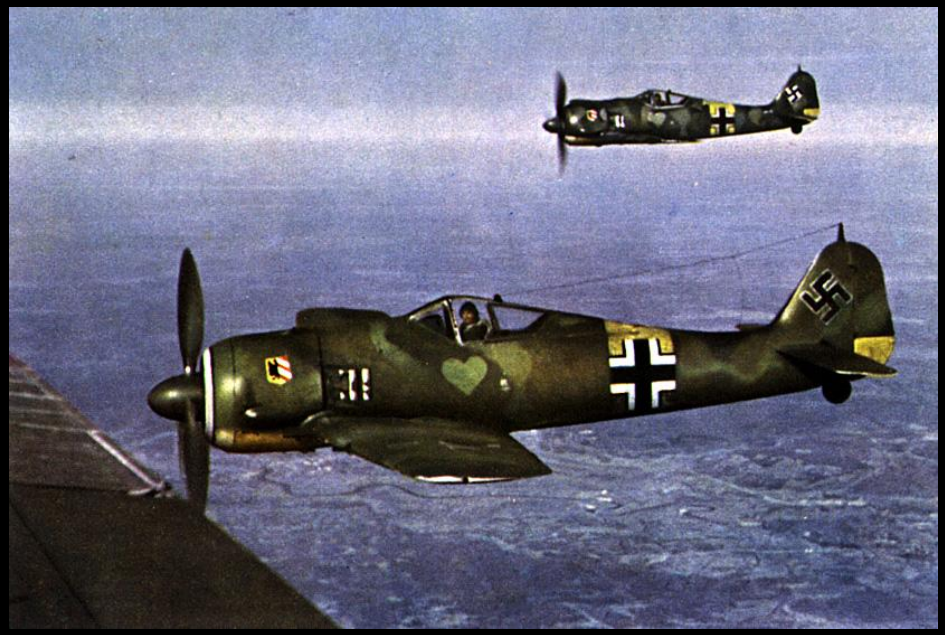


Storia dei Corticosteroidi

Nel 1563 Eustachio scopre l'esistenza delle ghiandole surrenali, nel 1849 Addison attribuisce la pelle bronzea a malfunzionamento delle ghiandole.

The Nobel Prize in Physiology or Medicine 1950

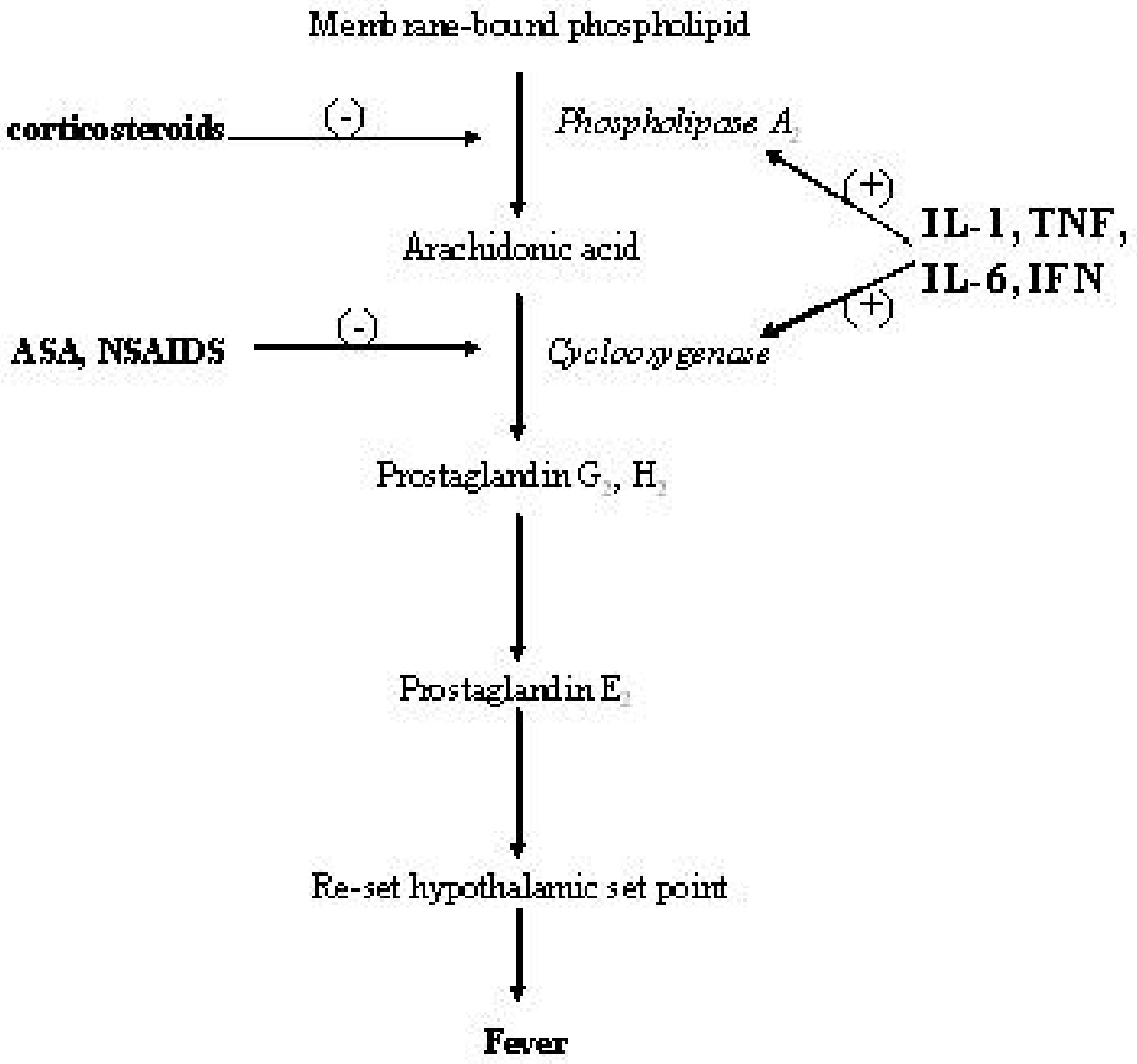
Edward Calvin Kendall

Tadeus Reichstein

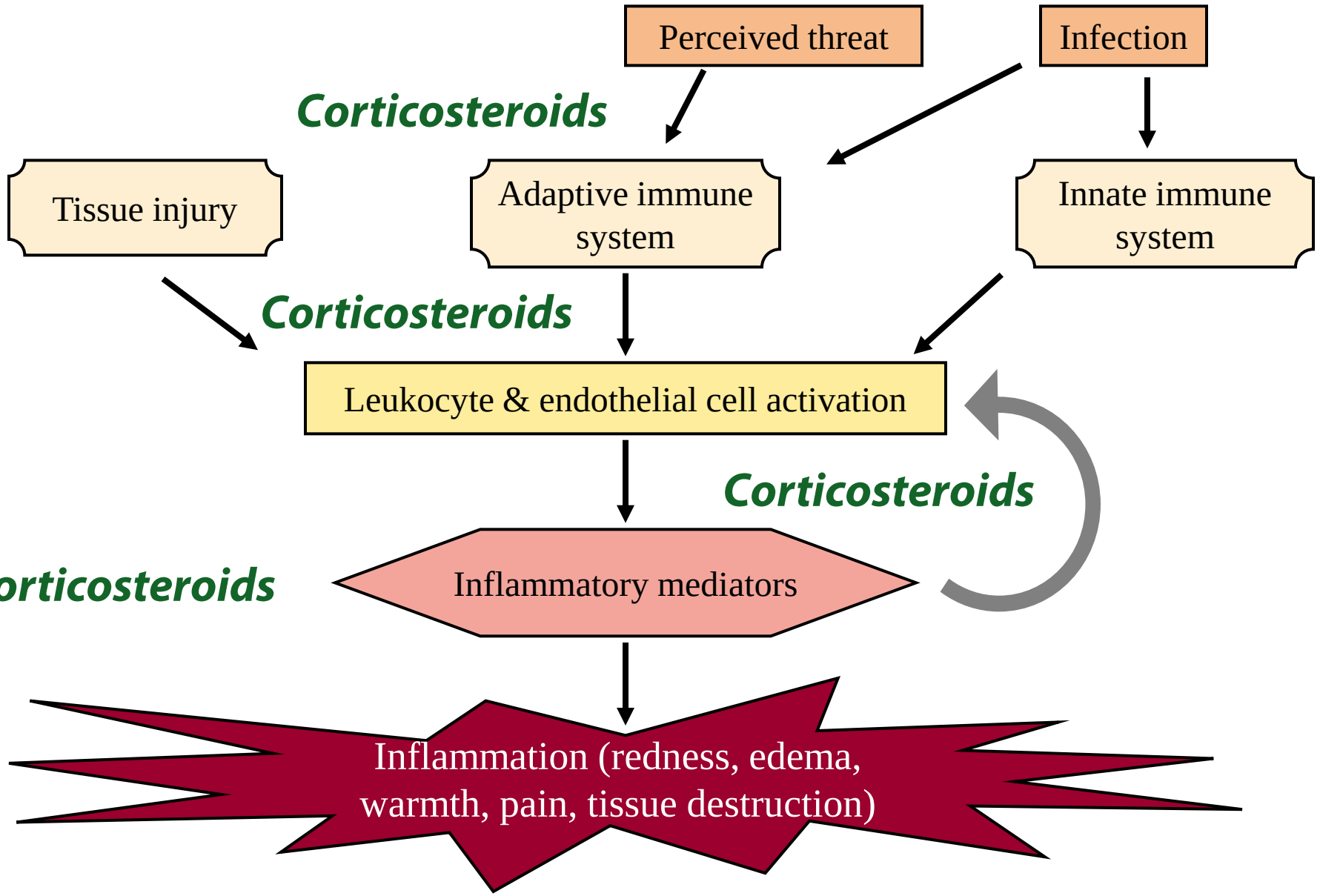
Philip Showalter Hench

They appeared to act, not by removing the causes of the diseases responsive thereto, but by suppressing in large measure the reactions of the tissues to the irritating agents. Although the hormones influenced greatly the reversible part of these diseases, the pathologic physiology (the “fire,” the active inflammation which causes symptoms), they exerted no influence on the irreversible part, the pathologic anatomy or residual ‘ashes’.

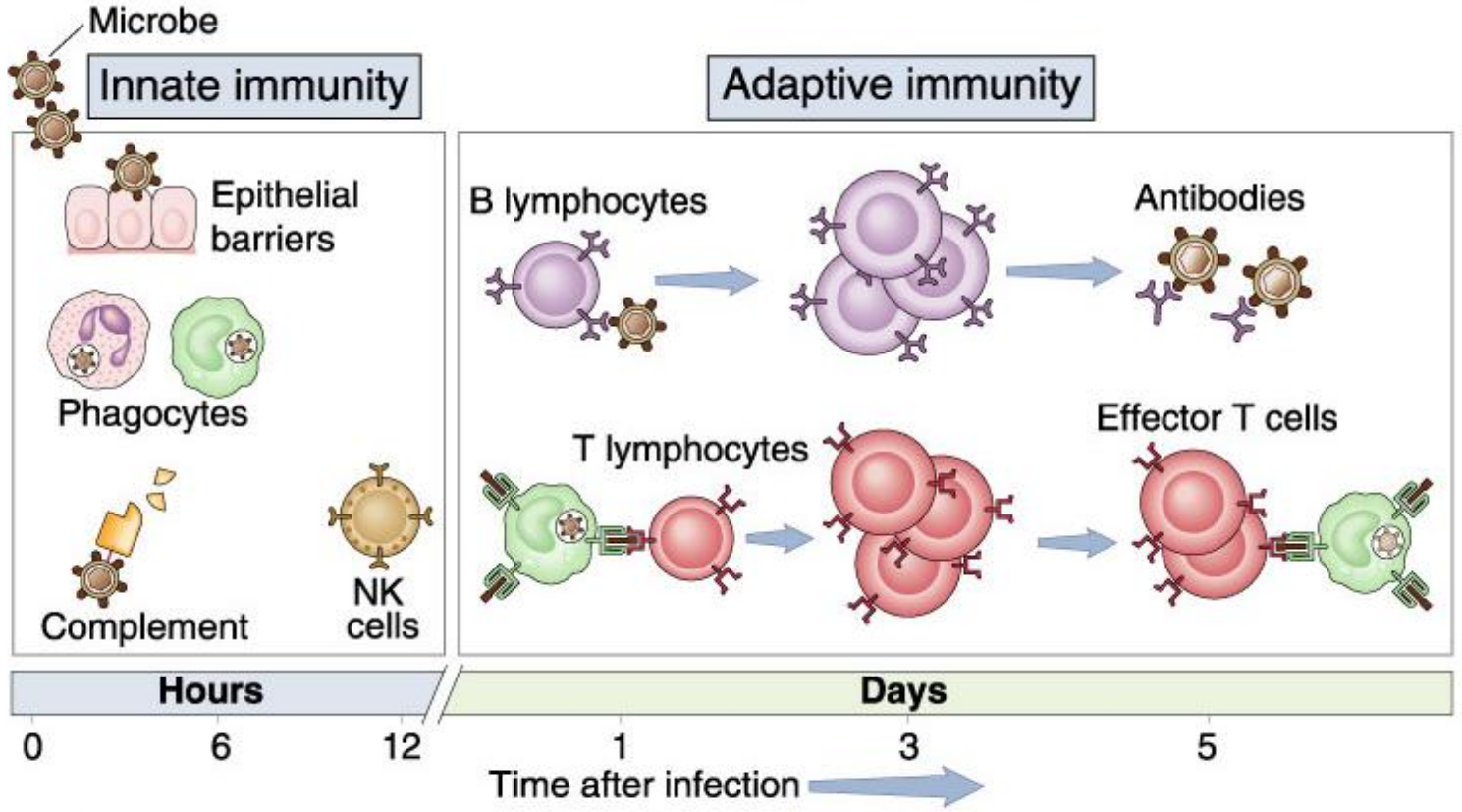
Hench PS. Cortisone, hydrocortisone and corticotropin; some facts and speculations with special reference to rheumatoid arthritis. Trans Assoc Life Insur Med Dir Am 1951; 35: 5-33.


Membrane-bound phospholipid
corticosteroids
(-)
Phospholipase A2
(+)
IL-1, TNF,
IL-6, IFN
Arachidonic acid
(+)
ASA, NSAIDS
(-)
Cyclooxygenase
Prostaglandin G2, H2
Prostaglandin E2
Re-set hypothalamic set point
Fever

The Mighty Corticosteroids

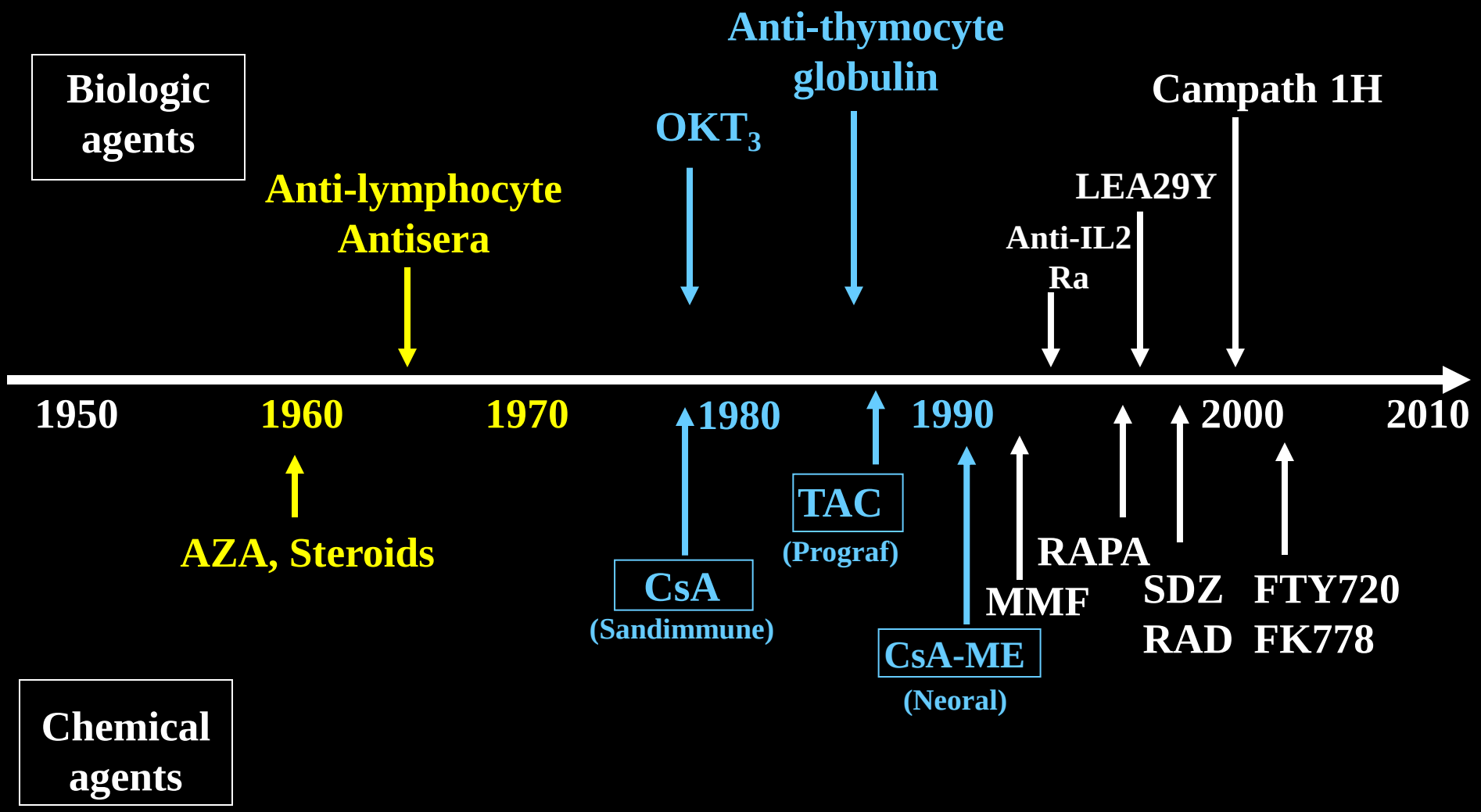


Glucocorticoids Are Powerful Immuno-suppressants

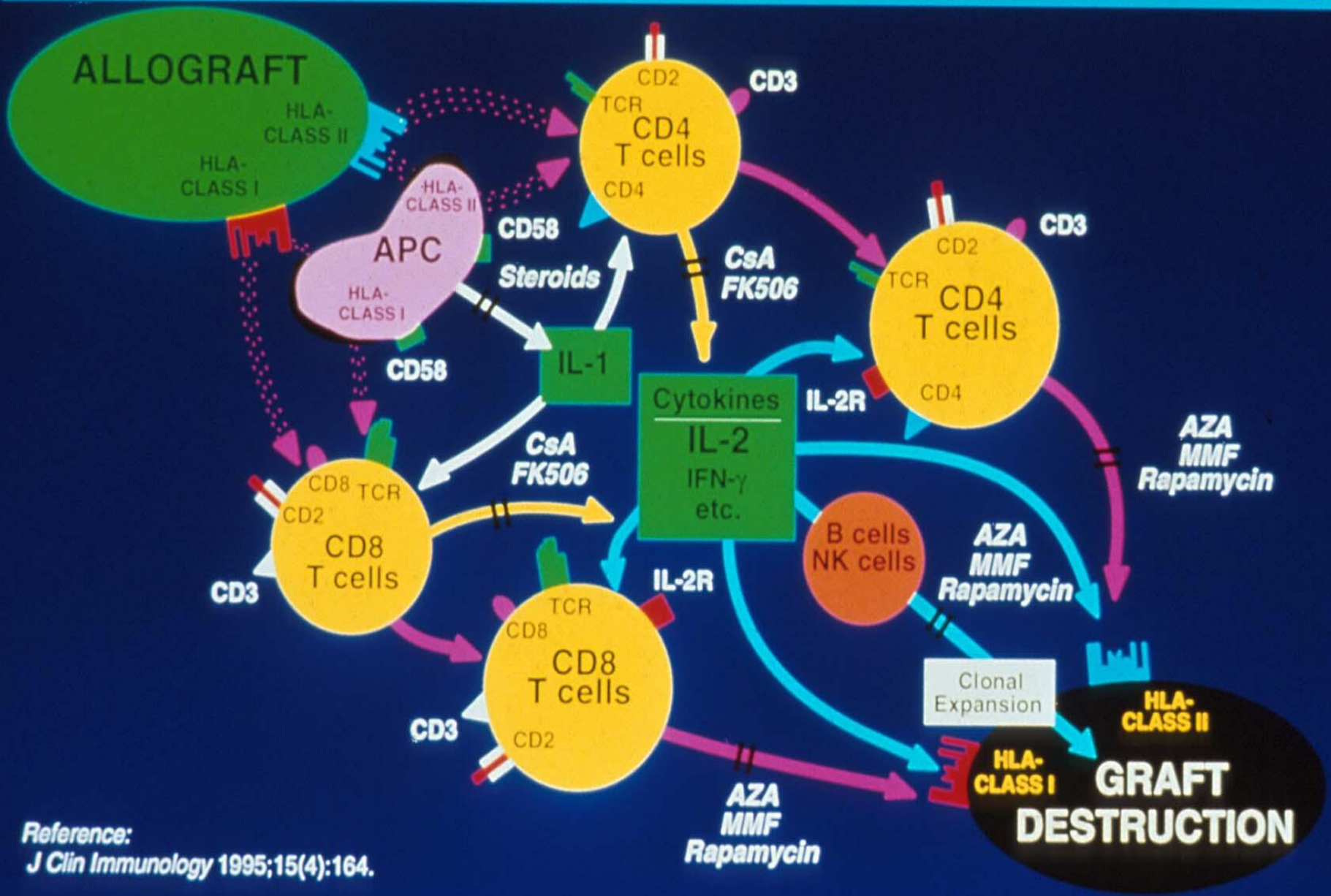


Corticosteroids affect nearly every facet of immune function, although less inhibition of humoral arm than cell-mediated arm; they also induce apoptosis in rapidly-dividing leukocytes

DEVELOPMENTS IN IMMUNOSUPPRESSION



Immunosuppressive Activity



Reference:
J Clin Immunology 1995;15(4):164.

Table 8

Side Effect Profiles of Immunosuppressive Drugs

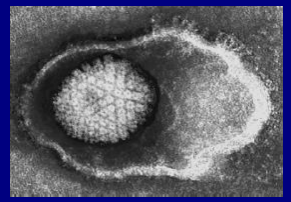
	CsA	Tac	Srl	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal insufficiency	++	++	∅	∅	∅
Hyperlipidemia	++	+	+++	++	∅
Hyperkalemia	+++	+++	∅	∅	∅
Tremor	∅	+	∅	∅	∅
Hirsutism	+	∅	∅	∅	∅
Gingival hyperplasia	+	∅	∅	∅	∅
Hypophosphatemia	++	++	+	∅	∅
Osteoporosis	±	±	∅	+++	∅
Malignancy	+	+	?	∅	+

CsA, cyclosporin; Tac, tacrolimus; Srl, Sirolimus; Ster, Steroids; MMF, mycophenolate mofetil.

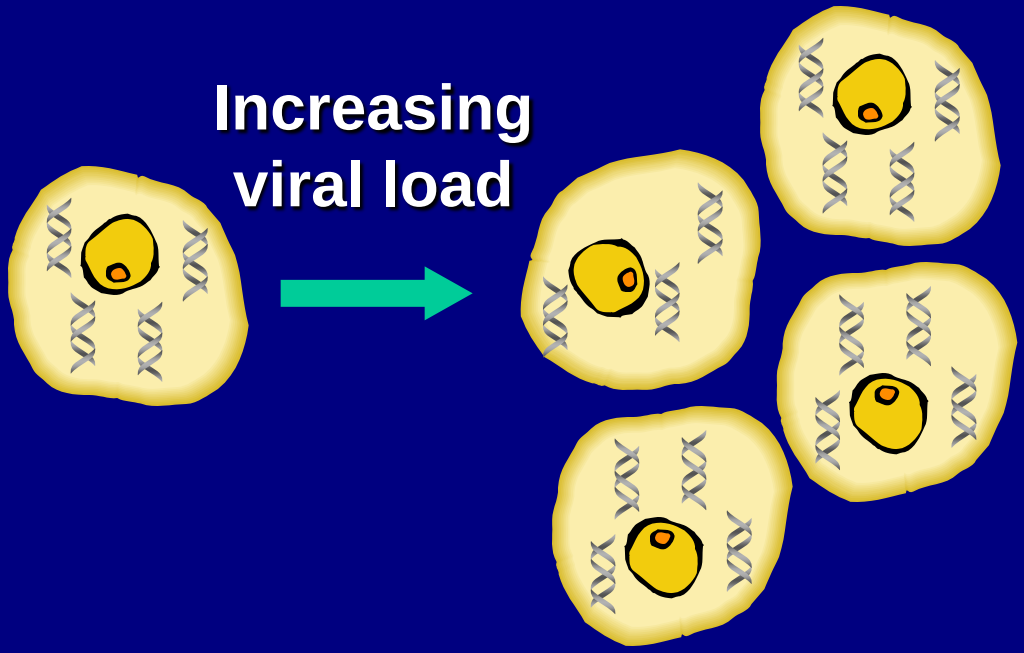
Adapted from Dr Martin Zand, University of Rochester.

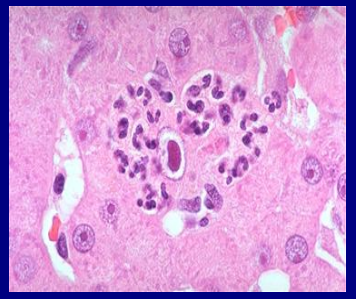
Steroids
CsA

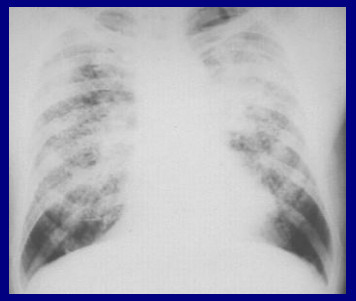
MMF

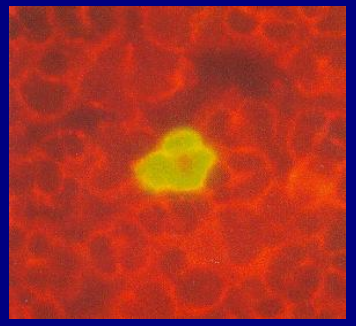


Increasing
viral load









CMV INFECTION

CMV DISEASE

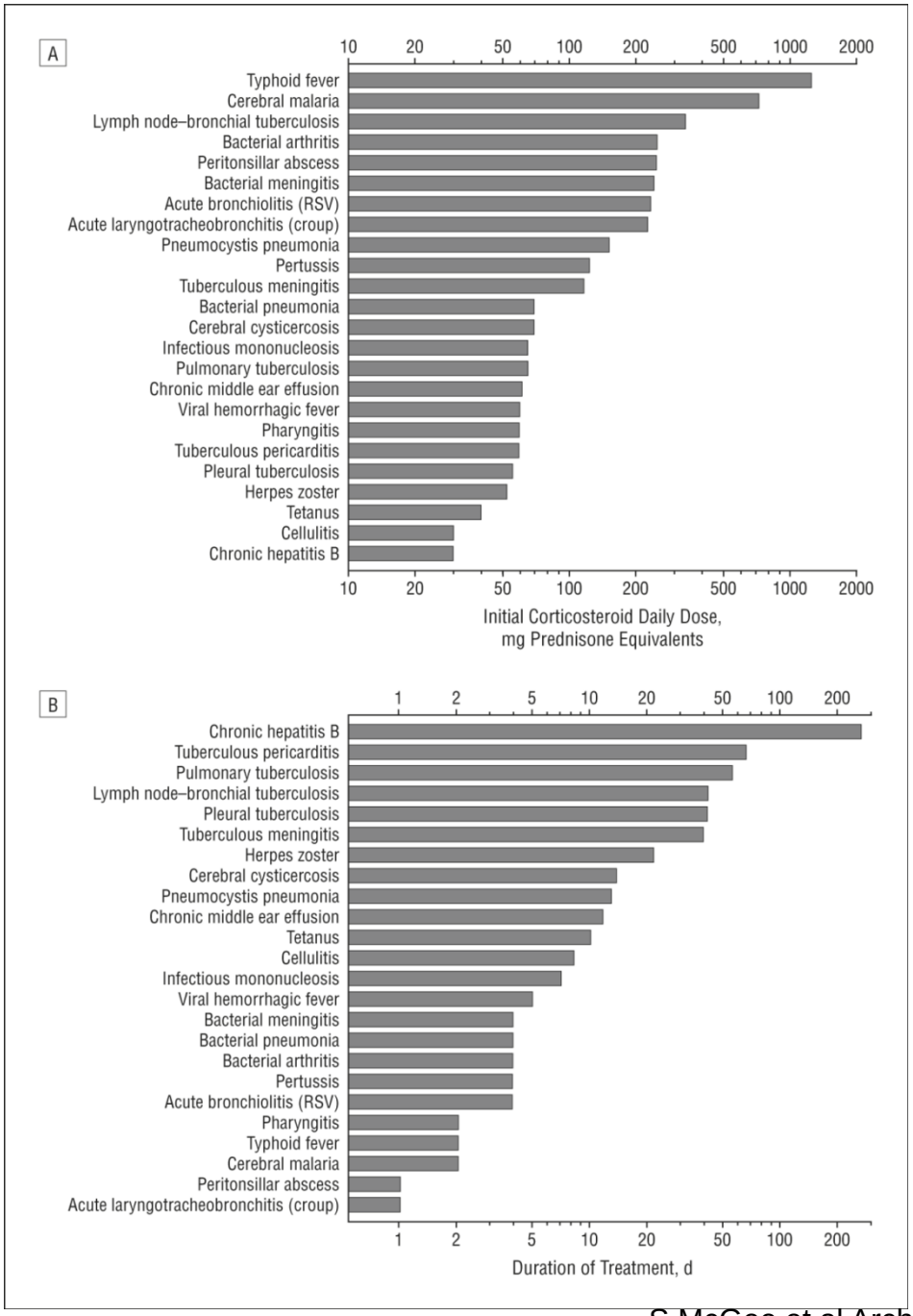
Clinicians have generally avoided prescribing corticosteroids for active infection because of their known immunosuppressive effects and concern about long-term complications.

S.McGee et al Arch Intern Med. 2008;168(10):1034-1046.

SPECIAL ARTICLE

Use of Corticosteroids in Treating Infectious Diseases

Steven McGee, MD; Jan Hirschmann, MD



S.McGee et al Arch Intern Med. 2008;168(10):1034-1046

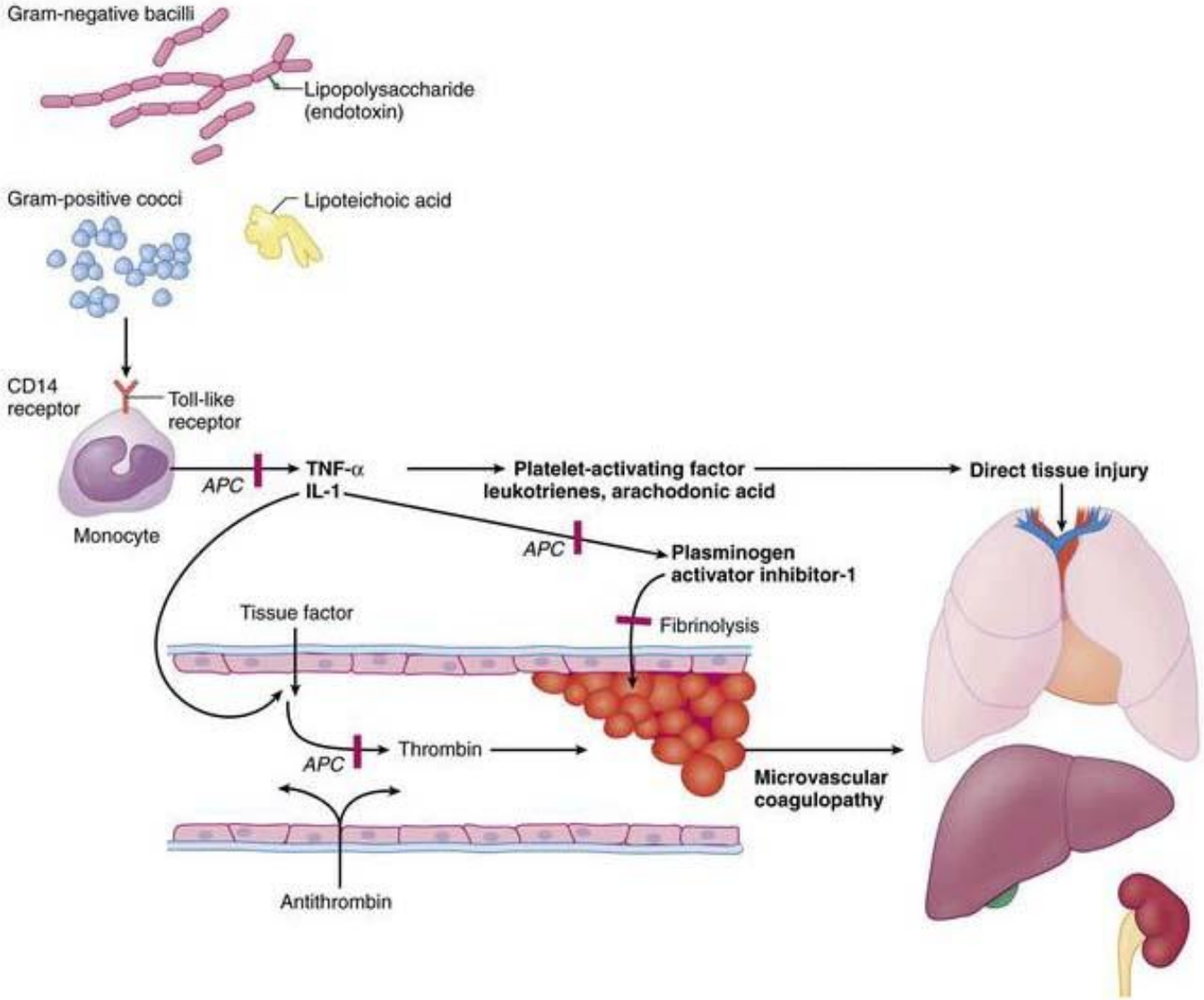
Bacterial (Nontuberculous) Infections and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Table 2. Bacterial (Nontuberculous) Infections and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Source	No. of Patients	Type of Patients	Corticosteroid, Initial Daily Dose	Duration of Treatment, d
		Bacterial Meningitis		
Molyneux et al, 2002[65]	602	Children with bacterial meningitis	Dexamethasone IV, 0.8 mg/kg[a]	2
Scarborough et al, 2007[66]	465	Adults with bacterial meningitis	Dexamethasone IV, 32 mg[a]	4
Nguyen et al, 2007[67]	435	Adults with bacterial meningitis	Dexamethasone IV, 0.8 mg/kg	4
Peltola et al, 2007[68]	329	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg	2
de Gans and van de Beek, 2002[69]	301	Adults with bacterial meningitis	Dexamethasone IV, 40 mg[a]	4
Lebel et al, 1988[70]	200	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg	4
Wald et al, 1995[71]	143	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg	4
Schaad et al, 1993[72]	115	Children with bacterial meningitis	Dexamethasone IV, 0.8 mg/kg[a]	2
DeLemos and Haggerty, 1969[73]	109	Children with bacterial meningitis	Methylprednisolone IV, 160 mg	3
Odio et al, 1991[74]	101	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg[a]	4
Qazi et al, 1996[75]	89	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg[a]	4
Belsey et al, 1969[76]	86	Children with bacterial meningitis	Dexamethasone IV, 1.2 mg/m^2	4
Thomas et al, 1999[77]	60	Adults with bacterial meningitis	Dexamethasone IV, 40 mg	3
Lebel et al, 1989[78]	60	Children with bacterial meningitis	Dexamethasone IV, 0.6 mg/kg	4
Kanra et al, 1995[79]	53	Children with pneumococcal meningitis	Dexamethasone IV, 0.6 mg/kg	4
		Bacterial Pneumonia		
Wagner et al, 1956[80]	113	Adults with uncomplicated pneumococcal pneumonia	Hydrocortisone PO, 260 mg[b]	5
Kirby et al, 1960[81c]	42	Adults with pneumococcal pneumonia	Methylprednisolone PO, 32 mg[b]	4
Confalonieri et al, 2005[82]	46	Adults admitted to ICU with severe community-acquired pneumonia	Hydrocortisone IV, 200-mg loading dose, then 10 mg/h	7
Marik et al, 1993[83]	30	Adults admitted to ICU with severe community-acquired pneumonia	Hydrocortisone IV, 10 mg/kg	1
		Bacterial Arthritis		
Odio et al, 2003[84]	123	Children with septic arthritis	Dexamethasone IV, 0.6 mg/kg	4
		Pharyngitis		
Bulloch et al, 2003[85]	184	Children with acute pharyngitis, < 48 h	Dexamethasone PO, 0.6 mg/kg	1
Hahn et al, 1950[86]	174	Military recruits with acute pharyngitis, < 31 h	Cortisone IM, 50 or 100 mg	5
Olympia et al, 2005[87]	143	Children with acute pharyngitis	Dexamethasone PO, 0.6 mg/kg	1
Wei et al, 2002[88]	111	Adults with acute pharyngitis	Dexamethasone PO or IV, 10 mg	1
Marvez-Valls et al, 1998[89]	92	Adults with acute pharyngitis	Betamethasone IM, 12 mg	1
Niland et al, 2006[90]	90	Children with acute pharyngitis	Dexamethasone PO, 0.6 mg/kg	3
O'Brien et al, 1993[91]	58	Adults with acute pharyngitis	Dexamethasone IM, 10 mg	1
		Peritonsillar Abscess		
Ozbek et al, 2004[92]	62	Adults with peritonsillar abscess	Methylprednisolone, 2-3 mg/kg	1
		Cellulitis		
Bergkvist and Sjobeck, 1997, 1998[93,94]	112	Adults hospitalized with cellulitis	Prednisolone, 30 mg[b]	8
		Chronic Middle Ear Effusion		
Podoshin et al, 1990[95]	136	Children with effusion after otitis media, > 2 mo duration	Prednisone, 1 mg/kg[b]	14
Berman et al, 1990[96]	53	Children with effusion after otitis media, > 6 wk duration	Prednisone, 1-2 mg/kg	7
		Typhoid Fever		
Hoffman et al, 1984[97]	38	Children and adults with severe typhoid fever	Dexamethasone IV, 3 mg/kg	2
		Tetanus		
Payda et al, 1988[98]	63	Children and adults in ICU with severe tetanus	Prednisolone (parenteral), 40 mg	10
		Pertussis		
Roberts et al, 1992[99]	11	Infants with pertussis	Dexamethasone, 0.3 mg/kg	4

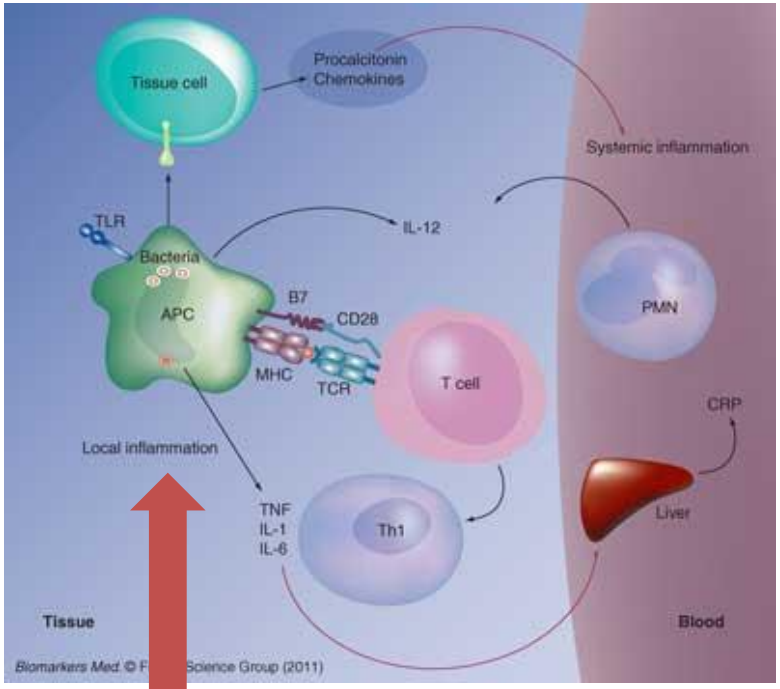
Abbreviations: ICU, intensive care unit; IM, intramuscular; IV, intravenous; PO, oral.
[a]The initial dose of corticosteroids was administered before antibiotics.
[b]The initial daily dose was subsequently tapered.
[c]The study was double-blinded and placebo-controlled but does not clearly state whether it was randomized.

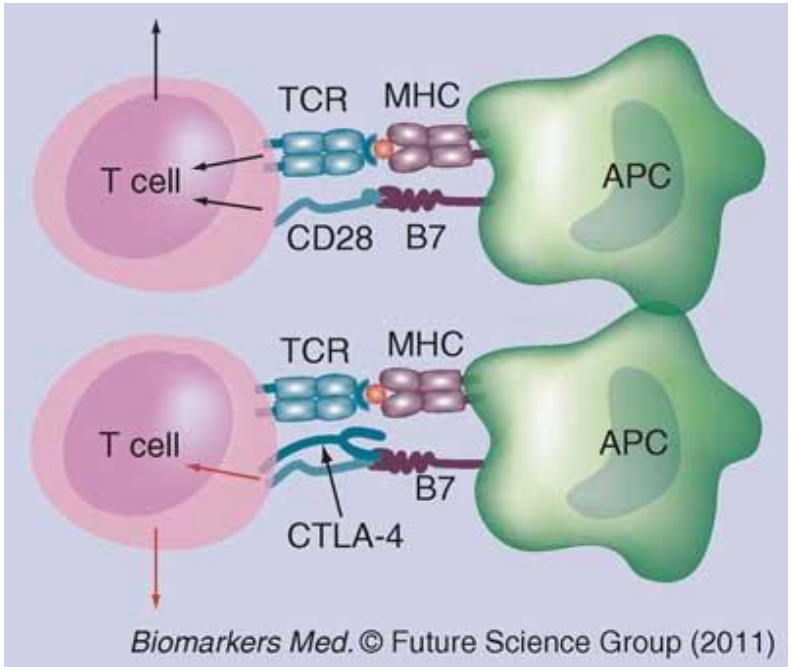
S.McGee et al Arch Intern Med. 2008;168(10):1034-1046.


Gram-negative bacilli
Lipopolysaccharide (endotoxin)
Gram-positive cocci
Lipoteichoic acid
CD14 receptor
Toll-like receptor
Monocyte
APC
TNF-α
IL-1
Platelet-activating factor
leukotrienes, arachodonic acid
Direct tissue injury
APC
Plasminogen activator inhibitor-1
Tissue factor
Fibrinolysis
APC
Thrombin
Microvascular coagulopathy
Antithrombin

Pro-inflammatory Phase of Sepsis

Immunosuppressive Phase of Sepsis





STEROIDS

Steroids for Septic Shock*

Back From the Dead? (Pro)

Robert A. Balk, MD, FCCP

CHEST / 123 / 5 / MAY, 2003

Cronin L et al. Crit Care Med 1995

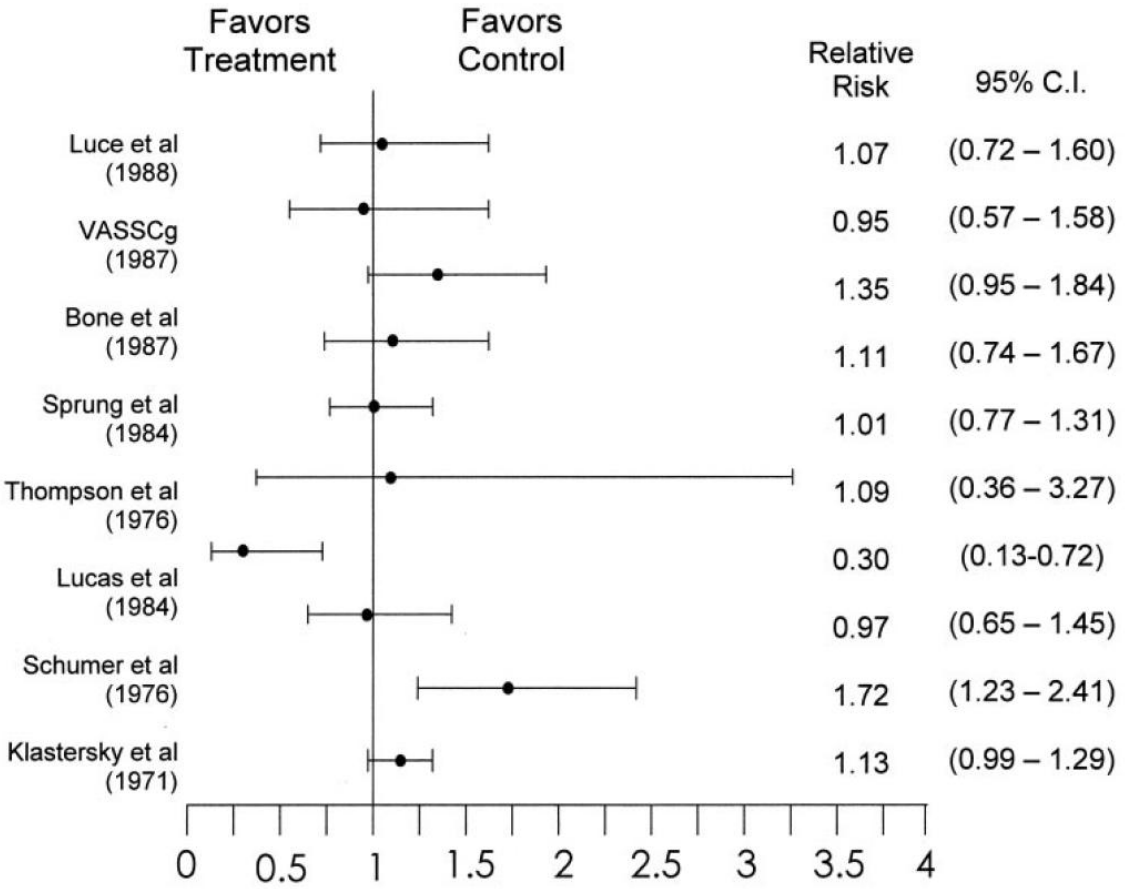


FIGURE 1. Review evidence on benefit of high-dose early administration of corticosteroids in sepsis and shock. Reprinted with permission from Cronin et al.[3] CI = confidence interval; VASSCg = Veterans Administration Systemic Sepsis Cooperative Study Group.

The review critically evaluated a pool of 124 relevant articles on this topic using the techniques of evidence-based medicine and concluded that there was *no convincing evidence* that *high-dose early administration of corticosteroids in patients with severe sepsis and septic shock was beneficial*

Reversal of late septic shock with supraphysiologic doses of hydrocortisone

Bollaert, Pierre-Edouard MD, PhD; Charpentier, Claire MD; Levy, Bruno MD; Debouverie, Marc MD; Audibert, Gerard MD; Larcan, Alain MD, PhD

Crit Care Med 1998

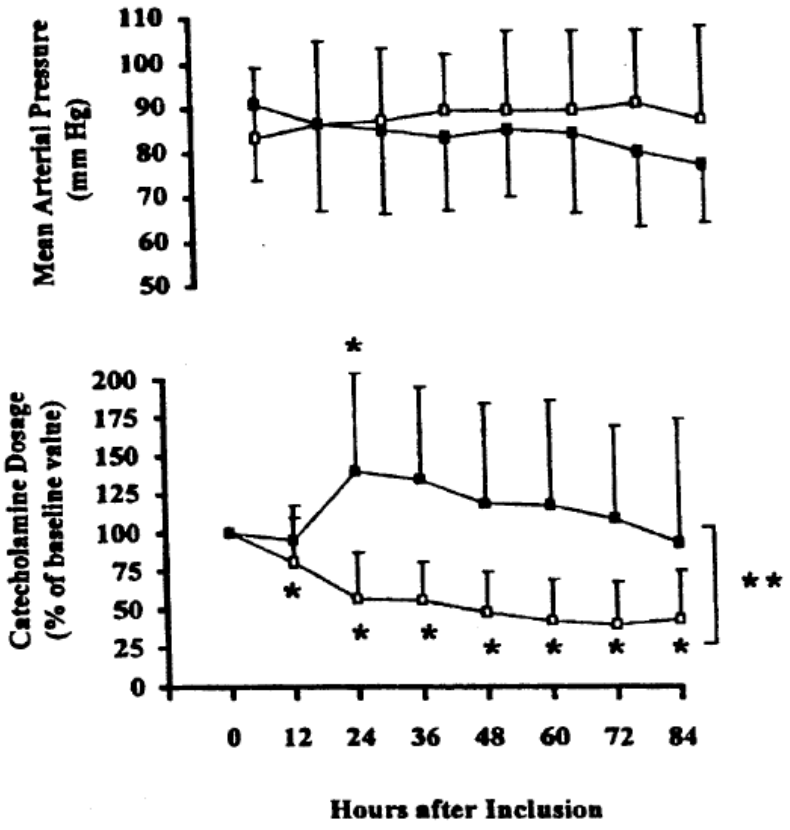


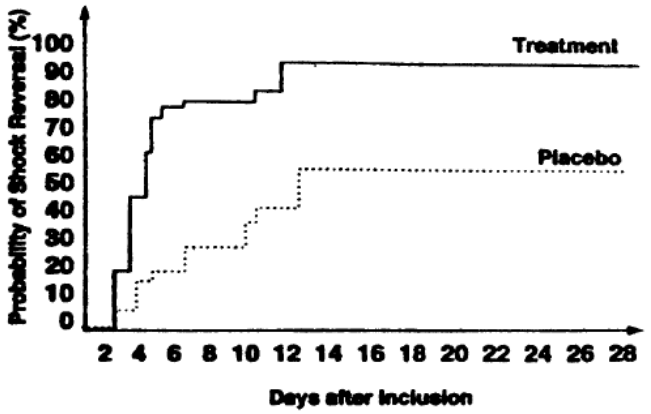
FIGURE 2. Evolution of hemodynamic parameters and catecholamine dosage over time. Reprinted with permission from Bollaert et al.[28]

Significant decrease in the cumulated amount of catecholamines perfused in the treatment group compared with baseline ($p < .001$) and placebo group ($p = .002$)

Reversal of late septic shock with supraphysiologic doses of hydrocortisone

Bollaert, Pierre-Edouard MD, PhD; Charpentier, Claire MD; Levy, Bruno MD; Debouverie, Marc MD; Audibert, Gerard MD; Larcan, Alain MD, PhD

Crit Care Med 1998



28-day reversal of shock was significantly higher in the treatment group (p = .005)

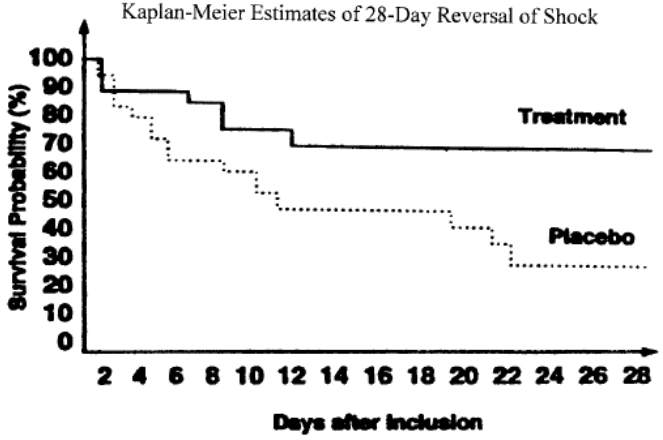


FIGURE 3. Kaplan-Meier curves of shock reversal and mortality over the 28-day study. Reprinted with permission from Bollaert et al.[28]

Overall 28-day mortality was seven (32%) of 22 treated patients and 12 (63%) of 19 placebo patients, a difference of 31% (95% confidence interval 1% to 61%; p = .045)

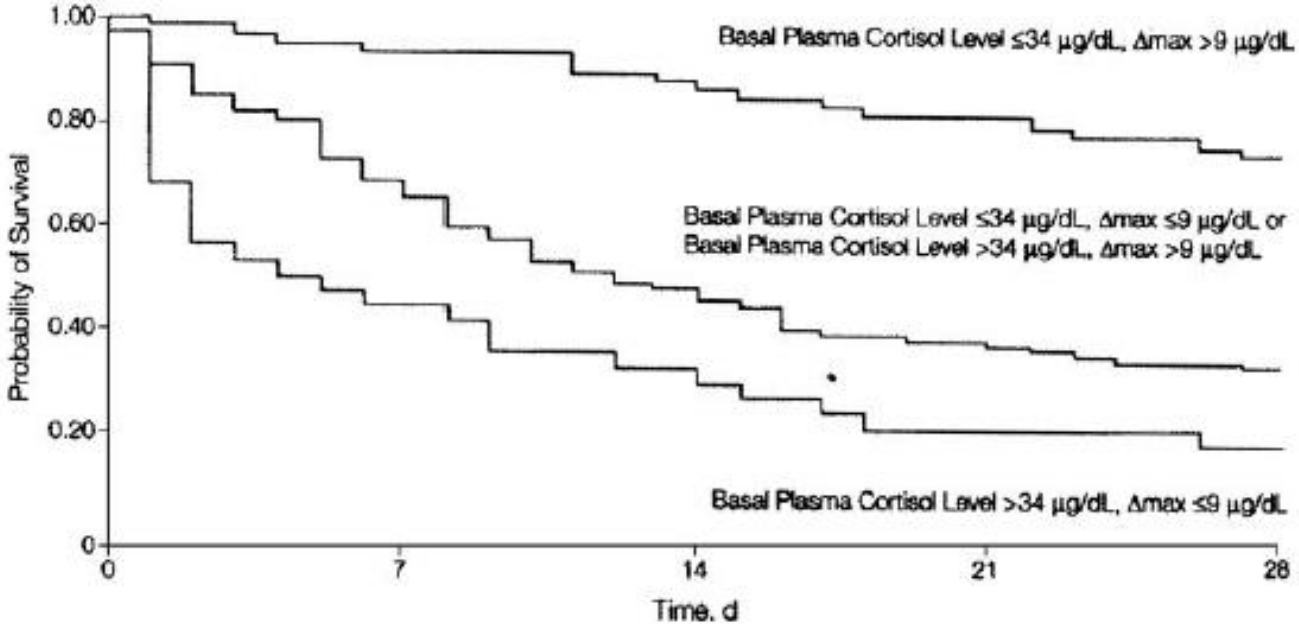


FIGURE 8. Survival curves of septic shock patients according to basal plasma cortisol level and maximum response to corticotropin stimulation test. Reprinted with permission from Annane et al.[30] Δmax = difference between baseline and post-ACTH cortisol levels.

These findings support the concept that some patients with severe sepsis and septic shock have "relative" adrenal insufficiency and may benefit from supplemental therapy with corticosteroids.

Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000; 283:1038–1045

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 10, 2008 VOL. 358 NO. 2

Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

CONCLUSIONS

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)

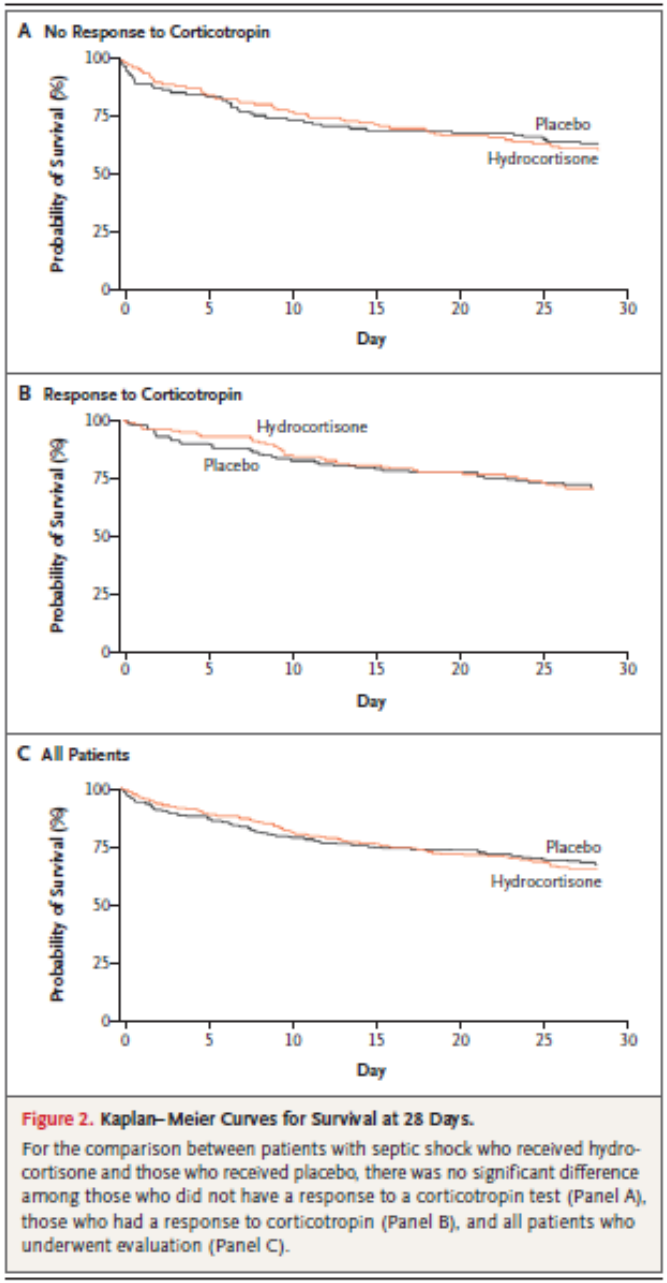


Figure 2. Kaplan–Meier Curves for Survival at 28 Days.

For the comparison between patients with septic shock who received hydrocortisone and those who received placebo, there was no significant difference among those who did not have a response to a corticotropin test (Panel A), those who had a response to corticotropin (Panel B), and all patients who underwent evaluation (Panel C).

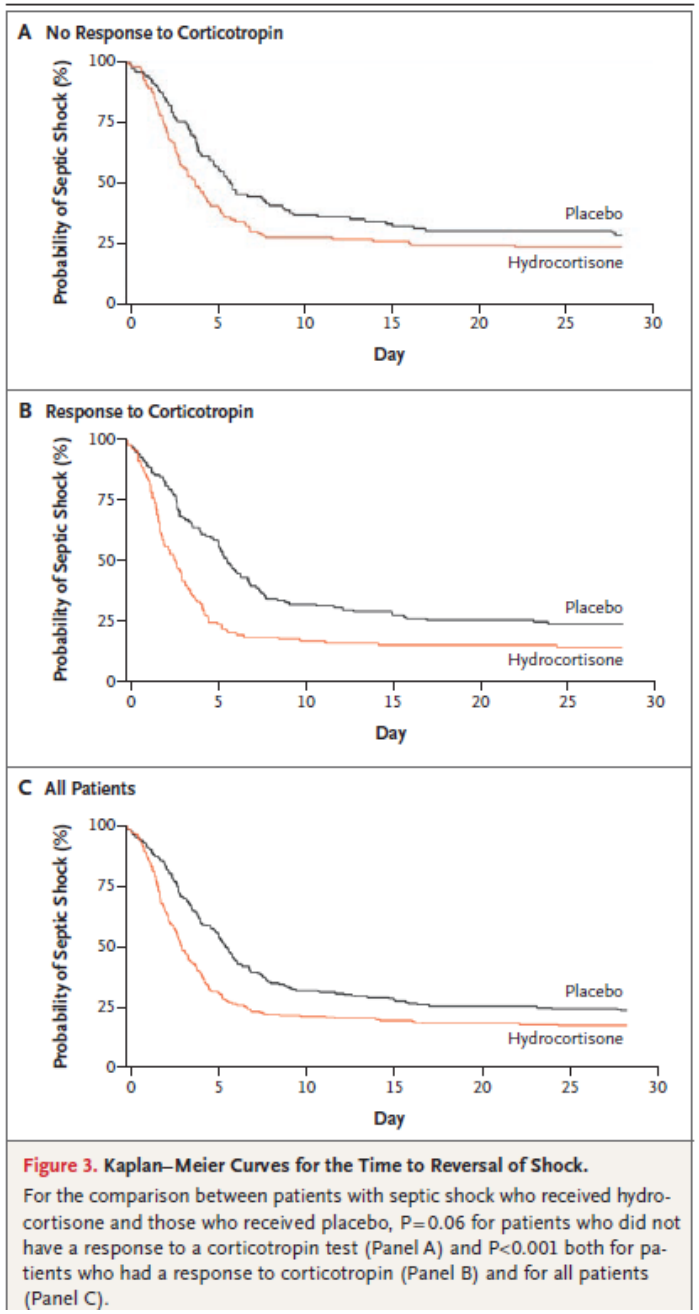


Figure 3. Kaplan–Meier Curves for the Time to Reversal of Shock.

For the comparison between patients with septic shock who received hydrocortisone and those who received placebo, P=0.06 for patients who did not have a response to a corticotropin test (Panel A) and P<0.001 both for patients who had a response to corticotropin (Panel B) and for all patients (Panel C).

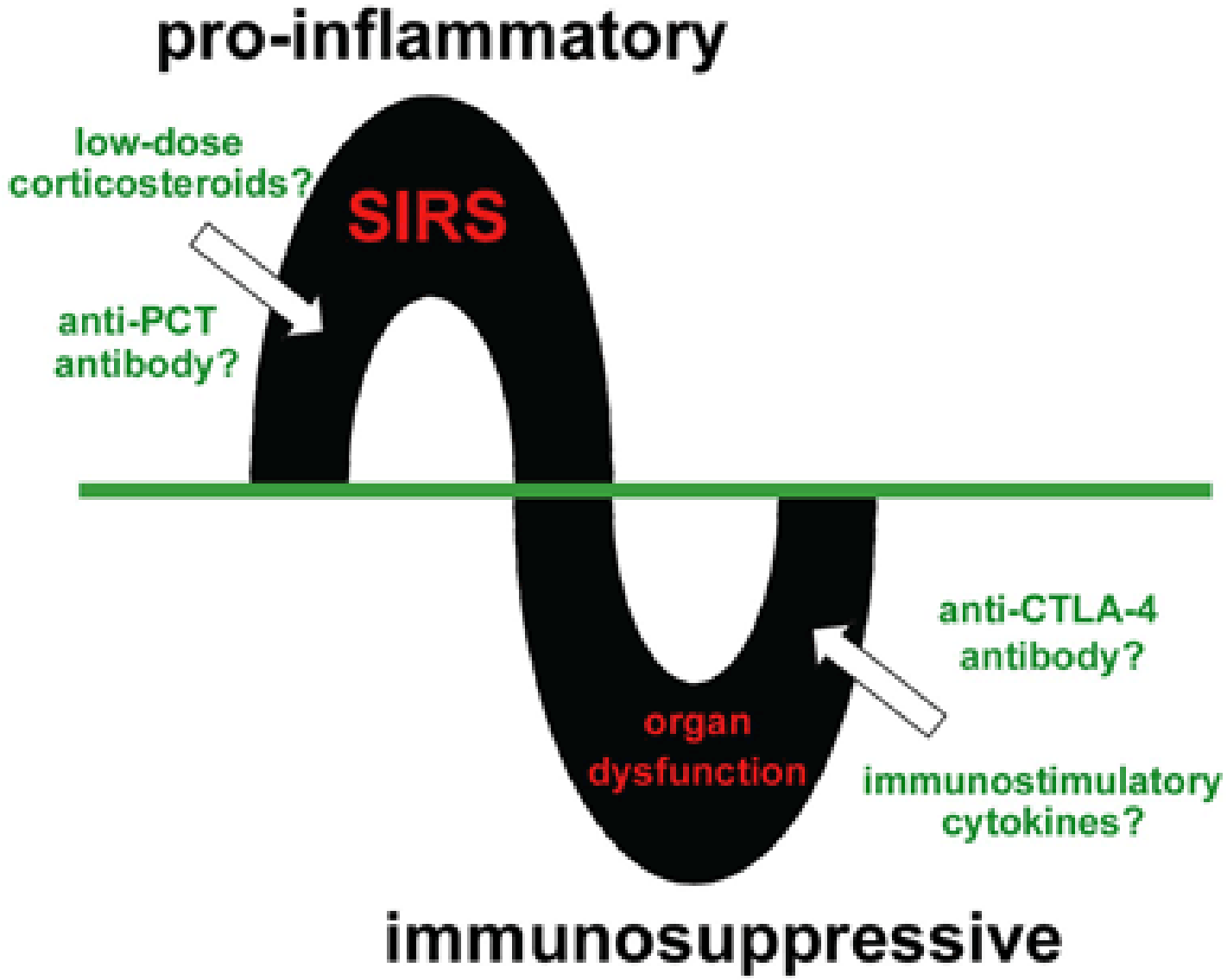
Surviving Sepsis Campaign

International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
Table of Contents

J. Corticosteroids

1. We suggest not using intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (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).


pro-inflammatory
low-dose corticosteroids?
SIRS
anti-PCT antibody?
anti-CTLA-4 antibody?
organ dysfunction
immunostimulatory cytokines?
immunosuppressive

The New England
Journal of Medicine

VOLUME 347 NOVEMBER 14, 2002 NUMBER 20

DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

JAN DE GANS, PH.D., AND DIEDERIK VAN DE BEEK, M.D., FOR THE EUROPEAN DEXAMETHASONE IN ADULTHOOD BACTERIAL MENINGITIS STUDY INVESTIGATORS*

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DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

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TABLE 2. OUTCOMES EIGHT WEEKS AFTER ADMISSION, ACCORDING TO CULTURE RESULTS.*

OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
Streptococcus pneumoniae	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
Neisseria meningitidis	4/50 (8)	5/47 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20
Focal neurologic abnormalities				
All patients	18/143 (13)	24/119 (20)	0.62 (0.36–1.09)	0.13
S. pneumoniae	11/49 (22)	11/33 (33)	0.67 (0.33–1.37)	0.32
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	3/11 (27)	3/16 (19)	1.45 (0.36–5.92)	0.66
Negative bacterial culture	1/37 (3)	5/26 (19)	0.14 (0.02–1.13)	0.07
Hearing loss				
All patients	13/143 (9)	14/119 (12)	0.77 (0.38–1.58)	0.54
S. pneumoniae	7/49 (14)	7/33 (21)	0.67 (0.25–1.69)	0.55
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	2/11 (18)	1/16 (6)	2.91 (0.30–28.3)	0.55
Negative bacterial culture	1/37 (3)	1/26 (4)	0.70 (0.05–10.7)	1.00

IDSA GUIDELINES

2004

Practice Guidelines for the Management of Bacterial Meningitis

Allan R. Tunkel,[1] Barry J. Hartman,[2] Sheldon L. Kaplan,[3] Bruce A. Kaufman,[4] Karen L. Roos,[5] W. Michael Scheld,[6] and Richard J. Whitley[7]

However, we think that adjunctive dexamethasone should be initiated in all adult patients with suspected or proven pneumococcal meningitis, because assessment of the score may delay initiation of appropriate therapy. Dexamethasone should only be continued if the CSF Gram stain reveals gram-positive diplococci, or if blood or CSF cultures are positive for S. pneumoniae.

Adjunctive dexamethasone should not be given to adult patients who have already received antimicrobial therapy, because administration of dexamethasone in this circumstance is unlikely to improve patient outcome (A-I). The data are inadequate to recommend adjunctive dexamethasone to adults with meningitis caused by other bacterial pathogens, although some authorities would initiate dexamethasone in all adults, because the etiology of meningitis is not always ascertained at initial evaluation (B-III).

Corticosteroids for acute bacterial meningitis

The Cochrane Library

2013

Matthijs C Brouwer[1], Peter McIntyre[2], Kameshwar Prasad[3], Diederik van de Beek[1]

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Authors' conclusions

Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality. Data support the use of corticosteroids in patients with bacterial meningitis in high-income countries. We found no beneficial effect in low-income countries.

Figure 9. Forest plot of comparison: 1 All patients, outcome: 1.1 Mortality.

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bademosi 1979	12	24	11	28	2.6%	1.27 [0.69, 2.34]
Belsey 1969	2	43	1	43	0.3%	2.00 [0.19, 21.24]
Bennett 1963	16	38	22	47	5.0%	0.90 [0.56, 1.46]
Bhaumik 1998	1	14	3	16	0.7%	0.38 [0.04, 3.26]
Ciana 1995	8	34	12	36	3.0%	0.71 [0.33, 1.51]
de Gans 2002	11	157	21	144	5.6%	0.48 [0.24, 0.96]
DeLemos 1969	2	54	1	63	0.2%	2.33 [0.22, 25.03]
Girgis 1989	21	225	43	245	10.4%	0.53 [0.33, 0.87]
Kanra 1995	2	29	1	27	0.3%	1.86 [0.18, 19.38]
Kilpi 1995	0	32	0	26		Not estimable
King 1994	0	50	1	51	0.4%	0.34 [0.01, 8.15]
Lebel 1988a	0	51	1	49	0.4%	0.32 [0.01, 7.68]
Lebel 1988b	0	51	0	49		Not estimable
Lebel 1989	0	31	1	30	0.4%	0.32 [0.01, 7.63]
Molyneux 2002	96	305	91	293	23.6%	1.01 [0.80, 1.29]
Nguyen 2007	22	217	26	218	6.6%	0.85 [0.50, 1.45]
Odio 1991	1	52	1	49	0.3%	0.94 [0.06, 14.65]
Peltola 2007	23	166	26	163	6.7%	0.87 [0.52, 1.46]
Qazi 1996	12	48	5	41	1.4%	2.05 [0.79, 5.33]
Sankar 2007	0	12	1	13	0.4%	0.36 [0.02, 8.05]
Scarborough 2007	129	231	120	228	30.6%	1.06 [0.90, 1.26]
Schaad 1993	0	60	0	55		Not estimable
Thomas 1999	3	31	5	29	1.3%	0.56 [0.15, 2.14]
Wald 1995	1	69	0	74	0.1%	3.21 [0.13, 77.60]
Total (95% CI)		**2024**		**2017**	**100.0%**	**0.92 [0.82, 1.04]**
Total events	362		393			

Heterogeneity: Chi² = 20.57, df = 20 (P = 0.42); I² = 3%

Test for overall effect: Z = 1.34 (P = 0.18)

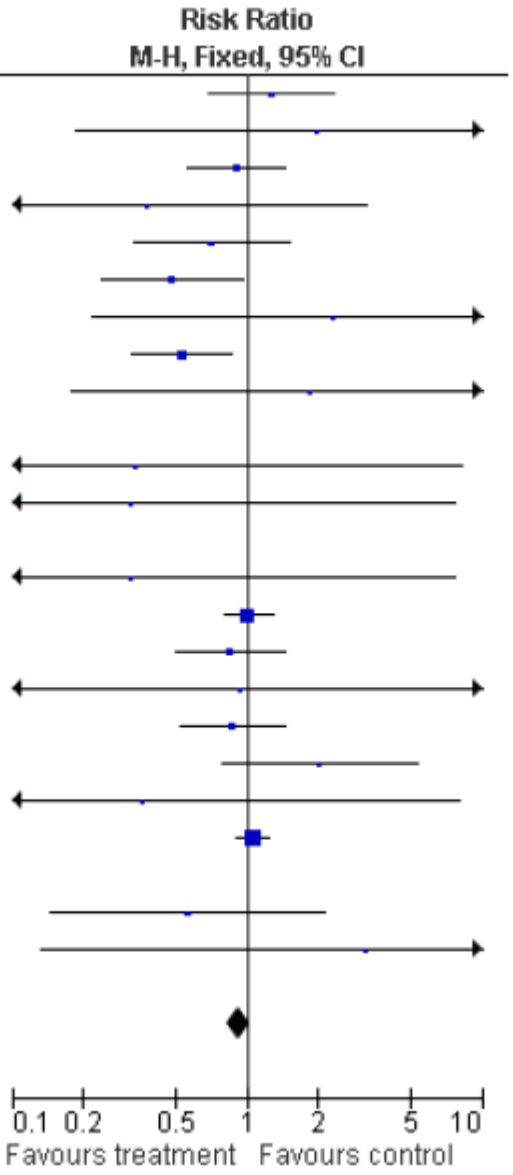


Figure 10. Forest plot of comparison: 1 All patients, outcome: 1.2 Severe hearing loss.

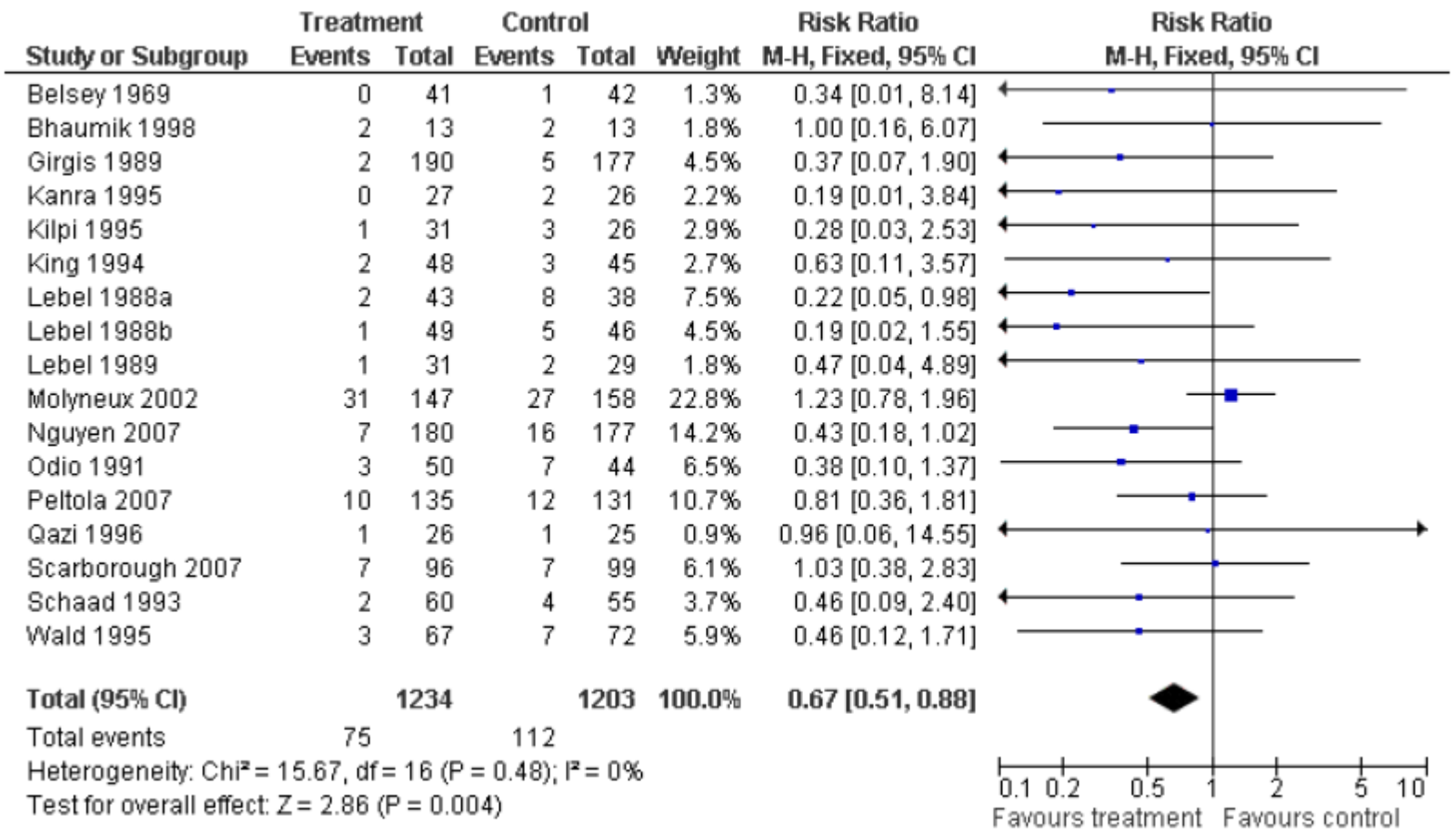
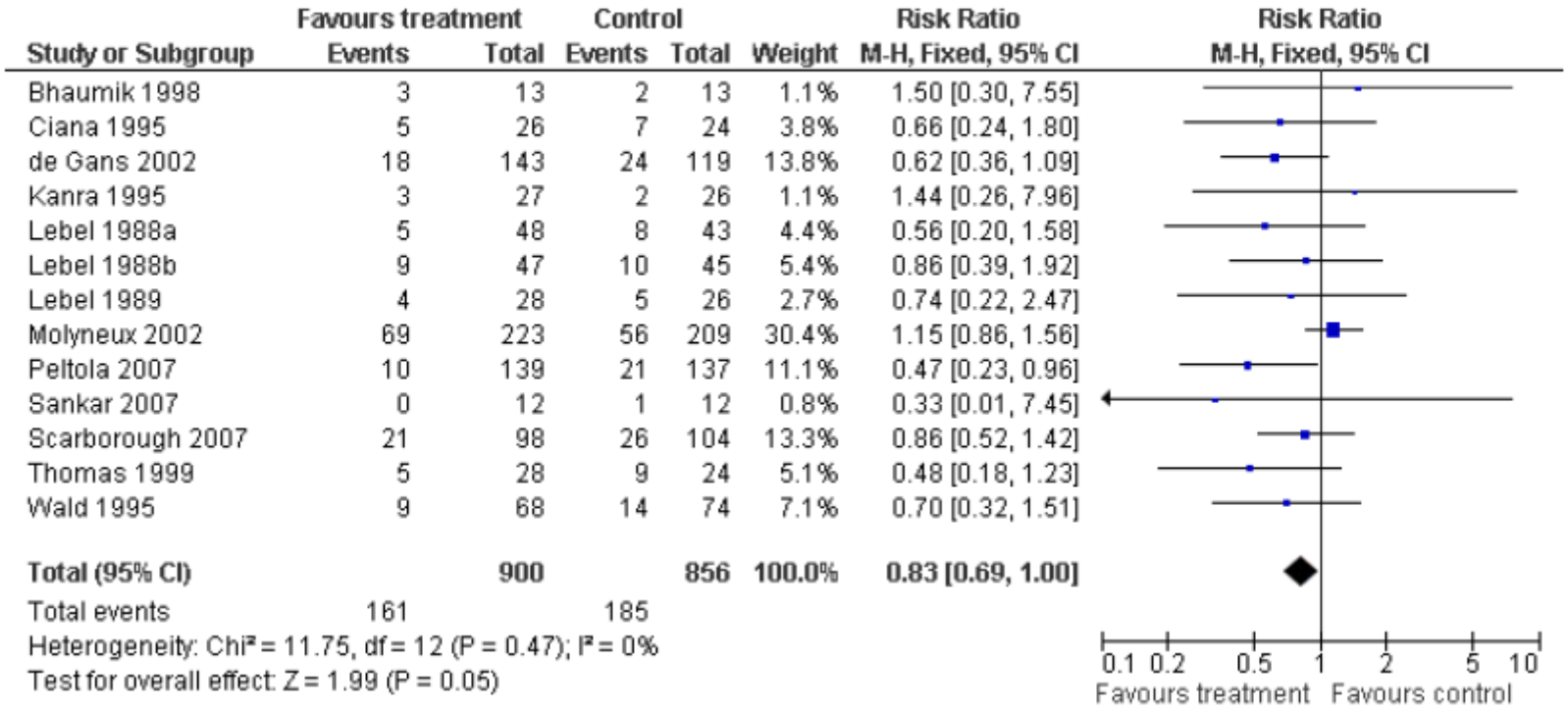


Figure 12. Forest plot of comparison: 1 All patients, outcome: 1.4 Short-term neurological sequelae.



Review article EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 17 (2013)

Should corticosteroids be used in bacterial meningitis in children?

Susanna Esposito, Margherita Semino, Irene Picciolli, Nicola Principi*

1. **In high-income countries dexamethasone has shown good results to prevent hearing loss in Hib meningitis if administered before or at the same time as the first dose of antibiotics.**

2. **Dexamethasone should be evaluated in pneumococcal meningitis: it may be less beneficial in children with delayed presentation to medical attention and may be unfavourable in case of cephalosporin-resistant pneumococci.**

3. **There is no evidence to recommend the use of corticosteroids in meningococcal meningitis.**

Bacterial meningitis in children

Xavier Sáez-Llorens, George H McCracken Jr

Lancet 2003

Panel 4: **Commonly-used supportive and adjunctive treatment in bacterial meningitis**

Rationale	Strategies	Cautions
Reduction of raised intracranial pressure	30º bed head elevation, antipyretic agents, avoidance of vigorous and frequent intratracheal suctioning and intubation, correction of hyponatraemia and SIADH, hyperventilation, use of mannitol, high-dose barbiturate therapy	Fluid restriction can be dangerous if patient has dehydration or hypovolaemia; significant reduction of $PaCO_2$ (<25 mm Hg) can affect cerebral blood flow; cardiac toxicity with pentobarbital
Control and prevention of seizures	Anticonvulsant drugs (lorazepam, diazepam, phenytoin, phenobarbital)	Respiratory depression and hypotension with benzodiazapines and phenobarbital; cardiac arrythmias with phenytoin
Amelioration of meningeal inflammation	Dexamethasone	Potential delayed eradication of highly-resistant pneumococci from CSF; rare risk of GI bleeding; possibly, long-term cognitive impairment due to cell apoptosis in hippocampus

CSF=cerebrospinal fluid. SIADH=syndrome of inappropriate secretion of anti-diuretic hormone. GI=gastrointestinal.

The Committee on Infectious Diseases of the American Academy of Pediatrics on the use of steroids for pneumococcal meningitis is as follows:
“For infants and children 6 weeks of age and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and possible risks. Experts vary in recommending the use of corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate clear benefit in children”

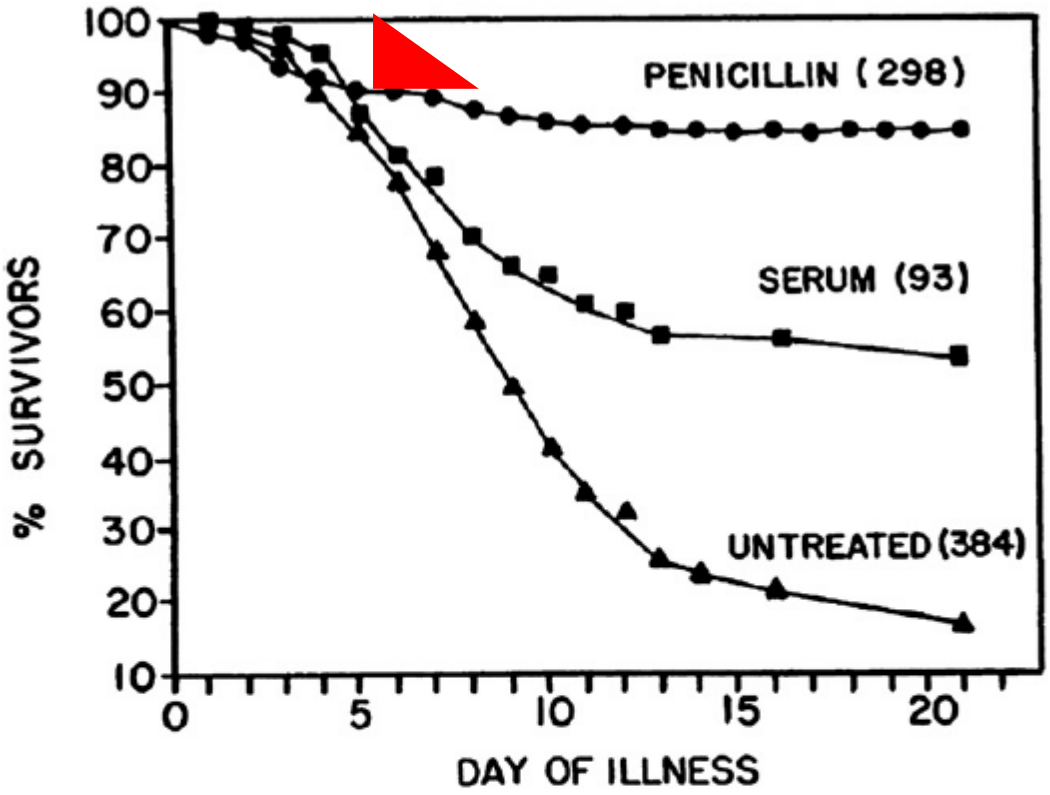


Figure 1 Effect of therapy in % survival in pneumococcal bactreremia. Numbers in parentheses indicate number of patients in each treatment category. Data for untreated and serum- treated patients derived from studies published in pre-antibiotic era. (Reproduced with permission from Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med* 1964; 60:759–776).

Review

Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2012.02554.x

Treatment with anti-inflammatory drugs in community-acquired pneumonia

S. C. A. Meijvis[1], E. M. W. van de Garde[2,3], G. T. Rijkers[4,5] & W. J. W. Bos[1]

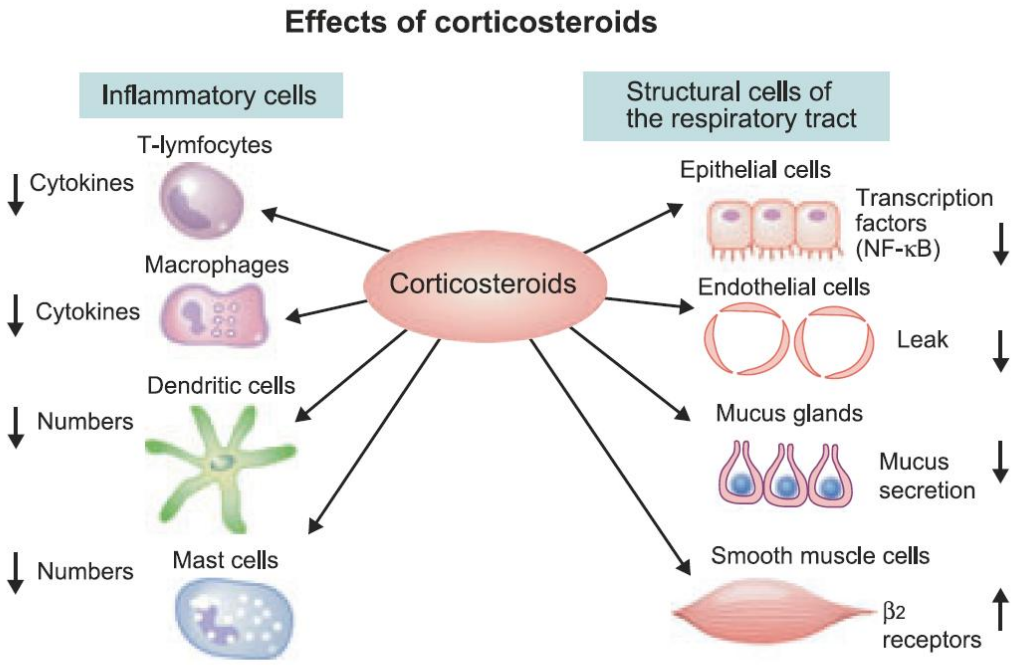


Fig. 4 *Overview of the cellular effects of corticosteroids.*

REVIEW Journal of Infection (2011) 63, 187–199

Immunomodulatory agents in the treatment of community-acquired pneumonia: A systematic review

Vicente F. Corrales-Medina [a,b,*], Daniel M. Musher [c,d,1]

Table 4 Effect of acute treatment with corticosteroids on outcomes in patients with pneumonia.

Author (Reference #)	Year	Nature of Study	Population	Intervention	Outcome	Effect of corticosteroids
Wagner[95]	1956	Randomized open-label clinical trial	113 hospitalized patients with pneumococcal pneumonia	Hydrocortisone 80 mg bolus followed by 60 mg/6 h × 3 doses, 40 mg/6 h × 4 doses, 20 mg/6 h × 4 doses, 10 mg/6 h × 4 doses, and 10 mg/12 h × 2 doses	Death in hospital	OR, 1.17 (0.07, 19.28)
McHardy[96]	1972	Randomized open-label clinical trial	126 not-severely-ill patients with pneumonia	Prednisolone 20 mg daily for 7 days	Death in hospital	OR, 1.41 (0.39, 5.09)
Marik[97]	1993	Randomized double-blinded clinical trial	30 hospitalized patients with severe CAP[a]	Hydrocortisone one bolus of 10 mg/kg before starting antibitotic therapy	Death in ICU	OR, 0.36 (0.04, 3.69)
Confalonieri[98]	2004	Randomized double-blinded clinical trial	48 hospitalized patients with severe CAP	Hydrocortisone 200 mg bolus followed by 240 mg continous infusion daily for 7 days	PaO_2:FiO_2 ratio improvement (>300 or ≥100 incerease), MODS score and development of delayed septic shock at day 8	Patients on steroid group had significantly better outcomes ($p < 0.05$ for each comparison)
Mikami[99]	2007	Randomized open-label clinical trial	31 hospitalized patients with CAP	Prednisolone 40 mg daily for 3 days	Length (days) of hospital stay	11.3 (±5.5) vs. 15.5 (±10.7), p 0.18, favoring perdnisolone
Snijders[100]	2010	Randomized double-blinded clinical trial	213 hospitalized patients with CAP	Prednisolone 40 mg daily for 7 days	Clinical cure at 30 days[b]	OR, 0.59 (0.32, 1.07)
Fernandez-Serrano[101]	2011	Randomized double-blinded clinical trial	56 hospitalized patients with severe CAP	Methyl-prednisolone 200 mg/bolus followed by 20 mg/6 h × 3 days, 20 mg/12 h × 3 days, and 20 mg/24 h × 3 days	Need for non-invasive positive pressure ventilation or mechanical ventilation by day 9	OR, 0.2 (0.02, 1.84)
Meijvis[102]	2011	Randomized double-blinded clinical trial	304 hospitalized patients with CAP	Dexamethasone 5 mg intravenously daily for 4 days	Length (days) of hospital stay	6.5 (IQR 5.0–9.0) vs. 7.5 (5.3–11.5), favoring dexamethasone

MODS denotes multi-organ dysfunction syndrome.
IQR denotes inter-quartile range.
[a] Community-acquired pneumonia (CAP) is by strict definition only; otherwise "pneumonia" is stated.
[b] Defined as resolution or improvement of symptoms and clinical signs related to pneumonia.

Our search yielded 8 RCTs that specifically addressed this issue (Table 4).[95–102] These trials are characterized by heterogeneity among their populations, dosing regimens and outcome measures. None has conclusively demonstrated a beneficial effect of corticosteroid therapy on CAP-associated mortality. However, 1 showed a significant one-day reduction in hospital stay,[102] 3 reported faster resolution of clinical symptoms with steroid use,[98,99,101] and 2 suggested less need for mechanical ventilation with this intervention in severely ill patients.[97,98] A high-quality meta-

Corticosteroids	Further study needed to determine value in treating pneumonia of all severity as well as severe disease specifically

Corticosteroids for pneumonia (Review)

Chen Y, Li K, Pu H, Wu T

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 3

AUTHORS' CONCLUSIONS

Implications for practice

In patients with pneumonia, corticosteroids may relieve symptoms but the evidence is weak. In severe pneumonia, corticosteroids can also be used to improve oxygenation and reduce the use of mechanical ventilation. However, there is insufficient evidence to confirm whether they can reduce mortality and resolve pneumonia. We do not recommend the use of steroids for respiratory syncytial virus-infected children with pneumonia because there is no significant benefit for the patient. However, we do recommend corticosteroids for *M. pneumoniae* infected children because corticosteroids can significantly relieve clinical symptoms and prevent relapse of the disease.

Corticosteroids for preventing postherpetic neuralgia (Review)

The Cochrane Library

2013

Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C

THE COCHRANE COLLABORATION®

Authors' conclusions

There is moderate quality evidence that corticosteroids given acutely during zoster infection are ineffective in preventing postherpetic neuralgia. In people with acute herpes zoster the risks of administration of corticosteroids do not appear to be greater than with placebo, based on moderate quality evidence. Corticosteroids have been recommended to relieve the zoster-associated pain in the acute phase of disease. If further research is designed to evaluate the efficacy of corticosteroids for herpes zoster, long-term follow-up should be included to observe their effect on the transition from acute pain to postherpetic neuralgia. Future trials should include measurements of function and quality of life.

Tuberculosis and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Table 3. Tuberculosis and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Source	No. of Patients	Type of Patients	Corticosteroid, Initial Daily Dose	Duration of Treatment, d
		Pulmonary Tuberculosis		
US Public Health Service Trials, 1960, 1965[100,101]	1674	Adults with pulmonary tuberculosis	Prednisolone, 20 mg[a]	35 or 63
Mayanja-Kizza et al, 2005[102]	187	HIV-positive patients with pulmonary tuberculosis	Prednisolone, 2.75 mg/kg[a]	56
Johnson et al, 1965[103]	102	Veterans with pulmonary tuberculosis	Methylprednisolone, 16 mg[a]	84
Weinstein and Koler, 1959[104]	100	Adults with pulmonary tuberculosis	Prednisolone, 20 mg[a]	68
		Lymph Node–Bronchial Tuberculosis		
Nemir et al, 1963, 1967[105,106]	117	Children with primary tuberculosis and suspected endobronchial lymph node disease	Prednisone, 3 mg/kg[a]	37
		Pleural Tuberculosis		
Elliott et al, 2004[107]	197	HIV-positive adults with pleural tuberculosis	Prednisolone, 50 mg[a]	56
Galarza et al, 1995[108]	117	Adults with pleural tuberculosis	Prednisone, 1 mg/kg[a]	30
Wyser et al, 1996[109]	70	Adults with pleural tuberculosis	Prednisone, 0.75 mg/kg[a]	28-42
Lee et al, 1988[110]	40	Adults with pleural tuberculosis	Prednisolone, 0.75 mg/kg[a]	54
		Tuberculous Meningitis		
Thwaites et al, 2004[111]	545	Adults with tuberculous meningitis	Dexamethasone IV, 0.3 mg/kg or 0.4 mg/kg[a]	42 or 56
Girgis et al, 1991[112]	160	Children and adults with tuberculous meningitis	Dexamethasone IM, 12 mg or 8 mg for children < 25 kg[a]	42
Schoeman et al, 1997, 2001[113,114]	116	Children with tuberculous meningitis	Prednisone, 2 mg/kg or 4 mg/kg	30
Escobar et al, 1975[115]	99	Children with tuberculous meningitis	Prednisone, 10 mg/kg[a] or 1 mg/kg	30
Kumarvelu et al, 1994[116]	47	Children and adults with tuberculous meningitis	Dexamethasone IV, 16 mg[a]	42
O'Toole et al, 1969[117]	23	Children and adults with tuberculous meningitis	Dexamethasone parenteral, 9 mg[a]	28
		Tuberculous Pericarditis		
Strang et al, 1988, 2004[118,119]	198	Adults with tuberculous pericardial effusion	Prednisolone, 60 mg[a]	77
Strang et al, 2004, 1987[119,120]	114	Adults with tuberculous constrictive pericarditis	Prednisolone, 60 mg[a]	77
Hakim et al, 2000[121]	58	HIV-positive adults with tuberculous pericardial effusion	Prednisolone, 60 mg[a]	42

Abbreviations: HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous.
[a] The initial daily dose was subsequently tapered.

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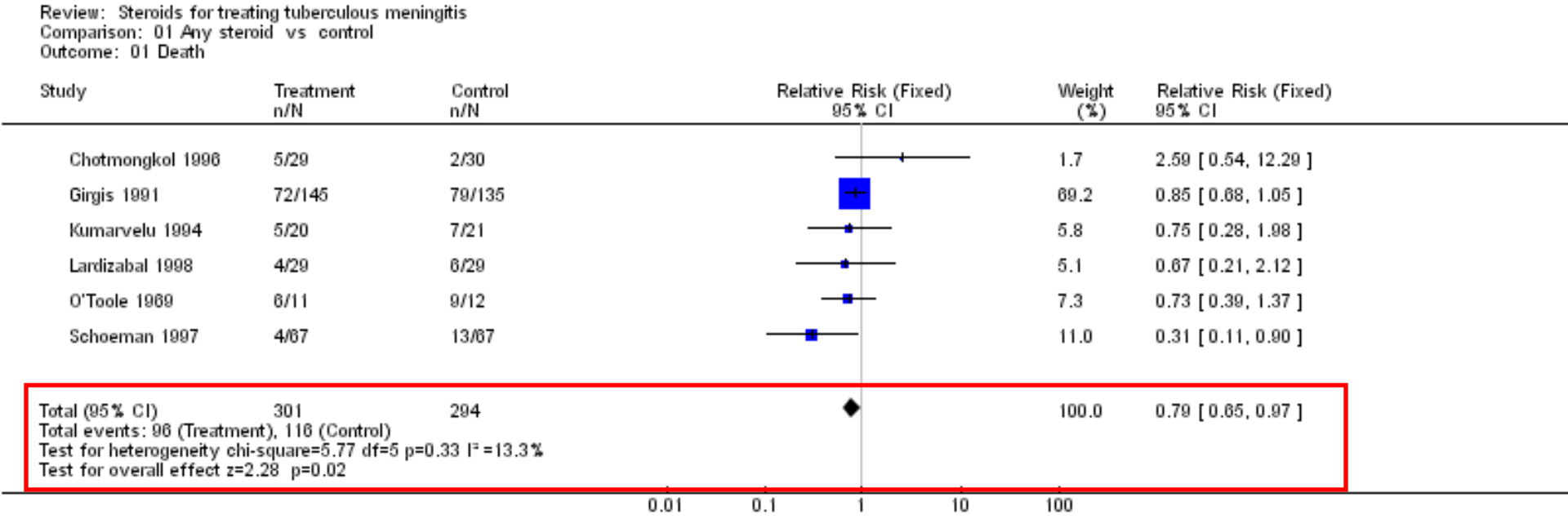
Arch Intern Med. 2008;168(10):1034-1046.

Any steroid vs control

Death



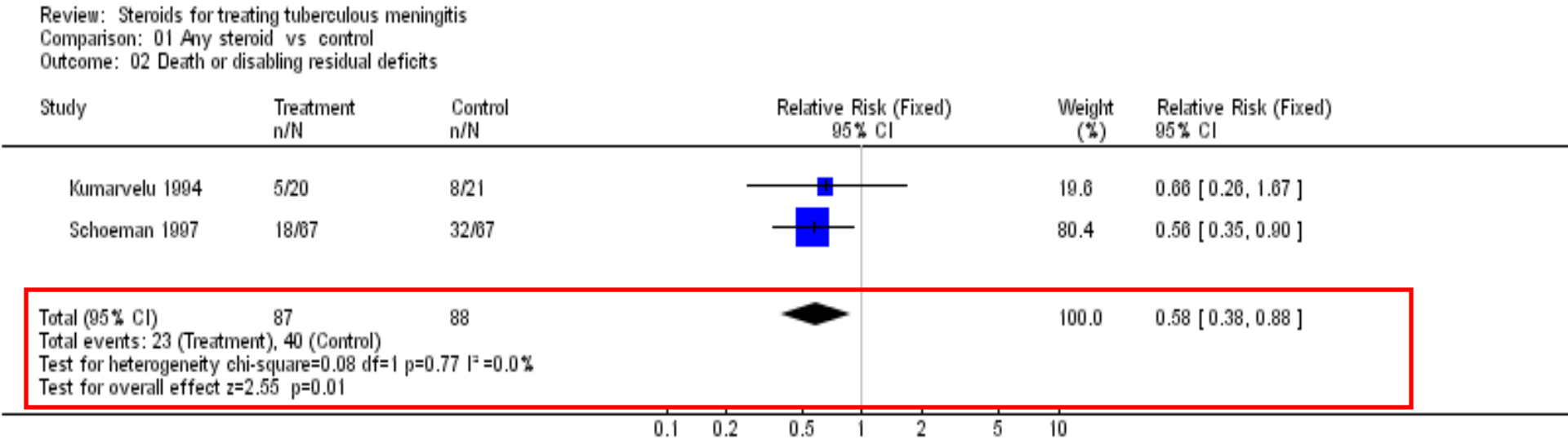
EER: 96/301= 31.89% CER: 116/294= 39.46%

ARR: 39.46%-31.89%= 7.57% **NNT: 1/0.0757= 13.2**

The Cochrane Database of Systematic Reviews 2005 Issue 4

Any steroid vs control

Death or disabling residual deficits



EER: 23/87= 26.44% CER: 40/88= 45.45%

ARR: 45.45%-26.44%= 19.01% **NNT: 1/0.1901= 5.3**

The Cochrane Database of Systematic Reviews 2005 Issue 4

EVIDENCE-BASED REVIEW

The use of adjunctive corticosteroids in the treatment of pericardial, pleural and meningeal tuberculosis: Do they improve outcome?

D.J. Evans[a,b,*]

Respiratory Medicine (2008)

1. Cochrane reviews have summarized the evidence for adjunctive corticosteroids in the treatment of tuberculous pericarditis, meningitis and pleural effusion.

2. These reviews have shown ***improved mortality for pericarditis and meningitis***, but inconclusive effects for pericardial constriction and ongoing neurological disability.

3. Rapid improvements in clinical parameters for pleural effusion were not supported by any lasting improved outcomes for these patients.

Curr HIV/AIDS Rep (2012) 9:238–250
DOI 10.1007/s11904-012-0129-5

CO-INFECTIONS (C BENSON, SECTION EDITOR)

Management of the Immune Reconstitution Inflammatory Syndrome

Graeme Meintjes · James Scriven · Suzaan Marais

Appropriate management of IRIS requires recognition of the condition and exclusion of differential diagnoses, particularly additional infections and OI drug resistance.

Most clinicians use corticosteroids for life-threatening forms of mycobacterial and fungal IRIS.

Corticosteroids and NSAIDs provide symptom relief and there is clinical trial evidence demonstrating that prednisone reduces morbidity in paradoxical TB-IRIS.

Corticosteroids are generally avoided in viral forms of IRIS.
Exceptions are local corticosteroids for CMV Immune recovery uveitis and systemic corticosteroids for life-threatening PML-IRIS complicated by cerebral edema.

From: **Use of Corticosteroids in Treating Infectious Diseases**

Table 4. Miscellaneous Infections and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Source	No. of Patients	Type of Patients	Corticosteroid, Initial Daily Dose	Duration of Treatment, d
		PCP		
Bozzette et al, 1990[122a]	251	HIV-infected adults with PCP	Prednisone, 80 mg[b]	21
Walmsley et al, 1995[123]	78	HIV-infected adults with PCP and moderate to severe hypoxemia	Methylprednisolone IV, 80 mg	10
Nielsen et al, 1992[124a]	59	HIV-infected adults with PCP and moderate to severe hypoxemia	Methylprednisolone IV, 2 mg/kg	10
Clement et al, 1989[125]	41	HIV-infected adults with PCP and severe hypoxemia	Methylprednisolone IV, 240 mg[b]	8
Montaner et al, 1990[126]	37	HIV-infected adults with PCP and moderate hypoxemia	Prednisone, 60 mg[a]	21
Gagnon et al, 1990[127]	23	HIV-infected adults with PCP and severe hypoxemia	Methylprednisolone IV, 160 mg	7
		Cerebral Malaria		
Warrell et al, 1982[128]	100	Adults and children with cerebral malaria	Dexamethasone IV, about 0.9-1.2 mg/kg	2
Hoffman et al, 1988[129]	38	Adults and children with cerebral malaria	Dexamethasone IV, 5.8 mg/kg	2
		Cerebral Cysticercosis		
Garg et al, 2006[130]	60	Adults and children with cerebral cysticercosis and new-onset seizures	Prednisolone, 1 mg/kg	14

Abbreviations: HIV, human immunodeficiency virus; IV, intravenous; PCP, pneumocystis pneumonia.
[a] Both landmark trials were randomized but not blinded, although the primary end points (death and the need for mechanical ventilation) are unlikely to be subject to bias.
[b] The initial daily dose was subsequently tapered.

Figure Legend:

Miscellaneous Infections and Corticosteroids: Randomized, Double-blind, Placebo-Controlled Trials

Arch Intern Med. 2008;168(10):1034-1046

Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection (Review)

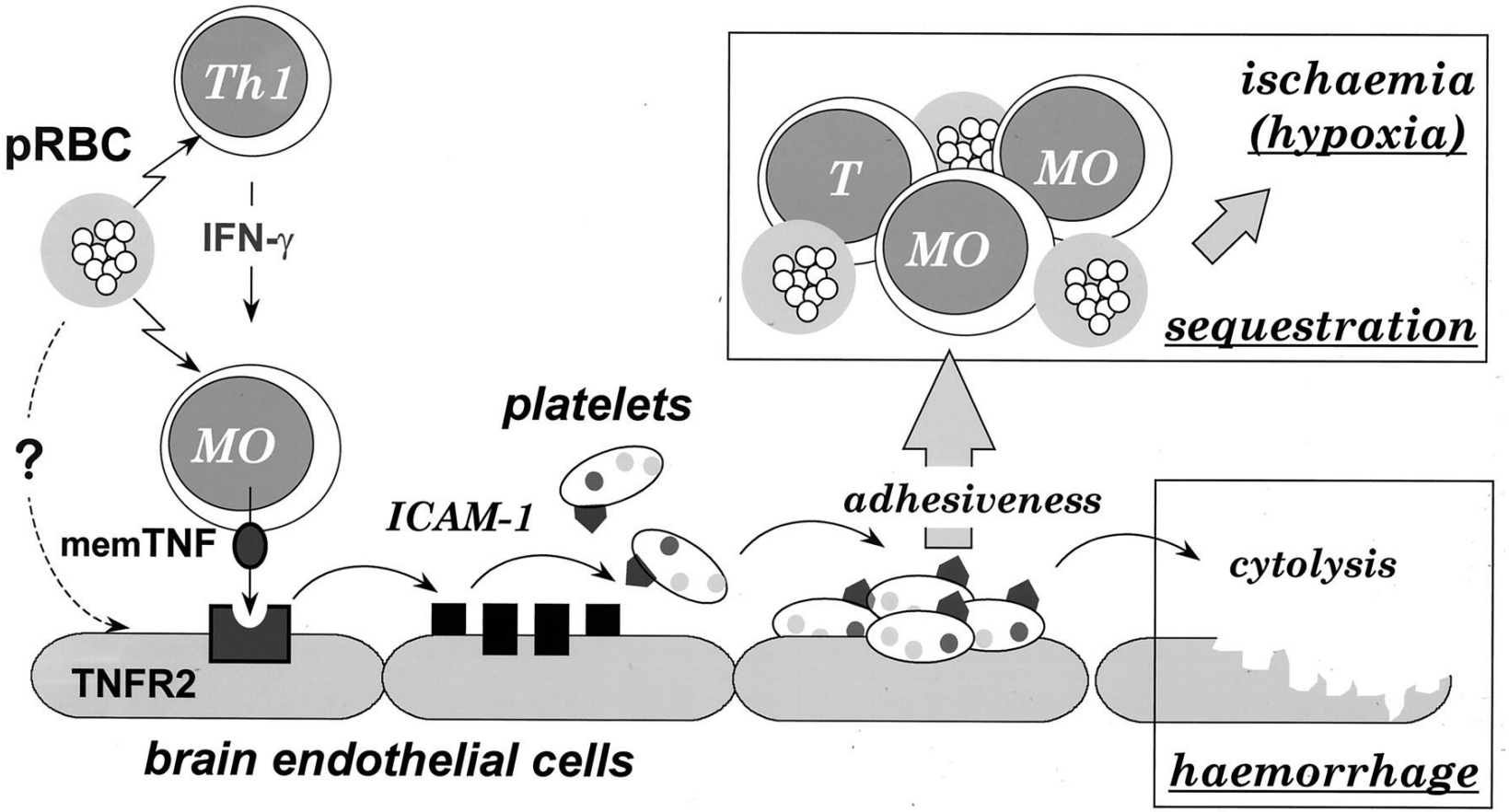
Briel M, Bucher H, Boscacci R, Furrer H

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2006, Issue 3

Authors' conclusions

The number and size of trials investigating adjunctive corticosteroids for HIV-infected patients with PCP is small, but evidence fron this review suggests a beneficial effect for patients with substantial hypoxemia.

Importance of other blood cells in the modulation of pRBC binding in the pathogenesis of CM. The malarial parasite (pRBC) stimulated the host immune response, notably an expansion of Th1 clones, leading to overproduction of IFN-γ.



Lou J et al. Clin. Microbiol. Rev. 2001;14:810-820

Steroids for treating cerebral malaria (Review)

Prasad K, Garner P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 1999, Issue 3

This review assesses the effects of corticosteroid drugs given for cerebral malaria, on death, life-threatening complications, and residual disability in survivors.

The authors included two trials with a total of 143 patients (both adults and children). There were no significant differences in the number of deaths between the corticosteroid and control groups, and data on clinical complications were difficult to assess. Neither trial examined disability.

Authors' conclusions

There is currently no evidence of benefit from corticosteroids, but the small number of participants means it is difficult to exclude an effect on death in either direction. Data on clinical complications are difficult to assess.

Table 5. Effects of Corticosteroids in Infections: 5 Groups

Group	Diseases
1: Treatment effective, improves survival	Bacterial meningitis Tuberculous meningitis Tuberculous pericarditis Severe typhoid fever Tetanus PCP, moderate or severe
2: Treatment effective, provides long-term benefits	Bacterial arthritis
3: Treatment effective, improves symptoms	Herpes zoster Infectious mononucleosis Acute laryngotracheobronchitis (croup) Pneumococcal pneumonia (not treated in ICU) Pharyngitis Peritonsillar abscess Cellulitis Chronic middle ear effusion Cerebral cysticercosis (single lesion) Pulmonary tuberculosis Lymph node–bronchial tuberculosis Pleural tuberculosis
4: Treatment ineffective or uncertain	Acute bronchiolitis (RSV) Viral hemorrhagic fever Pertussis Severe community-acquired pneumonia (treated in ICU)
5: Treatment harmful	Viral hepatitis Cerebral malaria

Abbreviations: ICU, intensive care unit; PCP, pneumocystis pneumonia; RSV, respiratory syncytial virus.

Arch Intern Med. 2008;168(10):1034-1046

SPECIAL ARTICLE

Use of Corticosteroids in Treating Infectious Diseases

Steven McGee, MD; Jan Hirschmann, MD

in addition to placebo or corticosteroids. For patients with bacterial meningitis, tuberculous meningitis, tuberculous pericarditis, severe typhoid fever, tetanus, or pneumocystis pneumonia with moderate to severe hypoxemia, treatment with corticosteroids improved patient survival (group 1 infections). For patients with bacterial arthritis, corticosteroids were also beneficial and reduced long-term disability (group 2 infections). For about a dozen other infections, corticosteroids significantly relieved symptoms (group 3 infections), and clinicians should consider using them if symptoms are substantial. Corticosteroids were harmful in 2 infections, viral hepatitis and cerebral malaria (group 5 infections). We conclude that corticosteroids are beneficial and safe for a wide variety of infections, although courses longer than 3 weeks should be withheld from patients with concomitant human immunodeficiency virus infection and low CD4 counts.

Arch Intern Med. 2008;168(10):1034-1046

MALATTIE INFETTIVE E STEROIDI: SI O NO?

UNA QUESTIONE ANCORA APERTA !