ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Acute encephalitis
ICU management

Romain Sonneville, M.D., Ph.D.
Intensive care medicine
Bichat university hospital, Paris, France

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

université PARIS DIDEROT PARIS 7

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Acute encephalitis

- « Encephalitis » encompasses a broad range of infectious and/or autoimmune pathophysiologic processes

=> Inflammation of brain parenchyma

=> Acute brain dysfunction

- Strictly, the diagnosis is established only by histopathologic examination of brain tissue

- Brain tissue is (usually) not available for examination unless brain biopsy or post mortem examination are performed

- Indirect markers of brain inflammation
  - CSF leukocyte count or protein levels
  - Neuroimaging (MRI) changes

Diagnostic criteria for encephalitis

Major criterion (required)
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified
Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)
Documented fever ≥38°C (100.4°F) within the 72 hours before or after presentation
Generalized or partial seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF leukocyte count ≥5/mm^3
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

A. Venkatesan, Clin Infect Dis 2013

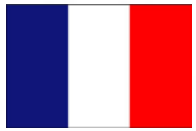
Beyond Viruses: Clinical Profiles and Etiologies Associated with Encephalitis

Clin Infect Dis, 2006

C. A. Glaser,[1] S. Honarmand,[1] L. J. Anderson,[3] D. P. Schnurr,[1] B. Forghani,[1] C. K. Cossen,[1] F. L. Schuster,[1] L. J. Christie,[1] and J. H. Tureen[2]

- **1998-2005: 1570 patients (adults and children)**
- **ICU admission 58%**

Infectious Encephalitis in France in 2007: A National Prospective Study



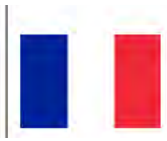
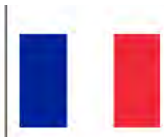
Clin Infect Dis 2009

Alexandra Mailles[1] and Jean-Paul Stahl,[2] on behalf of the Steering Committee and the Investigators Group[a]

[1]Institut de Veille Sanitaire, Saint-Maurice, and [2]Infectious Diseases Unit, University Hospital of Grenoble, Grenoble, France

- **2007: 253 patients (adults)**
- **ICU admission 46%**

Epidemiology of acute encephalitis

Study	n	Design	Main causes	Unknown cause
Glaser CA 2006 	1570	Prospective Multicenter	HSV1, enterovirus, *M. pneumoniae*	63%
Stahl JP 2009 	253	Prospective Multicenter	HSV1, VZV *Mycobacterium tuberculosis*	48%
Granerod J 2010 	203	Prospective Multicenter	HSV1 Immune-mediated	37%
Thakur KT 2013 	103	Retrospective Single center **ICU**	HSV1, VZV Immune-mediated	47%
Sonneville R 2014 	279	Retrospective Single center **ICU**	HSV1, VZV, *Mycobacterium tuberculosis* Immune-mediated	32%

Acute encephalitis in the ICU

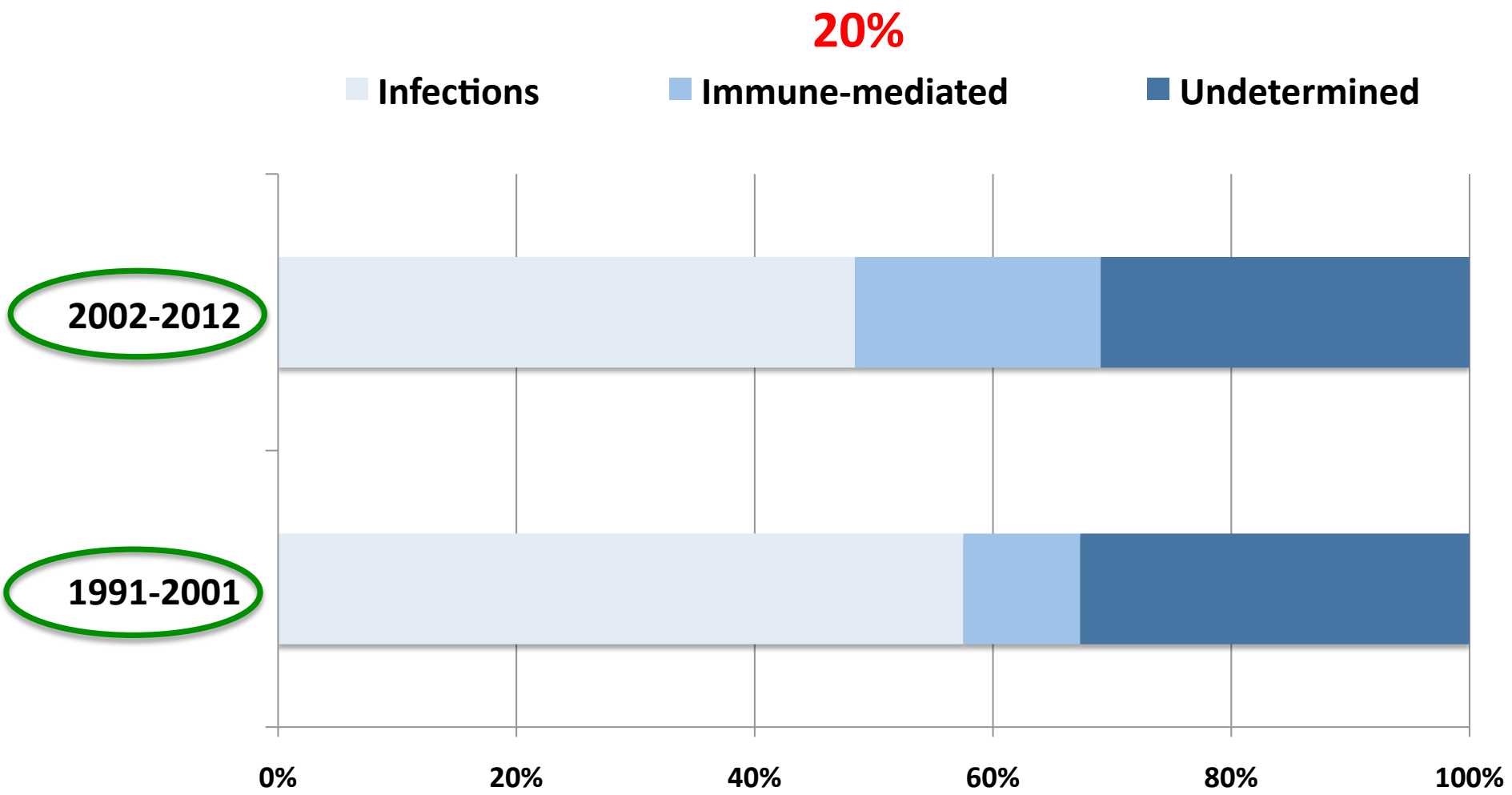
CAUSES	N = 279
INFECTIONS	149 (53%)
TB	65 (23%)
HSV-1	40 (14%)
VZV	14 (5%)
Listeria	19 (7%)
Other	11 (4%)
IMMUNE-MEDIATED	41 (15%)
ADEM	24 (9%)
Anti-NMDAR	6 (2%)
Other	11 (4%)
UNKNOWN	89 (32%)

Data are n (%)

Bichat Medical ICU
1991-2012

R Sonneville, Eur J Neurol 2014

Temporal trends of encephalitis in the ICU



R Sonneville, Eur J Neurol 2014

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

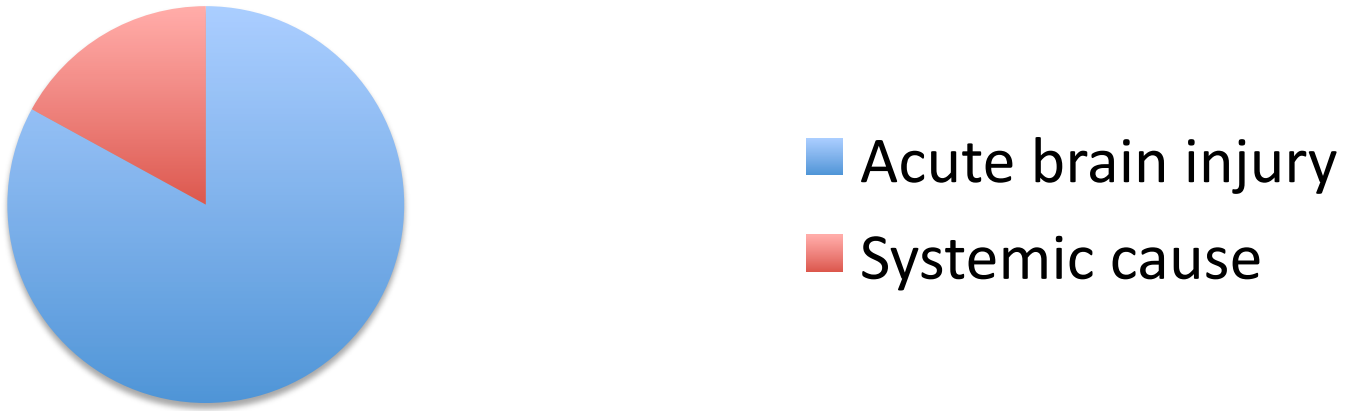
Outcomes of encephalitis in ICU patients

N=279 patients

Poor outcome at 3 months (mRS score 4-6): 71 (25%) patients

Hospital mortality 47 (17%) patients

Causes of death



Duration of mechanical ventilation in ICU survivors : 12 (6-28) days

Outcome of and Prognostic Factors for Herpes Simplex Encephalitis in Adult Patients: Results of a Multicenter Study

Franck Raschilas,[1,2] Michel Wolff,[2] Frédérique Delatour,[3] Cendrine Chaffaut,[4] Thomas De Broucker,[5] Sylvie Chevret,[4] Pierre Lebon,[1] Philippe Canton,[6] and Flore Rozenberg,[1] for the French Herpes Simplex Encephalitis Study Group[a]

IMPACT OF SPECIFIC THERAPY ON OUTCOME

Adverse outcome at 6-month : 84 adults

Variables	OR	CI 95%	p
SAPS 2 > 27	3.7	1.3-10.6	0.014
Admission – Acyclovir therapy > 2 days	3.1	1.1-9.1	0.037

Clin Infect Dis 2002

Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

577 patients with anti-NMDA receptor encephalitis
ICU admission 75%

Table 3: Factors associated with good outcome (mRS 0–2)

Multivariable analysis			
Stay in intensive care unit	<0·0001	0·12 (0·06–0·22)	394
Time until start of treatment (log_e)	<0·0001	0·62 (0·50–0·76)	394
Follow-up	<0·0001	..	394
4 months†	..	0·04 (0·02–0·06)	224
8 months†	<0·0001	0·20 (0·12–0·35)	110
12 months†	0·0044	0·37 (0·21–0·66)	32
18 months†	0·0066	0·76 (0·42–1·37)	22
24 months†	0·36	1·00	6
Maximum mRS	0·51	..	394

M Titulaer, Lancet Neurol 2013

Prognostic factors in encephalitis

IMPACT OF SECONDARY COMPLICATIONS +++

144 patients (mainly children) with Japanese encephalitis
Referral center, Ho Chi Minh (1994-1997)
Factors associated with poor outcome (severe disability or death)
Multiple logistic regression

Variable	aOR	95% CI
Coma	5.9	1.8-18.7
≥ 1 witnessed convulsion	6.3	1.5-26.0
Herniation syndrome	32.3	9.1-115.4
Ill for ≥ 7 days	13.0	3.5-48.2

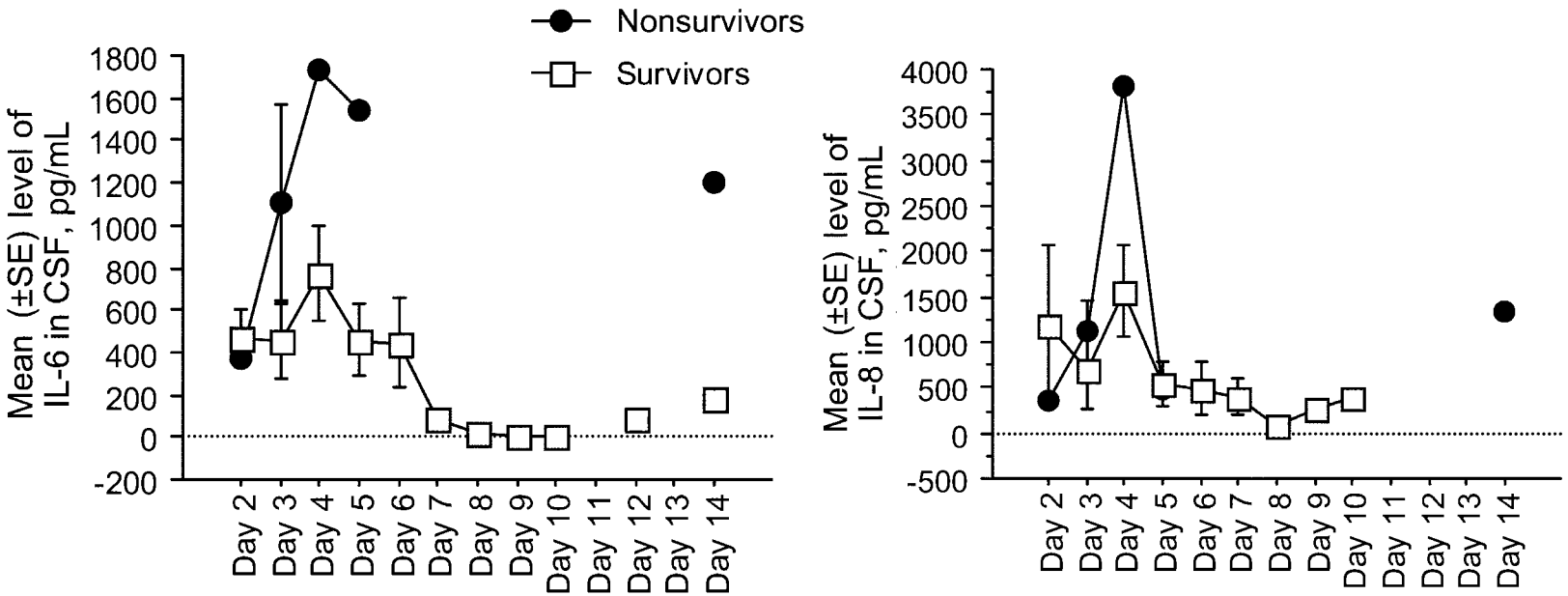
T. Solomon, Brain 2002

Prognostic factors in encephalitis

IMPACT OF CSF INFLAMMATION +++

118 patients with Japanese encephalitis

Elevated levels of proinflammatory cytokines and chemokines in the CSF are associated with poor outcome



PM White, J Inf Dis 2004

Prognostic factors in encephalitis

103 adult patients with all-cause encephalitis
ICU
Johns Hopkins, USA (1997-2011)
Factors associated with ICU mortality

Died before discharge (n = 19)	OR	95% CI	Average marginal effects, %	*p* Value
Age ≥65 y	2.10	0.44-10.02	7.47	0.35
Male	3.63	0.97-13.54	13.00	0.04
Thrombocytopenia	6.28	1.41-28.03	18.54	0.01
Cerebral edema	18.06	3.14-103.92	29.20	<0.01
Status epilepticus	8.16	1.55-43.10	21.19	0.01
Immunosuppression	1.86	0.27-12.6	6.28	0.50
Charlson comorbidity	1.16	0.84-1.60	1.49	0.37

A Venkatesan, Neurology 2012

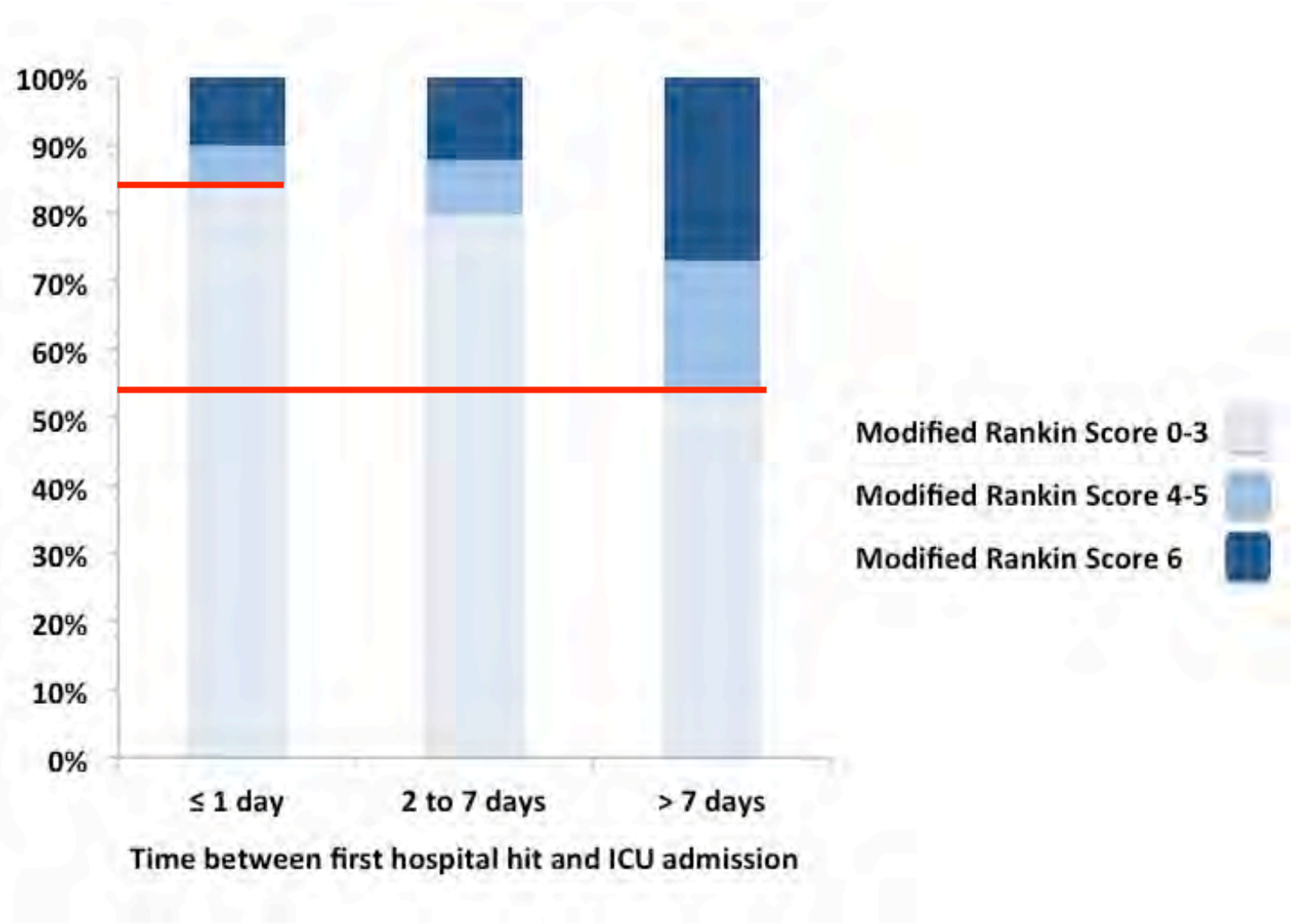
Prognostic factors in encephalitis

279 adult patients with all-cause encephalitis
Bichat medical ICU, Paris, France (1991-2012)
Poor outcome (mRS=4-6): 71 (25%) patients at day 90

Variable	**Odd Ratio**	**95% CI**
KNAUS score 3-4	6.3	2.0-21.2
Coma	7.1	3.1-17.0
Temperature (per °C)	0.7	0.5-0.9
Aspiration pneumonia	4.0	1.5-11.0
CSF protein levels, per 1 g/l	1.6	1.2-2.1
Time between hospital and ICU admission, days	1.04	1.01-1.07

R Sonneville, Eur J Neurol 2014

Prognostic factors in encephalitis



R Sonneville, Eur J Neurol 2014

How to improve outcome ?

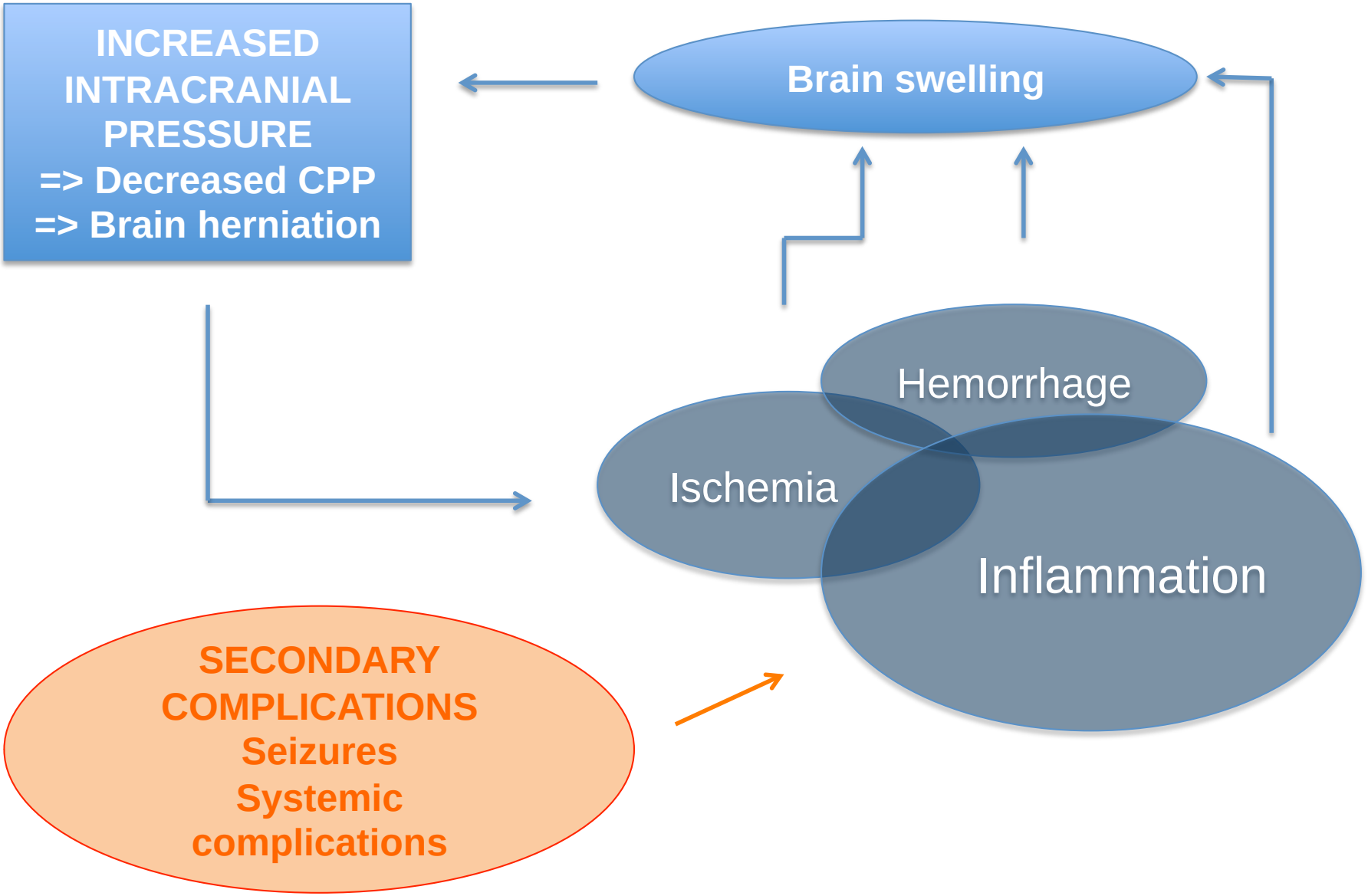
- Timely identification of causes of encephalitis deserving specific therapy
- Early ICU admission
- Detection and control of secondary complications
  - Cerebral oedema, herniation
  - Seizures
  - Systemic complications

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Acute brain dysfunction in encephalitis



Acute brain dysfunction in encephalitis

CONCERNS ABOUT INCREASED ICP AND MASS EFFECTS
SHOULD PROMPT IMMEDIATE CT SCAN IMAGING

DIFFUSE CEREBRAL OEDEMA

BRAIN HERNIATION

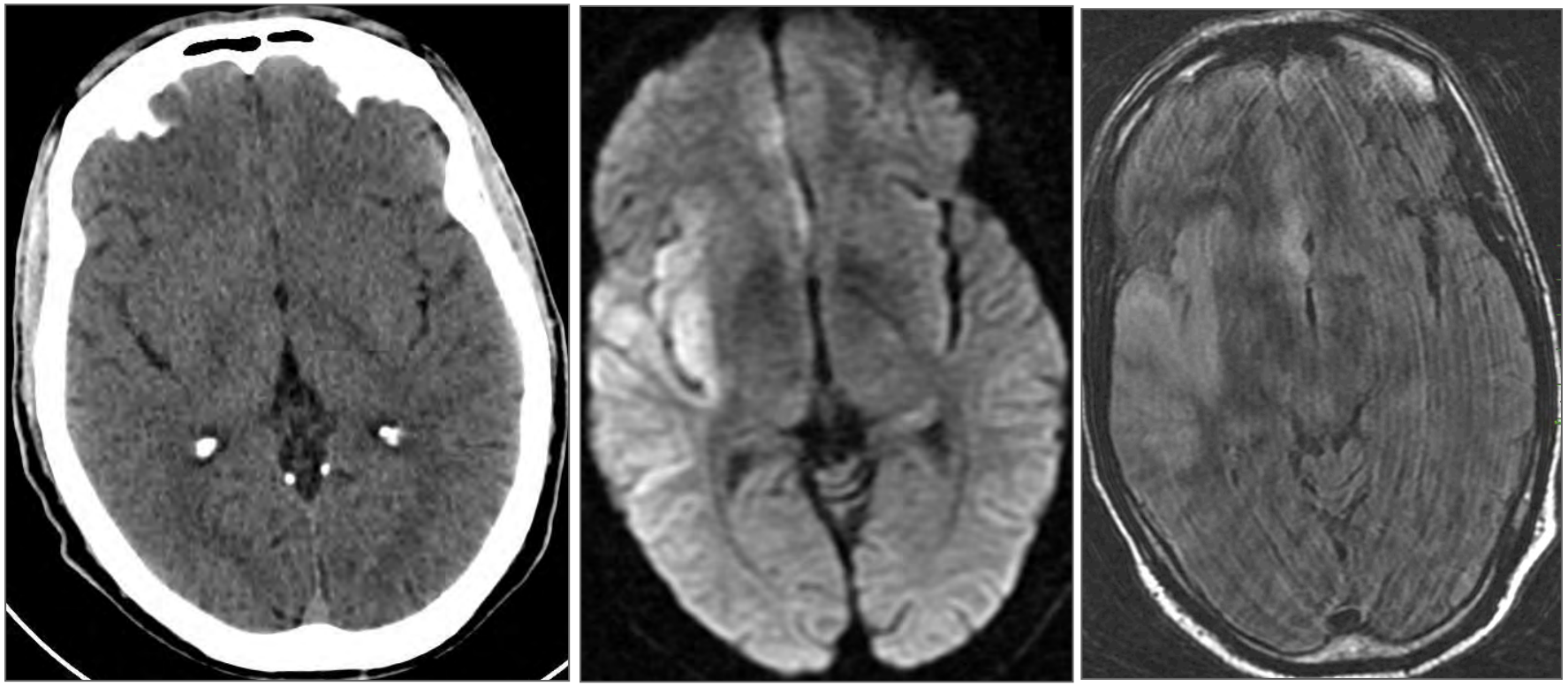
The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America

“ MRI is the most sensitive neuroimaging test to evaluate patients with encephalitis” (A-I)

- MRI is more sensitive and specific (vs. CT)
- Diffusion-weighted/FLAIR imaging is superior to conventional MRI for the detection of early signal abnormalities (HSV, enterovirus, West-Nile)
- Some characteristic neuroimaging patterns have been observed in patients with encephalitis caused by specific agents (HSV, flavivirus, enterovirus)
- ADEM & other Immune-mediated encephalitis +++

MRI in acute encephalitis

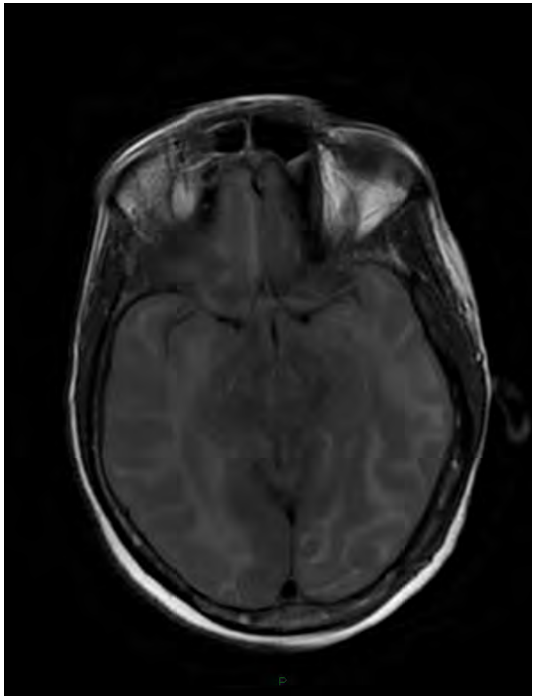
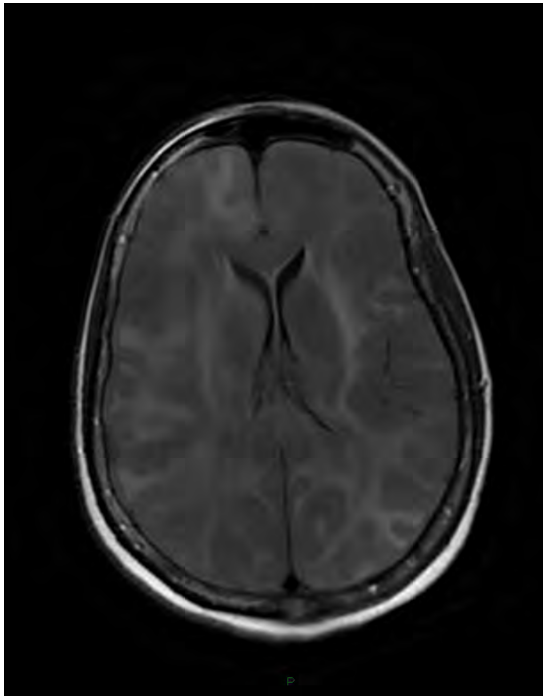
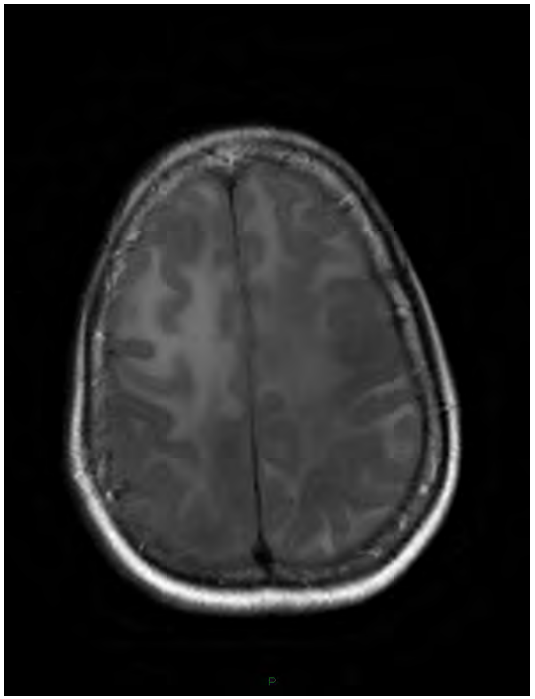
EARLY SIGNS OF BRAIN SWELLING



HSV1

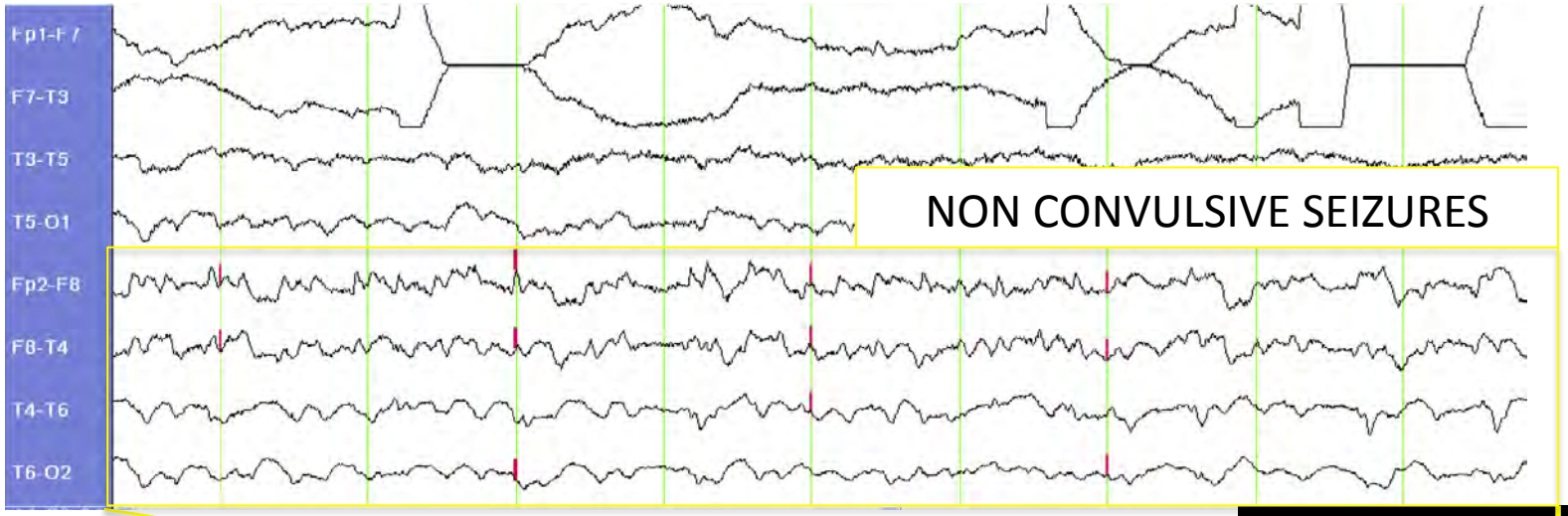
MRI in acute encephalitis

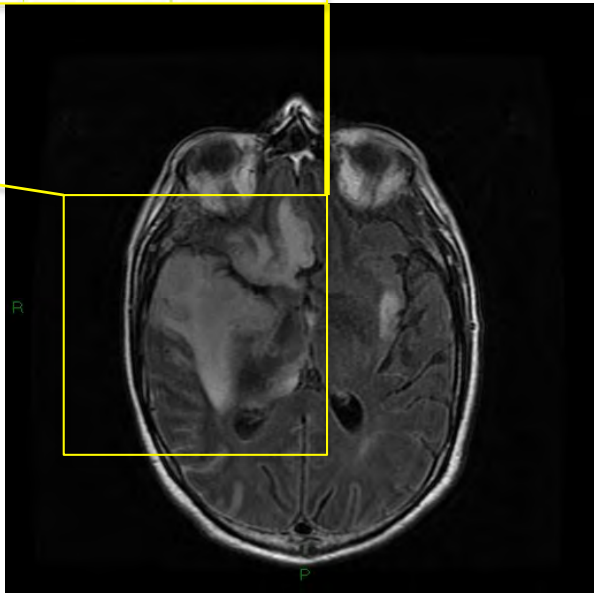
DIFFUSE VASOGENIC OEDEMA

Diffuse white matter hyperintensities, relative sparing of cortex
An increase in extracellular water => measurable increase in diffusion
(elevated ADC, not shown)

Acute brain dysfunction in encephalitis





60 yr-old man
Acute onset of fever
GCS score 10
Left hemiparesis
CSF 70 cell / microL, prot 0.8g/l
Positive CSF PCR for HSV-1

The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America

14. Electroencephalography (EEG) is rarely helpful in establishing an etiology in patients with encephalitis, but it has a role in identifying patients with nonconvulsive seizure activity who are confused, obtunded, or comatose and should be performed in all patients with encephalitis (A-III).

Tunkel Clin Inf Dis 2008

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Case

- 19-year old girl, no medical history
- Admitted to the ER

  Headache, fever 38.6°C

  Delirium

  No focal sign

  GCS 14

  « normal CT scan »

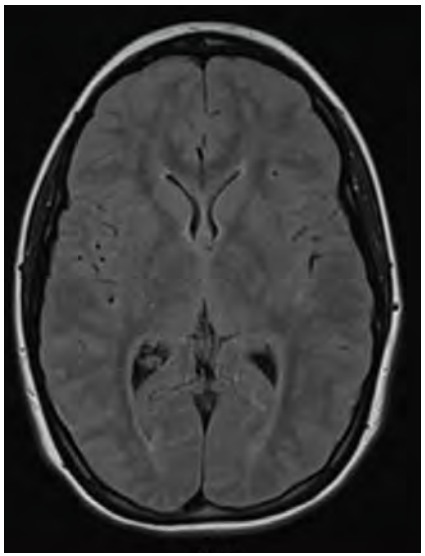
  CSF :

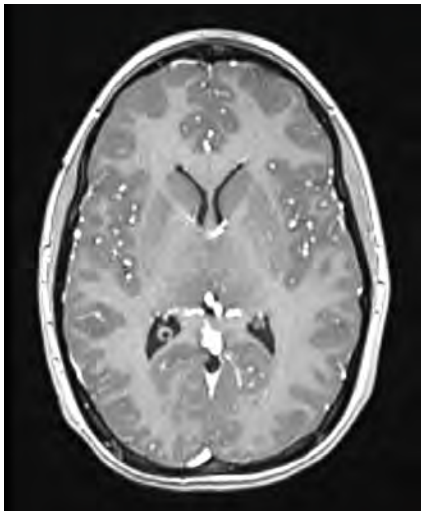
  68 cells /microL (60% lympho.)

  Prot 0.58g/l

  Glucose 3.7mmol/l

=> IV Acyclovir, IV amoxicillin



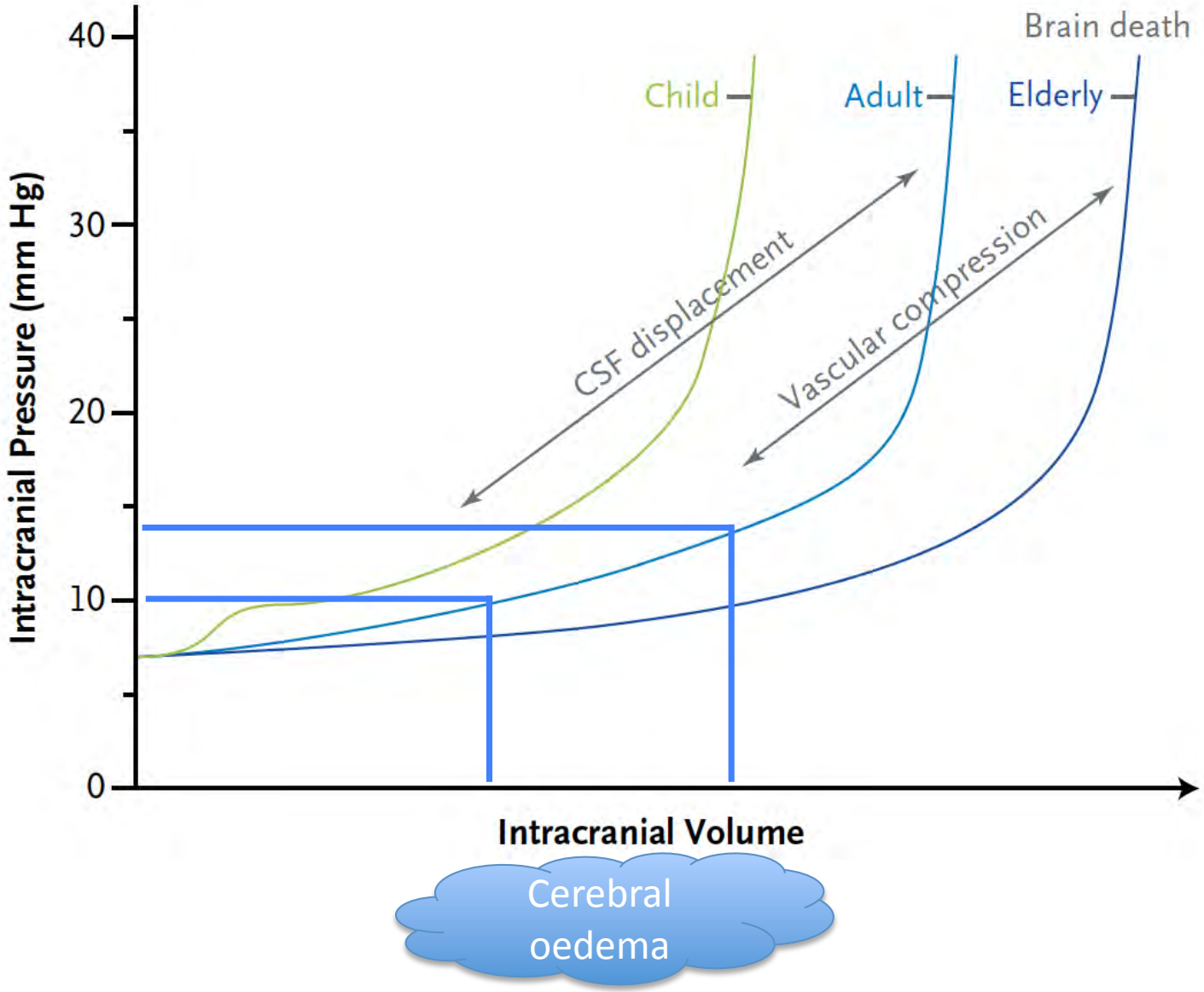


Case

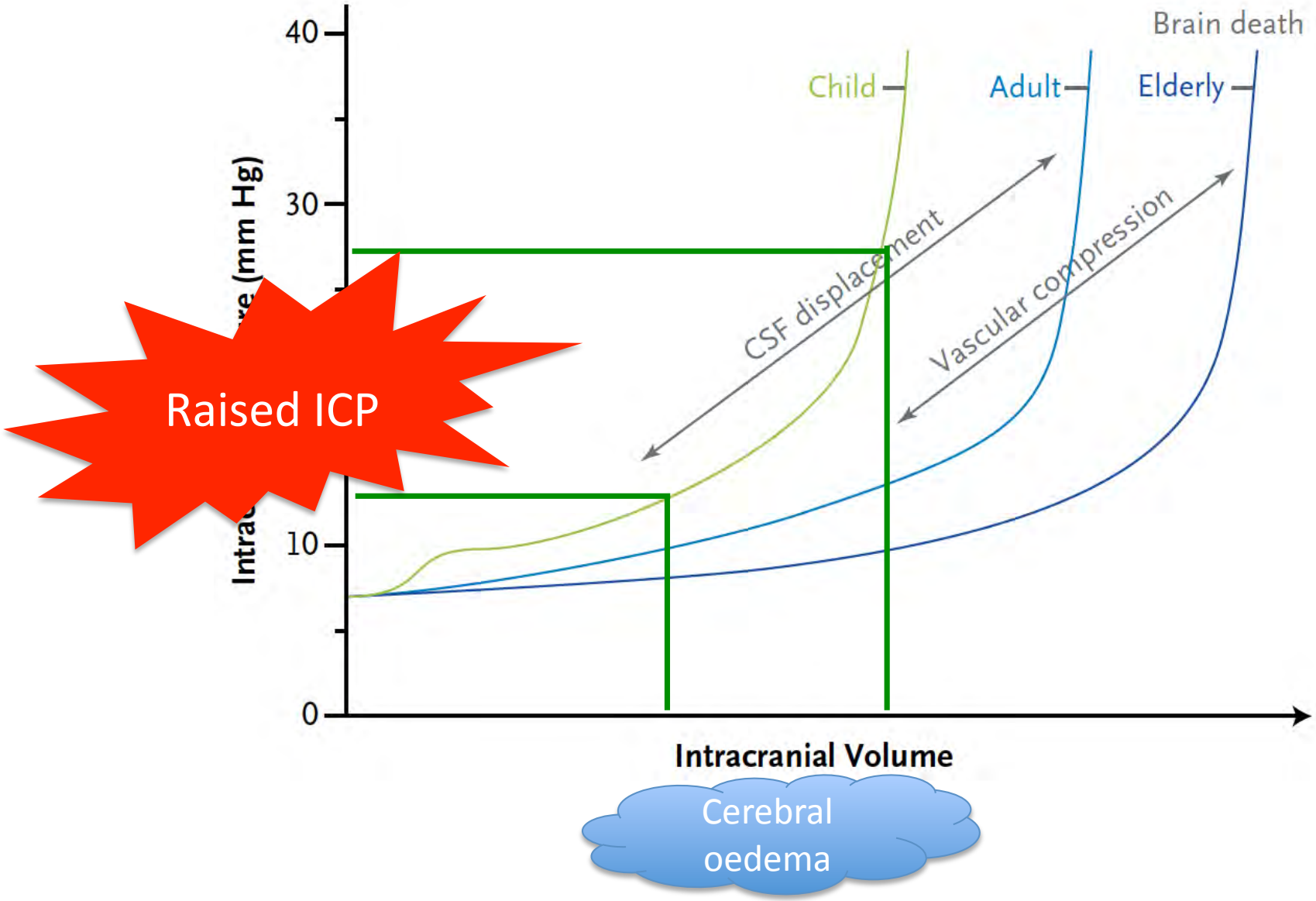
NEUROLOGICAL DETERIORATION
ON DAY 3
GCS 8
ICU ADMISSION
MECHANICAL VENTILATION

SEVERE INTRACRANIAL
HYPERTENSION ON DAY 5
Bilateral pupillary dilation
Reactivity to light +

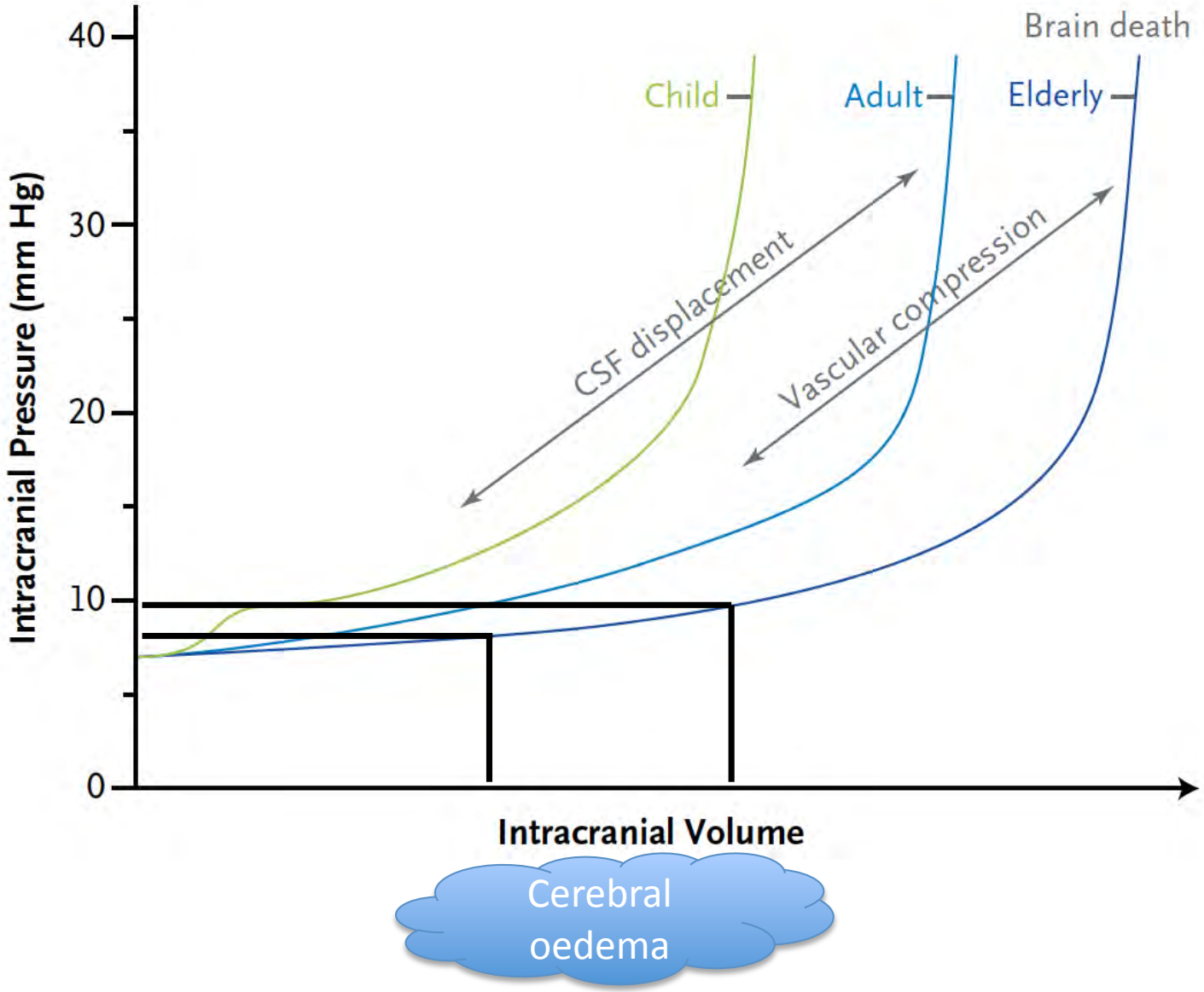
Relationship between pressure and volume within the cranium



Relationship between pressure and volume within the cranium



Relationship between pressure and volume within the cranium



Early therapeutic goals in the ICU

- Head of the bed elevated > 30 degrees

(to facilitate cerebral venous drainage)

- Respiratory care
  - PaO_2 > 80 mmHg, SpO_2 > 94%
  - Normocapnia: $PaCO_2$ 35-40 mmHg

- Sedation

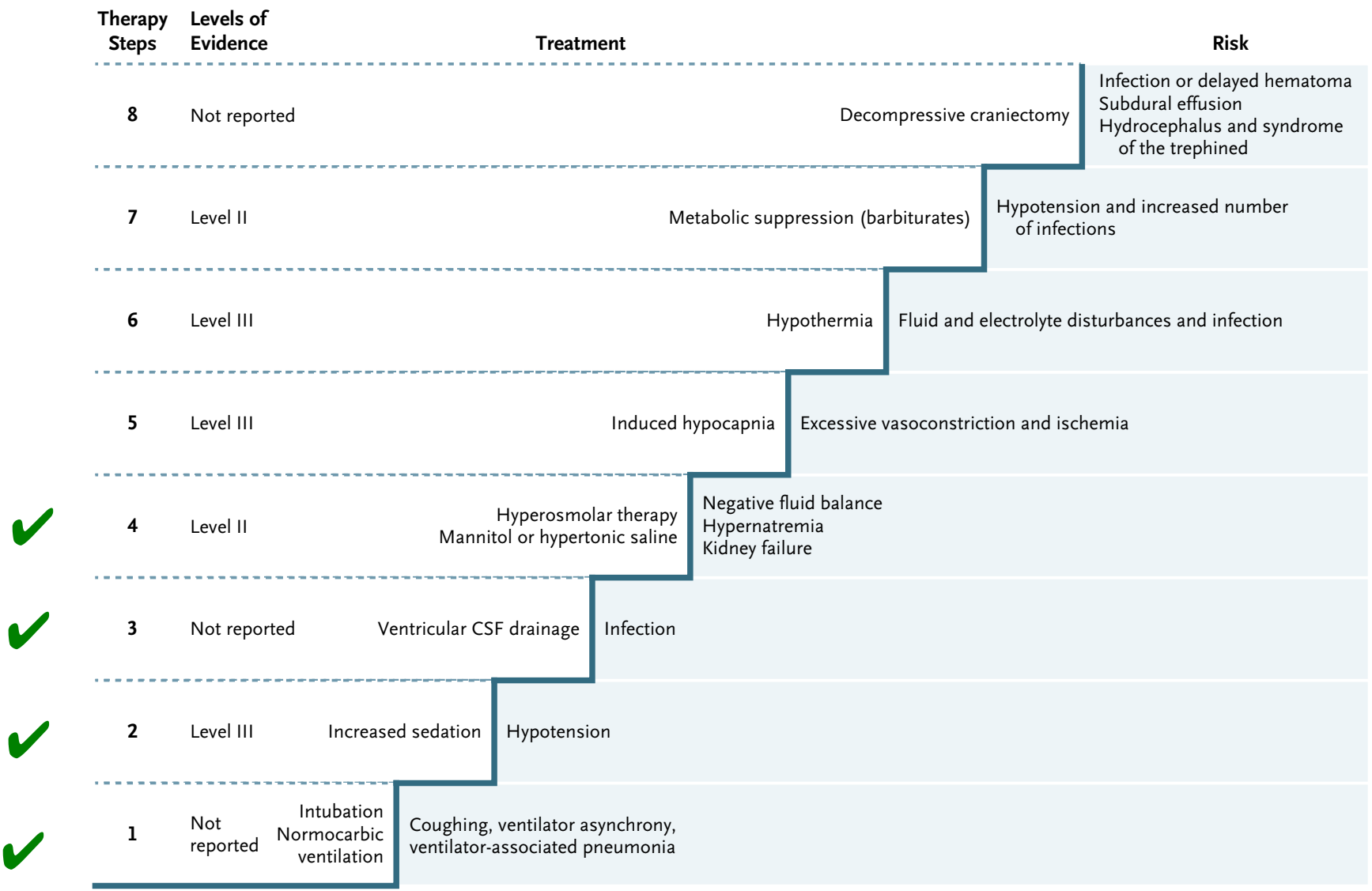
- Hemodynamics: MAP 70-80mmHg

Hyperosmolar therapy in raised intracranial pressure

If mass effect from significant cerebral edema is noted, hyperosmolar therapy with the use of mannitol or hypertonic saline may be necessary

Indication	Typical dosing/administration[a]
Cerebral edema[e8]	Mannitol 0.25 to 1 g/kg bolus every 4–6 hours
	Hypertonic saline
	Active brain herniation, 23% saline (30 mL bolus via central venous access)
	Maintenance, 2%–3% saline (250–500 mL boluses or continuous venous infusion; 3% saline via central venous access)

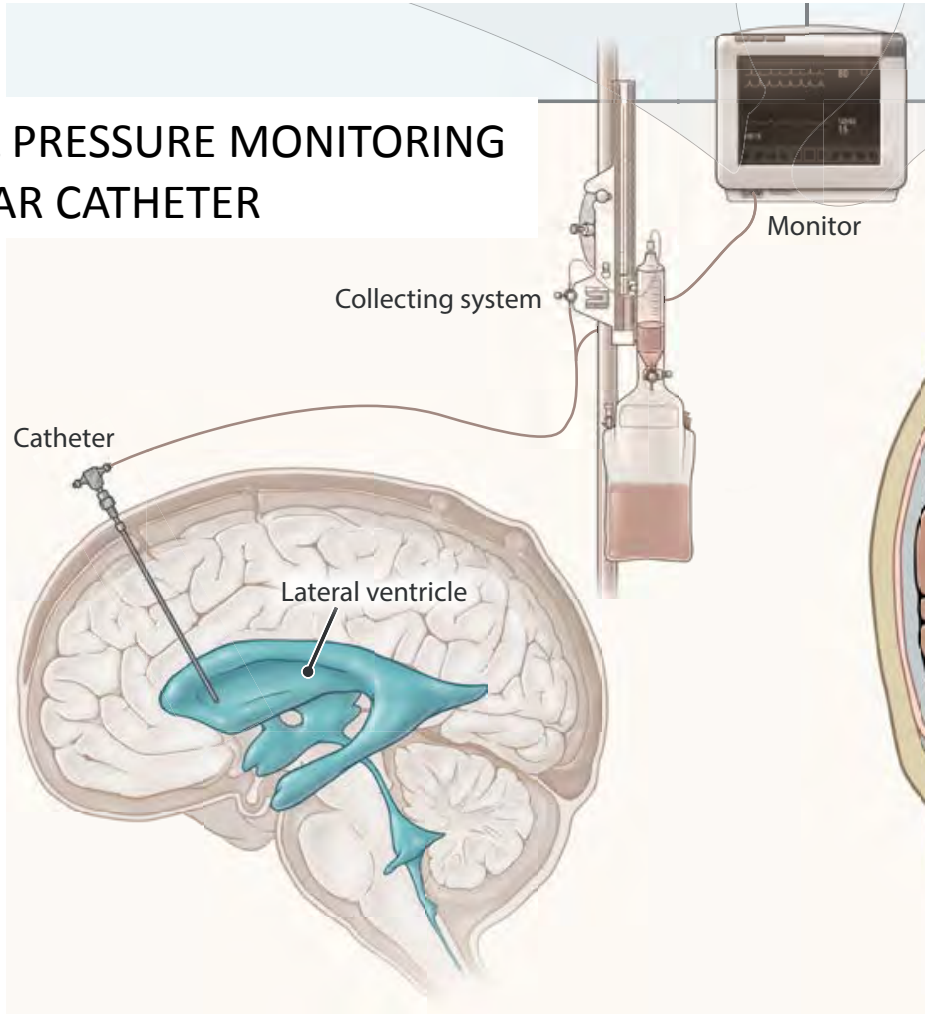
Treatment of raised intracranial presssure



N. Stocchetti, New Eng J Med 2014

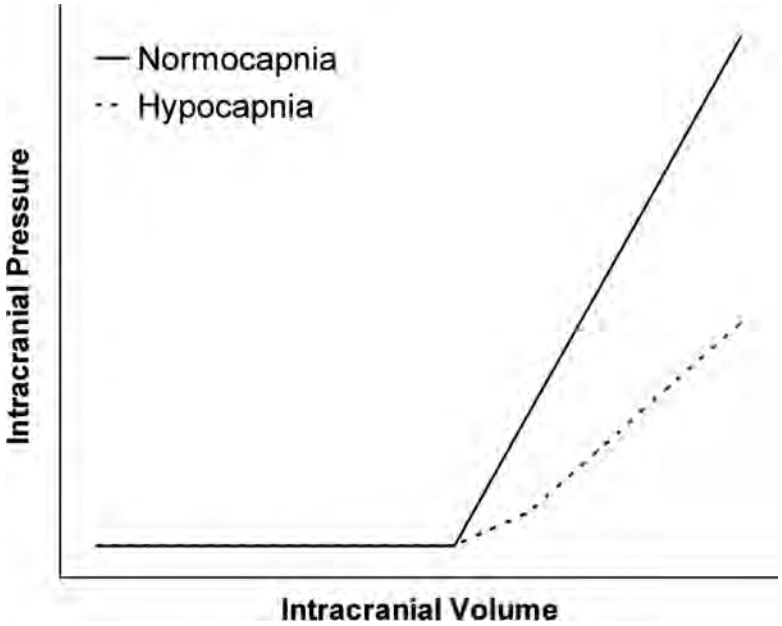
Treatment of raised intracranial presssure

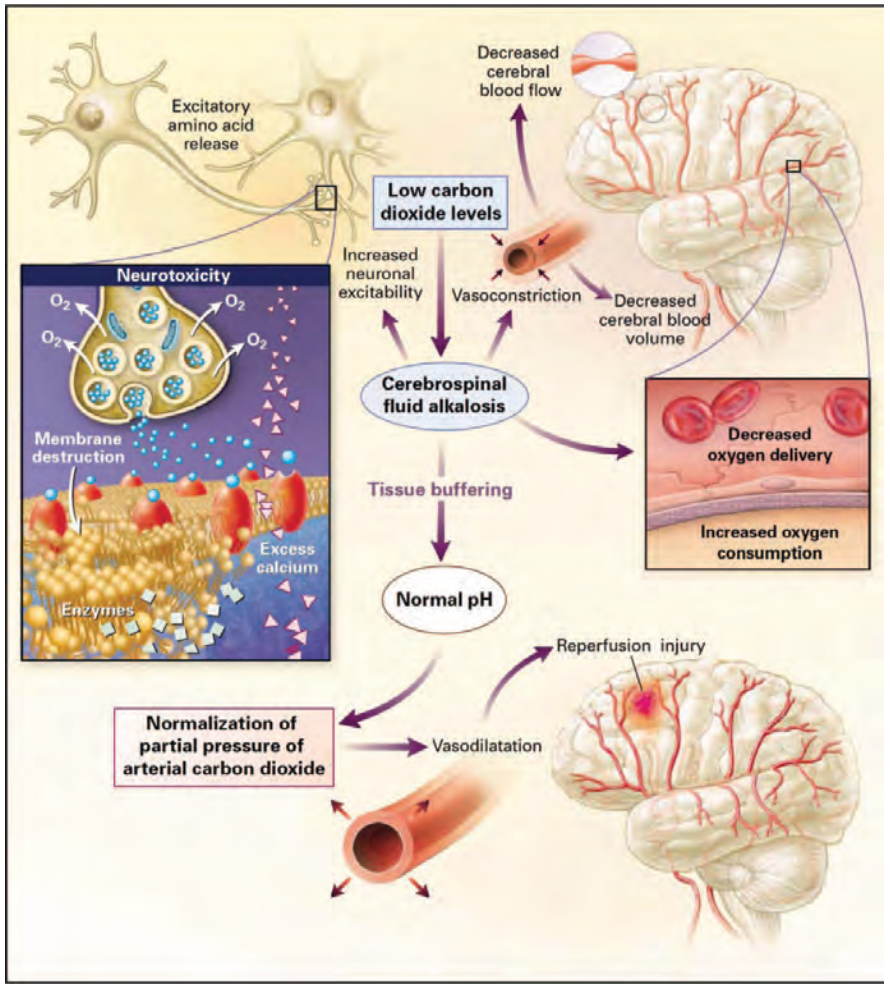
INTRACRANIAL PRESSURE MONITORING
BY VENTRICULAR CATHETER



N. Stocchetti, New Eng J Med 2014

Hypocapnia and the injured brain: More harm than benefit





G Curley, Crit Care Med 2010

Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial

275 adult patients

RCT Oral glycerol 75ml x 4 / day vs. placebo

The trial was stopped early on the advice of the data and safety monitoring board after a planned interim analysis

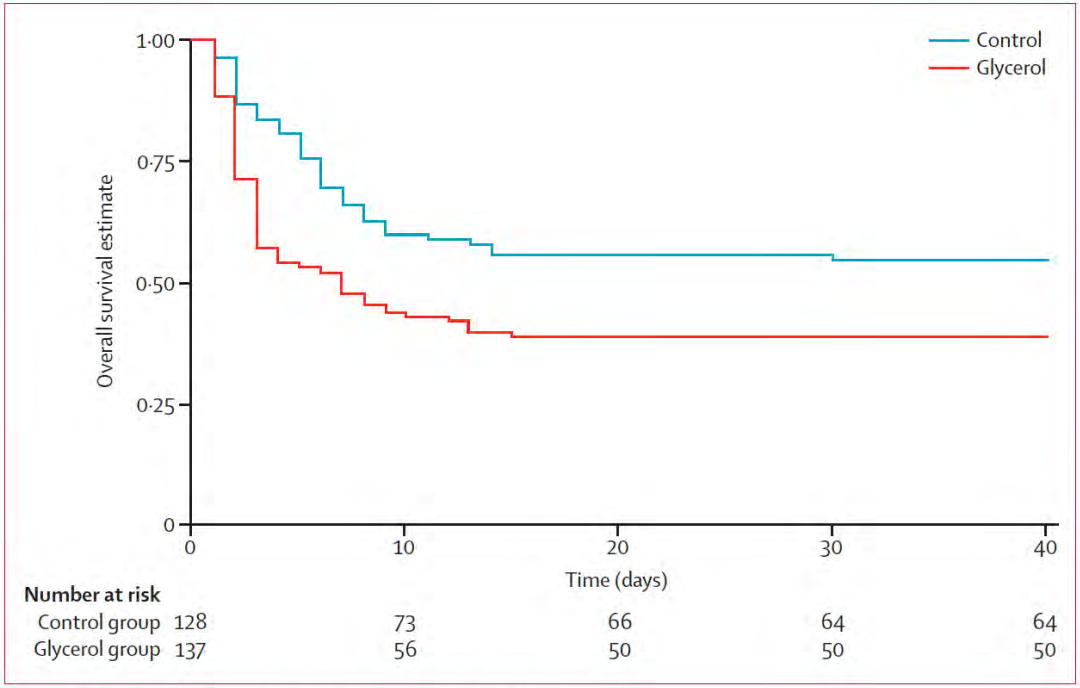


Figure 2: Kaplan-Meier survival estimates for glycerol *vs* control

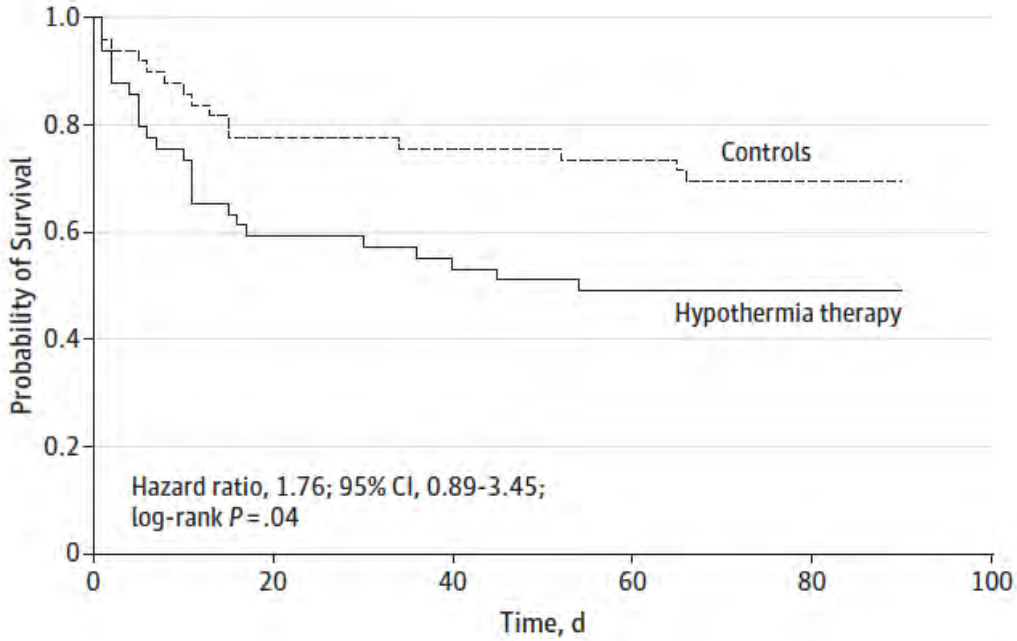
KMB Ajdukiewicz, Lancet Infectious Diseases 2011

Induced Hypothermia in Severe Bacterial Meningitis
A Randomized Clinical Trial

98 adult comatose patients with meningitis

RCT induced hypothermia 32-34° for 48H versus standard care

The trial was stopped early on the advice of the data and safety monitoring board after a planned interim analysis



No. at risk					
Controls	49	40	38	37	36
Hypothermia therapy	49	31	27	25	25

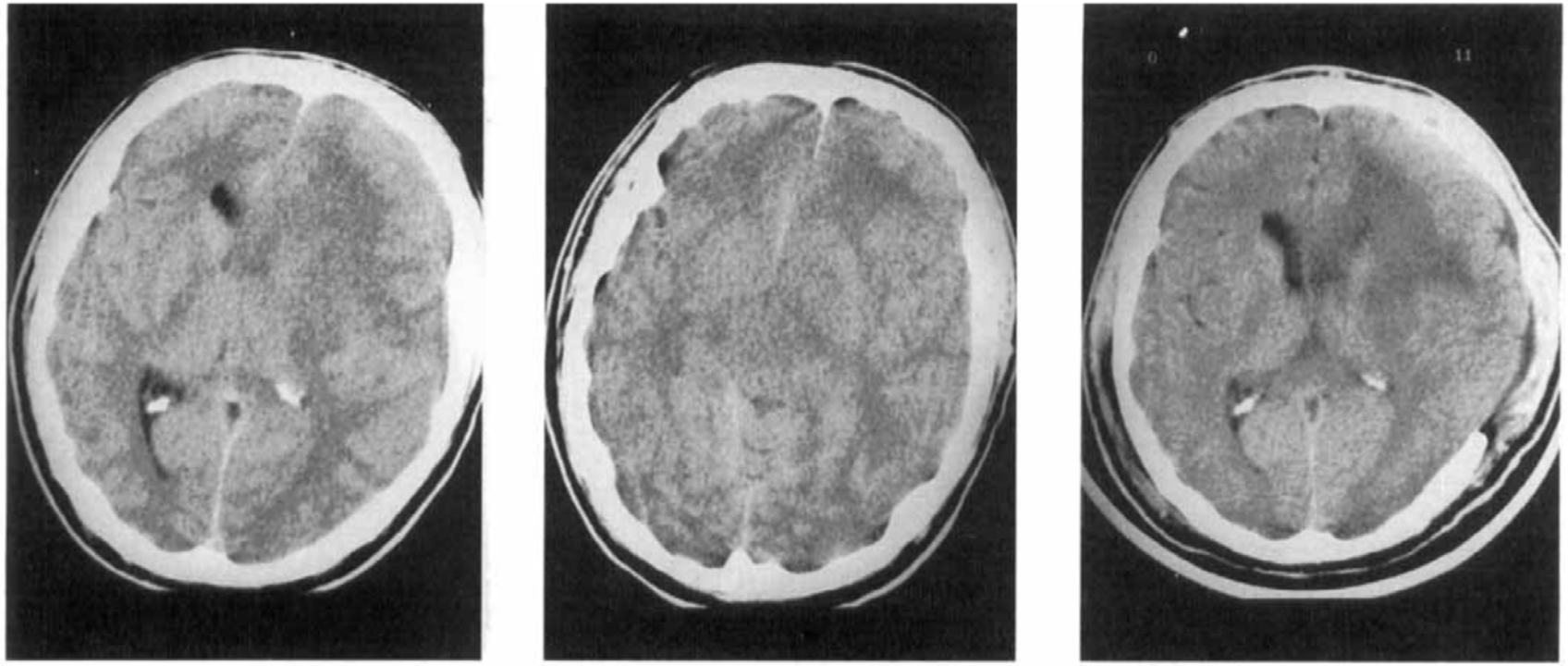
B Mourvillier, JAMA 2013

Decompressive craniectomy for encephalitis

Craniectomy:

An aggressive treatment approach in severe encephalitis

S. Schwab, MD; E. Jünger, MD; M. Spranger, MD; A. Dörfler, MD; F. Albert, MD; H.H. Steiner, MD; and W. Hacke, MD



Neurology 1999

Decompressive craniectomy for encephalitis

N=48 patients

Literature review of published cases

39 (81%) had a favorable functional recovery

Only two patients (4%) died after surgical treatment

	Good outcome	**Poor outcome**	**p**
Cause			0.02
Bacterial	9 (23)	7 (78)	
Viral	24 (62)	2 (22)	
Unkown	6 (15)	0 (0)	

J Perez Bovet, Acta Neurochirurgica 2012

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Seizures in patients with acute encephalitis

- 290 adult patients with encephalitis
- Bichat medical ICU, Paris, France (1991-2013)

- Seizures : 99/290 (34%)

  – Clinical presentation
    - Convulsive seizures : 4/5
    - Non convulsive seizures : 1/5

  – Type
    - Isolated seizures (n=44)
    - Non refractory status epilepticus (n=42)
    - Refractory status epilepticus (n=13)

NEUROCRITICAL CARE

Seizures after acute brain injury —more than meets the eye

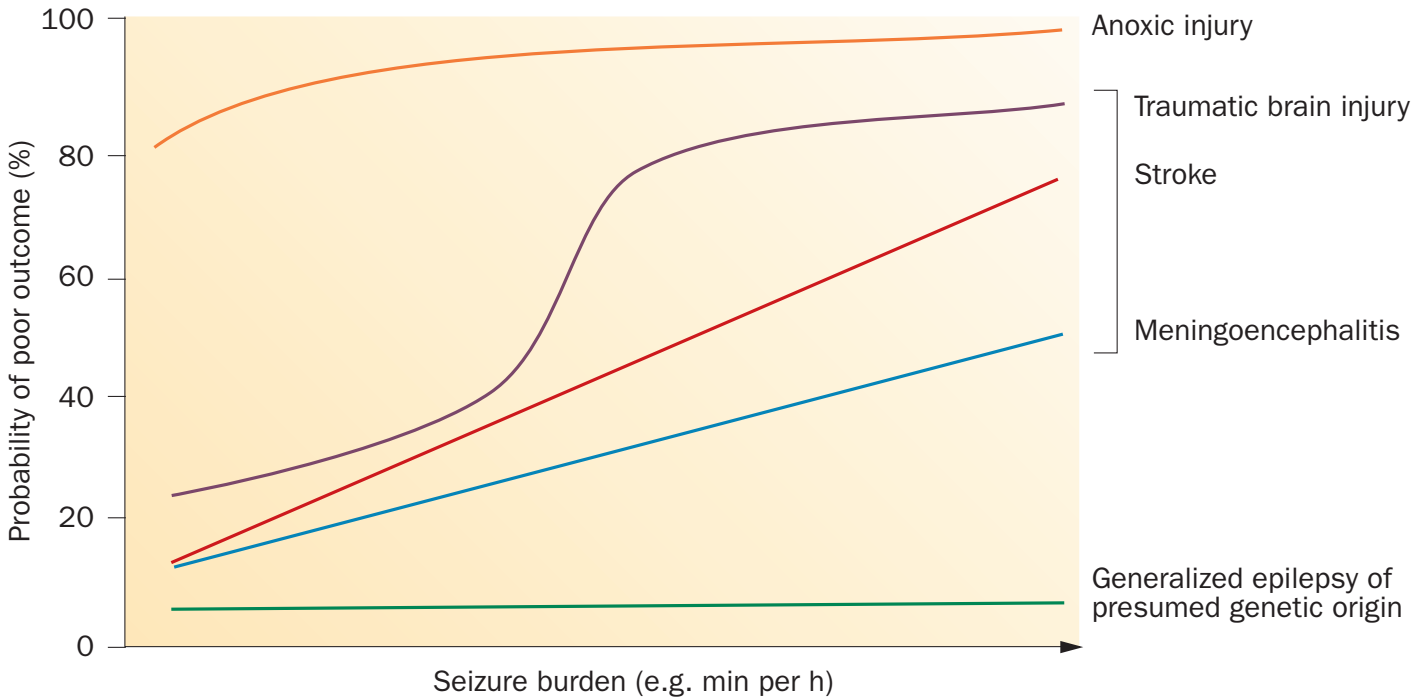


Figure 1 | Schematic illustration of potential relationships between seizure burden and outcome. The potential deleterious effects of seizures in the context of acute brain injury are likely to depend on the underlying aetiology. The probability of poor outcome might increase linearly or exponentially with increasing seizure burden, or a threshold might exist, above which seizures are harmful.

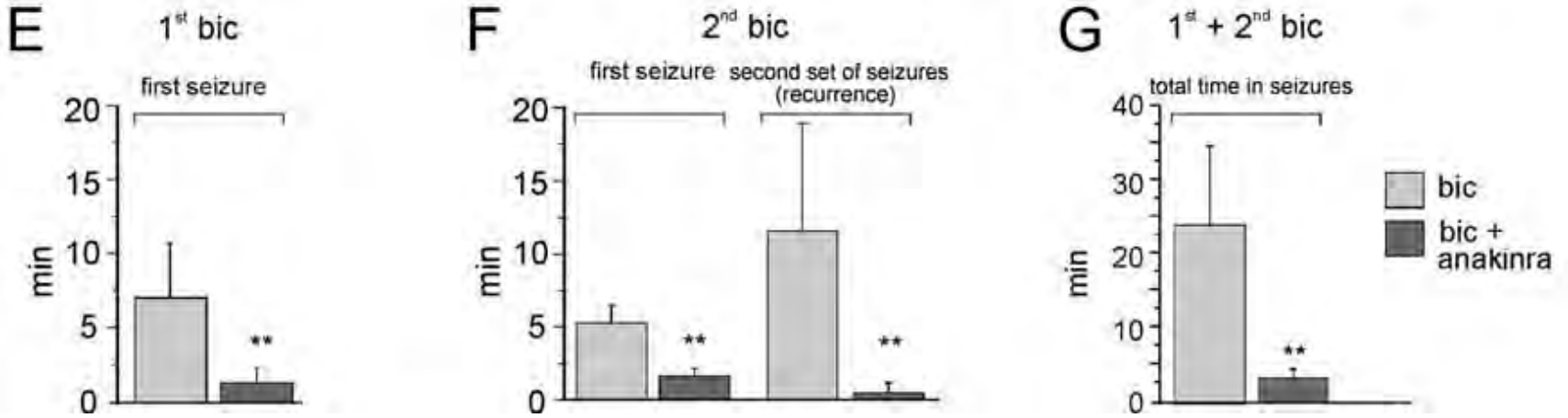
CD Hahn, Nature Review Neurol 2013

Seizure-Induced Brain-Borne Inflammation Sustains Seizure Recurrence and Blood–Brain Barrier Damage

Laura Librizzi, PhD,[1] Francesco Noè, PhD,[2] Annamaria Vezzani, PhD,[2]
Marco de Curtis, MD,[1] and Teresa Ravizza, PhD[2]

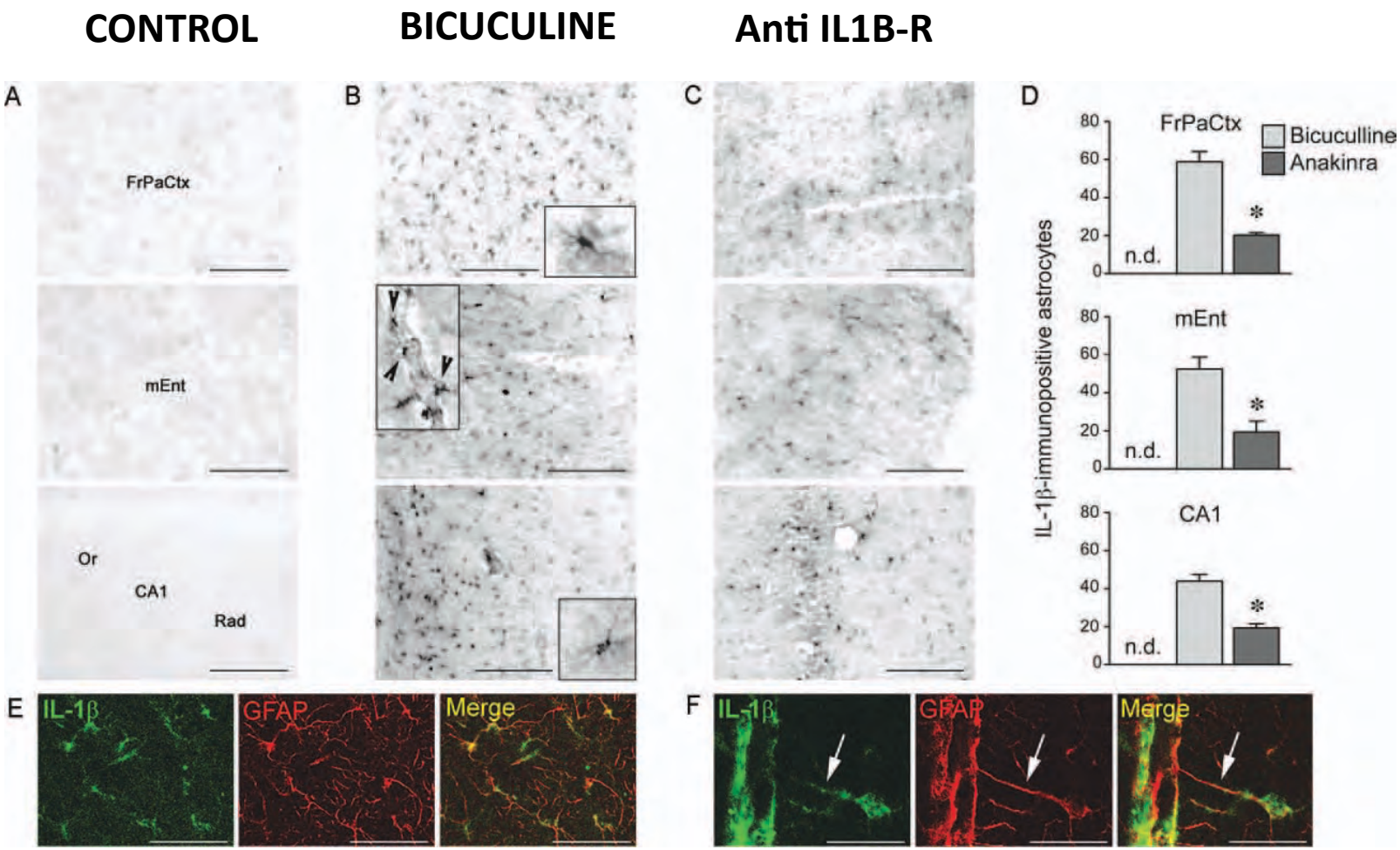
Epileptiform activity was induced by arterial perfusion of bicuculline in the in vitro isolated guinea pig brain.

The effects of arterially perfused anakinra, a human recombinant IL-1b receptor antagonist, were investigated on epileptiform discharges, brain inflammation, and BBB damage.



Annals Neurol 2012

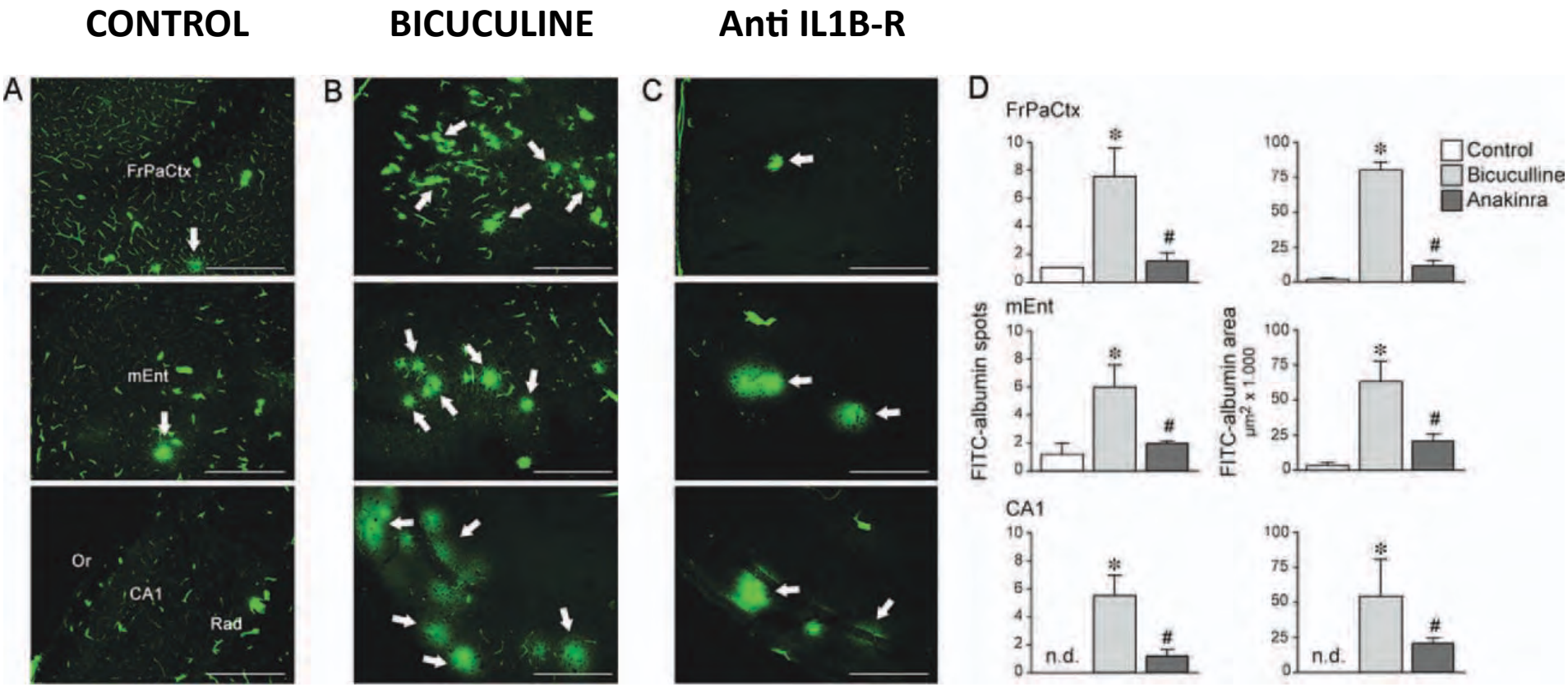
Seizure induction in the absence of extracerebral factors promoted the release of IL-1b from brain resident cells and enhanced its biosynthesis in astrocytes.



Seizure-induced brain inflammation was evaluated by quantitative immunohistochemical analysis of interleukin (IL)-1b in parenchymal cells.

Annals Neurol 2012

Anakinra rapidly terminated seizures, prevented their recurrence, and resolved seizure-associated BBB breakdown



BBB damage was assessed by extravasation of intravascular fluorescein isothiocyanate– albumin.

Annals Neurol 2012

Seizures in patients with acute encephalitis

290 adult patients with encephalitis

Bichat medical ICU, Paris, France (1991-2013)

Factors associated with seizures, multivariate analysis

Variable	**OR**	**95%CI**
GCS < 13	3.2	1.6-6.4
Cortical involvement on CT	7.0	3.4-14.7
Cause		
Immune-mediated (n=42)	1	-
Infectious (n=155)	0.4	0.2-1
Undetermined (n=93)	1.1	0.4-2.9
WBC > 10 000 / microL	1.3	0.7-2.5
CSF < 100 cells / microL	1.6	0.8-2.9
Natremia	1.0	1.0-1.1
N of organ failure(s)	1.1	0.7-1.8

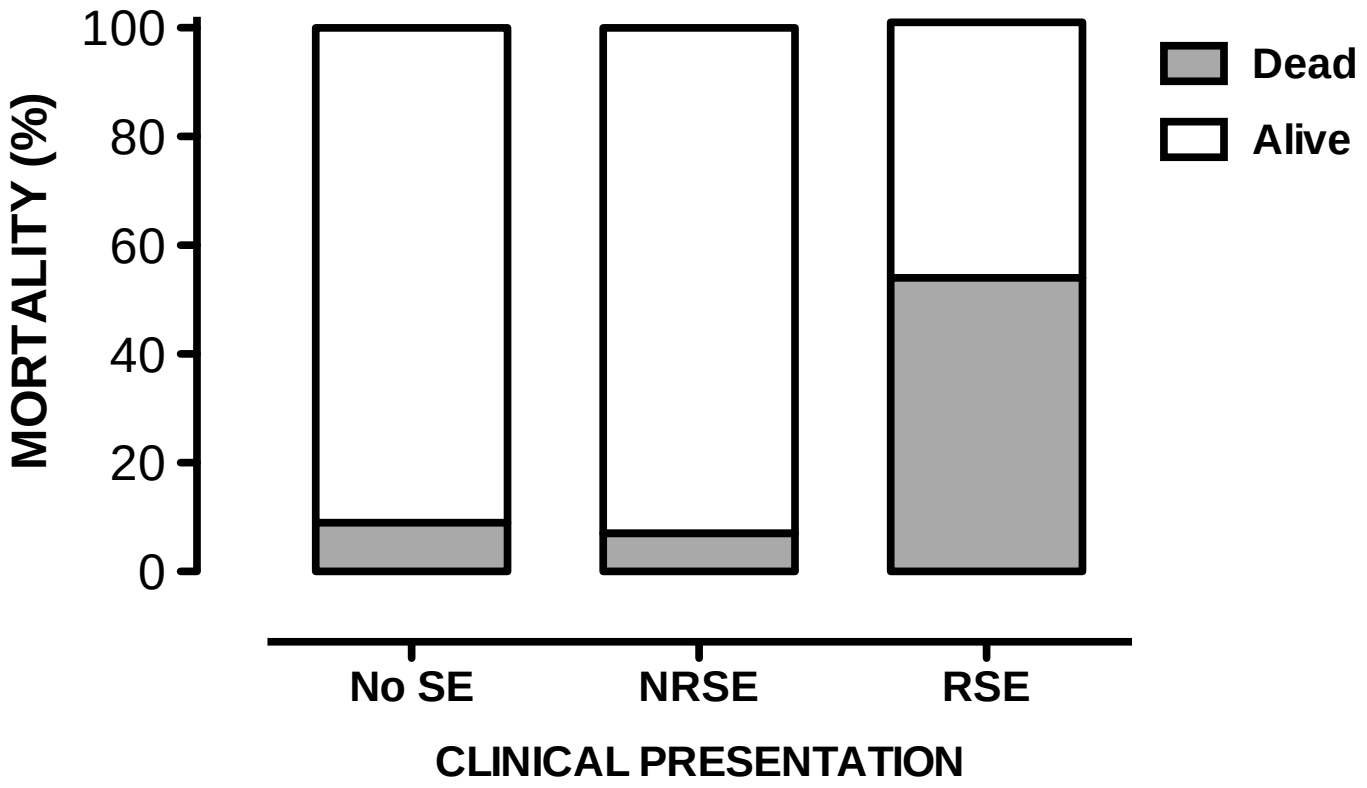
Seizures in patients with acute encephalitis

Seizures and status epilepticus[e12]	
First line, initial dosing	Lorazepam 0.1 mg/kg IV up to 4 mg per dose
	Midazolam 0.25 mg/kg IM up to 10 mg maximum
	Diazepam 0.15 mg/kg IV up to 10 mg per dose
Second line, initial dosing	Fosphenytoin 20 mg PE/kg IV
	Levetiracetam 1,000–3,000 mg IV
	Valproate sodium, 20–40 mg/kg IV
Third line, loading dose	Propofol 1–2 mg/kg
	Phenobarbital 20 mg/kg IV
	Pentobarbital 5–15 mg/kg IV

- There is little evidence to guide the AED choice as 2nd-line therapy.
- Patients who do not respond to 2nd line therapy should be sedated and intubated as for other causes of status epilepticus.
- DO NOT UNDERTREAT PATIENTS ++++

A Venkatesan, Neurology Clin Practice, 2014

Seizures in patients with acute encephalitis



Seizures in patients with acute encephalitis

Single center, retrospective study

147 patients with refractory status epilepticus

NYC, Columbia, USA

Risk factors for super refractory status epilepticus

Multivariate analysis

	SRSE n = 31	RSE n = 116	Odds ratio (95% CI)	*P*-value
Age, years[1]	48 (+/-20)	61 (+/-17)	0.96 (0.94, 0.98)	0.001*
Women, n (%)	17 (55)	78 (67)		
Race, n (%)				
White	15 (48)	52 (45)	-	-
Non white	16 (52)	64 (55)	-	-
History of epilepsy, n (%)	8 (26)	38 (33)		
Etiology, n (%)				
Acute	16 (52)	70 (60)	-	-
Encephalitis	12 (35)	13 (11)	4.35 (1.7, 11.09)	0.002*
Intracerebral hemorrhage	1 (3)	31 (27)	0.09 (0.011, 0.69)	0.021
Stroke	1 (3)	4 (3)		
Toxic-metabolic	1 (3)	11 (9)		
Traumatic brain injury	1 (3)	11 (9)		

D. Pugin Crit Care 2014

Periodic Epileptiform Discharges (PEDs)

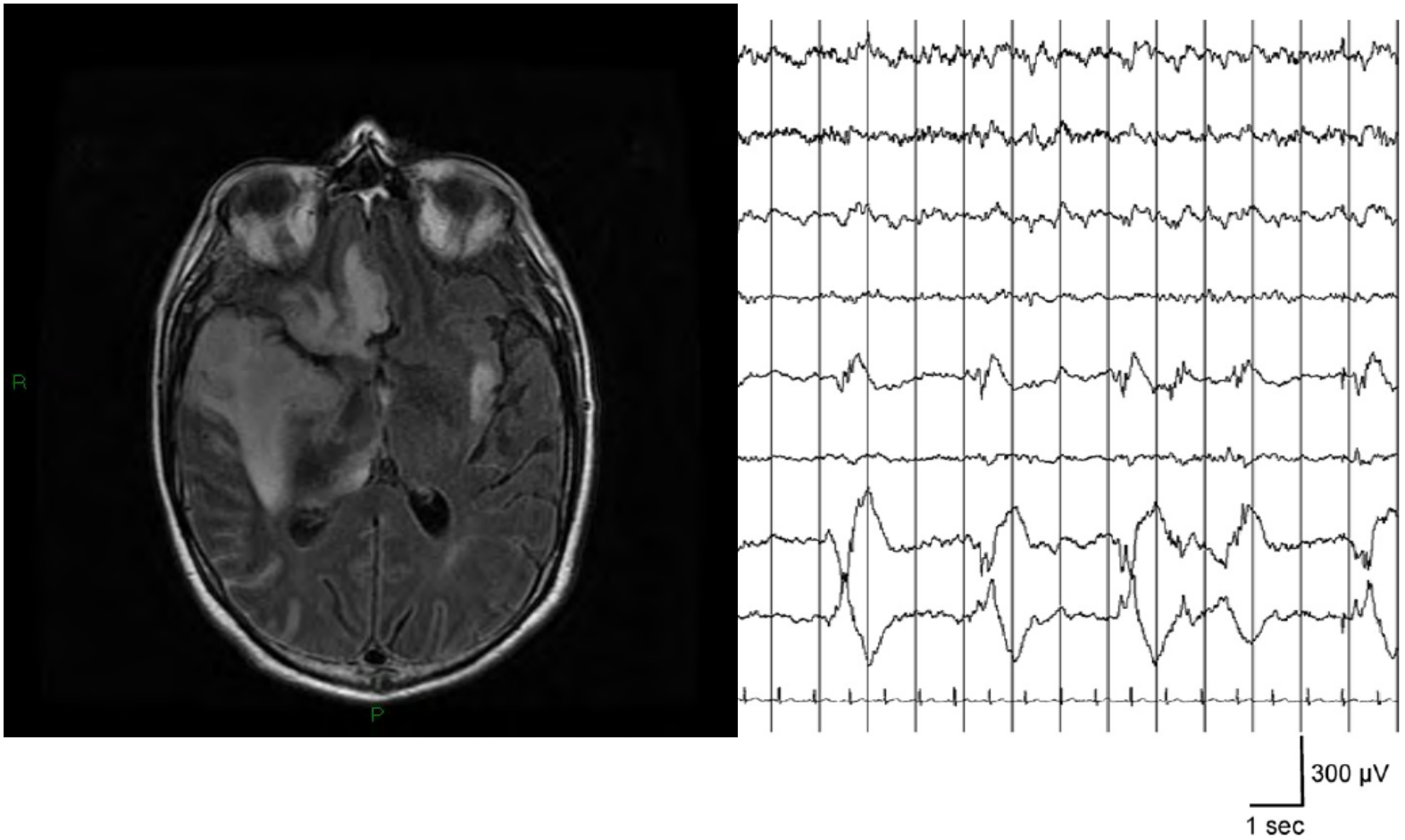


Figure 3 Diagnostic différentiel d'état de mal : PLEDs. Extrait d'un tracé EEG, en montage bipolaire longitudinal, comportant huit électrodes, chez une patiente présentant une confusion fébrile dans le cadre d'une méningoencéphalite herpétique. L'EEG montre des PLEDS qui prédominent dans la région temporale gauche. Il s'agit de potentiels lents très amples, mêlés à des activités moins amples et plus rapides, se répétant de façon pseudopériodique toutes les deux à trois secondes. Dans cet exemple, il n'y a pas de figures épileptiques associées aux PLEDs, ni de décharges de pointes, montrant que cette méningoencéphalite n'est pas compliquée de crise ni d'un EME.

Continuous Electroencephalographic Monitoring in Critically Ill Patients With Central Nervous System Infections

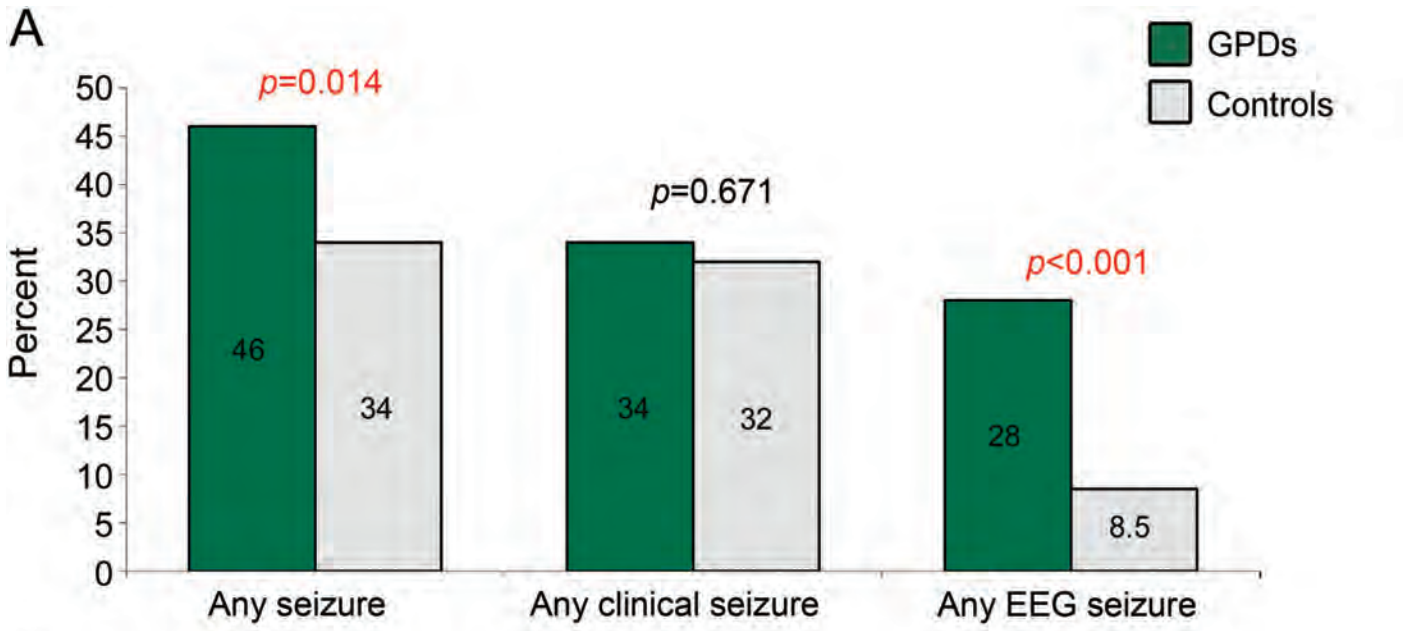
42 patients with primary CNS infection
Electrographic seizures : 14 (33%)
PEDs : 17 (40%)

PREDICTORS OF OUTCOME	OR	p-value
Stupor or coma	5.4	0.04
Electrographic seizures, n (%)	5.9	0.02
PEDs (periodic epileptiform discharges)	6.1	0.01

E Carrera, Arch Neurol 2008

Generalized periodic discharges in the critically ill

A case-control study of 200 patients



B Foreman, Neurology 2012

ICU management of acute encephalitis

KEYPOINTS

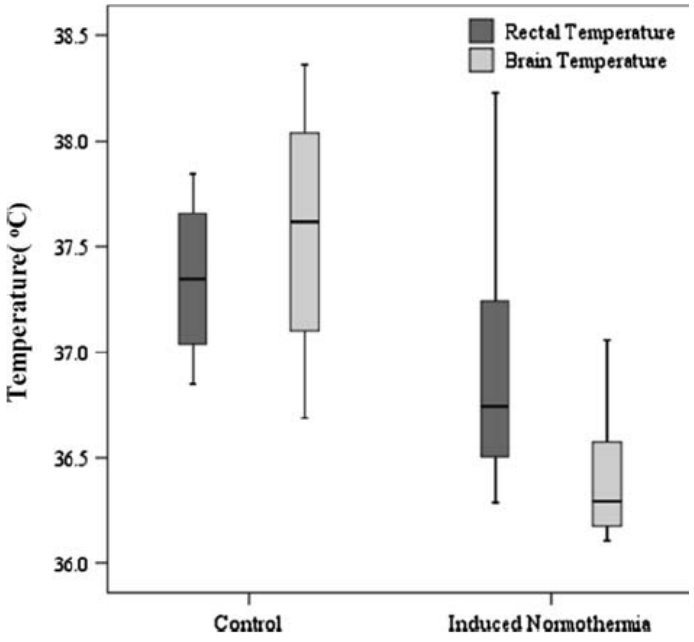
- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

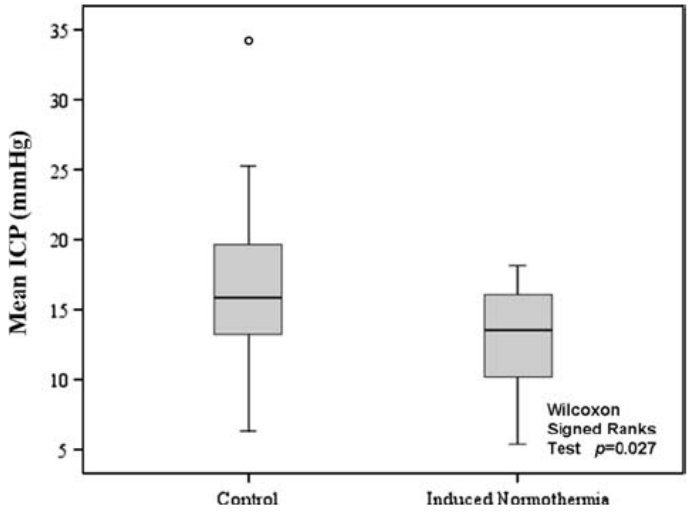
neurocritical care society Neurocrit Care
DOI 10.1007/s12028-009-9213-0

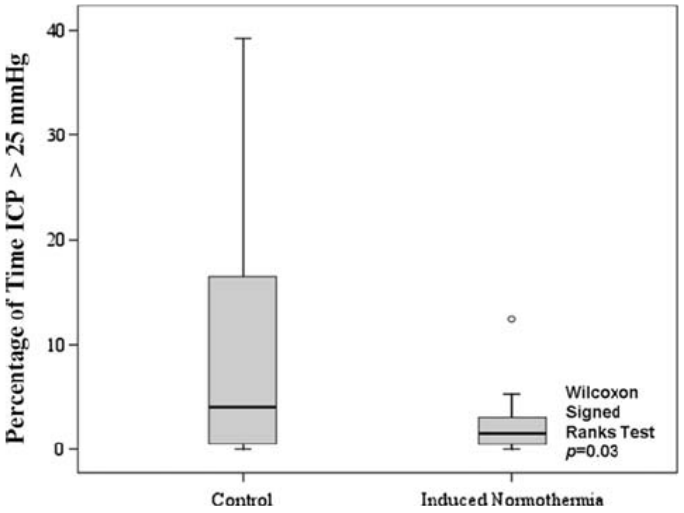
ORIGINAL ARTICLE

Induced Normothermia Attenuates Intracranial Hypertension and Reduces Fever Burden after Severe Traumatic Brain Injury

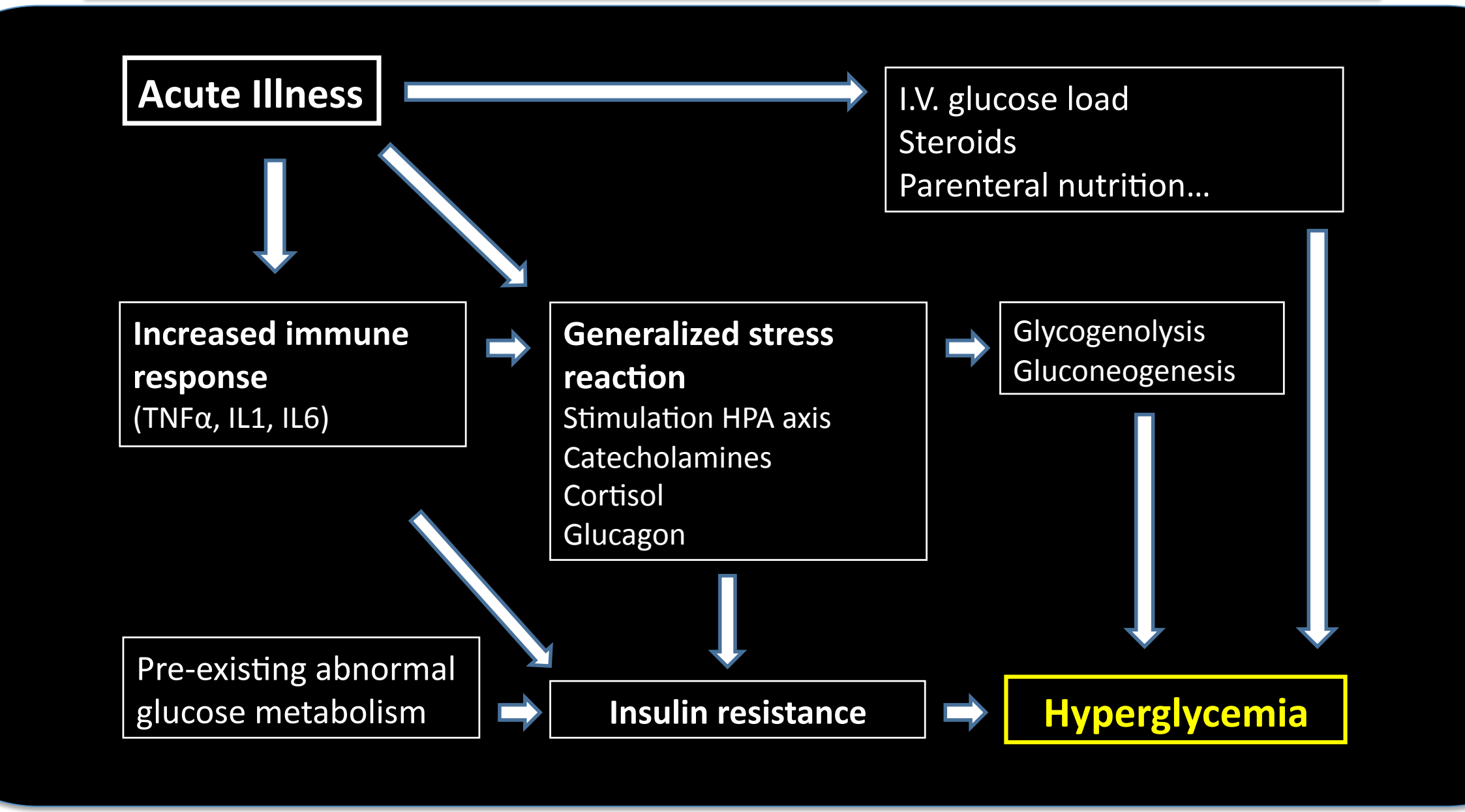
Ava M. Puccio · Michael R. Fischer · Brian T. Jankowitz · Howard Yonas · Joseph M. Darby · David O. Okonkwo



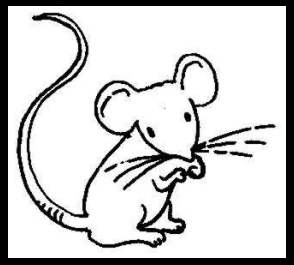




Hyperglycemia in critical illness



Mouse model of polymicrobial sepsis



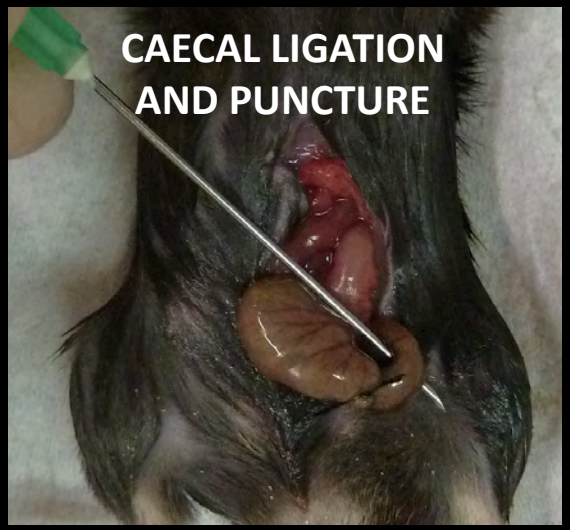
HYPERGLYCEMIA > 150 mg/dL

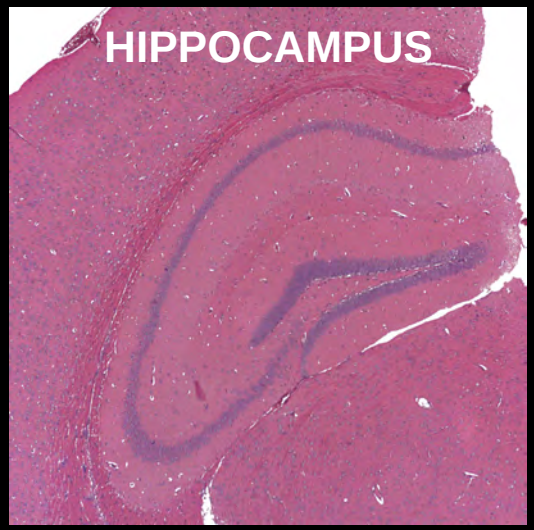
Broad spectrum antibiotics
IV fluid resuscitation

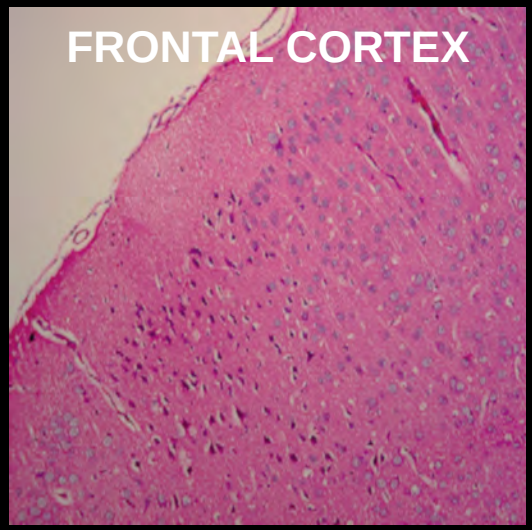
NORMOGLYCEMIA 80-110 mg/dL

Sacrifice day 5

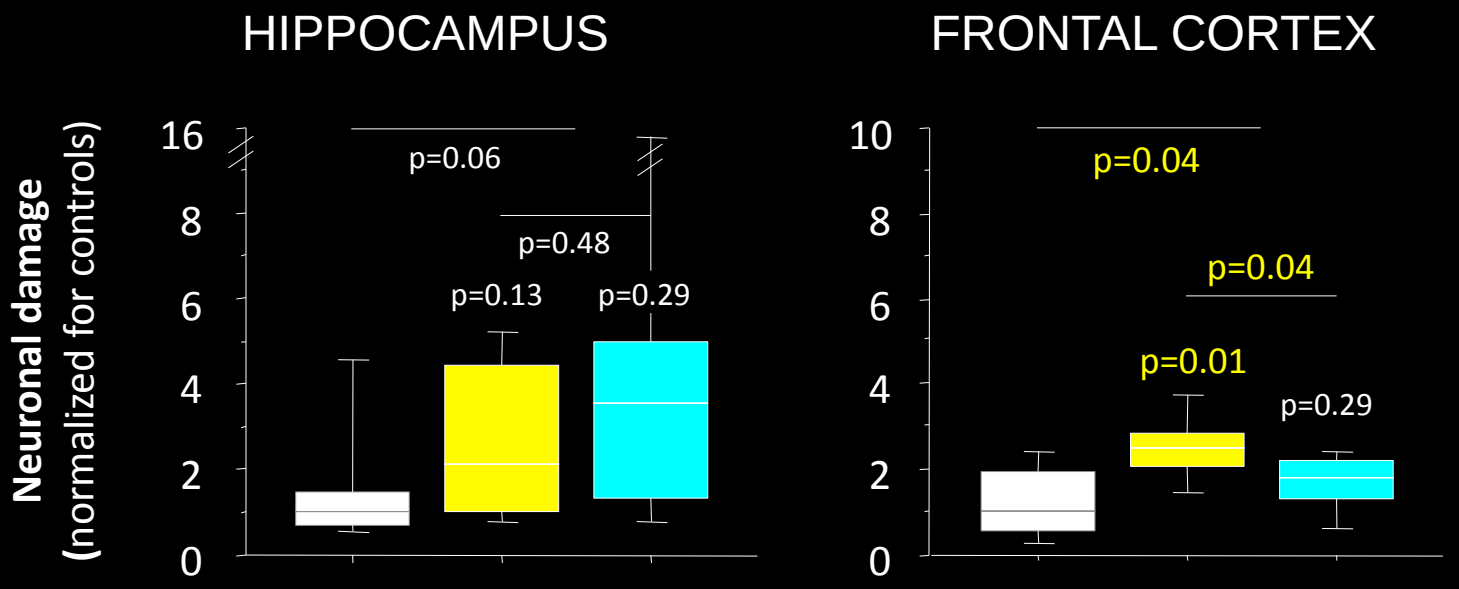
Wild type mice
General anesthesia
Jugular vein catheterization
Sepsis induced by peritonitis





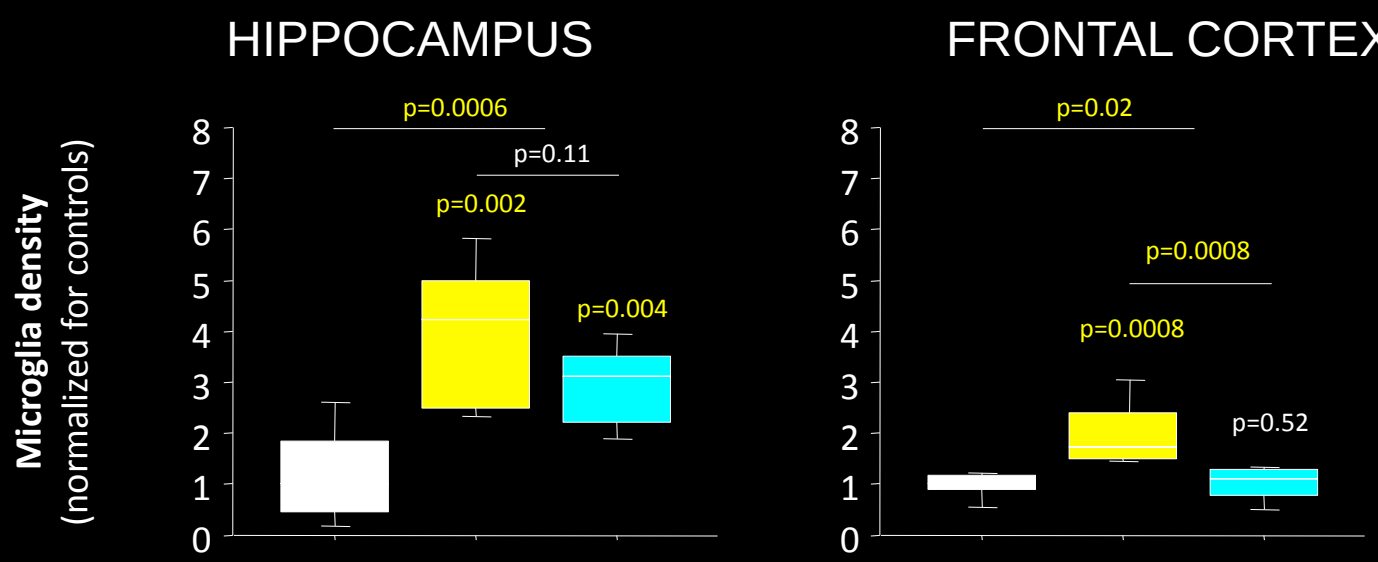


Glucose and neuronal damage



Control Moderate hyperglycemia Normoglycemia

Blood glucose and microglial activation



Early microglial changes during sepsis

SEPSIS MODEL (Peritonitis, CLP)

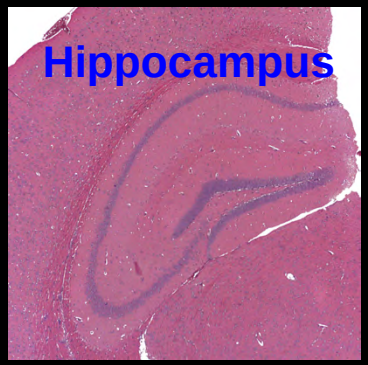
Severe clinical phenotype
Multiple caecal punctures
No antibiotics
Subcutaneous rehydration

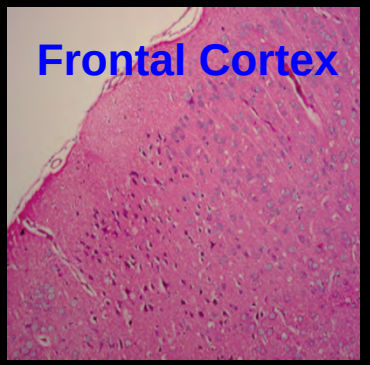
SEPSIS
(CLP)

SHAM SURGERY
(anesthesia, skin incision)

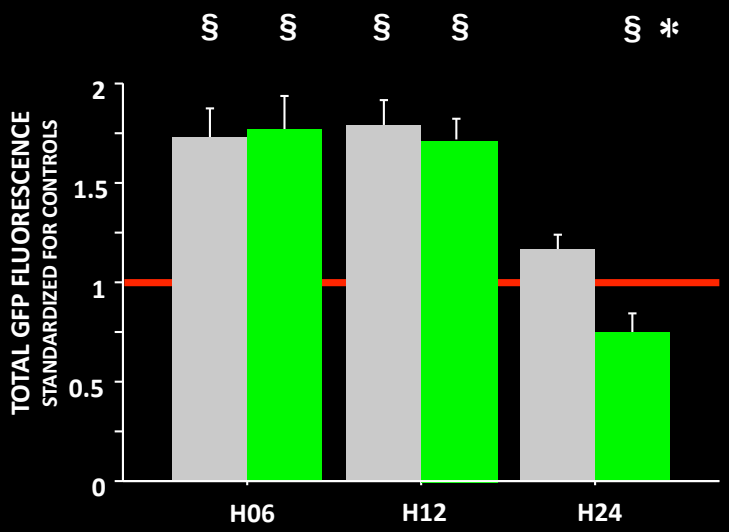
CLINICAL PARAMETERS
before sacrifice
(locomotor activity, body T°, sickness behavior score)

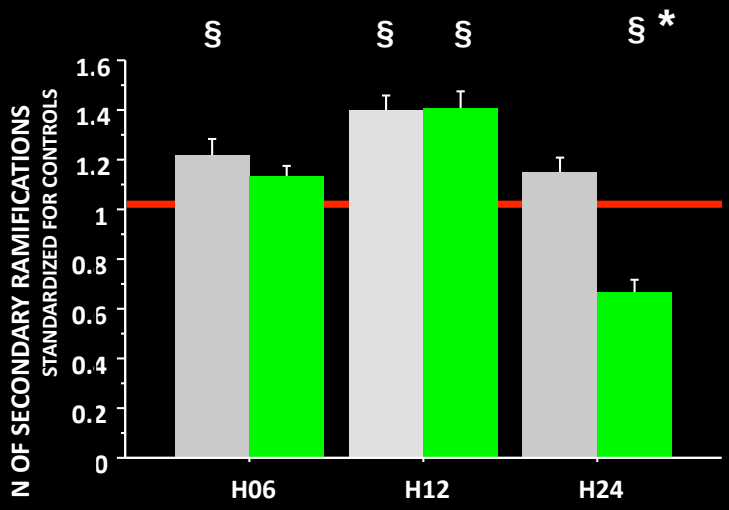
SACRIFICE AT 6, 12 or 24 H
NEURONAL DAMAGE

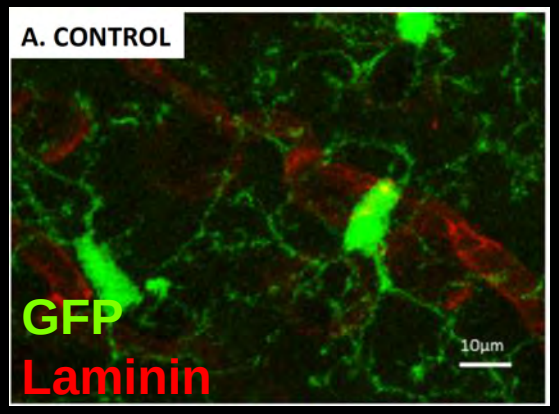


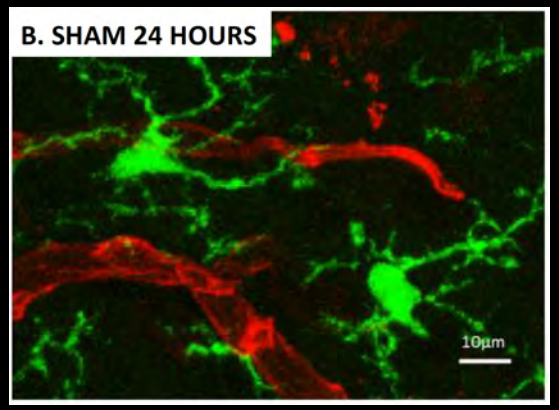


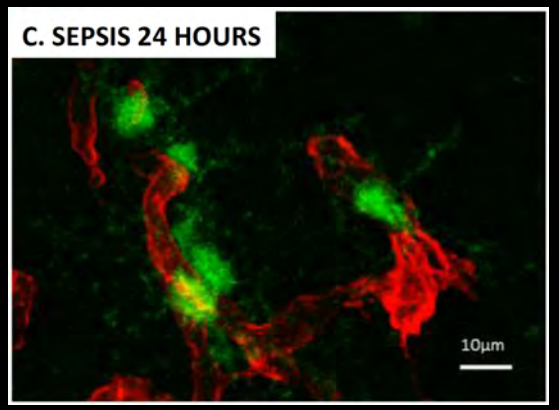
Microglial changes in sepsis











SHAM

SEPSIS

§ : p<0.05 vs. healthy controls

* : p<0.05 vs. sham

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Case

Patient 57 yrs, no medical history

22/10 : Angina, amoxicillin

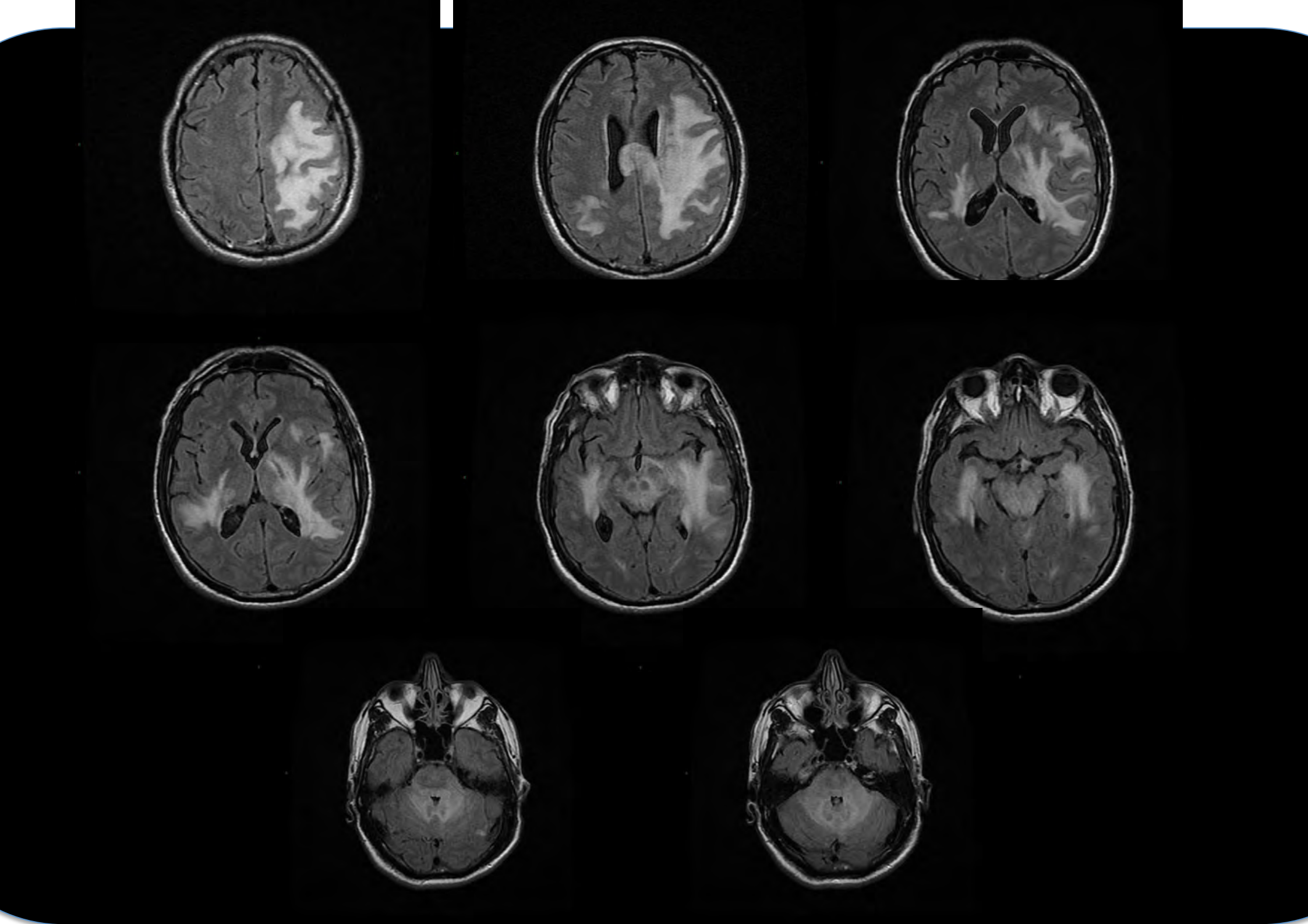
29/10 : fever, gait disturbances=> ER

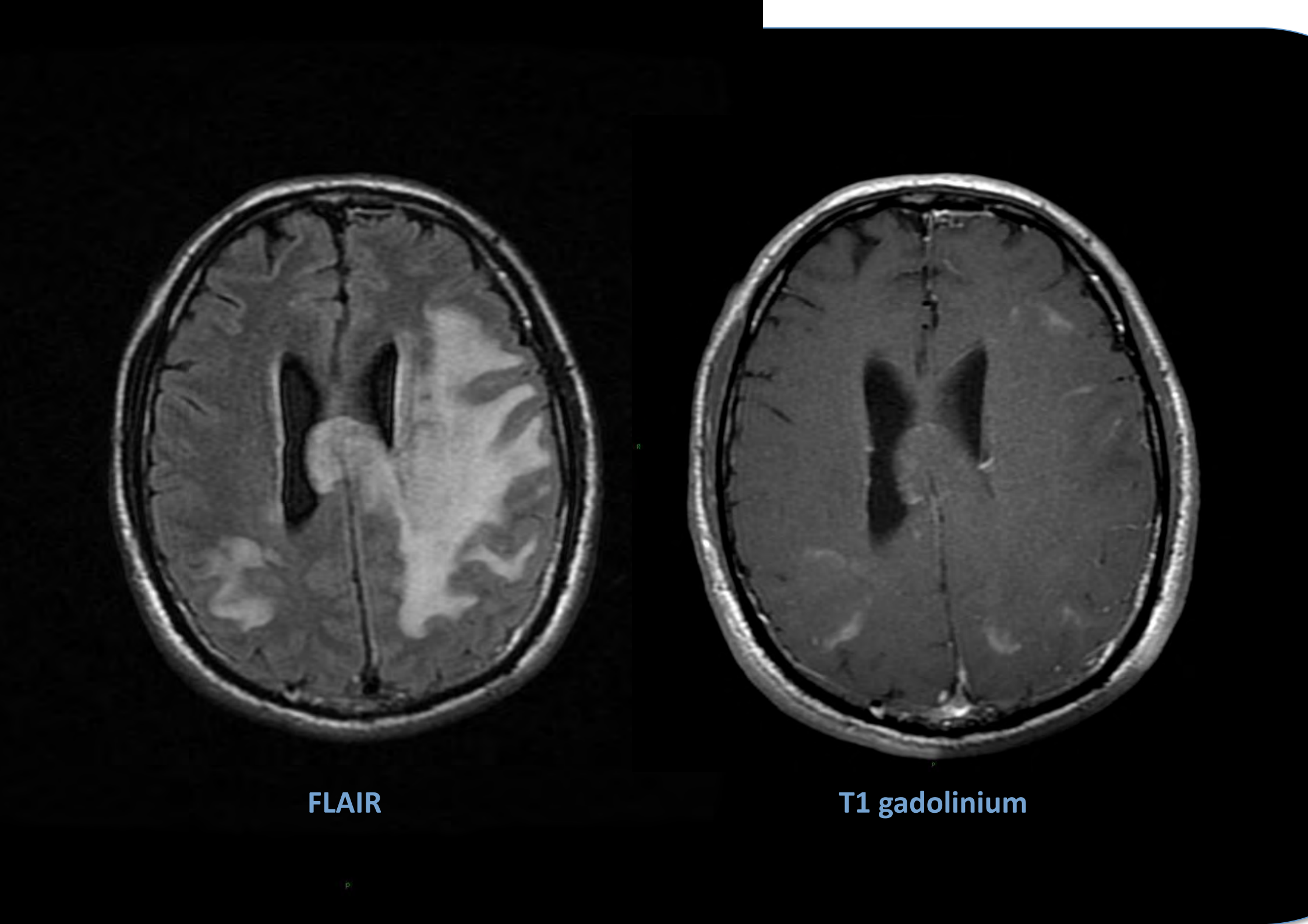
GCS 10, T°39°C, nuchal rigidity, right hemiparesis

Normal CT scan…..

CSF : 1500 cell /mm^3 (79% polynuclear cells), Protein levels 1,72 g/l, normal glucose levels – Negative direct examination

⇒ intubation / MV
⇒ IV cefotaxime
⇒ IV amoxicilline – gentamicine
⇒ IV aciclovir




FLAIR
T1 gadolinium

Acute disseminated encephalomyelitis (ADEM)

Pathophysiology

MOLECULAR MIMICRY

« viral » infection

Pathogene = structure homology with myelin components

MBP (Myelin Basic Protein)

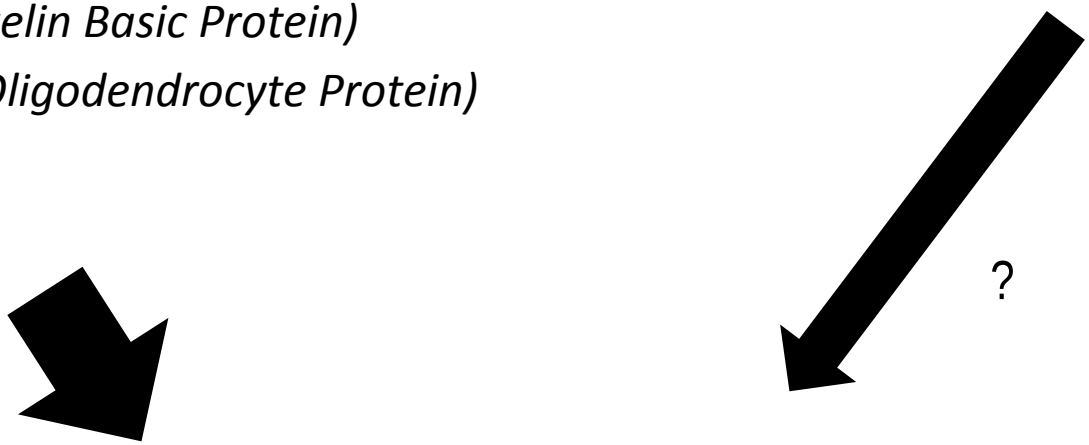
MOG (Myelin Oligodendrocyte Protein)

PRIMITIVE CNS INFECTION

Neurotropic pathogen

BBB disruption

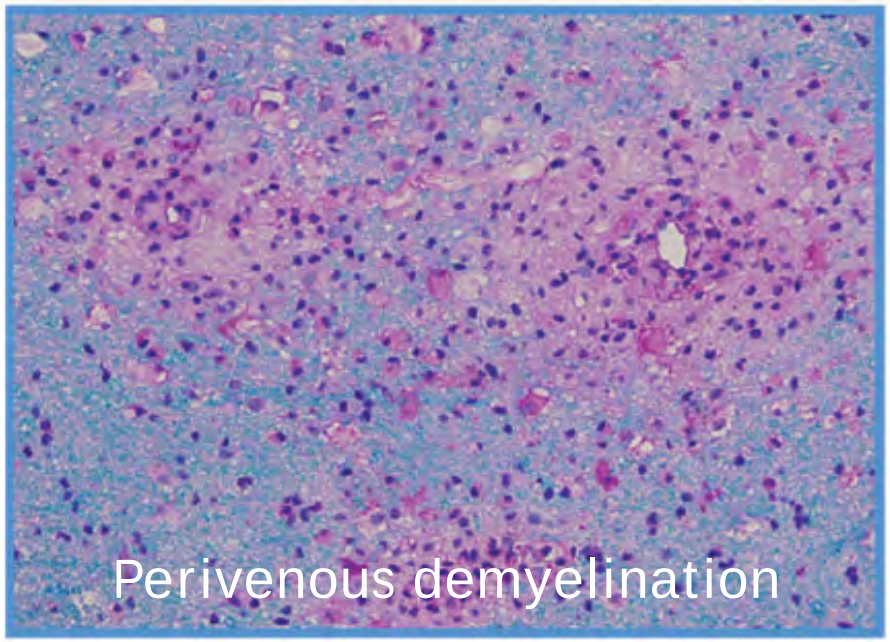
CNS Ab release in peripheral circulation

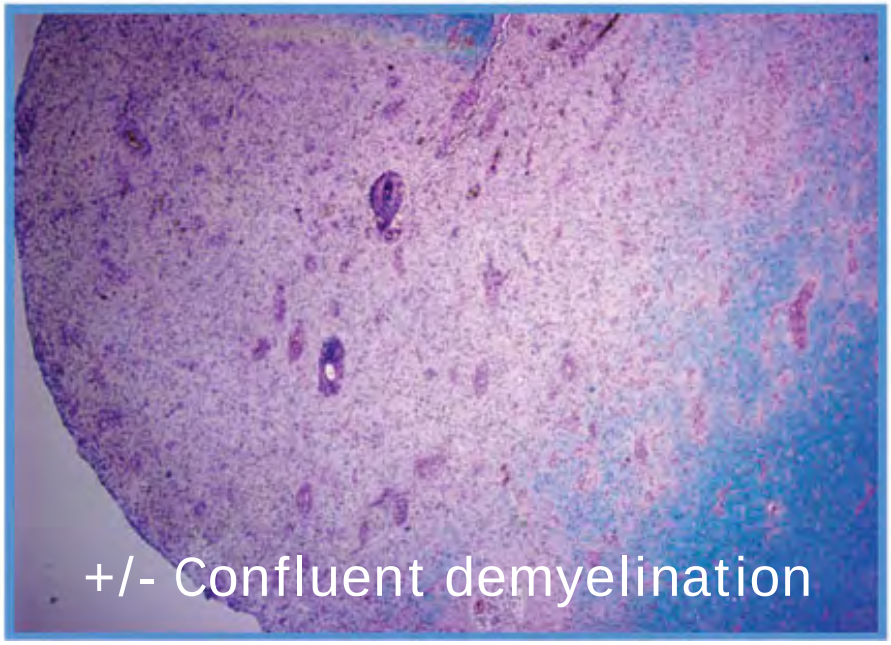


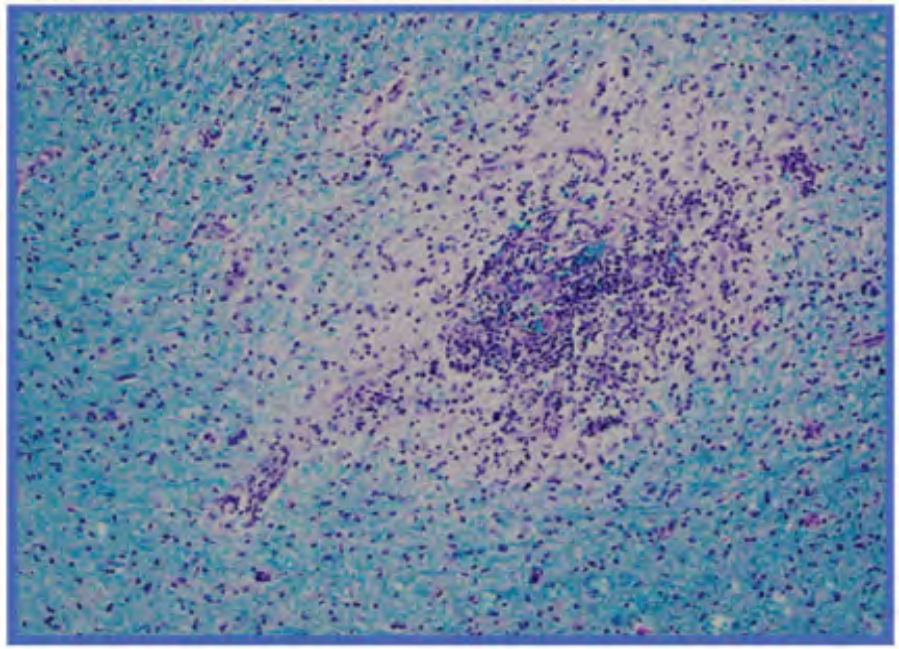
Auto-immune response against CNS components

Tunkel, Clinical Infectious Diseases 2007


Perivenous sleeve of inflammation







- Perivenous distribution
- White matter lesions
- Cellular infiltrate
- Demyelination
- Axons and arteries spared
- No evidence of previous demyelination

NP Young, Brain 2010

Cortical microglial activation without cortical demyelination

« Depressed level of consciousness is a more specific clinical criterion for pathologically confirmed ADEM than encephalopathy, which overdiagnosed ADEM among MS patients. »

A distinct neuropathological pattern (60% patients) may be the correlate of depressed level of consciousness in ADEM

NP Young, Brain 2010

ADEM in the ICU

Parameter	All patients ($n = 20$)
Age, years	37 (27–51)[a]
Fernale sex, *n* (%)	11 (55)
Preceding infectious disease, *n* (%)	14 (70)
Latency period, days	8 (6–14)
SAPS II	33 (15–45)
MV, *n* (%)	14 (70)
Temperature, °C	39 (38–39)
Neck stiffness, *n* (%)	10 (50)
GCS	7 (4–13)
Seizures, *n* (%)	6 (30)
Motor deficit, *n* (%)	17 (85)
Spinal card symptoms, *n* (%)	11 (55)

R Sonneville, Intensive Care Med 2007

IDSA GUIDELINES

ADEM

Although not fully assessed in randomized, placebo-controlled trials **high-dose intravenous corticosteroids (methylprednisolone, 1 g IV/day, 3–5 days) are generally recommended for ADEM**

Reports of successful treatment with PLEX have also been documented, although no data from randomized trials are available.

PLEX should be considered in patients who respond poorly to corticosteroids

The use of intravenous immunoglobulin has been reported for the treatment of ADEM.

This approach may be considered in patients who have not responded to corticosteroids or PLEX

Tunkel CID 2008

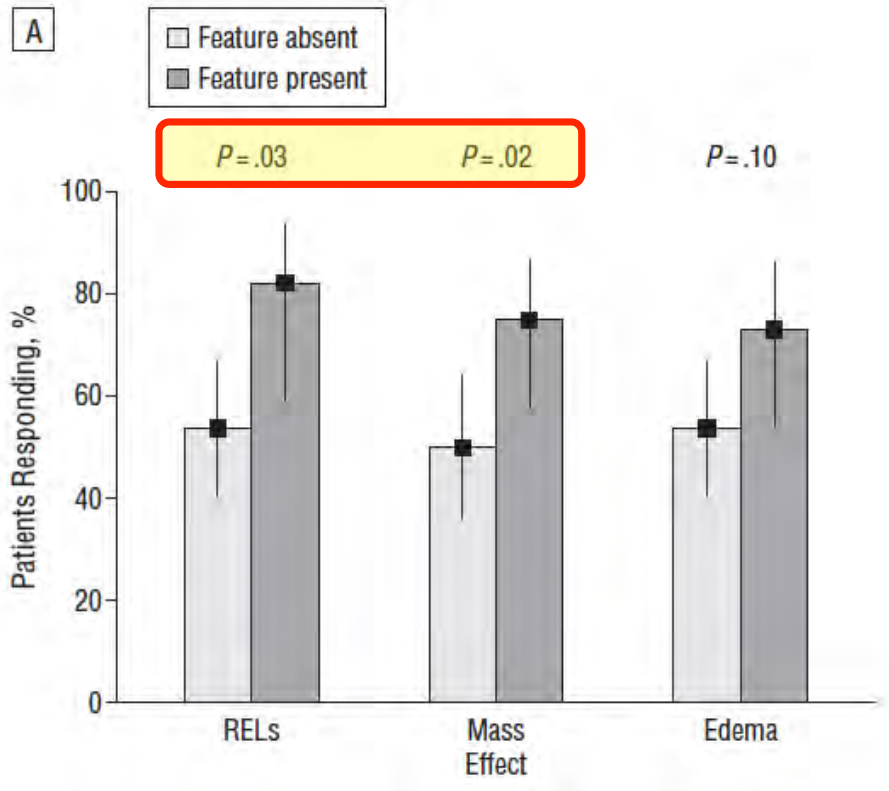
Beneficial Plasma Exchange Response in Central Nervous System Inflammatory Demyelination

Setty M. Magaña, BS; B. Mark Keegan, MD; Brian G. Weinshenker, MD; Bradley J. Erickson, MD, PhD; Sean J. Pittock, MD; Vanda A. Lennon, MD, PhD; Moses Rodriguez, MD; Kristine Thomsen, BA; Stephen Weigand, MS; Jay Mandrekar, PhD; Linda Linbo, RN; Claudia F. Lucchinetti, MD

n=153 patients with acute steroïd-refractory CNS inflammatory demyelinating diseases

Table 3. Unadjusted Logistic Regression Models of Clinical Features Associated With Plasma Exchange Response Among All 153 Patients

Feature	PLEX Response Rate, %	OR (95% CI)	*P* Value
Sex			.68
Female	58	1 [Reference]	
Male	61	1.16 (0.58-2.32)	
Time from index attack to PLEX, d			.89
≤20	60	1 [Reference]	
21-60	60	1.03 (0.51-2.07)	
>60	55	0.81 (0.31-2.14)	
EDSS score at index attack			.98
<8	59	1 [Reference]	
≥8	58	0.99 (0.51-1.94)	
Deep tendon reflexes			.001
Flaccid or absent	31	1 [Reference]	
Brisk or normal	66	4.28 (1.78-10.26)	



REL: ring enhancement lesions

Arch Neurol. Published online March 14, 2011.

Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies

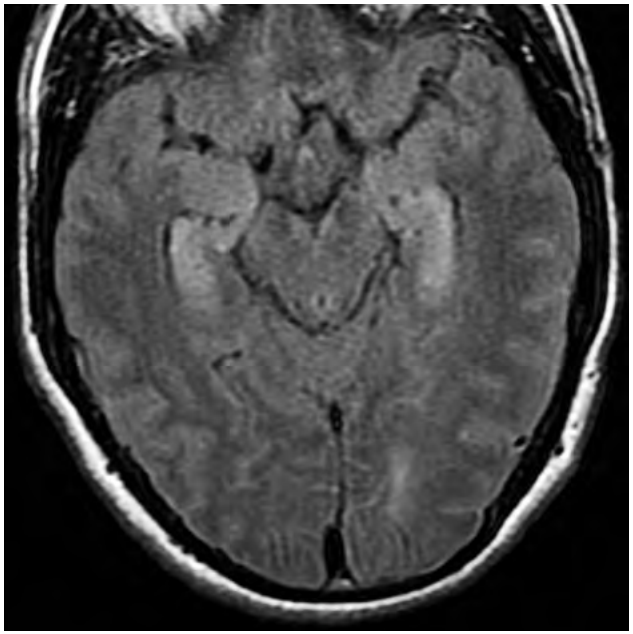
100 patients

	Patients
Women and girls	91
Median age, range (years)	23, 5–76
Prodromal symptoms (information available for 84 patients)	72
Symptom presentation	
Psychiatric (first seen by psychiatrist)	77
Neuropsychiatric (first seen by neurologists)	23
Seizures	
Any type	76
Generalised tonic-clonic	45
Partial complex	10
Other*	30
Dyskinesias and movement disorders	
Any type	86
Orofacial	55
Choreoathetoid and complex movements with extremities, abdomen or pelvis	47
Abnormal postures (dystonic, extension), muscle rigidity, or increased tone	47
Other†	25
Autonomic instability‡	69
Central hypoventilation	66

Dalmau Lancet Neurol 2008

Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies

Findings of 100 pts with encephalitis and NR1-NR2 antibodies

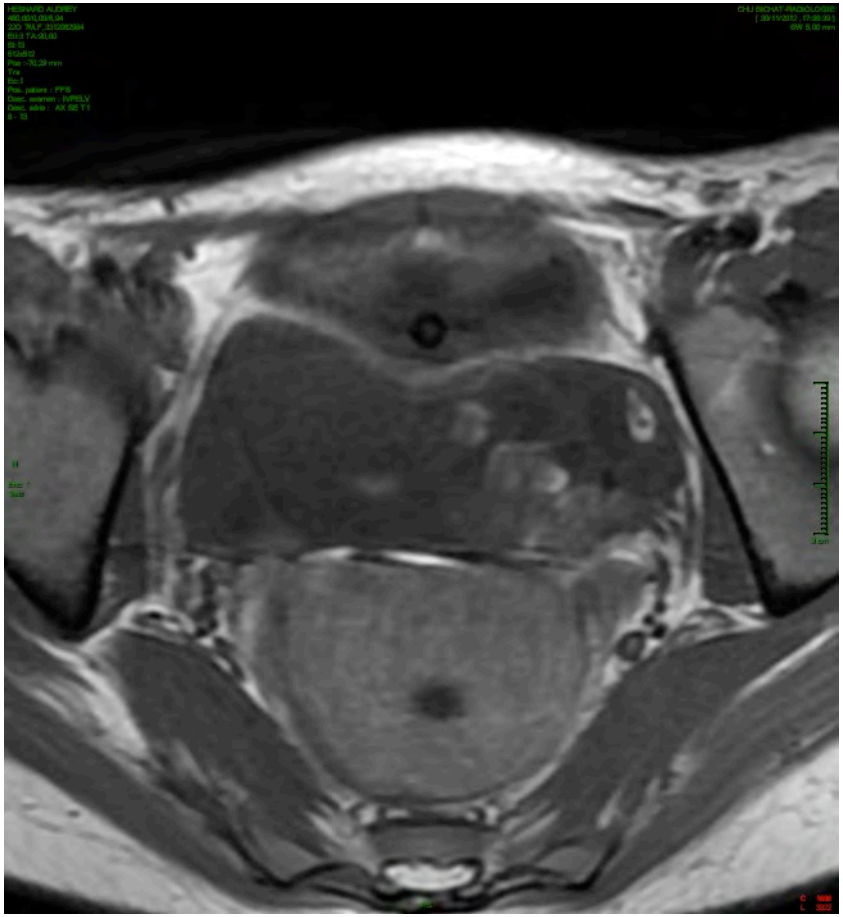


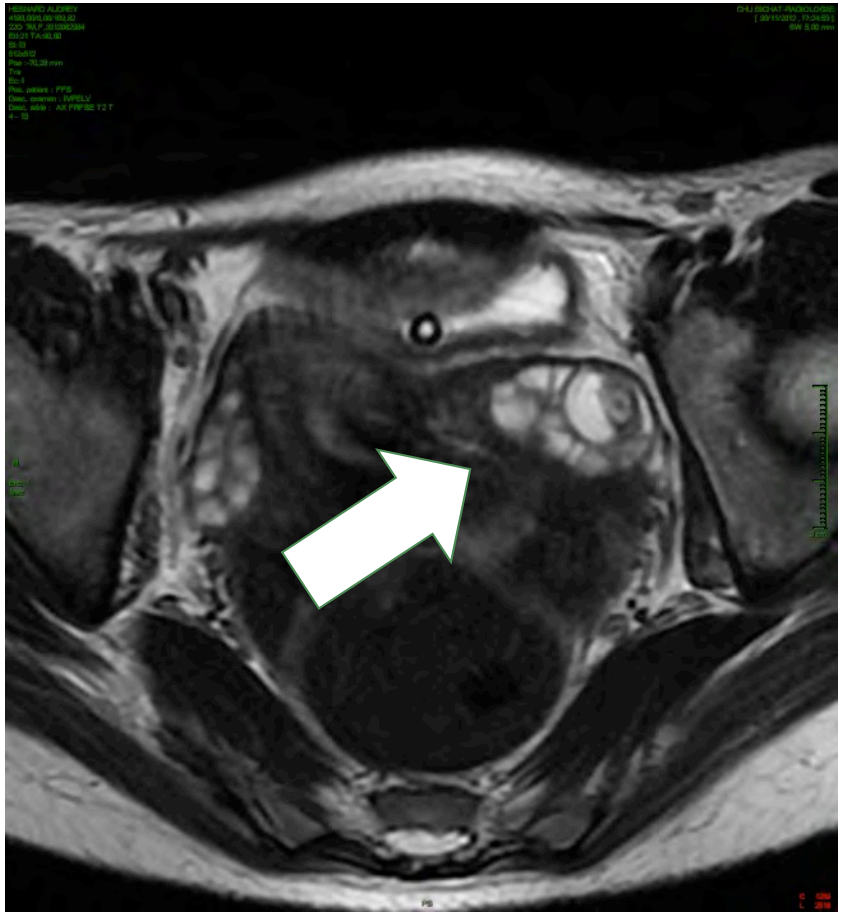
Brain MRI	
Total with abnormal findings	55
Medial temporal lobes	22
Cerebral cortex	17
Cerebellum	6
Brainstem	6
Basal ganglia	5
Contrast enhancement in cortex, meninges, basal ganglia	14
Other†	8

MRI Normal in 45% of patients

Dalmau Lancet Neurol 2008

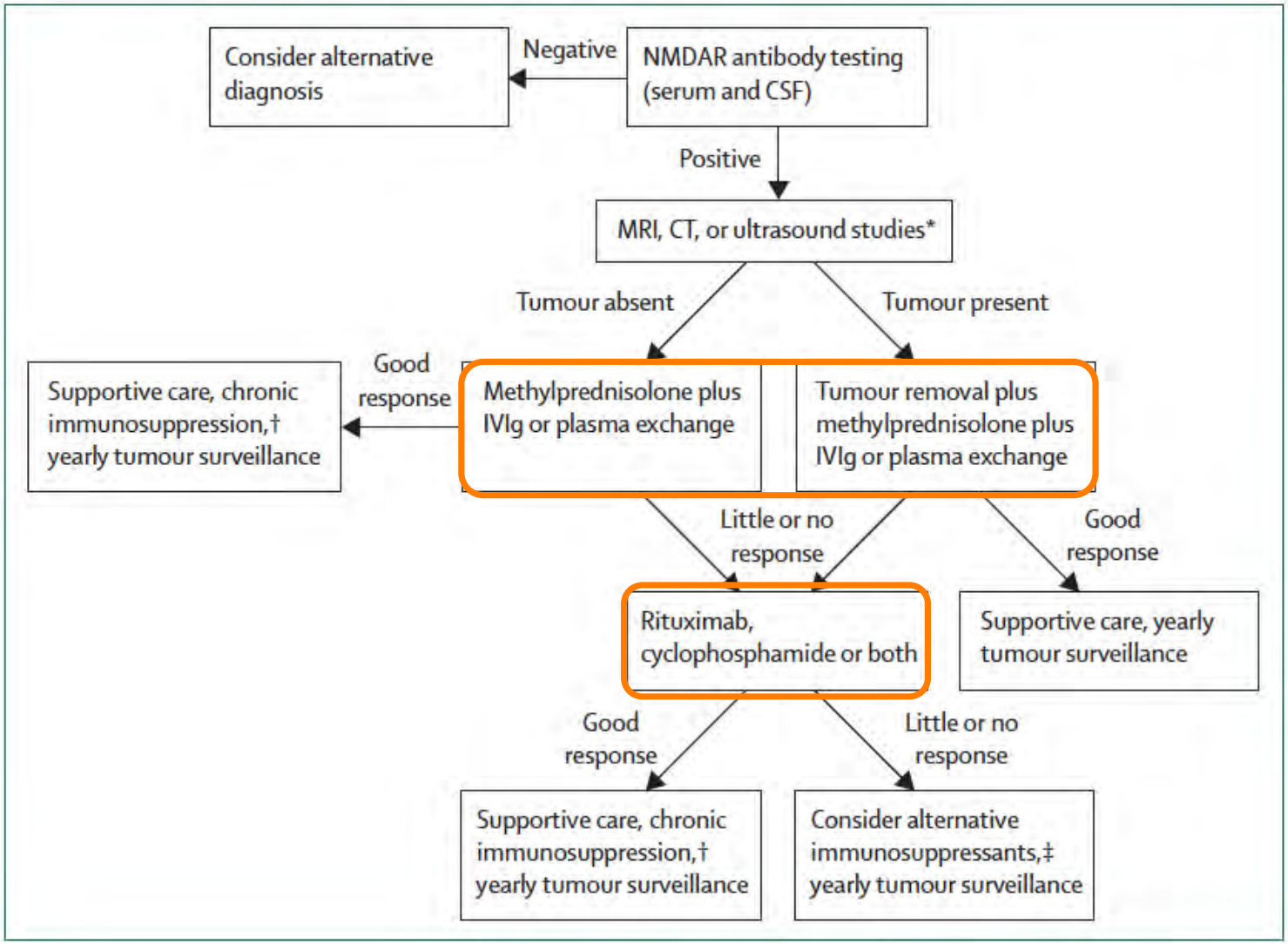
PELVIS MRI





Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis

Josep Dalmau, Eric Lancaster, Eugenia Martinez-Hernandez, Myrna R Rosenfeld, Rita Balice-Gordon



Lancet Neurology 2011

ICU management of acute encephalitis

KEYPOINTS

- Encephalitis patients frequently require ICU admission
- Prognostic factors and the impact of secondary complications on outcome
- Understanding brain dysfunction
- Care in the ICU
  - Cerebral oedema
  - Seizures / status epilepticus
  - Systemic complications
- Specific causes requiring anti-inflammatory therapy
- Conclusions

Conclusions

- Patients with acute encephalitis and altered level of consciousness may benefit from early ICU admission
- Understanding the mechanism of brain dysfunction +++
- Prevention and control of cerebral edema represents a major therapeutic goal
- Other complications that may worsen brain inflammation +++
  - Seizures
  - Systemic complications
    - Fever
    - Hyperglycemia
    - Sepsis

White Light, Jackson Pollock 1954