II MEETING DELLE NEUROSCIENZE TOSCANE

SNO Scienze Neurologiche Spedaliere

Società dei Neurologi, Neurochirurghi e Neuroradiologi Ospedalieri

Sin Società Italiana di Neurologia

Il trattamento delle crisi e degli stati epilettici nel Dipartimento di Emergenza

Dr. Marco Paganini
CdRR Diagnosi e Terapia dell'Epilessia
Neurologia 2 AOUC-Firenze

CRISI EPILETTICA

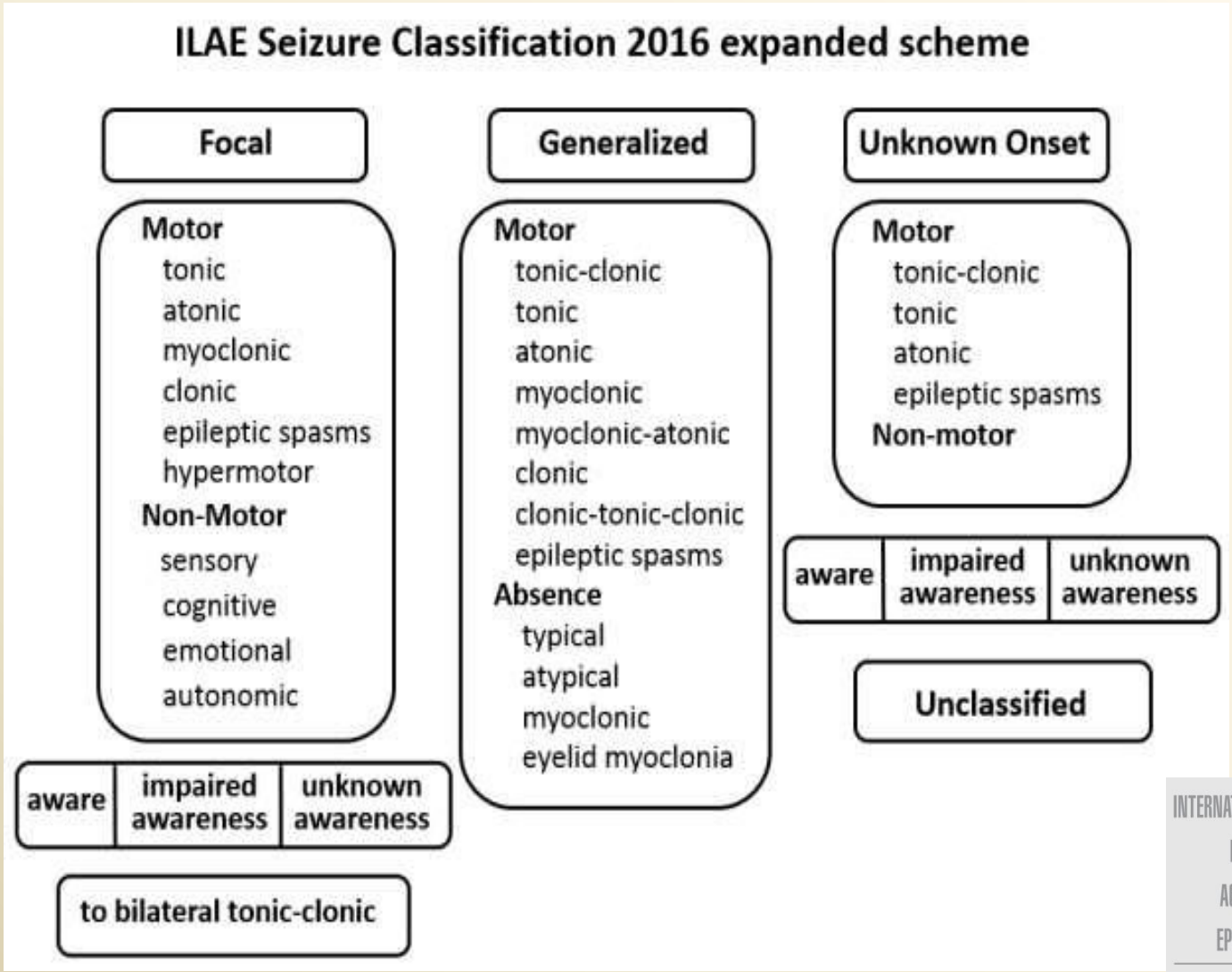
"A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"

The term transient is used as demarcated in time, with a **clear start and finish.**

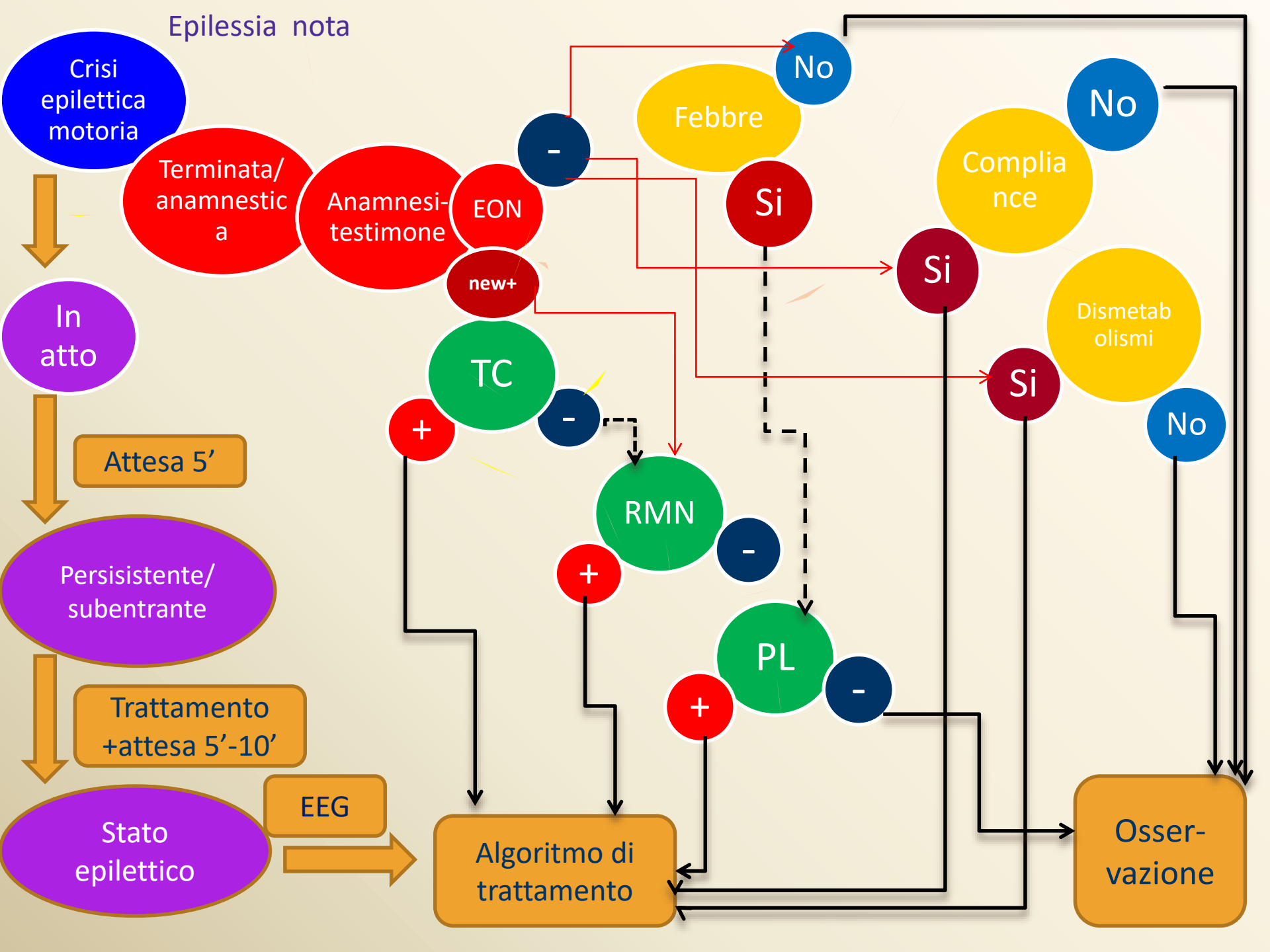
Robert S. Fisher
Department of Neurology & Neurological Sciences, Stanford University School of Medicine

Fisher et al, 2005

Crisi epilettiche: classificazione ILAE 2016



INTERNATIONAL LEAGUE AGAINST EPILEPSY
Established 1909


Epilessia nota
Crisi epilettica motoria
Terminata/ anamnestica
Anamnesi-testimone
EON
new+
In atto
Attesa 5’
Persisistente/ subentrante
Trattamento +attesa 5’-10’
Stato epilettico
EEG
TC
RMN
PL
Febbre
Si
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Compliance
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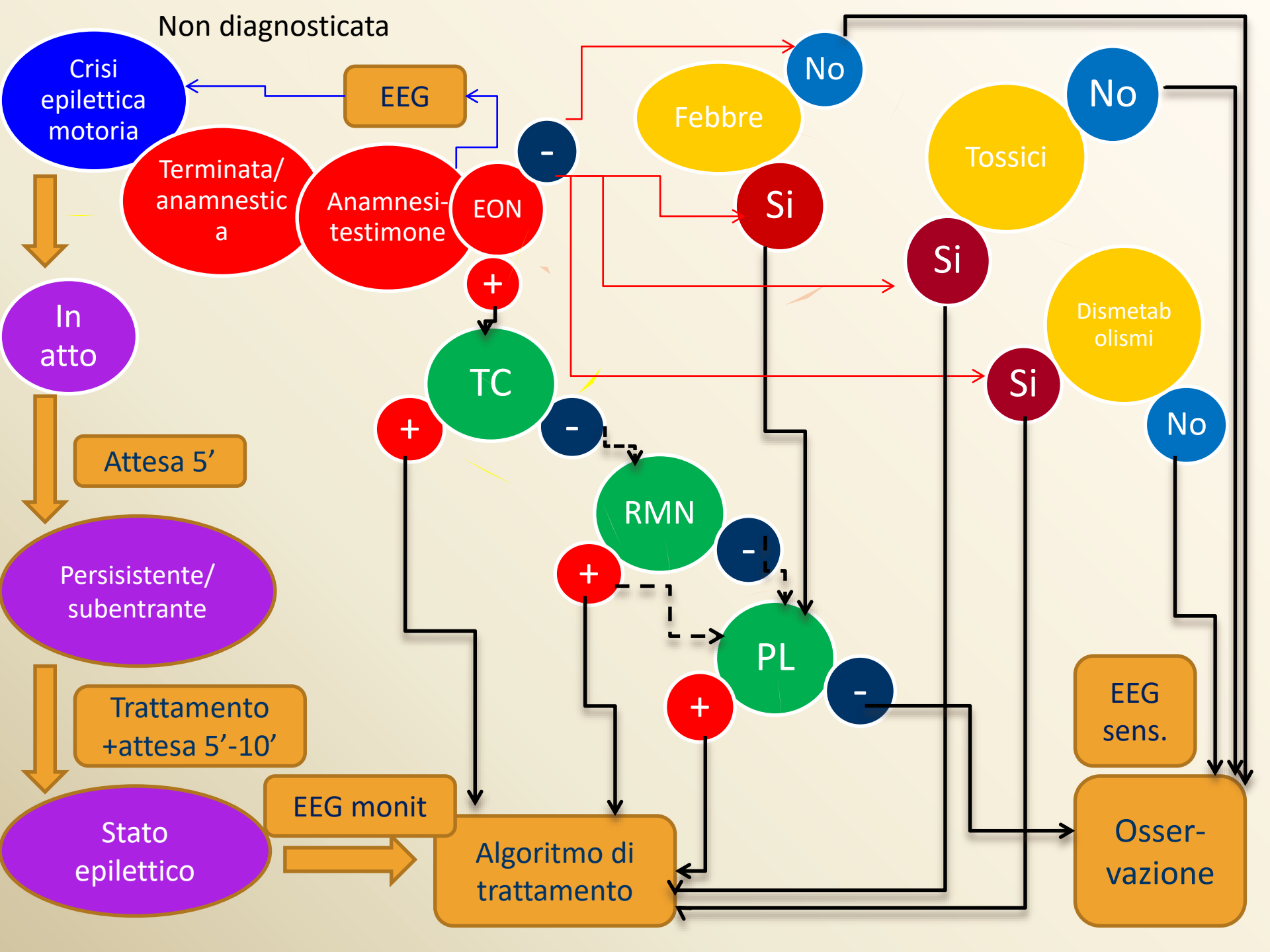
Dismetabolismi
Si
No
Algoritmo di trattamento
Osser-vazione


Non diagnosticata
Crisi epilettica motoria
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Terminata/ anamnestica
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Dismetabolismi
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Attesa 5’
RMN
+
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Persisistente/ subentrante
PL
+
-
EEG sens.
Trattamento +attesa 5’-10’
EEG monit
Stato epilettico
Algoritmo di trattamento
Osser-vazione

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

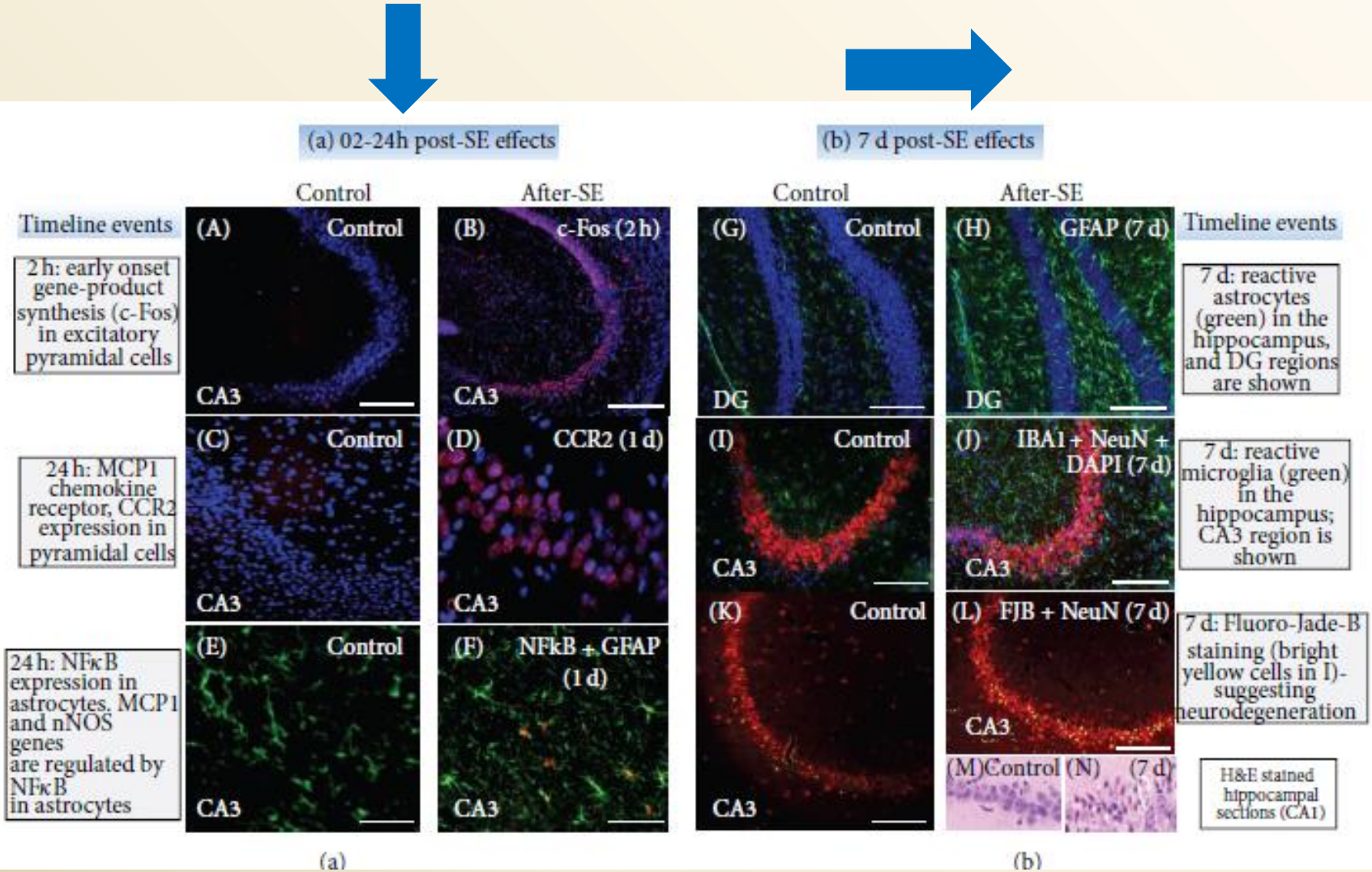
E. Trinka, H. Cock, D. Hesdorffer, A. O. Rossetti, I. E. Scheffer, S. Shinnar, S. Shorvon, and D.l H. Lowenstein

Epilepsia, 56(10):1515–1523, 2015

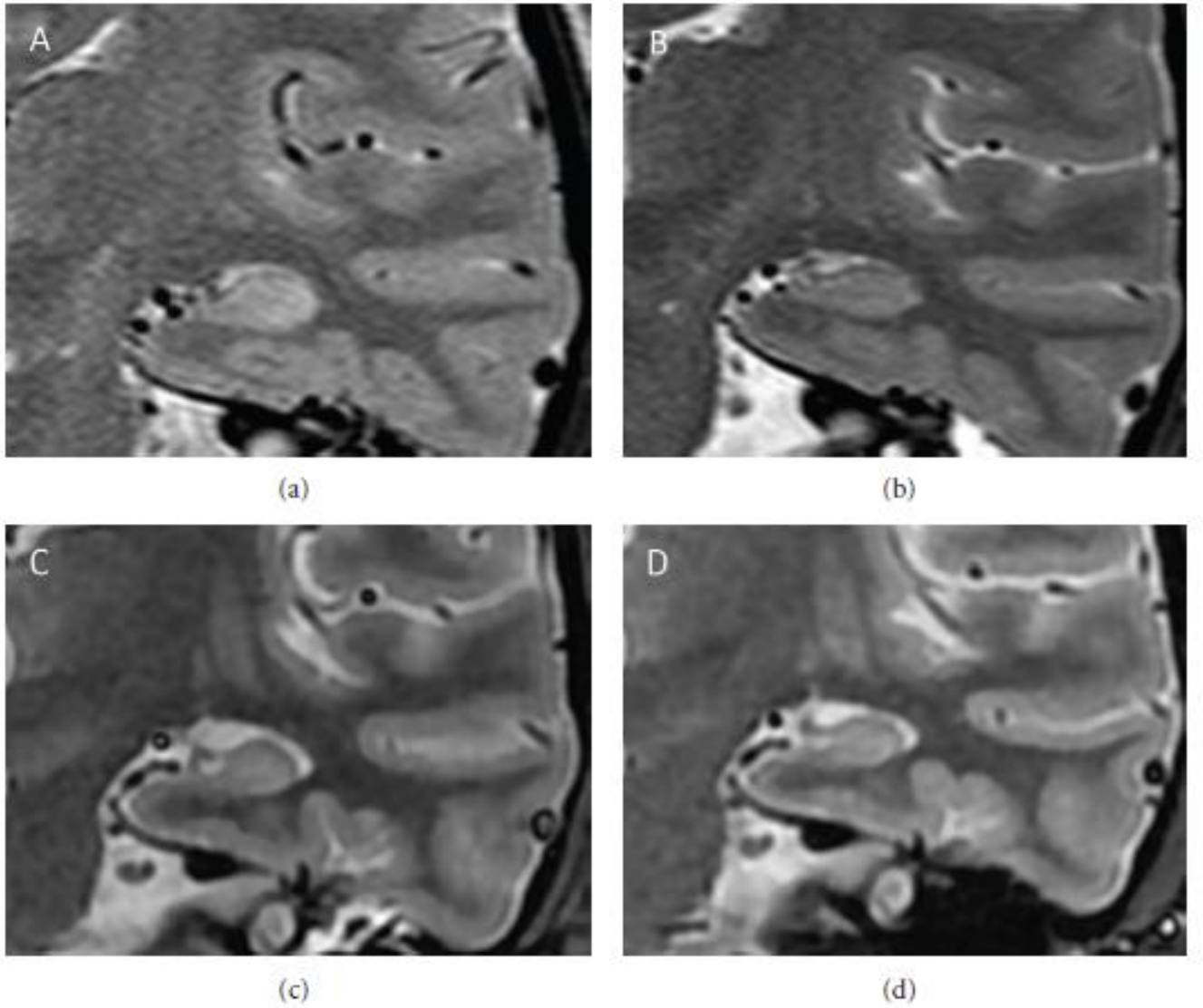
- SE was defined as a "a condition characterized by an epileptic seizure that is **sufficiently prolonged or repeated** at sufficiently brief intervals so as to produce an unvarying and **enduring epileptic condition."**

- SE is not a disease entity but rather a symptom with a myriad of etiologies.

BioMed Research International
Volume 2015, Article ID 745613, 20 pages



BioMed Research International
Volume 2015, Article ID 745613, 20 pages



Review Article

Temporal Lobe Epilepsy after Refractory Status Epilepticus: An Illustrative Case and Review of the Literature

J. Gordon Boyd,1 Derek B. Debicki,2 and G. Bryan Young2

hippocampus appears bright and somewhat edematous 10 days after the onset of status epilepticus (a). Thirty days after the onset of refractory status epilepticus (b), the edema has resolved, and the hippocampus appears atrophic.
At 2 (c) and 6 (d) months after the onset of status epilepticus, progressive hippocampal atrophy is noted.

Epilepsy Research and Treatment Volume 2012, Article ID 209701, 6 pages

The therapeutic principle “time is brain” applies not only for stroke but also for status epilepticus, as the prognosis of SE worsens with increasing duration of seizure activity

(Madzar et al. J Neurol 2016;263(March (3))485–91) Towne AR, et al. Epilepsia 1994;35(1):27–34)

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

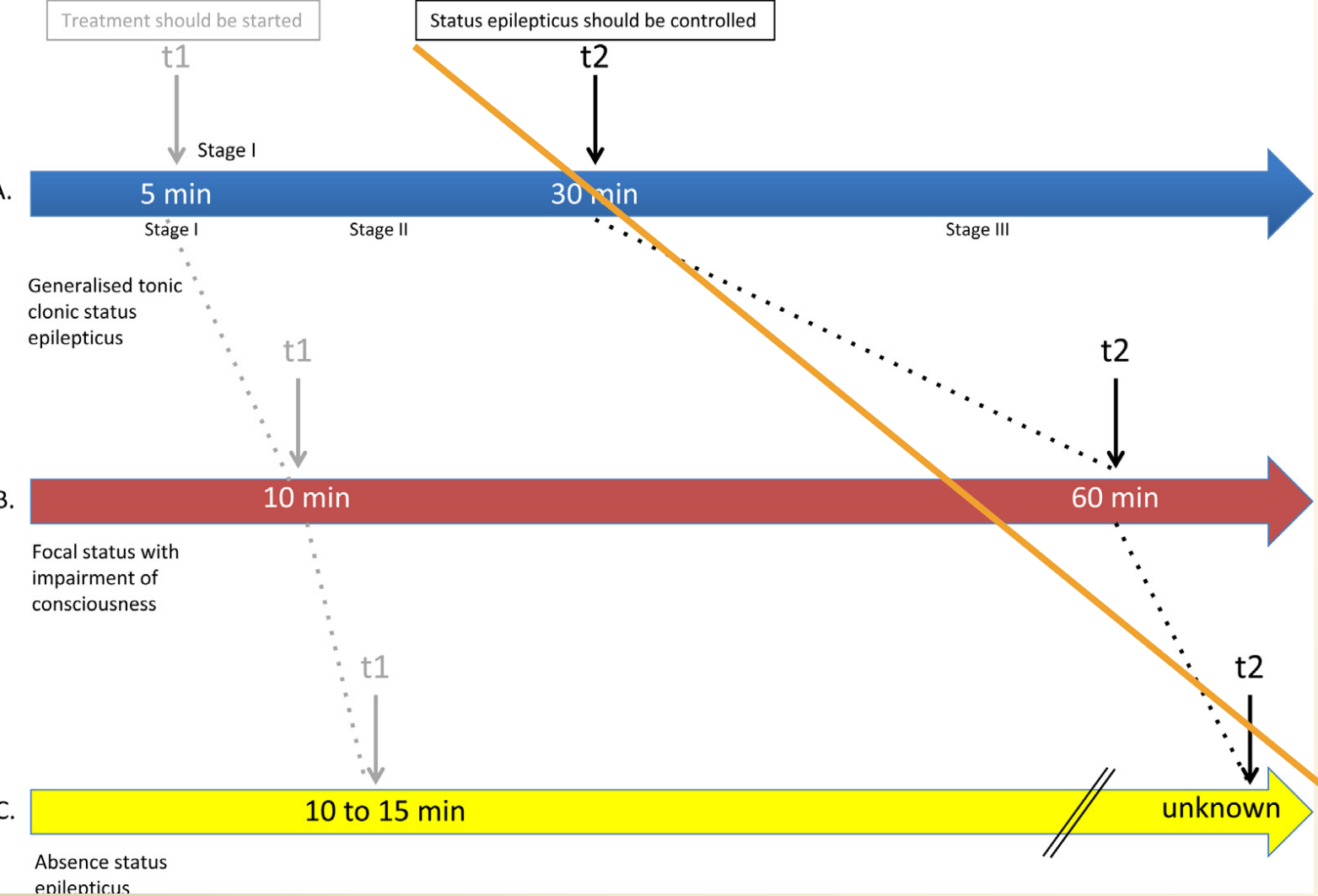
Epilepsia, 56(10):1515–1523, 2015
doi: 10.1111/epi.13121

SE definition is conceptual, with two operational dimensions:

- length of the seizure time point (**t1**) at which the seizure should be regarded as an "**abnormally prolonged seizure.**"
- second time point (**t2**) is the time of ongoing seizure activity beyond which there is a **risk of long-term consequences.**

division into two time points has clear clinical implications:

- **t1** determines the time at which treatment should be considered or started,
- **t2** determines how aggressively treatment should be implemented to prevent long-term consequences



Operational dimensions with **t1 indicating the time that emergency treatment of SE should be started and t2 denoting the time at which long term consequences may be expected**. Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity. Time (t2), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits). For generalized tonic clonic status the stages have been added (stage I 5–10 min; stage II 10–30 min; stage III 30–30 min)

E. Trinka, R. Kälviäinen / Seizure 44 (2017) 65–73

- Studies with video-EEG recordings suggest that the majority of convulsive generalised tonic-clonic seizures terminate prior to two minutes.
- (Jenssen *et al*., 2006). 579 seizures recorded on video- EEG monitoring in 159 adults All the primary and majority of secondary generalised tonic-clonic seizures **terminated before 5 minutes**
- *two of the secondary generalised tonic-clonic seizures lasted longer than 10 minutes*

- DeLorenzo *et al*., (1999). SE cases lasting>10 and <29 minutes
  - 42% of the seizures stopped spontaneously and patients did not receive treatment,
  - 58% received AED treatment
  - mortality of group that stopped seizing spontaneously was zero and only 5.8% in the treated group

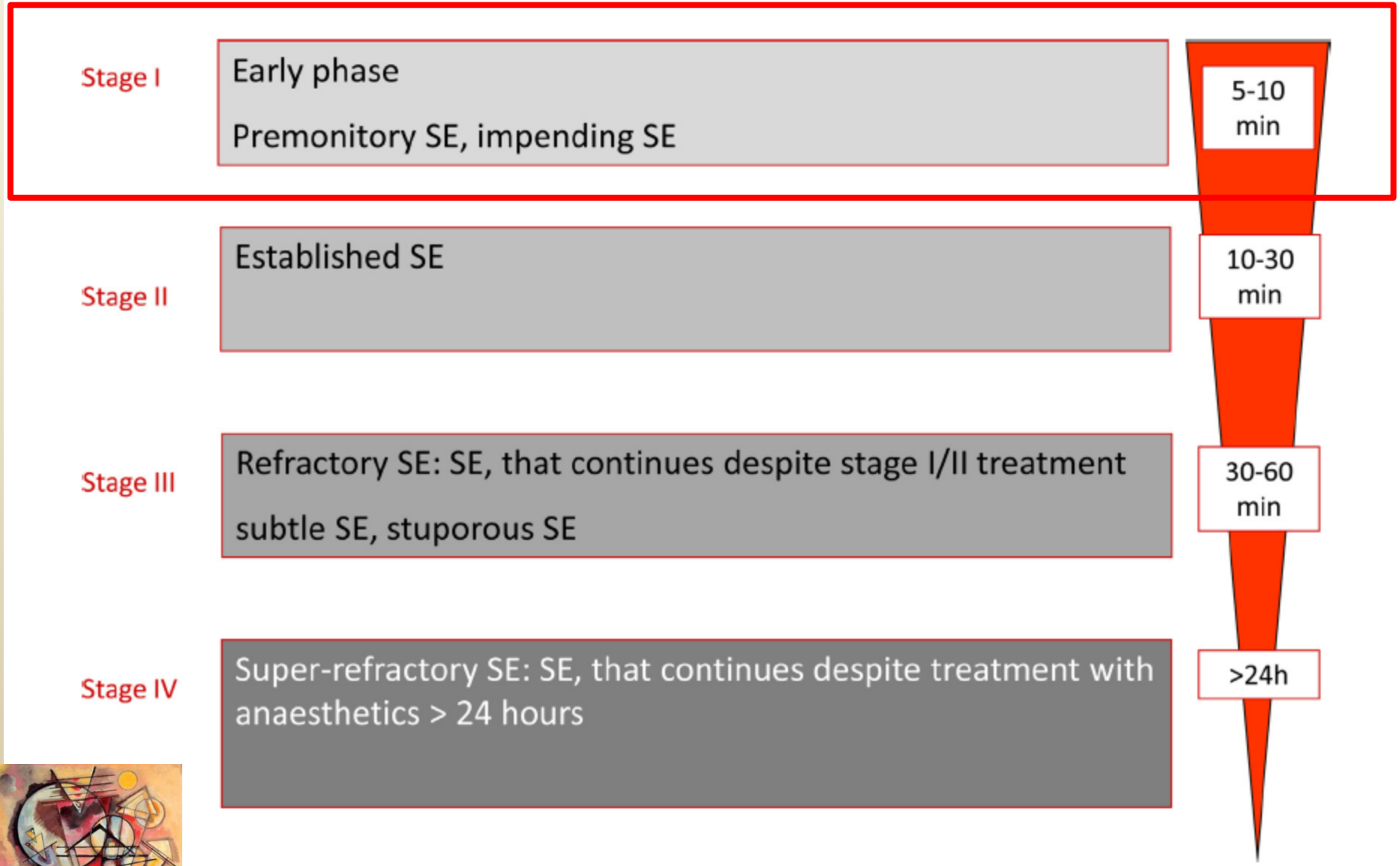


Fig. 2. Clinical course of convulsive status epilepticus.

E. Trinka et al. Drugs (2015) 75:1499–1521

Pharmacotherapy for Status Epilepticus

- **Initial treatment** of early status epilepticus (SE) with intravenous lorazepam or intramuscular midazolam is able to control seizures in **63–73 %;**

- buccal midazolam may be an alternative whenever intravenous or intramuscular application of other benzodiazepines is not possible

Early Status Epilepticus: Stage I

- I farmaci antiepilettici (FAE) indicati come di prima-linea nello SE sono le benzodiazepines:
  - Pre-hospital management Time (Still seizing after 5 min. Impending / early status epilepticus)
    - **Lorazepam** 2 mg IV over 2 min up to 0.1 or 1.5 mg/kg

    If no IV access
    - **Midazolam** 10 mg IM/intranasal/buccal (using IV solution)
    - **Diazepam** 20 mg per rectum (using IV solution)

    ABC (airway, breathing, circulation) Obtain IV access Check finger stick glucose Glucose 33% Monitoring: O2, HR, BP, EKG , Give thiamine 100 mg IV prior to dextrose

Seizure 47 (2017) 17–24

E. Trinka et al. Drugs (2015) 75:1499–1521

Early Status Epilepticus: Stage I

- ..benzodiazepine:
  - **Clonazepam (IV)** più lipofilico del lorazepan e meno del diazepam
    - **Emivita di 17–55 h** buona rapidità di azione
  - **Midazolam** (IV, Intramuscular e(IM), Intranasale,Buccale) multiple vie di somministrazione in virtù della idrosolubilità
    - Valutato efficace e sicuro quanto il lorazepam e.v.: arrivo in DEA, senza crise e senza necessità di ulteriore somministrazione nel **73.4 %** (329/448) dei casi nel gruppo midazolam IM nel **63.4 %** (282/ 445) nel gruppo lorazepam EV
    - Similmente riguardo alla necessità di intubazione endotracheale (14.1 % gruppo midazolam IM e 14.4 % lorazepam EV) ed alla ricorrenza di crisi (11.4 % midazolam IM e 10.6 %,lorazepam EV)
    - È considrata una pratica ed efficace alternativa all'uso del lorazepam EV in ambito pre-ospedaliero

E. Trinka et al. Drugs (2015) 75:1499–1521

Early Status Epilepticus: Stage I

- La terapia iniziale con singolo bolo alla dose piena di benzodiazepina è preferibile all'uso di dosi ridotte refratte
- le dosi refratte sono associate ad un aumento del rischio di insufficienza respiratoria e gravate di una maggiore incidenza di insuccesso terapeutico

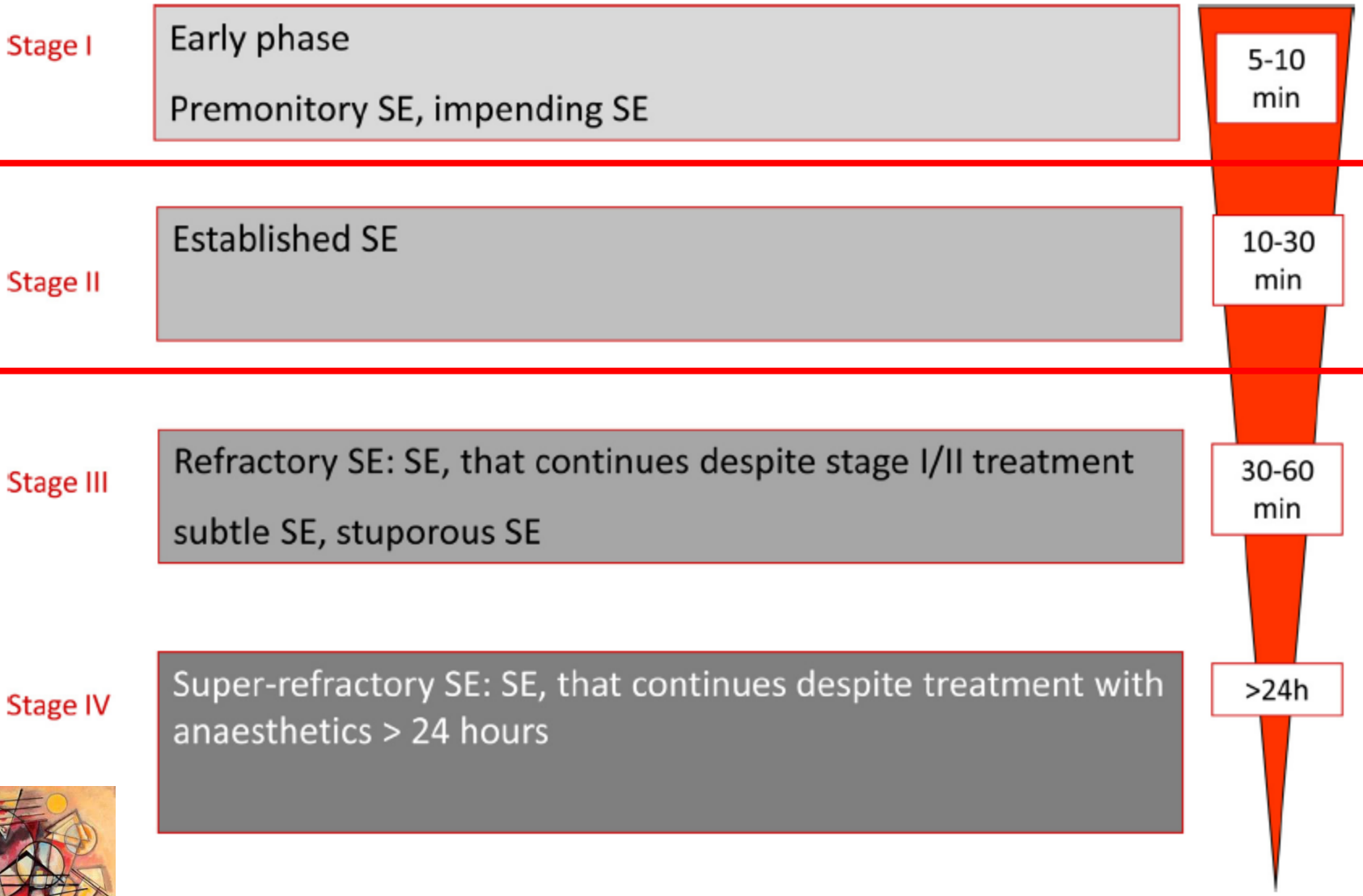


Fig. 2. Clinical course of convulsive status epilepticus.

Established Status Epilepticus: Stage II

Tutti i farmaci vengono sominstrati EV

- Valproate: 20–40 mg/kg (over 10 min). Additional dose 20 mg/kg over 5 mins,
- Levetiracetam: 1000–4000 mg over 5–15 min Additional dose 1500–3000 mg
- Phenytoin: 15–20 mg/kg (50 mg/min). Additional dose 5–10 mg/kg
- Lacosamide: 400 mg IV(over a few mins). Additional dose 200 mg over 10 min

I boli addizionali vengono somministrati in persistenza della crisi

G. Zaccara et al. / Seizure 47 (2017) 17–24

E. Trinka et al. Drugs (2015) 75:1499–1521

Established Status Epilepticus: Stage II

- **Acido Valproico (IV)** efficacia largo spettro su tutti i tipi di crisi, elevato legame proteico nel plasma(90 %)
  - il picco plasmatico si raggiunge in pochi minuti , rapido inizio d'azione
  - Metabolismo epatico (glucuronidazione and betaossidation, in minor misura omega ossidazione)
  - Emivita 12 h
  - Inibizione del citocromo P450
  - Il tasso di risposta nell'abrogare lo SE è del **70.9 %** (601/848; 95 % CI 67.8–73.9)
  - eventi avversi più gravi sono rari e costituiti dalla encefalopatia acuta talora correlata ad anomalie epatiche ed iperammoniemia; trombocitopenia and pancreatite acuta emorragica (J Clin Med. 2016 May; 5(5): 49. Published online 2016 Apr 25.)

E. Trinka et al. Drugs (2015) 75:1499–1521

Established Status Epilepticus: Stage II

- **Levetiracetam (IV)** largo spettro di azione su tutti i tipi di crisi ,basso potenziale di interazioneifarmacologiche,basso metabolismo epatico ,escrezione prevalentemente urinaria, l basso legame proteico plasmatico (<10 %)
  - Tasso molto basso di effetti collaterali (prevalentemente sonnolenzae sedazione, raramente agitazione /allucinazioni and trombocitopenia)
  - Efficacia relativa **68.5 %** (95 % CI 56.2–78.7), confrontata con fenobarbital 73.6 % (95 % CI 58.3–84.8 %), fenitoin 50.2 % (95 % CI 34.2–66.1), e valproate 75.7 % (95 % CI 63.7–84.8)
  - non ci sono studi "testa a testa" con i farmaci vecchi , (J Clin Med. 2016 May; 5(5): 49. Published online 2016 Apr 25)
  - Richiede aggiustamento posologico nell'insufficienza renale, (J Clin Med. 2016 May; 5(5): 49. Published online 2016 Apr 25)
  - Uno studio pilota suggerisce la possibilità che sia efficace anche nella fase I del SE

Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study.

Misra UK, Kalita J, Maurya PK.

.

- randomised, open-label study comparing IV LEV 20 mg/kg over 15 minutes with lorazepam 0.1 mg/kg over 2 to 4 minutes in patients with early SE, both regimens were equally effective
- Lorazepam, however, was associated with a significantly higher need for artificial ventilation

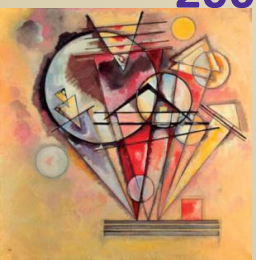
J Neurol 2012;259:645-8

J Clin Med. 2016 May; 5(5): 49. Published online 2016 Apr 25.

Established Status Epilepticus: Stage II

Lacosamide.

- .selectively enhancing the slow inactivation of voltage-gated sodium channels ..
- ..its high rate of off-label use for refractory status epilepticus is likely due to its availability in the IV form..
- There are no studies specifically looking at lacosamide in ESE . efficacy in SE (19 studies, 10 single case-reports and 9 case-series) looking at a total of 136 patients.
- ..**overall success of aborting status of 56%.**
- ..most common side effects were mild sedation and hypotension.
- Yasiry and Shorvon… concluded that there was insufficient data at this time
- A randomized trial of lacosamide and fosphenytoin (TRENdS) for NCSE is still being analyzed
- **most commonly used bolus dose is 400 mg IV, followed by a daily dose of 200–400 mg given in divided doses**



Established Status Epilepticus: Stage II

- **Phenitoina/Fosphenitoina (IV)**
  - Necessita di glicole propilenico e si una soluzione alcalina per prevenirne la precipitazione in soluzione causando irritazioni locali, tromboflebiti nel punto di iniezione, compartment syndrome, and 'purple glove syndrome, necrosi in caso di stravaso
  - Solo nove studi presenti in letteratura inclusi i quattro randomizzati
  - Non ci sono differenze fra fenitoina e valproato nell' interruzione delle crisi cliniche (RR 1.31, 95 % CI 9.93–1.84), e nella libertà da crisi a 24 h (RR 0.96; 95 % CI 0.88–1.06),
  - Un tasso maggiore di effetti indesiderati con la fenitoina (RR 0.31; 95 % CI 0.12–0.85)
  - La fosfofenitoina è il precursore idrosolubile (somministrabile in infusione fino a 50 mg/min; richiede 15' per la conversione a molecola attiva)

E. Trinka et al. Drugs (2015) 75:1499–1521

Established Status Epilepticus: Stage II

- **Fenobarbital (IV, IM)** ha studi controllati nello SEC, il fenobarbital EV è afficace almeno quanto la combinazione di diazepam e fenitoina
  - Non inferiore al lorazepam nel trattamento iniziale dello SE initial treatment of SE
  - L'effetto di depressione respiratorla centrale in associazine con le benzodiazepina nel limita l'utilità clinica.
  - main disadvantages are sedation, respiratory depression, and hypotension (respiration and blood pressure monitored while receiving the bolus J Clin Med. 2016 May; 5(5): 49. Published online 2016 Apr 25.)
  - recommended adult IV loading dose of phenobarbital is **10 mg/kg** (doses up to 20 mg/kg have been used and recommended)

rate of 100 mg/min, up to a total amount of 700 mg in 7 min; respiration and blood pressure have to be monitored

Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus

Francesco Brigo a,b,∗, Nicola Bragazzi c,d, Raffaele Nardone b,e, Eugen Trinka e,

Efficacy of : LEV (68.5%; 95% CI: 56.2–78.7%) and VPA (75.7%; 95% CI: 63.7–84.8%) were found to be comparable with that of phenobarbital (73.6%; 95% CI: 58.3–84.8%) and somewhat higher than that of PHT (50.2%; 95% CI: 34.2–66.1%)

Epilepsy & Behavior 64 (2016) 110–115

Challenges in the treatment of convulsive status epilepticus

Gaetano Zaccaraa,*, Gianfranco Giannasib, Roberto Oggionic, Eleonora Rosatid, Luciana Tramacerea, Pasquale Palumbod, on behalf of the convulsive status epilepticus study group of the uslcentro Toscana, Italy1 a Unit of Neurology, Department of Medicine, Uslcentro Toscana Health Authority, Firenze, Italy

- In the early stages, the most important issue is time. In the prehospital setting, IM midazolam may be preferable due to the rapidity of administration which offsets the faster effect of IV formulations
- In stage 2, established status epilepticus, phenytoin can no longer be considered as the first choice. While phenytoin does not seem more effective, and perhaps is less effective than valproate, it is certainly associated with several risks and is not easy to administer

Seizure 47 (2017) 17–24

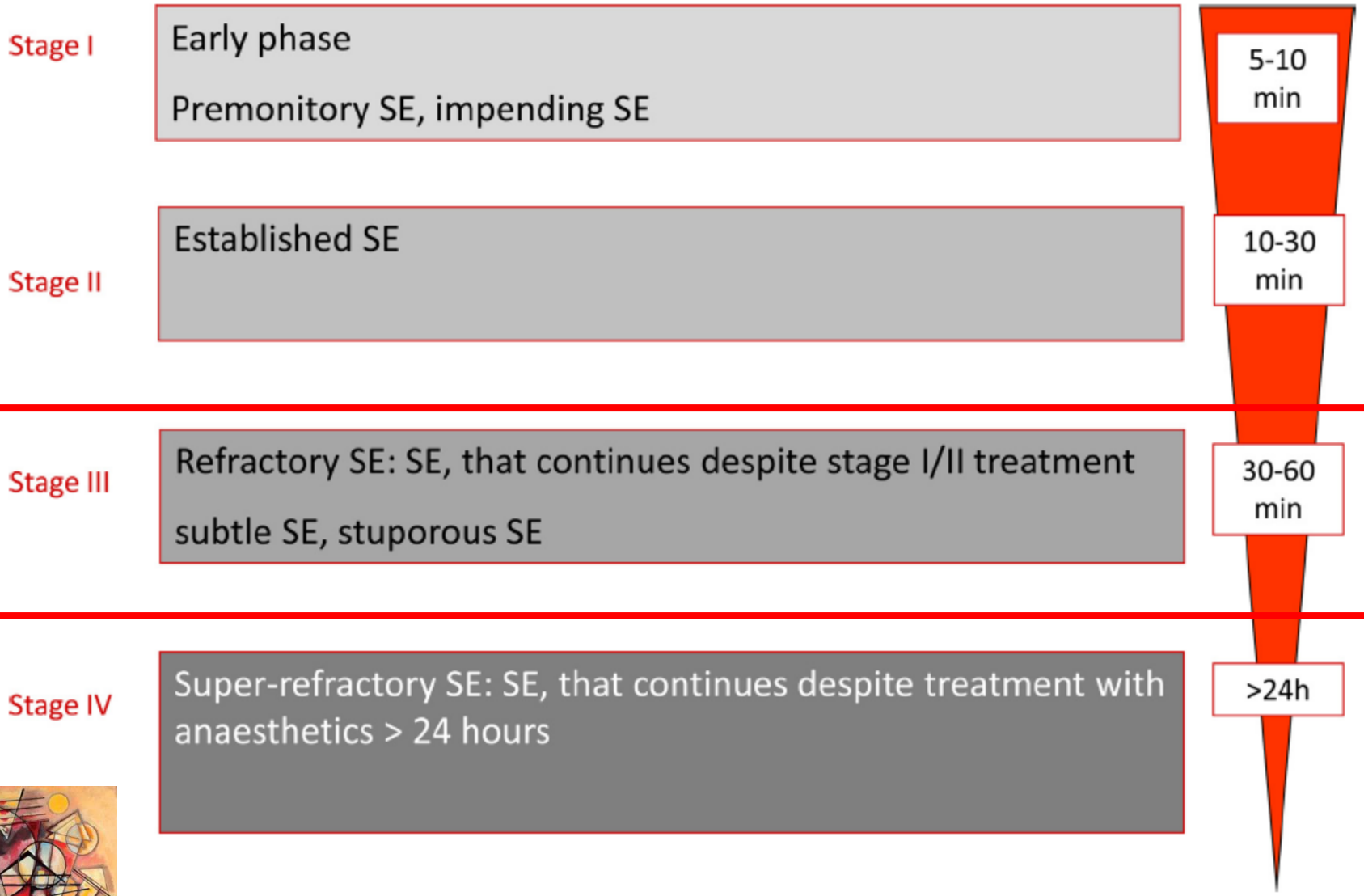


Fig. 2. Clinical course of convulsive status epilepticus.

E. Trinka et al. Drugs (2015) 75:1499–1521

….it has now been commonly accepted to designate **established SE** as ‘‘benzodiazepine-resistant SE’’

…. while the term **refractory SE** is used, when treatment with benzodiazepines and one or more IV AEDs have failed.

E. Trinka et al. Drugs (2015) 75:1499–1521

Refractory Status Epilepticus: Stage III

- 31–43 % of patients enter the refractory stage
- IV anesthetic drugs (thiopental/pentobarbital, midazolam, or propofol) are commonly used
- recommendations at this stage depend on retrospective case series and uncontrolled studies
- two systemic reviews, none of the treatments currently available was superior to another
- rate of cardiovascular and metabolic complications seemed to be lowest with midazolam and highest with barbiturates
- Propofol may be associated with an infusion syndrome,
- use of anesthetics in refractory and super-refractory SE was associated with more infections during SE (43 % vs. 11 %; p = 0.0001) and a 2.9-fold relative risk for death (2.88; 95 % CI 1.45–5.73)

Refractory Status Epilepticus: Stage III

- **Midazolam (Continuous IV Infusion)** Continuous midazolam and diazepam infusions were equally effective for cessation of SE, midazolam was associated with a higher seizure recurrence rate and mortality
  - half of the patients required mechanical ventilation
  - 40 % of patients in both groups had hypotension.
  - median maximum dose was **0.4 mg/kg/h** (interquartile range [IQR] 0.2, 1.0) for the high-dose group and 0.2 mg/kg/h (IQR 0.1, 0.3) for the low-dose group ($p<0.001$), with a similar duration of infusion
  - Withdrawal seizures (48 h) less frequent in the high-dose group (15 vs. 64 %; odds ratio (OR) 0.10; 95 % CI 0.03–0.27)
  - mortality was lower in the high-dose group (40 vs. 62 %; OR 0.34; 95 % CI 0.13–0.92) compared with the low-dose group.

E. Trinka et al. Drugs (2015) 75:1499–1521

Refractory Status Epilepticus: Stage III

- **Propofol** acting as an N-methyl-Daspartate (NMDA) antagonist in vitro, with a shorter duration of action and lower tendency to accumulate
  - may cause hypotension
  - reduces intracranial pressure and brain metabolic requirements
  - prolonged use has been reported to cause the so called ‘‘propofol infusion syndrome,’’ which includes potentially fatal myocardial failure with lactic acidosis, hypertriglyceridemia, and rhabdomyolysis, with an observed incidence of around 1 %
  - treatment duration of less than 48 h and doses of no more than 5 mg/kg/h are recommended

robust evidence on the role of propofol…is still lacking

E. Trinka et al. Drugs (2015) 75:1499–1521

Refractory Status Epilepticus: Stage III

- **Thiopental, Pentobarbital** acting as GABA-A agonists, with enhanced inhibitory neurotransmission
  - prolonged duration of action.. long recovery time
  - cause hypotension and cardiorespiratory depression
  - require the use of additional drugs to control pressure and breathing, as well as immuno suppression
  - associated with longer mechanical ventilation respect to propofol
  - no difference with respect to control of seizure activity, infections, and arterial hypotension
  - achieved seizure control in 64 % (midazolam 78 %, propofol 68 %)
  - death rate during treatment in 19 % (midazolam 2 %, propofol 8 %)
  - barbiturates should be restricted to the most severe forms of refractory SE

Challenges in the treatment of convulsive status epilepticus

Gaetano Zaccaraa,*, Gianfranco Giannasib, Roberto Oggionic, Eleonora Rosatid, Luciana Tramacerea, Pasquale Palumbod, on behalf of the convulsive status epilepticus study group of the uslcentro Toscana, Italy1 a Unit of Neurology, Department of Medicine, Uslcentro Toscana Health Authority, Firenze, Italy

- In stages 3 (refractory CSE), and 4 (super-refractory CSE), thiopental or pentobarbital (in the USA) are strong inducers which may affect several treatments They also have a long half-life, a lot of adverse effects and, where possible, should be avoided.
- From a theoretical point of view, a combination of ketamine with midazolam or propofol might also be interesting to assess in randomized studies

Seizure 47 (2017) 17–24

Epilepsy & Behavior 70 (2017) 177–181

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Brief Communication

Treatment of refractory and super-refractory status epilepticus with brivaracetam: A cohort study from two German university hospitals

Adam Strzelczyk [a,b,*], Isabel Steinig [a], Laurent M. Willems [a], Philipp S. Reif [a], Christian Senft [c], Martin Voss [d], Bernadette Gaida [e], Felix von Podewils [e,1], Felix Rosenow [a,b,1]

Conclusion: Based on these cases and previous data from animal experiments, BRV may prove useful in SE treatment, and trials would be warranted to examine BRV's efficacy in treating SE and how this efficacy might be influenced by co-administration with levetiracetam.

synaptic vesicle protein 2A (SV2A)

Brexanolone as Adjunctive Therapy in Super-Refractory Status Epilepticus

Eric S. Rosenthal, MD,[1] Jan Claassen, MD, PhD,[2] Mark S. Wainwright, MD, PhD,[3] Aatif M. Husain, MD,[4] Henrikas Vaitkevicius, MD,[5] Shane Raines, MS,[6] Ethan Hoffmann, BA,[7] Helen Colquhoun, MD,[7] James J. Doherty, PhD,[7] and Stephen J. Kanes, MD, PhD[7]

The results .. demonstrate that despite the rare nature of SRSE and the variability of clinical treatment, an interventional study in critically ill SRSE patients is feasible, and brexanolone appears well tolerated in the sample of patients studied. Furthermore, this open-label trial demonstrated the ability to observe the clinical response of SRSE during and following brexanolone infusion; clinical improvement was observable despite significant baseline neurological and systemic morbidity, past refractoriness to multiple baseline AEDs, and past dependence on one or more baseline TLAs for seizure control.

Allopregnanolone

ANN NEUROL 2017;82:342–352

#1: Benzodiazepines:
- Diazepam
- Lorazepam
- Midazolam

#2: Phenytoins and Valproic Acid:
- Phenytoin
- Fosphenytoin
- Valproic acid

#3: Other medications (Second-line Adjuncts)
- Levetiracetam
- Lacosamide
- Phenobarbital
- Ketamine

#4: IV Anesthetics
- Midazolam
- Propofol
- Barbiturates: pentobarbital, thiopental

#5: Adjunctive Treatments:
- Hypothermia
- ECT
- Ketogenic diet

Management of SE. ECT, electroconvulsive therapy; IV, intravenous.

Status Epilepticus
What's New?
Danya Khoujah, MBBS,
Michael K. Abraham, MD, MS*

Emerg Med Clin N Am 34 (2016) 759–776

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD1,2, Alomi O. Parikh, BA1, Colin Ellis, MD1, Jennifer S. Myers, MD2,3, Brian Litt, MD

- From time of seizure onset, the median delays to paramedic arrival ranged 12.5 minutes (IQR 18, range 0-95) to 30 minute
- hospital presentation ranged 30 minutes (range 5-120) to 1 hour 45 minutes
- Prior to reaching the emergency department (ED), antiepileptic medication was administered to 34% (16/47) to 51% (56/109) of patients
- When out-of-hospital first-line therapy was administered, the median delay was 1 hour 10 minutes

'Accepted Article **Annals of Neurology**

Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD1,2, Alomi O. Parikh, BA1, Colin Ellis, MD1, Jennifer S. Myers, MD2,3, Brian Litt, MD

- >30 minute delay to first-line treatment was observed for 17% (26/157) to 64% (97/151) of patients
- median delays to first-line therapy ranging from 30 minutes to 70 minutes
- median delays to second-line treatment ranged from 69 minutes to 3 hours
- median delays to third-line treatment ranged from 2 hours 38 minutes to 3 hour

study of international practice observed that 16% of patients received third-line therapy within one hour

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- delay to first-line drug was best explained by delay in calling paramedics and the clumsiness of administering rectal medication
- delay to second-line therapy was largely because paramedics did not have the ability to administer IV fosphenytoin
- delay to third-line therapy might be attributable to diagnostic delay
- Due to improper drug choice, dosage, or sequence, *29% (13/45) to 61% (77/126) of patients* were not treated according to protocol

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COMMON VIOLATION OF THE PROTOCOL

- More than two administrations of benzodiazepines 23% (41/179) to 49% (23/47) of pediatric

- Furthermore, it may be that one element of adherence (drug sequence) is more important than another drug dose.

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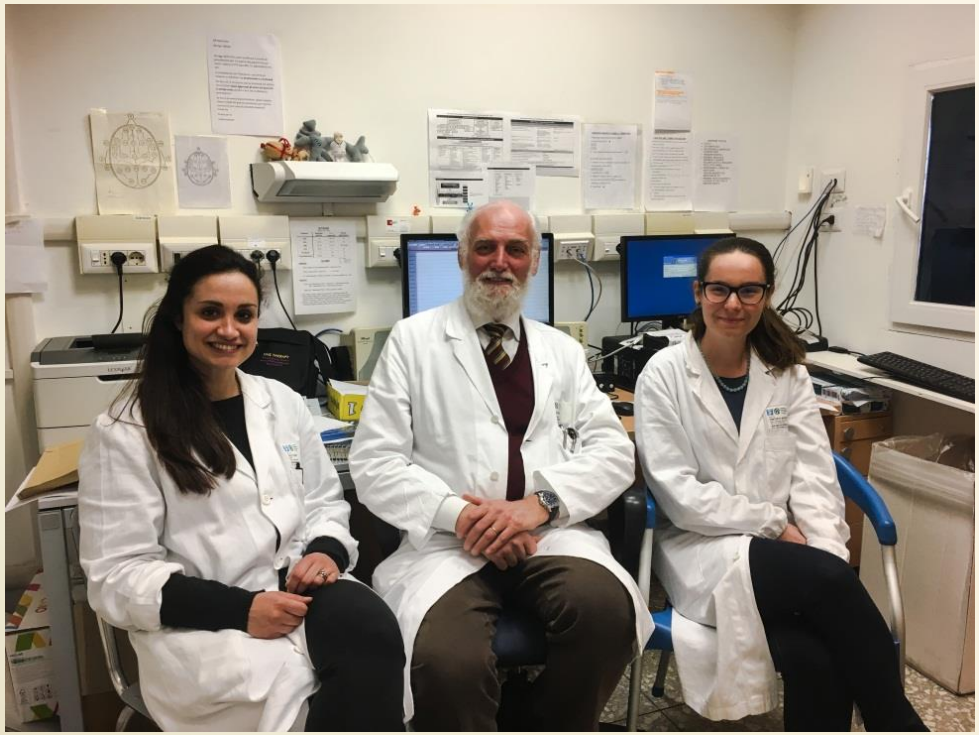
The patient's hospital course from the pre-hospital setting, continuing through the ED, and ultimately the time spent in an intensive care unit (ICU) can be greatly affected by the choices the emergency physician makes

AZIENDA OSPEDALIERO-UNIVERSITARIA CAREGGI
DIPARTIMENTO NEUROMUSCOLOSCHELETRICO E DEGLI ORGANI DI SENSO

S.O.D. di NEUROLOGIA II
C.d.R.R. per la Diagnosi e la Terapia dell'Epilessia



Grazie per l'attenzione!

Classification of Status Epilepticus propose

- Four axes :
  - 1 Semiology
  - 2 Etiology
  - 3 EEG correlates
  - 4 Age

  At initial presentation, the approximate **age** of the patient and the **semiology** will be immediately assessable.

  EEG recordings will not be available in many settings, particularly at presentation.

  However, the EEG will affect choice and aggressiveness of treatment, prognosis, and clinical approaches, so an **EEG should be sought** where possible and **as early as possible**

Table 2. Axis I: Classification of status epilepticus (SE)

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
- A.2.a. With coma
- A.2.b. Without coma

A.3 Focal motor
- A.3.a. Repeated focal motor seizures (Jacksonian)
- A.3.b. Epilepsia partialis continua (EPC)
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
- B.2.a. Generalized
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. Focal
  - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
  - B.2.b.b Aphasic status
  - B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
  - B.2.c.a Autonomic SE

Axis 1: Semiology

Refers to the clinical presentation:

- The presence or absence of prominent motor symptoms (Convulsive [A] or non convulsive[B] forms of SE)
- The degree (qualitative or quantitative) of impaired consciousness
- **NCSE** is divided into those patients with and without coma following two broad clinical categorie
  ‘‘ictally comatose’’,
  ‘‘walking wounded’’

Axis 2: Etiology

Table 4. Etiology of status epilepticus
Known (i.e., symptomatic)
Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)
SE in defined electroclinical syndromes
Unknown (i.e., cryptogenic)

The term "**known**" or "symptomatic" is used for SE caused by a known disorder, which can be structural, metabolic, inflammatory, infectious, toxic, or genetic

temporal relationship, the subdivisions acute, remote, and progressive can be applied

The term "unknown" or "cryptogenic" is used in its strict original meaning: unknown cause.

Table 3. Currently indeterminate conditions (or "boundary syndromes")
Epileptic encephalopathies
Coma with non evolving epileptiform EEG pattern[a]
Behavioral disturbance (e.g., psychosis) in patients with epilepsy
Acute confusional states, (e.g., delirium) with epileptiform EEG patterns

[a]Lateralized and generalized periodic discharges with monotonous appearance are not considered as evolving EEG patterns.[26,27]

The term "idiopathic" or "genetic" is not applicable to the underlying etiology of SE.
The assumption that the term "unknown" is "presumably" symptomatic or genetic is inappropriate.

List of Etiologies That May Cause Status Epilepticus (Not Exhaustive)

Cerebrovascular diseases

a) Ischemic stroke
b) Intracerebral bleeding
c) Subarachnoid bleeding
d) Subdural hematoma
e) Epidural hematoma
f) Sinus venous thrombosis and cortical venous thrombosis
g) Posterior reversible leukoencephalopathy syndrome
h) Vascular dementia

CNS infections

a) Acute bacterial meningitis
b) Chronic bacterial meningitis
c) Acute viral encephalitis (including Japanese B encephalitis, herpes simplex encephalitis, human herpesvirus 6)
d) Progressive multifocal leukoencephalopathy (PML)
e) Cerebral toxoplasmosis
f) Tuberculosis
g) Neurocysticercosis
h) Cerebral malaria
i) Atypical bacterial infections
j) HIV-related diseases
k) Prion diseases (Creutzfeldt-Jakob disease, CJD)
l) Protozoal infections
m) Fungal diseases
n) Subacute sclerosing panencephalitis
o) Progressive Rubella encephalitis

List of Etiologies That May Cause Status Epilepticus (Not Exhaustive)

Neurodegenerative diseases

a) Alzheimer's disease
b) Corticobasal degeneration
c) Frontotemporal dementia

Intracranial tumors

a) Glial tumors
b) Meningioma
c) Metastases
d) Lymphoma
e) Meningeosis neoplastica
f) Ependymoma
g) Primitive neuroectodermal tumor (PNET)

Cortical dysplasias

a) Focal cortical dysplasia (FCD) II, tuberous sclerosiscomplex (TSC), hemimegalencephaly, hemihemimegalencephaly
b) Gangliоglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor (DNET)
c) Periventricular nodular heterotopia (PNH) and other nodular heterotopias
d) Subcortical band heterotopia spectrum
e) Lissencephaly
f) Familial and sporadic polymicrogyria
g) Familial and sporadic schizencephaly
h) Infratentorial malformations (e.g., dentate dysplasia, mamillary dysplasia, etc.)

List of Etiologies That May Cause Status Epilepticus (Not Exhaustive)

Head trauma

a) Closed head injury
b) Open head injury
c) Penetrating head injury

Alcohol related

a) Intoxication
b) Alcohol withdrawal
c) Late alcohol encephalopathy with seizures
d) Wernicke encephalopathy

Intoxication

a) Drugs
b) Neurotoxins
c) Heavy metals

Withdrawal of or low levels of antiepileptic drugs

Cerebral hypoxia or anoxic

Metabolic disturbances (e.g., electrolyte imbalances,glucose imbalance, organ failure, acidosis, renal failure,hepatic encephalopathy, radiation encephalopathy, etc.)

Autoimmune disorders causing SE

a) Multiple sclerosis
b) Paraneoplastic encephalitis
c) Hashimoto's encephalopathy
d) Anti-NMDA (N-methyl-D-aspartate) receptor encephalitis
e) Anti–voltage–gated potassium channel receptor
f) encephalitis (including anti–leucine–rich glioma
g) inactivated 1 encephalitis)
h) Anti-glutamic acid decarboxylase antibody associated
i) encephalitis
j) Anti–alpha–amino–3–hydroxy–5–methylisoxazole–
k) a-propionic acid receptor encephalitis
l) Seronegative autoimmune encephalitis
m) Rasmussen encephalitis
n) Cerebral lupus (systemic lupus erythematosus)
o) CREST (calcinosis, Raynaud phenomenon, esophageal
p) dysmotility, sclerodactyly, telangiectasia) syndrome
q) Adult-onset Still's disease
r) Goodpasture syndrome
s) Thrombotic thrombocytopenic purpura (Moschcowitz
t) syndrome, Henoch Sch€onlein purpura)

List of Etiologies That May Cause Status Epilepticus (Not Exhaustive)

Mitochondrial diseases causing SE

a) Alpers disease
b) Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
c) Leigh syndrome
d) Myoclonic encephalopathy with ragged red fibers (MERRF)
e) Neuropathy, ataxia, and retinitis pigmentosa (NARP)

Chromosomal aberrations and genetic anomalies

a) Ring chromosome 20
b) Angelman syndrome
c) Wolf-Hirshhorn syndrome
d) Fragile X syndrome
e) X-linked mental retardation syndrome
f) Ring chromosome 17
g) Rett syndrome
h) Down syndrome (trisomy 21)
i) Neurocutaneous syndromes
j) Sturge-Weber syndrome

List of Etiologies That May Cause Status Epilepticus (Not Exhaustive)

Metabolic disorders

a) Porphyria
b) Menkes disease
c) Wilson disease
d) Adrenoleukodystrophy
e) Alexander disease
f) Cobalamin C/D deficiency
g) Ornithine transcarbamylase deficiency
h) Hyperprolinemia
i) Maple syrup urine disease
j) 3-Methylcrotonyl Coenzyme A carboxylase deficiency
k) Lysinuric protein intolerance
l) Hydroxyglutaric aciduria
m) Metachromatic leukodystrophy
n) Neuronal ceroid lipofuscinosis (types I, II, III,
o) including Kufs disease)
p) Lafora disease
q) Unverricht-Lundborg disease
r) Sialidosis (type I and II)
s) Morbus Gaucher
t) Beta ureidopropionase deficiency
u) 3-Hydroxyacyl CoenzymeAdehydrogenase deficiency
v) Carnitine palmitoyltransferase deficiency
w) Succinic semialdehyde dehydrogenase deficiency

Others

a) Familial hemiplegic migraine
b) Infantile onset spinocerebellar ataxia (SCA)
c) Wrinkly skin syndrome
d) Neurocutaneous melanomatosis
e) Neuroserpin mutation
f) Wolfram syndrome
g) Autosomal recessive hyperekplexia
h) Cockayne syndrome
i) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
j) Robinow syndrome
k) Malignant hyperpyrexia

Axis 3: Electroencephalographic correlates

- EEG is overloaded with movement and muscle artifact in the convulsive forms of SE and thus of limited clinical value,
- it is indispensable in the diagnosis of NCSE, as the clinical signs (if any) are often subtle and nonspecific
- Currently there are no evidence-based EEG criteria for SE

Axis 3: Electroencephalographic correlates

- Proposed terminology to describe EEG patterns in SE:
  - **Location**: generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal
  - **Name of the pattern**: Periodic discharges, rhythmic delta activity or spike-and-wave/sharp-and-wave plus subtypes.
  - **Morphology**: sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity.
  - **Time-related features**: prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static).
  - **Modulation:** stimulus-induced vs. spontaneous.
  - **Effect of intervention** (medication) on EEG.

Table 5. SE in selected electroclinical syndromes according to age

SE occurring in neonatal and infantile-onset epilepsy syndromes
Tonic status (e.g., in Ohtahara syndrome or West syndrome)
Myoclonic status in Dravet syndrome
Focal status
Febrile SE
SE occurring mainly in childhood and adolescence
Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies; see Appendices 1–3)
Tonic status in Lennox-Gastaut syndrome
Myoclonic status in progressive myoclonus epilepsies
Electrical status epilepticus in slow wave sleep (ESES)
Aphasic status in Landau-Kleffner syndrome
SE occurring mainly in adolescence and adulthood
Myoclonic status in juvenile myoclonic epilepsy
Absence status in juvenile absence epilepsy
Myoclonic status in Down syndrome
SE occurring mainly in the elderly
Myoclonic status in Alzheimer's disease
Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease
De novo (or relapsing) absence status of later life

These forms of SE may be encountered prevalently in some age groups, but not exclusively.

Axis 4: Age

1 .Neonatal (0 to 30 days).

2 .Infancy (1 month to 2 years).

3 .Childhood (> 2 to 12 years).

4 .Adolescence and adulthood (> 12 to 59 years).

5 .Elderly (≥ 60 years).