Corticoïdes dans les Encéphalites en Réanimation ?

Romain Sonneville

Journée OUTCOMEREA

30/11/2023

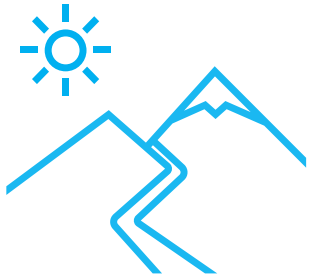
APHP, Hôpital Bichat Claude Bernard, Paris
Intensive Care Medicine

Conflicts of interest

Research Grants:

- French Ministry of Health.
- LFB

Roadmap



- Introduction
- Viral encephalitis ?
- Autoimmune encephalitis ?
- Acute bacterial meningitis ?
- Other causes ?
- Perspectives

	Encephalitis	Meningitis
Inflammation	**Brain parenchyma**	**Subarachnoid space**
Causes	**Viral** Immune-mediated	**Bacterial** Viral
Altered mental status	**+**	+/-
Fever	**+**	**+**
Meningism	+/-	**+**
Focal signs	+/-	+/-
Seizures	+/-	+/-

ORIGINAL

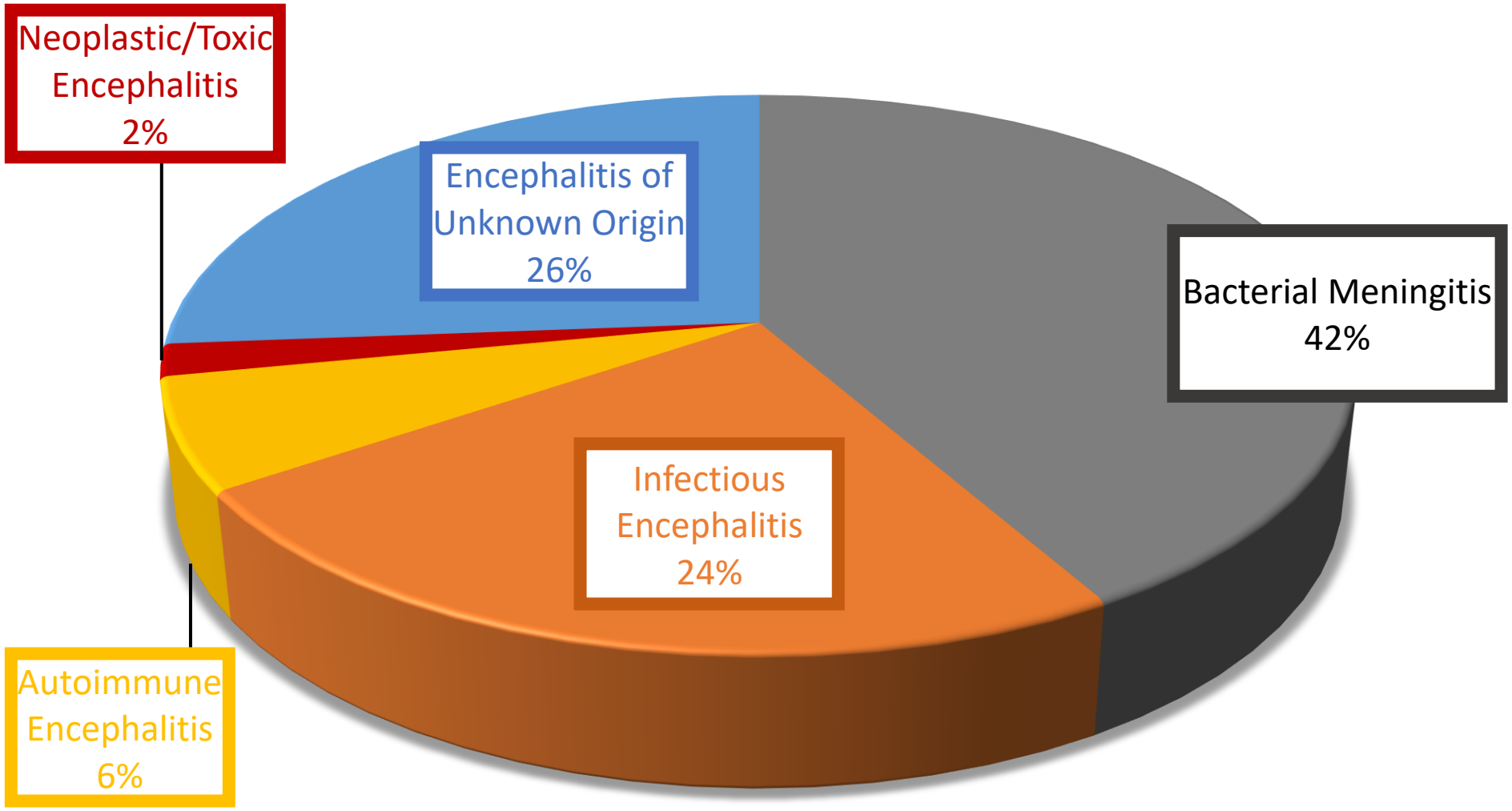
Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study

Romain Sonneville[1,2,30*], Etienne de Montmollin[1,2], Damien Contou[3], Ricard Ferrer[4], Mohan Gurjar[5], Kada Klouche[6], Benjamine Sarton[7], Sophie Demeret[8], Pierre Bailly[9], Daniel da Silva[10], Etienne Escudier[11], Loic Le Guennec[12], Russel Chabanne[13], Laurent Argaud[14], Omar Ben Hadj Salem[15], Martial Thyrault[16], Aurélien Frerou[17], Guillaume Louis[18], Gennaro De Pascale[19], Janneke Horn[20], Raimund Helbok[21,31], Guillaume Geri[22], Fabrice Bruneel[23], Ignacio Martin-Loeches[24], Fabio Silvio Taccone[25], Jan J. De Waele[26], Stéphane Ruckly[27], Quentin Staiquly[27], Giuseppe Citerio[28,29] and Jean-François Timsit[1,2] on behalf of the EURECA Investigator Study Group

Results

Patients (n=589)

Aetiological groups



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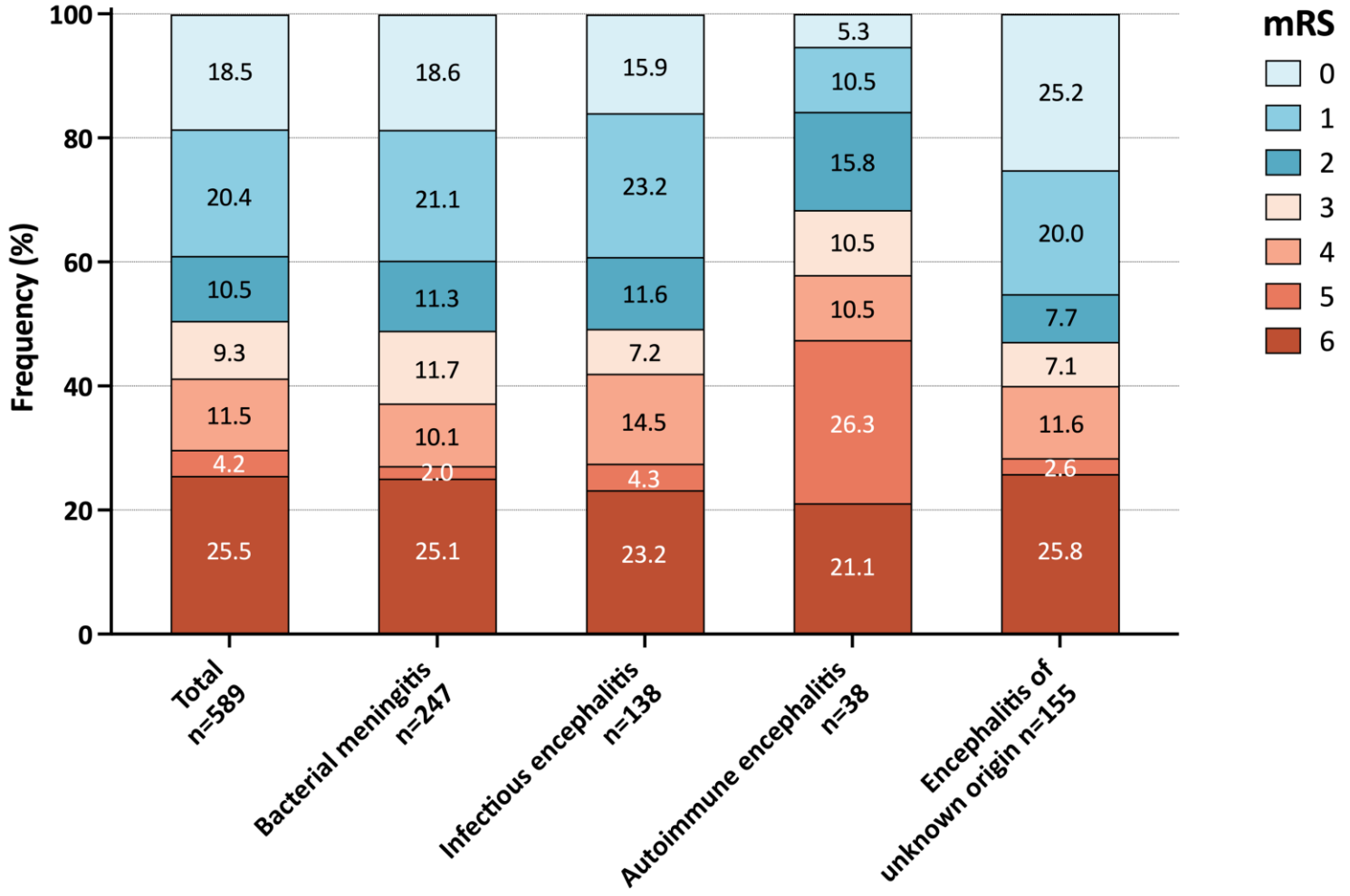
Categories	n (%)
Acute bacterial meningitis	**247 (41·8)**
Streptococcus pneumoniae	148 (25)
Neisseria meningitidis	17 (2·9)
Listeria monocytogenes	14 (2·4)
Other causes**	68 (11·5)
Infectious encephalitis	**140 (23·7)**
Viral causes	101 (17·1)
Herpes simplex virus 1/2	49 (8·3)
Varicella zoster virus	21 (3·6)
Enterovirus	3 (0·5)
Other causes	28 (4·7)
Subacute bacterial causes	25 (4·2)
Mycobacterium tuberculosis	16 (2·7)
Other causes	9 (1·5)
Fungal/parasitic causes	14 (2·4)
Toxoplasma gondii	7 (1·2)
Cryptococcus neoformans	3 (0·5)
Aspergillus spp.	2 (0·3)
Other causes***	2 (0·5)
Autoimmune	**38 (6·4)**
Anti N-methyl-D-aspartate Receptor antibody	16 (2·7)
Acute disseminated encephalomyelitis	7 (1·2)
Other causes**	15 (2·5)
Neoplastic/toxic	**11 (1·9)**
Unknown origin	**155 (26·2)**

Day-90 outcomes



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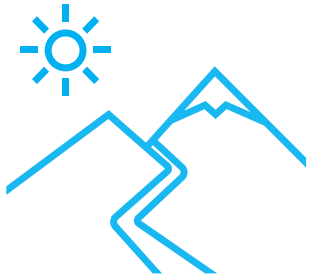
Roadmap



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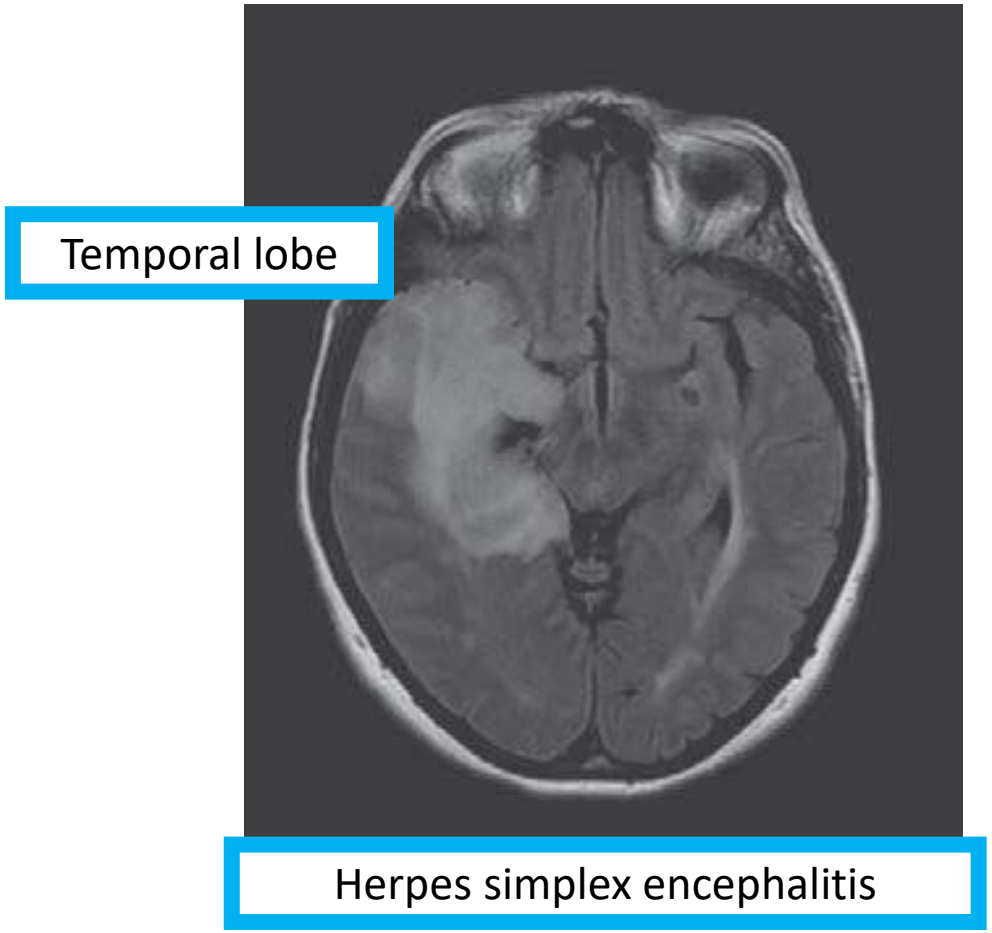
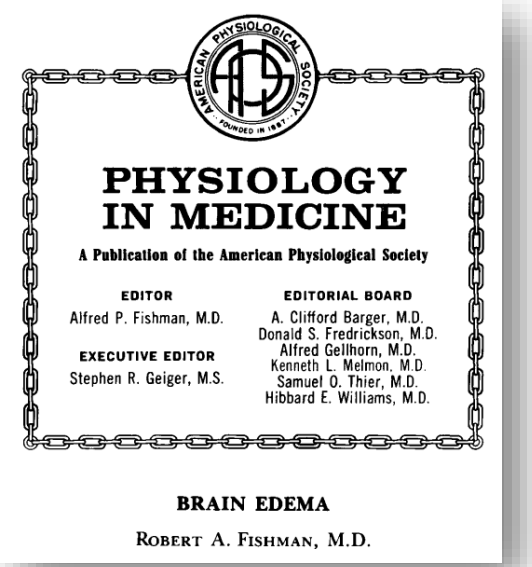
Encephalitis

Inflammation	**Brain parenchyma**
Causes	**Viral** Immune-mediated
Altered mental status	**+**
Fever	**+**
Meningism	+/-
Focal signs	+/-
Seizures	+/-




PHYSIOLOGY IN MEDICINE

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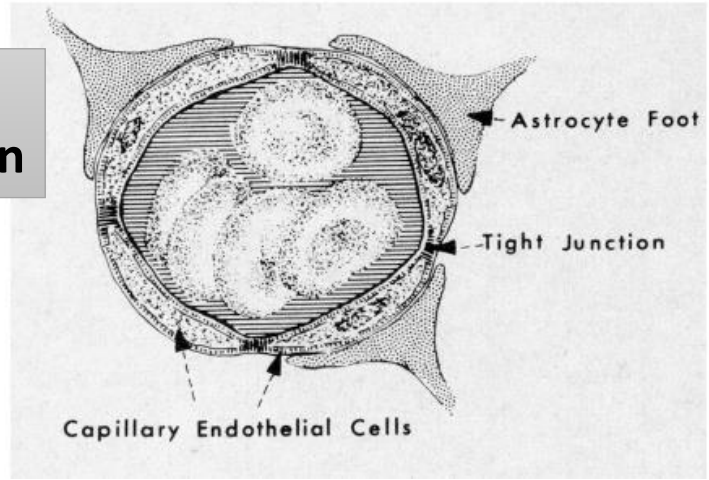
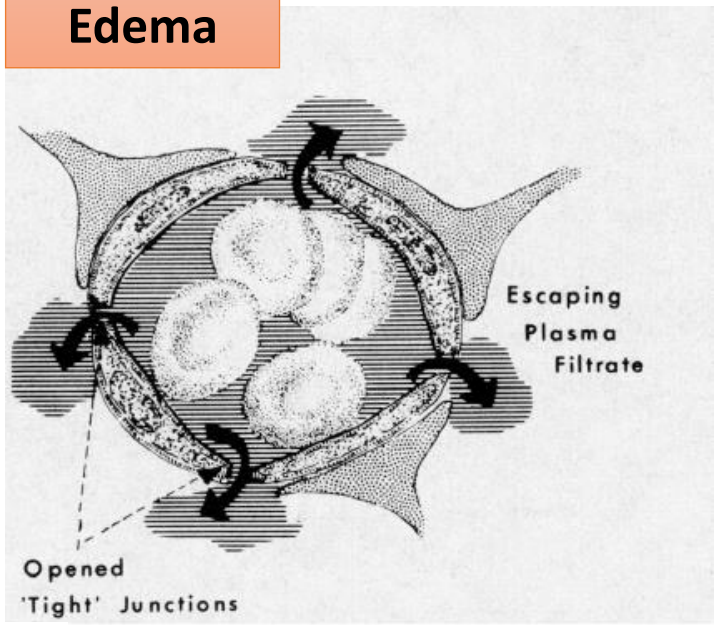
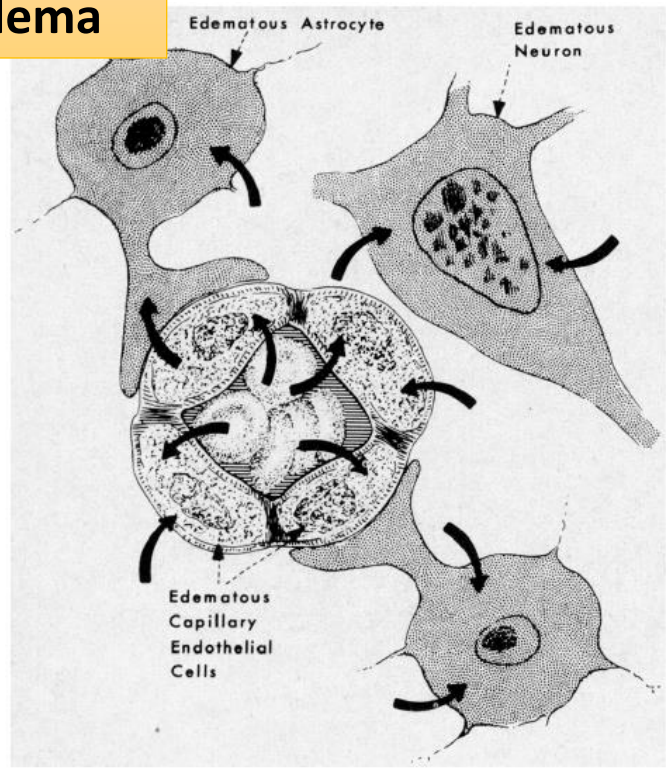
Normal Situation



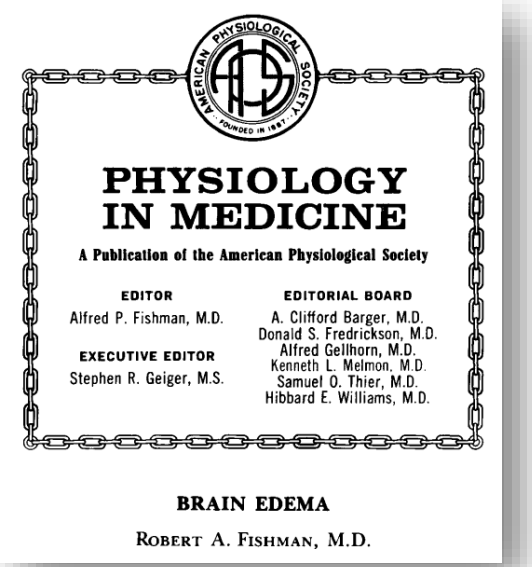
Vasogenic Edema



Cytotoxic Edema



New Eng J Med 1975



Feature	Vasogenic	Cytotoxic	Interstitial
Disorders	Abscess Meningitis / Encephalitis Brain tumor TBI , hemorrhage	Cerebral hypoxia Infarction Hypoosmolality	Obstructive hydrocephalus
Pathogenesis	Increased capillary permeability	Cellular swelling	Block of CSF absorption
Main location	White matter	Gray and white matter	Periventricular
Edema composition	Plasma filtrate including proteins	Increased intracellular water and Na+	CSF
Extracellular fluid volume	Increased	Decreased	Increased
Capillary permeability to large molecules	Increased	Normal	Normal
Rx : Steroids	?	No effect	Uncertain

New Eng J Med 1975

Steroids for Encephalitis ?

UPs

Anti-inflammatory effects

Edema reduction

Immunomodulation

Cellular stabilization

Neuroprotective effects

DOWNs

Fluid retention and edema

Immunosuppression

Electrolyte imbalance

Gastrointestinal issues

Neuropsychological effects

Glucose metabolism changes

Pharmacologic Characteristics of Corticosteroids

Sophie Samuel, PharmD[1], Thuy Nguyen, PharmD[1], H. Alex Choi, MD[2]

[1]Department of Pharmacy, Memorial Hermann Texas Medical Center, Houston, TX;
[2]Department of Neurosurgery and Neurology, The University of Texas Medical School at Houston, Houston, TX, USA

Table 1. Corticosteroid comparison chart

	Equivalent glucocorticoid dose (mg)	Potency relative to hydrocortisone		Half-life duration of action (hours)
		Anti-inflammatory	Mineralo-corticoid	
Glucocorticoids				
Short acting				
Hydrocortisone*	20	1	1	8-12
Cortisone acetate	25	0.8	0.8	8-12
Intermediate acting				
Prednisone	5	4	0.8	12-36
Prednisolone	5	4	0.8	12-36
Methylprednisolone*	4	5	0.5	12-36
Long acting				
Dexamethasone*	0.75	30	0	36-54
Mineralocorticoid				
Fludrocortisone	0	15	150	24-36

*These medications are also available for intravenous administration. Doses of intravenous medications are not equivalent to oral

REVIEW
J Neurocrit Care 2017;10(2):53-59
https://doi.org/10.18700/jnc.170035

VIDARABINE VERSUS ACYCLOVIR THERAPY IN HERPES SIMPLEX ENCEPHALITIS

RICHARD J. WHITLEY, M.D., CHARLES A. ALFORD, M.D., MARTIN S. HIRSCH, M.D.,
ROBERT T. SCHOOLEY, M.D., JAMES P. LUBY, M.D., FRED Y. AOKI, M.D., DANIEL HANLEY, M.D.,
ANDRE J. NAHMIAS, M.D., SENG-JAW SOONG, P.D.,
AND THE NIAID COLLABORATIVE ANTIVIRAL STUDY GROUP*

Table 1. Demographic Characteristics and Selected Findings in 69 Patients with Biopsy-Proved Herpes Simplex Encephalitis.

CHARACTERISTICS	TREATMENT GROUP	
	VIDARABINE	ACYCLOVIR
	no. of patients (%)	
No. of patients	37 (54)	32 (46)
Sex		
Male	20 (54)	23 (72)
Female	17 (46)	9 (28)
Age		
>6 months–10 yr	5 (14)	8 (25)
11–20 yr	3 (8)	7 (22)
21–30 yr	3 (8)	3 (9)
31–40 yr	4 (11)	3 (9)
41–50 yr	3 (8)	1 (4)
51–60 yr	5 (14)	3 (9)
>60 yr	14 (37)	7 (22)
Race		
White	36 (97)	28 (88)
Black	0 (0)	1 (3)
Other	1 (3)	3 (9)
History of labial herpes*	3 (8)	4 (13)
Seizures†	25 (68)	22 (69)
Focal	10 (40)	9 (41)
Generalized	4 (16)	5 (23)
Both	11 (44)	8 (36)
Glasgow coma score		
≤6	12 (32)	8 (25)
7–10	12 (32)	16 (50)
>10	13 (35)	8 (25)
Therapy of cerebral edema		
None	8 (22)	8 (25)
Corticosteroids	9 (24)	10 (31)
Mannitol	3 (8)	2 (6)
Both	17 (46)	12 (38)
	mean (±SE) days (% of patients)	

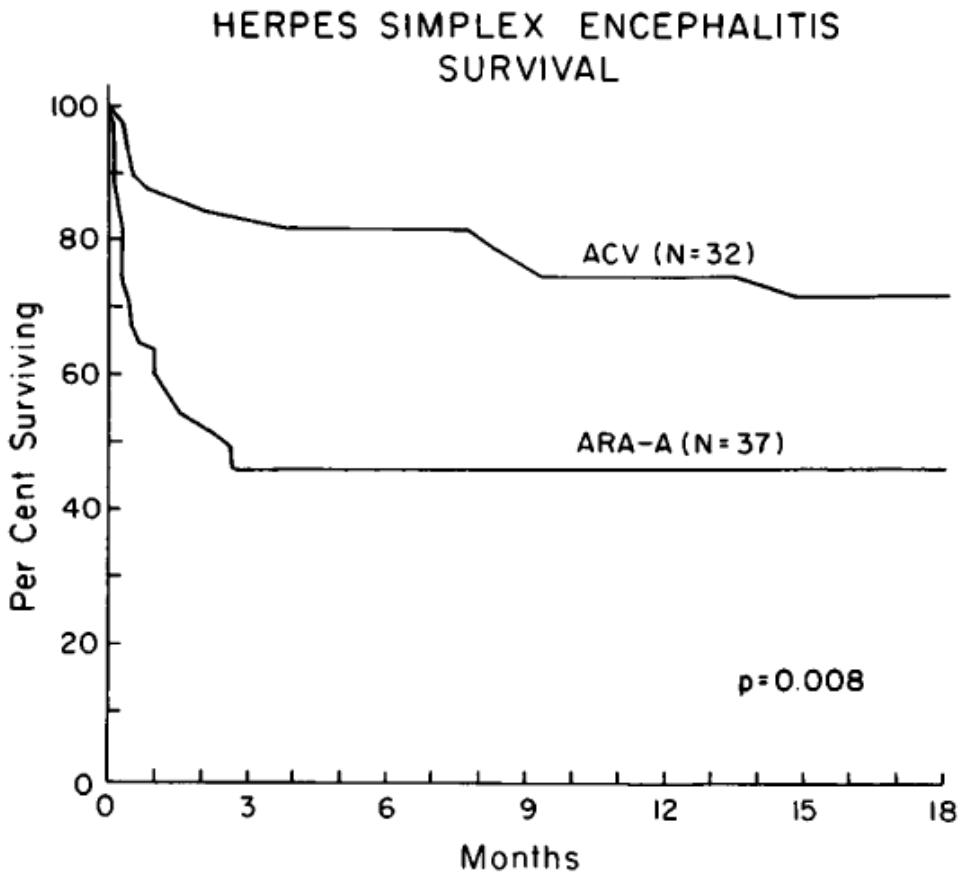


Figure 1. Comparison of Survival in Patients with Biopsy-Proved Herpes Simplex Encephalitis Treated with Vidarabine (ARA-A) or Acyclovir (ACV); P = 0.008.

New Eng J Med 1986

PAPER

Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis

S Kamei, T Sekizawa, H Shiota, T Mizutani, Y Itoyama, T Takasu, T Morishima, K Hirayanagi

See Editorial Commentary, p 1469

J Neurol Neurosurg Psychiatry 2005;**76**:1544–1549. doi: 10.1136/jnnp.2004.049676

Retrospective Study
45 pts with HSV encephalitis treated with acyclovir

Table 3 Results for the estimation of predictors of outcome in herpes simplex encephalitis by single and multiple logistic regression analyses

Variable	Unit of increase	Spearman's rank correlation against outcome	Single logistic regression analysis		Multiple logistic regression analysis	
			Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
(1) Sex	NA	0.266	0.992 (0.30 to 3.29)	0.989	–	–
(2) Age	1 year	0.605	1.075 (1.03 to 1.12)	0.001*	1.088 (1.02 to 1.16)	0.006*
(3) Days after onset at initiation of aciclovir	1 day	0.305	1.097 (0.92 to 1.31)	0.144	–	–
(4) Modified value of GCS score at initiation of aciclovir†	1 score	0.602	1.424 (1.14 to 1.77)	0.002*	1.452 (1.08 to 1.95)	0.014*
(5) Initial leucocyte cell count in CSF‡ (maximum values in serial CSFs)	0–10	0.245 (0.284)	1.00 (reference)	0.566 (0.719)	–	–
	11–100		0.200 (0.02 to 2.03) (0.275 (0.03 to 2.90))			
	101–300		0.200 (0.02 to 2.58) (0.250 (0.02 to 3.34))			
	⩾301/μl		0.300 (0.03 to 3.63) (0.375 (0.03 to 4.71))			
(6) Initial CSF protein‡ (maximum values in serial CSFs)	⩽50	0.253 (0.246)	1.00 (reference)	0.441 (0.388)	–	–
	51–100		0.444 (0.07 to 2.74) (0.650 (0.10 to 4.18))			
	⩾101 mg/dl		0.292 (0.04 to 1.94) (0.311 (0.05 to 2.11))			
(7) Corticosteroid administration	0=given 1=not given	0.521	3.467 (0.99 to 12.09)	0.041*	8.964 (1.13 to 70.99)	0.038*
(8) Detection of lesion by initial CT	0=absent 1=present	0.562	6.222 (1.45 to 26.65)	0.044*	3.690 (0.43 to 31.85)	0.235
(9) Detection of lesion by initial MRI	0=absent 1=present	0.567	5.400 (0.59 to 49.27)	0.135	–	–
(10) Detection of PLEDs on EEG	0=absent 1=present	0.269	1.050 (0.32 to 3.44)	0.936	–	–

Adjunctive steroids in adults with encephalitis: a propensity score analysis

Ambreen Allana[1] · Mohammed Samannodi[1,2] · Michael A. Hansen[3] · Stacia DeSantis[4] · Lauren T. Ho[5] · Rodrigo Hasbun[1]

230 adult patients with **Encephalitis**

Adjunctive steroids given in **121 (52.6%)** patients and associated with :

- ICU admission
- Invasive mechanical ventilation
- More severe neurologic presentation
- White matter changes on MRI

Etiologies, (*n*) (%) (*n* = 230)	*N* (%) (*n* = 230)	Patients that received steroids by etiology, *n* (%) (*n* = 121)
Unknown etiology	111 (48.3)	55 (49.5)
Viral etiology	65 (28.2)	26 (40.0)
West Nile virus	24	9
Herpes simplex virus	21	7
Varicella zoster virus	10	5
Cytomegalovirus	4	1
JC virus	1	1
Enterovirus	1	1
Autoimmune etiology	28 (12.1)	26 (92.8)
Anti-NMDA receptor antibodies	26	
Anti-VGKC antibodies	2	
Bacterial etiology	13 (5.6)	7 (53.8)
Mycobacterium tuberculosis	3	2
Treponema pallidum	2	0
Streptococci pneumonia	2	2
Beta hemolytic streptococci	1	0
Staphylococcus aureus	1	0
Coagulase negative Staphylococcus	1	1
Group A beta hemolytic streptococci	1	1
Brucella spp.	1	0
Rickettsia ricketsii	1	1
Parasitic etiology	5 (2.2)	5 (100.0)
Toxoplasma gondii	5	5
Fungal etiology	3 (1.3)	3 (100.0)
Cryptococcus neoformans	2	2
Coccidiodes immitis	1	1

NMDA anti-*N*-methyl-D-aspartate, *VKGC* voltage-gated potassium channel antibodies, *JC* John Cunningham virus

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230 adult patients with **Encephalitis**

Adjunctive steroids

- Prescribed in 52.6%
- Not associated with outcome ….

Table 5 Independent prognostic factors of an adverse clinical outcome in 230 adults with encephalitis by Logistic Regression

Clinical variable	Adjusted odds ratio	95% confidence interval	*P* value[b]
Cerebral edema[c]	6.55	1.37–31.40	**0.02**
Meningeal enhancement[c]	2.02	0.84–4.84	0.12
GCS < 8[d]	14.86	3.71–59.42	**< 0.001**
Abnormal exam[e]	1.65	0.59–4.63	0.34
Seizures	1.10	0.53–2.29	0.80
Fever > 38.4 C	2.54	1.21–5.32	**0.01**
ICU admission[f]	1.85	0.75–4.58	0.18
Respiratory failure/intubation	0.24	0.08–0.70	**0.009**

Adverse clinical outcome defined by a Glasgow Outcome Scale (GOS) 1–4. GOS 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability) or 5 (mild disability)

[b]All statistically significant outcomes signified by bolding the *P* value

[c]Seen on magnetic resonance imaging

[d]*GCS* Glasgow Coma Scale

[e]Abnormal examination = includes acute focal deficits, seizures, GCS < 15

[f]*ICU* intensive care unit

Interpretation Adjunctive steroids are used more frequently in sicker patients and are not associated with improved clinical outcomes.

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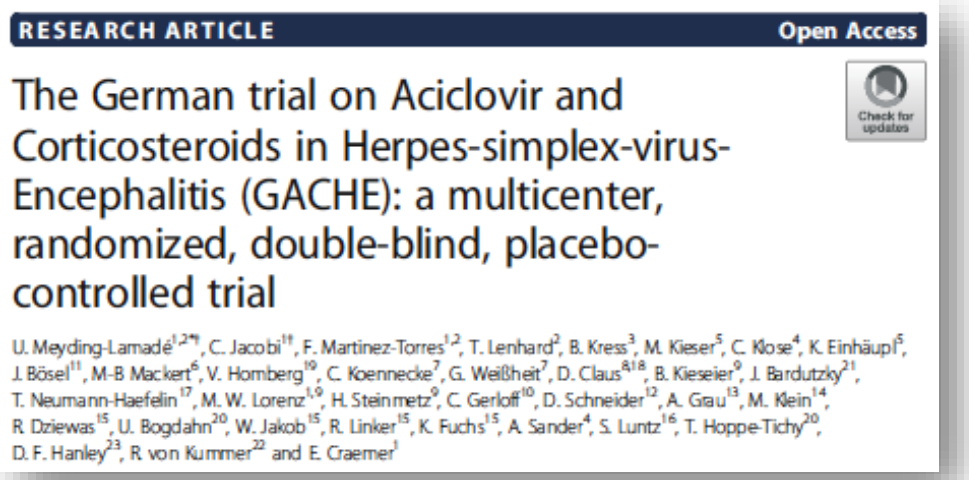


RESEARCH ARTICLE Open Access

The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial

U. Meyding-Lamadé[1,2*†], C. Jacobi[1†], F. Martinez-Torres[1,2], T. Lenhard[3], B. Kress[3], M. Kieser[5], C. Klose[4], K. Einhäupl[5], J. Bösel[11], M-B Mackert[6], V. Homberg[19], C. Koennecke[7], G. Weißheit[7], D. Claus[8,18], B. Kieseier[9], J. Bardutzky[21], T. Neumann-Haefelin[17], M. W. Lorenz[1,9], H. Steinmetz[9], C. Gerloff[10], D. Schneider[12], A. Grau[13], M. Klein[14], R. Dziewas[15], U. Bogdahn[20], W. Jakob[15], R. Linker[15], K. Fuchs[15], A. Sander[4], S. Luntz[16], T. Hoppe-Tichy[20], D. F. Hanley[23], R. von Kummer[22] and E. Craemer[1]

RCT DXM 10mg x 4 / j pdt 4 jours vs. placebo

Treatment arms

All patients were treated with aciclovir intravenously at a dosage of 10 mg/kg body weight every 8 hours with an infusion time of 1 h, if patients had a normal renal function. In case of reduced creatinine clearance (< 60 ml/min) the aciclovir dosage was adapted. In addition, they received the study medication, either intravenous Dexamethasone at a dosage of 40 mg every 24 h for 4 days, or placebo that was identical in appearance to the active drug.

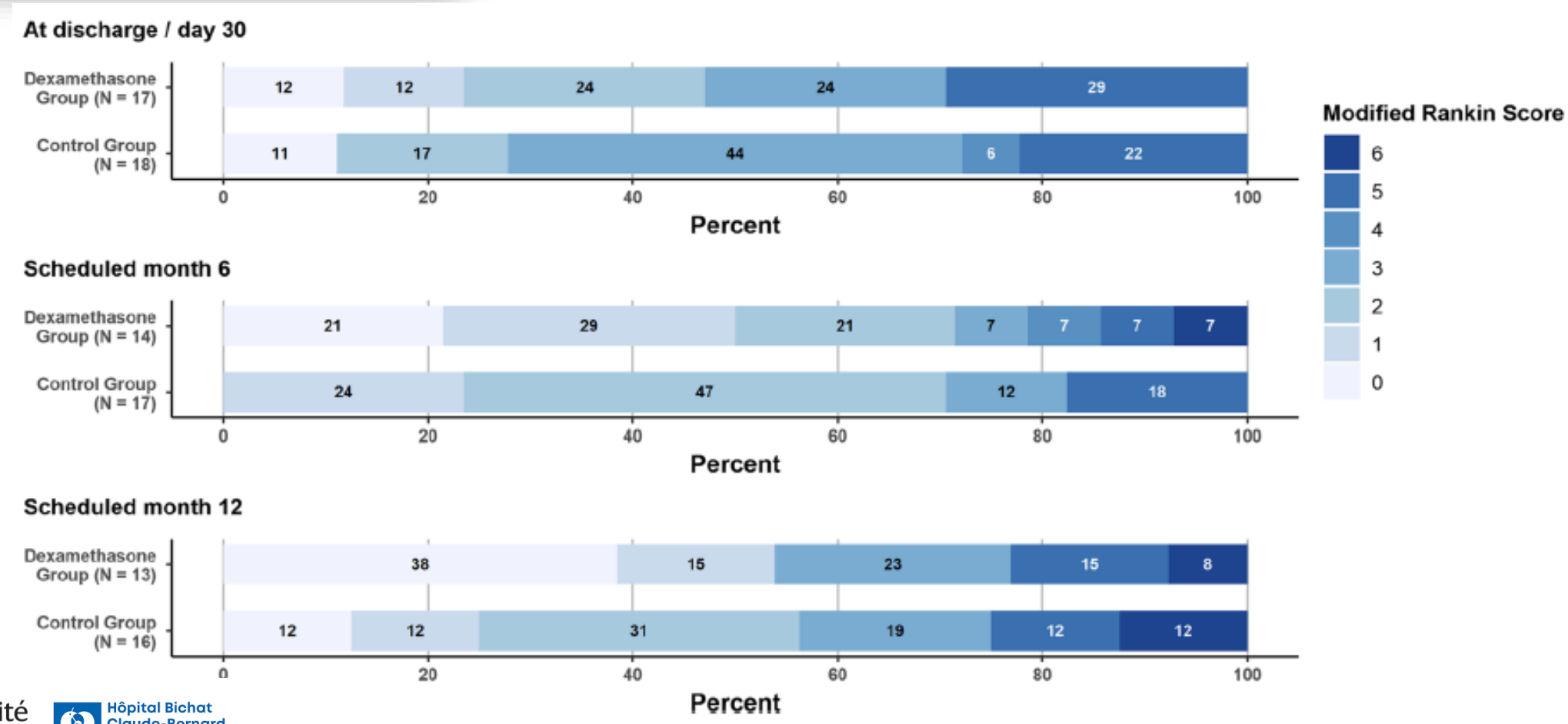
	Placebo *N* = 19	Dexamethasone *N* = 19
Gender		
male	10 (52.6%)	11 (57.9%)
female	9 (47.4%)	8 (42.1%)
Age		
Mean +/− SD	58.6 +/− 15.0	61.6 +/− 12.1
Focal neurological signs		
yes	12 (63.2%)	15 (78.9%)
Seizures within last 5 days		
yes	11 (57.9)	11 (57.9%)
Result of PCR		
positive	19 (100.0%)	19 (100.0%)

RESEARCH ARTICLE Open Access

The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial

U. Meyding-Lamadé[1,2*†], C. Jacobi[1†], F. Martinez-Torres[1,2], T. Lenhard[2], B. Kress[3], M. Kieser[5], C. Klose[4], K. Einhäupl[5], J. Bösel[11], M-B Mackert[6], V. Homberg[19], C. Koennecke[7], G. Weißheit[7], D. Claus[8,18], B. Kieseier[9], J. Bardutzky[21], T. Neumann-Haefelin[17], M. W. Lorenz[1,9], H. Steinmetz[9], C. Gerloff[10], D. Schneider[12], A. Grau[13], M. Klein[14], R. Dziewas[15], U. Bogdahn[20], W. Jakob[15], R. Linker[15], K. Fuchs[15], A. Sander[4], S. Luntz[16], T. Hoppe-Tichy[20], D. F. Hanley[23], R. von Kummer[22] and E. Craemer[1]

RCT DXM 10mg x 4 / j pdt 4 jours vs. placebo



2023

2019

Open access Protocol

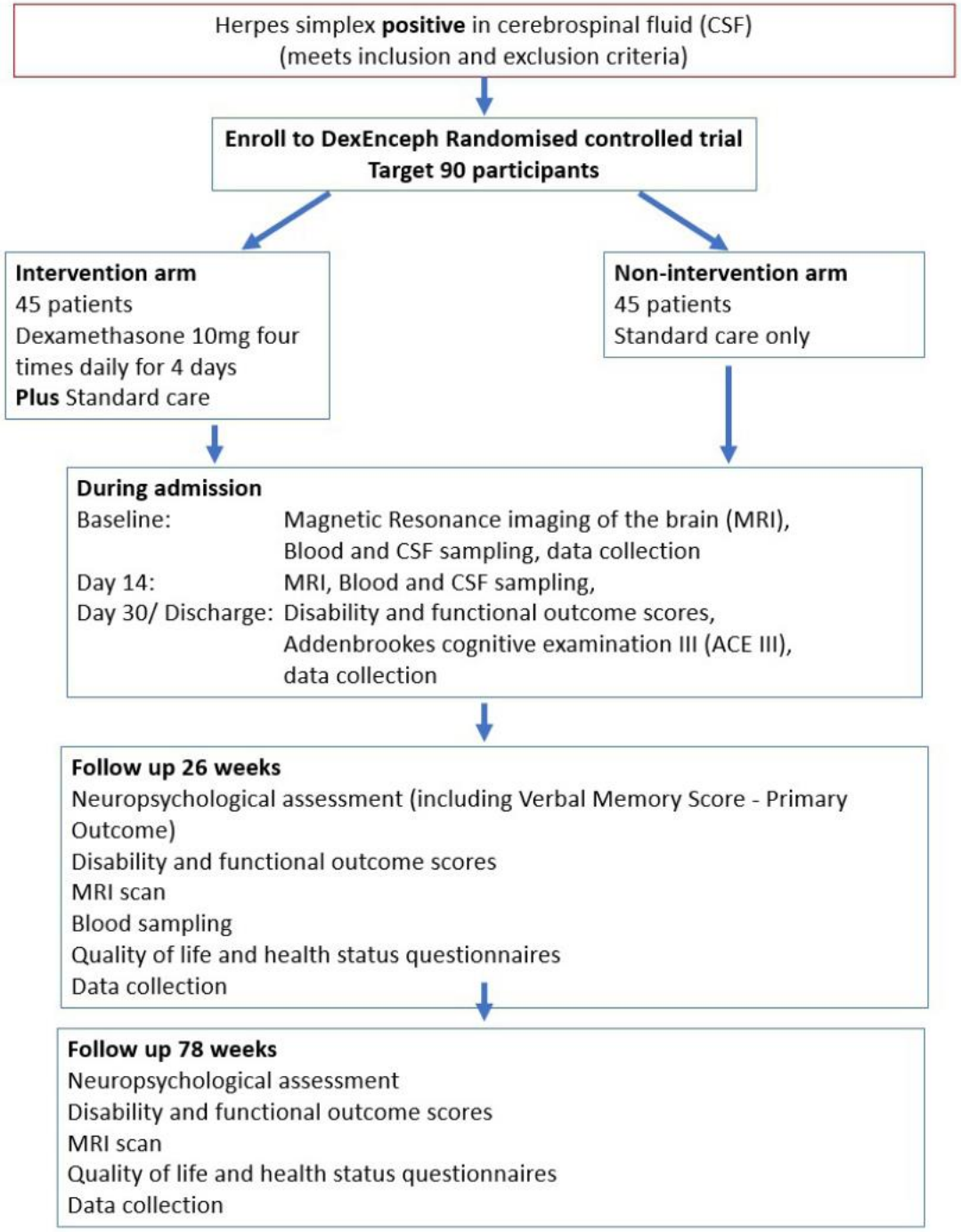
BMJ Open

Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis

Thomas Whitfield ,[1] Cristina Fernandez,[1] Kelly Davies,[2] Sylviane Defres,[1,3,4] Michael Griffiths,[1,5] Cory Hooper,[1] Rebecca Tangney,[6] Girvan Burnside,[7] Anna Rosala- Hallas,[7] Perry Moore,[8] Kumar Das,[9] Mark Zuckerman,[10] Laura Parkes,[11] Simon Keller,[6] Neil Roberts,[12] Ava Easton,[13] Saber Touati,[14] Rachel Kneen,[15,16] J P Stahl,[17] Tom Solomon[18,19]

RCT
DXM 10mg x 4 / j pdt 4 jours
vs.
placebo

?



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Steroids for the treatment of viral encephalitis: a systematic literature review and meta-analysis

Emira Hodzic[1] · Rodrigo Hasbun[2] · Alejandro Granillo[2] · Anna R. Tröscher[3] · Helga Wagner[1] · Tim J. von Oertzen[3,4] · Judith N. Wagner[3,4]

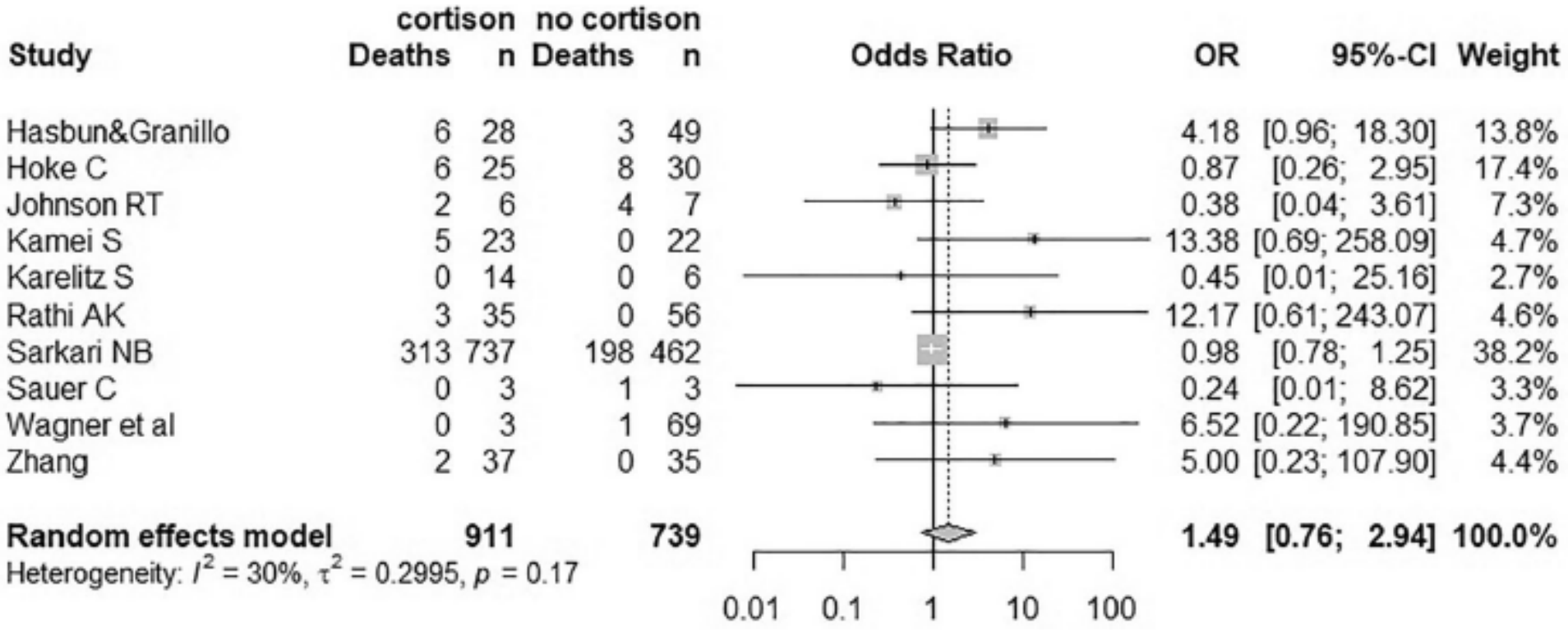
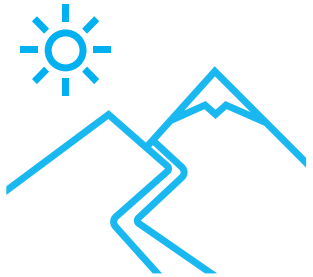


Fig. 3 Forest Plot of the odds ratio (OR) for the risk of dying in patients who received steroids (C.P.) vs. those who did not (no C.P.)

Roadmap



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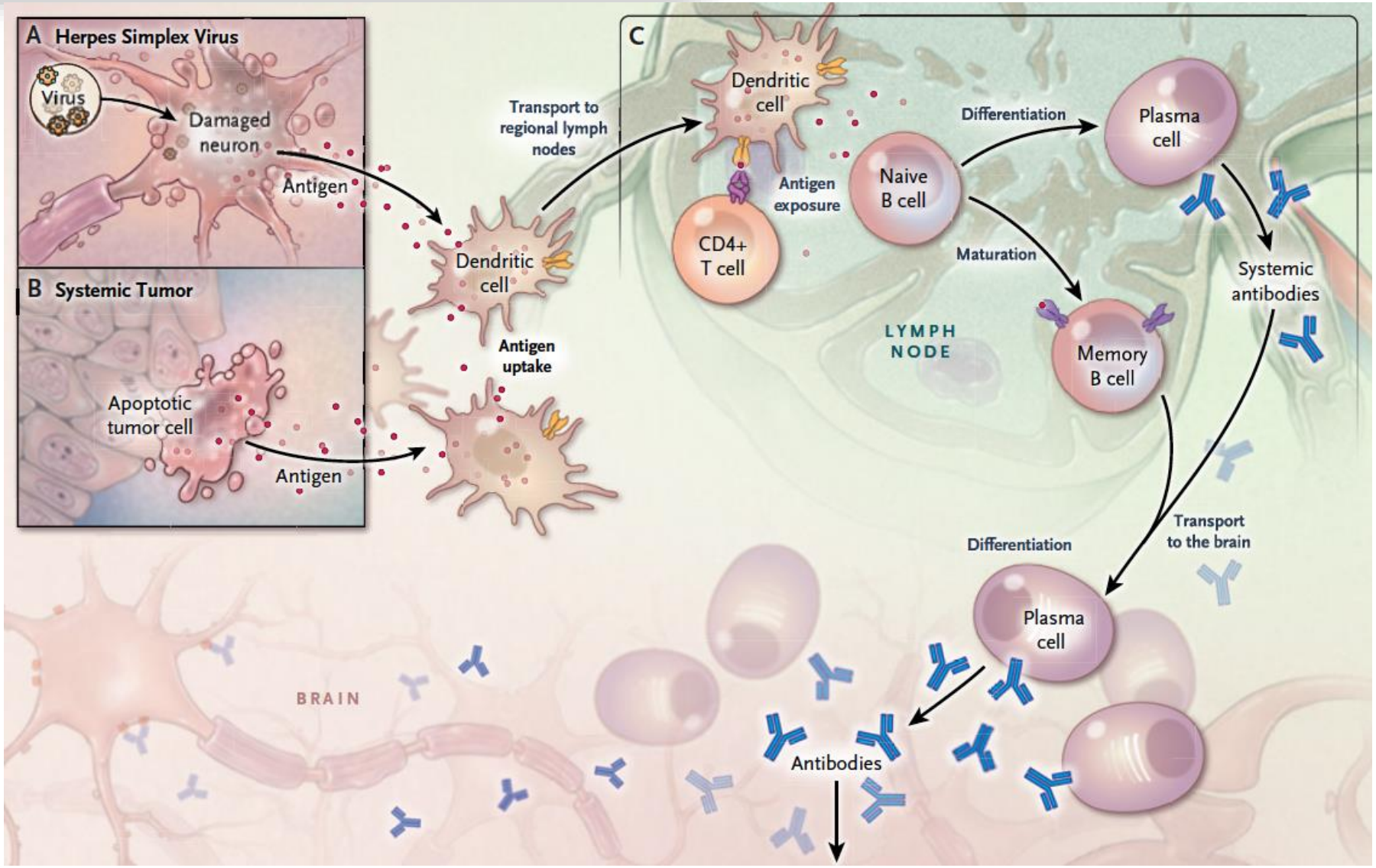
Antibody-Mediated Encephalitis

Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D.



New Eng J Med 2018

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18*], and Romain Sonneville[16,19*]; on behalf of the ENCEPHALITICA Study Group[‡]

Multivariate analysis of factors of good neurological outcome at 6 months (mRS < 2)

Variable	Odds Ratio (95% CI)	*P* Value
First-line immunotherapy		0.008
Late immunotherapy	Reference	
Early* intravenous immunoglobulin administration only	3.33 (0.66–16.79)	0.14†
Early* steroid administration only	4.96 (0.76–32.23)	0.09†
Early* combined immunotherapy‡ administration	16.16 (3.32–78.64)	<0.001†
Second-line immunotherapy	0.19 (0.05–0.69)	0.01
White blood cells in first CSF		0.04
>50 cells/mm^3	Reference	
5–50 cells/mm^3	3.97 (1.16–13.65)	0.03†
<5 cells/mm^3	9.83 (1.07–90.65)	0.04†

*before ICU admission or following 8 days of ICU admission

Université Paris Cité

Hôpital Bichat Claude-Bernard AP-HP

Am j Resp Crit Care Med 2017

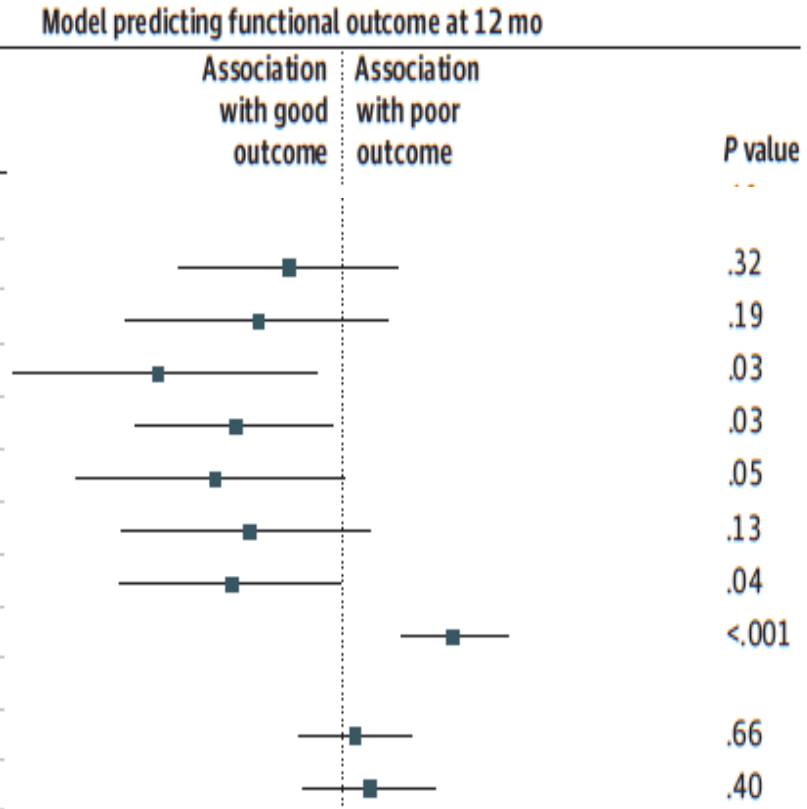
JAMA Neurology | Original Investigation

Use and Safety of Immunotherapeutic Management of *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
A Meta-analysis

Margherita Nosadini, MD, PhD; Michael Eyre, MD; Erika Molteni, PhD; Terrence Thomas, MD; Sarosh R. Irani, MD, PhD; Josep Dalmau, MD, PhD; Russell C. Dale, MD, PhD; Ming Lim, MD, PhD; and the International NMDAR Antibody Encephalitis Consensus Group

N=1552 patients

ICU admission 51%



Characteristic	OR (95% CI)	P value
First-line treatment		
Corticosteroids only	0.61 (0.22-1.65)	.32
IVIG only	0.46 (0.13-1.50)	.19
TA only	0.18 (0.05-0.79)	.03
Corticosteroids and IVIG	0.37 (0.15-0.91)	.03
Corticosteroids and TA	0.31 (0.09-1.01)	.05
IVIG and TA	0.43 (0.13-1.28)	.13
Corticosteroids, IVIG, and TA	0.36 (0.13-0.97)	.04
No immunotherapy within 30 d of disease onset	0.74 (1.70-4.53)	<.001
Second-line treatment		
Rituximab	1.12 (0.67-1.89)	.66
Cyclophosphamide	1.29 (0.69-2.33)	.40

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JAMA Neurol 2021

Review

Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management

Hesham Abboud ,[1,2] John C Probasco,[3] Sarosh Irani ,[4] Beau Ances,[5] David R Benavides,[6] Michael Bradshaw,[7,8] Paulo Pereira Christo,[9] Russell C Dale,[10] Mireya Fernandez-Fournier,[11] Eoin P Flanagan ,[12] Avi Gadoth,[13] Pravin George,[14] Elena Grebenciucova,[15] Adham Jammoul,[14] Soon-Tae Lee,[16] Yuebing Li,[14] Marcelo Matiello,[17,18] Anne Marie Morse,[19] Alexander Rae-Grant,[14] Galeno Rojas,[20,21] Ian Rossman,[22] Sarah Schmitt,[23] Arun Venkatesan,[3] Steven Vernino,[24] Sean J Pittock ,[12] Maarten J Titulaer ,[25] Autoimmune Encephalitis Alliance Clinicians Network

Box 1 Best practice recommendations summary for acute management of autoimmune encephalitis (AE)

Severe presentation* = combination therapy

*severe NMDARE, refractory status epilepticus, severe dysautonomia …

FIRST LINE
High dose corticosteroids
+
IgIV or PLEX

No improvement ?

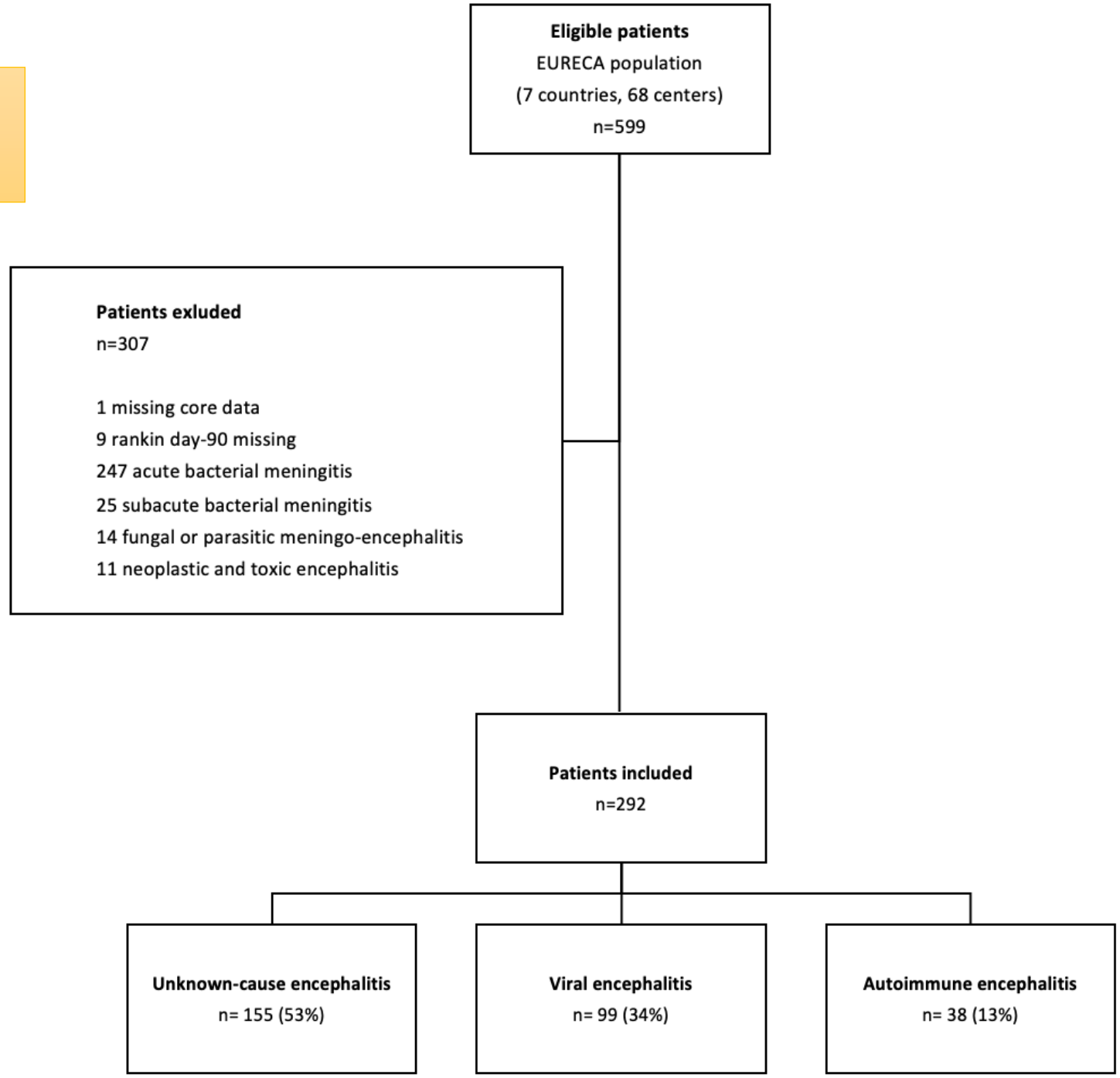
SECOND LINE
Rituximab
OR
Cyclophosphamide

IVIg first if agitation or bleeding disorders
PLEX first if hyponatremia, high risk of thrombosis, or brain/spinal demyelination

Rituximab in known or highly suspected antibody-mediated immunity (e.g. NMDARE)
Cyclophosphamide in case of cell-mediated immunity (classical paraneoplastic syndromes)

J Neurol Neurosurg Psychiatry 2021

IMMUNO-EURECA
DESC Marie Cantier



IMMUNO-EURECA
DESC Marie Cantier

Variable	All patients n=292	Viral n=99	Autoimmune n=38	Unknown-cause n=155	*p* value
IV METHYLPREDNISOLONE BOLUS (steroids)	60 (20.5)	8 (8.1)	33 (86.8)	19 (12.3)	**<.0001**
Time from ICU admission to start, days	4 [2 ; 8]	4.5 [1.5 ; 12.5]	2.5 [1 ; 8]	6 [2 ; 8]	0.3603
Duration of treatment, days	5 [3 ; 6]	4 [2 ; 5.5]	5 [4 ; 8]	5 [3 ; 5]	0.1339
INTRAVENOUS IMMUNOGLOBULINS (IVIg)	32 (11)	3 (3)	21 (56.8)	8 (5.2)	**<.0001**
Time from ICU admission to start, days	6 [2 ; 11]	2 [1 ; 6]	5 [2 ; 13]	7.5 [4.5 ; 9]	0.3228
Duration of treatment, days	5 [5 ; 5]	5 [1 ; 5]	5 [5 ; 5]	5 [4 ; 5]	0.0623
PLASMA EXCHANGES (PLEX)	24 (8.2)	1 (1)	20 (54.1)	3 (1.9)	**<.0001**
Time from ICU admission to start, days	14 [9 ; 27]	20 [20 ; 20]	13 [9 ; 34]	17 [14 ; 25]	0.7891
Nb of plasma exchange	8 [5 ; 10]	4 [4 ; 4]	8 [6.5 ; 10]	1 [1 ; 8]	0.0814

IMMUNO-EURECA
DESC Marie Cantier

Therapeutic	All patients n=292	mRS 0-2 n=146	mRS 3-6 n=146	*p* value
IV METHYLPREDNISOLONE BOLUS (steroids)	60 (20.5)	20 (13.7)	40 (27.4)	**0.0056**
Dose at initiation (mg/day)	1000 [750 ; 1000]	1000 [1000 ; 1000]	1000 [310 ; 1000]	0.7168
Time from ICU admission to start, days	4 [2 ; 8]	4 [2 ; 7]	4 [1 ; 9]	0.8966
Duration of treatment, days	5 [3 ; 6]	5 [3 ; 9.5]	5 [3.5 ; 6]	0.9743
INTRAVENOUS IMMUNOGLOBULINS (IVIg)	32 (11)	11 (7.6)	21 (14.4)	0.0905
Dose at initiation (g/kg/day)	0.4 [0.4 ; 0.4]	0.4 [0.4 ; 0.5]	0.4 [0.4 ; 0.4]	0.6203
Time from ICU admission to start, days	6 [2 ; 11]	4 [3 ; 9]	6 [2 ; 13]	0.7401
Duration of treatment, days	5 [5 ; 5]	5 [5 ; 5]	5 [5 ; 5]	0.7774
PLASMA EXCHANGES (PLEX)	24 (8.2)	5 (3.4)	19 (13)	**0.0046**
Volume at initiation (ml/kg)	45 [30 ; 60]	30 [30 ; 30]	47.5 [30 ; 60]	0.4014
Time from ICU admission to start, days	14 [9 ; 27]	9 [8 ; 17.5]	15.5 [12 ; 34]	0.1354
Nb of plasma exchange	8 [5 ; 10]	10 [8 ; 10]	7 [5 ; 10]	**0.0489**

IMMUNO-EURECA
DESC Marie Cantier

Impact of early immunotherapy and other indicators of poor functional outcome (mRS 3-6) at day-90
Multivariate logistic regression

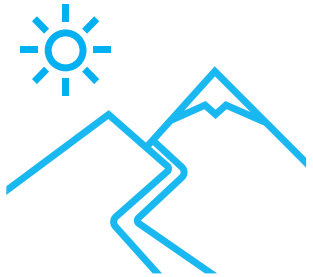
Variable	Odds Ratios	95% CI	p value
Early immunotherapy (≤ 7days from ICU admission)			0.0325
No early immunotherapy (reference)	1	-	
Early Monotherapy	2.224	[1.060 ; 4.667]	
Early combined therapy	3.251	[0.868 ; 12.177]	
Age > 60 years	2.112	[1.257 ; 3.548]	0.0047
Immunosuppression	2.143	[1.132 ; 4.055]	0.0192
Hospital to ICU admission delay > 1 day	1.395	[0.841 ; 2.316]	0.1973
Motor GCS ≤ 2	2.584	[1.299 ; 5.143]	0.0068
Hemiparesis/hemiplegia	1.654	[0.804 ; 3.402]	0.1716
Respiratory failure	2.194	[1.067 ; 4.512]	0.0327
Cardiovascular failure	1.982	[0.952 ; 4.130]	0.0676

2 questions ?

- Steroids for **all-cause encephalitis** (n=292) ?

- (Early) combined therapy for (suspected/confirmed) **autoimmune causes (n=38) ?**

Roadmap



- Introduction
- Viral encephalitis ?
- Autoimmune encephalitis ?
- Acute bacterial meningitis ?
- Other causes ?
- Perspectives

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*

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

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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

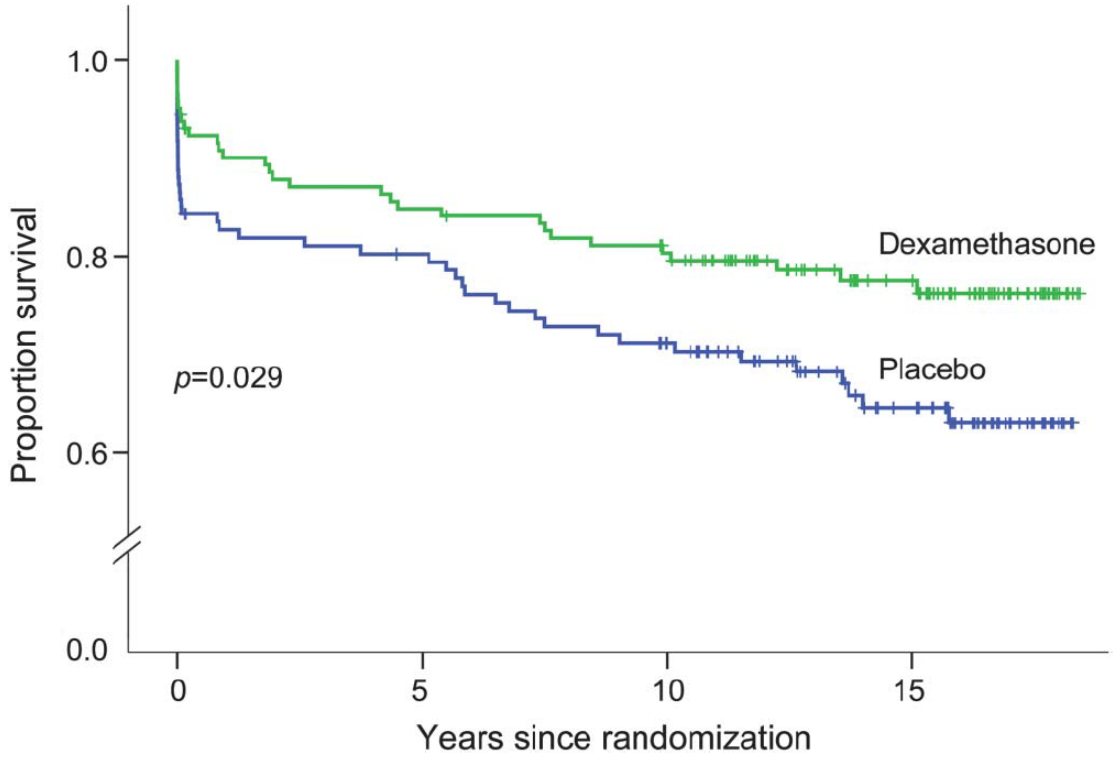
Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

	1998-2002	2006-2008	p
DXM use	11 (3%)	217 (79%)	<0.001
Mortality	107 (30%)	61 (22%)	0.018
Adverse outcome	177 (50%)	109 (39%)	0.016
Hearing loss	55 (22%)	25 (11%)	0.005
Systemic complications	134 (38%)	117 (42%)	NS

Mc Brouwer, Neurology 2010

Dexamethasone and long term survival in bacterial meningitis

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



D Fritz,
Neurology 2013

Corticosteroids for acute bacterial meningitis

	RR	95% CI
Mortality*	0.90	0.80-1.01
Mortality in adults**	0.74	0.53-1.05
Mortality in patients with *S. pneumoniae* meningitis	0.84	0.72-0.98
Hearing loss	0.74	0.63-0.87
Neurological sequelae	0.83	0.69-1.00

* p= 0.07, ** p= 0.09

There was no beneficial effect of corticosteroid therapy in low-income countries.

THE COCHRANE COLLABORATION®

Brouwer MC et al. Cochrane Database Syst Review 2015

ORIGINAL ARTICLE

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. L. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

Grade A recommendations

Empiric treatment with dexamethasone is strongly recommended for all adults

(10 mg q6h for 4 days) with acute bacterial meningitis in the setting of high income countries

Treatment with dexamethasone is strongly recommended to be initiated with the first dose of antibiotic treatment.

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESCMID guideline 2015 : diagnosis and treatment of acute bacterial meningitis

Dexamethasone for pneumococcal meningitis

(1783 patients, 2006-2018)

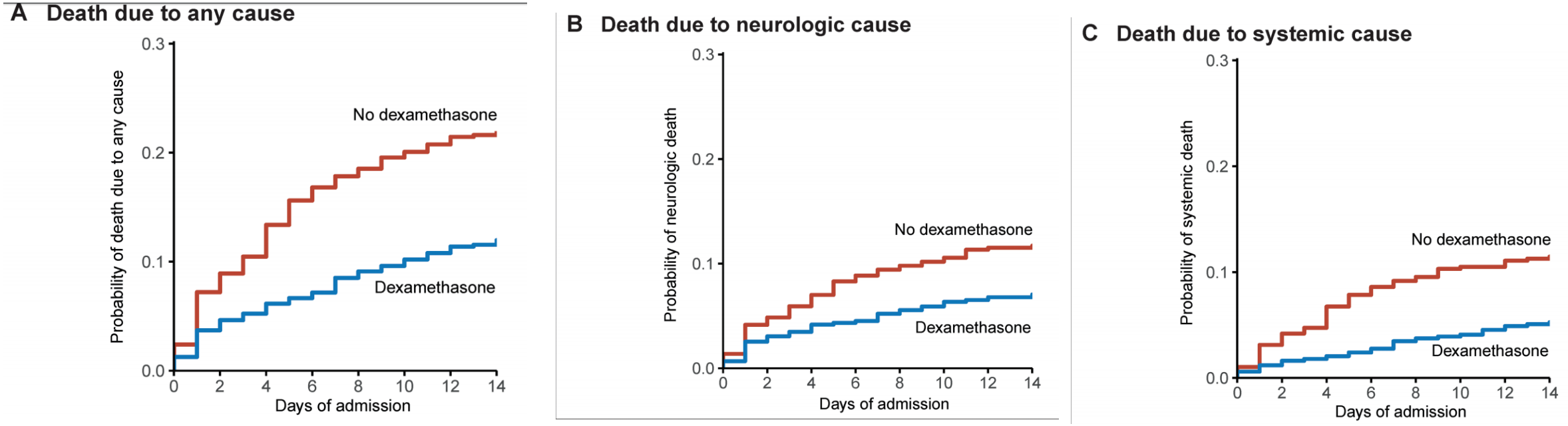


Figure 4. Effect of dexamethasone on survival in pneumococcal meningitis. (A) Kaplan-Meier estimates stratified for the use of dexamethasone for overall mortality, and death from (B) systemic and (C) neurological complications. P values of the respective log-rank tests were all < 0.0001.

DLH Koelman et coll. Clin Infect Dis 2022

ORIGINAL

Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study

S. pneumoniae: 60%

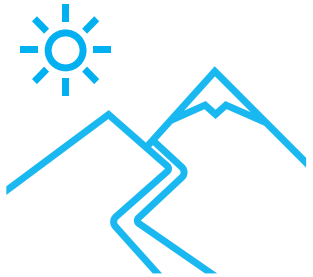
B. Bacterial Meningitis

Variable	OR [IC 95%]	pvalue
Age >60	1.577 [0.873 ; 2.850]	0.1312
Immunodepression	1.624 [0.806 ; 3.272]	0.1746
Admission hospital-ICU delay >1	1.477 [0.760 ; 2.873]	0.2502
GCS Motor <=3	2.556 [1.311 ; 4.982]	**0.0059**
SOFA respiratory 3-4	1.830 [0.839 ; 3.991]	0.1287
SOFA cardiovascular 3-4	1.603 [0.808 ; 3.178]	0.1769
Hemiparesis	3.515 [1.419 ; 8.706]	**0.0066**
Cefotaxime/Ceftriaxone on D1	0.434 [0.201 ; 0.940]	**0.0343**
Acyclovir on D1	0.543 [0.256 ; 1.154]	0.1126
Adjunctive steroids on D1	0.772 [0.405 ; 1.470]	0.4303

Evolution défavorable Rankin$_m$: 3-6

68% des patients

Roadmap



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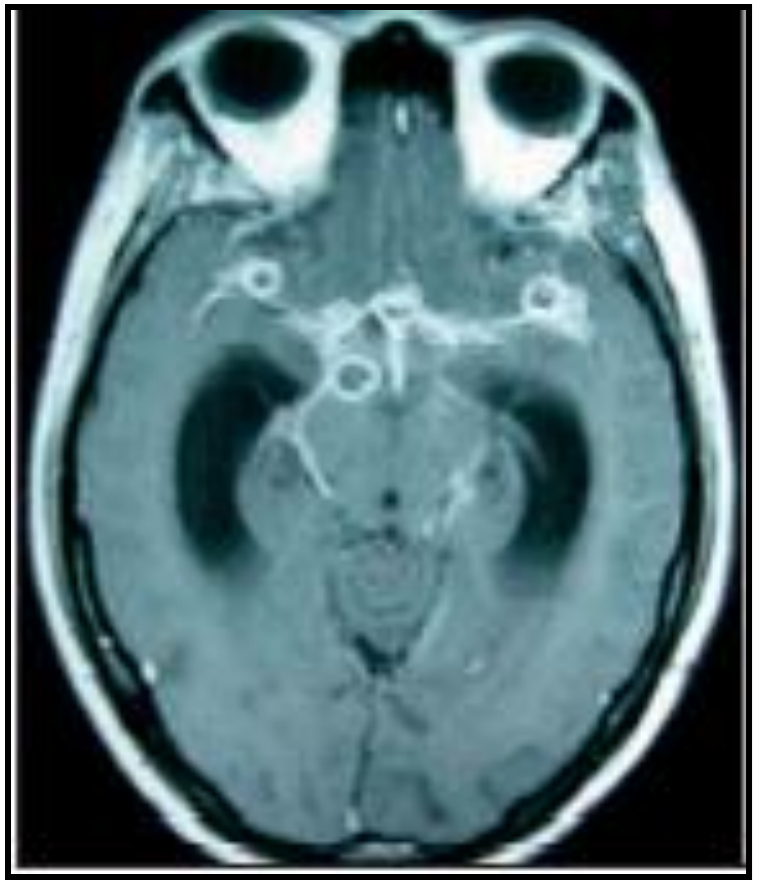
Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Guy E. Thwaites et al., N Engl J Med 2004 ; 351 : 1741-51



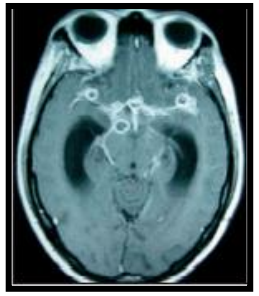
The NEW ENGLAND JOURNAL of MEDICINE

Corticothérapie

Critères modifiés du BMRC	Clinique	Protocole thérapeutique
I	GCS 15 signes focaux : 0	**TTT IV 2 SEMAINES** DXM 0.3 mg/kg semaine 1 0.2mg/kg semaine 2 **Puis TTT PO 4 semaines**
II	GCS 11-14 ou GCS 15 + signes focaux	**TTT IV 4 SEMAINES** DXM 0.4mg/kg/j semaine 1 0.3mg/kg/j semaine 2 0.2mg/kg/j semaine 3 0.1mg/kg/j semaine 4 **Puis TTT PO 4 SEMAINES** DXM 4 mg / j Décroissance 1mg/j par semaine
III	GCS < 11	

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

The NEW ENGLAND JOURNAL of MEDICINE



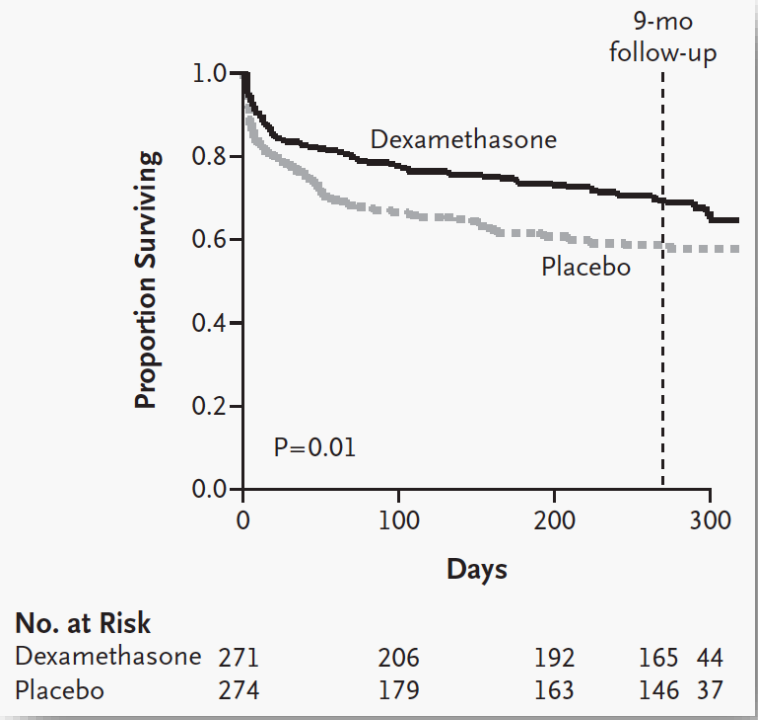


Table 3. Outcomes of 545 Patients Nine Months after Randomization.

Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

Guy E. Thwaites, N Engl J Med 2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2023 VOL. 389 NO. 15

Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D., Dau T.T. Huong, M.Sc., Nguyen T.T. Hiep, M.D., Lam H.B. Ngoc, B.Sc., Dang V. Thanh, M.D., Nguyen T. Thanh, M.D., Anna L.S. Wardhani, B.Sc., Kartika Maharani, M.D., Cakra P. Gasmara, M.D., Nguyen H.H. Hanh, M.D., Pham K.N. Oanh, M.D., Riwanti Estiasari, Ph.D., Do D.A. Thu, B.Sc., Ardiana Kusumaningrum, M.D., Le T. Dung, M.D., Do C. Giang, Ph.D., Dang T.M. Ha, Ph.D., Nguyen H. Lan, M.D., Nguyen V.V. Chau, Ph.D., Nguyen T.M. Nguyet, B.Sc., Ronald B. Geskus, Ph.D., Nguyen T.T. Thuong, Ph.D., Evelyne Kestelyn, M.P.H., Raph L. Hamers, Ph.D., Nguyen H. Phu, Ph.D., and Guy E. Thwaites, F.R.C.P., for the ACT HIV Investigators*

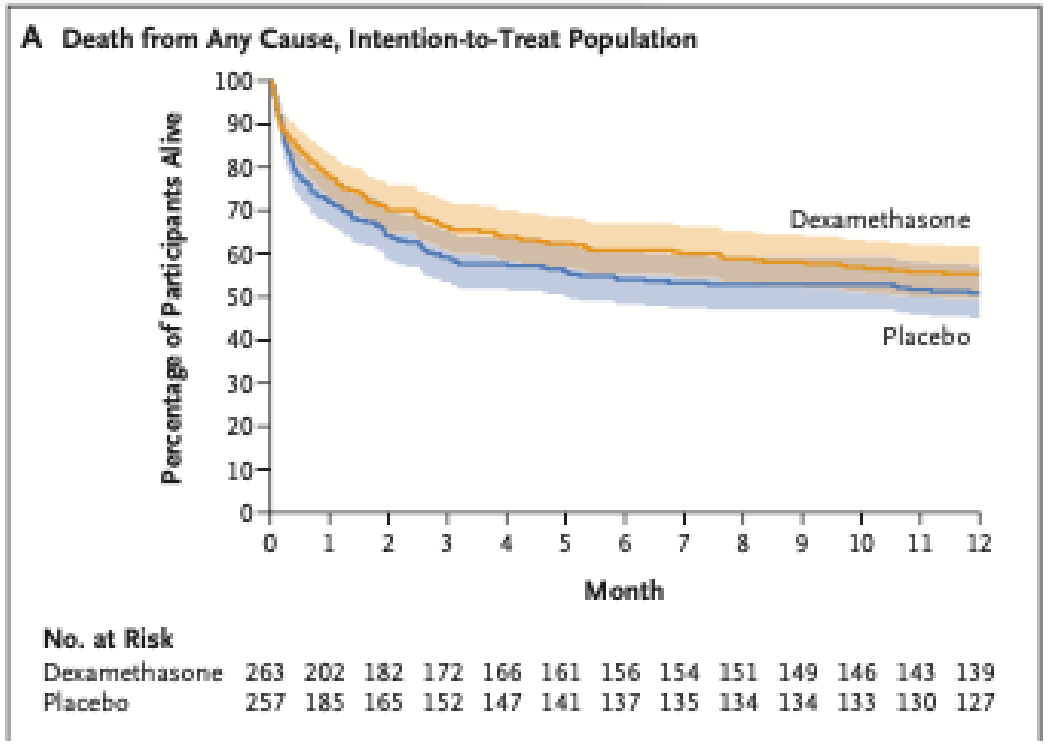


Table 2. Death from Any Cause in Prespecified Subgroups in the Intention-to-Treat Population.*

Subgroup	Dexamethasone (N=263)	Placebo (N=257)	Hazard Ratio (95% CI)
	no. of deaths/no. of participants		
Overall	116/263	126/257	0.85 (0.66–1.10)†
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
LTA4H genotype‡			
TT	12/25	11/26	1.06 (0.47–2.41)
CT	49/117	59/114	0.72 (0.49–1.05)
CC	38/84	36/80	1.04 (0.66–1.63)
Antituberculosis-drug resistance§			
MDR or rifampin monoresistance	7/10	5/6	0.66 (0.21–2.11)
Isoniazid resistance without MDR	6/14	13/20	0.56 (0.21–1.49)
No or other resistance	22/52	13/45	1.58 (0.79–3.13)
ART status at enrollment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 Mo of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrollment			
≤50 per cubic millimeter	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimeter	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimeter	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimeter	11/37	15/36	0.70 (0.32–1.52)

New Eng J Med 2023

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

Outcome and Analysis Population	Dexamethasone (N=224)	Placebo (N=226)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Death by week 10: primary outcome — no./total no. (%)†				
Intention-to-treat population	106/224 (47)	93/226 (41)	1.11 (0.84–1.47)	0.45‡
Disability at 10 wk in intention-to-treat population — no./total no. (%)				
Good outcome**	28/222 (13)	55/220 (25)	0.42 (0.25–0.69)	<0.001
Intermediate outcome	53/222 (24)	46/220 (21)		
Severe disability	35/222 (16)	26/220 (12)		
Death	106/222 (48)	93/220 (42)		
Disability at 6 mo in intention-to-treat population — no./total no. (%)				
Good outcome††	40/223 (18)	68/223 (30)	0.49 (0.31–0.77)	0.002
Intermediate outcome	40/223 (18)	34/223 (15)		
Severe disability	15/223 (7)	12/223 (5)		
Death	128/223 (57)	109/223 (49)		

New Eng J Med 2016

Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study

Caroline Charlier, Élodie Perrodeau, Alexandre Leclercq, Benoît Cazenave, Benoît Pilmis, Benoît Henry, Amanda Lopes, Mylène M Maury, Alexandra Moura, François Goffinet, Hélène Bracq Dieye, Pierre Thouvenot, Marie-Noëlle Ungeheuer, Mathieu Tourdjman, Véronique Goulet, Henriette de Valk, Olivier Lortholary, Philippe Ravaud, Marc Lecuit, on behalf of the MONALISA study group

3-month mortality for neurolisteriosis (n=252)		
Female sex	2·68 (1·24–5·83)	0·013
Age (years)	1·35 (0·99–1·85)	0·058
Ongoing organ neoplasia	4·58 (1·53–13·73)	0·007
Recent major weight loss	2·65 (1·08–6·55)	0·034
Multi-organ failure	3·08 (1·25–7·58)	0·014
Aggravation of any pre-existing organ dysfunction	2·75 (1·23–6·16)	0·014
Influenza-like symptoms	0·47 (0·20–1·12)	0·087
Mechanical ventilation	2·89 (1·31–6·37)	0·009
Monocytopenia <200 cells per µL	3·57 (1·24–10·23)	0·018
Positive blood cultures	3·67 (1·60–8·40)	0·002
Protein concentration in the CSF	1·18 (0·99–1·41)	0·062
Adjunctive dexamethasone for meningitis	4·58 (1·50–13·98)	0·008

Lancet Infect Dis 2017; 17: 510–19

Adjunctive dexamethasone treatment in adults with listeria monocytogenes meningitis: a prospective nationwide cohort study

Matthijs C. Brouwer* and Diederik van de Beek**

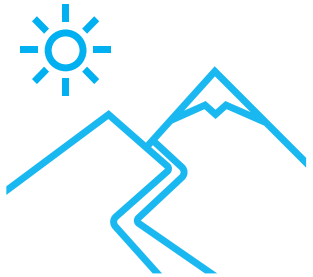
162 out of 2664 episodes (6%) of community-acquired bacterial meningitis episode were caused by *L. monocytogenes*

Variable	Univariable analysis		Multivariable analysis
	OR (95% CI)	*P*-value	OR (95% CI)
Age (per year increase)	1.04 (1.01-1.06)	0.002	1.04 (1.01-1.06)
Male sex	1.19 (0.61–2.29)	0.61	
Immunocompromised state[a]	0.95 (0.50–1.79)	0.88	
Glasgow Coma Scale (per point increase)	0.90 (0.79–1.01)	0.07	0.91 (0.80–1.06)
C-reactive protein (per 10 mg/L)	1.02 (0.98–1.05)	0.31	
CSF leukocyte count (per 100 cells/mm^3)	1.00 (0.97–1.02)	0.67	
Adequate initial antibiotic regimen[a]	0.33 (0.14–0.79)	0.01	0.44 (0.17–1.09)
Dexamethasone 10 mg QID 4 days[a,b]	0.40 (0.21–0.76)	0.005	0.40 (0.19–0.81)

[a]Reference categories: no immunocompromised state, no adequate initial antibiotic regimen and no dexamethasone treatment according to standard prot for 4 days started with 1st dose of antibiotics.

Table 3: **Results of univariable and multivariable analysis of risk factors for unfavourable outcome in *L. monocytogenes* meningitis.**

Roadmap



- Introduction
- Viral encephalitis ?
- Autoimmune encephalitis ?
- Acute bacterial meningitis ?
- Other causes ?
- Perspectives

Early Adjunctive Steroids ?

Yes !

Acute Bacterial Meningitis

De Gans, New Eng J Med 2002

(Reduced mortality and disability)

Tuberculous Meningitis

Thwaites, New Eng J Med 2004

(Reduced mortality)

Donovan, New Eng J Med 2023

(HIV+ patients)

Maybe ?

Viral (HSV) Encephalitis

Ongoing DEXENCEPH trial…

(Improved cognitive function ?)

Listeria monocytogenes meningitis ?

Brouwer, eClinical Med 2023

(Reduced mortality and disability)

No !

Cryptococcal Meningitis

Beardsley, New Eng J Med 2016

(More disability, more adverse events)

SeizURe PRophylaxIs and adjunctive Steroids in meningoEncephalitis "SURPRISE"

PHRC-N 2023 LI