Acute encephalitis
ICU management

Romain Sonneville, M.D., Ph.D.
Intensive care medicine
Bichat university hospital, Paris, France
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
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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
or inflammation, toxic exposures, or metabolic derangements (table e-1 at Neurology.org/cp). Such conditions need to be aggressively investigated in all patients with suspected encephalitis. Given the range of conditions that cause and mimic encephalitis, obtaining a thorough history is crucial. Important historical points include the presence of recent illness, ill contacts, unusual exposures (including occupational, vector, and animal), outdoor activities, and ingestions. It is critical to elicit travel history, both recent and remote, since agents such as rabies or malaria can become symptomatic long after initial exposure.

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/mm³ |
| | 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

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. Tureen2

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

Infectious Encephalitis in France in 2007: A National Prospective Study

Alexandra Mailles1 and Jean-Paul Stahl,2 on behalf of the Steering Committee and the Investigators Group*  
1Institut de Veille Sanitaire, Saint-Maurice, and 2Infectious Diseases Unit, University Hospital of Grenoble, Grenoble, France

- **2007: 253 patients (adults)**
- **ICU admission 46%**
Epidemiology of acute encephalitis

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Main causes</th>
<th>Unknown cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaser CA 2006</td>
<td>1570</td>
<td>Prospective Multicenter</td>
<td>HSV1, enterovirus, <em>M. pneumoniae</em></td>
<td>63%</td>
</tr>
<tr>
<td>Stahl JP 2009</td>
<td>253</td>
<td>Prospective Multicenter</td>
<td>HSV1, VZV <em>Mycobacterium tuberculosis</em></td>
<td>48%</td>
</tr>
<tr>
<td>Granerod J 2010</td>
<td>203</td>
<td>Prospective Multicenter</td>
<td>HSV1 Immune-mediated</td>
<td>37%</td>
</tr>
<tr>
<td>Thakur KT 2013</td>
<td>103</td>
<td>Retrospective Single center ICU</td>
<td>HSV1, VZV Immune-mediated</td>
<td>47%</td>
</tr>
<tr>
<td>Sonneville R 2014</td>
<td>279</td>
<td>Retrospective Single center ICU</td>
<td>HSV1, VZV, <em>Mycobacterium tuberculosis</em> Immune-mediated</td>
<td>32%</td>
</tr>
</tbody>
</table>
# Acute encephalitis in the ICU

## Causes

<table>
<thead>
<tr>
<th>Causes</th>
<th>N = 279</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIONS</td>
<td>149 (53%)</td>
</tr>
<tr>
<td>TB</td>
<td>65 (23%)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>40 (14%)</td>
</tr>
<tr>
<td>VZV</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Listeria</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>IMMUNE-MEDIATED</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>ADEM</td>
<td>24 (9%)</td>
</tr>
<tr>
<td>Anti-NMDAR</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>89 (32%)</td>
</tr>
</tbody>
</table>

Data are n (%)  

R Sonneville, Eur J Neurol 2014
Temporal trends of encephalitis in the ICU

20%

- Infections
- Immune-mediated
- Undetermined

2002-2012

1991-2001

R Sonneville, Eur J Neurol 2014
ICU management of acute encephalitis

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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
Outcomes 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

IMPACT OF SPECIFIC THERAPY ON OUTCOME

Adverse outcome at 6-month: 84 adults

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS 2 &gt; 27</td>
<td>3.7</td>
<td>1.3-10.6</td>
<td>0.014</td>
</tr>
<tr>
<td>Admission – Acyclovir therapy &gt; 2 days</td>
<td>3.1</td>
<td>1.1-9.1</td>
<td>0.037</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Table 3: Factors associated with good outcome (mRS 0–2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariable analysis</strong></td>
</tr>
<tr>
<td>Stay in intensive care unit</td>
</tr>
<tr>
<td>Time until start of treatment (log$_{10}$)</td>
</tr>
<tr>
<td>Follow-up</td>
</tr>
<tr>
<td>4 months†</td>
</tr>
<tr>
<td>8 months†</td>
</tr>
<tr>
<td>12 months†</td>
</tr>
<tr>
<td>18 months†</td>
</tr>
<tr>
<td>24 months†</td>
</tr>
<tr>
<td>Maximum mRS</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma</td>
<td>5.9</td>
<td>1.8-18.7</td>
</tr>
<tr>
<td>≥ 1 witnessed convulsion</td>
<td>6.3</td>
<td>1.5-26.0</td>
</tr>
<tr>
<td>Herniation syndrome</td>
<td>32.3</td>
<td>9.1-115.4</td>
</tr>
<tr>
<td>Ill for ≥ 7 days</td>
<td>13.0</td>
<td>3.5-48.2</td>
</tr>
</tbody>
</table>

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
# Prognostic factors in encephalitis

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

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

A Venkatesan, Neurology 2012
# Prognostic factors in encephalitis

279 adult patients with all-cause encephalitis
Poor outcome (mRS=4-6): 71 (25%) patients at day 90

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

R Sonneville, Eur J Neurol 2014
Prognostic factors in encephalitis
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

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  Systemic complications

• Specific causes requiring anti-inflammatory therapy

• Conclusions
Acute brain dysfunction in encephalitis

- INCREASED INTRACRANIAL PRESSURE
  - => Decreased CPP
  - => Brain herniation

SECONDARY COMPLICATIONS
- Seizures
- Systemic complications

Brain swelling
- Hemorrhage
- Ischemia
- Inflammation
Acute brain dysfunction in encephalitis

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

DIFFUSE CEREBRAL OEDEMA

BRAIN HERNIATION
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).
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• 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
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

Raised ICP

Cerebral oedema
Relationship between pressure and volume within the cranium

- Child
- Adult
- Elderly
- CSF displacement
- Vascular compression

Cerebral oedema
Early therapeutic goals in the ICU

- Head of the bed elevated > 30 degrees (to facilitate cerebral venous drainage)

- Respiratory care
  - $\text{PaO}_2 > 80\, \text{mmHg, SpO}_2 > 94%$
  - Normocapnia: $\text{PaCO}_2 35-40\, \text{mmHg}$

- Sedation

- Hemodynamics: MAP 70-80 mmHg
If mass effect from significant cerebral edema is noted, hyperosmolar therapy with the use of mannitol or hypertonic saline may be necessary

<table>
<thead>
<tr>
<th>Indication</th>
<th>Typical dosing/administrationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edemaa8</td>
<td>Mannitol 0.25 to 1 g/kg bolus every 4–6 hours</td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline</td>
</tr>
<tr>
<td></td>
<td>Active brain herniation, 23% saline (30 mL bolus via central venous access)</td>
</tr>
<tr>
<td></td>
<td>Maintenance, 2%-3% saline (250–500 mL boluses or continuous venous infusion; 3% saline via central venous access)</td>
</tr>
</tbody>
</table>
The new england journal of medicine

n engl j med

370;22
nejm.org may 29, 2014

2126

and intracranial pressure through multiple mechanisms. In the first minutes of infusion, mannitol and hypertonic saline expand the plasma volume, decrease blood viscosity, and reduce the cerebral blood volume. Once plasma osmolarity increases, a gradient across the blood–brain barrier is established, and water is extracted from the brain. This effect may last for up to several hours, until the osmotic equilibrium is reestablished. The integrity of the blood–brain barrier is a prerequisite for the efficacy of hyperosmolar agents. Mannitol is an osmotic diuretic and may cause dehydration and hypovolemia. Hypertonic saline may cause abrupt increases in the sodium plasma concentration. Comparisons between mannitol and hypertonic saline for the treatment of increased intracranial pressure have not shown a clear superiority of one option over the other.

Induced arterial blood hypocarbia (hyperventilation) reduces intracranial pressure at the expense of decreasing cerebral blood flow as a result of vasoconstriction. Hyperventilation carries a serious risk of cerebral ischemia. For this reason, current guidelines recommend additional monitoring for cerebral ischemia (e.g., by the monitoring of oxygen saturation in the jugular bulb and of brain-tissue oxygenation) when hyperventilation is used.

### Therapy Steps

<table>
<thead>
<tr>
<th>Therapy Steps</th>
<th>Levels of Evidence</th>
<th>Treatment</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not reported</td>
<td>Intubation, Normocarbic ventilation</td>
<td>Coughing, ventilator asynchrony, ventilator-associated pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>Level III</td>
<td>Increased sedation</td>
<td>Hypotension</td>
</tr>
<tr>
<td>3</td>
<td>Not reported</td>
<td>Ventricular CSF drainage</td>
<td>Infection</td>
</tr>
<tr>
<td>4</td>
<td>Level II</td>
<td>Hyperosmolar therapy (mannitol or hypertonic saline)</td>
<td>Negative fluid balance, Hypernatremia, Kidney failure</td>
</tr>
<tr>
<td>5</td>
<td>Level III</td>
<td>Induced hypocapnia</td>
<td>Excessive vasoconstriction and ischemia</td>
</tr>
<tr>
<td>6</td>
<td>Level III</td>
<td>Hypothermia</td>
<td>Fluid and electrolyte disturbances and infection</td>
</tr>
<tr>
<td>7</td>
<td>Level II</td>
<td>Metabolic suppression (barbiturates)</td>
<td>Hypotension and increased number of infections</td>
</tr>
<tr>
<td>8</td>
<td>Not reported</td>
<td>Decompressive craniectomy</td>
<td>Infection or delayed hematoma, Subdural effusion, Hydrocephalus and syndrome of the trephined</td>
</tr>
</tbody>
</table>

**Figure 3. Staircase Approach to the Treatment of Increased Intracranial Pressure.** The level of therapy in patients with raised intracranial pressure is increased step by step, with more aggressive interventions when there is no response. The sequence of interventions may vary among different institutions; every intervention is associated with adverse effects. Shown are the levels of evidence that underpin various approaches to treatment. Levels of evidence are based on the criteria for classification of evidence, as used in international guidelines.

The revised guidelines for the management of severe traumatic brain injury and the surgical guidelines for the management of such injury do not contain any evidence on ventricular drainage of cerebrospinal fluid (CSF) or the use of decompressive craniectomy. Level I evidence shows that decompressive craniectomy is effective in reducing intracranial pressure but may worsen the long-term outcome and is associated with several complications. Among them is the syndrome of the trephined, in which a sunken skull flap develops with a (poorly understood) neurologic deterioration.

N. Stocchetti, New Eng J Med 2014
Intracranial causes of increased intracranial pressure

- Mass lesions (e.g., traumatic hematomas, tumors)
- Edema
- Vasodilatation
- Disturbed central spinal/fluid circulation

At equilibrium:
The sum of the 3 intracranial components (cerebrospinal/fluid + cerebral tissue + blood content) is constant, corresponding to a normal (10–15 mm Hg) intracranial pressure.

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
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
Decompressive craniectomy for encephalitis

Craniektomy:
An aggressive treatment approach in severe encephalitis

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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Good outcome</th>
<th>Poor outcome</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Bacterial</td>
<td>9 (23)</td>
<td>7 (78)</td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>24 (62)</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (15)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

J Perez Bovet, Acta Neurochirurgica 2012
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• 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)
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.
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, PhD2

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

Seizure-induced brain inflammation was evaluated by quantitative immunohistochemical analysis of interleukin (IL)-1β in parenchymal cells.
Anakinra rapidly terminated seizures, prevented their recurrence, and resolved seizure-associated BBB breakdown.

BBB damage was assessed by extravasation of intravascular fluorescein isothiocyanate–albumin.
Seizures in patients with acute encephalitis

290 adult patients with encephalitis  
Bichat medical ICU, Paris, France (1991-2013)  
Factors associated with seizures, multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS &lt; 13</td>
<td>3.2</td>
<td>1.6-6.4</td>
</tr>
<tr>
<td>Cortical involvement on CT</td>
<td>7.0</td>
<td>3.4-14.7</td>
</tr>
<tr>
<td>Cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune-mediated (n=42)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Infectious (n=155)</td>
<td>0.4</td>
<td>0.2-1</td>
</tr>
<tr>
<td>Undetermined (n=93)</td>
<td>1.1</td>
<td>0.4-2.9</td>
</tr>
<tr>
<td>WBC &gt; 10 000 / microL</td>
<td>1.3</td>
<td>0.7-2.5</td>
</tr>
<tr>
<td>CSF &lt; 100 cells / microL</td>
<td>1.6</td>
<td>0.8-2.9</td>
</tr>
<tr>
<td>Natremia</td>
<td>1.0</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>N of organ failure(s)</td>
<td>1.1</td>
<td>0.7-1.8</td>
</tr>
</tbody>
</table>
Seizures in patients with acute encephalitis

<table>
<thead>
<tr>
<th>Seizures and status epilepticus&lt;sup&gt;12&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line, initial dosing</strong></td>
</tr>
<tr>
<td>Lorazepam 0.1 mg/kg IV up to 4 mg per dose</td>
</tr>
<tr>
<td>Midazolam 0.25 mg/kg IM up to 10 mg maximum</td>
</tr>
<tr>
<td>Diazepam 0.15 mg/kg IV up to 10 mg per dose</td>
</tr>
<tr>
<td><strong>Second line, initial dosing</strong></td>
</tr>
<tr>
<td>Fosphenytoin 20 mg PE/kg IV</td>
</tr>
<tr>
<td>Levetiracetam 1,000–3,000 mg IV</td>
</tr>
<tr>
<td>Valproate sodium, 20–40 mg/kg IV</td>
</tr>
<tr>
<td><strong>Third line, loading dose</strong></td>
</tr>
<tr>
<td>Propofol 1–2 mg/kg</td>
</tr>
<tr>
<td>Phenobarbital 20 mg/kg IV</td>
</tr>
<tr>
<td>Pentobarbital 5–15 mg/kg IV</td>
</tr>
</tbody>
</table>

- There is little evidence to guide the AED choice as 2<sup>nd</sup>-line therapy.
- Patients who do not respond to 2<sup>nd</sup> 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

<table>
<thead>
<tr>
<th></th>
<th>SRSE n = 31</th>
<th>RSE n = 116</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years¹</td>
<td>48 (+/−20)</td>
<td>61 (+/−17)</td>
<td>0.96 (0.94, 0.98)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>17 (55)</td>
<td>78 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (48)</td>
<td>52 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non white</td>
<td>16 (52)</td>
<td>64 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of epilepsy, n (%)</td>
<td>8 (26)</td>
<td>38 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>16 (52)</td>
<td>70 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>12 (35)</td>
<td>13 (11)</td>
<td>4.35 (1.7, 11.09)</td>
<td>0.002²</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1 (3)</td>
<td>31 (27)</td>
<td>0.09 (0.011, 0.69)</td>
<td>0.021</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3)</td>
<td>4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic-metabolic</td>
<td>1 (3)</td>
<td>11 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>1 (3)</td>
<td>11 (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pugin et al. Critical Care 2014, 18:R103 Page 3 of 7

http://ccforum.com/content/18/3/R103

Single center, retrospective study
147 patients with refractory status epilepticus
NYC, Columbia, USA

Risk factors for super refractory status epilepticus

Multivariate analysis
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 PLED qui prédominent dans la région temporaire 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.
42 patients with primary CNS infection  
Electrographic seizures: 14 (33%)  
PEDs: 17 (40%)

<table>
<thead>
<tr>
<th>PREDICTORS OF OUTCOME</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stupor or coma</td>
<td>5.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Electrographic seizures, n (%)</td>
<td>5.9</td>
<td>0.02</td>
</tr>
<tr>
<td>PEDs (periodic epileptiform discharges)</td>
<td>6.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

E Carrera, Arch Neurol 2008
Generalized periodic discharges in the critically ill
A case-control study of 200 patients

- A prior study documented 64.0% mortality, with GPDs vs controls (patients with first seizure/total patients consecutively monitored on cEEG).
- CSE (A) Comparison of seizure occurrence at any time in patients with GPDs vs controls (%).
- B) Comparison of seizures during study.
- Overall in-hospital mortality for GPD patients.
- Generalized periodic discharges were strongly associated with nonconvulsive seizures.
- Conclusion:
- Results:
- Methods:
- Generalized periodic discharges in the critically ill patients are increasingly recognized on continuous EEG monitoring; their relationship to seizures and prognosis remains unclear.
- A total of 46% of patients with generalized periodic discharges had a seizure during their study.
- Excluding those, 46.7% of patients as ours (18.9%), it included 7 with burst-suppression patterns, which we excluded. Burst-suppression is associated with poor outcome, especially after CA, and all 7 patients died. Excluding those, 14.5% in our study.
- Multivariate predictors of worse outcome were cardiac arrest, coma, nonconvulsive status epilepticus, and seizures. Generalized periodic discharges were not after matching for age, etiology, and level of consciousness.
- Underlying pathophysiology and clinical significance remain unclear. Reports have correlated generalized periodic discharges with destructive focal lesions, usually acute, and seizures. Generalized periodic discharges had nonconvulsive status epilepticus, vs 7% of controls.
- Lateralized periodic epileptiform discharges (also known as periodic lateralized epileptiform discharges [PLEDs]) have been seen in a third of both groups.
- A total of 27% of patients with generalized periodic discharges had a convulsive status epilepticus, 11% had nonconvulsive status epilepticus, and 14% had convulsive seizures.
- Excluding those, 46% of patients with generalized periodic discharges had a seizure during their study.
- Multivariate predictors of worse outcome were cardiac arrest, coma, nonconvulsive status epilepticus, and seizures.
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
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. Durby · David O. Okonkwo

![Graphs showing temperature and intracranial pressure comparisons between control and induced normothermia groups.](image-url)
Acute Illness

Pre-existing abnormal glucose metabolism

Increased immune response (TNFα, IL1, IL6)

Generalized stress reaction
  - Stimulation HPA axis
  - Catecholamines
  - Cortisol
  - Glucagon

Insulin resistance

Hyperglycemia

I.V. glucose load
Steroids
Parenteral nutrition...

Glycogenolysis
Gluconeogenesis

Hyperglycemia in critical illness
Mouse model of polymicrobial sepsis

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

CAECAL LIGATION AND PUNCTURE

HYPERGLYCEMIA > 150 mg/dL
Broad spectrum antibiotics
IV fluid resuscitation
NORMOGLYCEMIA 80-110 mg/dL

Sacrifice day 5

HIPPOCAMPUS
FRONTAL CORTEX
Glucose and neuronal damage

Neuronal damage (normalized for controls)

**HIPPOCAMPUS**

- Control
- Moderate hyperglycemia
- Normoglycemia

**FRONTAL CORTEX**

- Control
- Moderate hyperglycemia
- Normoglycemia

*Significance levels (p-values)*:
- **HIPPOCAMPUS**: p=0.06, p=0.13, p=0.29
- **FRONTAL CORTEX**: p=0.04, p=0.01, p=0.29

*Note*: For glucose and neuronal damage, p=0.29.
Blood glucose and microglial activation

**Microglia density (normalized for controls)**

**HIPPOCAMPUS**
- Control
- Moderate hyperglycemia
- Normoglycemia

**FRONTAL CORTEX**
- Control
- Moderate hyperglycemia
- Normoglycemia

$p=0.002$  
$p=0.004$  
$p=0.11$  
$p=0.0008$  
$p=0.52$  
$p=0.0008$  
$p=0.0006$  
$p=0.02$
Early microglial changes during sepsis

SEPSIS MODEL (Peritonitis, CLP)
Severe clinical phenotype
Multiple caecal punctures
No antibiotics
Subcutaneous rehydration

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

SACRIFICE AT 6, 12 or 24 H
NEURONAL DAMAGE

Hippocampus
Frontal Cortex
Microglial changes in sepsis

A. CONTROL

GFP Laminin

B. SHAM 24 HOURS

C. SEPSIS 24 HOURS

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 /mm³ (79% polynuclear cells), Protein levels 1,72 g/l,
     normal glucose levels – Negative direct examination

⇒ intubation / MV
⇒ IV cefotaxime
⇒ IV amoxicillin – gentamicine
⇒ IV aciclovir
Acute disseminated encephalomyelitis (ADEM)
**Pathophysioloogy**

**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 demyelination

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

NP Young, Brain 2010
"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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37 (27–51)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Preceding infectious disease, n (%)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Latency period, days</td>
<td>8 (6–14)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>53 (15–45)</td>
</tr>
<tr>
<td>MV, n (%)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>39 (38–39)</td>
</tr>
<tr>
<td>Neck stiffness, n (%)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>GCS</td>
<td>7 (4–13)</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Motor deficit, n (%)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Spinal cord symptoms, n (%)</td>
<td>11 (55)</td>
</tr>
</tbody>
</table>

R Sonneville, Intensive Care Med 2007
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.
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 steroid-refractory CNS inflammatory demyelinating diseases

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

<table>
<thead>
<tr>
<th>Symptom presentation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric (first seen by psychiatrist)</td>
<td>77</td>
</tr>
<tr>
<td>Neuropsychiatric (first seen by neurologists)</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seizures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type</td>
<td>76</td>
</tr>
<tr>
<td>Generalised tonic-clonic</td>
<td>45</td>
</tr>
<tr>
<td>Partial complex</td>
<td>10</td>
</tr>
<tr>
<td>Other*</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dyskinesias and movement disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type</td>
<td>86</td>
</tr>
<tr>
<td>Orofacial</td>
<td>55</td>
</tr>
<tr>
<td>Choreoathetoid and complex movements with extremities, abdomen or pelvis</td>
<td>47</td>
</tr>
<tr>
<td>Abnormal postures (dystonic, extension), muscle rigidity, or increased tone</td>
<td>47</td>
</tr>
<tr>
<td>Other†</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autonomic instability‡</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Central hypoventilation</td>
<td>66</td>
</tr>
</tbody>
</table>

Dalmau Lancet Neurol 2008
### Table 1: Clinical Information

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, low-grade fever, or non-specific viral-like illness within 2 weeks before hospital admission</td>
<td>86 patients</td>
</tr>
<tr>
<td>Prominent psychiatric symptoms, including anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts, and visual or auditory hallucinations</td>
<td>77 patients</td>
</tr>
<tr>
<td>Short-term memory loss or seizures alone or associated with psychiatric manifestations</td>
<td>23 patients</td>
</tr>
</tbody>
</table>

### Results

- **Table 1 summarises the clinical information.** 86 patients who could be assessed had headache, low-grade fever, or a non-specific viral-like illness within 2 weeks before hospital admission. 77 patients presented with prominent psychiatric symptoms, including anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts, and visual or auditory hallucinations. 23 patients presented with short-term memory loss or seizures alone or associated with psychiatric manifestations.

- **During the first 3 weeks of symptom presentation, 76 patients had seizures.** 88 patients developed decreased consciousness, progressing to a catatonic-like state, with periods of akinesis alternating with agitation, and diminished or paradoxical responses to stimuli (eg, no response to pain but resisting eye opening). Some patients mumbled unintelligible words or had echolalia. Eye contact or visual tracking was absent or inconsistent. During this clinical stage, large proportions of patients developed dyskinesias, autonomic instability, and central hypoventilation (median time of ventilatory support, 8 weeks; range 2–40 weeks).

- **Orofacial dyskinesias were the most common.** These included grimacing, masticatory-like movements, and forceful jaw opening and closing, resulting in lip and tongue injuries or broken teeth. 37 patients had cardiac dysrhythmias, including tachycardia or bradycardia, with prolonged pauses in seven patients; four needed pacemakers. 52 patients had dyskinesias.

### Table 2: Characteristics and Clinical Features

<table>
<thead>
<tr>
<th>Test</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG (information for 92 patients)</td>
<td>55</td>
</tr>
<tr>
<td>Total with abnormal findings</td>
<td>92</td>
</tr>
<tr>
<td>Slow activity*</td>
<td>71</td>
</tr>
<tr>
<td>Epileptic activity</td>
<td>21</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>55</td>
</tr>
<tr>
<td>Total with abnormal findings</td>
<td>92</td>
</tr>
<tr>
<td>Medial temporal lobes</td>
<td>22</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>17</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>6</td>
</tr>
<tr>
<td>Brainstem</td>
<td>6</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>5</td>
</tr>
<tr>
<td>Contrast enhancement in cortex, meninges, basal ganglia</td>
<td>14</td>
</tr>
<tr>
<td>Other†</td>
<td>8</td>
</tr>
<tr>
<td>CSF</td>
<td>95</td>
</tr>
<tr>
<td>Total with abnormal findings</td>
<td>92</td>
</tr>
<tr>
<td>Lymphocytic pleocytosis‡</td>
<td>91</td>
</tr>
<tr>
<td>Increased protein concentration§</td>
<td>32</td>
</tr>
<tr>
<td>Oligoclonal bands positive (information for 39 patients)</td>
<td>26</td>
</tr>
<tr>
<td>Tumour (information for 98 patients)</td>
<td>58</td>
</tr>
<tr>
<td>All</td>
<td>58</td>
</tr>
<tr>
<td>Women</td>
<td>35</td>
</tr>
<tr>
<td>Mature teratoma of the ovary</td>
<td>35</td>
</tr>
<tr>
<td>Immature teratoma of the ovary</td>
<td>14</td>
</tr>
<tr>
<td>Radiologically demonstrated teratoma</td>
<td>4</td>
</tr>
<tr>
<td>Other‡</td>
<td>3</td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td>Immature teratoma of the testis</td>
<td>1</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Treatment</td>
<td>100</td>
</tr>
<tr>
<td>Tumour resection</td>
<td>51</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>92</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>76</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>62</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>34</td>
</tr>
<tr>
<td>Rituximab</td>
<td>10</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Only supportive care</td>
<td>2</td>
</tr>
</tbody>
</table>

*EEG delta or theta activity, generalized or in frontotemporal regions.
†Other areas of abnormal signal in MRI FLAIR/T2: four corpus callosum, two hypothalamus, one periventricular, one multifocal white-matter change.
‡Median 32 cells/μL, range 5–480 cells/μL.
§Median 67 mg/dL, range 49–213 mg/dL.
¶One sex-cord stromal tumour, one neuroendocrine tumour, one teratoma of the mediastinum.
||Seven chemotherapy, three electroconvulsive therapy.

**MRI Normal in 45% of patients**

Dalmau Lancet Neurol 2008
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