SALA POLISSENA B

EMERGENZE NEUROLOGICHE

Moderatori: **Rosa Intermite– Vincenzo Natale**

Gaetano Zaccara

La gestione dello stato epilettico

XII congresso nazionale
simeu
RICCIONE 13-15 MAGGIO 2022

Emergenze neurologiche

La gestione dello stato epilettico

Gaetano Zaccara, Firenze

XII congresso nazionale
simeu
RICCIONE 13-15 MAGGIO 2022

Definizione di Stato epilettico (SE) secondo le ultime linee guida dell'International League Against Epilepsy (ILAE) del 2015

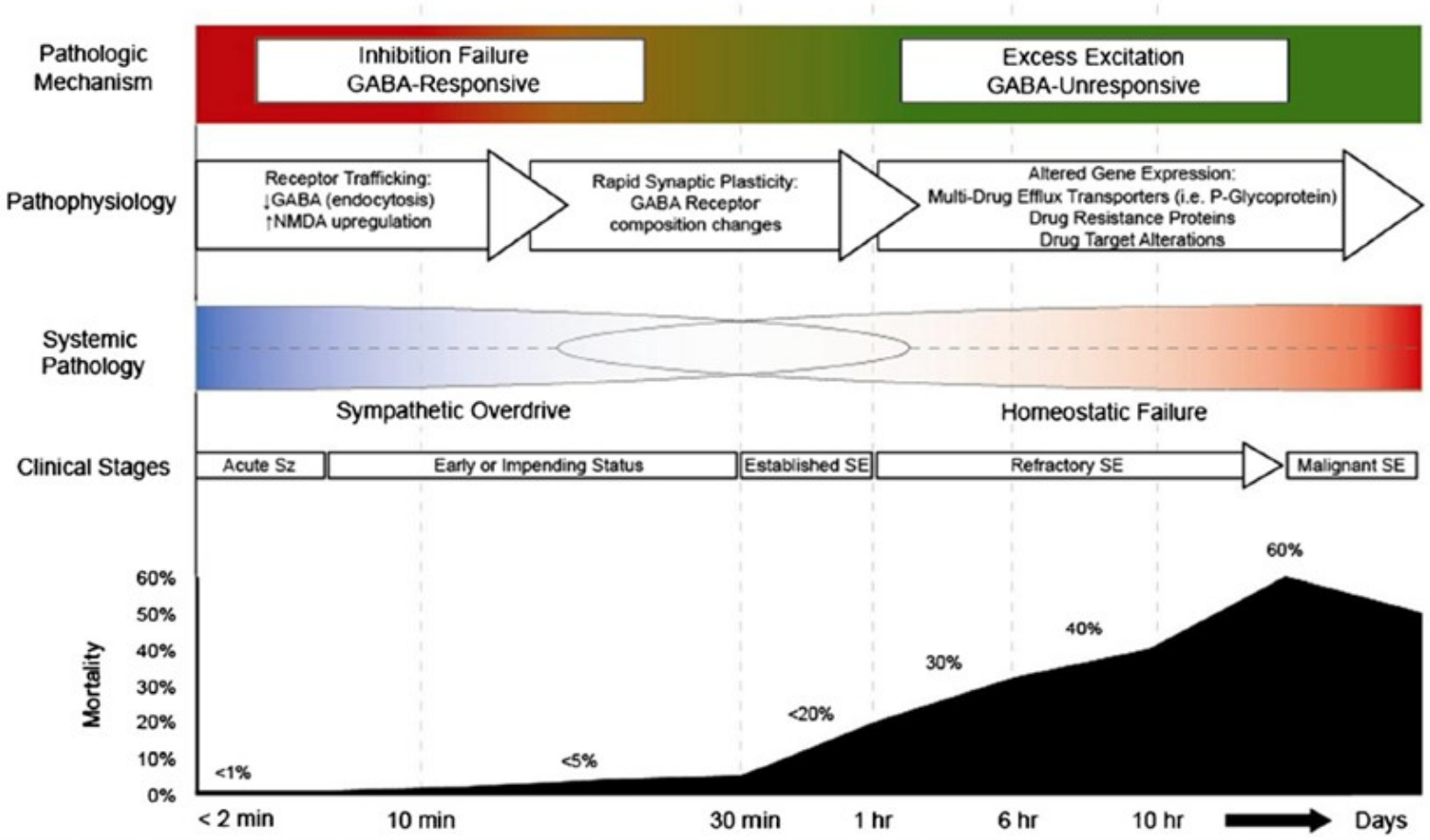
"Lo SE è una condizione risultante sia dal fallimento dei meccanismi responsabili della cessazione della crisi sia dall'inizio di meccanismi che portano ad una anormale prolungamento della crisi epilettica (*dopo un tempo t1*). Questa è una condizione che può avere conseguenze a lungo termine (*dopo un tempo t2*), come morte neuronale, danno neuronale, e alterazioni delle connessioni neuronali, che dipendono dal tipo e dalla durata della crisi"

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

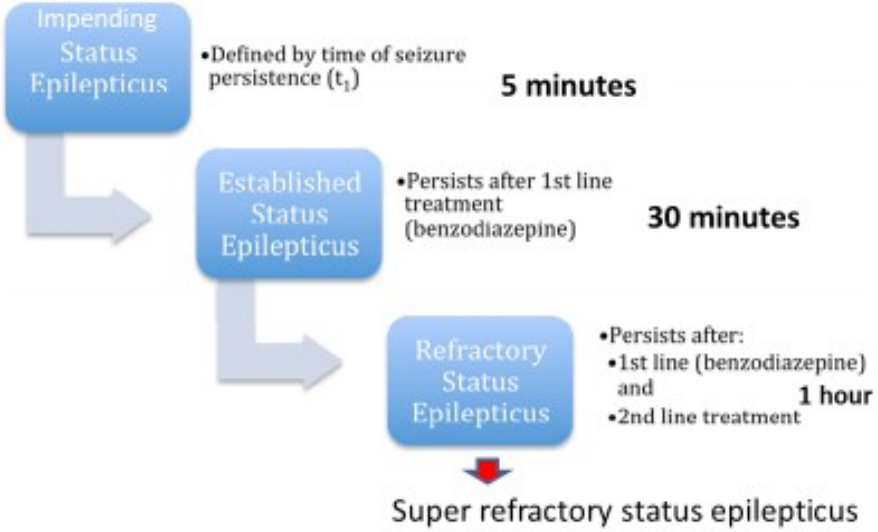
Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional 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

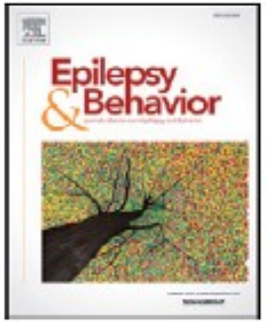
[a]Evidence for the time frame is currently limited and future data may lead to modifications.

The pathophysiology of status epilepticus (SE)



La crisi è durata più di 5 minuti oppure si è verificata una seconda crisi prima che il paziente abbia potuto riprendere coscienza





Management of status epilepticus in adults. Position paper of the Italian League against Epilepsy

Fabio Minicucci [a,*,1], Monica Ferlisi [b,1], Francesco Brigo [c,d], Oriano Mecarelli [e], Stefano Meletti [f,g], Umberto Aguglia [h], Roberto Michelucci [i], Massimo Mastrangelo [j], Nicola Specchio [k], Stefano Sartori [l], Paolo Tinuper [m,n]

Epilepsy & Behavior 102 (2020) 106675

Challenges in the treatment of convulsive status epilepticus

Gaetano Zaccara[a,*], Gianfranco Giannasi[b], Roberto Oggioni[c], Eleonora Rosati[d], Luciana Tramacere[a], Pasquale Palumbo[d], on behalf of the convulsive status epilepticus study group of the uslcentro Toscana, Italy[1]

Seizure 47 (2017) 17–24

Members of the convulsive status epilepticus study group of the uslcentro Toscana, Italy. Paola Bartalucci, Alessandra Borgheresi, Roberto Campostrini, Barbara Chiocchetti, Massimo Cincotta, Fabio Daviddi, Giovanni Del Sorbo, Lucia Devito, Camilla Ferrari, Maria Lombardi, Marco Monfardini, Mario Rugna, Emma Sirabella, Milena Taglioli, Laura Tirelli, Gino Volpi.

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

5-20 min
Initial therapy phase

A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

Glaucer et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

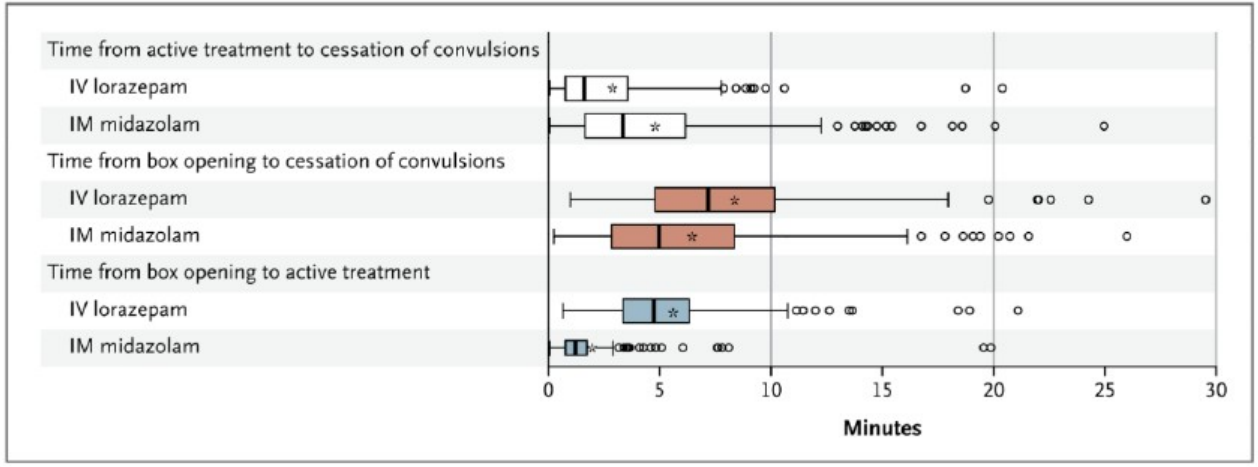
Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

N Engl J Med. 2012 February 16; 366(7): 591–600.

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D. for the NETT

Double-blind, randomized, noninferiority trial

Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector (10 mg IM midazolam or intravenous infusion (4 mg IV lorazepam)



At the time of arrival in the emergency department, seizures were absent in **73.4**% subjects in the intramuscular-midazolam group and in **63.4**% in the intravenous-lorazepam group ($P<0.001$ for both noninferiority and superiority).

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

20-40 min
Second therapy phase

There is no evidence based preferred second therapy of choice (Level U):

Choose one of the following second line options and give as a single dose

- Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR
- Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
- Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U)

If none of the options above are available, choose one of the following (if not given already)

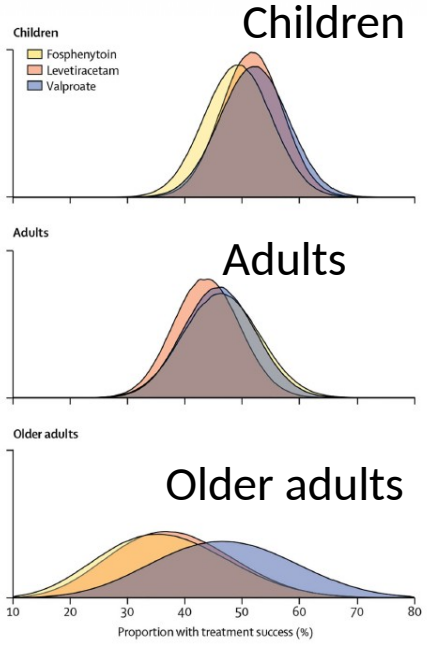
- Intravenous phenobarbital (15 mg/kg, max dose, Level B)

Glaucer et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial

Chamberlain et al., Lancet. 2020 Apr 11;395(10231):1217-1224.

Patients included: 225 children, 186 adults, and 51 older adults. 175 (38%) patients randomly assigned to levetiracetam, 142 (31%) to fosphenytoin, and 145 (31%) to valproate.
No differences were detected in efficacy or primary safety outcome by drug within each age group. With the exception of endotracheal intubation in children, secondary safety outcomes did not significantly differ by drug within each age group



Posterior probabilities of success by age and treatment groups for the primary outcome

Why we prefer levetiracetam over phenytoin for treatment of status epilepticus

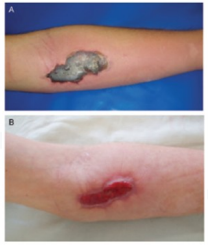
Acta Neurol Scand. 2018;1–5.

G. Zaccara[1] | F. S. Giorgi[2] | A. Amantini[3] | G. Giannasi[4] | R. Campostrini[4] | F. Giovannelli[5] | M. Paganini[6] | P. Nazerian[7] | on behalf of the Tuscany study group on seizures in the emergency department and status epilepticus in adults

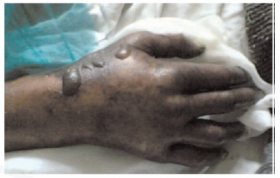
PROBLEMS AND SAFETY OF THE ADMINISTRATION OF IV LOADING DOSE OF PHENY TOIN

Loading dose required	**Effect delayed;** Serious cutaneous adverse effects
Electrocardiogram and blood pressure should be monitored	Severe hypotension and cardiac arrhythmias
Blood levels may be misleading	Wrong dose adjustment
Should be administered into a large peripheral or central vein	Local reactions Purple glove syndrome
Strong enzyme inducer	Makes several coadministered drugs less effectives

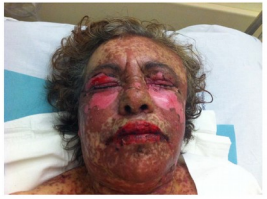
Local reaction

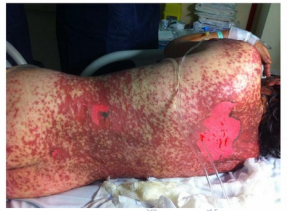


Purple glove



Toxic epidermal necrolysis





JPPT | Editorial

Status Epilepticus: The Slow and Agonizing Death of Phenytoin

J Pediatr Pharmacol Ther 2020;25(1):4–6

Elizabeth A. Hall, PharmD; James W. Wheless, BScPharm, MD; and Stephanie J. Phelps, BScPharm, PharmD

Since its introduction in 1950, phenytoin (PHT) has been the premier parenteral anticonvulsant used in the management of generalized convulsive status epileptics (GCSE) that is refractory to benzodiazepines.
However, after more than half a century of use, there continues to be insufficient evidence-based data to support its efficacy over other anticonvulsants as a first-line agent in pediatric or adult patients with GCSE. This coupled with its **narrow mechanism of action, complex pharmacokinetics and pharmacogenomics, drug-drug interactions, unique adverse effects, and formulation issues** that make administration difficult mandates that PHT be replaced by safer and superiorly effective anticonvulsants for the treatment of GCSE when benzodiazepines are ineffective.

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

40-60 min
Third therapy phase

Refractory Status epilepticus

There is no clear evidence to guide therapy in this phase (Level U):
Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).

Glaucer et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

Raoul Sutter, MD
Stephan Marsch, MD, PhD
Peter Fuhr, MD
Peter W. Kaplan, MB, BS, FRCP
Stephan Rüegg, MD

Anesthetic drugs in status epilepticus: Risk or rescue?

A 6-year cohort study

Neurology® 2014;82:656-664

To evaluate the risks of continuously administered IV anesthetic drugs on the outcome of adult patients with status epilepticus (SE).

Prospective observational cohort study

Of 171 patients, 37% were treated with continuously administered IV anesthetic drugs.

Patients with anesthetic drugs had more infections during SE and a 2.9-fold relative risk for death independent of possible confounders

Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee.

Lacosamide

Lacosamide: 400 mg IV(over a few mins). Additional dose 200 mg over 10 mins

Thirty-two clinical trials were reported using IV lacosamide as treatment for SE (3 class III and 29 class IV). They used different definitions of RSE, and some included a large proportion of focal SE or electrographic NCSE cases.

- **Two studies involved patients who had only received a benzodiazepine prior to lacosamide** (**established** SE).
- **Sixteen studies** on adults or on both children and adults examined the efficacy of LCM in the treatment of convulsive Resistant Status Epilepticus (2 class III and 14 class IV studies)

For children and adults with CRSE, it is possible that lacosamide (at a loading dose of 10 mg/ Kg) is effective at stopping *Resistant* SE (level C; 2 class III, 14 class IV studies). For adults with *established* CSE, insufficient evidence exists to support that lacosamide and valproate are equally effective as second line treatment (level U, 1 class III study).

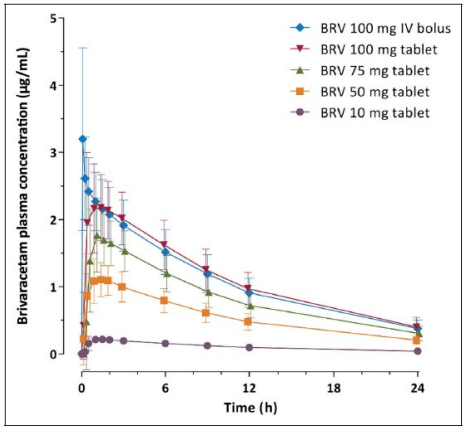
Vossler et al., Epilepsy Curr. 2020 Sep;20(5):245-264.

Intravenous Brivaracetam in the Management of Acute Seizures in the Hospital Setting: A Scoping Review

J Intensive Care Med. 2022, 1-13

Kiwon Lee, MD, FACP, FAHA, FCCM[1], Pavel Klein, MD, FAAN, FAES[2], Prashant Dongre, MD[3], Eun Jung Choi, MD, PhD[3], and Denise H. Rhoney, PharmD, FCCP, FCCM, FNCS[4]

Twelve studies were included for analysis.



IV BRV was generally well tolerated in patients with acute seizures, with a low incidence of individual TEAEs classified as **behavioral disorders**. Although outside of the approved label, findings from several studies suggest that IV BRV reduces seizures and is generally **well tolerated in patients with status epilepticus.**

IV BRV acts fast, with 100 mg 2-min bolus achieving a tmax in approximately 5 min, and **suppression of epileptiform activity on EEG in a median of 2 min** in patients with photosensitive epilepsy

Respiratory depression and cardiorespiratory adverse events were not observed

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

40-60 min
Third therapy phase

Refractory status epilepticus

There is no clear evidence to guide therapy in this phase (Level U):
Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).

Glaucer et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee

Midazolam: Thirty-three original studies identified, 0 were class I or II, 4 were class III, and 29 were class IV.
Pentobarbial Thiopental: Forty-four original studies published between 1967 and 2019. Two were class III and the other 42 were class IV.
Propofol: Literature between 1988 and 2019 yielded 28 articles (2 class 3, 26 class IV)
Ketamine: Twenty-five class IV studies included 14 case reports and 11 case series.

In all cases there was insufficient evidence that showed efficacy of any drug or a significant difference in any comparison in refractory status epilepticus (level U)

Vossler et al., Epilepsy Currents 2020, Vol. 20(5) 245-264

Comparison of Intravenous Anesthetic Agents for the Treatment of Refractory Status Epilepticus

	Mechanism of Action	Half-Life (Hrs) and protein bibding	Drug Interactions	Adverse Reactions
Midazolam	GABA agonist	2–7 94%-97%	CYP 3A4 substrate	Hypotension Respiratory depression
Propofol	GABA agonist; NMDA antagonist	0.5-7	N/A	Hypotension Respiratory depression Propofol Related Infusion Syndrome Increase Triglycerides
Pentobarbital	GABA agonist; Barbiturate	biphasic: about 4 hours in first phase and up to 50 hours in the second phase	CYP 2A6 inducer	Hypotension Respiratory depression Paralytic ileus Immune suppression Hepatic/pancreatic dysf
Ketamine	NMDA antagonist	2.5	CYP 2C9 & 3A4 substr	Hypertension Hypersalivation Hallucinations

Pharmacotherapy for Nonconvulsive Seizures and Nonconvulsive Status Epilepticus

Drugs (2021) 81:749–770

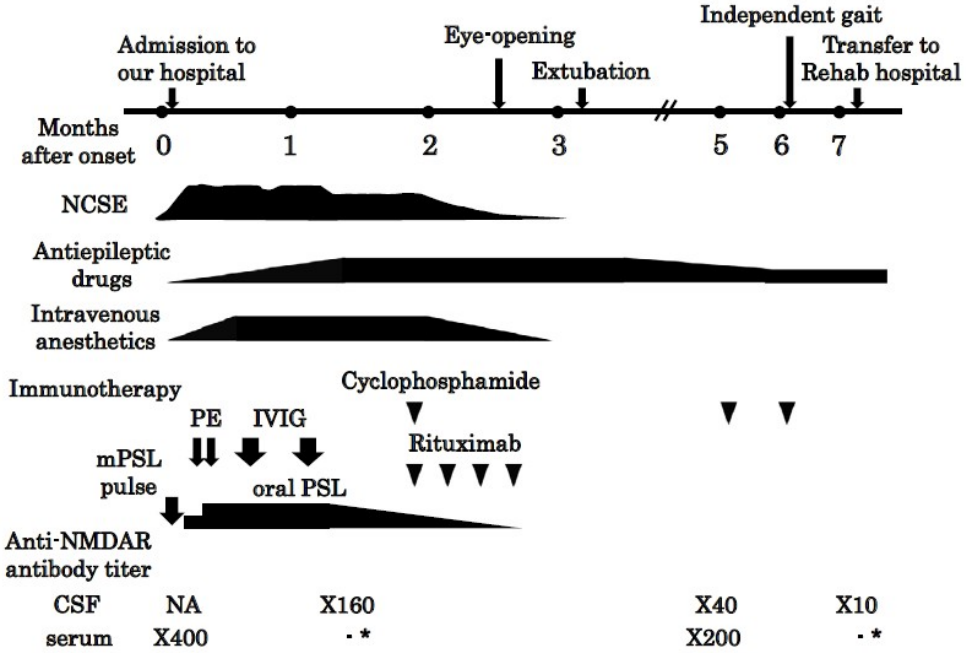
Pablo Bravo[1] · Aparna Vaddiparti[1] · Lawrence J. Hirsch[1]

May treatment strategy be influenced by different kinds of nonconvulsive status epilepticus?

- NCSE that follows convulsive SE.
- NCSE with coma or stupor.
- NCSE without coma or stupor.

Refractory Status Epilepticus Caused by Anti-NMDA Receptor Encephalitis that Markedly Improved Following Combination Therapy with Rituximab and Cyclophosphamide

Masato Kadoya, Hiroyuki Onoue, Akiko Kadoya, Katsunori Ikewaki and Kenichi Kaida



Clinical course of the present patient. The NCSE disappeared after the initiation of second-line immunotherapy. The titer of anti-NMDA receptor antibodies in the CSF decreased in association with the improvements in the encephalitis.

(Intern Med 54: 209-213, 2015)

La maggiori criticità cliniche ed organizzative nella gestione dello stato epilettico

- Stesura di protocolli operativi che tengano conto delle recenti linee guida
- Il rispetto dei tempi per l'esecuzione delle procedure diagnostiche e terapeutiche
- La scelta dei farmaci anche in considerazione delle interazioni farmacocinetiche e farmacodinamiche e delle comorbidità
- La definizione di percorsi ospedalieri

Prehospital Treatment of Status Epilepticus in the United States

Guterman et al., **JAMA** November 16, 2021 Volume 326, Number 19

Benzodiazepine type and dose	No. (%) of encounters				
	All (N = 9174)[a]	Intramuscular route	Intranasal route	Intravenous route	Other route[b]
Midazolam, mg					
<5	3289 (42.9)	648 (8.5)	559 (7.3)	2061 (26.9)	21 (0.3)
5	3809 (49.7)	1677 (21.9)	788 (10.3)	1331 (17.4)	13 (0.2)
>5 and <10	22 (0.3)	6 (0.1)	3 (<0.1)	13 (0.2)	0
10	541 (7.1)	310 (4.0)[c]	154 (2.0)	72 (1.0)	5 (0.1)
>10	4 (0.1)	0	0	4 (0.1)	0
Total	7665	2641	1504	3481	39
Lorazepam, mg					
<2	331 (26.2)	40 (3.2)	18 (1.4)	268 (21.2)	5 (0.4)
2	890 (70.4)	188 (14.9)	47 (3.7)	640 (50.6)	15 (1.2)
>2 and <4	2 (0.2)	1 (0.1)	0	1 (0.1)	0
4	35 (2.8)	13 (1.0)	2 (0.2)	18 (1.4)[c]	2 (0.2)
>4	6 (0.5)	3 (0.2)	2 (0.2)	1 (0.1)	0
Total	1264	245	69	928	22
Diazepam, mg					
<6	207 (84.5)	18 (7.4)	25 (10.2)	162 (66.1)	2 (0.8)
≥6 and <10[d]	38 (15.5)	2 (0.8)	2 (0.8)	29 (11.8)[c]	5 (2.0)
Total	245	20	27	191	7

- Prehospital status epilepticus treatment was rarely consistent with expert guidelines.
- The majority of patients received benzodiazepine doses **lower than recommended**, and many were treated via **a route not recommended**.

The relevance of timing in nonconvulsive status epilepticus: A series of 38 cases☆

Epilepsy & Behavior 82 (2018) 11–16

Álvaro Gutiérrez-Viedma [a,b,c,*], Beatriz Parejo-Carbonell [a,c], María-Luz Cuadrado [a,b,c], Irene Serrano-García Belén Abarrategui [a,c,1], Irene García-Morales [a,b,c]

Assessment of the precise relationship between timing in nonconvulsive status epilepticus (NCSE) management and its outcome.

Cross-sectional prospective study of 38 admitted NCSE

- The median time to treatment initiation was 5 h, and the median time to first electroencephalography assessment was 18.5 h
- In the cases with out-of-hospital onset (n=24), the median time to hospital arrival was 2.8 h.
- The median time to NCSE control was 16.5 h

There were pervasive delays in all phases of NCSE management.

Timing Is Everything: Where Status Epilepticus Treatment Fails

ANN NEUROL 2017;82:155–165

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1]
Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

Minority of patients receive treatment before arrival in the hospital
Unreliable administration and dosage of benzodiazepines as the first-line agent
Journey to hospital is often prolonged
Delays in diagnosis of status epilepticus (EEG)
Difficult to retrospectively assess seizure duration and clinical decision making
Limited and laborious data collection
Health system and institution-specific factors impact protocol adherence

Potential drug–drug interactions when managing status epilepticus patients in intensive care: A cohort study

Clémentine Le Roux[1,2] | Alexandre Destère[1] | Sarah Hervy[3] | Célia Lloret-Linares[1,4] | Jean Reignier[5] | Pascal Caillet[3] | Pascale Jolliet[2] | Bruno Mégarbane[1,6] | David Boels[1,2,3]

Br J Clin Pharmacol. 2022;88:2408–2418.

BJCP

BRITISH PHARMACOLOGICAL SOCIETY

Observational bi-centric cohort study including all SE patients admitted to the ICU in the period 2016–2020.

- 431 SE patients were included and **5504 potential DDIs were identified** including 1772 DDIs (33%) between ASDs, 2610 DDIs (47%) between ASDs and previous usual treatments (PUTs), and 1067 DDIs (20%) between ASDs and ICU treatments (ICUTs).
- **DDIs were moderate (n = 4871), major (n = 562) or severe (n = 16). All patients exhibited potential DDIs, which were major-to-severe DDIs in 47% of the cases.**
- DDIs were pharmacokinetic (n = 1972, 36%), mostly involving cytochrome P450 modulators, and pharmacodynamic (n = 3477, 64%), mainly leading to increased sedation. ASD/PUT DDIs were the most frequent and severe.
- Age, PUT and ASD drug numbers and length of ICU stay were significantly associated with increased DDI number.

Regione Toscana

ARS TOSCANA
agenzia regionale di sanità

OTGC
ORGANISMO TOSCANO GOVERNO CLINICO

PERCORSO ASSISTENZIALE
PER LA PRESA IN CARICO
DELLE PERSONE CON EPILESSIA

CAPITOLO QUINTO – L'epilessia nella Emergenza/Urgenza

L'osservazione in DEA

- Tutti i pazienti con crisi epilettiche in serie o che presentino uno stato epilettico "incipiens" dovrebbero essere ricoverati in un presidio ospedaliero dotato di rianimazione e ove sia possibile eseguire almeno una TC cranio in urgenza.
- Dovrebbe inoltre essere possibile eseguire **in tempi rapidi un EEG e richiedere consulenza neurologica**
- Il trattamento farmacologico nei pazienti in stato epilettico resistenti alle benzodiazepine dovrebbe essere concordato con il neurologo, se presente, ed in determinati casi la consulenza può essere anche solo telefonica.

Firenze, 4 giugno, 2019

Raccomandazioni concernenti l'uso dell'EEG

Dovrebbe essere possibile **utilizzare l'EEG come indagine da eseguire in emergenza.** La non disponibilità dell'EEG non dovrebbe tuttavia ritardare il trattamento di questi pazienti.

- Nel paziente che rimane non responsivo dopo il trattamento iniziale, l'EEG dovrebbe essere utilizzato per **differenziare la sedazione farmaco-indotta da una condizione di persistenza di crisi**.
- L'EEG dovrebbe essere usato anche per monitorare **l'effetto del trattamento dei pazienti in SE refrattario**, in particolare nelle forme non convulsive.

Clinical pathways of epileptic seizures and status epilepticus: results from a survey in Italy

Neurol Sci. 2020 Jun;41(6):1571-1575.

Gaetano Zaccara[1] · Giuseppe Citerio[2,3] · Alfredo Del Gaudio[4] · Monica Ferlisi[5] · Francesco Rocco Pugliese[6] · Danilo Toni[7]

- A survey of physicians from all parts of Italy on the management of patients with epileptic seizures or status epilepticus in the hospital
- **Epileptologists managed patients with epilepsy, acute seizures, and status epilepticus in 35%, 21%, and 16% of cases, respectively**.
- **Diagnostic, therapeutic, and assistance pathways (PDTA) were available in about 50% of hospitals**.

	Professionals included in a formal PDTA ($n = 87$)*
Epileptologists/neurologists, emergency physicians	23 (26%)
Epileptologists/neurologists, emergency physicians, intensivists	48 (55%)
Epileptologists/neurologists, emergency physicians, intensivists, specialist in internal medicine	16 (18%)
Other specialists	–

Grazie per l’attenzione