Meningite acute batteriche: quando lo steroide

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Meningite batterica

- **2.6-6 casi x100000 abitanti/anno nelle aree sviluppate**
- **Incidenza 10 volte superiore nelle aree in via di sviluppo**
- **Circa 700.000 casi per anno**
- **170.000 morti per anno**
- **Sequele in variabile proporzione di sopravvissuti**

Murray DJ, WHO 2010

Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis

Karen Edmond, Andrew Clark, Viola S Korczak, Colin Sanderson, Ulla K Griffiths, Igor Rudan

Few data sources are available to assess the global and regional risk of sequelae from bacterial meningitis. We aimed to estimate the risks of major and minor sequelae caused by bacterial meningitis, estimate the distribution of the different types of sequelae, and compare risk by region and income. We systematically reviewed published papers from 1980 to 2008. Standard global burden of disease categories (cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus) were labelled as major sequelae. Less severe, minor sequelae (behavioural problems, learning difficulties, unilateral hearing loss, hypotonia, diplopia), and multiple impairments were also included. 132 papers were selected for inclusion. The median (IQR) risk of at least one major or minor sequela after hospital discharge was 19·9% (12·3–35·3%). The risk of at least one major sequela was 12·8% (7·2–21·1%) and of at least one minor sequela was 8·6% (4·4–15·3%). The median (IQR) risk of at least one major sequela was 24·7% (16·2–35·3%) in pneumococcal meningitis; 9·5% (7·1–15·3%) in *Haemophilus influenzae* type b (Hib), and 7·2% (4·3–11·2%) in meningococcal meningitis. The most common major sequela was hearing loss (33·9%), and 19·7% had multiple impairments. In the random-effects meta-analysis, all-cause risk of a major sequela was twice as high in the African (pooled risk estimate 25·1% [95% CI 18·9–32·0%]) and southeast Asian regions (21·6% [95% CI 13·1–31·5%]) as in the European region (9·4% [95% CI 7·0–12·3%]; overall I^2=89·5%, p<0·0001). Risks of long-term disabling sequelae were highest in low-income countries, where the burden of bacterial meningitis is greatest. Most reported sequelae could have been averted by vaccination with Hib, pneumococcal, and meningococcal vaccines.

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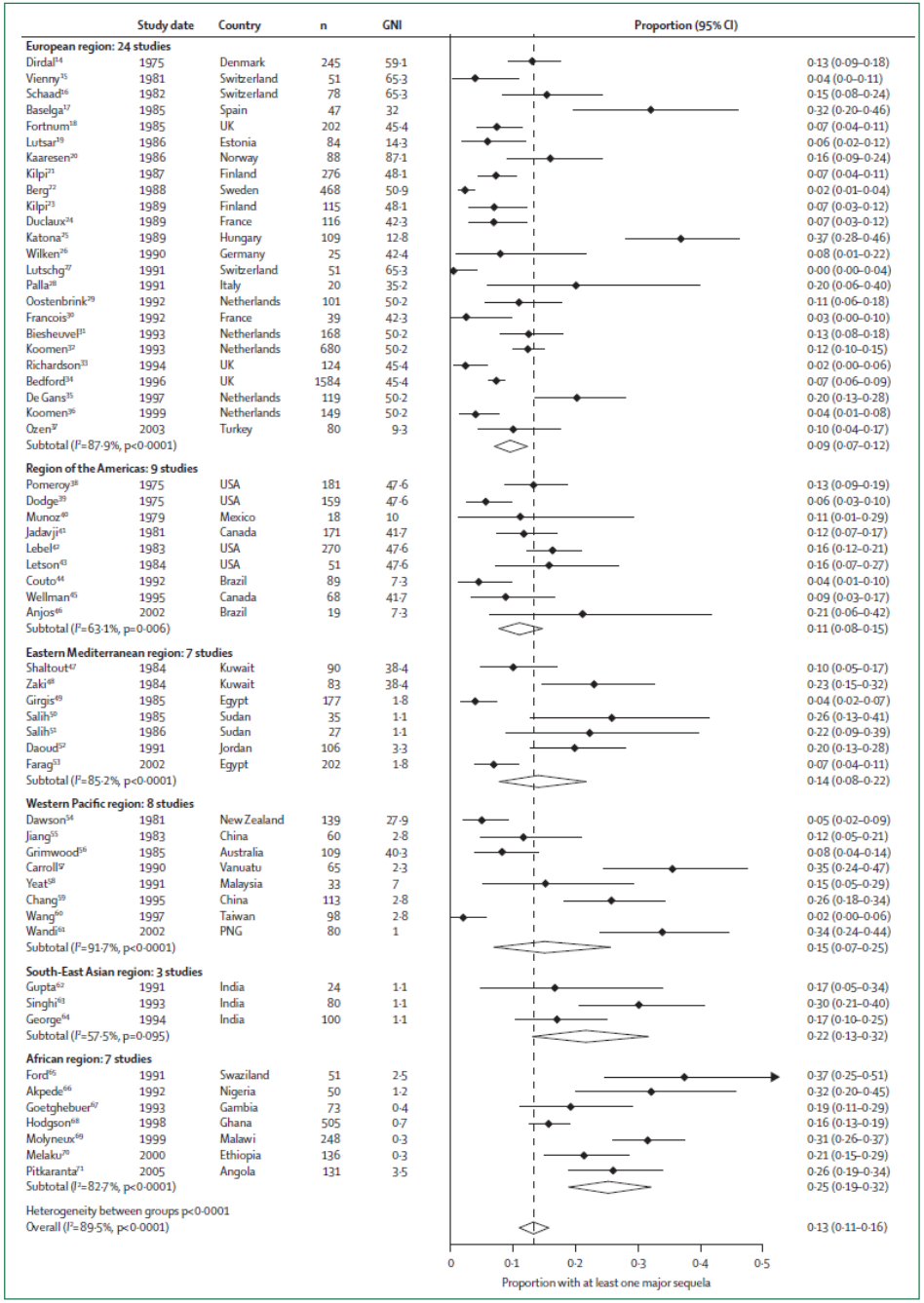
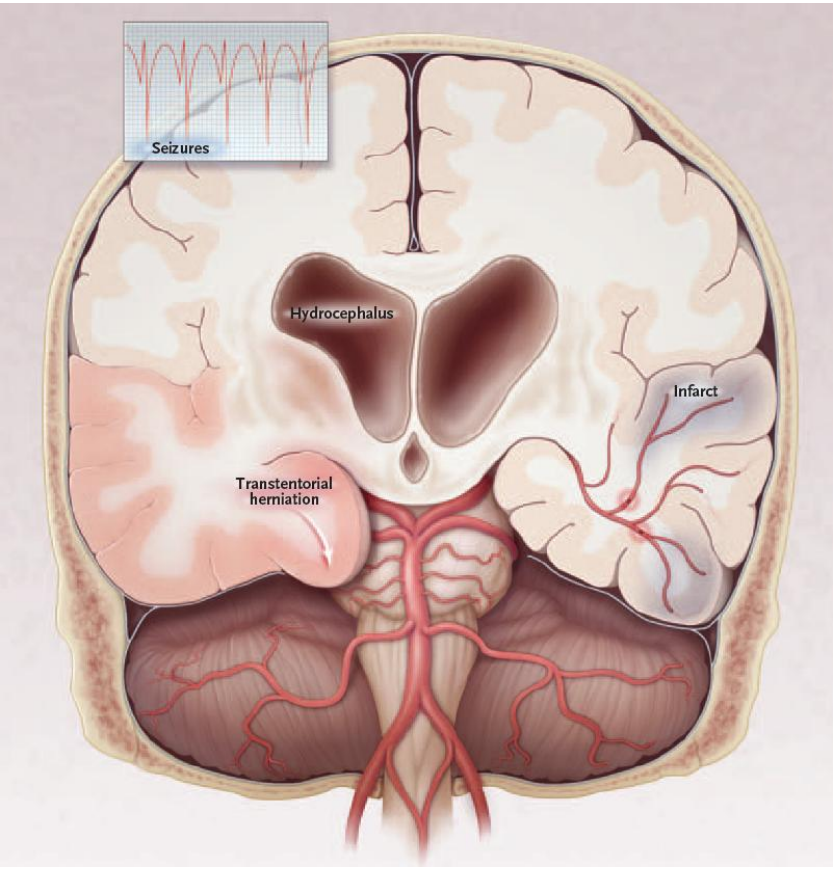
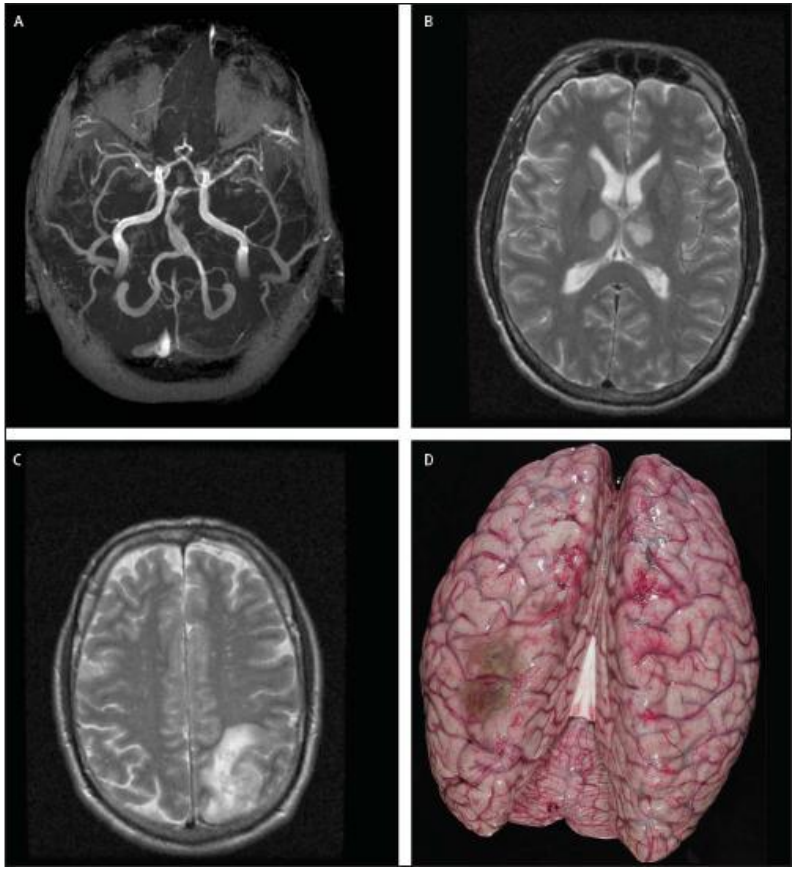


Edmond, Lancet Infect Dis 2010

PRINCIPALI COMPLICANZE DELLA MENINGITE BATTERICA





Weisfeldt Lancet neurology 2006
Van de Beek NEJM 2006

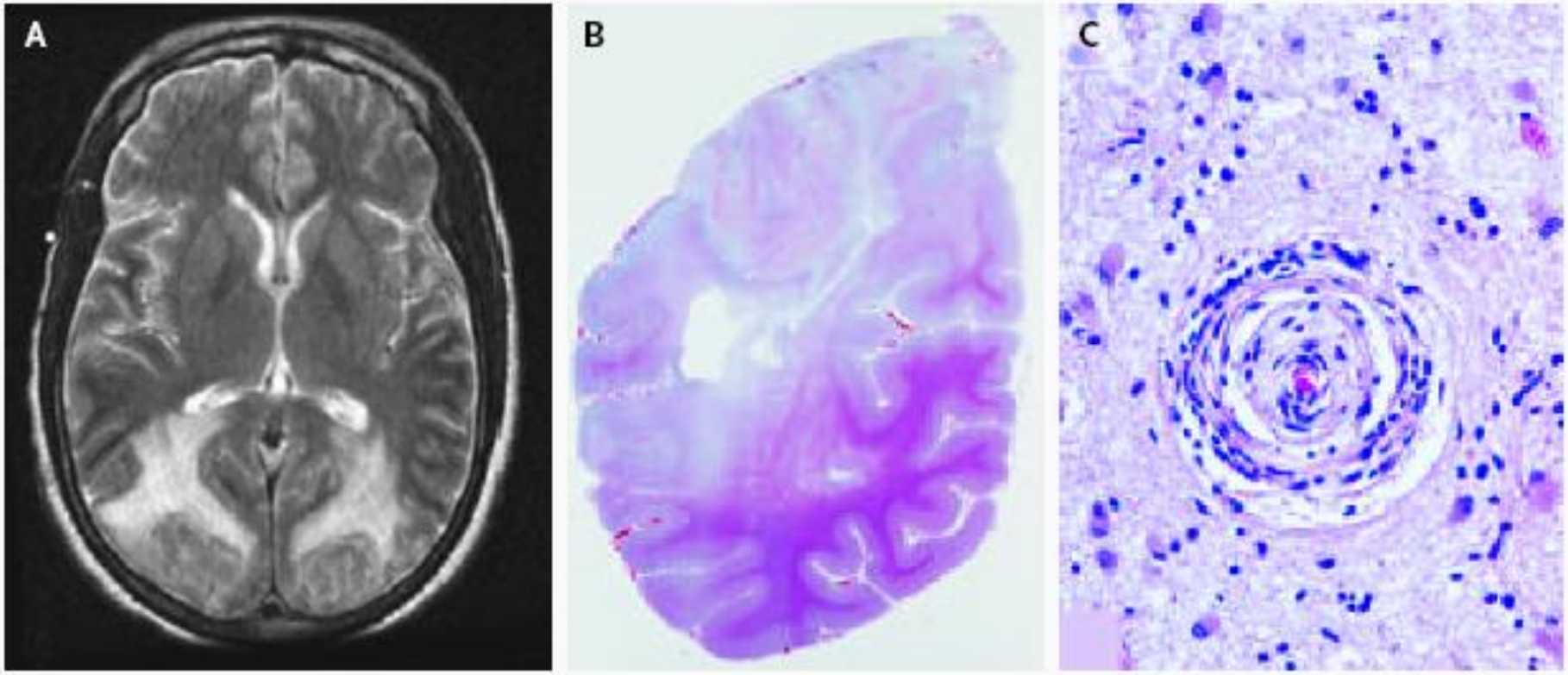
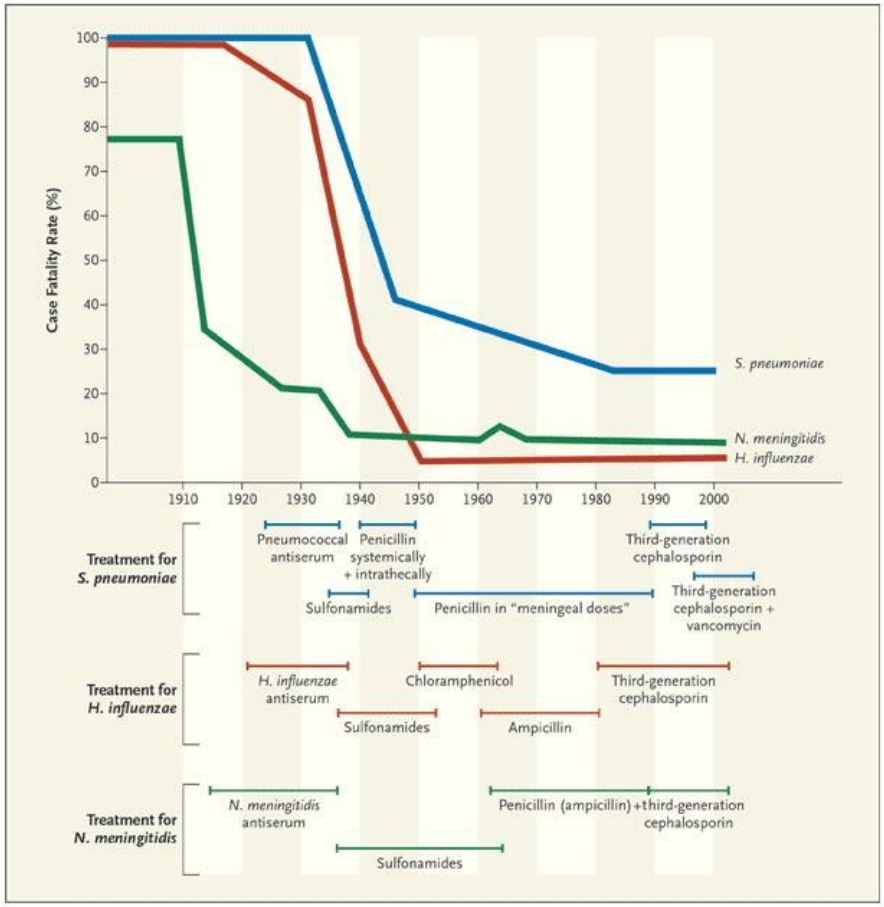


Figure 2. Cerebrovascular Complications in Bacterial Meningitis.

In Panel A, T_2-proton-density–weighted magnetic resonance imaging of the brain shows a transverse view of a hyperintense signal of the posterior lobes that indicates cerebral edema. In Panel B, a postmortem coronal view of the left posterior lobe of the same patient shows large areas of confluent necrosis involving the upper part of the hemisphere, as indicated by the loss of staining for hematoxylin and eosin. In Panel C, the microscopic substrate in the posterior lobe of this patient shows a small, almost completely obstructed vessel in the cortex with perivascular lymphocytic infiltration (endarteritis obliterans) that is surrounded by gliosis.



Swartz, NEJM 2004

Terapia adiuvante delle meningiti batteriche: ruolo degli steroidi

0019-9567/08/$08.00+0 doi:10.1128/IAI.00856-07

Mechanisms of Dexamethasone-Mediated Inhibition of Toll-Like Receptor Signaling Induced by *Neisseria meningitidis* and *Streptococcus pneumoniae*[▽]

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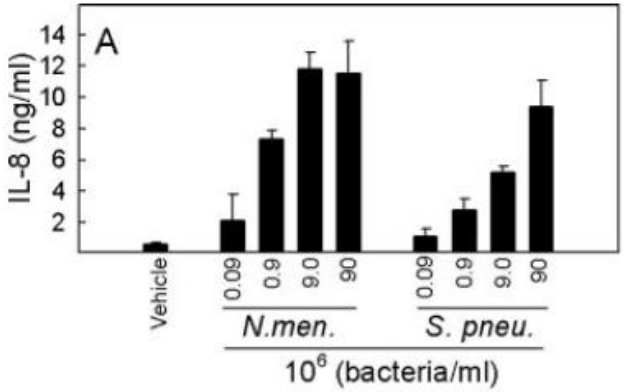
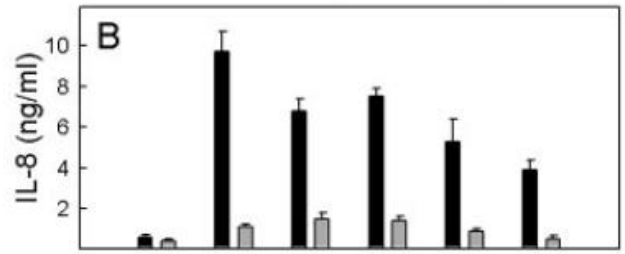
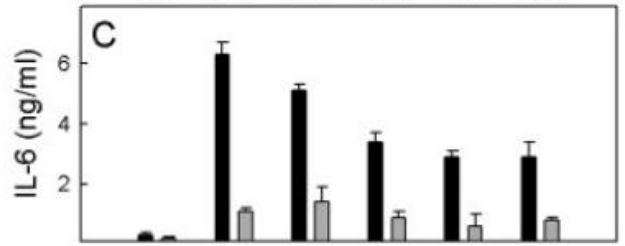
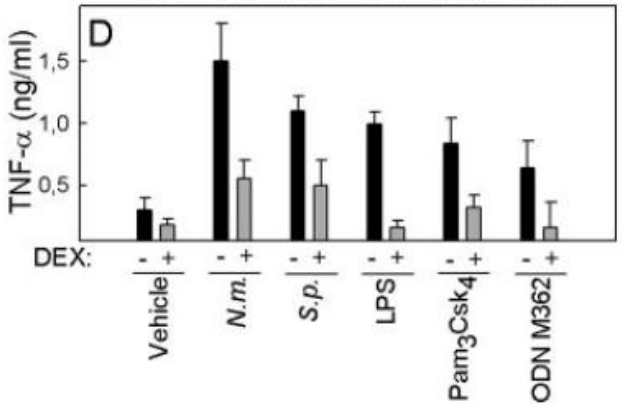
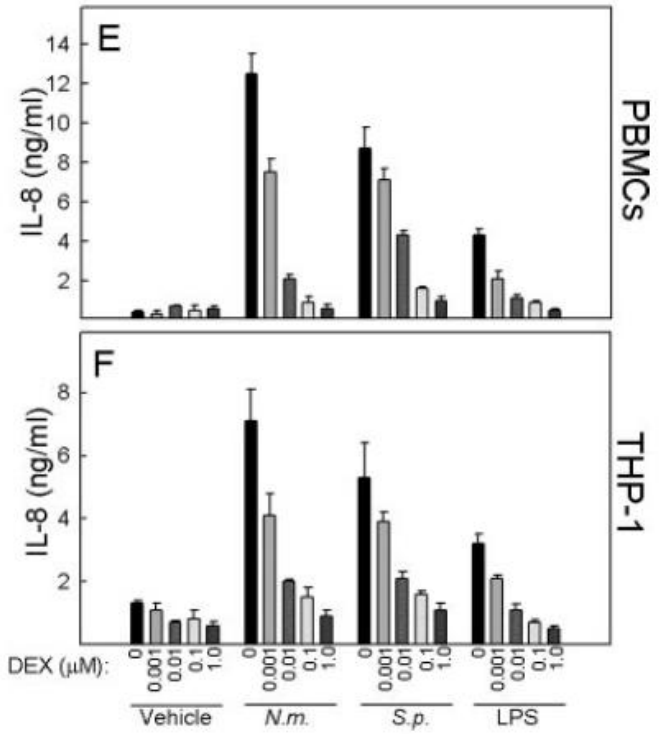
Excessive inflammation contributes to the pathogenesis of bacterial meningitis, which remains a serious disease despite treatment with antibiotics. Therefore, anti-inflammatory drugs have important therapeutic potential, and clinical trials have revealed that early treatment with dexamethasone significantly reduces mortality and morbidity from bacterial meningitis. Here we investigate the molecular mechanisms behind the inhibitory effect of dexamethasone upon the inflammatory responses evoked by *Neisseria meningitidis* and *Streptococcus pneumoniae*, two of the major causes of bacterial meningitis. The inflammatory cytokine response was dependent on Toll-like receptor signaling and was strongly inhibited by dexamethasone. Activation of the NF-κB pathway was targeted at several levels, including inhibition of IκB phosphorylation and NF-κB DNA-binding activity as well as upregulation of IκBα synthesis. Our data also revealed that the timing of steroid treatment relative to infection was important for achieving strong inhibition, particularly in response to *S. pneumoniae*. Altogether, we describe important targets of dexamethasone in the inflammatory responses evoked by *N. meningitidis* and *S. pneumoniae*, which may contribute to our understanding of the clinical effect and the importance of timing with respect to corticosteroid treatment during bacterial meningitis.

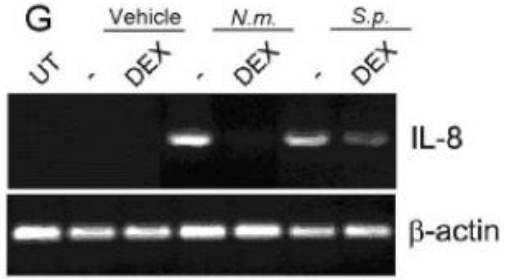




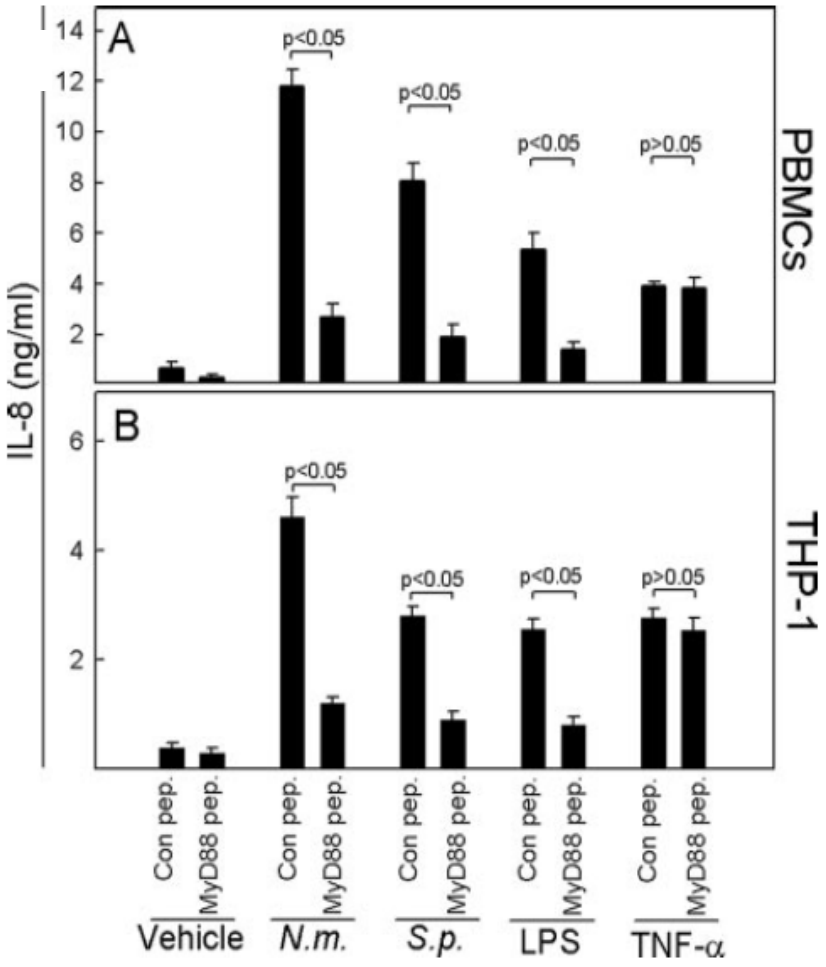








Mogensen Infect, Immun 2008



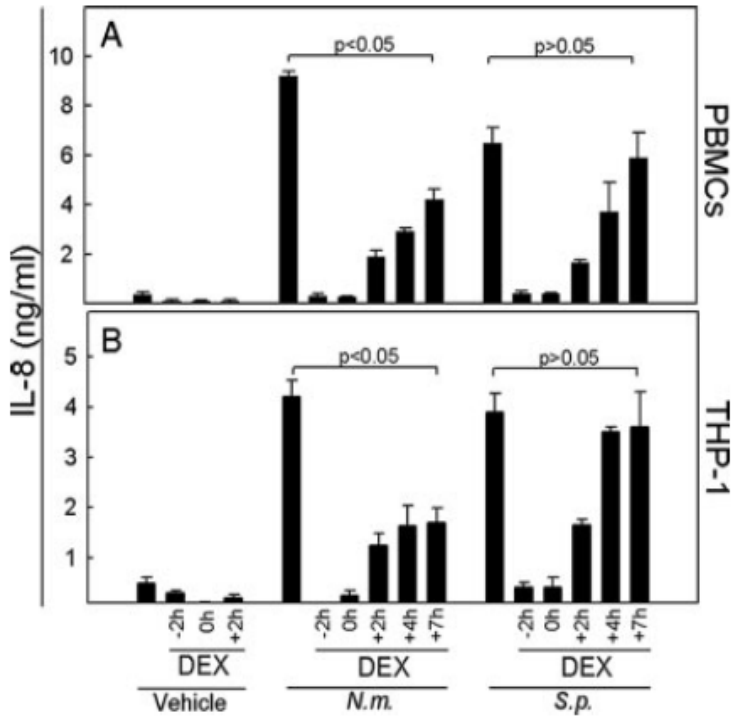


FIG. 3. *N. meningitidis* and *S. pneumoniae* display differential sensitivity to timing of dexamethasone treatment with respect to induction of cytokine expression. PBMCs (A) or THP-1 cells (B) were treated with 1.0 μM of dexamethasone at the indicated time points before stimulation with 9×10^7 bacteria/ml of *N. meningitidis* (*N.m.*) or *S. pneumoniae* (*S.p.*). At 20 h poststimulation, supernatants were harvested and levels of IL-8 were determined. The data are shown as

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Dexamethasone Aggravates Hippocampal Apoptosis and Learning Deficiency in Pneumococcal Meningitis in Infant Rats

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- **Il Desametazone non modifica il tasso di killing batterico a 22 e 30 h.**
- **Non modifica il tasso di morte spontanea**
- **Non modifica l'incidenza di convulsioni nelle prime 30 h**

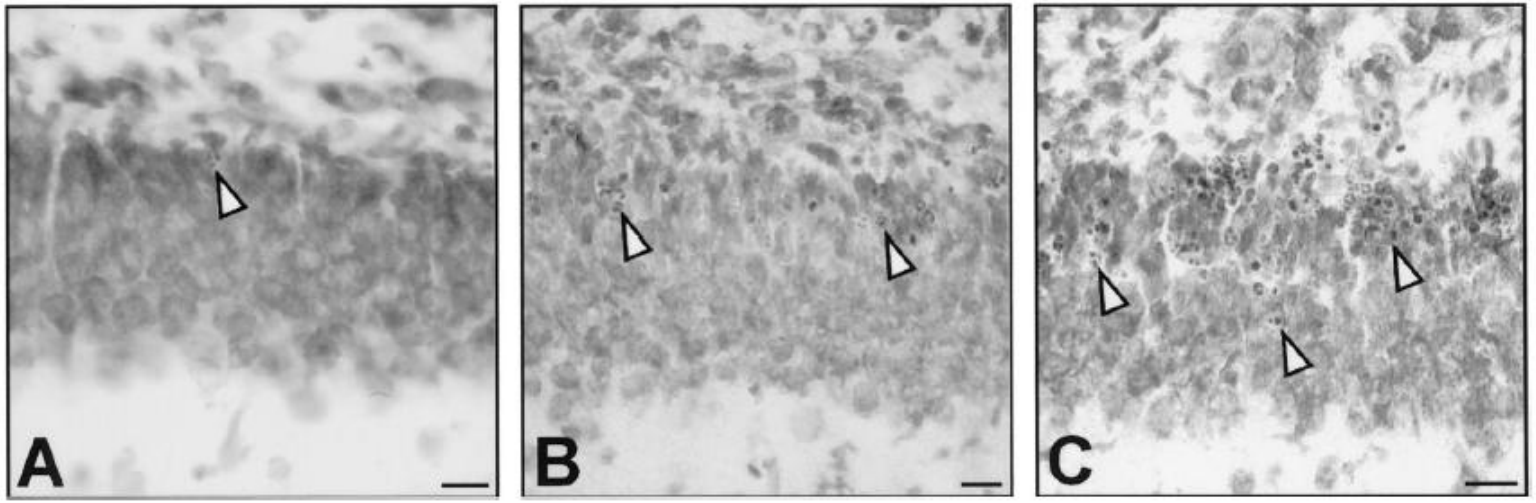


Figure 1. Hippocampal dentate gyrus histology of infant rats suffering from pneumococcal meningitis at 34 h after infection. *A*) In the dentate gyrus of uninfected controls physiologic occurrence of neuronal apoptosis is sporadically visible by the formation of condensed and fragmented nuclei (*arrowhead*). *B*) In infected vehicle treated rats formation of apoptotic bodies is characteristically observed in the inner rim of the dentate gyrus (*arrowheads*) at 34 h after infection. *C*) Treatment with dexamethasone markedly increased the occurrence of apoptotic bodies (arrowheads) in the hippocampal dentate gyrus. Cresyl violet; original magnification × 300; bar 50 μm.

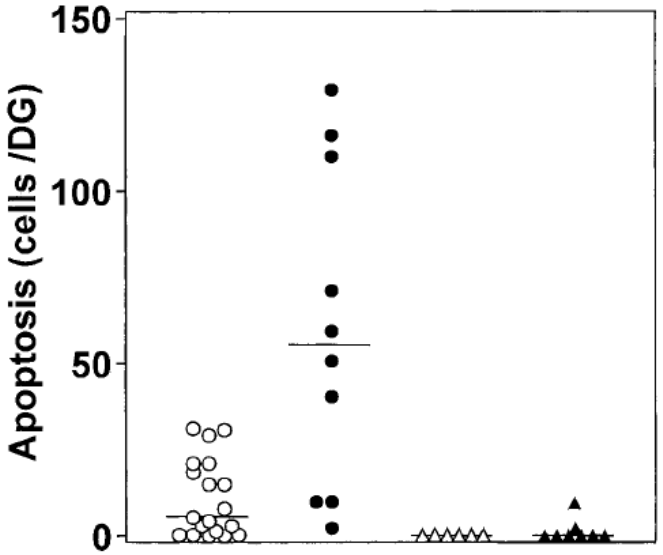
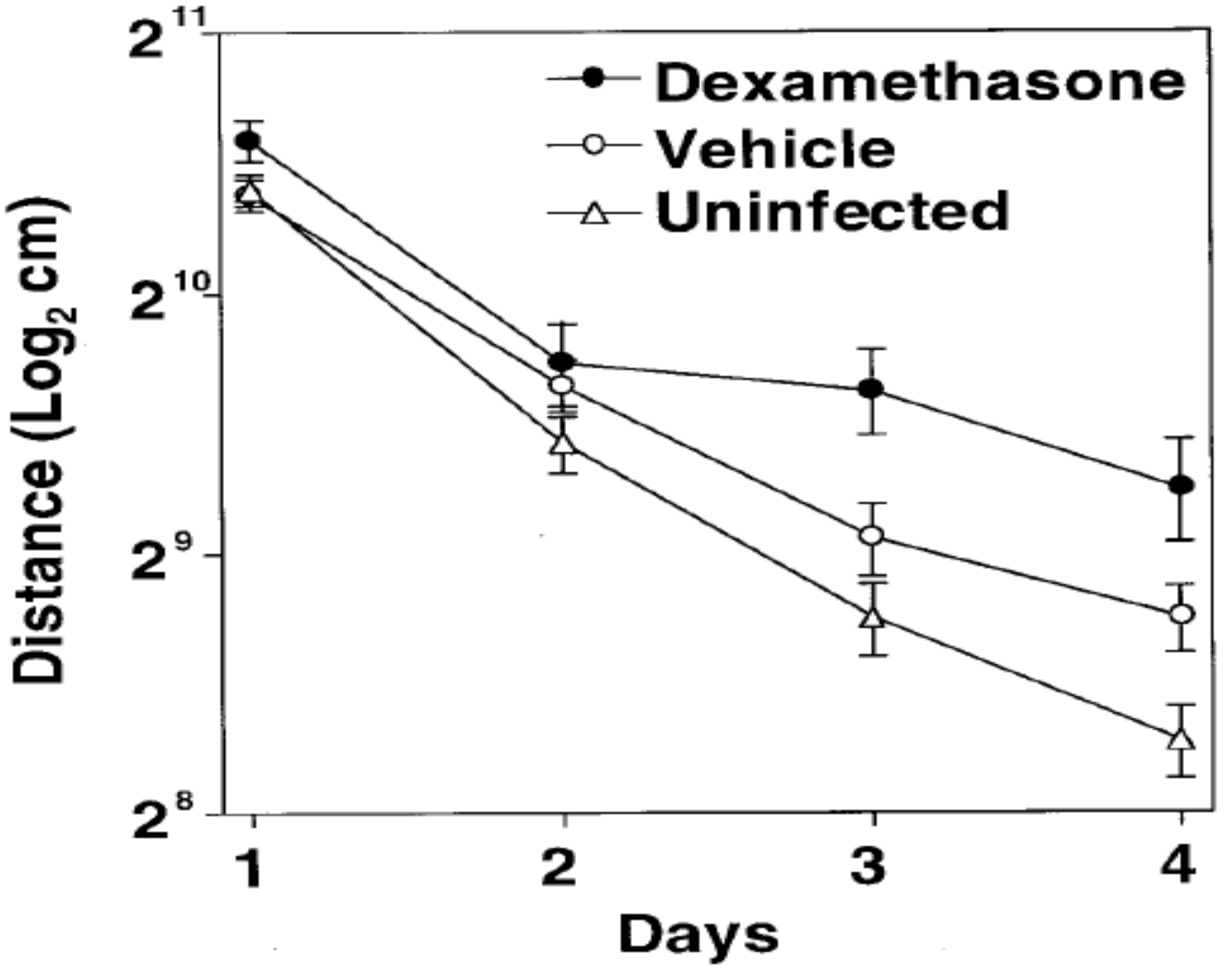


Figure 2. Effect of dexamethasone on hippocampal apoptosis in infant rats with pneumococcal meningitis. Dexamethasone significantly increased apoptosis in infected animals ($p < 0.01$, Mann-Whitney rank-sum test). In uninfected animals no effect was observed. (○, infected vehicle treated; ●, infected dexamethasone treated; △, uninfected vehicle treated; ▲, uninfected dexamethasone treated).



Leib, Pediatric research 2003

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PLoS one

Adjunctive Dexamethasone Affects the Expression of Genes Related to Inflammation, Neurogenesis and Apoptosis in Infant Rat Pneumococcal Meningitis

Cornelia Blaser[1], **Matthias Wittwer**[2], **Denis Grandgirard**[1], **Stephen L. Leib**[1]*

1 Institute for Infectious Diseases, University of Bern, Bern, Switzerland, **2** Spiez Laboratory, Spiez, Switzerland

Abstract

Streptococcus pneumoniae is the most common pathogen causing non-epidemic bacterial meningitis worldwide. The immune response and inflammatory processes contribute to the pathophysiology. Hence, the anti-inflammatory dexamethasone is advocated as adjuvant treatment although its clinical efficacy remains a question at issue. In experimental models of pneumococcal meningitis, dexamethasone increased neuronal damage in the dentate gyrus. Here, we investigated expressional changes in the hippocampus and cortex at 72 h after infection when dexamethasone was given to infant rats with pneumococcal meningitis. Nursing Wistar rats were intracisternally infected with *Streptococcus pneumoniae* to induce experimental meningitis or were sham-infected with pyrogen-free saline. Besides antibiotics, animals were either treated with dexamethasone or saline. Expressional changes were assessed by the use of GeneChip® Rat Exon 1.0 ST Arrays and quantitative real-time PCR. Protein levels of brain-derived neurotrophic factor, cytokines and chemokines were evaluated in immunoassays using Luminex xMAP® technology. In infected animals, 213 and 264 genes were significantly regulated by dexamethasone in the hippocampus and cortex respectively. Separately for the cortex and the hippocampus, Gene Ontology analysis identified clusters of biological processes which were assigned to the predefined categories "inflammation", "growth", "apoptosis" and others. Dexamethasone affected the expression of genes and protein levels of chemokines reflecting diminished activation of microglia. Dexamethasone-induced changes of genes related to apoptosis suggest the downregulation of the Akt-survival pathway and the induction of caspase-independent apoptosis. Signalling of pro-neurogenic pathways such as transforming growth factor pathway was reduced by dexamethasone resulting in a lack of pro-survival triggers. The anti-inflammatory properties of dexamethasone were observed on gene and protein level in experimental pneumococcal meningitis. Further dexamethasone-induced expressional changes reflect an increase of pro-apoptotic signals and a decrease of pro-neurogenic processes. The findings may help to identify potential mechanisms leading to apoptosis by dexamethasone in experimental pneumococcal meningitis.

Citation: Blaser C, Wittwer M, Grandgirard D, Leib SL (2011) Adjunctive Dexamethasone Affects the Expression of Genes Related to Inflammation, Neurogenesis and Apoptosis in Infant Rat Pneumococcal Meningitis. PLoS ONE 6(3): e17840. doi:10.1371/journal.pone.0017840

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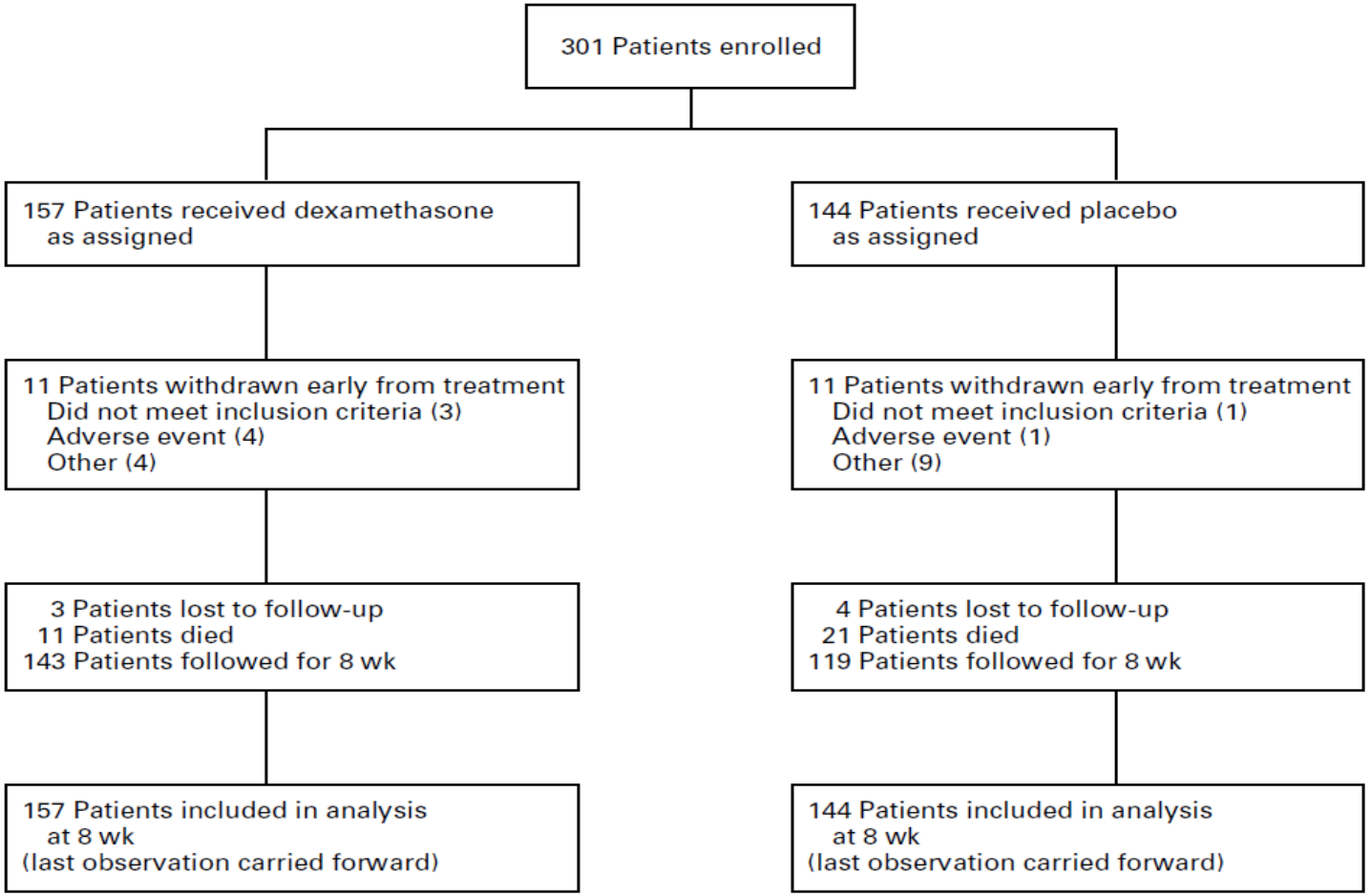
DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

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



Patients were randomly assigned to receive dexamethasone sodium phosphate (Oradexon), at a dose of 10 mg given every six hours intravenously for four days, or placebo that was identical in appearance to the active drug. The study medication was given 15 to 20 minutes before the parenteral administration of antibiotics. After the interim analysis, the protocol was amended to allow administration of the study medication with the antibiotics.

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

De Gans, NEJM 2002

TABLE 4. UNFAVORABLE OUTCOME AT EIGHT WEEKS ACCORDING TO THE SCORE ON THE GLASGOW COMA SCALE ON ADMISSION.*

COMA SCORE AND CULTURE RESULTS	DEXAMETHASONE	PLACEBO	RELATIVE RISK (95% CI)	P VALUE
	no./total no. (%)			
Score of 12 to 14				
All patients	8/80 (10)	8/80 (10)	1.00 (0.40–2.53)	1.00
Streptococcus pneumoniae	1/15 (7)	2/11 (18)	0.37 (0.04–3.55)	0.56
Neisseria meningitidis	3/27 (11)	4/34 (12)	0.94 (0.23–3.87)	1.00
Score of 8 to 11				
All patients	7/52 (13)	14/41 (34)	0.39 (0.18–0.89)	0.03
S. pneumoniae	6/27 (22)	12/23 (52)	0.43 (0.19–0.95)	0.04
N. meningitidis	1/17 (6)	0/9 (0)	—	1.00
Score of 3 to 7				
All patients	8/25 (32)	14/23 (61)	0.53 (0.27–1.02)	0.08
S. pneumoniae	8/16 (50)	12/16 (75)	0.67 (0.38–1.17)	0.27
N. meningitidis	0/6	1/4 (25)	—	0.40

*Higher scores indicate a better level of consciousness. CI denotes confidence interval.

De Gans, NEJM 2002

Dexamethasone and long-term survival in bacterial meningitis

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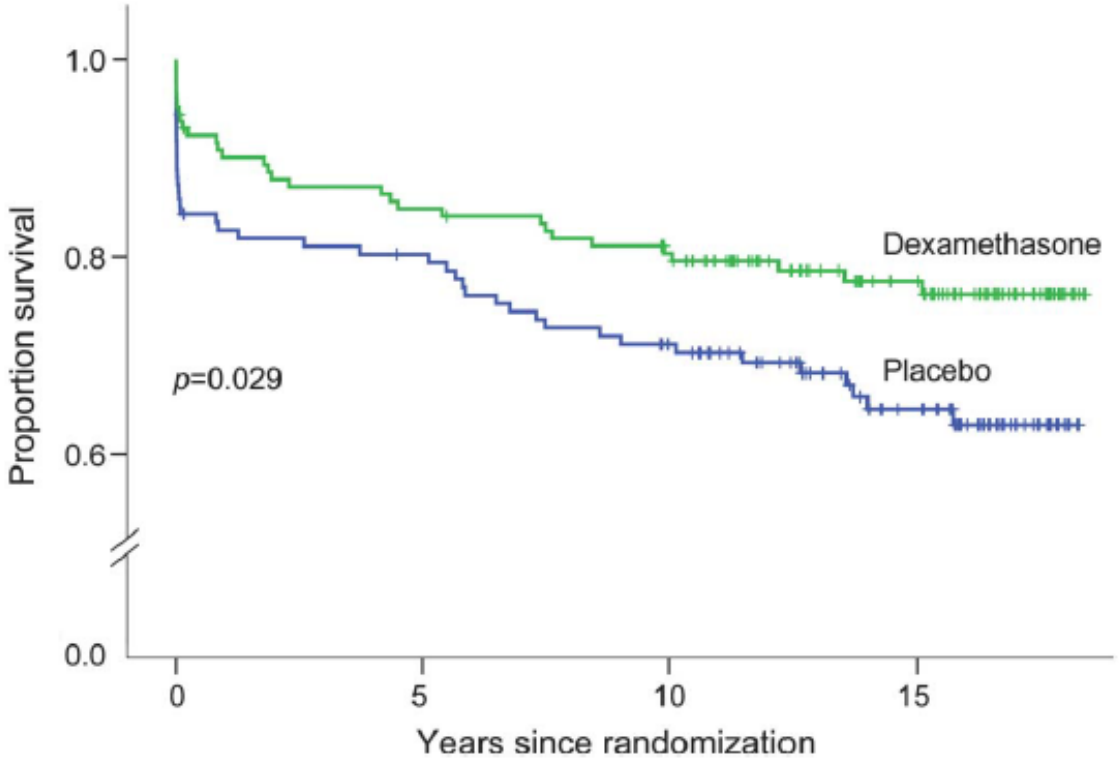
Figure **Kaplan-Meier survival estimates according to study group (adjunctive dexamethasone therapy vs placebo) for adult patients with community-acquired bacterial meningitis.**



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PLoS one

Dexamethasone and Long-Term Outcome of Tuberculous Meningitis in Vietnamese Adults and Adolescents

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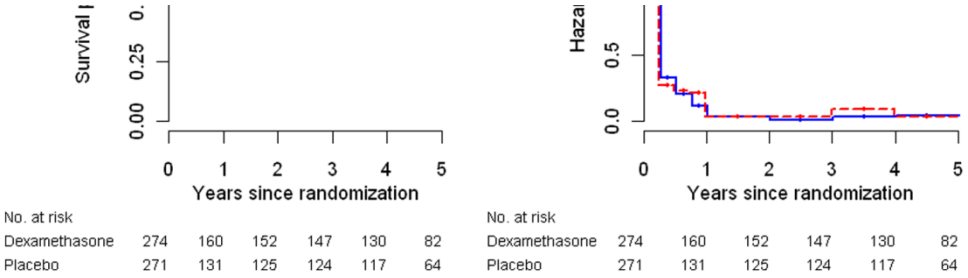

Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

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ABSTRACT

Background: In this nationwide prospective cohort study, we evaluated the implementation of adjunctive dexamethasone therapy in Dutch adults with pneumococcal meningitis.

Methods: From March 2006 through January 2009, all Dutch patients over 16 years old with community-acquired pneumococcal meningitis were prospectively evaluated. Outcome was classified as unfavorable (defined by a Glasgow Outcome Scale score of 1 to 4 points at discharge) or favorable (a score of 5). Clinical characteristics and outcome were compared with a similar nationwide cohort of 352 patients with pneumococcal meningitis from a previous period before guidelines recommended dexamethasone therapy (1998–2002). A multivariable prognostic model was used to adjust for differences in case mix between the 2 cohorts.

Results: We evaluated 357 episodes with pneumococcal meningitis in 2006–2009. Characteristics on admission were comparable with the earlier cohort (1998–2002). Dexamethasone was started with or before the first dose of antibiotics in 84% of episodes in 2006–2009 and 3% in 1998–2002. At discharge, unfavorable outcome was present in 39% in 2006–2009 and 50% in 1998–2002 (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.46–0.86; $p = 0.002$). Rates of death (20% vs 30%; $p = 0.001$) and hearing loss (12% vs 22%; $p = 0.001$) were lower in 2006–2009. Differences in outcome remained after adjusting for differences in case mix between cohorts.

Conclusions: Dexamethasone therapy has been implemented on a large scale as adjunctive treatment of adults with pneumococcal meningitis in the Netherlands. The prognosis of pneumococcal meningitis on a national level has substantially improved after the introduction of adjunctive dexamethasone therapy.

Classification of evidence: This study provides Class III evidence that dexamethasone (10 mg IV, given every 6 hours for 4 days started before or with the first dose of parenteral antibiotics) reduced the proportion of patients with unfavorable outcomes (Glasgow Outcome Scale score of 1 to 4) in the 2006–2009 cohort, as compared to the 1998–2002 cohort (39% vs 50%; OR 0.63; 95% CI 0.46–0.86; $p = 0.002$). Mortality rate (20% vs 30%; absolute risk difference 10%; 95% CI 4%–17%; $p = 0.001$) was also lower in 2006–2009. *Neurology*® 2010;75:1533–1539

Table 2 Characteristics of intravenous dexamethasone treatment[a]

Characteristics	2006–2009	1998–2002	Absolute difference (%)
No. of episodes	357	352	
Dexamethasone received	329 (92)	59 (17)	+75[b]
Dexamethasone 10 mg every 6 hours for 4 days, started before or with first dose of antibiotics	276 (77)	11 (3)	+74[b]
Dexamethasone started before or with first dose of antibiotics, all dosages and durations	301 (84)	11 (3)	+81[b]
Dexamethasone 10 mg every 6 hours for 4 days, started at any time	299 (84)	11 (3)	+81[b]

[a] Data are number of episodes (%).

[b] *p* Value for differences between cohorts <0.001.

Brouwer, Neurology 2010

Table 3 Clinical course, mortality, disability, and neurologic findings at discharge[a]

Characteristics	2006–2009	1998–2002	Difference (%)	*p* Value
No. of episodes	357	352		
Clinical course, n (%)				
Neurologic complications[b]	239 (60)	263 (75)	−15	<0.001
Seizures	60/344 (17)	85/349 (24)	−7	0.025
Cardiorespiratory failure	133 (37)	134 (38)	−1	0.823
Score on Glasgow Outcome Scale, n (%)				
1 (death)	71 (20)	107 (30)	−10	0.001
2 (vegetative state)	0	3 (1)	−1	
3 (severe disability)	18 (5)	17 (5)	0	
4 (moderate disability)	50 (14)	50 (14)	0	
5 (no or minor disability)	218 (61)	175 (50)	+11	0.002
Neurologic findings at discharge, n (%)				
Cranial nerve palsy	47/280 (17)	67/243 (28)	−11	0.003
Hearing impairment	33/280 (12)	55/243 (22)	−10	0.001
Focal cerebral deficits	32/280 (11)	26/243 (11)	0	0.791

[a] Neurologic examination was performed in 243 of 245 surviving patients of cohort 1998–2002 and 280 of 285 surviving patients of cohort 2006–2009.
[b] Neurologic complications were defined as impairment of consciousness, seizures, or focal neurologic abnormalities.

Brouwer, Neurology 2010

Adjunctive dexamethasone in adults with meningococcal meningitis

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ABSTRACT

Objectives: We evaluated the implementation and effectiveness of adjunctive dexamethasone in adults with meningococcal meningitis.

Methods: We compared 2 Dutch prospective nationwide cohort studies on community-acquired meningococcal meningitis. A total of 258 patients with CSF culture-proven meningitis were enrolled between 1998 and 2002, before routine dexamethasone therapy was introduced, and 100 patients from March 2006 to January 2011, after guidelines recommended dexamethasone.

Results: Dexamethasone was administered in 43 of 258 (17%) patients in the 1998–2002 cohort and in 86 of 96 (90%) patients in the 2006–2011 cohort ($p < 0.001$), and was started with or before the first dose of antibiotics in 12 of 258 (5%) and 85 of 96 (89%) patients ($p < 0.001$). Rates of unfavorable outcome were similar between cohorts (12 of 100 [12%] vs 30 of 258 [12%]; $p = 0.67$), also after correction for meningococcal serogroup. The rates of hearing loss (3 of 96 [3%] vs 19 of 237 [8%]; $p = 0.10$) and death (4 of 100 [4%] vs 19 of 258 [7%]; $p = 0.24$) were lower in the 2006–2011 cohort, but this did not reach significance. The rate of arthritis was lower in patients treated with dexamethasone (32 of 258 [12%] vs 5 of 96 [5%], $p = 0.046$). Dexamethasone was not associated with adverse events.

Conclusions: Adjunctive dexamethasone is widely prescribed for patients with meningococcal meningitis and is not associated with harm. The rate of arthritis has decreased after the implementation of dexamethasone.

Classification of evidence: This study provides Class III evidence that adjuvant dexamethasone in adults with meningococcal meningitis does not increase negative outcomes such as deafness, death, or negative Glasgow Outcome Scale measures. *Neurology*® 2012;79:1563–1569

Table 2 Characteristics of IV dexamethasone treatment[a]

Characteristic	2006–2011, 96 episodes	1998–2002, 258 episodes	Absolute difference, %
Dexamethasone received	86 (90)	43 (17)	+73[b]
Dexamethasone 10 mg every 6 hours for 4 days, started before or with first dose of antibiotics	78 (81)	12 (5)	+76[b]
Dexamethasone started before or with first dose of antibiotics, all dosages and durations	85 (89)	12 (5)	+84[b]
Dexamethasone 10 mg every 6 hours for 4 days, started at any time	79 (82)	12 (5)	+77[b]

[a] Data are number of episodes (percentage).
[b] *p* Value for differences between cohorts <0.001.

Table 4 Clinical course, mortality, disability, and neurologic findings at discharge[a]

Characteristic	2006–2011, 100 episodes	1998–2002, 258 episodes	Difference, %[b]
Clinical course			
Neurologic complications	43 (43)	105/258 (41)	+2
Cardiorespiratory failure	18 (18)	44 (17)	+1
Score on Glasgow Outcome Scale			
1 (death)	4 (4)	19 (7)	−3 ($p = 0.24$)
2 (vegetative state)	0	0	0
3 (severe disability)	0	4 (2)	−2
4 (moderate disability)	8 (8)	7 (3)	+5
5 (no or minor disability)	88 (88)	228 (88)	0
Neurologic findings at discharge			
Cranial nerve palsy	6/96 (6)	6/238 (3)	+3
Hearing impairment	3/96 (3)	19/237 (8)	−5 ($p = 0.10$)
Focal cerebral deficits	4/96 (4)	4 (2)	+2

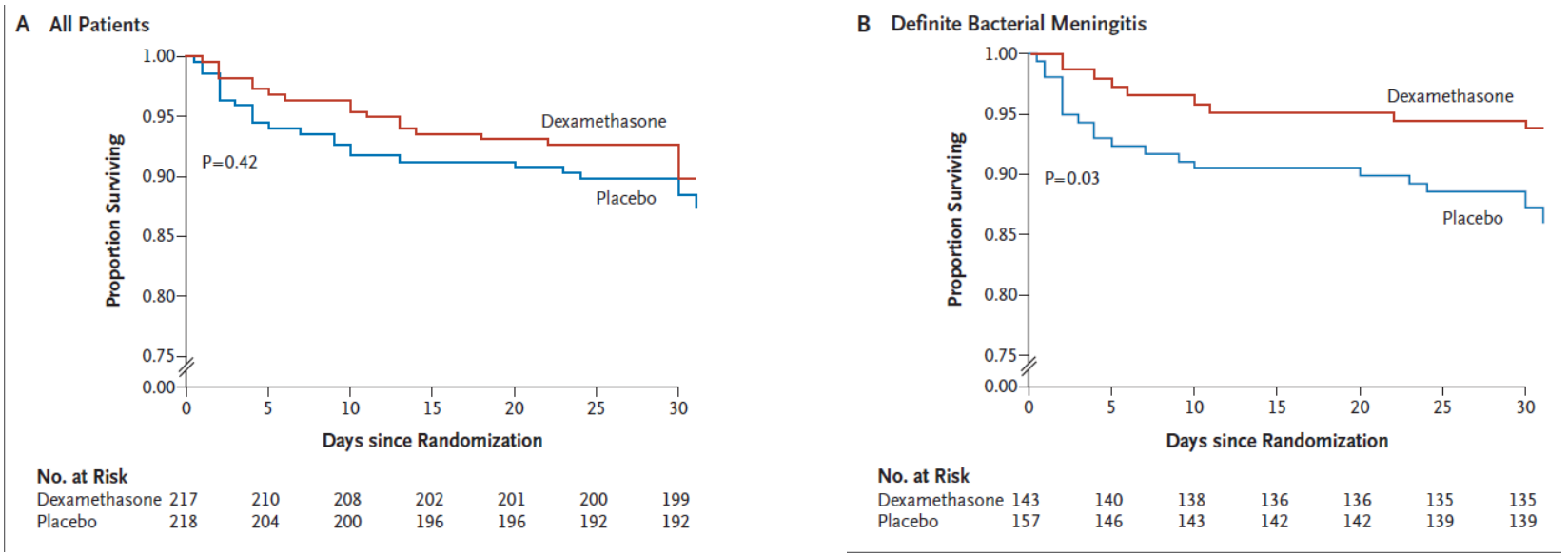
[a] Data are presented as n/N (%).
[b] *p* Value for all >0.05.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 13, 2007 VOL. 357 NO. 24

Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis

Nguyen Thi Hoang Mai, M.D., Tran Thi Hong Chau, M.D., Guy Thwaites, M.D., Ly Van Chuong, M.D., Dinh Xuan Sinh, M.D., Ho Dang Trung Nghia, M.D., Phung Quoc Tuan, M.D., Nguyen Duy Phong, M.D., Nguyen Hoan Phu, M.D., To Song Diep, M.D., Nguyen van Vinh Chau, M.D., Nguyen Minh Duong, M.D., James Campbell, Constance Schultsz, M.D., Chris Parry, M.D., M. Estee Torok, M.D., Nicholas White, F.R.C.P., Nguyen Tran Chinh, M.D., Tran Tinh Hien, M.D., Kasia Stepniewska, Ph.D., and Jeremy J. Farrar, F.R.C.P.



Nguyen, NEJM 2007

Table 4. Relative Risk of Death for the Independent Predictors among Patients with Definite or Probable Meningitis.

Variable	Relative Risk of Death (95% CI)*	P Value
Age (per year)	1.03 (1.02–1.05)	0.001
Hemiparesis (yes or no)	3.40 (1.54–7.49)	0.002
Glasgow Coma Scale score (per unit increase)†	0.84 (0.76–0.93)	0.002
Streptococcus suis meningitis (yes or no)	0.16 (0.05–0.53)	0.003
Duration of symptoms (per day)	1.10 (1.04–1.15)	0.001
Definite bacterial meningitis (yes or no)		
Treated with placebo	1.00	
Treated with dexamethasone	0.22 (0.08–0.58)	0.002
Probable bacterial meningitis (yes or no)		
Treated with placebo	0.15 (0.04–0.58)	0.006
Treated with dexamethasone	0.38 (0.15–0.96)	0.04

Nguyen, NEJM 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Corticosteroids for Bacterial Meningitis in Adults in Sub-Saharan Africa

Matthew Scarborough, M.R.C.P., Stephen B. Gordon, M.D., Christopher J.M. Whitty, F.R.C.P., Neil French, Ph.D., Yasin Njalale, Dip.Med.Sci., Alex Chitani, Dip.Med.Sci., Timothy E.A. Peto, Ph.D., David G. Lalloo, F.R.C.P., and Eduard E. Zijlstra, Ph.D.

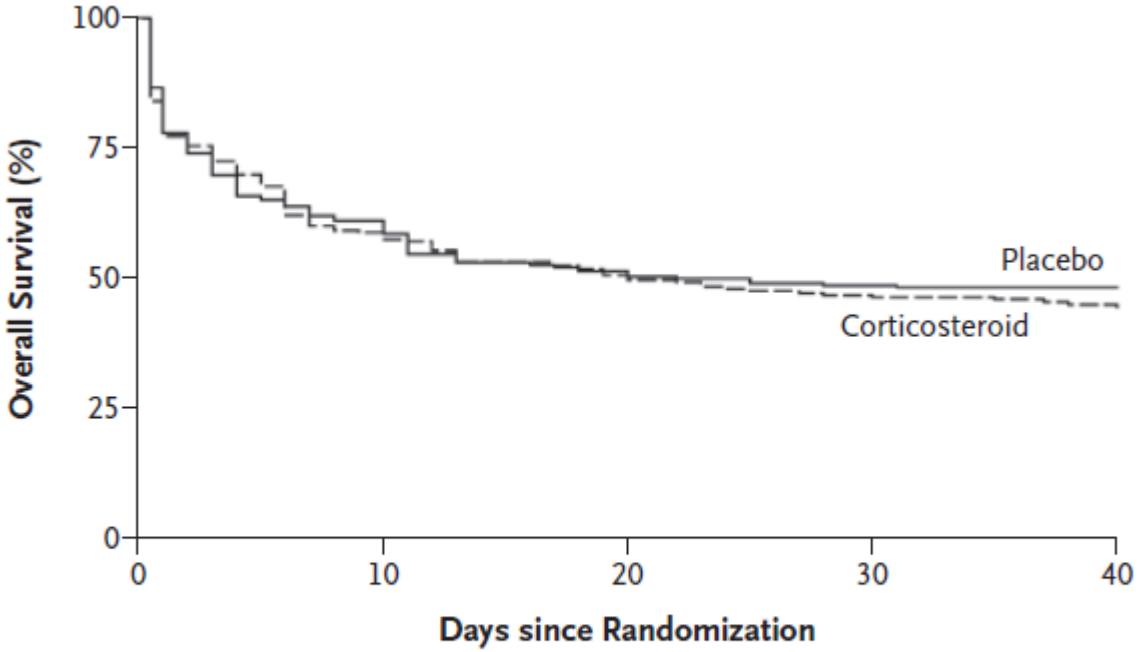


Figure 2. Kaplan–Meier Estimates of Survival for 459 Patients through Day 40.

Scarborough, NEJM 2007

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Corticosteroid (N=233)	Placebo (N=232)	Intramuscular Ceftriaxone (N=230)	Intravenous Ceftriaxone (N=235)
Age — yr	32.3±10.1	32.6±11.4	32.4±10.9	32.6±10.6
Male sex — no. (%)	122 (52)	108 (47)	115 (50)	115 (49)
Glasgow Coma Scale score†	10.7±3.5	10.8±3.3	11±3.4	10.4±3.4
Hemoglobin — g/dl	10.4±2.8	10.7±3.1	10.5±3.0	10.7±2.8
Median time to presentation — hr (interquartile range)	72 (48–120)	72 (48–144)	72 (48–144)	72 (48–120)
Previous treatment with antimicrobial agents — no. (%)‡				
Oral	35 (15)	42 (18)	34 (15)	43 (18)
Parenteral	48 (21)	47 (20)	49 (21)	46 (20)
Not known	4 (2)	8 (3)	6 (3)	6 (3)
Microbiologic diagnosis — no. (%)				
Proven bacterial	158 (68)	167 (72)	155 (67)	170 (72)
Streptococcus pneumoniae	130 (56)	145 (62)	131 (57)	144 (61)
Neisseria meningitidis	10 (4)	10 (4)	13 (6)	7 (3)
Other gram-negative organisms§	15 (6)	10 (4)	9 (4)	16 (7)
Other¶	3 (1)	2 (1)	2 (1)	3 (1)
Probable bacterial (no organism identified)	52 (22)	50 (22)	56 (24)	46 (20)
Not bacterial meningitis	23 (10)	15 (6)	19 (8)	19 (8)
Cryptococcal meningitis‖	12 (5)	8 (3)	8 (3)	12 (5)
Mycobacterium tuberculosis	6 (3)	1 (0.4)	5 (2)	2 (1)
Not meningitis	5 (2)	6 (3)	6 (3)	5 (2)
Positive blood culture — no. (%)**	82 (35)	68 (29)	69 (30)	81 (34)
Blood culture unavailable — no. (%)	6 (3)	5 (2)	3 (1)	8 (3)
HIV-positive — no./total no. tested (%)	194/216 (90)	195/218 (89)	191/215 (89)	198/219 (90)
HIV status not known — no. (%)	17 (7)	14 (6)	15 (7)	16 (7)
Randomly assigned to receive intramuscular ceftriaxone — no. (%)	117 (50)	113 (49)		
Randomly assigned to receive corticosteroids — no. (%)			117 (51)	116 (49)

Scarborough, NEJM 2007

Table 2. Association between Baseline Characteristics and Mortality at 40 Days.

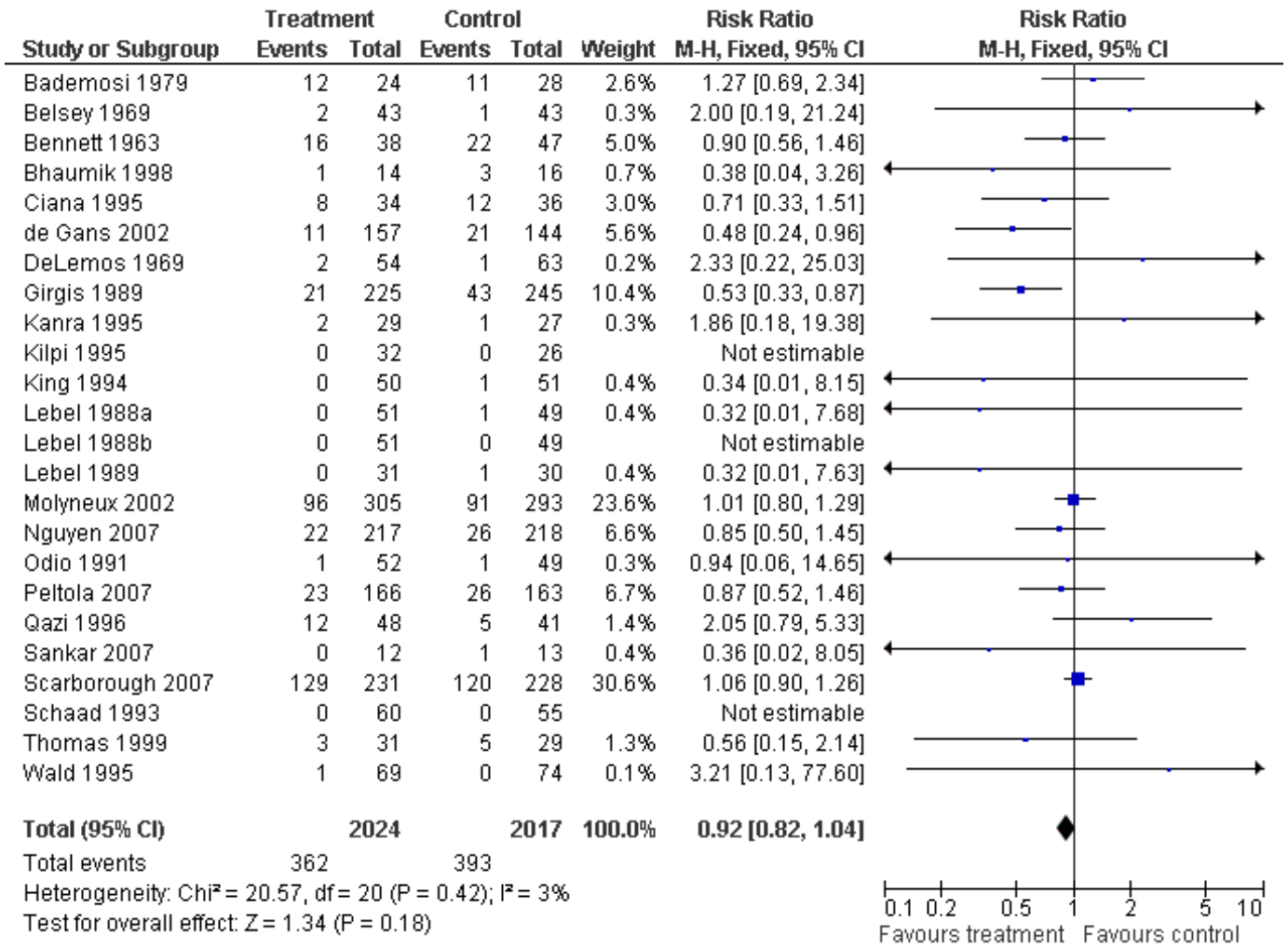
Characteristic	Univariate Analysis		Multivariate Analysis*	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Male sex	1.09 (0.75–1.57)	0.67	0.98 (0.62–1.55)	0.94
Age ≥32 yr†	1.92 (1.32–2.79)	0.001	1.96 (1.24–3.10)	0.004
Glasgow Coma Scale score <12‡	2.77 (1.90–4.06)	<0.001	4.10 (2.51–6.69)	<0.001
Hemoglobin <10 g/dl§	1.82 (1.23–2.69)	0.003	2.19 (1.39–3.45)	0.001
>48-hr history¶	1.64 (1.07–2.50)	0.02	1.48 (0.87–2.49)	0.14
Pneumococcal infection	0.76 (0.52–1.10)	0.15	0.56 (0.34–0.93)	0.02
Previous treatment with antibiotics	1.19 (0.81–1.75)	0.364	0.93 (0.58–1.49)	0.76
HIV-positive	1.96 (1.05–3.69)	0.035	1.35 (0.67–2.72)	0.40

Scarborough, NEJM 2007

Corticosteroids for acute bacterial meningitis (Review)

Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D

THE COCHRANE COLLABORATION®


Treatment
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
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)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

European Journal of Neurology 2009, **16:** 662–673 doi:10.1111/j.1468-1331.2009.02615.x

REVIEW ARTICLE

Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials

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Keywords:
central nervous system,
corticosteroids,
S. pneumoniae

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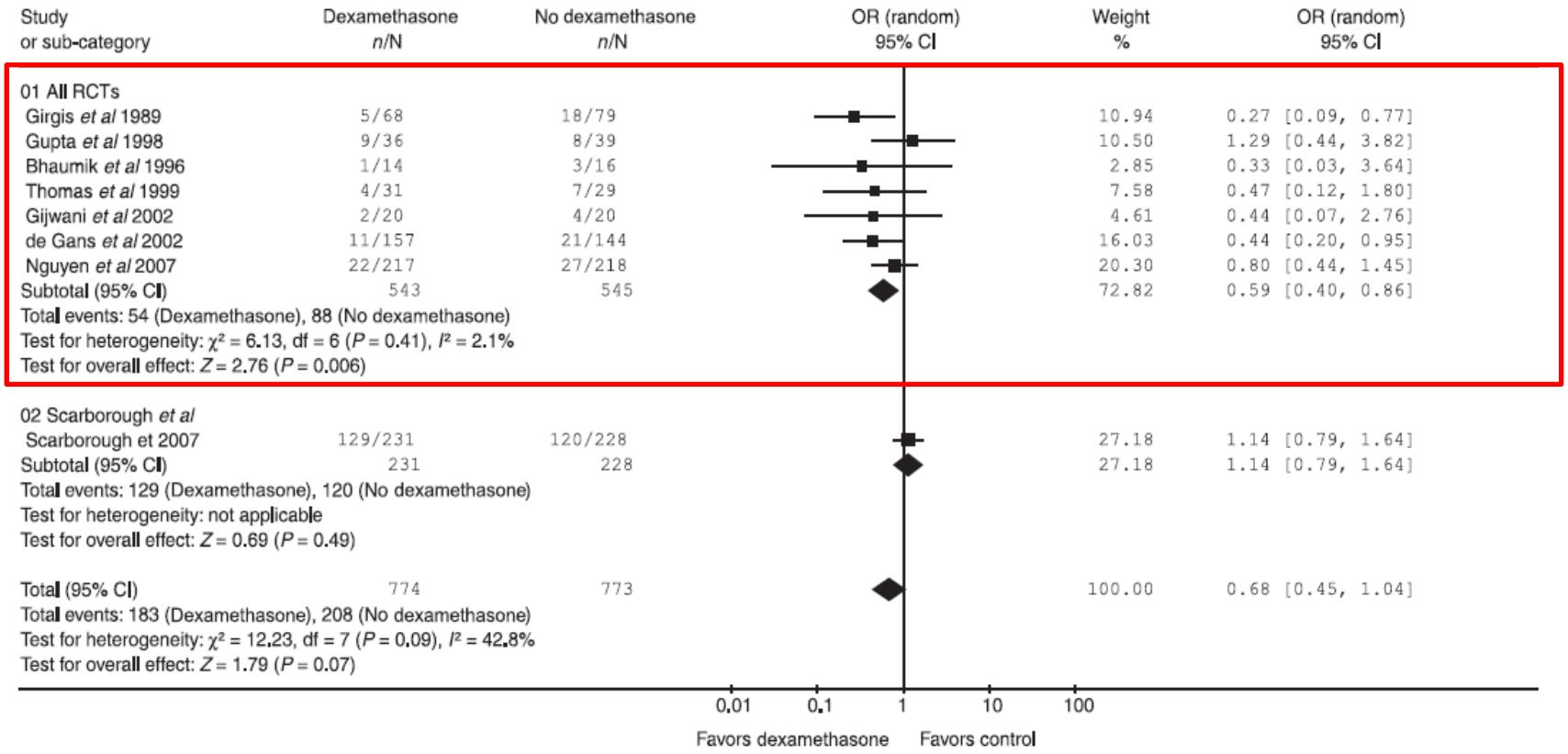
The objective of this review was to study the effectiveness of dexamethasone for the treatment of adult patients with bacterial meningitis. Data was extracted from randomized controlled trials (RCTs) comparing dexamethasone with placebo or no treatment and pooled using meta-analysis techniques. Treatment with dexamethasone was associated with a non-significant lower mortality than placebo or no treatment [odds ratio (OR) = 0.68, 95% confidence interval (CI) 0.45–1.04]. If a RCT conducted in Malawi was excluded from the analysis, dexamethasone was associated with lower mortality than placebo or no treatment (OR = 0.58, 95% CI 0.40–0.83). Dexamethasone was associated with lower mortality in patients with definite meningitis (OR = 0.55, 95% CI 0.31–0.96), short duration of symptoms (OR = 0.61, 95% CI 0.38–1.00), *Streptococcus pneumoniae* meningitis (OR = 0.26, 95% CI 0.08–0.78), patients in countries with high (OR = 0.45, 95% CI 0.23–0.87) and medium Human Development Index (OR = 0.65, 95% CI 0.42–1.00). No benefit was seen in patients with longer duration of symptoms (OR = 0.80, 95% CI 0.47–1.36) or no antibiotic use (OR = 0.68, 95% CI 0.36–1.28). Dexamethasone was associated with fewer episodes of hearing impairment in high quality RCTs (OR = 0.64, 95% CI 0.43–0.94). The currently available evidence suggests that dexamethasone should be administered to all adult patients with bacterial meningitis. Large studies are needed to clarify the role of the duration of symptoms, disease severity, and antibiotic administration before the initiation of treatment with dexamethasone on modifying the outcomes.



Vardakas E. J. Neurology 2009

Comparison or Outcome	No. of studies	Patients, *n*/*N* (%) corticosteroids versus placebo/no treatment	Effect estimate OR (95% CI)
Mortality (total)	10	211/836 (25.2) vs. 241/848 (28.4)	0.83 (0.66–1.06)
Mortality (Jadad >2)	6	187/742 (25.2) vs. 215/745 (28.9)	0.68 (0.44–1.05)
Symptoms >2 days	6	152/535 (28.4) vs. 160/551 (29.0)	0.94 (0.70–1.26)
Prior antibiotics	5	99/441 (22.4) vs. 123/470 (26.2)	0.81 (0.58–1.13)
Definite	8	135/581 (23.2) vs. 172/619 (27.8)	0.67 (0.43–1.04)
Probable	6	48/175 (27.4) vs. 42/149 (28.2)	1.11 (0.60–2.06)
High HDI	3	31/226 (13.7) vs. 50/220 (22.7)	0.56 (0.33–0.95)
Medium to low HDI	7	180/610 (29.5) vs. 191/628 (30.4)	0.93 (0.71–1.21)
Double blind	6	184/694 (26.5) vs. 201/686 (29.3)	0.86 (0.66–1.12)
Concealment of allocation	5	182/674 (27.0) vs. 197/666 (29.6)	0.88 (0.67–1.14)
N. meningitidis	5	7/115 (6.1) vs. 9/119 (7.6)	0.83 (0.30–2.33)
S. pneumoniae	8	105/301 (34.9) vs. 142/321 (44.2)	0.45 (0.21–0.96)

HDI, human developing index.

Vardakas E. J. Neurology 2009

Adjunctive dexamethasone in meningitis: does value depend on clinical setting?

Bacterial meningitis causes 170 000 deaths worldwide per year and, in low-income and middle-income countries, is ranked fourth as a cause of disability,[1] emphasising the need for clear evidence-based recommendations to guide acute management. Despite more than 20 clinical trials of adjunctive corticosteroid therapy in bacterial meningitis over the past 50 years,[2] absence of significant benefit in most individual studies, diverse steroid and antibiotic regimens, and concerns about generalisability to all causative organisms have fuelled continued debate. A Cochrane review on bacterial meningitis, based on trials reported to the end of 2003, concluded that use of adjunctive dexamethasone in bacterial meningitis was justified in all adults but only in children in high-income countries.[2] It called for additional studies among adults in low-income countries and for a

McIntyre, Lancet Neurology 2010

Influenza delle varianti del gene regolatore l'espressione del recettore per gli steroidi (GLCCI1)

Table 1 Mortality rates by patient genotype and dexamethasone treatment.

	CC/CT genotype	TT genotype	OR (95% CI)	*P*-value
All white patients				
Standard DXM	15/349 (4%)	9/87 (10%)	2.57 (1.09–6.09)	0.032
No DXM	10/79 (13%)	4/27 (15%)	1.20 (0.34–4.20)	0.780
Immunocompetent white patients				
Standard DXM	7/271 (3%)	6/67 (9%)	3.71 (1.20–11.43)	0.002
No DXM	7/61 (12%)	4/23 (17%)	1.62 (0.43–6.17)	0.267
White patients with pneumococcal meningitis				
Standard DXM	13/261 (5%)	7/63 (11%)	2.35 (0.90–6.15)	0.083
No DXM	6/47 (13%)	4/21 (19%)	1.61 (0.40–6.43)	0.297

Brouwer, *J. infection* 2012

Possono terapie antibiotiche ugualmente efficaci dal punto di vista microbiologico incidere sull'outcome?

Short-term rifampicin pretreatment reduces inflammation and neuronal cell death in a rabbit model of bacterial meningitis*

Annette Spreer, MD; Raimond Lugert, PhD; Valentin Stoltefaut; Anna Hoecht; Helmut Eiffert, MD, PhD; Roland Nau, MD

Objective: In bacterial meningitis, severe systemic and local inflammation causes long-term impairment and death of affected patients. The current antibiotic therapy relies on cell wall–active beta-lactam antibiotics, which rapidly sterilize the cerebrospinal fluid (CSF). However, beta-lactams inhibit cell wall synthesis, induce bacteriolysis, and thereby evoke a sudden release of high amounts of toxic and proinflammatory bacterial products. Because tissue damage in bacterial meningitis is the result of bacterial toxins and the inflammatory host response, any reduction of free bacterial compounds promises to prevent neuronal damage.

Design: In vitro experiments and randomized prospective animal study.

Setting: University research laboratories.

Subjects: Streptococcus pneumoniae broth cultures and New Zealand White rabbits.

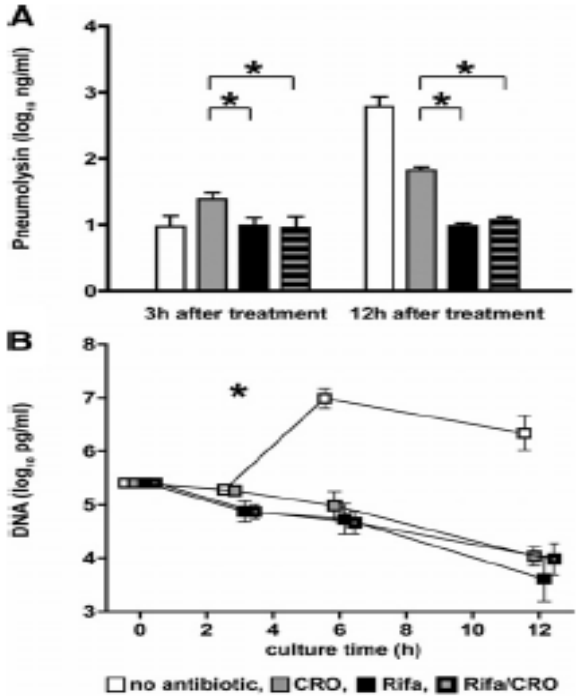
Interventions: We evaluated a concept to improve bacterial meningitis therapy in which a short-term pretreatment with the protein synthesis–inhibiting antibiotic rifampicin precedes the standard antibiotic therapy with ceftriaxone. First, logarithmically growing pneumococcal cultures were subdivided and exposed to different antibiotics. Then, rabbits suffering from pneumococcal meningitis were randomized to receive rifampicin pretreatment or ceftriaxone alone.

Measurements and Main Results: In pneumococcal cultures, quantitative immunoblotting and real-time polymerase chain reaction revealed a reduced release of pneumolysin and bacterial DNA by rifampicin pretreatment for 30 minutes in comparison with ceftriaxone treatment alone. *In vivo*, a 1-hour rifampicin pretreatment reduced the release of bacterial products and attenuated the inflammatory host response, as demonstrated by decreased CSF levels of prostaglandin E2 and total protein and increased glucose CSF/plasma ratios. Rifampicin pretreatment reduced infection-associated neuronal apoptotic cell loss compared with ceftriaxone-treated controls.

Conclusions: A short-term pretreatment with rifampicin reduced the beta-lactam–induced release of deleterious bacterial products, attenuated inflammation, and thereby decreased neuronal cell loss in experimental bacterial meningitis. This concept has the potential to reduce inflammation-associated neuronal injury in bacterial meningitis and should be evaluated in a clinical trial. (Crit Care Med 2009; 37:2253–2258)

KEY WORDS: *Streptococcus pneumoniae*; meningitis; rabbit model; nonbacteriolytic antibiotics; meningeal inflammation; neuronal apoptosis

CONCENTRAZIONE DELLE PNEUMOLISINE E TERAPIA SOMMINISTRATA



Spreer, CCM 2009

Killing bacteria softly in the cerebrospinal fluid may be advantageous in bacterial meningitis*

Bacterial meningitis affects all age groups and continues to be a significant cause of disability and loss of life despite improvements in prophylaxis and therapy during the past 25 years. The Hib vaccine has led to a virtual disappearance of *Haemophilus influenzae* serotype b meningitis in countries in which it has been adopted in the childhood immunization program. An analogous protein-conjugated vaccine against *Streptococcus pneumoniae* covering seven major serotypes holds a similar promise and has reduced the number of pneumococcal meningitis cases in the United States by ~30% (1).

ful effect in severely ill patients has been suggested (5, 6). These observations may indicate a detrimental side effect of β-lactam antibiotics in patients still out of reach of intensive supportive care, which could be the result of augmentation of the inflammatory response elicited by antibiotic bacterial killing.

The inflammatory response associated with bacterial meningitis is an obvious target for adjunctive therapy. Glucocorticosteroids, when administered before or together with the first dose of antibiotics, have a confirmed protective effect on hearing loss in children in high-income countries (7), but this effect has become

means to modulate the inflammatory response. The use of nonbacteriolytic antibiotics in the therapy of meningitis is another approach to decrease the potential harmful effect of antibiotic bacterial killing. In this issue of *Critical Care Medicine*, Spreer et al (17) demonstrate, using a rabbit meningitis model, that rifampicin administered 1 hour before the initial dose of ceftriaxone causes less brain damage and reduces the release of immunogenic pneumococcal cell wall fragments compared with therapy with ceftriaxone alone. During the past decade, the group from Germany has extensively addressed this issue with a series of experimental

Schønheyder, CCM 2009

Slow initial β-lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial

Tuula Pelkonen, Irmeli Roine, Manuel Leite Cruzeiro, Anne Pitkäranta, Matti Kataja, Heikki Peltola

	Number of patients assessed	Cefotaxime infusion				Cefotaxime boluses with oral paracetamol (n=180)	
		With oral paracetamol (n=183)		With oral placebo (n=180)		Odds ratio (95% CI)	p
		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		
Total mortality							
Intention-to-treat overall	723	0·80 (0·52–1·24)	0·32	1·10 (0·72–1·68)	0·67	1·00 (0·65–1·53)	>0·99
Per-protocol overall	499	0·84 (0·50–1·43)	0·53	1·13 (0·67–1·89)	0·66	1·06 (0·64–1·77)	0·82
Intention-to-treat *S pneumoniae*	184	0·66 (0·31–1·42)	0·29	0·76 (0·33–1·75)	0·51	0·99 (0·43–2·26)	0·97
Per-protocol *S pneumoniae*	160	0·64 (0·27–1·50)	0·30	0·83 (0·34–2·04)	0·69	1·26 (0·53–2·99)	0·61
48 h							
Intention-to-treat overall	723	0·45 (0·26–0·77)	0·003	0·89 (0·55–1·43)	0·63	1·00 (0·63–1·60)	>0·99
Per-protocol overall	499	0·48 (0·26–0·91)	0·02	1·01 (0·58–1·77)	0·97	1·06 (0·61–1·83)	0·84
Intention-to-treat *S pneumoniae*	184	0·57 (0·25–1·31)	0·19	0·93 (0·39–2·23)	0·87	1·38 (0·59–3·22)	0·45
Per-protocol *S pneumoniae*	160	0·57 (0·22–1·44)	0·23	0·90 (0·35–2·30)	0·82	1·59 (0·66–3·87)	0·30
72 h							
Intention-to-treat overall	723	0·52 (0·32–0·85)	0·009	0·80 (0·51–1·27)	0·35	0·97 (0·62–1·53)	0·91
Per-protocol overall	499	0·55 (0·30–0·99)	0·04	0·97 (0·57–1·68)	0·92	1·01 (0·59–1·71)	0·98
Intention-to-treat *S pneumoniae*	184	0·65 (0·29–1·43)	0·28	0·82 (0·35–1·94)	0·65	1·09 (0·47–2·51)	0·84
Per-protocol *S pneumoniae*	160	0·60 (0·25–1·47)	0·27	0·85 (0·34–2·13)	0·73	1·32 (0·55–3·18)	0·53

Table 4: **Mortality in hospital, overall and at 48 and 72 h, in the whole series and in children with pneumococcal meningitis for three study treatment groups**

Lancet Inf Dis 2011

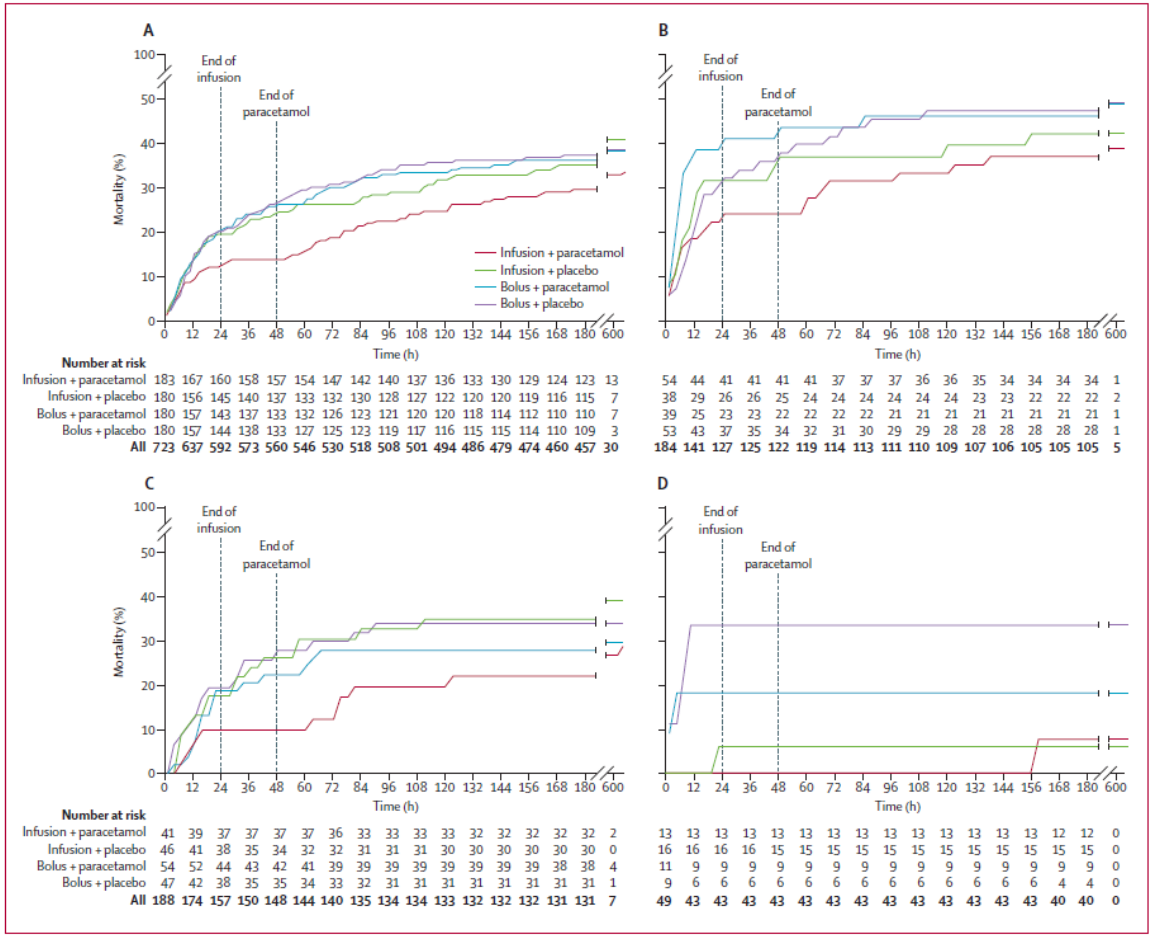


***Figure 2*: Mortality curves for per-protocol population**

(A) All children (n=723), (B) with pneumococcal (n=184), (C) with *Haemophilus influenzae* type b (n=188), and (D) with meningococcal meningitis (n=49).

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Early Vancomycin Therapy and Adverse Outcomes in Children With Pneumococcal Meningitis

Steven C. Buckingham, Jonathan A. McCullers, Jorge Luján-Zilbermann, Katherine M. Knapp, Karen L. Orman and B. Keith English

Pediatrics 2006;117;1688
DOI: 10.1542/peds.2005-2282

TABLE 3 Associations of Vancomycin Start Time With Outcome Variables

Outcome	Vancomycin Start Time, *n/N* (%)		*P*[a]	Odds Ratio (95% Confidence Interval)
	<2 h	>2 h		
Mortality	3/54 (6)	3/44 (7)	.99	0.80 (0.15–4.19)
Hearing loss	24/32 (75)	8/27 (30)	.0007	7.1 (2.3–22.5)
Other neurologic deficit	6/50 (12)	6/40 (15)	.76	0.77 (0.23–2.61)

[a] Fisher's exact test.

Antimicrobial Agents and Chemotherapy

Attenuation of Cerebrospinal Fluid Inflammation by the Nonbacteriolytic Antibiotic Daptomycin versus That by Ceftriaxone in Experimental Pneumococcal Meningitis

Denis Grandgirard, Kevin Oberson, Angela Bühlmann, Rahel Gäumann and Stephen L. Leib

Antimicrob. Agents Chemother. 2010, 54(3):1323. DOI: 10.1128/AAC.00812-09.
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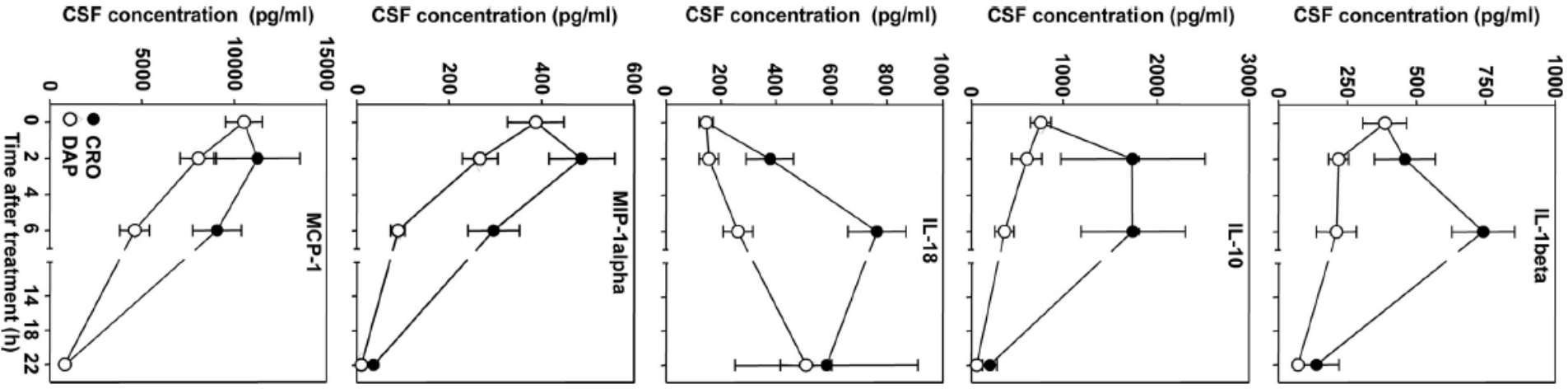

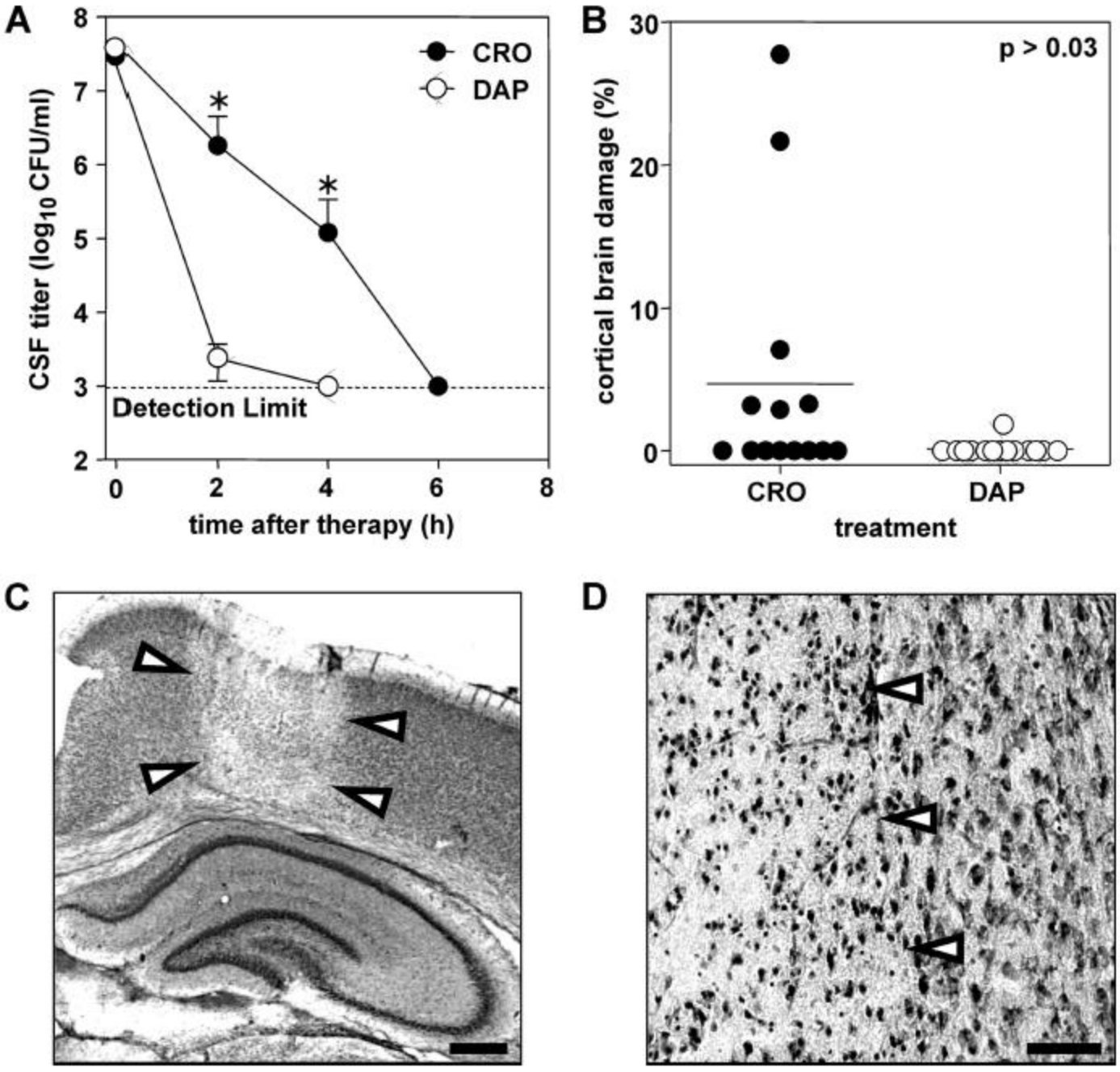
A
CSF titer (log_{10} CFU/ml)
time after therapy (h)
CRO
DAP
Detection Limit
*
*
B
cortical brain damage (%)
p > 0.03
CRO
DAP
treatment
C
D

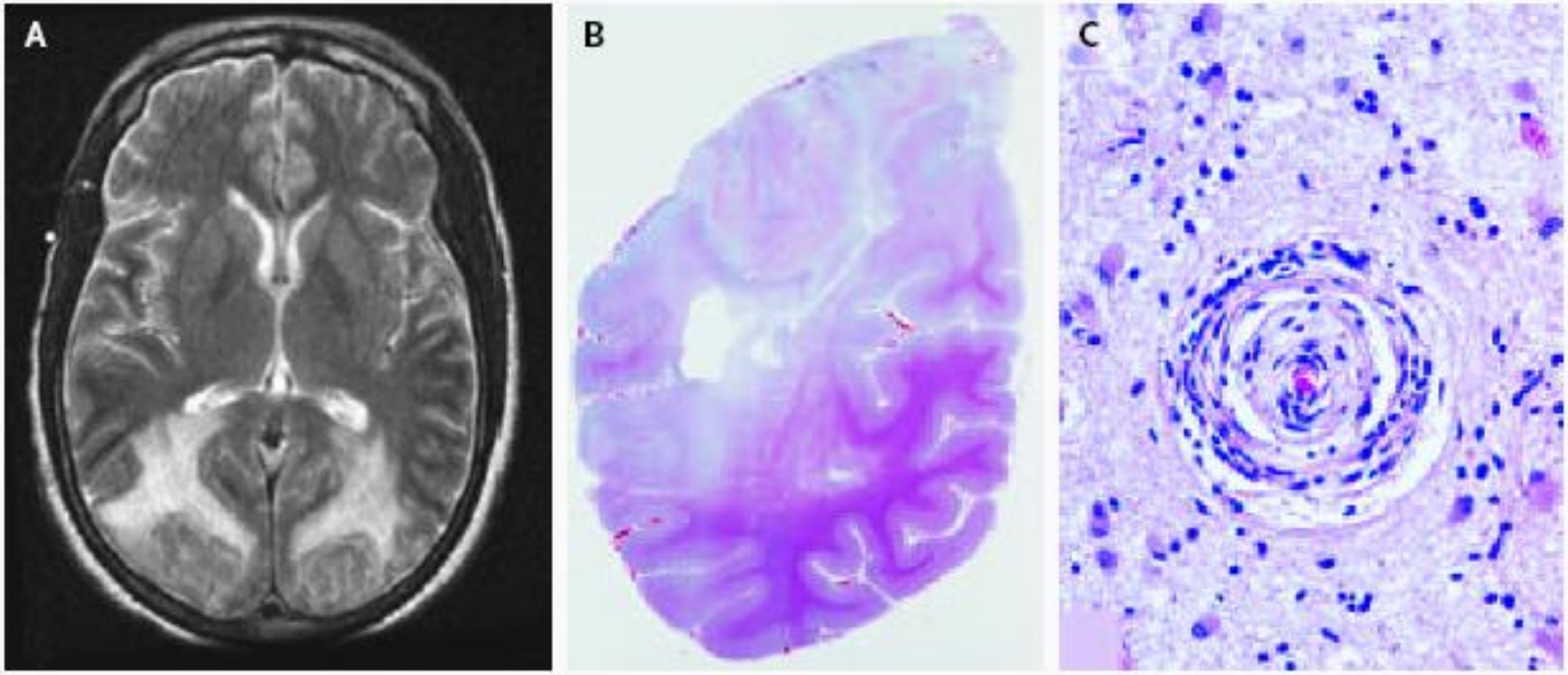

Figure 2. Cerebrovascular Complications in Bacterial Meningitis.

In Panel A, T_2-proton-density–weighted magnetic resonance imaging of the brain shows a transverse view of a hyperintense signal of the posterior lobes that indicates cerebral edema. In Panel B, a postmortem coronal view of the left posterior lobe of the same patient shows large areas of confluent necrosis involving the upper part of the hemisphere, as indicated by the loss of staining for hematoxylin and eosin. In Panel C, the microscopic substrate in the posterior lobe of this patient shows a small, almost completely obstructed vessel in the cortex with perivascular lymphocytic infiltration (endarteritis obliterans) that is surrounded by gliosis.

Conclusioni

- **L'uso dello steroide deve essere considerato nelle aree ad alto HDI, il Desametazone deve essere preferito per la sua buona capacità di passare la barriera emato-encefalica e per la sua attività anti-edemigena**
- **L'utilizzo deve essere limitato ai primi 4 giorni di terapia come suggerito dalle linee guida (IDSA, EFNS, NICE)**
- **I pazienti con meningite pneumococcica sono la migliore popolazione target**
- **Almeno nelle area a basso HDI, l'uso non è efficace negli HIV positivi che presentano già un deficit della risposta immune**
- **E' importante assieme allo steroide utilizzare farmaci non batteriolitici per limitare il rilascio di prodotti batterici**