Refractory status epilepticus

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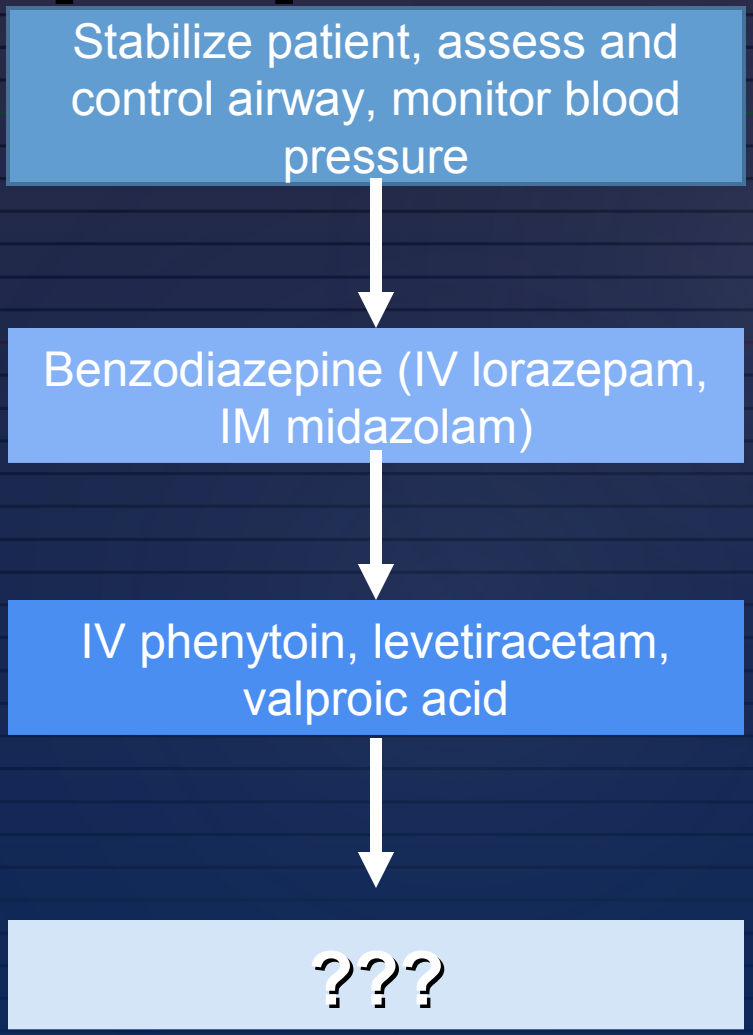
Refractory status epilepticus

- **Refractory status epilepticus**: Prolonged seizure activity that fails to respond to a first line agent (usually a benzodiazepine) and a second line medication

Status epilepticus treatment



Meierkord H, et al. *Eur J Neurol*. 2010 Mar;17(3):348-55.
Glauser T, et al. *Epilepsy Curr*. 2016 Jan-Feb;16(1):48-61.
Brophy GM, et al. *Neurocrit Care*. 2012 Aug;17(1):3-23.

Refractory status epilepticus

- Data on treatment = relatively limited
- Expert consensus guidelines: Convulsive status epilepticus → more aggressive therapy?
  - More clear risk of neuronal injury and death, based on animal data

Meldrum BS, Horton RW. *Arch Neurol*. 1973 Jan;28(1):1-9.
Meierkord H, et al. *Eur J Neurol*. 2010 Mar;17(3):348-55.
Meldrum BS, Brierley JB. *Arch Neurol*. 1973 Jan;28(1):10-7.

Refractory status epilepticus

- Convulsions, motor manifestations of status epilepticus diminish with time
  - 16 patients convulsive status epilepticus at time of onset
  - By the time placed on IV anesthetic agent, 100% were nonconvulsive
- Continuous EEG monitoring is necessary to guide treatment in patients with status epilepticus
  - 89-92% seizures subclinical

Claassen J, Hirsch LJ, Emerson RG, et al. *Epilepsia*. 2002 Feb;43(2):146-53
Meierkord H, et al. *Eur J Neurol*. 2010 Mar;17(3):348-55.
Claassen J, Hirsch LJ, Emerson RG, et al. *Neurology*. 2001 Sep 25;57(6):1036-42

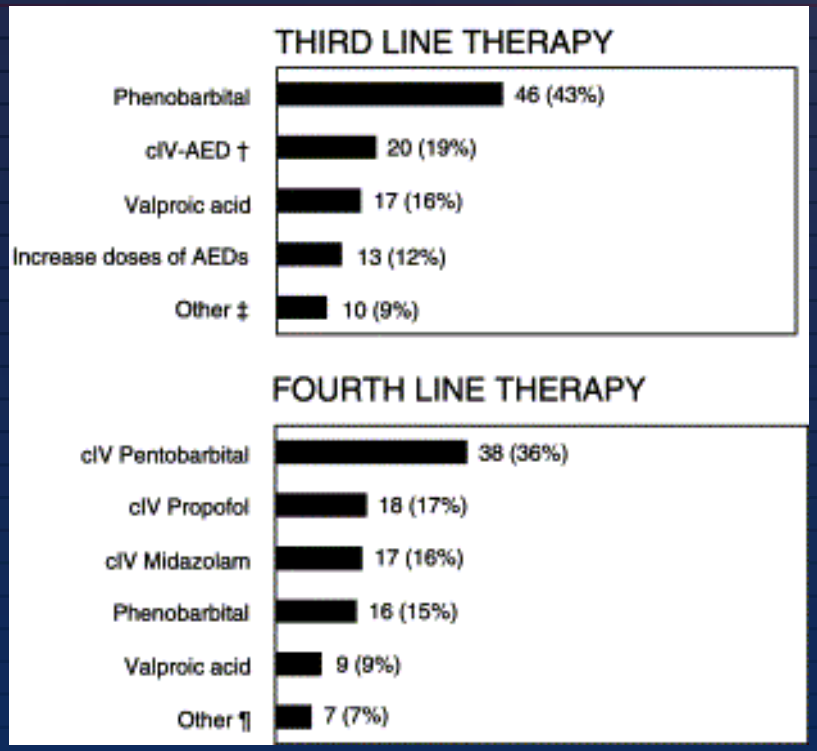
Consequences

- Mortality ranges from 23-61%
  - 2.7x higher mortality in older patients
  - Higher mortality in patients with status epilepticus due to anoxia
  - Improved mortality in patients with seizures due to pre-existing epilepsy, alcohol abuse
- Morbidity in > 90% of survivors

DeLorenzo RJ, et al. *Neurology*. 1996; 46: 1029-32
Towne AR, et al. *Epilepsia*. 1994;5:27-36.
Claassan J, *Neurology*. 2001;57(6):1036–42
Mayer SA, et al. *Arch Neurol*. 2002;59(2):205–10.

How do we treat?

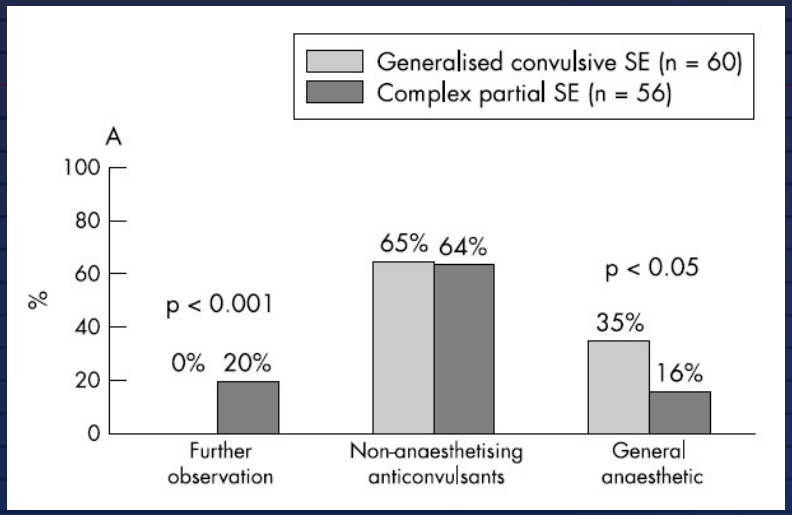
- Significant variability in practice!
- 2003 survey in the U.S. for patient in generalized convulsive status epilepticus:



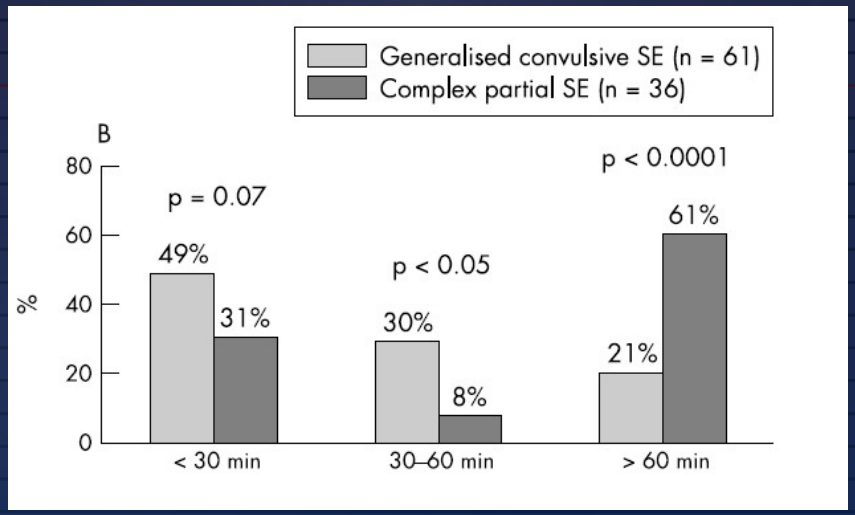
Claassen J, Hirsch LJ, Mayer SA. *J Neurol Sci*. 2003 Jul 15;211(1-2):37-41.

Variability in treatment

- 2003 survey of European neurologists:



Treatment after failure of 1st and 2nd line agents

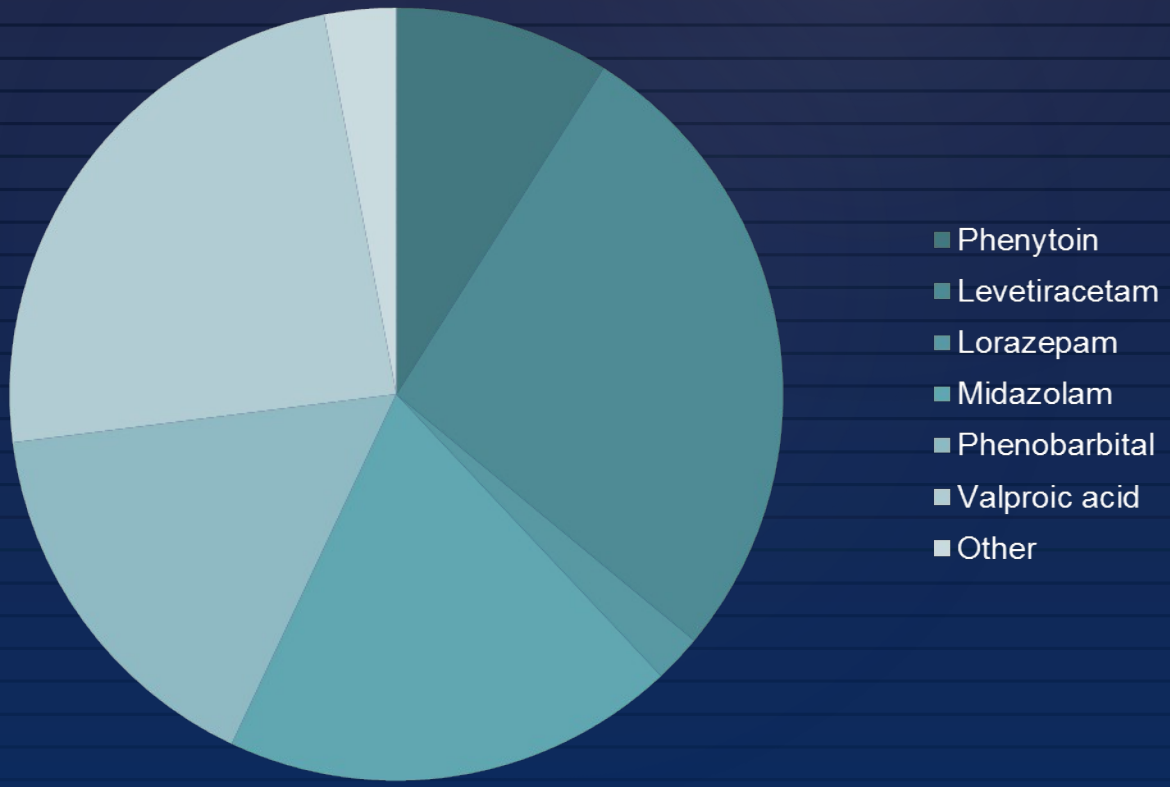


Time point after onset of status epilepticus at which anesthesia is used

Holtkamp M, et al. *J Neurol Neurosurg Psychiatry*. 2003 Aug;74(8):1095-9.

Variability in treatment

- From 2012 survey of U.S. and Canadian neurologists' preferred 1st, 2nd and 3rd line agents in treating status epilepticus:



Abend N et al., *Neurocritical Care* 2010

Current treatment

Treatment options include treatment with a different 2nd line antiepileptic drug or an IV anesthetic agent

- Propofol
- Midazolam
- Pentobarbital
- +/- Ketamine*
- Thiopental (not available in the U.S.)

* Recommended in European Federation of Neurologic Society guidelines, but not recommended by Neurocritical Care Society or American Epilepsy Society guidelines

Anesthetics: weighing the risks

- Risk versus benefit
- Prolonged seizures → worse outcomes
- IV anesthetics / therapeutic coma not benign
  - IV benzodiazepines → ↑ hospital stays, ↑ intubation
  - IV anesthetics → 2.6x mortality, 3.9x infection
  - Controlling for etiology, age and epilepsy, IV anesthetics → 9x mortality ↑, 6.8x disability ↑
  - One study → no association between IV anesthetics and outcome

Young GB, Jordan KG, Doig GS. *Neurology*, 1996 Jul; 47 (1): 83-9.
Alvarez V, et al. *Neurology*. 2016 Oct 18;87(16):1650-1659.
Spatola M, Alvarez V, Rossetti AO. Epilepsia. 2013 Aug;54(8):e99-e102.
Sutter R, Marsch S, Fuhr P, et al. *Neurology*. 2014 Feb 25;82(8):656-64.
Marchi NA, et al. *Crit Care Med*. 2015 May;43(5):1003-9.

Midazolam IV infusion

- Advantages:
  - Short half life (1.5 to 3.5 hours)
    - Rapid titration
    - Can be withdrawn quickly
  - Less hypotension than pentobarbital

- Disadvantages:
  - ~ 50% of patients have breakthrough sz as midazolam is tapered

Propofol IV infusion

- Advantages:
  - Rapid onset (<1 minute) & elimination
  - Less hypotension than pentobarbital

- Disadvantages:
  - Risk of “propofol infusion syndrome”, a rare possibly fatal syndrome of acidosis, hyperkalemia and rhabdomyolysis with prolonged use

Pentobarbital / thiopental infusion

- Advantages:
  - Very effective (only 12% breakthrough seizures)

- Disadvantages:
  - Hypotension common – most patients will require vasopressor agents
  - Long half life (20 – 60 hours) → patients in prolonged coma

Propofol vs. midazolam vs. pentobarbital

- Study of 193 patients with RSE → no difference in mortality between agents
- Pentobarbital → fewer breakthrough seizures but greater hypotension, longer time intubated

Claasen J et al., Epilepsia 2003.

Anesthetic agents in SE

	Midazolam (N=55)	Propofol (N=35)	Pentobarbital (N=106)	Total (N=196)
Acute treatment failure	17%	26%	8%	13%
Breakthrough seizures	49%	20%	12%	24%
Hypotension → pressors	31%	38%	68%	54%
Treatment failure	11%	4%	3%	18%
Mortality	46%	52%	48%	48%

Claasen J et al., Epilepsia 2003.

Ketamine infusion

- Ketamine advantages:
  - Does not produce cardiac depression, hypotension
  - Short half life (2-3 hours)

- Possible concerns regarding increased intracranial pressure (ICP)
  - Children sedated with ketamine for lumbar puncture had higher ICPs
  - Meta-analysis of 7 studies found no effect of ketamine on ICP

Ben Yehuda Y, Watemberg N. *J Child Neurol*. 2006 Jun;21(6):441-3.
Zeiler FA, et al. *J Crit Care*. 2014 Dec;29(6):1096-106.
Zeiler FA, et al. *Neurocrit Care*. 2014 Aug;21(1):163-73.

Ketamine infusion

- Largest study: Retrospective 58 patients at 10 centers
  - Ketamine → "possibly" or "probably" contributed to seizure control in 32%
  - No response to ketamine seen:
    - In patients seizing for > 8 days
    - In patients who had already failed 7 or more drugs
  - Mortality rate 43%, slightly lower than with other IV sedative medications

Gaspard N, et al. *Epilepsia* 2013 Aug;54(8):1498-503.

Ketamine infusion

- Meta-analysis of 22 studies:
  - Ketamine → electrographic seizure resolution in 56.5% adult, 63.5% pediatric patients
  - Low incidence of adverse effects (3% adults)

Zeiler FA, et al. *Neurocrit Care*. 2014 Jun;20(3):502-13.

Other possibilities?

	Number of cases	Comments
Allopregnanolone	2	In ongoing clinical trials
Cannabidiol	2	
CSF drainage		Older therapy
Electroconvulsive therapy	8	87% success
Hypothermia	9	High rate of complications
Immunotherapy	--	Unknown effectiveness
Inhaled anesthetics	27	41% success
Lidocaine	300+, widely used	47-56% success
Magnesium	3	
Neurosurgery	36	75% success
Stiripental	5	60% success
Trancranial magnetic stimulation	21	74% success rate
Vagus nerve stimulator	4	Unclear success

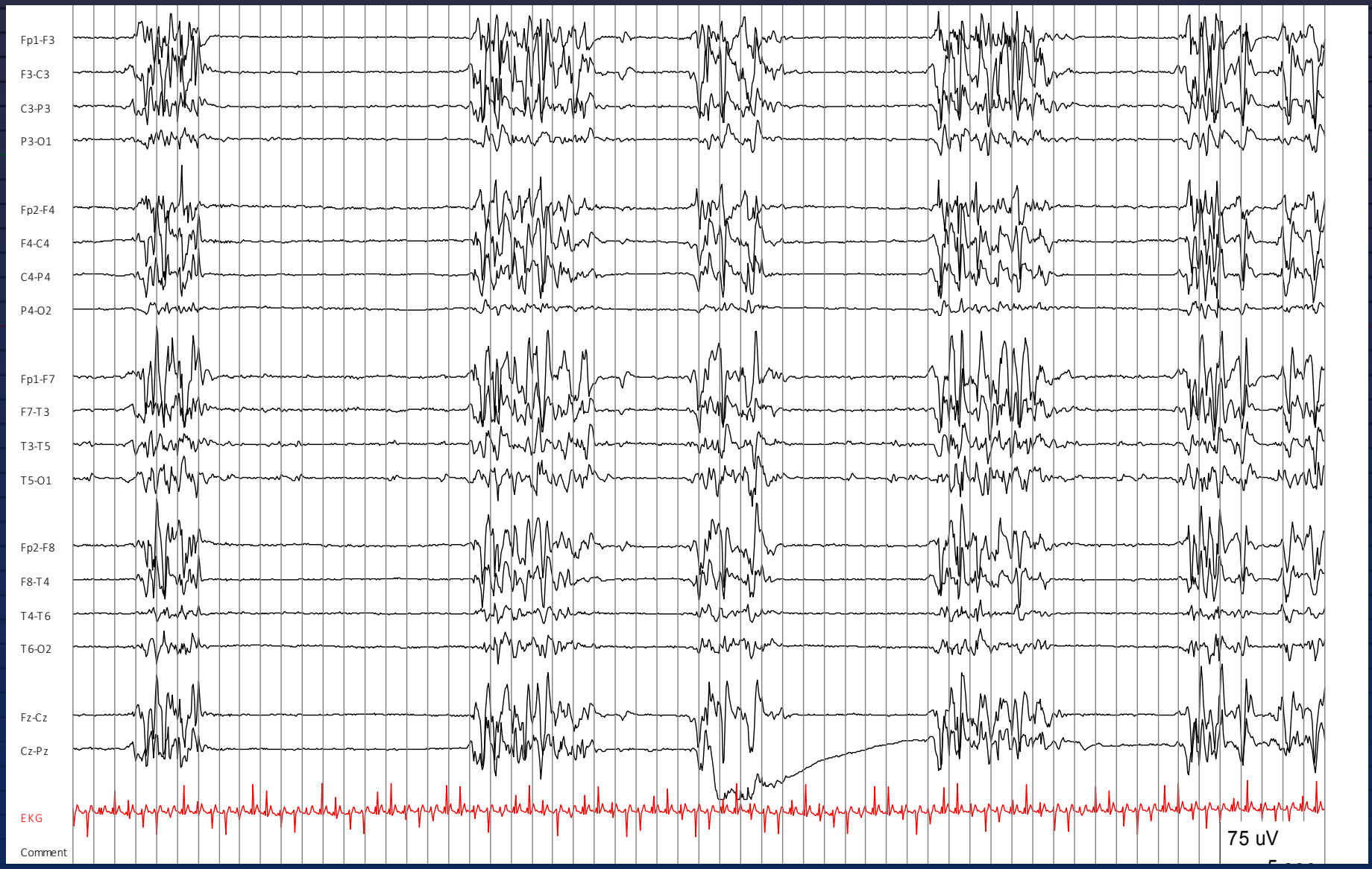
Ferlisi M, Shorvon S. *Brain*. 2012 Aug;135(Pt 8):2314-28.

Depth of suppression

- When initiating treatment with IV anesthetic agents, disagreement about depth of sedation:
  - EFNS guidelines: Titrate to either burst-suppression or isoelectric EEG
  - NCS guidelines: Titrate to burst-suppression (8-20 second intervals), diffuse beta, seizure cessation or isoelectric EEG

Meierkord H, et al. *Eur J Neurol*. 2010 Mar;17(3):348-55.

Brophy GM, et al. *Neurocrit Care*. 2012 Aug;17(1):3-23.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F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
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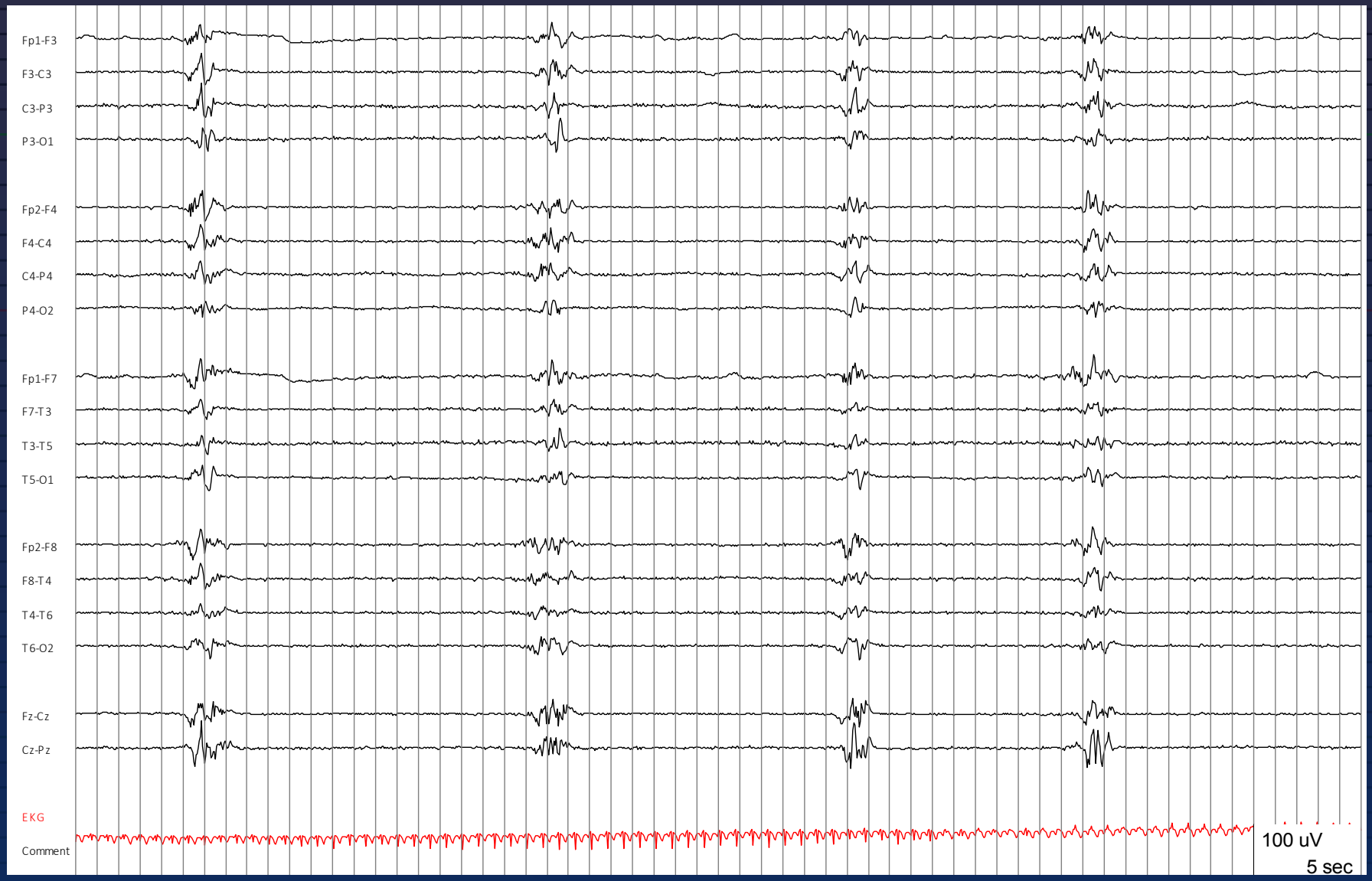
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
EKG
Comment
75 uV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F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
EKG
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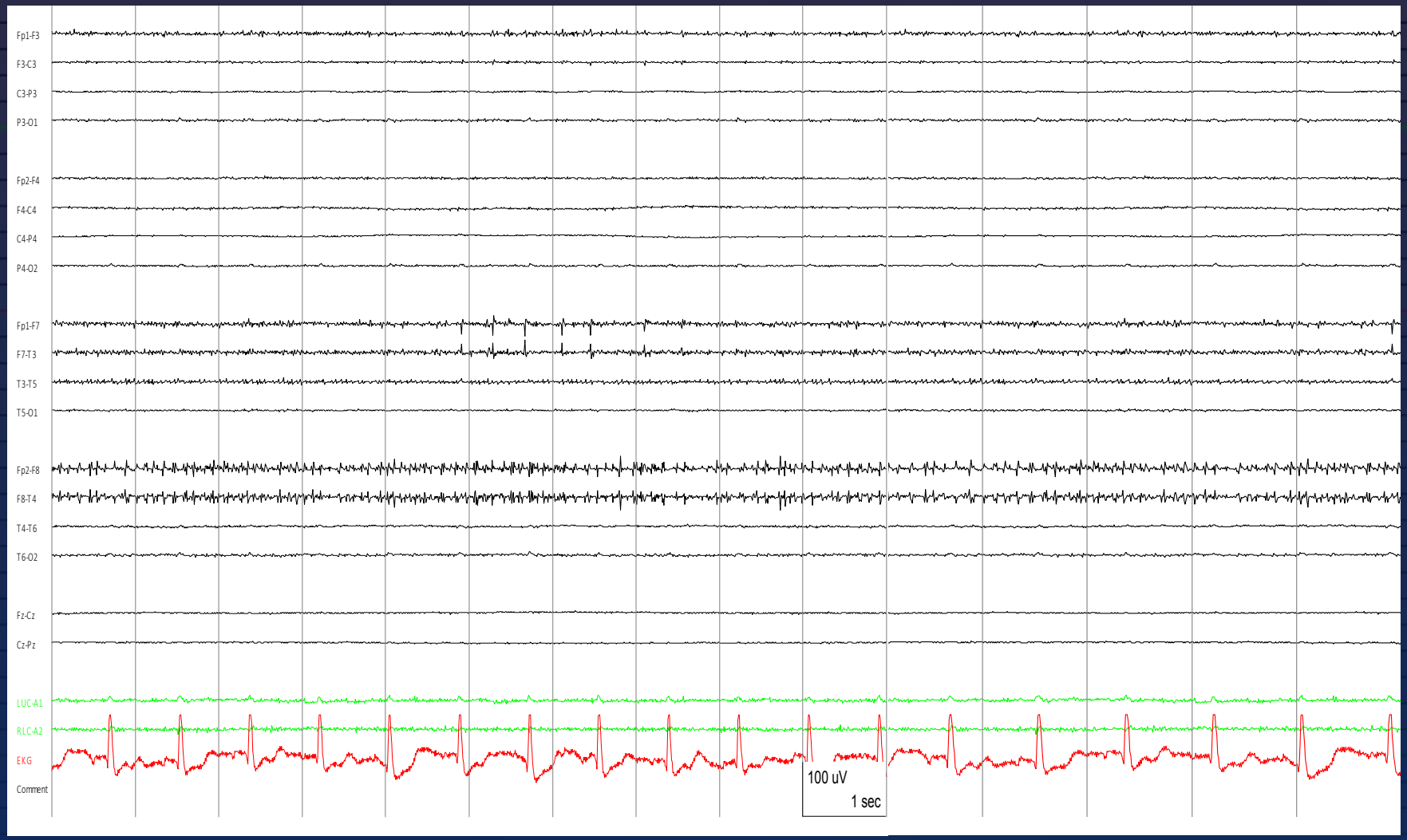
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
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F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
LUC-A1
RLC-A2
EKG
Comment
100 uV
1 sec

Depth of suppression

Study of 37 pts with RSE weaned off anesthetic agents:

- 17 successful weans, 20 unsuccessful weans
  - Interburst interval, burst-suppression ratio, length of bursts did not predict successful weans
  - Epileptiform activity within bursts → decreased success
  - Lower amplitude bursts (< 125 μV) → increased success

Krishnamurthy KB, Drislane FW. *Epilepsia*. 1999 Jun;40(6):759-62.

Outcome after refractory status

Outcome	n = 596
Death	207 (35%)
Severe neurological deficit	79 (13%)
Mild neurological deficit	80 (13%)
Undefined neurological deficit	22 (4%)
Recovery to baseline	208 (35%)

Ferlisi M, Shorvon S. *Brain*. 2012 Aug;135(Pt 8):2314-28.

NORSE

- **N**ew **O**nset **R**efractory **S**tatus **E**pilepticus:
  - First described in a group of young women in Singapore
  - Previous healthy patients
  - Etiology unknown (at least initially) despite extensive investigation for infectious etiologies

NORSE

- NORSE features:
  - CSF: mild lymphocytosis or normal CSF
  - EEG: Repetitive, refractory seizures with focal, multifocal or generalized epileptiform activity
  - Imaging: Highly variable abnormalities, but many patients are normal

Wilder-Smith EP, et al. *Ann Acad Med Singapore*. 2005 Aug;34(7):417-20.
Costello DJ, Kilbride RD, Cole AJ. *J Neurol Sci*. 2009 Feb 15;277(1-2):26-31.

NORSE

Largest case series: 130 cases

- 52% cryptogenic → higher rate of tx failure
- 18% paraneoplastic
- 19% nonparaneoplastic autoimmune
- 7.7% infectious
- 3.3% other

Gaspard N, et al. *Neurology*. 2015 Nov 3;85(18):1604-13.

NORSE

- Bimodal age distribution (median ages 28.5 and 65.6)
- Female predominance 2:1 (especially in older patients)
- 38% → more than 2 IV anesthetic agents
- 54% of cryptogenic cases → immunotherapy, 69% of cases with an identified etiology received immunotherapy
- Anesthetics → more complications, **BUT** length of status epilepticus was associated with a higher degree of complications

Gaspard N, et al. *Neurology*. 2015 Nov 3;85(18):1604-13.

FIRES

Fever-**I**nduced **R**efractory **E**pilepsy **S**yndrome

- Refractory seizures begin a few days after an infection in previously healthy children
- Cryptogenic etiology
- Surviving patients have significant cognitive deficits after resolution of seizures

FIRES

- Subjects:
  - 77 patients with FIRES
  - Median age 8 year old
- Etiology:
  - Most → extensive metabolic and infectious workup
  - Only 35% tested for autoimmune etiologies
- Treatment:
  - Median of 8 AEDs
  - 39% received IVIg
  - 38% received steroids
    - Immunotherapy was reported to be beneficial in only rare cases

Kramer U, et al. *Epilepsia*. 2011 Nov;52(11):1956-65
Kramer U, et al. *Epilepsia*. 2011 Oct;52 Suppl 8:28-30.

FIRES

- None of the agents used shortened the disease course, except:
  - **Ketogenic diet** (25% efficacy, used in 5% of cases)
  - IVIg (effective in 6.7% of patients)

- Increased time spent in burst suppression → worse cognitive outcome

Kramer U, et al. *Epilepsia*. 2011 Nov;52(11):1956-65
Kramer U, et al. *Epilepsia*. 2011 Oct;52 Suppl 8:28-30.

FIRES vs. NORSE

	NORSE	FIRES
Age	18-81 (peaks at 29 & 66 years)	2-17 (median 8) years
Gender	F>M (4:1-2:1)	M>F (3:2)
Preceding fever?	34-71%	100%
Autoimmune etiology?	34-37%	4% (but only 35% of patients tested)
CSF	Abnormal 73%	Abnormal 57%
MRI	62% abnormal	32% abnormal early in illness
Outcome	62% poor outcome / deceased	70% poor outcome / deceased
Post-STE epilepsy	92% survivors	97% of survivors

Sakuma H, et al. *Acta Neurol Scand*. 2010 Apr;121(4):251-6.
Shyu CS, et al. *Brain Dev*. 2008 May;30(5):356-61.
Wilder-Smith EP, et al. *Ann Acad Med Singapore*. 2005 Aug;34(7):417-20.
Gaspard N, et al. *Neurology*. 2015 Nov 3;85(18):1604-13.
Mikaeloff Y, et al. *Epilepsy Res*. 2006 Apr;69(1):67-79.
van Baalen A, et al. *Epilepsia*. 2010 Jul;51(7):1323-8.
Kramer U, et al. *Epilepsia*. 2011 Nov;52(11):1956-65.

FIRES and NORSE

- Both conditions → inflammation on brain biopsy
- Both conditions → development of refractory epilepsy
- Different gender ratios, response to treatment in two conditions
- Increased understanding of autoimmune disease may provide etiology for previously “cryptogenic” cases

Sakuma H, et al. *Acta Neurol Scand*. 2010 Apr;121(4):251-6.
Shyu CS, et al. *Brain Dev*. 2008 May;30(5):356-61.
Wilder-Smith EP, et al. *Ann Acad Med Singapore*. 2005 Aug;34(7):417-20.
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Mikaeloff Y, et al. *Epilepsy Res*. 2006 Apr;69(1):67-79.
van Baalen A, et al. *Epilepsia*. 2010 Jul;51(7):1323-8.
Kramer U, et al. *Epilepsia*. 2011 Nov;52(11):1956-65.

Conclusions

- Treatment of refractory status epilepticus remains challenging due to limited data
- Trials of second line agents and IV anesthetics are reasonable treatment options
- The optimal depth of sedation for patients being treated with IV anesthetics is uncertain
- NORSE and FIRES remain challenging entities to treat. Understanding about these conditions is limited.