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Algorithme thérapeutique pour l'état de mal épileptique

Les jeudis de formation continue de médecine interne générale

Martigny – 17 novembre

Dr Vincent Alvarez – Service de neurologie – Hôpital du Valais

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Plan

- **Qu'est-ce que l'état de mal épileptique**
  - Définition
  - Physiopathologie
- **Prise en charge initiale**
- **Traitement de 2ème**
- **Survol de la suite…**
- **Algorithme de traitement**

Etat de mal épileptique: Definition

- **1ère apparition du mot “Status epilepticus” est en 1868 dans une retranscription de Bazire d’une conférence donnée par Trousseau:**
  - “You have heard of cases in which the attacks have lasted **two or three days**, and have terminated in **death**. This is the condition which has been termed status epilepticus at La Pitié-Salpétrière… characterized not by a single attack but a series of attacks.”

Neligan & Shorvon.The History of Status epilepticus and its Treatment. ***Epilepsia***. 2009; 50 Suppl 3: 56-58 |

Etat de mal épileptique: Definition

- **Neurocritical care Society:**
  - **5 min** or more of (i) continuous clinical and/or electro- graphic seizure activity or (ii) recurrent seizure activity **without recovery** (returning to baseline) between seizures. Brophy ***Neurocrit care*** 2012

- **International League Against Epilepsy** Trinka **Epilepsia** 2015:

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

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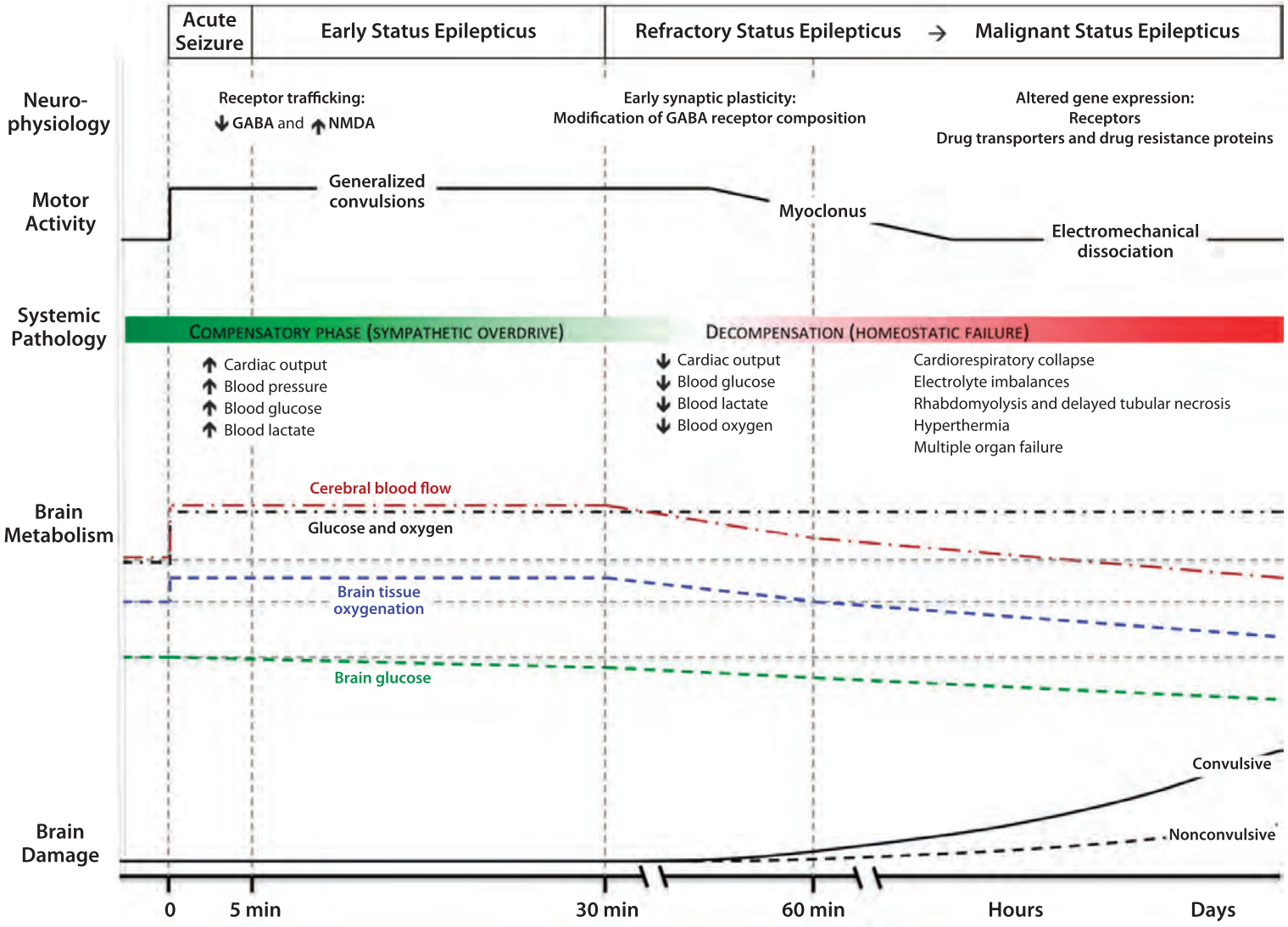
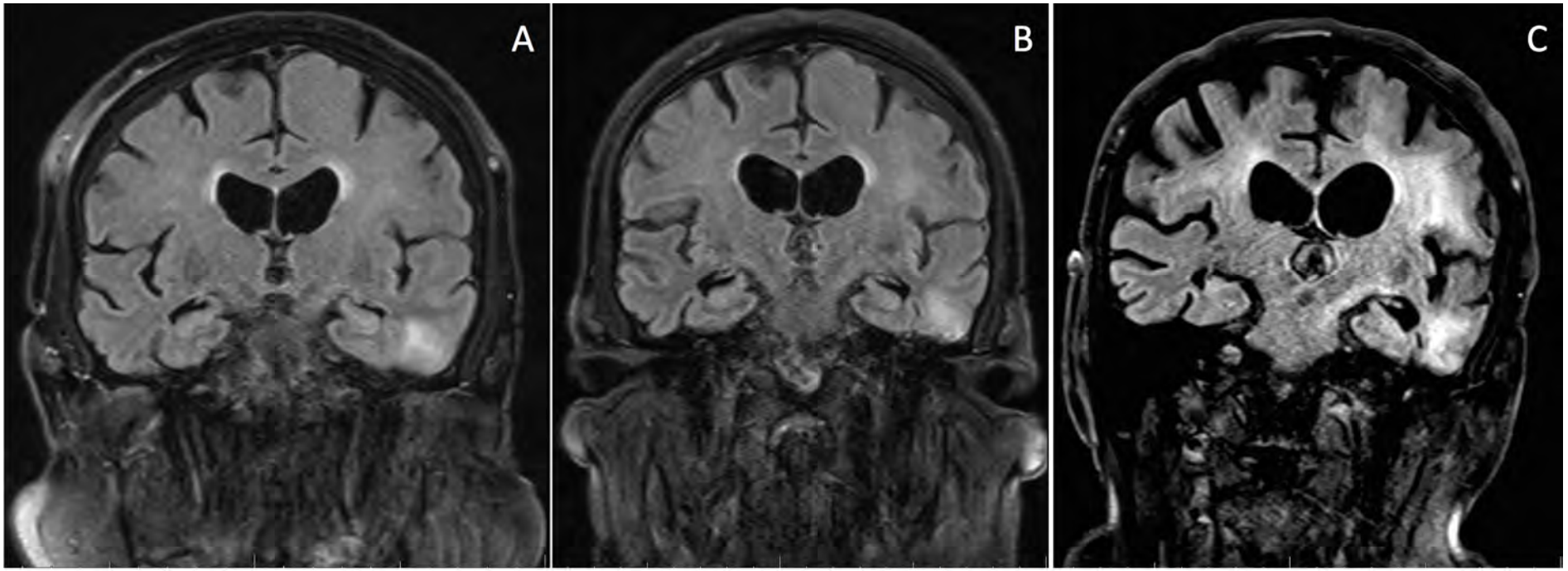
Physiopathologie



Hirsch & Gaspard. Status epilepticus. ***Continuum***. 2013; 19 (Epilepsy): 769-794

Physiopathology

- **Neuronal injury in human?**
  - Radiology
    - Hippocampal abnormalities on MRI (22/199) after a febrile SE Shinnar et al. 2012
    - DWI MRI, brain atrophy, laminar necrosis or mesial temporal sclerosis described Huang et al. 2009



Day 2: Isolated sz. Start of LEV

Day 5: LEV, VPA, LCS. And finally PROP/MDZ

Day 7: SE recurs with weaning sedation

Day 15: **MRI B**

At 3 month: **MRI C**. Conscious, but no contact. Under LEV, LCS, TPM

Fall with small left temporal contusion

Day 5: SE start with ongoing left temporal sz

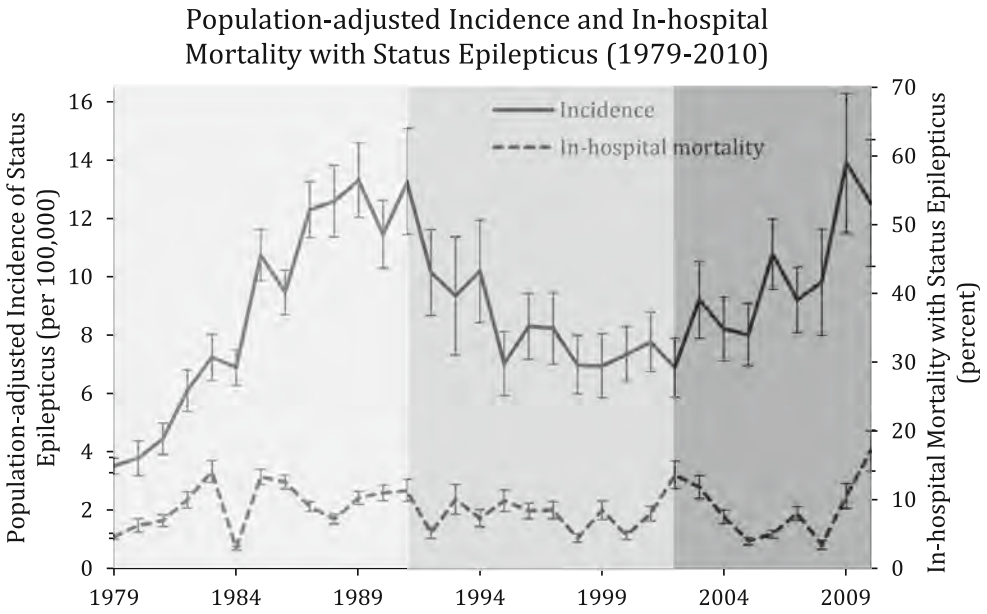
Day 6: **MRI A**

Day 11: SE stops, but breakthrough sz

At 5 months: Died from a pneumonia in rehabilitation

Etat de mal épileptique: épidemiologie

- **L'état de mal épileptique est la 2ème urgence neurologique potentiellement mortelle la plus fréquente après l'AVC**
- **Incidence de 10 à 40 cas pour 100'000 personne par année** **Coeytaux et al. 2000; DeLorenzo et al. 1996**



Dham et al. 2014

Etat de mal épileptique: Classification

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TABLE 12-1 Classification of Status Epilepticus According to Clinical and EEG Findings

		Ictal EEG Activity	
Motor Activity	**Consciousness**	**Generalized**	**Focal/Lateralized**
Intense (convulsive)	Markedly to severely impaired	Tonic-clonic Tonic Clonic Myoclonic (with absence, or in coma)	Hemiconvulsive
	Normal to mildly impaired	Myoclonic (usually in primary generalized epilepsy)	Epilepsia partialis continua
Absent or subtle (nonconvulsive)	Markedly to severely impaired	Absence (including typical, atypical, and late-onset) Subtle or purely electrographic (in coma)	Complex partial Subtle or purely electrographic (in coma)
	Normal to mildly impaired	Absence (including typical, atypical, and late-onset)	Simple partial (including aura continua) or mild or intermittent complex partial

Etat de mal épileptique: étiologie

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Table 1. List of diagnostic categories and their frequencies as definitive SE etiology

Underlying etiology after complete workup (n = 212)	n	%
Total, n = 212		
ASD-related (nonadherence, recent change or low levels)	34	16.04
Brain tumor without acute change (no change or increase in tumor load)	28	13.21
Acute hemorrhagic cerebrovascular event	21	9.91
Known epilepsy (non structural) without provocative factors (breakthrough seizures)	16	7.55
Remote ischemic cerebrovascular event	14	6.6
Unclassified[a]	13	6.13
CNS infection (meningitis or encephalitis)	12	5.66
Unknown origin	11	5.19
Toxic-metabolic	10	4.72
Systemic infection/sepsis	10	4.72
Remote hemorrhagic cerebrovascular event	8	3.77
Acute TBI	7	3.3
Acute ischemic cerebrovascular event	5	2.36
Remote TBI	6	2.83
Alcohol related (withdrawal or intoxication)	6	2.83
Brain tumor with acute change (bleeding, recent biopsy/surgery or rapid increase in edema)	5	2.36
Benzodiazepine withdrawal	4	1.89
Neurodegenerative disease	2	0.94
Other drugs known to reduce seizure threshold	0	0

ASD, antiseizure drug; CNS, central nervous system; TBI, traumatic brain injury.

[a]Unclassified includes: three multiple sclerosis, two confirmed and one possible posterior reversible encephalopathy syndrome (PRES), two tumoral meningitis, one NMDA encephalitis, one neurosarcoidosis, one eclampsia, one arteriovenous malformation without bleeding, and one case of microangiopathic hemolytic anemia.

- La non-adhérence au traitement chez un patient souffrant d'épilepsie reste la cause la plus fréquente

- 45% des étiologies nécessitent des prises en charges spécifiques.

Alvarez **Epilepsia** 2014

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Prise en charge initiale

Critical care treatment	Timing (minutes post seizure onset)	Goals	Rationale/references
Non-invasive airway protection and gas exchange with head positioning	Immediate (0–2 min)	Maintain airway patency, avoid snoring, administer O_2	[40, 76–79]
Intubation (if airway/gas exchange compromised or elevated ICP suspected)	Immediate (0–10 min)	Establish secure oxygenation and ventilation	Expert opinion
Vital signs: O_2 saturation, BP, HR	Immediate (0–2 min)	Establish and support baseline vital signs	[80–81]
Vasopressor support of BP if SBP <90 mmHg or MAP <70	Immediate (5–15 min)	Support CPP	Expert opinion
Finger stick blood glucose	Immediate (0–2 min)	Diagnose hypoglycemia	
Peripheral IV access	Immediate (0–5 min)	Establish medication route	[80–82]
1. Emergent initial AED therapy (i.e. benzodiazepine)		1. Stop seizure	
2. Fluid resuscitation		2. Establish euvolemia	
3. Nutrient resuscitation (thiamine given before dextrose; dextrose)		3. Reverse thiamine deficiency, treat hypoglycemia	
Urgent SE control therapy with AED	Immediate after initial AED given (5–10 min)	Stop seizure	[80–82]
Neurologic exam	Urgent (5–10 min)	Evaluate for mass lesion, acute intracranial process	Expert opinion
Triage lab test panel (see Table 2)	Immediate (5 min)	Diagnose life threatening metabolic condition	Expert opinion
Refractory SE treatment	Urgent (20–60 min after 2nd AED)	Stop seizures; treatment strategies based on individual patient response and AED concentrations (if applicable)	Expert opinion
Urinary catheter	Urgent (0–60 min)	Evaluate systemic circulation	Expert opinion
Continuous EEG	Urgent (15–60 min)	Evaluate for NCSE if not waking up after clinically obvious seizures cease	[50, 73, 75]
Diagnostic testing (selection depends on clinical presentation)	Urgent (0–60 min)	Evaluate for mass lesions, meningitis, encephalitis	Expert opinion
CT			
LP			
MRI			
Intracranial pressure monitoring (depending on clinical presentation)	Urgent (0–60 min of imaging diagnosis)	Measure and control ICP	Expert opinion

AED antiepileptic drug; *BP* blood pressure; *CPP* cerebral perfusion pressure; *CT* computed tomography; *EEG* electroencephalogram; *HR* heart rate; *ICP* intracranial pressure; *LP* lumbar puncture; *MAP* mean arterial pressure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure

Etat de mal épileptique: treatment

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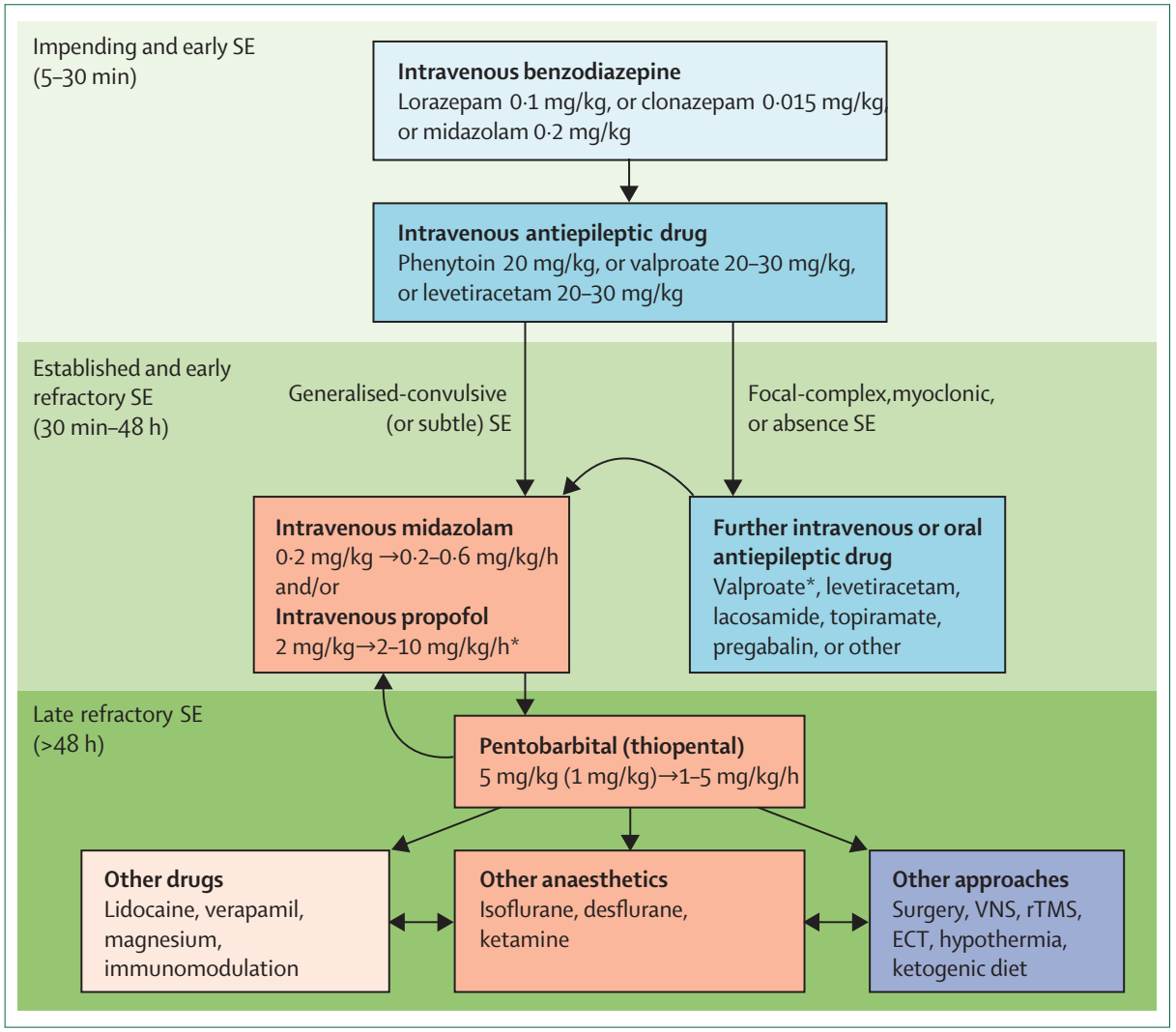

1ère ligne: les benzodiazépines

- **Leppik et al. 1983**
  - 70 adults with convulsive SE
  - SE episode were in controlled in
    - 89% with LZP
    - 76% with DZP
- **Treiman et al. 1998 ("The VA affairs study)**
  - 384 patients
  - SE episode were in controlled in:
    - 64.9% with **LZP 0.1mg/kg**
    - 58.2% with PB 15mg/kg
    - 55.8% with DZP 0.15 mg/kg + PHT 18 mg/kg
    - 43.6% with PHT 18 mg/kg
- **Alldrege et al. 2001**
  - 205 adult patients
  - SE episode were in controlled in:
    - 21% with placebo
    - 42.5% with DZP
    - 59.1% with LZP
- **Silbergleit et al. 2012 (RAMPART)**
  - 893 adults and pediatric
  - SE was controlled in:
    - 63.4% for iv LZP 4 mg
    - 73.4% for **im** MDZ 10 mg

1ère ligne: les benzodiazépines

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Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	[a, level A
Phenytoin/fo	[b, level A
Phenobarbita	[b, level A
Valproate so	[b, level A
Levetiracetam	Class IIb, level C

Clonazepam (Rivotril) ?

Clonazepam pour l'état de mal: quelles évidences?

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- **Comparaison de CLZ, LZP et MDZ** Alvarez **Epilepsia** 2015
  - 177 patients, prospective, 4 centres

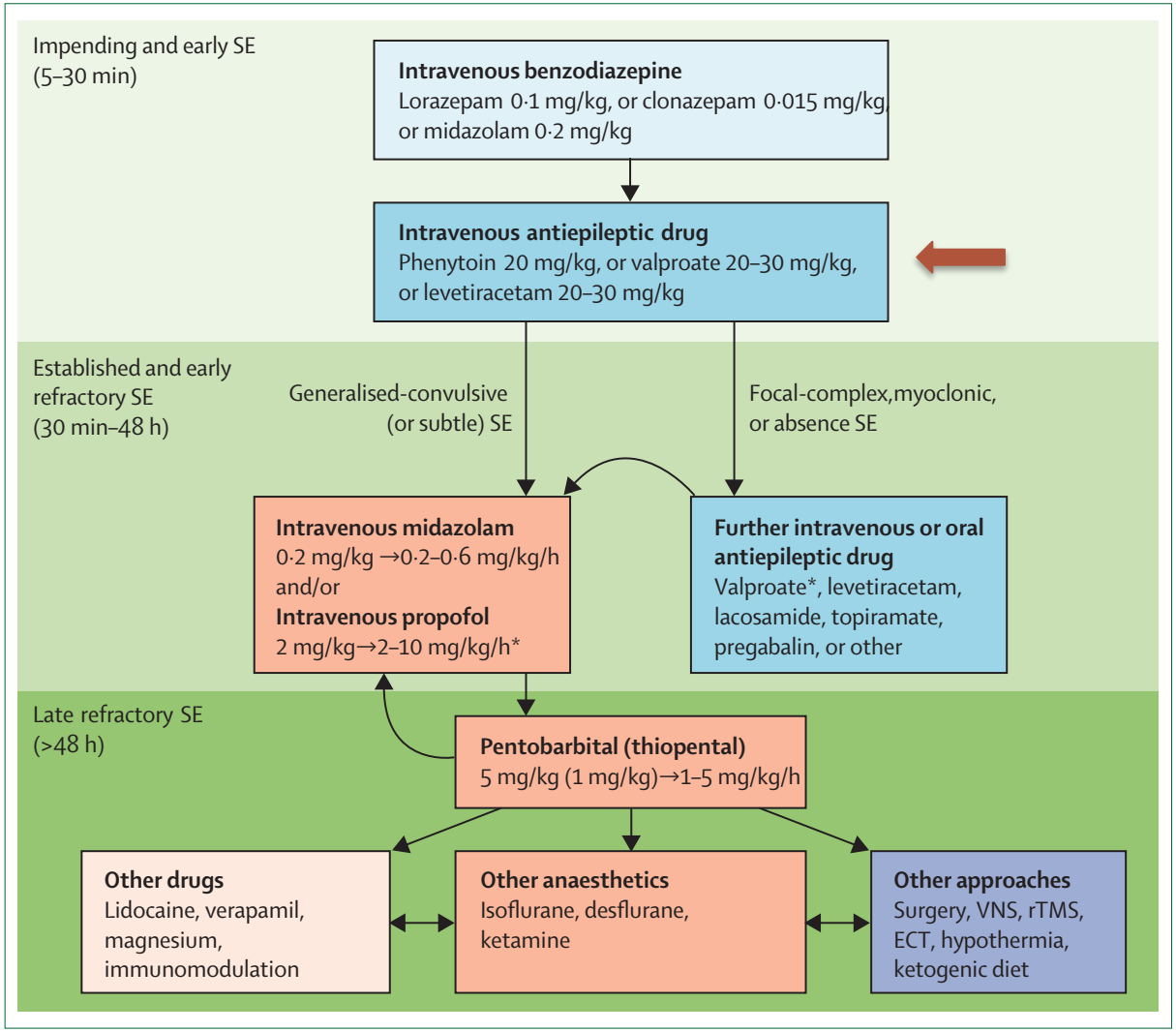
KEY POINTS

- Clonazepam seems to be an effective alternative to lorazepam and midazolam as first-line treatment of status epilepticus.
- Lorazepam is underdosed in the majority of cases.
- Practice variability of initial treatment influences the risk of refractoriness and the number of antiseizure drugs used but not outcome at hospital discharge.

1ère ligne: résumé pratique

- MDZ im 10 mg pour adulte
- CLZ iv 0.015 mg/kg -> 1 mg pour adulte (ev répéter)
- Si disponible LZP 0.1 mg/kg (4 mg d’abord, à répéter)

2ème ligne



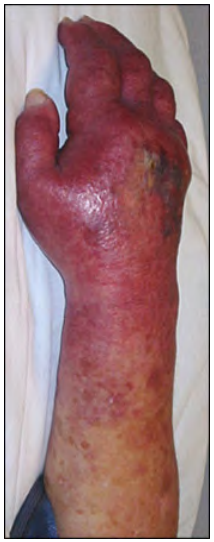
Rossetti & Lowenstein. Management of refractory status epilepticus in adults: still more questions than answers. ***Lancet Neurol***. 2011; 10: 922-930

2ème ligne de traitment

- **A admistrer si crises subsistent après les BZD**
- **A adminstrer également si réponse pour éviter récidives**
  - En règle général toujours associé à la première ligne
- **Choix entre certains AED non sédatifs disponibles iv:**
  - Phénytoïne
  - Valproate
  - Levetiracetam
  - (Lacosamide)

2ème ligne: phénytoïne

- **Dose:**
  - 20 mg/kg, si pas d'effet, re-charge avec 5-10 mg/kg
    - Alkaline (pH 12)
    - Vitesse de perfusion limitée par hypotension (1.5%) et arrhythmies (2%)
    - **Max 50 mg/min, voire même 20mg/min** chez les > de 70 ans.
    - Monitoring ECG et TA indispensable
- **Controler les taux**
- **CAVE:**
  - purple glove syndrome
- **fos-phenytoin?**
  - Avantages pas clairs et $$$$
  - pas disponible en CH



2ème ligne: Valproate

- **Dose:**
  - Charge 20-40 mg/kg jusqu'à 200 mg/min
- **Pas d'hypotension, ni d'arrhythmies, ni réaction allergique**
- **Efficacité:**
  - rapportée jusqu'à 87% Gilad Acta Neurol Scandinavia 2000
  - Et bien toléré… Sinha Neurology 2000
- **Action dès 30 minutes**
- **CAVE:**
  - Peut provoquer une hyperammoniémie
    - Parfois démasque des déficience en OCT ou autre anomalie du cycle de Krebs
  - chez patients avec maladie hépatique et chez les enfants
  - Pancréatite
  - Risque théorique augmenté d'hémorragie car baisse la fct plaquettaire in vitro

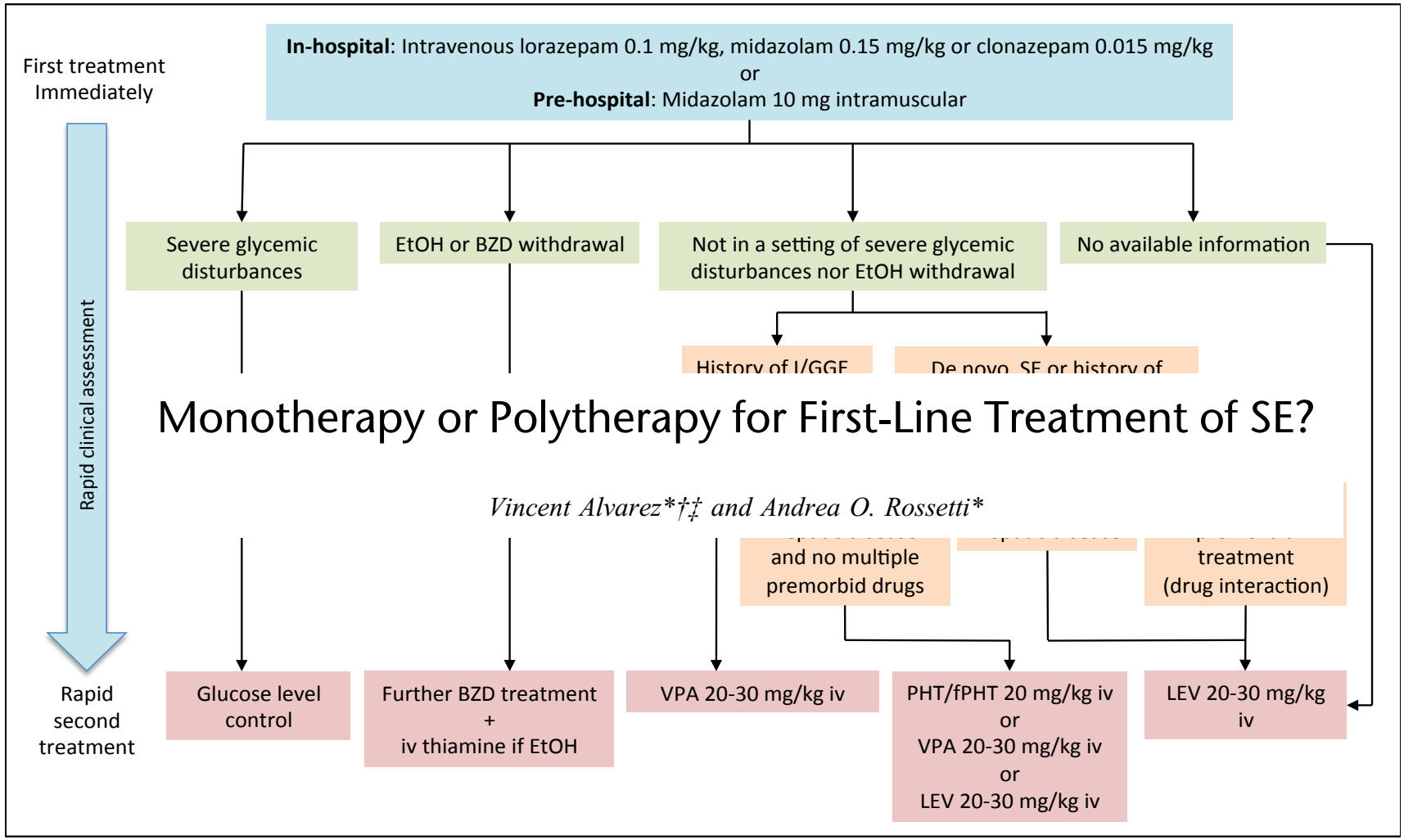
2ème ligne: Levetiracetam

- **Dose:**
  - Charge entre 20 et 60 mg/kg
- **10 études**
  - Dose 250-2500mg
  - Efficacité dans les études prospectives: 44-75%
  - Etudes retrospectives: 52-94%
- **CAVE comorbidité psychiatrique**
  - Rarement un problème en phase hyper-aigue

2ème ligne: lequel choisir?

- **Une seule étude rétrospective qui compare les 3 après un échec des BZD** Alvarez **Epilepsia** 2011
  - Echec de la 2ème ligne:
    - VPA 20 mg/kg: 25.42%
    - PHT 20 mg/kg: 44.2%
    - LEV 20 mg/kg: 48.27%
    - Après correction pour les facteurs confondants, le VPA reste significtivement meilleur que le LEV (OR: 2.69 pour un échec de la 2ème ligne si le Keppra est choisi)
- **ESETT (Established Status Epilepticus Treatment Trial)**
  - Clinicaltrial.gov : NCT01960075
  - Randomisation entre les trois
  - Enrolle depuis octobre 2015
    → Fin 2019

Traitement initiale: attitude pragmatique



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Première ligne seule ou combinée d'emblée?

Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial

Lancet Neurol 2016; 15: 47–55

*Vincent Navarro, Christelle Dagron, Caroline Elie, Lionel Lamhaut, Sophie Demeret, Saïk Urien, Kim An, Francis Bolgert, Jean-Marc Tréluyer, Michel Baulac, Pierre Carli, for the SAMUKeppra investigators**

	Clonazepam plus levetiracetam (n=68)	Clonazepam plus placebo (n=68)	RR (95% CI)	p value
Primary outcome				
Seizure cessation within 15 min of the onset of treatment				
Modified intention-to-treat analysis	50/68 (74%)	57/68 (84%)	0·88 (0·74–1·05)	0·14
Per-protocol analysis	46/61 (75%)	50/58 (86%)	0·87 (0·73–1·04)	0·14
Secondary outcomes*				
Time between the first injection and cessation of convulsions, min†	3 (0–50)	5 (0–41)	..	0·97
Need for a second injection of clonazepam after 5 min	28/67 (42%)	28/65 (43%)	0·97 (0·65–1·44)	0·88
Need for injection of an antiepileptic drug after 15 min	19/67 (28%)	15/65 (23%)	1·23 (0·68–2·21)	0·49
Patients with waking signs at 35 min‡	22/56 (39%)	21/51 (41%)	0·95 (0·60–1·51)	0·84
Endotracheal intubation for general anaesthesia at 35 min	9/68 (14%)	12/67 (18%)	0·95 (0·82–1·09)	0·45
Seizures at hospital arrival	1/68 (1%)	2/66 (3%)	0·49 (0·05–5·23)	0·62
Patients awake at hospital arrival‡	29/39 (74%)	31/44 (70%)	0·87 (0·43–1·75)	0·69
Seizure recurrence during stay in hospital	7/67 (10%)	13/68 (19%)	0·55 (0·23–1·28)	0·16
Length of hospital stay, days				
Overall	10 (1–15)	10 (1–15)	..	0·95
In intensive care unit	3 (0–15)	3 (1–15)	..	0·74
Post-hoc analyses				
Delay between the first and second injection of clonazepam, min	8 (5–25)	10 (5–25)		0·73
Cessation of convulsions at 35 min	55/68 (81%)	55/68 (81%)	1·00 (0·85–1·18)	1
Prehospital seizure recurrence in patients with seizure cessation within 35 min of the onset of treatment‡	9/42 (21%)	11/49 (22%)	0·95 (0·44–2·08)	0·91
Neurological state at 15 days after admission to hospital, or earlier if discharged from hospital				
Death§	3/66 (5%)	4/65 (6%)	0·74 (0·17–3·17)	0·72
New neurological deficit¶	1/63 (2%)	8/61 (13%)	0·12 (0·02–0·94)	0·016

Data are in n/N (%) or median (minimum/maximum values) unless otherwise indicated. RR=relative risk. *Comparison of the time between the first injection and signs of awakening was not presented because of missing data (data not available in four of 30 awake patients [13%] in the levetiracetam group and seven of 28 awake patients [25%] in the placebo group). Comparison of Glasgow Coma Scale for patients without waking signs at 35 min was not presented because that population was too small (data available for 19 patients in the levetiracetam group and 11 patients in the placebo group). †In patients with seizures that stopped after the onset of the treatment. ‡In patients without endotracheal intubation; waking signs are defined as either eyes opening or hand shaking in response to speech. §No death was judged to be a consequence of the drug treatments. ¶In alive patients.

***Table 2*: Primary, secondary, and post-hoc outcomes**

3ème ligne

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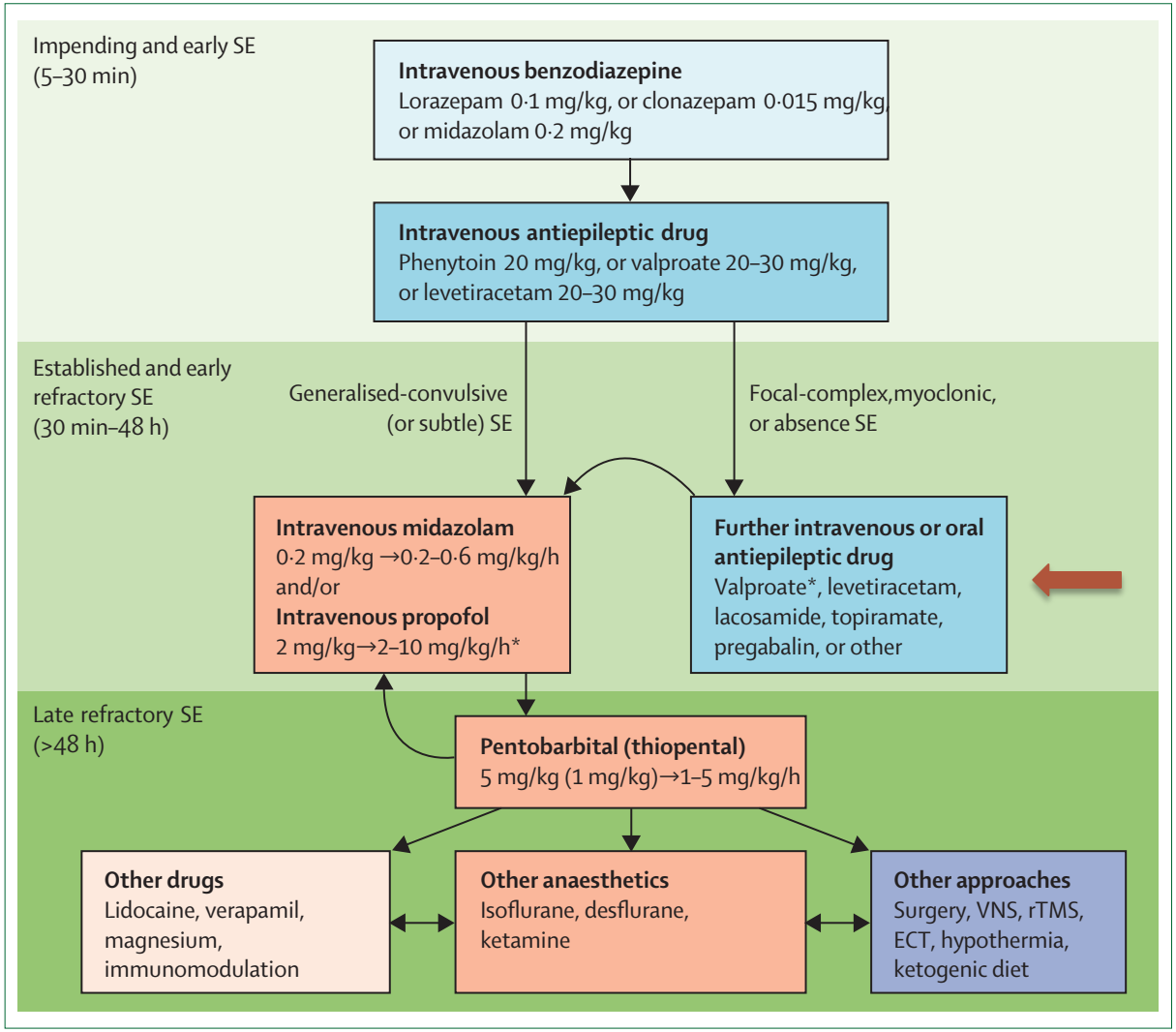


Rossetti & Lowenstein. Management of refractory status epilepticus in adults: still more questions than answers. ***Lancet Neurol***. 2011; 10: 922-930

“3ème ligne” : coma

- **Supprimer complètement l’activité épileptique**
  - Hautes doses de « GABAergique » nécessaires et donc intubation
- **Nécessite un monitoring EEG**
  - **“Seizures suppression”**
    - « compliqué » à monitorer
  - **“Burst-Suppression”**
    - Plus simple, mais peut-être en lien avec un état hyperexcitable Amzica **Epilepsia** 2009
  - **“Suppression”**
    - probablement pas nécessaire et grosse doses de sédatifs nécessaires
  - AUCUNE ÉVIDENCE pour choisir entre un de ces 3 patterns est mieux qu’un autre Classen **Epilepsia** 2003 (review)
- **Quelle molécule utiliser?**
  - Propofol, dormicum, barbiturique, kétamine,…?

Coma thérapeutique et mortalité

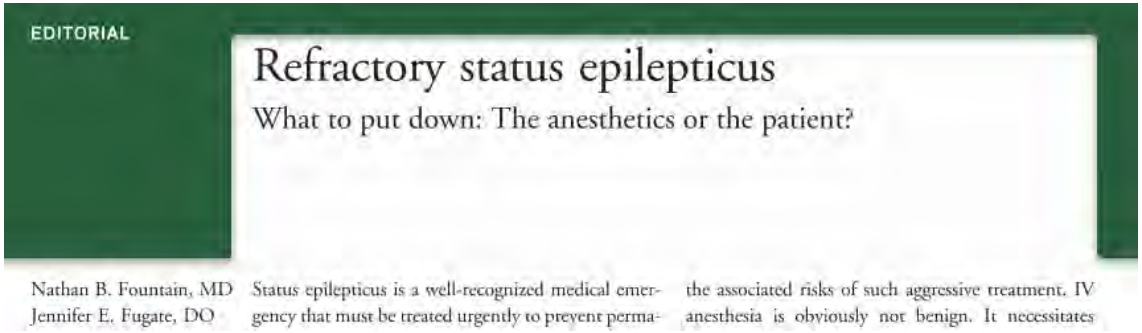
- **The treatment**
  - Impact on mortality:
    - **Therapeutic coma using anesthetic drugs**
      - retrospective assessment of 126 SE patients treated in intensive care units
        - IVAD → OR: 8.65 Kowalski et al. 2012
      - prospective cohort of 171 SE treated in ICU
        - IVAD → RR: 2.9 Sutter et al. 2014
      - prospective cohort of 467 patients
        - IVAD → RR: 9.1 Marchi et al. 2015

Coma thérapeutique et mortalité

- **The treatment**
  - Impact on mortality:
    - Does **therapeutic coma** using anesthetic drugs increased mortality?

Coma thérapeutique et mortalité

- **The treatment**
  - Impact on mortality:
    - **Therapeutic coma using anesthetic drugs**



EDITORIAL

Refractory status epilepticus

What to put down: The anesthetics or the patient?

Nathan B. Fountain, MD
Jennifer E. Fugate, DO

Status epilepticus is a well-recognized medical emergency that must be treated urgently to prevent perma-

the associated risks of such aggressive treatment. IV anesthesia is obviously not benign. It necessitates

EPILEPSY CURRENTS

Current Literature

in Clinical Science

Finding the Lesser of Two Evils: Treating Refractory Status Epilepticus

Factor associated with mortality

- **The treatment**
  - "Cultural differences"?
    - **Use of IVAD in SE**:
      - 5% in Germany Kellinghaus et al. 2012
      - 8% in Italy Vignatelli et al. 2005
      - 10.7% in Switzerland Marchi et al. 2015
      - 22% in France Aranda et al. 2010
      - 31% in the USA Claassen et al. 2002
      - 36% in the USA Cook et al. 2012
    - **Use of IVAD in RSE**:
      - 30% in Switzerland Novy et al. 2010
      - 43% in Switzerland Sutter et al. 2013
      - 87.3% in the USA Hocker et al. 2013

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Différences culturelles ?

VS

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Therapeutic coma for status epilepticus

Differing practices in a prospective multicenter study

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ABSTRACT

Objective: Our aim was to analyze and compare the use of therapeutic coma (TC) for refractory status epilepticus (SE) across different centers and its effect on outcome.

Methods: Clinical data for all consecutive adults (>16 years) with SE of all etiologies (except postanoxic) admitted to 4 tertiary care centers belonging to Harvard Affiliated Hospitals (HAH) and the Centre Hospitalier Universitaire Vaudois (CHUV) were prospectively collected and analyzed for TC details, mortality, and duration of hospitalization.

Results: Two hundred thirty-six SE episodes in the CHUV and 126 in the HAH were identified. Both groups were homogeneous in demographics, comorbidities, SE characteristics, and Status Epilepticus Severity Score (STESS); TC was used in 25.4% of cases in HAH vs 9.75% in CHUV. After adjustment, TC use was associated with younger age, lower Charlson Comorbidity Index, increasing SE severity, refractory SE, and center (odds ratio 11.3 for HAH vs CHUV, 95% confidence interval 2.47–51.7). Mortality was associated with increasing Charlson Comorbidity Index and STESS, etiology, and refractory SE. Length of stay correlated with STESS, etiology, refractory SE, and use of TC (incidence rate ratio 1.6, 95% confidence interval 1.22–2.11).

Conclusions: Use of TC for SE treatment seems markedly different between centers from the United States and Europe, and did not affect mortality considering the whole cohort. However, TC may increase length of hospital stay and related costs.

Classification of evidence: This study provides Class III evidence that for patients with SE, TC does not significantly affect mortality. The study lacked the precision to exclude an important effect of TC on mortality. ***Neurology*® 2016;87:1650–1659**

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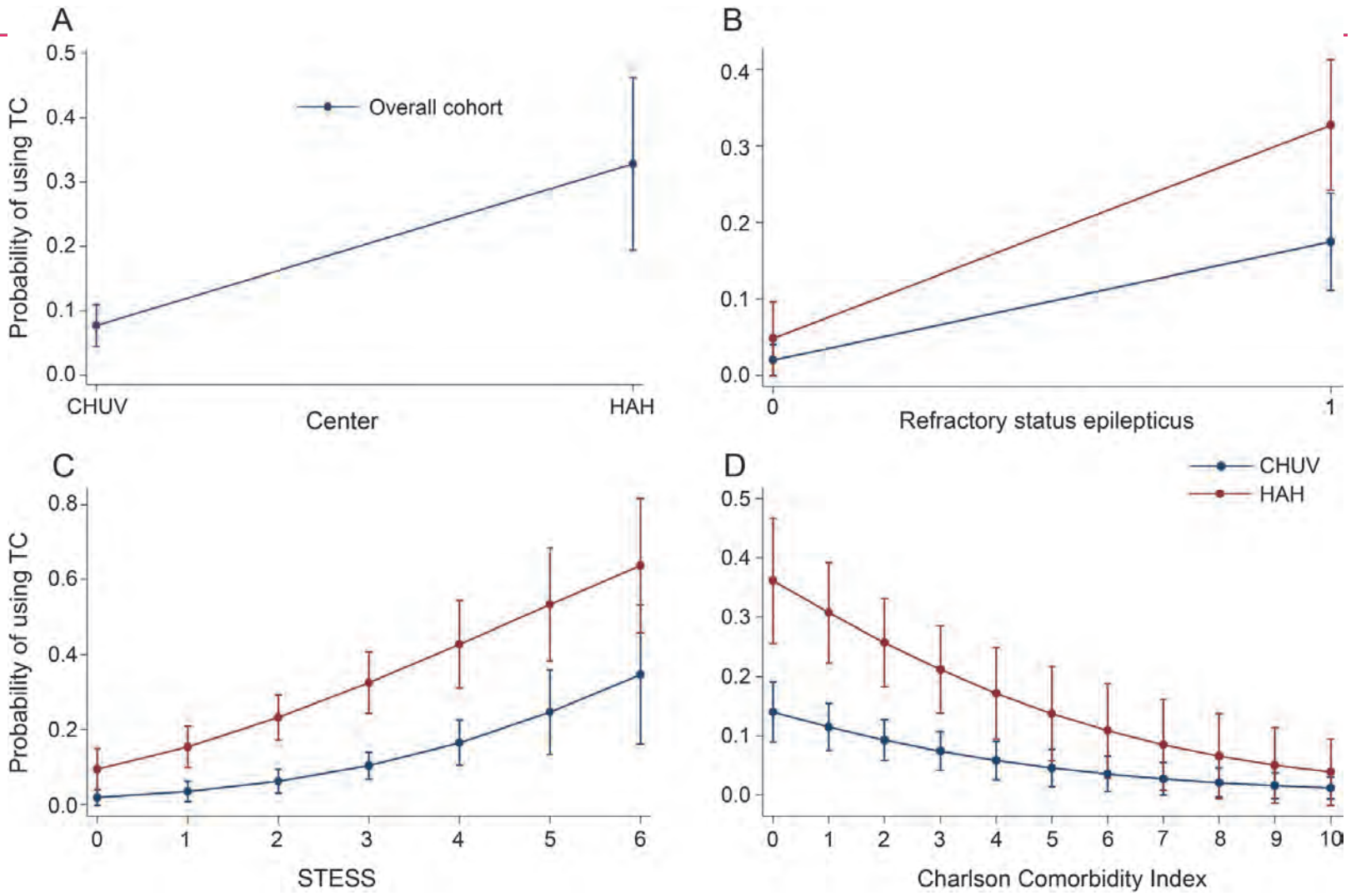
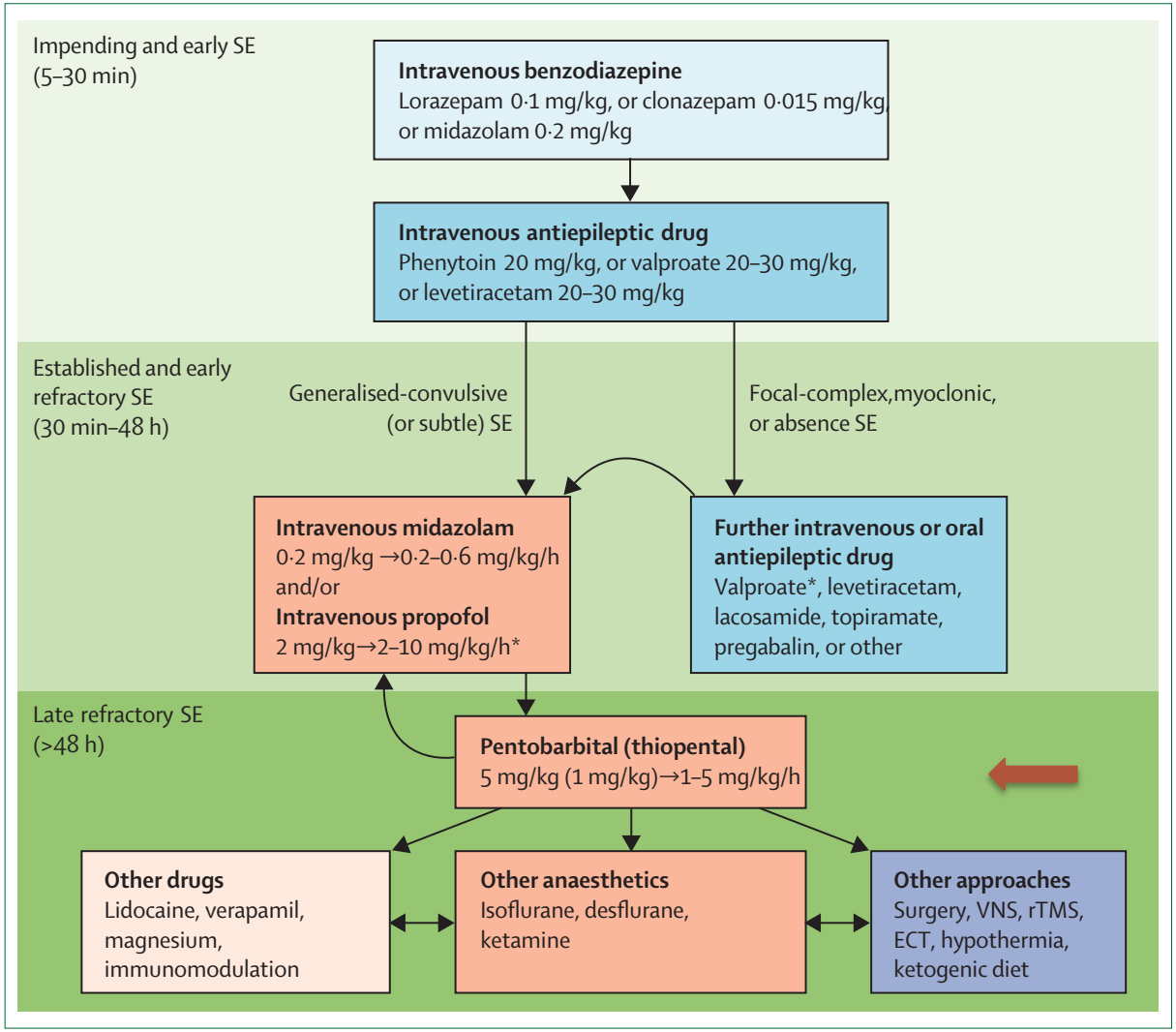
Figure 1 Adjusted margin probability for using TC comparing the 2 groups: HAH in red and CHUV in blue



(A) Overall probability by groups. (B) Probability by refractory status epilepticus. (C) Probability at equally spaced STESS values. (D) Probability at equally spaced Charlson Comorbidity Index values. Vertical axes represent probability of reaching outcome (using TC) based on the multivariate logistic regression model from table 2. CHUV = Centre Hospitalier Universitaire Vaudois; HAH = Harvard Affiliated Hospitals; STESS = Status Epilepticus Severity Score; TC = therapeutic coma.

Et après…



Rossetti & Lowenstein. Management of refractory status epilepticus in adults: still more questions than answers. ***Lancet Neurol***. 2011; 10: 922-930

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Conclusions:

- **L'état de mal épileptique (> 5min de convulsions ou crises) est une URGENCE neurologique**

- **Voir l'état de mal comme la manifestation d'un problème cérébral**
  - Chercher la cause

- **Algorithme de traitement pour la phase aigue**

Merci pour votre attention!

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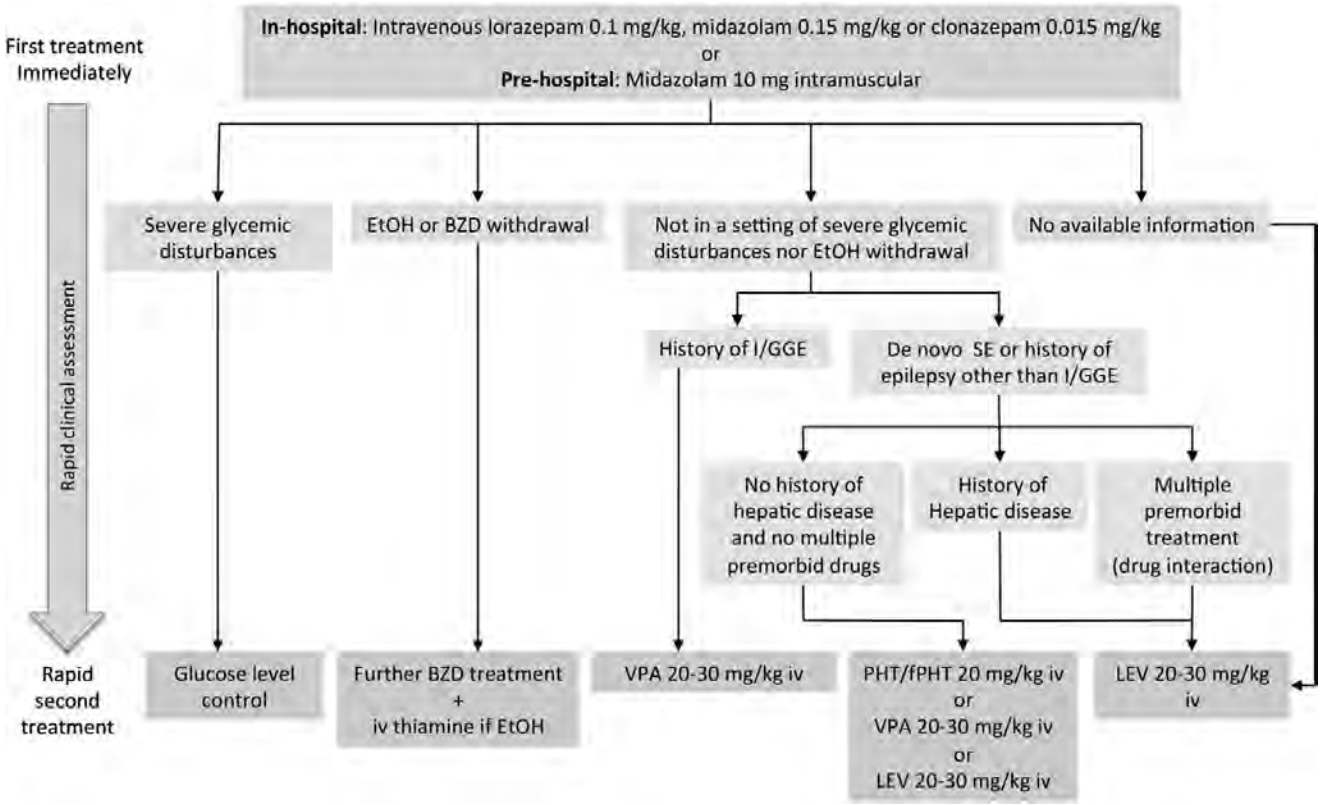

FIG. 1. Proposed rational algorithm for early seizure management in status epilepticus in adults. EtOH, ethyl alcohol; GGE, generalized genetic epilepsy; LEV, Levetiracetam; VPA, valproic acid; BZD, benzodiazepines; SE, status epilepticus; PHT, phenytoin; fPHT, fosphenytoin.