Status epileptikus

Ur ett intensivvårdsperspektiv

Läkemedelsbehandling av epilepsi – behandlingsrekommendation

INFORMATION FRÅN LÄKEMEDELSVERKET 3:2019

Anfallsbrytande behandling och behandling av status epilepticus

Status epilepticus (SE) är ett tillstånd med långvariga eller tätt återkommande epileptiska anfall, som kan innebära en risk för negativa långtidseffekter. Den allvarligaste formen är konvulsivt (tonisk-kloniskt) SE, som fordrar akut behandling för att minska en hög risk för allvarliga systemkomplikationer. Konvulsivt SE kännetecknas av långvariga eller upprepade tonisk-kloniska anfall (med fokal, generaliserad eller okänd start) under fem minuter eller mer. Det är viktigt att behandla konvulsivt SE tidigt i förloppet och med tillräckligt höga läkemedelsdoser, eftersom tillståndet är svårare att bryta ju längre det varar. I allmänhet rekommenderas att man inleder behandling när ett anfall pågått i fem minuter.

Tidigt
Etablerat
Refraktärt
status EP

Tabell V. Läkemedelsalternativ vid tidigt konvulsivt SE.
Läkemedlen listas i bokstavsordning med föreslagna doser för barn och vuxna.

Förstahandsval vid SE		
Läkemedel	**Administrationssätt**	**Föreslagen dos**
Diazepam	Intravenöst	0,15–0,25 mg/kg upp till 10 mg totalt (kan upprepas en gång vid utebliven effekt)
Lorazepam	Intravenöst	0,07–0,10 mg/kg upp till 4 mg totalt (kan upprepas en gång vid utebliven effekt)
Midazolam	Intravenöst	0,20 mg/kg upp till 7,5 mg totalt
Midazolam	Intramuskulärt	0,20 mg/kg upp till 10 mg totalt
Andrahandsval vid SE*		
Läkemedel	**Administrationssätt**	**Föreslagen dos**
Midazolam	Buckalt	0,3 mg/kg upp till 10 mg totalt
Midazolam	Nasalt	0,3 mg/kg upp till 7,5 mg totalt
Diazepam	Rektalt (klysma)	0,2–0,5 mg/kg upp till 20 mg totalt

*Används särskilt prehospitalt och som inledande behandling vid svårigheter att etablera venös infart.

Tabell VI. Läkemedelsalternativ vid etablerat konvulsivt SE.
Läkemedlen listas i bokstavsordning med föreslagna doser för barn och vuxna.

Läkemedel	Administrationssätt	Föreslagen dos
Fenobarbital*	Intravenöst	15–20 mg/kg upp till 1 000 mg
Fosfenytoin	Intravenöst	15–20 mg FE/kg upp till 1 500 mg FE (Fosfenytoindos anges som fenytoinnatriumekvivalenter, FE)
Levetiracetam	Intravenöst	30–60 mg/kg upp till 4 500 mg
Valproat	Intravenöst	20–40 mg/kg upp till 3 000 mg

*Fenobarbital används i svensk praxis huvudsakligen för yngre barn.

Var sker oftast denna behandling?
Är intensivvården inblandad?

Refraktär status epilepticus

- Kräver intensivvård
  - Varför?

Läkemedelsbehov leder till;

- Övervakning av vitalparametrar
- Behov av respirator
- Risk för behov av blodtryckshöjande LM
- Behov av nutrition
- Behov av frekvent provtagning och övervakning
- Övervakning med kontinuerligt EEG

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SUPPLEMENT ARTICLE

Epilepsia

Anesthetic drugs for the treatment of status epilepticus

Sara Hocker

Hocker S. Anesthetic drugs for the treatment of status epilepticus. *Epilepsia*. 2018;00:1–5. https://doi.org/10.1111/epi.14498

Tidig behandling ger bättre behandlingssvar och bättre outcome

intravenous anesthetic drug (CIVAD). Current guidelines support the use of anesthetic drugs as the third line pharmacologic therapy in generalized convulsive SE (GCSE) but differ in the strength of their recommendations.[5-7] The European Federation of Neurologic Societies guideline advises that anesthesia be postponed in favor of further nonanesthetizing antiseizure drugs in complex partial SE (now focal nonconvulsive SE [NCSE] with impaired consciousness)[5] but do not address the indications for anesthesia in focal and nonconvulsive forms.

När?

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Först när ingenting annat fungerar - det finns risker

Efter första och andrahandspreparat…

- Tillägg av droger som ännu inte använts till patienten (valproat, fosfenytoin, levetiracetam, lacosamid, eller fenobarbital
- Kontinuerligt intravenöst anestesiläkemedel (CIVAD)

TABLE 1 Proposed indications for initiation of CIVADs

SE Type	Indication for initiation of a CIVAD	Other considerations
GCSE	Failure of a benzodiazepine[a] + 1 additional antiseizure drug[a]	Priority is rapid seizure control utilizing anesthetics if needed
NCSE in coma	Failure of a benzodiazepine[a] + 2 additional antiseizure drugs[a]	Consider certainty regarding EEG pattern and clinical history; discontinuation of potential drug triggers and correction of metabolic derangements should be attempted before initiation of a CIVAD
Focal motor or focal NCSE (with consciousness impairment)	Failure of a benzodiazepine[a] + ≥2 additional antiseizure drugs[a]	Consider IV phenobarbital loading prior to initiation of a CIVAD
Epilepsia partialis continua	Consider in patients with a good prognosis if functionally limiting or painful and refractory to a benzodiazepine[a] + ≥2 additional antiseizure drugs[a]	Rarely indicated
Absence status epilepticus	Not indicated	

CIVAD, continuous intravenous anesthetic drug; EEG, electroencephalographic; GCSE, generalized convulsive status epilepticus; IV, intravenous; NCSE, nonconvulsive status epilepticus; SE, status epilepticus.

[a]Dosed according to published guidelines.

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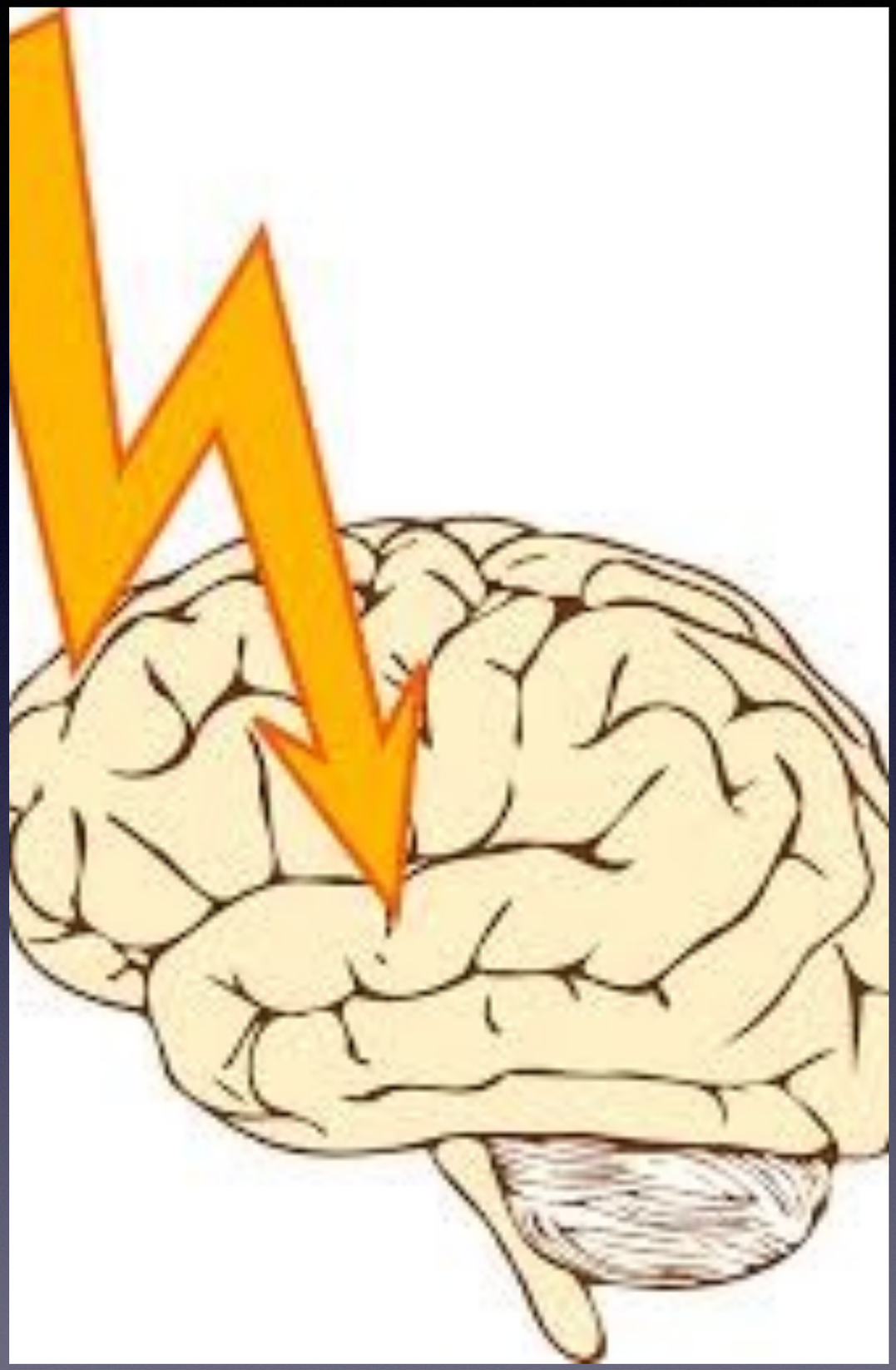
Balans mellan risk och nytta



Furthermore, anesthetics are very effective antiseizure drugs. Initiation of a CIVAD may avoid worsening pharmacoresistance to antiseizure drugs and limit both excitotoxic neuronal injury and systemic complications while allowing time for treatment targeting the cause of the seizures. Conversely, anesthetic use has been consistently

zures. Conversely, anesthetic use has been consistently associated with longer hospital lengths of stay, death, and worse functional outcomes,[8-10] and evidence supporting their use is limited. All CIVADs cause respiratory depression, which must be managed with endotracheal intubation for airway protection and mechanical ventilation. They all cause some degree of hypotension, which must be managed with vasopressors, involving their inherent risks. The

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Tabell VII. Läkemedelsalternativ vid intensivvårdsbehandling av refraktärt konvulsivt SE.
Läkemedlen listas i bokstavsordning med föreslagna doser för barn och vuxna.

Läkemedel	Administrationssätt	Förslag till inledande dosering
Midazolam	Intravenöst	Bolusdos 0,2 mg/kg följt av infusion 0,05–0,4 mg/kg/tim
Propofol	Intravenöst	Bolusdos 2 mg/kg följt av infusion 1–3 mg/kg/tim
Tiopental	Intravenöst	Bolusdos 2–3 mg/kg följt av infusion 2–5 mg/kg/tim

Midazolam

Midazolam	Enhance of GABAA transmission

- Ackumulering (obesitas, njursvikt)
- Tachyfylaxi

Tachyphylaxis, accumulation in renal insufficiency

Barbiturates, propofol and midazolam are commonly used in refractory SE [41] but it is extremely difficult to achieve bust suppressions with midazolam (Class IV).

Propofol

Enhance of GABAA transmission, sodium channel blockade

- Risk för propofol infusion syndrome
- Hypotension vanligt

in patients with heart failure. The propofol infusion syndrome (PRIS) causes lactic acidosis, rhabdomyolysis, lipemia, hyperkalemia, renal failure, and rapid cardiovascular collapse.

Propofol infusion syndrome, cardiorespiratory depression, bradyarrhythmia

Seizure-like phenomena and propofol

A systematic review

Bernhard Walder, MD; Martin R. Tramèr, MD, DPhil; and Margitta Seeck, MD

NEUROLOGY 2002;58:1327–1332

There is evidence that SLP may happen in patients with and without epilepsy receiving propofol. The time point of the occurrence of SLP (mainly during induction and emergence or delayed; almost never during maintenance) suggests that a change in the cerebral concentration of propofol may be causal.

Thiopental

Potentiation of GABAA transmission, AMPA receptor blockade

- Ackumulering
- Hypotension - behov av vasopressorer
- Paralytisk ileus
- Ökad risk för pneumoni
- Risk för leverpåverkan

Significant accumulation, cardiorespiratory depression, paralytic ileus, infection, megaloblastic anemia, hepatotoxicity, Stevens–Johnson syndrome

vid längre tids användning. Tiopental bör betraktas som ett andrahandsval för de flesta patienter med hänsyn till komplicerad farmakokinetik och hög komplikationsrisk vid långtidsanvändning.

Cochrane Library

Cochrane Database of Systematic Reviews

Propofol versus thiopental sodium for the treatment of refractory status epilepticus (Review)
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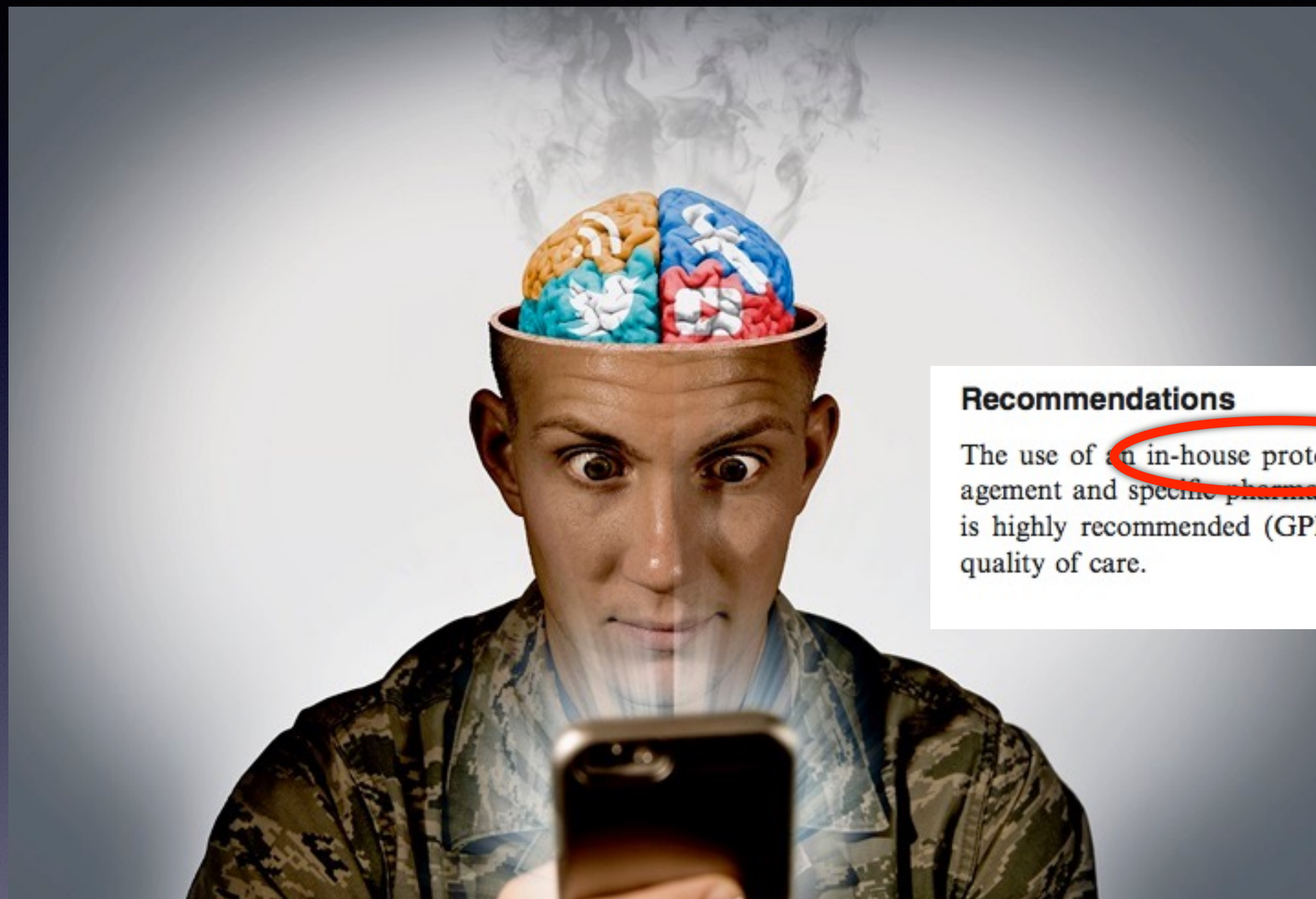
Propofol versus thiopental sodium for the treatment of refractory status epilepticus (Review)

Prabhakar H, Kalaivani M

Key results: There was no difference between the two drugs in their ability to control seizure activity. The only difference noted was the requirement for prolonged mechanical ventilation for patients in the thiopental sodium group. This could be due to the prolonged presence of the drug in the body due to its slow removal.

There is a lack of robust, randomised, controlled evidence to clarify the efficacy of propofol and thiopental sodium compared to each other in the treatment of RSE. There is a need for large RCTs for this serious condition.



Recommendations

The use of an in-house protocol for the general management and specific pharmacological treatment of SE is highly recommended (GPP) to provide the highest quality of care.

After initiation of a CIVAD, it is standard practice to target electrographic seizure control or burst suppression for 24-48 hours prior to a gradual withdrawal of the CIVAD.[6] Limited evidence suggests that EEG back-

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Behandla så länge som nödvändigt, men så kort tid som möjligt…

Säkerställ adekvat underhållsbehandling med antiepileptika och behandling av bakomliggande orsaker. Därefter, vanligen efter 12–24 timmars EEG-mässig anfallsfrihet, trappas narkosbehandlingen ut.

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Andra behandlingar?

Hypotermi

Hypothermia has been used as an adjunct to pharmacologic therapies in SE. Recently, the Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsivant Action after Convulsive Status Epilepticus (HYBERNATUS) trial found no benefit from hypothermia in patients with SE, with a higher incidence aspiration pneumonia (51 vs 45%) and ICU-acquired weakness, with a slightly lower incidence serious adverse events in the hypothermia group [72••]. It is unknown whether therapeutic normothermia, still believed to be important in nearly all acute neurologic emergencies, has a similar adverse effect profile.

Current Neurology and Neuroscience Reports (2018) 18: 7 https://doi.org/10.1007/s11910-018-0815-9

Andra behandlingar?

Ketogen kost

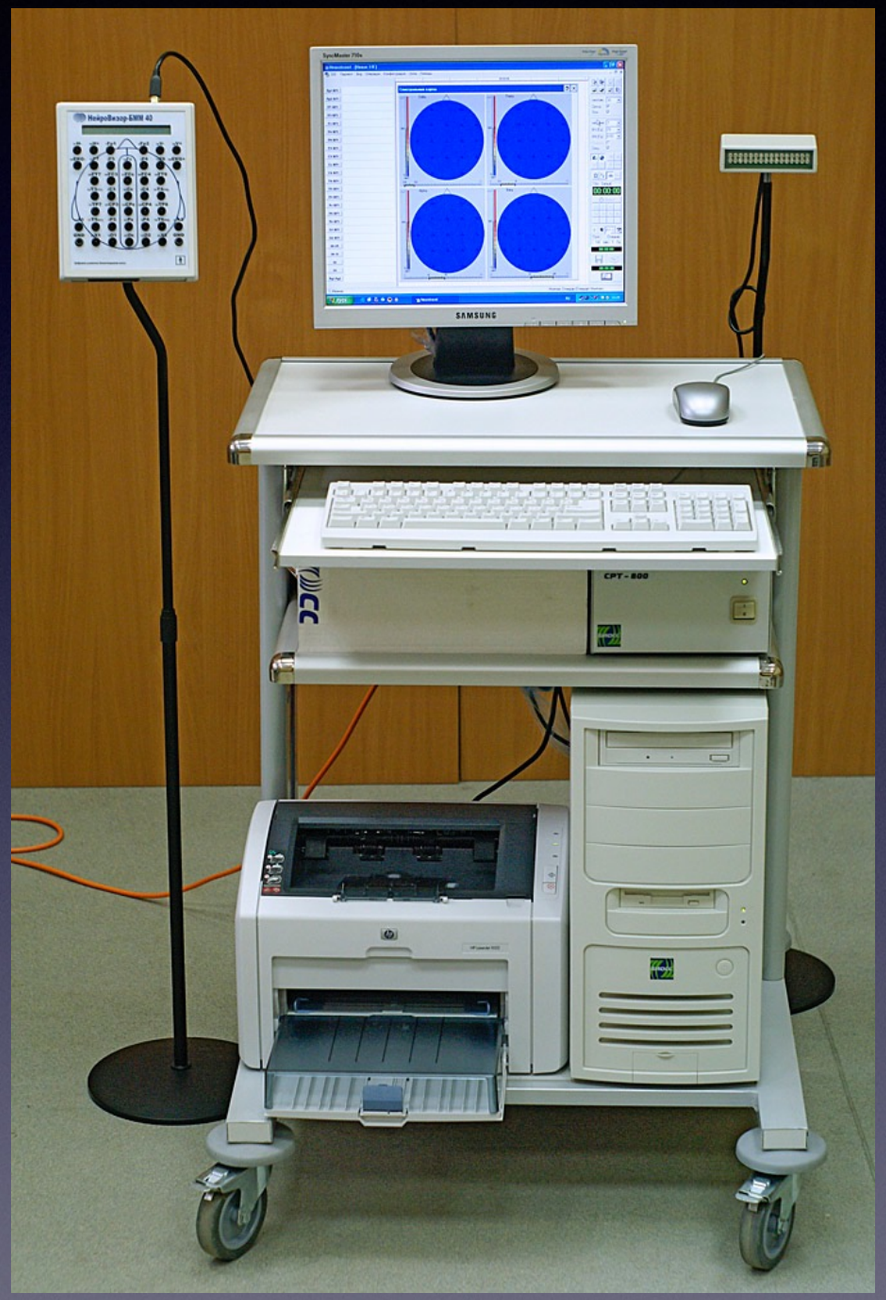
5. Conclusions

Ketogenic diets offer an increasingly needed adjunct to anti-epileptic drugs for management of chronic epilepsy and refractory status epilepticus in adults. Studies support feasibility, tolerability, and efficacy of the classic ketogenic diet and its variants in adults, although randomized control trials are needed. Potential complications and side effects of diet therapy are often preventable and manageable, nevertheless strategies are needed to improve adherence.

Clinical Neurophysiology Practice 2 (2017) 154–160

Ketogenic diet has shown promising results in adults with SRSE according to a recent phase II clinical trial [73••]. The

Current Neurology and Neuroscience Reports (2018) 18: 7 https://doi.org/10.1007/s11910-018-0815-9



EEG

Intensive Care Med (2013) 39:1337–1351
DOI 10.1007/s00134-013-2938-4

SYSTEMATIC REVIEW

Jan Claassen
Fabio S. Taccone
Peter Horn
Martin Holtkamp
Nino Stocchetti
Mauro Oddo

Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM

Recommendations for patients with convulsive SE

1. We recommend urgent EEG in patients with SE that do not return to functional baseline within 60 min after administration of seizure medication (strong recommendation, low quality of evidence—grade 1C).

Recommendations for patients with refractory SE

1. We recommend urgent (within 60 min) EEG in patients with RSE (strong recommendation, low quality of evidence—grade 1C).

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SYSTEMATIC REVIEW

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Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM

Recommendations for continuous EEG over intermittent EEG monitoring

1. We recommend cEEG for seizure detection in patients with RSE (strong recommendation, low quality of evidence—grade 1C).
2. We suggest cEEG for seizure detection in patients with SE that do not return to functional baseline within 60 min after administration of seizure medication

European Journal of Neurology 2010, **17:** 348–355 doi:10.1111/j.1468-1331.2009.02917.x

EFNS GUIDELINES/CME ARTICLE

EFNS guideline on the management of status epilepticus in adults

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Most authorities recommend administration of anaesthetic agents to a depth of anaesthesia which produces a burst suppression pattern in the EEG [41] (Class IV) or an isoelectric EEG [49]. Studies are needed in this area, as these issues give rise to ethically highly problematic decisions.

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”EEG-övervakning behövs för att säkerställa anfallsfrihet och övervaka sövningsdjup”

Förväntade komplikationer

Current Neurology and Neuroscience Reports (2018) 18: 7
https://doi.org/10.1007/s11910-018-0815-9

NEUROLOGY OF SYSTEMIC DISEASES (J BILLER, SECTION EDITOR)

CrossMark

Systemic Complications Following Status Epilepticus

Maximiliano A. Hawkes[1] · Sara E. Hocker[1]

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Summary Most systemic complications after SE are predictable. Anticipating their occurrence and respecting a number of simple guidelines may improve the prognosis of these patients.

Skilj på tidiga och sena komplikationer

drugs [6, 7, 8••, 9, 10]. While most early complications of SE are a consequence of catecholaminergic release [11], sustained muscle contraction, and mechanical injury, side effects of antiseizure medications and prolonged immobility are major contributors later on in the course of SE. Hence, optimal management of this condition relies on the anticipation of medical complications and side effect of medical therapies.

drugs [6, 7, 8••, 9, 10]. While most early complications of SE are a consequence of catecholaminergic release [11], sustained muscle contraction, and mechanical injury, side effects of antiseizure medications and prolonged immobility are major contributors later on in the course of SE. Hence, optimal management of this condition relies on the anticipation of medical complications and side effect of medical therapies.

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Tidiga komplikationer, cirkulation

- Frisättning av katekolaminer ger
  - högt BT
  - hög puls
  - ökad risk för arytmier
  - ökning av cerebralt blodflöde och förhöjt ICP

…fler tidiga komplikationer, metabolism

- Hyperglykemi
- Feber
- Tömda glykogendepåer
- Metabol acidos pga laktatproduktion
- Respiratorisk acidos pga koldioxidproduktion

…fler tidiga komplikationer, respiration

- Oregelbunden andning
- Aspiration
- Neurogent lungödem (upp till 30%)

Muskeloskeletala komplikationer

- Bett/sår i munnen (ca 20%)
- Frakturer (ca 1%)
  - skalle, näsa, klavikel vanligast om traumatiska
  - humerus och femur om icke-traumatiska

Sena komplikationer, cirkulation

- Hjärt”stunning”
- Hypotension

Sena komplikationer, infektion

- Vanligt!
  - Pneumoni
  - Sepsis
  - UVI

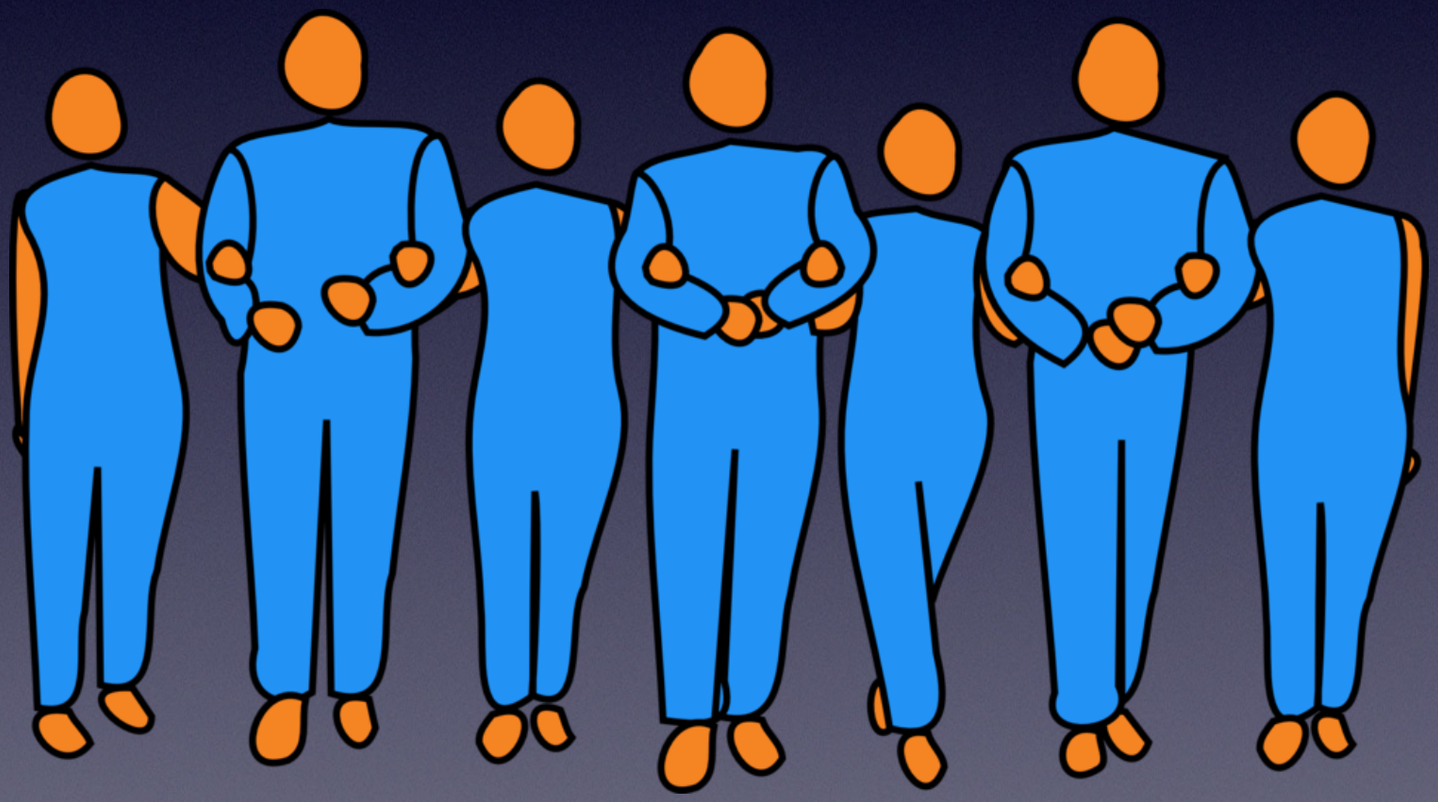
Sena komplikationer, njursvikt

- rhabdomyolys ger Acute Kidney Injury (AKI)

Sena komplikationer, hematologi

- Förhöjda leukocyter är vanligt!
- DIC - ovanligt men finns beskrivet

TEAMWORK



Neurogent lungödem

insult. Symptoms are present in the context of sympathetic activation (fever, tachycardia, hypertension, and leukocytosis) and usually resolve within 24 to 48 h of seizure control. Chest radiograph will reveal bilateral infiltrates (Fig. 1) [23].

1) Neurocardiogenic theory: the catecholaminergic surge causes myocardial stunning and increases the pressures on the left heart resulting in pulmonary edema.
2) Neurohemodynamic theory: a sudden increase in the systemic vascular resistance produces a shift of blood to the pulmonary circulation with fluid extravasation to the alveoli.
3) Blast theory: the abrupt rise in the pulmonary pressure causes barotrauma, disrupting the capillary walls, and causing fluid to leak into the alveoli. This theory also explains the exudative characteristic of the pulmonary edema.
4) Pulmonary venule adrenergic hypersensitivity theory: sympathetic surge directly stimulates α- and β-adrenergic receptors in the pulmonary vascular bed increasing the endothelial permeability causing pulmonary edema regardless of any systemic changes.

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