Status epilepticus - state of the art in diagnostic and therapeutic management.

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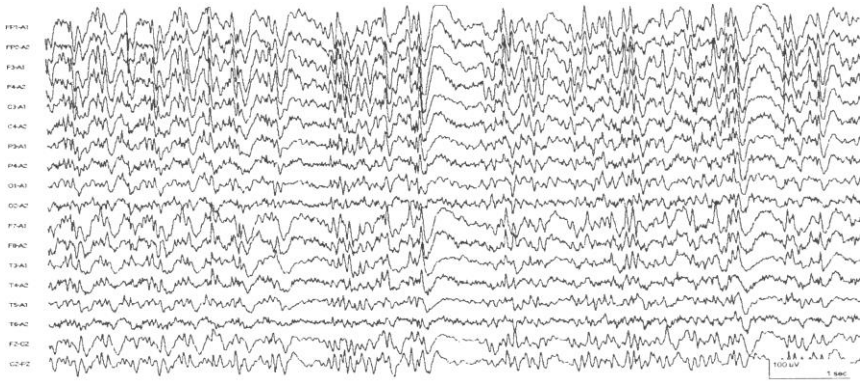

Within 30 min SE

- **increased** blood pressure, cardiac output, CBF

- **increased** blood glucose

A **prolonged SE (60min)** leads to **respiratory acidosis**,

➔ PaO_2 ↓ and $PaCO_2$ ↑
hypoxia and hypercapnia ➔ vasodilatation ➔
➔ ICP↑
➔ Hypotonia ➔ CPP ↓
➔ respiratory/metabolic acidosis
➔ hyperlactatemia
➔ hypoglycemia
➔ hyperglycemia
➔ hyperpyrexia

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blood gas analysis
pulse-oximetry is **not** sufficient

Duration of SE

Temporary systemic changes	Life threatening systemic changes	Death

Time point 1 (t_1)

"abnormally prolonged seizure"

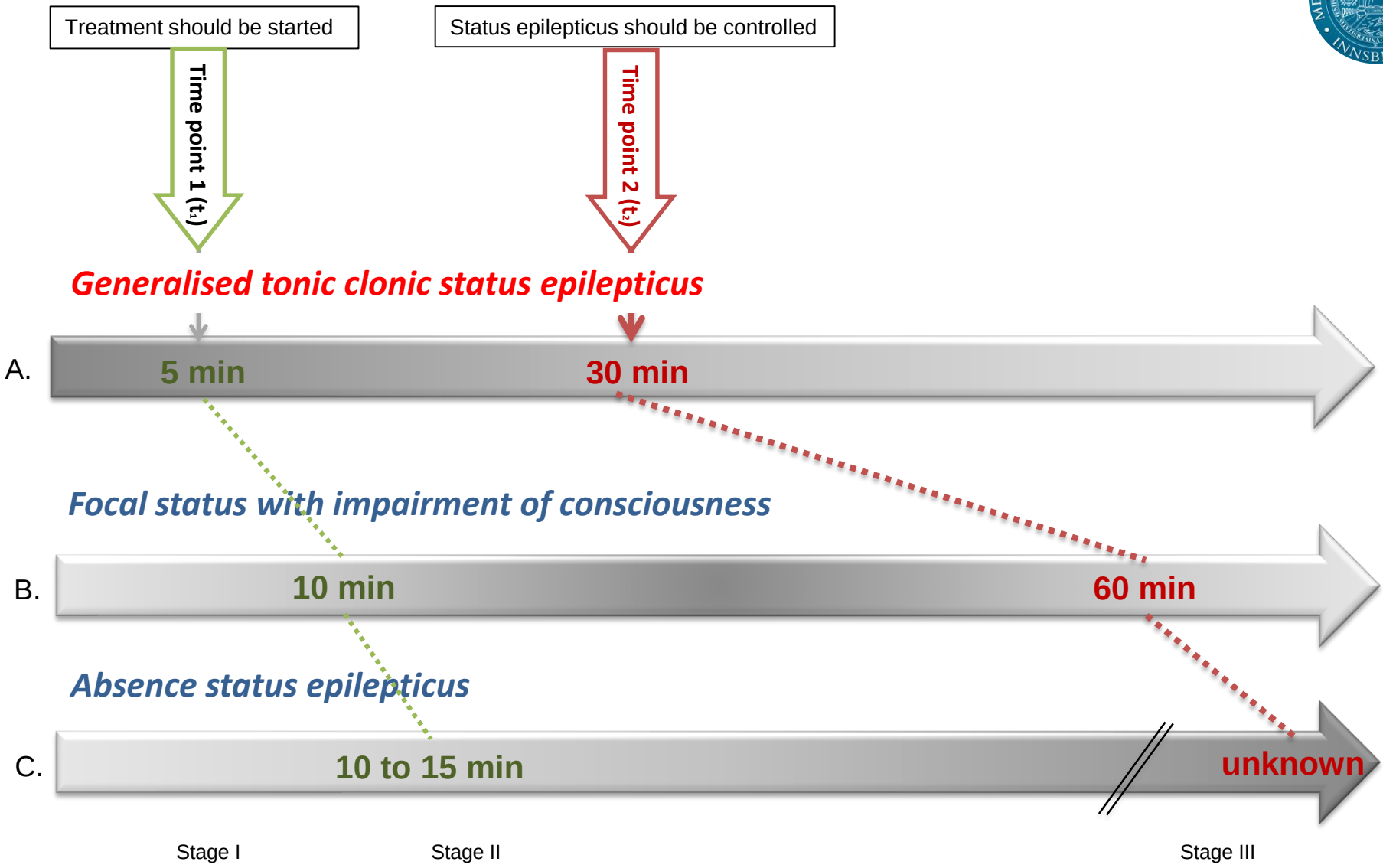
Start therapy

Time point 2 (t_2)

"risk of long-term consequences"

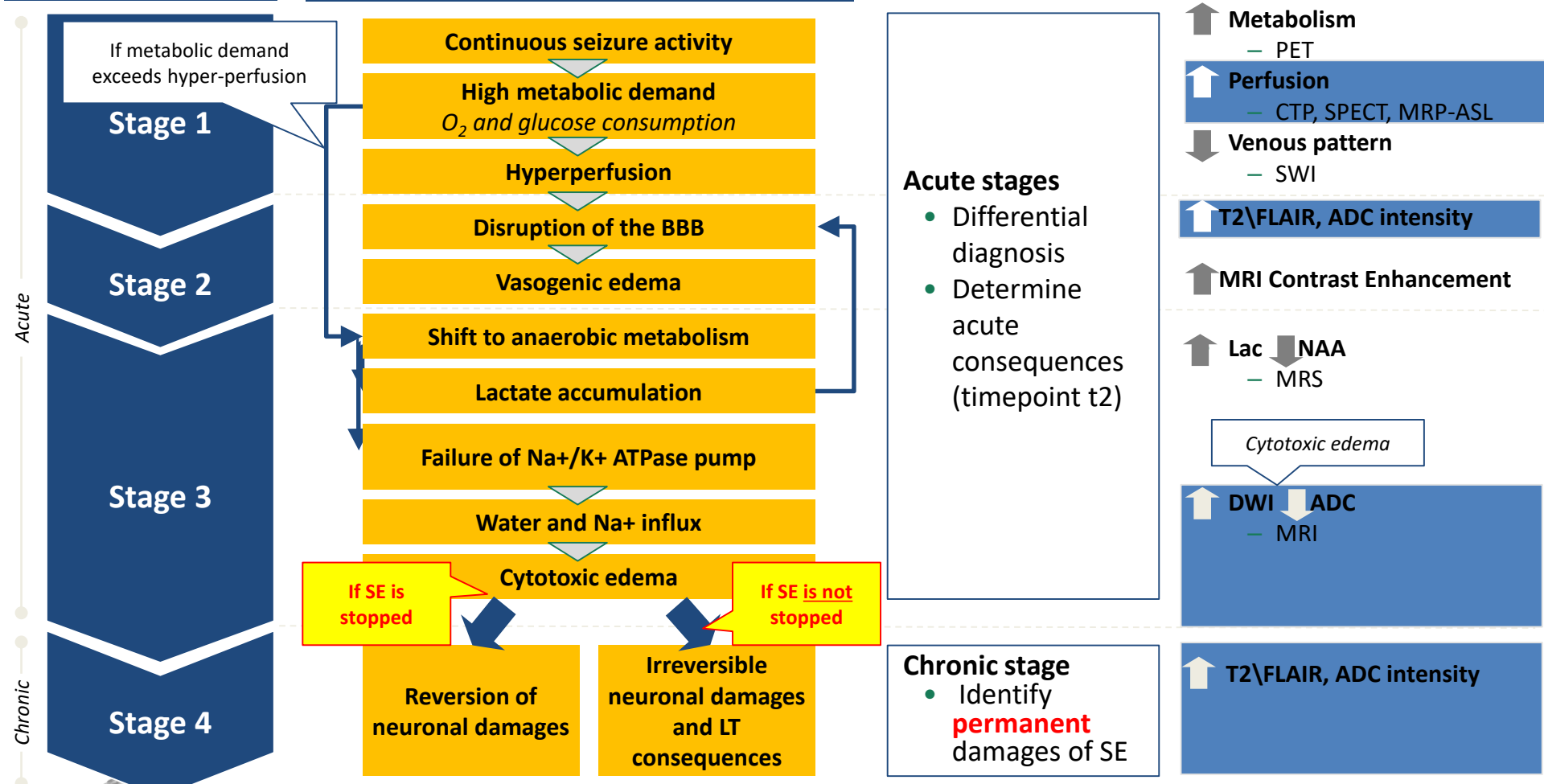
2nd- 3rd line therapy

Definition of SE



Modified from Trinka&Lowenstein 2015; Epigraph

Pathophysiology ➔ Neuroimaging of SE



Anas et al, Epilepsy Research, 2010; Yu et al, Brain Res Rew, 2008; Cole et al, Epilepsia, 2004; ***Giovannini and Trinka Epilepsia 2018***

All patients

- Fingerstick ***glucose*** and ***blood gas incl lactate***
- ***Monitor*** vital signs: O2 sat, Temp, BP, HR
- Head computed tomography (***CT***) scan
- Order ***laboratory*** test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, **AED levels**.
- Continuous electroencephalographic (***EEG***) monitoring if available

- IV access → draw blood
- administer O2; airway protection
- IV glucose?
- Thiamin

- Benzodiazepines, AED

Am. J. Trop. Med. Hyg., 88(1), 2013, pp. 127–131
doi:10.4269/ajtmh.2012.12-0447

Handheld Point-of-Care Cerebrospinal Fluid Lactate Testing Predicts Bacterial Meningitis in Uganda

Albert Majwala, Rebecca Burke, William Patterson, Relana Pinkerton, Conrad Muzoora, L. Anthony Wilson, and Christopher C. Moore*

Department of Internal Medicine, Mbarara Regional Referral Hospital, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda; Department of Medicine, Duke University School of Medicine, Durham, North Carolina; Department of Laboratory Medicine, University of Virginia School of Medicine, Charlottesville, Virginia; Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, Charlottesville, Virginia

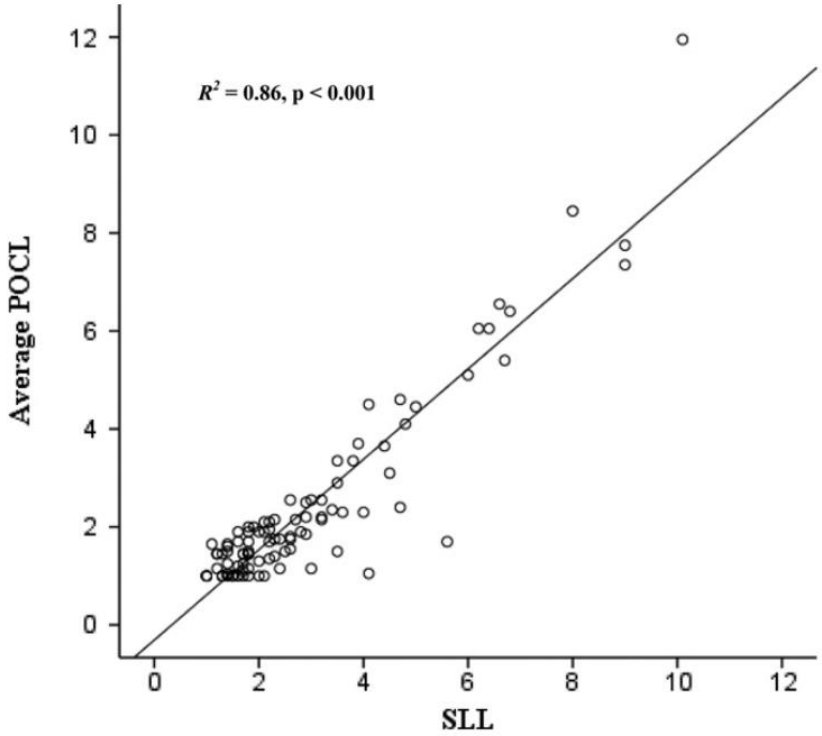


FIGURE 1. Scatter plot with regression line of average POCL and SLL results (in millimoles per liter) for CSF samples submitted to the clinical laboratory at the University of Virginia.

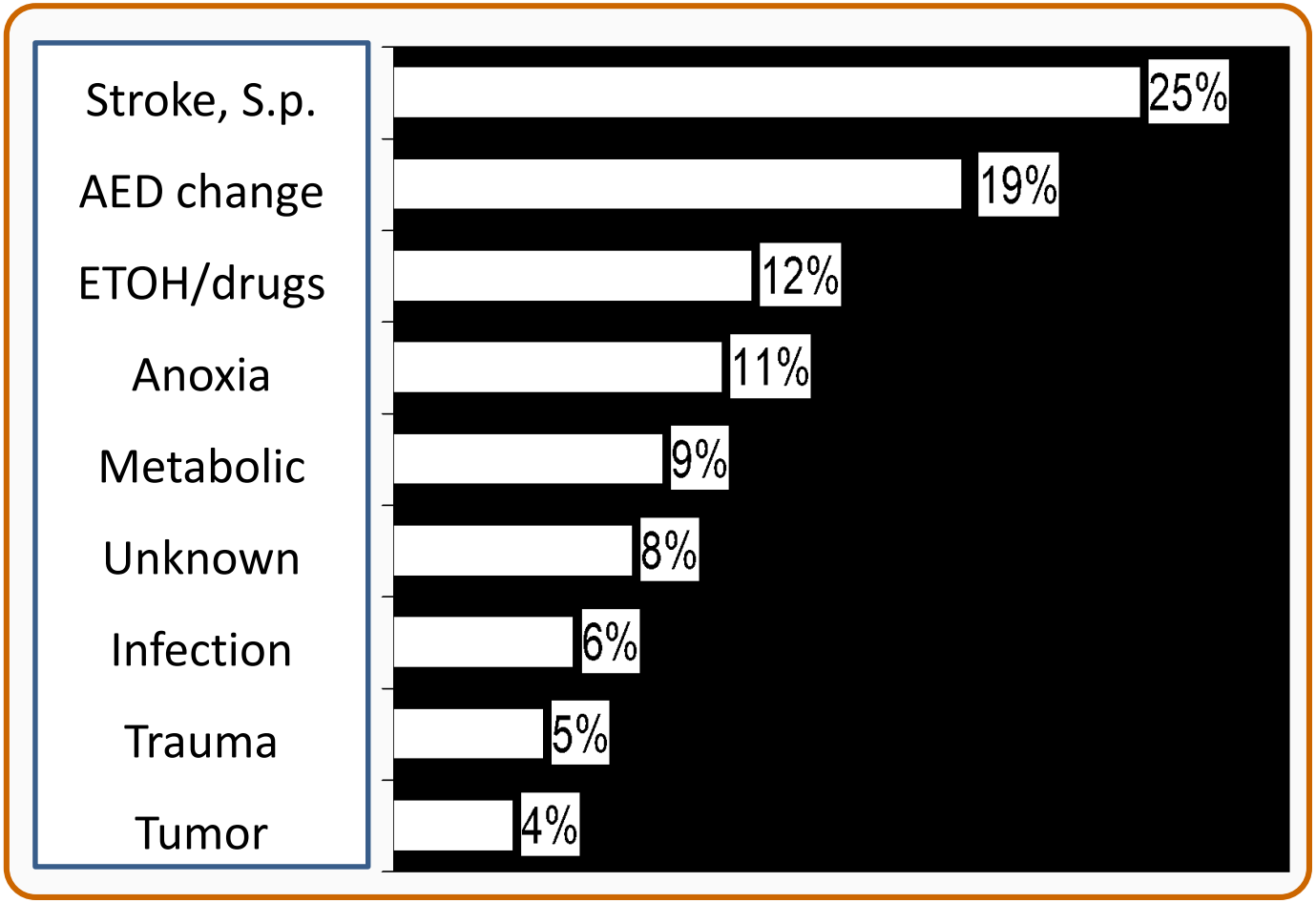
POCL: point of care lactate

SLL: standard laboratory lactate

Consider the following, based on clinical presentation

- Brain magnetic resonance imaging (***MRI***)
- Lumbar puncture (***LP***)
- Comprehensive ***toxicology*** panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine)
- Other ***laboratory tests***: liver function tests, serial troponins, type and hold, coagulation studies, ***arterial*** blood gas, AED levels, toxicology screen (urine and blood), and inborn errors of metabolism

SE: Etiology in adults in United States



DeLorenzo et al, Epilepsia '92

Seizure 51 (2017) 55–60

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Convulsive status epilepticus in a quaternary hospital paediatric intensive care unit (PICU) in South Africa: An 8 year review

Yavini Reddy[a,*], Yusentha Balakrishna[b], Lawrence Mubaiwa[a]

[a] Department of Paediatric Neurology, University of KwaZulu-Natal, Durban, South Africa
[b] Biostatistics Unit, South African Medical Research Council, Durban, South Africa

Table 2
Aetiology (n = 76).

Aetiology (n = 76)	n[%]
Acute Symptomatic	**65 (86)**
Infections	*40 (61)*
Gastroenteritis with metabolic derangements	*19 (29)*
Trauma related	*3 (5)*
Tumours	*2 (3)*
Intracerebral haematoma	*1 (2)*
Remote Symptomatic	**6 (8)**
Idiopathic Epilepsy Related	**1 (1)**
Prolonged Febrile	**3 (4)**
Unclassified	**1 (1)**


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Table 3
Infectious Aetiology Subgroup (n = 40).

Infectious Aetiology Subgroup (n = 40)	n [%]
Presumed viral encephalitis	18 (45)
Bacterial/Viral meningitis	10 (25)
Tuberculosis meningitis	5 (13)
Malaria	2 (5)
Sepsis	4 (10)
HIV Vasculitis	1 (2)

Treatment of SE

either / or

Stage 1
≤30 min

- Lorazepam 0,05mg/kg iv 2mg/min max 0.1mg/kg
- Diazepam 0,15mg/kg iv 5mg/min max 30mg
- Clonazepam 0.015mg /kg iv 0,5mg/min max 3mg
- Midazolam IM/IV 0.15mg/kg buccal/IN 0.2mg/kg
- Lorazepam buccal/IN 0.2mg/kg
  Diazepam rektal 10-30mg

either / or

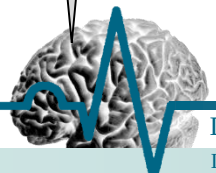
Stage 2
30-90 min

- Phenytoin 20mg/kg 50-100mg/min 5-7mg/kg/d
- **Valproic acid** 30mg/kg 10mg/kg/min 30-60mg/kg/d
- Levetiracetam* 30-60mg/kg 500mg/min 2-12g/d
- Lacosamide* 5mg/kg within 15 min 400-600mg/d
- Phenobarbital 20mg/kg 100mg/min 1-4mg/kg/d

either / or

Stage 3
>90/120 min

- Midazolam[1] 0,2mg/kg load 0,1-0,4mg/kg/h
- Propofol 2-3mg/kg load 5-10mg/kg/h
- Thiopental 5mg/kg load 3-7mg/kg/h



Meierkord et al. EFNS 2010; DGN Leitlinien 2017, ILAE Task Force, 2008, Hirsch et al. Continuum 2013, 1. Fernandez et al. Neurology 2014

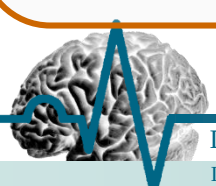
1. ***Intubation*** should be done after the administration of a **barbiturate bolus** of 3-5 mg/KG bw (e.g. Thiopental). This dosage usually allows sufficient "relaxation" to facilitate the placement of the endotracheal tube.

2. Neuromuscular blockade should **not** be given in these patients, however, if absolutely necessary, Vecuronium 0,1 mg/kg bw. can be considered.

3. Monitor body temperature, **maintain *normothermia***.

4. Pentobarbital 5-15 mg/KG bw. over 1 h (or **Thiopental** 3-7 mg/kg bw/h), then continue Pentobarbital 0,5-5 mg/KG/bw/h (or continue **Thiopental** at a rate of 1-3 mg/kg bw/h) until seizures are controlled.

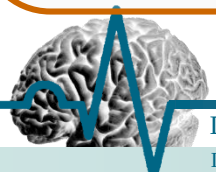
5. ***Monitor*** with **continuous** EEG



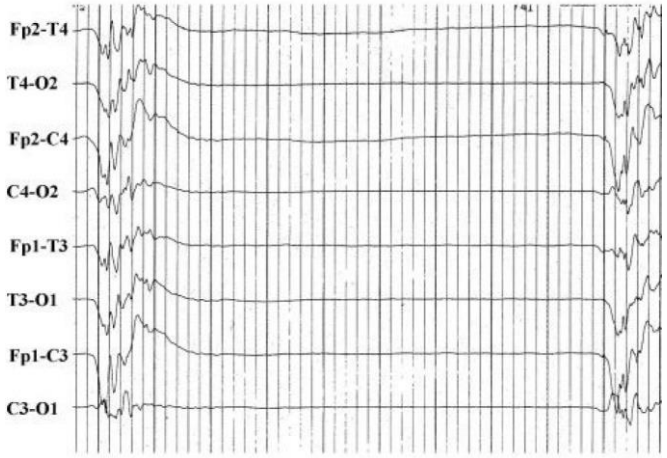
6. Intra-arterial line for ***blood gas*** **analysis, invasive** ***blood pressure*** **monitoring**

7. Invasive **hemodynamic monitoring**, e. g. PiCCO or even more invasive monitoring.

8. Titrate the dosage of barbiturates against ***EEG burst suppression*** pattern.



burst-suppression-EEG for at least 24 hours



Endpoints remain ***controversial*** and options include

- burst suppression
- complete background suppression
- seizure suppression

Withdrawal seizures:

restart ***MDZ*** or change to different cIV-AED

maximize other ***AEDs*** or add AED

Taper again after no seizures for 24-72 hrs

Bauerschmidt et al, Curr Opin Crit Care 2017, 23:122–127

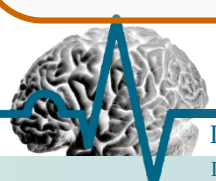
6. Intra-arterial line for **blood gas analysis, invasive blood pressure monitoring**

7. Invasive **hemodynamic monitoring**, e. g. PiCCO or even more invasive monitoring.

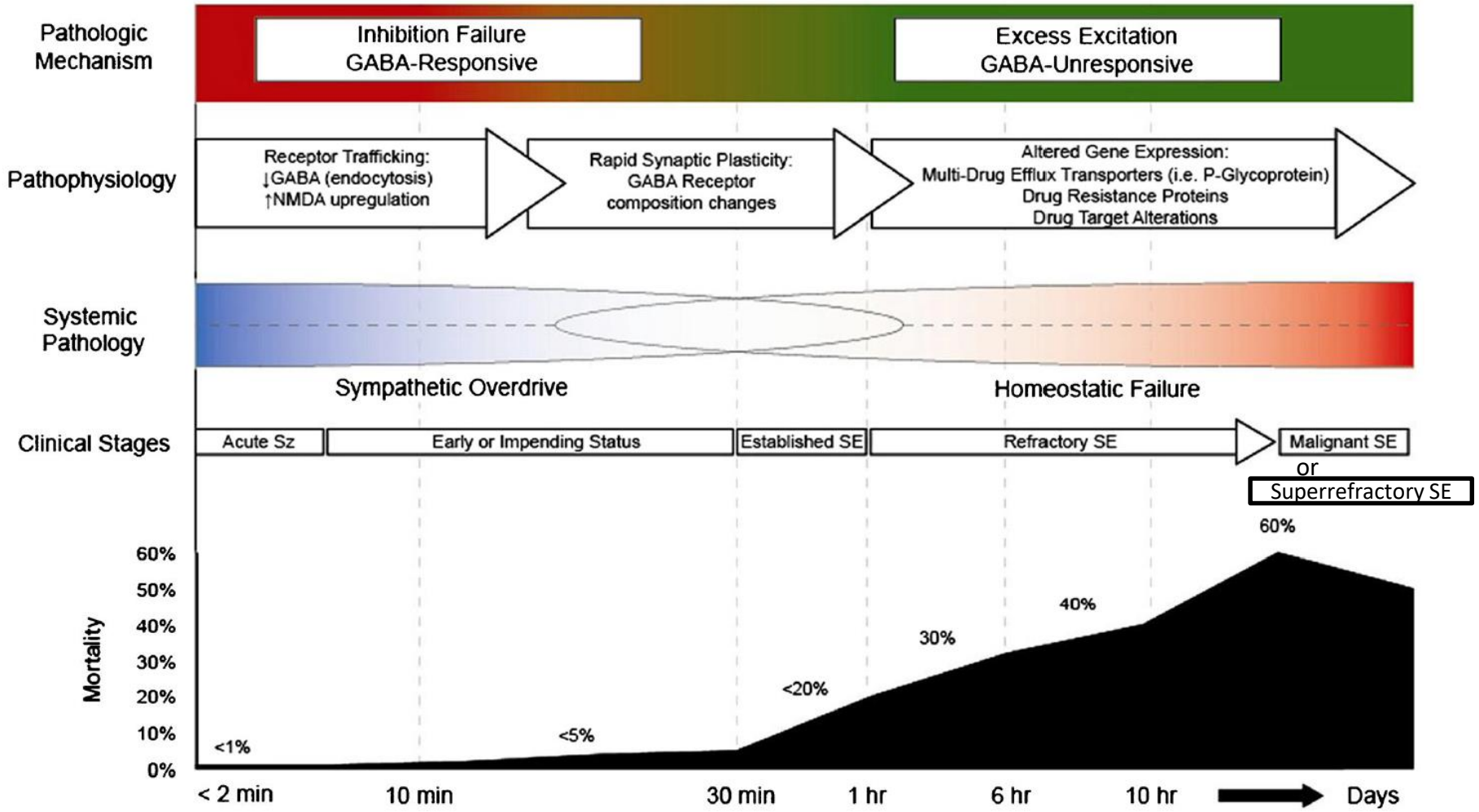
8. Titrate the dosage of barbiturates against **EEG burst suppression** pattern.

9. **Fluid management, aggressive fluid balancing,** if necessary **catecholamines**

10. **Monitoring** must be on high alert to recognize any **incipient nosocomial infection** (regular culturing of body fluids, regular C-reactive protein, procalitonin, WBC, etc.).



Receptor trafficking in prolonged seizure activity



Grover et al, Curr Treat Options Neurol (2016) 18: 11

Ketamine
Bolus: 0.5–4.5 mg/kg
M: up to 7,5 mg/kg/h

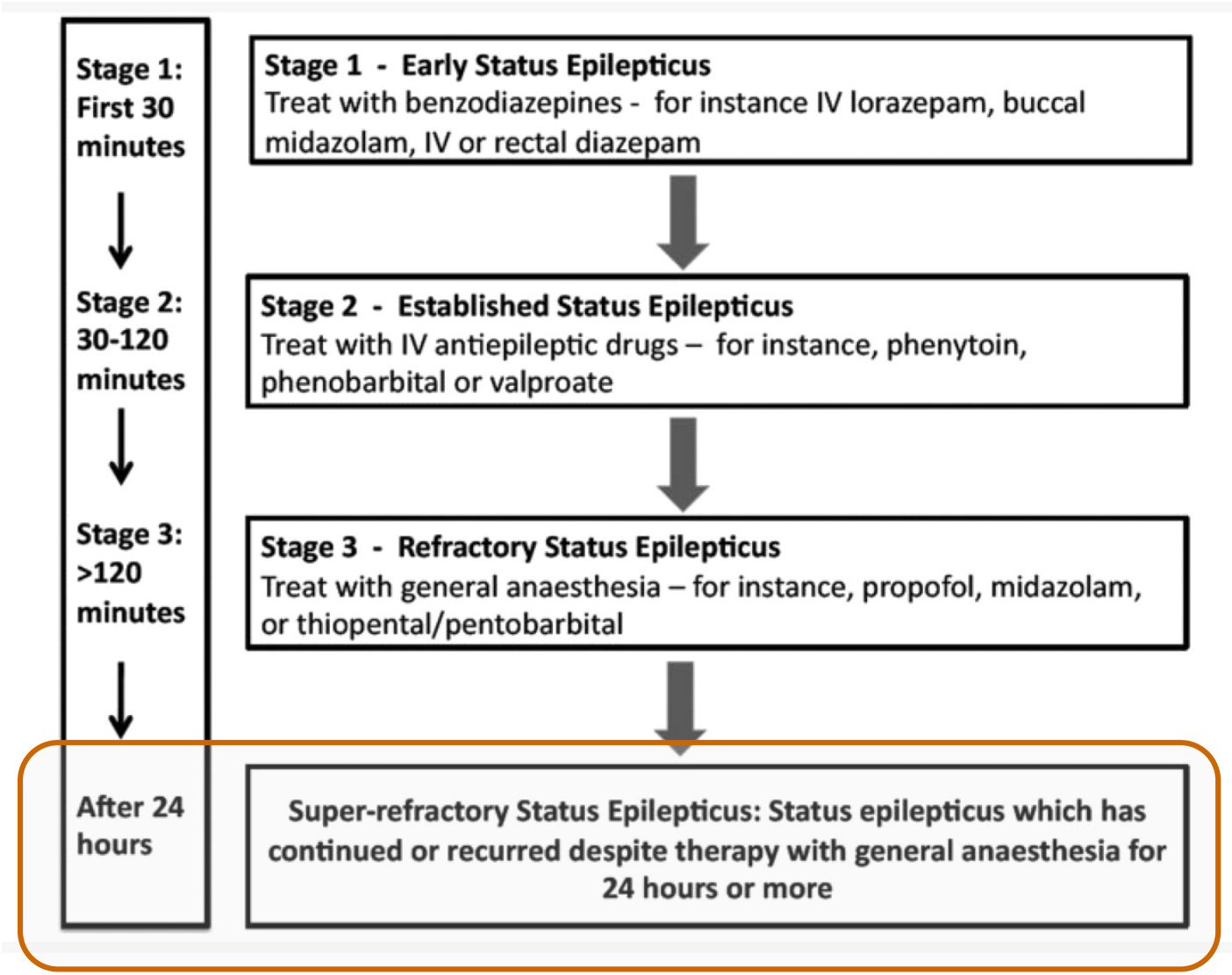
- NMDA antagonist

- ***Neuroprotective***
  - mechanism backed by animal data esp for prolonged SE
  - Barbiturates and benzos *work well* ***early*** in SE, not late
  - Ketamine is opposite, ***in SE >1h (=late)*** (expert opinion)

Borris 2000; Mazarati 1998, 1999

- ***Less hemodynamic side effects*** (compared to Barbiturates and Propofol)

Definition SRSE



Shorvon S , and Ferlisi M Brain 2011;134:2802-2818

Therapeutic options in SRSE

Table 1 The evidence base for treatments used in super-refractory status epilepticus

Therapy	Published cases in controlled or randomized studies (*n*)	Published cases in open series or as case reports (reports, *n*)
Pentobarbital/thiopental	9[a]	377 (32)
Midazolam	0	661 (29)
Propofol	14[a]	183 (34)
Ketamine	0	17 (8)
Inhalational anaesthetics	0	32 (11)
Hypothermia	0	10[c] (5)
Magnesium	0	11 (3)
Pyridoxine	0	14 (5)
Steroids/immunotherapy	0	50 (15)
Ketogenic diet	0	20 (6)
Transcranial magnetic stimulation	0	0
Vagal nerve stimulation	0	4 (4)
Deep brain stimulation	0	1[b] (1)
Resective neurosurgery	0	36 (15)
CSF drainage	0	1 (1)
Electroconvulsive therapy	0	8 (6)

Shorvon S , and Ferlisi M Brain 2011;134:2802-2818

Immunotherapy:

- 1000mg methylprednisolone for 3d followed by 1mg/kg/day for 1 week
- 30g IV Immunoglobulin for 3 to 5d
- 3 to 5 cycles Plasma exchange

Hypothermia: 32-35°C < 48h (neg. RCT!)

or

Ketogenic diet: (1:1 to 1:4)

ECT, CSF-drainage, withdrawal of AEDs and **others**

Trinka et al DRUGS 2015

Management of SE, RSE, SRSE – multimodal neuromonitoring?

Epilepsia, 54(Suppl. 6):57–60, 2013
doi: 10.1111/epi.12279

STATUS EPILEPTICUS 2013

Multimodal invasive monitoring in status epilepticus: What is the evidence it has a place?

*Raimund Helbok and †Jan Claassen

Periodic discharge >2Hz associated with ***brain tissue hypoxia***

Witch et al, JAMA Neurol. 2017 Mar 1;74(3):301-309

Epileptiform activity associated with ***metabolic distress***
(decreased CMD-glucose and increased CMD-LPR)

Vespa et al, Ann Neurol 2016;79:579–590

Modified from Helbok et al. 2013

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

Neurocrit Care (2012) 17:3–23

	GCSE	NCSE	RSE
Hospital mortality	9-21%	18-52%	23-62%
At 30d	19-27%	65%	39%
At 90d	19%		

Summary

- SE is an ***emergency*** and warrants ***immediate aggressive treatment***
- RSE, SRSE are still associated with ***high morbidity and mortality***
- Unclear how much ***additional damage*** caused by seizures but suggestive that seizures are not good for the acutely injured brain
- ***Neurotoxicity*** of SE
- Often will need ***cEEG monitoring*** for SE in ***ICU → call for multimodal neuromonitoring***
- ***Many treatment options***