5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 5

Refractory status epilepticus: What to do and how dangerous is it to the brain? (Level 2)

What to do when refractory SE does not stop? Third-line therapy

Andrea Rossetti
Lausanne, Switzerland

Email: andrea.rossetti@chuv.ch

Disclosure

Several medications discussed in this presentation are <u>not</u> FDA / EMA approved for status epilepticus

Summary

Background

3rd line treatment

Treatment beyond the lines

Treatment and prognosis

Conclusions

Summary

Background

3rd line treatment

Treatment beyond the lines

Treatment and prognosis

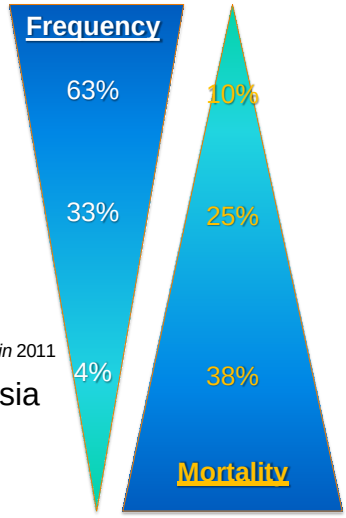
Conclusions

Refractory and super-refractory status epilepticus in adults: a 9-year cohort study

L. Delaj[1,2], J. Novy[1], P. Ryvlin[1], N. A. Marchi[1], A. O. Rossetti[1]

Acta Neurol Scand 2017: 135: 92–99

- Responsive
- Refractory Novy *Epilepsia* 2010
  resistant to BDZ and AED
- Superrefractory Shorvon&Ferlisi *Brain* 2011
  Resistant to 1st course of anesthesia

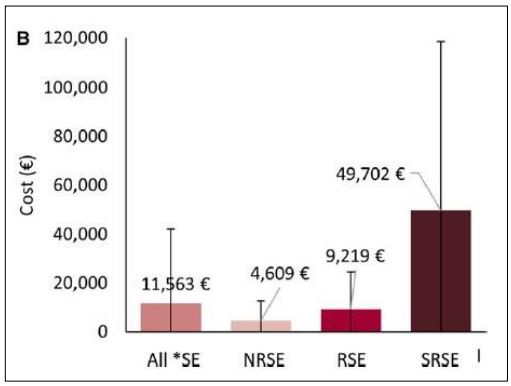


5

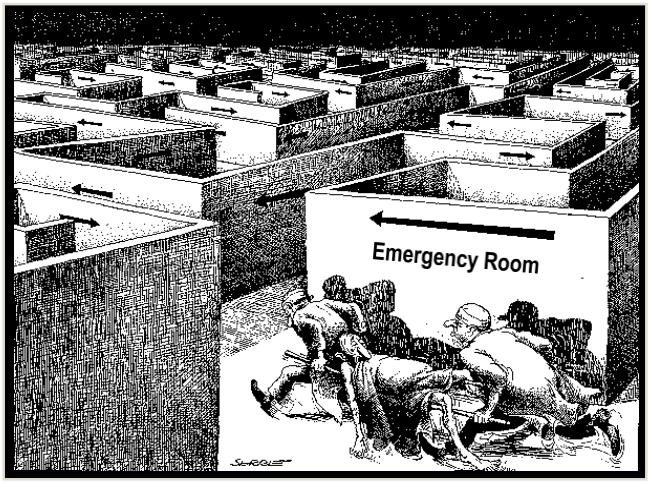
Costs, length of stay, and mortality of super-refractory status epilepticus: A population-based study from Germany

Epilepsia, 58(9):1533–1541, 2017

*†Adam Strzelczyk, ‡Sonja Ansorge, ‡Jana Hapfelmeier, §Vijayveer Bonthapally, ¶M. Haim Erder, and *†Felix Rosenow



6



Claude Serre, *Humour noir et hommes en blanc*, 1975

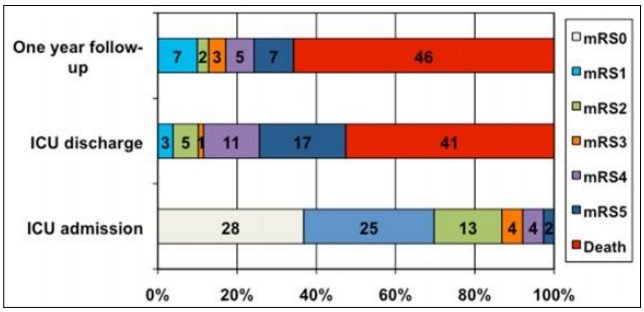
The longer **generalized** SE lasts, the harder it is to treat!
Fountain *J Clin Neurophysiol* 1995, Treiman *NEJM* 1998

7

Refractory SE and outcome

May be good even after prolonged RSE (15%-40%) !!

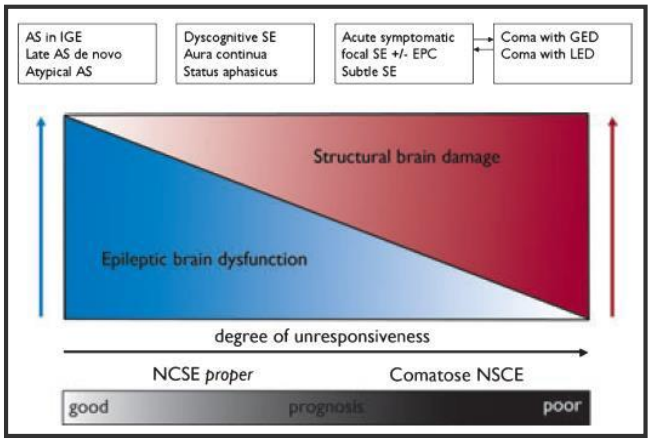
Cooper *Arch Neurol* 2009, Bausell *Neurology* 2011, Drislane *Epil Behav* 2011, Lai Crit Care 2015



Lai *Crit Care* 2015

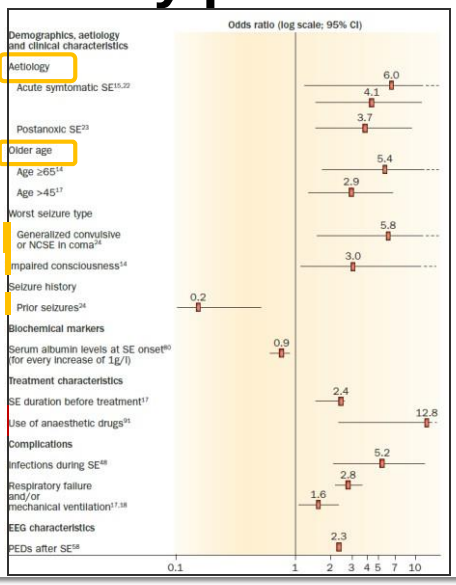
8

Non-convulsive SE and Coma



Bauer & Trinka *Epilepsia* 2010

Mortality predictors



Sutter *Nature Rev Neurol* 2013

10

Summary

Background

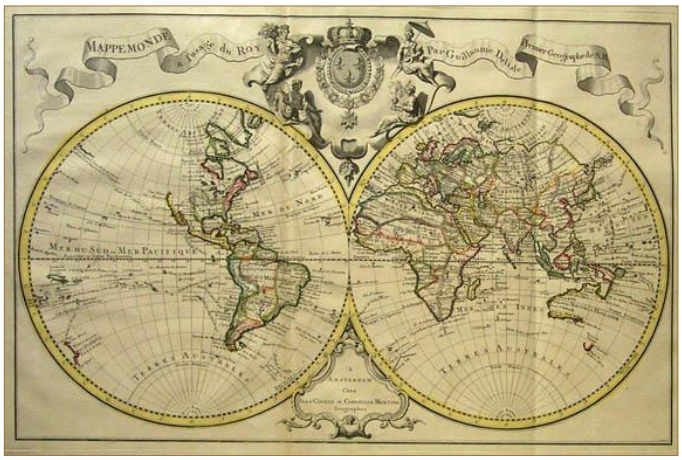
3rd line treatment

Treatment beyond the lines

Treatment and prognosis

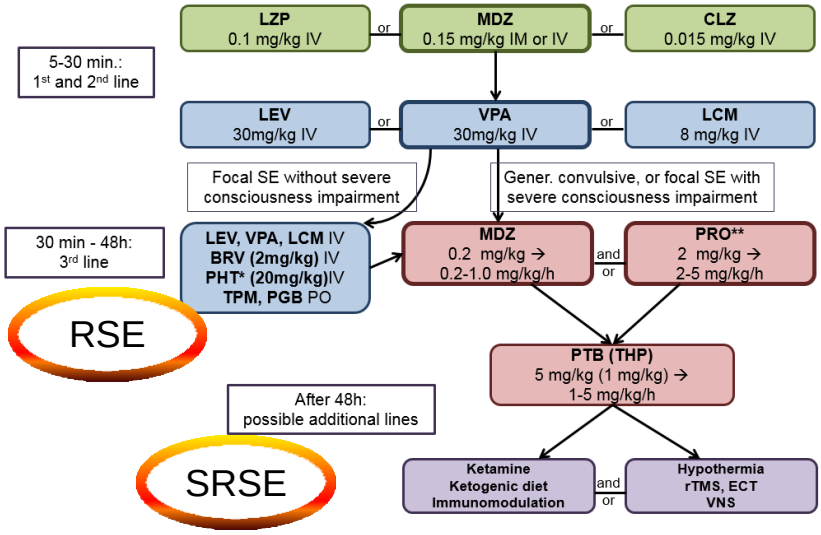
Conclusions

Evidence...?!



G. Delisle, *Mappemonde à l'usage du Roy*.
Covens & Mortier, Amsterdam, ca. 1730

SE treatment in Lausanne (2019)



13

3rd-line, adults, G and CP SE

Responders (23 pts., after BDZ+ AED) Rossetti *Neurocrit Care* 2011

PRO IV (EEG guided) : 43%
THP/PTB IV (EEG guided) : 22%
} non-significant

3rd-line, children, GSE

Responders (40 pts., after DZP+ PHT) Singhi *J Child Neurol* 2002

MDZ IV (clinically guided): 86%
DZP IV (cllinically guided): 89%
} non-significant

14

3rd-line, adults, retrospective

Responders (33 pts., after BDZ+ AED) Bellante *J Neurol* 2016

MDZ IV, 19 pts. (EEG guided) : 63%

THP IV, 14 pts. (EEG guided) : 64%

} non-significant

Adverse events (all $p<0.05$)

MDZ IV; infection: 26%, hypotension: 15%; ICU stay : 6d

THP IV; infection: 64%, hypotension: 57%; ICU stay : 15d

15

3rd line (anesthetics): overview

	BBT	PRO	MDZ
Mechanisms	$GABA_A$ (NMDA,Ca)	$GABA_A$ (NMDA ?,Ca)	$GABA_A$
Loading dose	THP 2-7mg/kg PTB 5-15 mg/kg	2 mg/kg	0.1-0.3 mg/kg
Maintenance	THP 3-5 mg/kg/h PTB 1-5 mg/kg/h	2-5(10) mg/kg/h	0.05-0.6 mg/kg/h
Elimination t1/2	THP 36h, PTB 22h	2h	0.5-50h
Drawbacks	Long wash-out	**PRIS**: check lactate, add BDZ	Habituation

Kress 1987, Van Ness 1990, Parke 1992, Orser 1995, Cremer 2001, Zhan 2001, Claassen 2001 & 2002, Walder 2002, Vasile 2003, Charlesworth 2004, Marik 2004, Rogawsky 2004, Rossetti 2004, Parviainen 2006, Zarovnaya 2007, Iyer 2009

16

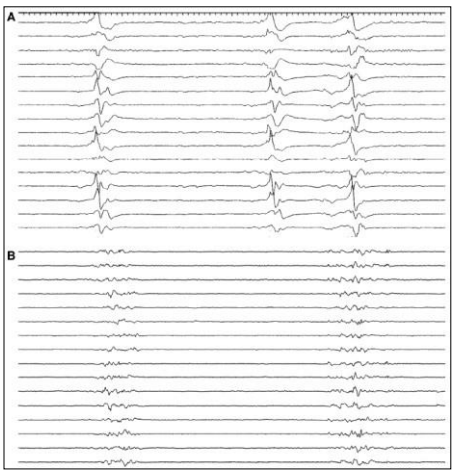
EEG targets

EEG defined endpoint	Rationale	Grade
Cessation of non-convulsive seizures	Recurrent non-convulsive seizures result in ongoing brain injury and worsen mortality	Class I, level B
Diffuse beta activity	Verifies effect of anesthetic agents	Class IIb, level C
Burst suppression 8–20 s intervals	Interruption of synaptic transmission of electrical activity	Class IIb, level C
Complete suppression of EEG	Interruption of synaptic transmission	Class IIb, level C

Brophy *Neurocrit Care* 2012

17

EEG targets



Successful anesthetic wean

- Interburst interval : no
- BS ratio : no
- Burst length : no
- Load of epil. bursts : p=0.008

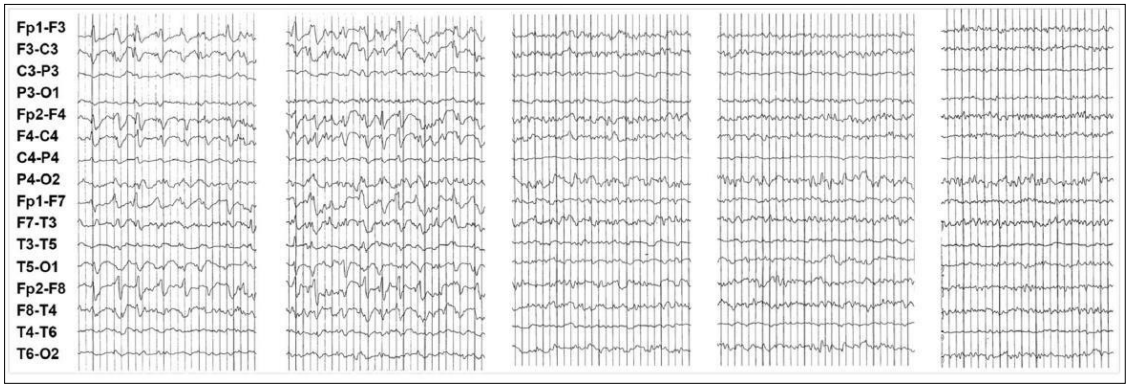
Johnson *Neurocrit Care* 2016

18

De Novo Generalized Periodic Discharges Related to Anesthetic Withdrawal Resolve Spontaneously

(*J Clin Neurophysiol* 2014;31: 194–198)

Amar B. Bhatt, Alexandra Popescu,† Elizabeth J. Waterhouse,‡ and Bassel W. Abou-Khalil**



19

Summary

Background

3rd line treatment

Treatment beyond the lines

Treatment and prognosis

Conclusions

20

Ketamine for Refractory Status Epilepticus: A Systematic Review

Anna Rosati[1] · Salvatore De Masi[2] · Renzo Guerrini[1]

CNS Drugs (2018) 32:997–1009

Table 2 GRADE assessment of the selected case series

Authors	No. of patients	Population (A/P)	Design	Outcome	Quality of evidence
Bleck et al. [29]	7	A	Retrospective	Resolution of SE	Very low[a]
Sing et al. [30]	14	A	Retrospective	Resolution of SE	Very low[a]
Gaspard et al. [31]	58 (60 SE)	A	Retrospective	Resolution of SE	Very low[a]
Gosselin-Lefebvre et al. [32]	9	A	Retrospective	Resolution of SE	Very low[a]
Synowiec et al. [33]	11	A	Retrospective	Resolution of SE	Very low[a]
Basha et al. [34]	11	A	Retrospective	Resolution of SE	Very low[a]
Sabharwal et al. [35]	67	A	Retrospective	Resolution of SE	Very low[a]
Höfler et al. [36]	42	A	Retrospective	Resolution of SE	Very low[a]
Mewasingh et al. [53]	5	P	Prospective	Resolution of SE	Low[b]
Kravljanac et al. [54]	6	P	Retrospective	Resolution of SE	Very low[a]
Al-Otaibi et al. [55]	5	P	Retrospective	Resolution of SE	Very low[a]
Rosati et al. [27]	12	P	Prospective	Resolution of SE	Low[b]
Rosati et al. [28]	9 (11 SE)	P	Prospective	Resolution of SE	Low[b]
Ilvento et al. [22]	13 (19 SE)	P	Prospective	Resolution of SE	Low[b]

21

Ketamine (+ GABA-ergic agent)

58 adults, retrospective, multi-center Gaspard *Epilepsia* 2013

- permanent RSE control in 7 (12%); 4 postanoxic; mortality 43%
- No response if given <0.9mg/kg/h, after >8 days

11 adults, retrospective, single-center Synowiec *Epilepsy Res* 2013

- RSE control in 7 (68%); mortality 18%
- All treated <8 days

42 adults, retrospective, single-center Höfler *CNS Drugs* 2016

- RSE controlled in 27 (64%); 9 postanoxic; mortality 45%
- Median treatment after 3d, no predictor of success

22

Ketogenic diet

10 adults, retrospective, multi-center Thakur *Neurology* 2014

- NG tube (?), 22d (median) after SE start
- Ketosis in 9, SE controlled in all (90%)

15 adults, prospective, multi-center Cervenka *Neurology* 2017

- NG tube, 10d (median) after SE start
- Ketosis in all at 2d (median), SE controlled in 11 (73%)

11 adults, retrospective, single-center Francis *Neurocrit Care* 2018

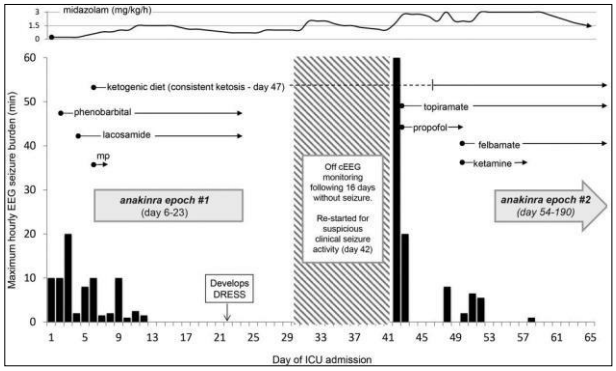
- NG tube (?), 1d ! (median) after SE start
- Ketosis in 10 at 1d (median), SE controlled in 8 (73%)

23

Anti IL-1β -R (anakinra)

First human report Kenney-Jung *Ann Neurol* 2016

- F, 32 months, healthy → FIRES
- 3 courses at 5mg/kg; good recovery at 12 months

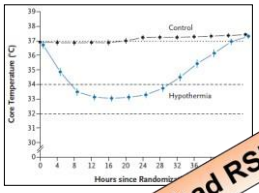


24

Hypothermia for Neuroprotection in Convulsive Status Epilepticus

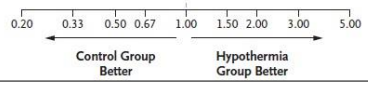
N Engl J Med 2016;375:2457-67

Stephane Legriel, M.D., Virginie Lemiale, M.D., Maleka Schenck, M.D.,



CAVE: only 25% had RSE !

Subgroup	Control Group	Hypothermia Group	Ratio for Primary Outcome (95% CI)
	no. with primary outcome/total no.		
All patients	56/130	67/138	1.22 (0.75–1.99)
Seizure duration at randomization			
≤60 min	46/99		1.17 (0.68–2.05)
>60 min	10/31	/35	1.58 (0.58–4.41)
Age at randomization			
≤65 yr	39/87	57/97	1.75 (0.98–3.16)
>65 yr	17/43	10/41	0.49 (0.19–1.25)



25

Intravenous Corticosteroids as an Adjunctive Treatment for Refractory and Super-Refractory Status Epilepticus: An Observational Cohort Study

Vasiliki Pantazou[1] · Jan Novy[1] · Andrea O. Rossetti[1]

CNS Drugs (2019) 33:187–192

Used de novo in 15/987 (1.5%) adult episodes (=12 pts)

	Total index episodes	Probable responders	Non-responders
SE episodes (*n*)	12	5	7
RSE episodes (*n*)	7	4	3
SRSE episodes (*n*)	5	1	4
Age (years) (median, range)	47 (20–90)	59 (45–79)	47 (20–90)
Female gender (*n*)	7	2	5
Aetiology			
Inflammatory	6	3	3
Other (neurodegenerative, acute lesion, unknown, etc.)	6	2	4
Seizure type			
Generalized	8	2	6
Focal (with or without consciousness impairment)	4	3	1

26

Transcranial Magnetic Stimulation for Status Epilepticus

Epilepsy Research and Treatment
Volume 2015, Article ID 678074, 10 pages

F. A. Zeiler,[1] M. Matuszczak,[2] J. Teitelbaum,[3] L. M. Gillman,[4,5] and C. J. Kazina[1]

21 pts (8 children); 10 (48%) responders
recurrence after TMS in 76% of responders

Reference	Study type	Oxford [29] level of evidence	GRADE [28, 30–33] level of evidence
Graff-Guerrero et al. [12]	Retrospective case series	4	D
Hyllienmark and Åmark [13]	Retrospective case report	4	D
Liu et al. [14]	Retrospective case series	4	D
Misawa et al. [15]	Retrospective case report	4	D
Morales et al. [16]	Retrospective case series	4	D
Naro et al. [17]	Retrospective case report	4	D
Rotenberg et al. [18]	Retrospective case series	4	D
Thordstein and Constantinescu [19]	Retrospective case report	4	D
Thordstein et al. [20]	Retrospective case series	4	D
Van Haerents et al. [21]	Retrospective case report	4	D
Wusthoff et al. [22]	Retrospective case report	4	D
Rotenberg et al. [23]	Retrospective case report	4	D

Rotenberg et al. [18] contains a series of patients including the case description from Rotenberg et al. [23]. Thus, the data from Rotenberg et al. [23] was not included in the final summary and analysis of data in order to avoid duplication of patient data.

27

VNS for refractory status epilepticus

F.A. Zeiler[a,b,*], K.J. Zeiler[b,c,1], J. Teitelbaum[b,c,2], L.M. Gillman[d,e,3], M. West[a,4]

Epilepsy Research (2015) 112, 100–113

27 pts. (18 children); responders: gener. SE 76%, focal SE 25%

Table 3 Oxford and GRADE level of evidence.

Reference	Study type	Oxford (Phillips et al., 2014) level of evidence	GRADE (Guyatt et al., 2008a,b,c,d; Schünemann et al., 2008; Jaeschke et al., 2008) level of evidence
Boon et al. (2007)[a]	Retrospective case report	4	D
De Benedictis et al. (2013)	Retrospective case series	4	D
De Herdt et al. (2009)[a]	Retrospective case report	4	D
Donahue et al. (2013)	Retrospective case series	4	D
Howell et al. (2012)	Retrospective case series	4	D
Lin and Ko (2012)	Retrospective case series	4	D
Malik and Hernandez (2004)	Retrospective case series	4	D
O'Neill et al. (2011)	Retrospective case report	4	D
Patwardhan et al. (2005)	Retrospective case report	4	D
Shatzmiller et al. (2011)	Retrospective case report	4	D
Soto et al. (2012)	Retrospective case report	4	D
Soto et al. (2009)	Retrospective case report	4	D
Thielemann (2009)	Retrospective case report	4	D
Vonck et al. (2007)[a]	Retrospective case report	4	D
Winston et al. (2001)	Retrospective case report	4	D
Zamponi et al. (2008)	Retrospective case series	4	D
Zimmerman et al. (2002)	Prospective cohort	4	D

[a] Boon et al. (2007), De Herdt et al. (2009) and Vonck et al. (2007) are publications on the same patient, with Boon et al. (2007) and Vonck et al. (2007) meeting abstracts. De Herdt et al. (2009) is the final, long term follow up on this patient.

28

Electroconvulsive therapy for refractory status epilepticus: A systematic review

Seizure 35 (2016) 23–32

F.A. Zeiler [a,*], M. Matuszczak [b,1], J. Teitelbaum [c,2], L.M. Gillman [d,e,3], C.J. Kazina [a,4]

19 pts. (4 children); 7 (37%) complete responders

Reference	Study type	Oxford[28] Level of Evidence	GRADE[29–34] Level of Evidence
Carrasco et al.[9]	Retrospective Case report	4	D
Cline et al.[10]	Retrospective Case Report	4	D
Fernandez-Torre et al.[11]	Retrospective case Report	4	D
Griesemer et al.[12]	Retrospective Case Series	4	D
Kamel et al.[13]	Retrospective Case Series	4	D
Koong et al.[14]	Retrospective Case Report	4	D
Lisanby et al.[15]	Retrospective Case Report	4	D
Moddel et al.[16]	Retrospective Case Series	4	D
Morales et al.[17]	Retrospective Case Report	4	D
Regenold et al.[18]	Retrospective Case Report	4	D
Savard et al.[19]	Retrospective Case Report	4	D
Shin et al.[20]	Retrospective Case Report	4	D
Viparelli et al.[21]	Retrospective Case Report	4	D
Wusthoff et al.[22]	Retrospective Case Report	4	D
Shin et al.[23]	Retrospective Case Report	4	D

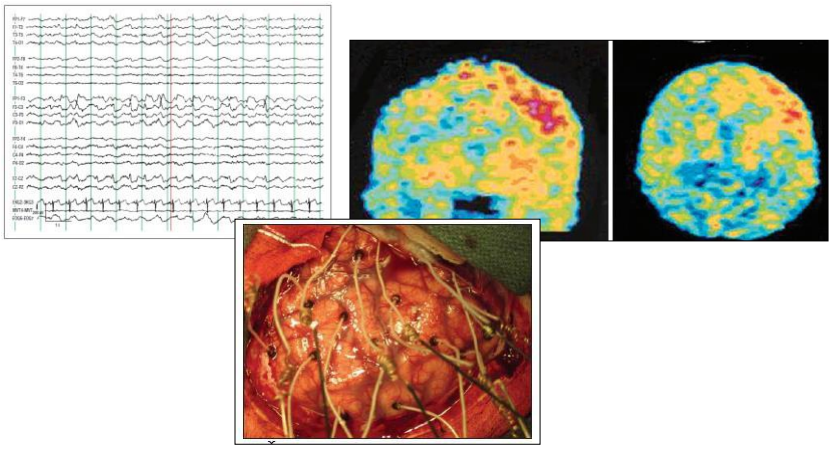
* Shin et al.[23] is a meeting abstract which contains the same patient data as Shin et al.[20]. Patient data from Shin et al[23] was not included in the final data analysis in order to avoid duplication of data.

29

Efficacy of Surgical Treatment of De Novo, Adult-Onset, Cryptogenic, Refractory Focal Status Epilepticus

Arch Neurol. 2006;63:895-901

Daniel J. Costello, MD, MRCPI; Mirela V. Simon, MD; Emad N. Eskandar, MD; Matthew P. Frosch, MD, PhD; Heidi L. Henninger, MD; Keith H. Chiappa, MD; Andrew J. Cole, MD, FRCPC



30

Summary

Background

3rd line treatment

Treatment beyond the lines

Treatment and prognosis

Conclusions

31

Complications of long ICU stay

Cereda *Neurocrit Care* 2009, Cooper *Arch Neurol* 2009, Sutter *Epilepsia* 2012

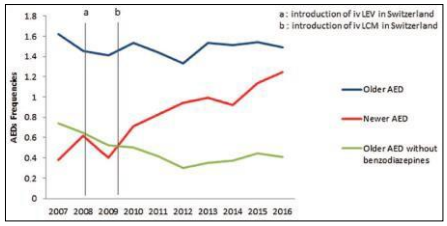
- **Infections**
- **ICU myopathy, neuropathy**
- Thrombosis, embolism
- Ileus
- AED side effects
- **…**

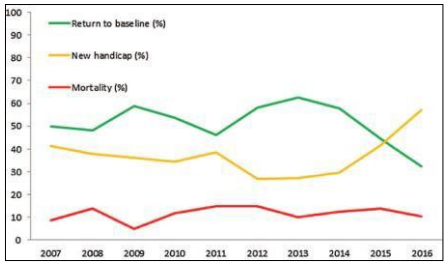
32

Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcomes in Comparison with Traditional Agents

Isabelle Beuchat[1] · Jan Novy[1] · Andrea O. Rossetti[1]

CNS Drugs 2017;31:327-334



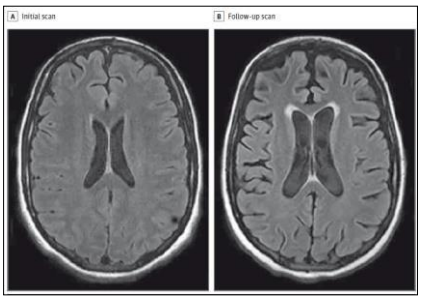


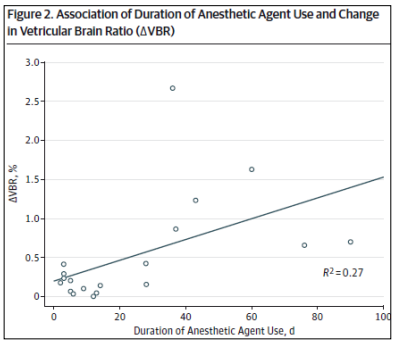
Lack of return to baseline independently associated to use of **newer AED** (OR=2.91, p<0.001)

Fatuzzo *Epilepsia* 2018

Duration of anesthetics and atrophy

Hocker *JAMA Neurol* 2016





19 pts, no correlation with survival

Does SE treatment influence prognosis?

	Poor outcome (GOS >2)		
	All SE Episodes		
Predictor	Odds Ratio	95% Confidence Interval	*p*
Third-line antiepileptic therapy	5.64	2.31–13.75	<.001
Age	1.06	1.03–1.09	<.001
First episode of SE	3.73	1.38–10.10	.010
First episode of seizure			NS
SE etiology: Acute CNS disease			NS
SE etiology: Subtherapeutic antiepileptic drug			NS

ICU-based, 144 episodes

Kowalski *Crit Care Med* 2012

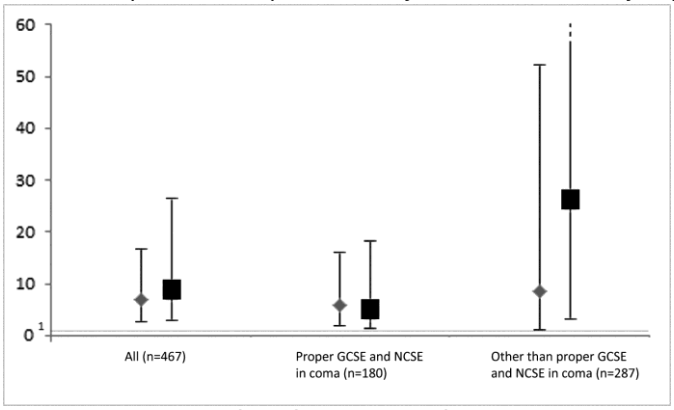
	Adjusted for SE duration, STESS,[a] critical conditions, nonanesthetic third-line AEDs		
	RR	95% CI	*p* Value
Death			
IVAD	2.88	1.45-5.73	0.003[b]
Number of IVADs	1.59	1.13-2.25	0.008[b]
No IVADs	Ref.		

ICU-based, 171 episodes

Sutter *Neurology* 2014

Does SE treatment influence prognosis?

Adjusted RR of therapeutic coma (new disability: diamonds; mortality: squares)



Hospit. cohort, 467 patients

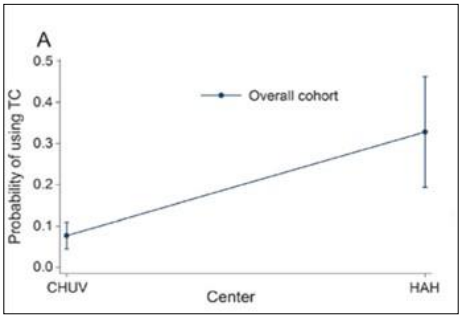
Marchi *Crit Care Med* 2015

Vincent Alvarez, MD
Jong Woo Lee, MD, PhD
M. Brandon Westover, MD, PhD
Frank W. Drislane, MD
Jan Novy, MD, PhD
Mohamed Faouzi, PhD
Nicola A. Marchi, MD
Barbara A. Dworetzky, MD
Andrea O. Rossetti, MD

Therapeutic coma for status epilepticus

Differing practices in a prospective multicenter study

Neurology® 2016;87:1650-1659



Mortality

- **Comorbiditiy: OR 1.18 (1.04-1.34)**
- **Severity : OR 1.54 (1.19-1.99)**
- **Fatal etiology: OR 2.60 (1.25-5.40)**
- **Refractoriness: OR 2.13 (1.01-4.50)**
- Coma: OR 1.62 (0.58-3.39)

Hospitalisation length

- **Severity: OR 1.10 (1.02-1.18)**
- **Fatal etiology: OR 1.60 (1.34-1.91)**
- **Refractoriness: OR 1.28 (1.06-1.55)**
- **Coma: OR 1.60 (1.22-2.11)**

Summary

Background

3rd line treatment

Treatment beyond the lines

Treatment and prognosis

Conclusions

Induce coma in which SE form?

Quickly in gen.-convulsive, deferred in focal, **never in absence**!

Which agent?

MDZ ≥ PRO > BBT

To which EEG target?

Seizure suppression or burst-suppression (1 / 10 sec.)

How long?

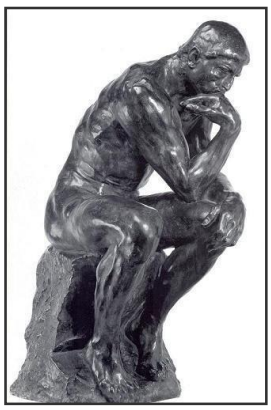
12-24 hours, then wean over 3-12 hours, (and again…)

Stopping treatment?

Only if evidence of permanent brain damage!

39

Take home messages...



Auguste Rodin, *Le penseur*, 1902, Paris

- **1st line has best evidence**
- **Biological background is determinant**
- **Adapt tt aggressiveness (~ intubation!)**
- **Think at <u>K</u>etamine, <u>K</u>etogenic diet**
- **<u>Target the etiology!</u>**

40

Merci !