UNIVERSITÀ DEGLI STUDI DI GENOVA

SCUOLA DI SCIENZE MEDICHE E FARMACEUTICHE

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia,

Genetica e Scienze Materno-Infantili (DINOGMI)

SCUOLA DI SPECIALIZZAZIONE IN PEDIATRIA

Tesi di Specializzazione:

Ketamine for benzodiazepine-refractory convulsive status epilepticus in the emergency department: a pediatric case series.

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Introduction

Status epilepticus (SE) represents a serious and potentially lethal neurological condition characterized by prolonged or repeated seizures without recovery of consciousness between episodes. In children, this condition is one of the most common neurological emergencies, with a significant risk of permanent neurological damage and mortality if not treated promptly and effectively. (1)

According to epidemiological studies, the risk of SE is particularly high in the pediatric population, with potentially devastating consequences for neurological development. (2)

First-line treatment for SE involves the use of benzodiazepines, which act as potent modulators of the GABA receptor, enhancing synaptic inhibition. However, approximately 30-40% of patients do not respond to this initial treatment, progressing to refractory status epilepticus (RSE), a condition that necessitates a more aggressive therapeutic approach. (3)

RSE is particularly concerning in pediatrics due to the limitations of conventional therapies, which include medications such as barbiturates, propofol, and valproic acid. These treatments carry the risk of severe side effects and require intensive monitoring.

After the failure of first- and second-line medications, hospitalization in an intensive care unit is usually indicated, along with continuous infusion of anesthetics.

In this context, interest in the use of ketamine as an alternative therapeutic option has grown significantly in recent years. Ketamine, originally

developed as a dissociative anesthetic, primarily acts as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, blocking glutamate-mediated excitotoxicity. This mechanism is one of the factors that may be implicated in the refractoriness of epileptic seizures.(4)

In addition to its anesthetic properties, ketamine has demonstrated potential anticonvulsant and neuroprotective effects, as well as synergistic effects with other antiepileptic medications, making it an interesting candidate for the management of RSE, particularly in pediatric populations where safe and effective therapeutic options are limited.

This explains the growing interest in ketamine as a second-line treatment for convulsive SE refractory to benzodiazepines in children, especially in light of its good tolerability and a safety profile that supports its use in emergency settings. (5)

These results represent a significant step toward the integration of ketamine into therapeutic guidelines for the management of RSE in children.

Until two years ago, the protocol for managing SE at the Emergency Department of the Giannina Gaslini Institute in Genoa did not include the use of ketamine. Second-line treatment relied on alternative medications such as levetiracetam, phenytoin, valproate, and phenobarbital. However, since November 2022, ketamine has been included as a second-line therapeutic option for cases of RSE in the institute's internal protocol, available to emergency department physicians.

The primary objective of this thesis is to analyze the introduction and use of ketamine as a second-line treatment for pediatric RSE within the emergency

department setting of the Gaslini Institute. Specifically, the administration methods of ketamine will be examined, and its efficacy and safety will be assessed in this clinical context.

Status Epilepticus

Definition and Classification

SE represents one of the most common and severe neurological emergencies in pediatrics.

The Task Force of the International League Against Epilepsy (ILAE) defines SE as a "condition resulting from the failure of mechanisms responsible for terminating seizures or from the initiation of mechanisms that lead to abnormally prolonged seizures."

SE can have long-term consequences, including neuronal death, neuronal injury, and alterations in neural networks, depending on the type and duration of the seizures.

According to classical definitions, SE is characterized by a seizure lasting more than 30 minutes or by two or more consecutive seizures without recovery of consciousness between episodes. (6)(7)

In clinical practice, however, a single seizure lasting longer than 5 minutes (in adults and children over 5 years old) should be considered SE. This timeframe is based on the recognition that timely treatment is crucial for preventing permanent neurological damage and improving clinical outcomes. The significance of this time interval lies in the fact that the first 5 minutes following the onset of a seizure is the period during which most seizures tend to resolve spontaneously. Beyond this period, therapeutic intervention is necessary, with an optimal treatment window occurring between 5 and 15 minutes from the onset of the seizure. After 30 minutes, the definition of SE becomes relevant in both epidemiological and pathophysiological contexts,

as well as regarding clinical outcomes. Indeed, the principle of "time is brain" applies to SE as well: as the duration of SE increases, there is progressive neuronal necrosis and edema of the neuropile. (8)(9)

Moreover, additional factors can contribute to brain damage during prolonged seizures, including cerebral hypoxia, hyperthermia, hypotension, hypoglycemia, acidosis, and failure of compensatory mechanisms (e.g., cerebral autoregulation). Thus, preventing secondary brain damage is imperative during SE.

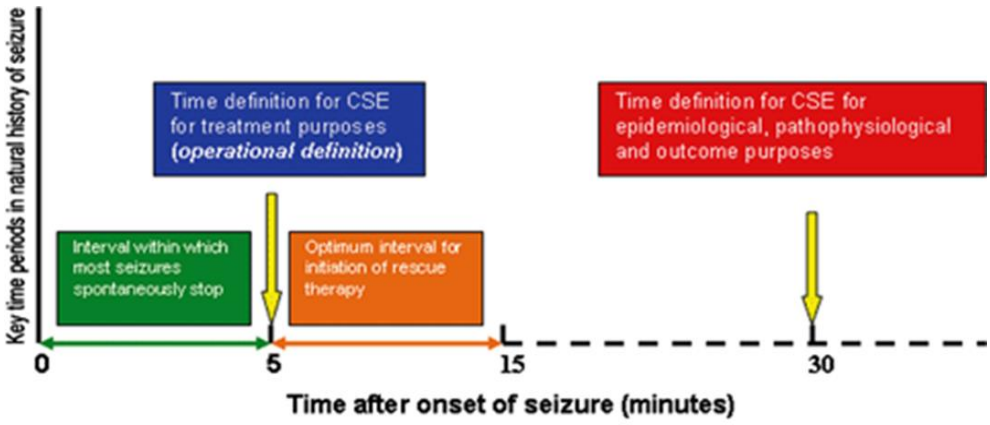


Figure 1. Temporal evolution of SE. *Epilepsia - vol 48 - The Epidemiology of Convulsive Status Epilepticus*

Regarding nomenclature and classification, we distinguish (1):

- Status Epilepticus (SE): A condition resulting from the failure of mechanisms responsible for terminating seizures or from the initiation of mechanisms that lead to abnormally prolonged seizures. This condition can have long-term consequences, including neuronal

death, neuronal damage, and alterations in neural networks, depending on the type and duration of the seizures.

- Refractory Status Epilepticus (RSE): Persistent SE despite the administration of at least two appropriately selected and dosed parenteral medications, including a benzodiazepine.
- Super Refractory Status Epilepticus (SRSE): SE that persists for at least 24 hours despite anesthetic treatment or recurs when attempting to withdraw from the anesthetic regimen.
- Prolonged Super-Refractory Status Epilepticus: SRSE that lasts for at least 7 days, including the continuous need for anesthetics.

Status epilepticus presents in different forms:

1. Convulsive Status Epilepticus: characterized by repeated generalized tonic-clonic seizures, with postictal depression of neurological function between seizures.
2. Non-Convulsive Status Epilepticus: in which seizures produce a continuous or fluctuating state of "epileptic twilight."
3. Repeated Partial Seizures: manifested as focal motor signs, focal sensory symptoms, or focal functional impairment (e.g., aphasia) not associated with altered consciousness (continuous partial epilepsy). (3)

Several scoring systems have been developed for the assessment of SE. Among the most commonly used, particularly in the adult population, is the Status Epilepticus Severity Score (STESS Score). (10)

The STESS Score is a clinical tool designed to assess the severity of status epilepticus and the risk of adverse outcomes. The score ranges from 0 to 6 and is based on various factors, including the level of consciousness, the type of seizure, the patient's age, and the presence of comorbidities or a history of previous seizures.

Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	>65 years	2
History of previous seizures	Yes	0
	No or unknown	1
TOTALE		0-6

Table 1. Status Epilepticus Severity Score (STESS Score)

The interpretation of the STESS Score is crucial for clinical management. Low scores (0-2) indicate a relatively low risk of complications, suggesting a favorable prognosis and standard monitoring. Intermediate scores (3-4) signal a moderate risk, requiring careful observation and possible therapeutic interventions. High scores (5-6) are associated with a high risk of negative outcomes, such as permanent neurological damage, and justify a more aggressive and timely therapeutic approach. The adoption of the STESS Score in the adult population has been shown to improve risk stratification

and optimize therapeutic decisions, contributing to more effective management of patients with SE.

Epidemiology

Regarding epidemiology, the incidence of SE is estimated to be between 10 and 25 cases per 100,000 children per year, with an increased risk of SE and associated mortality in younger children. Furthermore SE affects 10-20% of children with epilepsy.

In terms of mortality, it stands at 3% of all SE cases (rising to 17% in patients admitted to Intensive Care Units), but reaches 16-43% in cases of RSE and 12% in cases of super-refractory SE.

Finally, the likelihood of recurrence of an SE episode after the first event is 20% within the following four years, with a higher incidence in the first two years. (11) (12)(13)

Preexisting neurological conditions are a risk factor for the development of SE: between 56% and 60% of children presenting with SE were neurologically normal prior to the event, while the remainder had a preexisting neurological anomaly. This is less common in younger children (who more frequently present with febrile SE or acute symptomatic seizures) and more common in older children and adolescents. In fact, 60% of children over the age of 5 with SE have a preexisting neurological anomaly, compared to only 21% of children under 2 years old. (14)

Etiology

Regarding etiology, febrile SE is the most common cause in the pediatric population, accounting for about one-third of all SE cases in children between 6 months and 6 years of age.

Other causes of SE include:

- Infectious: such as bacterial meningitis or viral encephalitis;
- Metabolic: including hypoglycemia or hyperglycemia, hyponatremia or hypernatremia, hypocalcemia, and hypomagnesemia;
- Toxicological;
- Traumatic: including epidural, subdural, subarachnoid, or intraparenchymal hemorrhages;
- Vascular: such as arterial strokes or venous thrombosis;
- Preexisting epilepsy: where SE may be related to poor adherence or missed administration of baseline antiepileptic therapy, or to a concurrent infection;
- Central nervous system disorders: such as traumatic brain injury, stroke, malformations, or tumors. (14)

Current Guidelines for the Treatment of Pediatric Status Epilepticus

Recently, a comparative study conducted across ten pediatric research centers provided a detailed overview of the various treatment strategies for SE in pediatric emergency departments. (13)

Current treatment protocols for SE suggest a timely and stepwise management approach, emphasizing the importance of timing, efficacy, and safety of antiepileptic medications. (3,15)

The time-dependent protocol includes the following phases:

- 0-5 minutes: In this initial phase, corresponding to the onset of the seizure, it is essential to ensure patient stabilization.
- 5-20 minutes: During this time, the primary goal is to prevent progression to persistent SE. The administration of benzodiazepines is indicated to control the seizure and prevent the development of SE.
- 20-40 minutes: If the seizure persists, second-line therapies, such as phenytoin, valproate, levetiracetam, or phenobarbital, must be considered to interrupt the status epilepticus.
- 40-60 minutes: In cases of RSE that do not respond to previous treatments, the administration of general anesthesia should be considered for seizure control.

This stepwise approach allows for appropriate intervention based on the duration and severity of SE, optimizing the chances of a favorable clinical outcome and reducing the risk of neurological complications.(16)

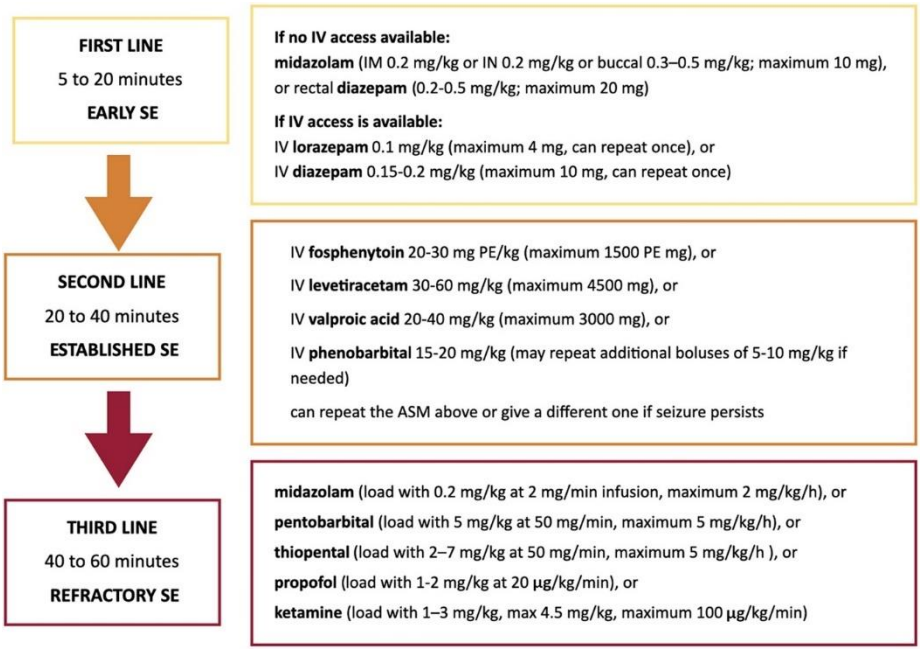


Figure 2. Pediatric SE timeline-based algorithm combining current guidelines and pathways. (16)

Treatment Objectives

The treatment of pediatric SE has three main objectives:

- Rapid interruption of seizures: The primary goal is to stop convulsive activity as quickly as possible. Current guidelines recommend initiating pharmacological treatment within the first 5 minutes of seizure onset. Timeliness is essential to prevent the development of RSE, a condition associated with a significant increase in mortality. (17)
- Prevention of complications: hypoxia, hypoglycemia, hyperthermia, metabolic acidosis, and hemodynamic instability. Continuous monitoring

of vital signs and early intervention to correct any abnormalities are essential to prevent secondary damage.

- Patient stabilization and prevention of recurrence: After stopping the seizures, it is crucial to stabilize the patient and monitor for potential seizure recurrence. This involves maintaining airway patency, cardiovascular stabilization, management of underlying causes of SE, and continuous electroencephalographic monitoring in more severe cases.

Phases of Treatment

The treatment of pediatric SE involves multiple phases, each requiring the use of specific classes of medications and therapeutic interventions. (11)(13)(18)

First line treatment

Benzodiazepines, which act as potent modulators of the GABA receptor, are the first line of treatment due to their rapid action and effectiveness in stopping convulsive seizures. Among the available options, midazolam, lorazepam, and diazepam are the most commonly used medications. Although there are variations in the specific choice of drug and route of administration across different centers, benzodiazepines remain the standardized first therapeutic option in all centers (level of evidence A, class I recommendation).

The importance of early administration of benzodiazepines stems from the fact that untimely treatment with first-line benzodiazepines is independently

associated with a higher frequency of deaths, increased use of continuous infusions, and prolonged duration of seizures. (19)

The most commonly used benzodiazepines are:

- Midazolam: Can be administered intranasally, buccally, intramuscularly, or intravenously (the first three routes are particularly useful in pre-hospital settings or emergency situations where venous access is not immediately available). The recommended dosage is 0.2 mg/kg, with a maximum of 4 mg per dose.
- Lorazepam: Considered the drug of choice in many hospital settings, as it has a slower onset of action compared to midazolam but a longer half-life which can reduce the need for additional doses. It is administered intravenously, with a recommended dosage of 0.1 mg/kg (maximum 4 mg per dose).
- Diazepam: Primarily used in pre-hospital settings where venous access is not available. The dosage for rectal administration is 0.15-0.2 mg/kg (maximum 10 mg per dose).

Side Effects and Contraindications. The use of benzodiazepines, while effective, is not without side effects. The most common include respiratory depression, hypotension, and, in some cases, excessive sedation. It is crucial to closely monitor patients during and after the administration of benzodiazepines, especially in neonates and infants, who are more susceptible to adverse effects.

Due to these side effects, the administration of benzodiazepines can only be repeated once, for a maximum of two total doses, including any given in the pre-hospital setting. In fact, the efficacy of a third dose would be limited, while the risk of respiratory depression would increase. (20)

Second line treatment

If benzodiazepines fail to terminate SE, the next step involves using non-benzodiazepine antiepileptic drugs, which constitute the second-line treatment. The most commonly used medications in this phase include fosphenytoin, levetiracetam, and phenobarbital.

- Fosphenytoin: This is a prodrug of phenytoin, administered either intravenously or intramuscularly. The recommended intravenous dosage is 20-30 mg PE/kg (maximum 1500 mg PE), with an infusion rate not exceeding 3 mg PE/kg/min. Fosphenytoin is preferred over phenytoin due to its improved safety profile, as it causes fewer local adverse reactions and has a lower risk of cardiac arrhythmias.
- Levetiracetam: Increasingly used as an alternative to fosphenytoin, levetiracetam is favored for its safety profile and ease of use. The recommended dosage is 30-60 mg/kg (maximum 4500 mg), administered intravenously over 15 minutes. It is generally well tolerated and does not require intensive monitoring of plasma concentrations, making it a favorable choice in acute settings.
- Phenobarbital: Traditionally used in pediatric SE, especially in neonates, with a dosage of 15-20 mg/kg administered intravenously.

However, its use is limited by side effects, including deep sedation and respiratory depression, which necessitate careful monitoring.

The choice of second-line medication depends on various factors, including drug availability, the clinical experience of the medical team, the patient's condition, and previous responses to treatments. Current guidelines recommend a flexible approach based on the specific clinical context.

Third line treatment

In cases of RSE, where the patient does not respond to first-line and second-line treatments, more aggressive therapies are employed, including the use of general anesthetics and other advanced treatments.

- Midazolam Continuous Infusion: Initial loading dose of 0.2 mg/kg (maximum 10 mg), followed by a continuous infusion of 0.2-0.3 mg/kg/hour.
- Thiopental and Propofol: These are used to induce a pharmacological coma in R SE. Thiopental is a short-acting barbiturate, administered with a loading dose of 3-5 mg/kg followed by continuous infusion. Propofol is an intravenous anesthetic administered with a loading dose of 1-2 mg/kg, followed by continuous infusion. Both medications require admission to an intensive care unit (ICU) with continuous EEG monitoring.
- Ketamine: Considered in some centers as a third-line option for RSE due to its anticonvulsant properties and relatively favorable safety profile in emergency settings. The recommended dosage varies, but it

typically involves a loading dose of 1-2 mg/kg followed by continuous infusion.

In more severe cases, ICU admission is essential, as continuous EEG monitoring, potential respiratory support, and management of systemic complications associated with prolonged SE are required.

International and National Guidelines

International League Against Epilepsy (ILAE) Guidelines

The guidelines from the International League Against Epilepsy (ILAE) are among the most authoritative references for managing pediatric SE. The ILAE recommends a structured approach to SE treatment, divided into phases that reflect the progression of therapeutic intervention based on the patient's response.

The ILAE emphasizes the importance of timely administration of benzodiazepines as the first-line treatment and provides detailed recommendations on dosages and administration routes. For second-line treatment, the ILAE recognizes the effectiveness of various antiepileptic drugs and encourages tailoring the treatment based on the patient's specific conditions and the availability of medications.

Recommendations from American Academy of Pediatrics (AAP)

The recommendations from the American Academy of Pediatrics (AAP) emphasize the importance of timely and appropriate intervention to prevent complications from SE. They provide detailed guidelines on how to manage

pediatric patients with SE, including recommendations for pre-hospital treatment, patient transport, and hospital management.

In particular, the AAP advocates for the use of intranasal or intramuscular midazolam in pre-hospital settings as an effective method to terminate seizures before the patient arrives at the hospital.

The AAP guidelines generally align with those of the International League Against Epilepsy (ILAE), but they place a greater emphasis on integrated patient management, which includes psychological support and family involvement.

European and Italian guidelines

European and Italian guidelines generally follow international recommendations, with some variations based on local practices and the availability of medications. Both emphasize the importance of interdisciplinary cooperation in the treatment of pediatric status epilepticus, involving neurologists, pediatricians, intensivists, and clinical pharmacists. There is a strong emphasis on the continuous education of healthcare professionals and the need for standardized protocols for the management of SE in all hospital settings

Final considerations

Clinical studies on SE often have limitations, such as the retrospective nature of the data, small sample sizes, the scarcity of trials conducted on pediatric patients, heterogeneity in etiology, age, and sample size, as well as

variability in dosages and medications used prior to or in conjunction with the studied drugs, and finally, the timing and duration of each therapy.

Current guidelines for the treatment of SE in pediatric research centers provide a diverse range of therapeutic approaches, with an increasing trend toward integrating medications like ketamine into refractory SE treatment protocols.

While there are still variations in practices among centers, the common denominator remains the importance of timely, multidisciplinary, and personalized intervention to improve outcomes for pediatric patients, especially considering the frequent significant delays in the initiation of treatment. (21)

The future of pediatric SE management will rely on ongoing clinical research and the dissemination of best therapeutic practices.

Ketamine

Interest in the use of ketamine for pediatric RSE has grown significantly in recent years due to its unique mechanism of action and relatively favorable safety profile compared to other therapeutic options.

Mechanism of action of ketamine

Ketamine, originally developed as a dissociative anesthetic, is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. This mechanism blocks glutamate-mediated excitotoxicity, which may be involved in the refractoriness of epileptic seizures. (4)

This mechanism may confer neuroprotective properties to ketamine, reducing the risk of neuronal damage associated with prolonged SE. Other advantages of ketamine include:

- When administered intravenously, it reaches peak plasma concentration within 1-5 minutes.
- A loss of consciousness occurs within 45 seconds after a single dose, lasting for 10-15 minutes; analgesia lasts about 40 minutes, and amnesia lasts for 1-2 hours.
- It has high liposolubility and low protein binding, allowing it to quickly penetrate the blood-brain barrier.
- It has a sympathomimetic effect (increasing heart rate and blood pressure).

- It improves cerebral perfusion pressure, making it safe even in neurological conditions.
- It does not induce respiratory depression, preventing the need for intubation in refractory SE.
- It maintains airway protective reflexes and cardiovascular stability.
- It is commonly used for procedures in emergency departments and in pre-hospital settings in pediatric populations.
- It has a synergistic effect with other medications (e.g., midazolam).
- It is low-cost and readily available.

The disadvantages of ketamine are limited. Psychiatric symptoms associated with ketamine use (such as hallucinations, delirium, vivid dreams, and blurred vision) are rare in children. The potential effect on intracranial pressure, often cited against ketamine, does not appear to be clinically relevant. It is now well recognized in clinical practice that ketamine can be used safely in cases of traumatic brain injury and non-traumatic neurological diseases.(16)

Safety and tolerability

The safety of ketamine, as documented in the 2011 guidelines, extends to the context of pediatric RSE. The main adverse events associated with ketamine are respiratory in nature (such as respiratory depression, apnea, and laryngospasm), but these are rare and manageable with appropriate monitoring. (22)(23)(24)(25)

Absolute contraindications for ketamine include:

- Age under 3 months (not specific to ketamine, but due to anatomical and reactivity differences in infants' airways).
- Known or suspected schizophrenia, even if stable or controlled with medication (it may exacerbate the condition).

Relative contraindications include:

- Major procedures that stimulate the posterior pharynx (e.g., endoscopy) increase the risk of laryngospasm, which does not occur with minor oropharyngeal procedures.
- History of airway instability, tracheal surgery, or tracheal stenosis (increased presumed risk of airway complications).
- Active lung infection or disease, including upper respiratory infections or asthma (higher risk of laryngospasm).
- Known or suspected cardiovascular diseases, including angina, heart failure, or hypertension (due to ketamine's sympathomimetic properties, including tachyarrhythmias).
- Masses, anomalies, or hydrocephalus of the central nervous system (doubtful increase in intracranial pressure with ketamine).
- Glaucoma or acute ocular injury (increased intraocular pressure with ketamine).
- Porphyria, thyroid disorders, or thyroid medications (enhanced sympathomimetic effects).

Several studies have highlighted the absence of fatal outcomes in children who inadvertently received doses of ketamine significantly higher than the therapeutic dose, ranging from 5 to 100 times, up to 450 mg/kg. Reported toxicities in these cases included prolonged sedation in some, and in others, episodes of transient apnea and/or desaturation that required intervention with oxygen therapy and brief non-invasive ventilation. (26)(27)(28)

Additionally, a systematic review documented cases of mortality associated with the use of ketamine, highlighting that no deaths were recorded in therapeutic contexts. Most reported fatalities were related to the use of the substance as a recreational drug, with the analyzed sample ages ranging from 2 to 65 years. (29)

Ketamina in SE

The FDA approved ketamine as an anesthetic in 1970, and since then, it has been widely used in emergency settings for sedation, intubation, agitation, and pain management.

Dissociative sedation is defined as a "cataleptic-like trance state characterized by profound analgesia and amnesia, while maintaining airway protective reflexes, spontaneous respiration, and cardiopulmonary stability." (25)

Ketamine is particularly used as an anesthetic agent in emergency settings due to its safety and effectiveness in providing dissociative sedation, which offers profound analgesia and amnesia while maintaining airway protective reflexes, spontaneous respiration, and cardiopulmonary stability. Therefore, it is frequently employed in short and painful procedures, especially those

requiring immobilization, such as facial sutures, fracture reductions, burn treatments, and abscess incisions. It is also used in pre-hospital settings for acute agitation or when analgesia or procedural sedation is needed.

Although the document "Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update" does not focus exclusively on pediatric RSE, these guidelines provide crucial information on ketamine management, including recommended dosages and safety protocols, which can be applicable in cases of SE treated in emergency departments. (25)

In recent years, research has focused on the use of ketamine not only as a dissociative sedative but also for its therapeutic potential in the context of epilepsy, leading to growing interest in ketamine as a second-line treatment for RSE unresponsive to benzodiazepines.

Recent animal studies investigating the pathophysiology of SE have highlighted rapid changes in receptor expression at the neuronal level, with alterations in their composition that could explain the self-sustaining nature of SE and the failure of medical therapy with benzodiazepines (the "receptor trafficking hypothesis").(30)(31)

In particular, it has been found that during prolonged seizures, the number and activity of GABA receptors progressively decrease, leading to a gradual failure of commonly used first- and second-line antiepileptic drugs (AEDs). (32)

At the same time, the number and activity of NMDA glutamatergic receptors increase, often leading to RSE.

These receptor changes explain the progressive resistance to benzodiazepines during SE and the potential role of NMDA receptor antagonists, such as ketamine (the only NMDA antagonist approved for use in humans as an intravenous medication).

Moreover, ketamine exerts neuroprotective effects that could mitigate neuronal damage induced by RSE, as demonstrated in studies using animal models. (33)(34)(35)

Ketamine, therefore, shows increasing promise in the treatment of RSE, with significant antiepileptic efficacy reported in 60-70% of cases.

Despite these positive results, it is essential to conduct further prospective studies to explore therapeutic regimens, efficacy, and safety of ketamine in the treatment of SE. Current evidence regarding ketamine use in SE is largely limited to case reports and retrospective studies. (16)

Only through systematic and well-designed research will it be possible to validate the use of ketamine as a viable therapeutic option for this complex condition. (36)(24)(37)

Management of Status Epilepticus in the Emergency Department of the Giannina Gaslini Institute in Genoa

At the Giannina Gaslini Institute, following the First London Meeting on Status Epilepticus (38), which recommended the adoption of written protocols for the management of convulsive SE in all units, developed in consultation with experts from other disciplines and potentially adapted to specific hospital settings, a research group on SE was established. This group consists of specialists in pediatric emergency medicine, neurology, and intensive care, and has initiated the development of the Gaslini Protocol for the management of SE.

The project has been structured through a systematic review of the literature, an analysis of available clinical and pharmacological resources, and the definition of a stepwise therapeutic algorithm.

The primary objectives of the protocol were to optimize therapeutic decisions and to use medications characterized by a rapid onset of action and a short duration, without significant adverse effects such as excessive sedation, respiratory depression, hypotension, and organ toxicity.

In 2019, ketamine was integrated into our timed treatment protocol as a second-line antiepileptic drug to be used after levetiracetam, applicable in the context of SE across all areas of the Institute (emergency department, intensive care, semi-intensive care, and various wards).

SE Protocol until November 2022

The management of SE at our Institute is based on a time-dependent protocol that outlines the administration methods and timing of medications, the diagnostic investigations to be performed, and the necessary specialist consultations.

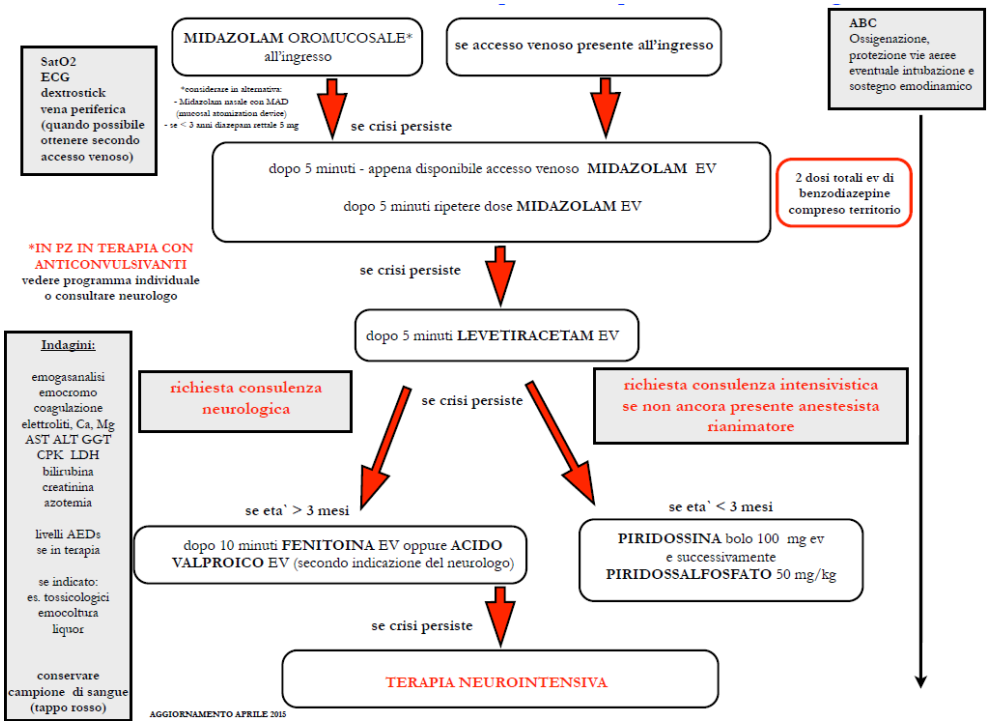


Figure 3. SE Protocol in our Institute until November 2022

Short-acting benzodiazepines are the first-line treatment for SE.

The administration of the first dose of benzodiazepines can occur via different routes depending on the clinical context. In home or community settings, when venous access is not available, midazolam is used via the oromucosal route (0.5 mg/kg, with a maximum of 10 mg) or intranasally (0.2 mg/kg, with a maximum of 5 mg), or diazepam can be given rectally (5 mg for patients < 3 years or < 10 kg; 10 mg for patients > 3 years or > 10 kg). If venous access

is available, the preferred treatment is intravenous midazolam (0.2 mg/kg, with a maximum of 5 mg).

Upon arrival in the Emergency Department (ED), it is crucial to implement initial care measures following the ABC protocol of first aid, which includes ensuring oxygenation, protecting the airway, and providing hemodynamic support. It is also essential to assess the patient's vital signs, including body temperature, oxygen saturation (SpO2), heart rate, and blood pressure; perform an electrocardiogram and a fingerstick glucose test; establish venous access as soon as possible; and conduct baseline blood tests, including blood gas analysis, possible levels of antiepileptic medications, and toxicological screening.

If the seizure persists after 5 minutes, it is indicated to repeat intravenous midazolam. The administration of benzodiazepines is limited to a maximum of two doses, including any that may have been given in the community.

In accordance with the protocol, the second-line medication is levetiracetam (due to its safety profile and rapid, effective action), to be administered at a dose of 30 mg/kg, simultaneously with the activation of a neurology consultation for an electroencephalogram (EEG) and intensive care consultation.

In the event of persistent seizures, the protocol stipulates:

- If age < 3 months: administration of a bolus of pyridoxine (100 mg IV), followed by continuous infusion of pyridoxal phosphate (50 mg/kg).

- If age > 3 months: administration of phenytoin (initial dose 15 mg/kg IV) or valproic acid (20-30 mg/kg), as indicated by the consulting neurologist, considering the contraindications of these two medications (long QT syndrome and atrioventricular block for phenytoin; liver or metabolic disorders and coagulopathies for valproic acid).

Intensive care treatment for SE is indicated in cases of RSE, where there is a lack of response to first- and second-line medications, and in the presence of systemic complications such as hemodynamic instability or respiratory depression. This treatment includes ventilatory and cardiovascular support, continuous EEG monitoring, advanced hemodynamic monitoring, pharmacological treatment of seizures (generally with continuous infusion therapies), and management of systemic complications.

New SE Protocol from November 2022

Since 2019, ketamine has been included as a second-line medication, after levetiracetam, for the management of SE refractory to benzodiazepines within the Institute.

As of November 2022, ketamine has been incorporated into the internal protocol flowchart for the management of RSE in the Emergency Department.

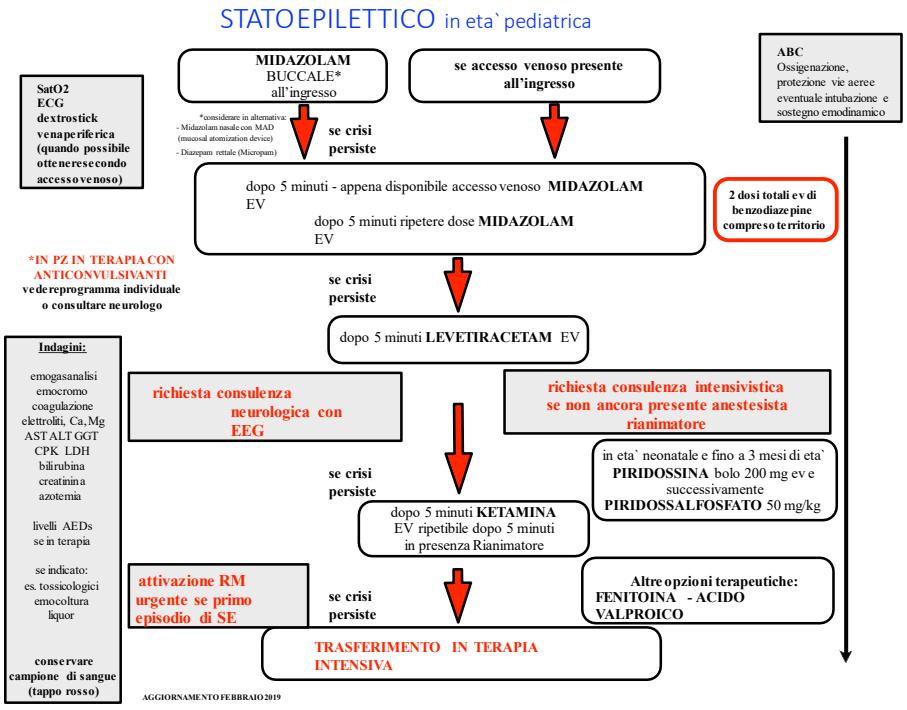


Figure 4. SE Protocol in our Institute from November 2022

The first phase of the protocol, which involves the use of short-acting benzodiazepines as first-line medications for the control of early convulsive seizures, remains unchanged. A maximum of two doses of benzodiazepines can still be administered at 5-minute intervals, including treatments given in pre-hospital settings.

The administration method and timing for the second-line medication, levetiracetam, remain the same. Levetiracetam continues to be given at the same dose, with a simultaneous request for a neurology consultation for an electroencephalogram (EEG) and intensive care consultation.

The new introduction is the use of ketamine as a second-line medication after the failure of levetiracetam. According to the new protocol, ketamine can be administered at a dose of 1-2 mg/kg, with the option to repeat the dose after 5 minutes, under the supervision of a resuscitator. However, for patients under 3 months of age, the use of pyridoxine in bolus, followed by pyridoxal phosphate, remains preferable.

If seizures persist despite two doses of ketamine, an urgent brain MRI is necessary (if this is the first episode of status epilepticus), and the patient should be transferred to intensive care.

Objectives of the study

The main objectives of our study are:

- To conduct a prospective study on a selected population of patients;
- To perform a descriptive analysis of the selected clinical cases;
- To evaluate adherence to and effectiveness of the new step-by-step protocol, in relation to the type and sequence of medications administered, dosage, timing, and method of administration;
- To analyze the efficacy and safety profile of the medications used, with particular attention to the introduction of ketamine as a second-line therapy.

Material and methods

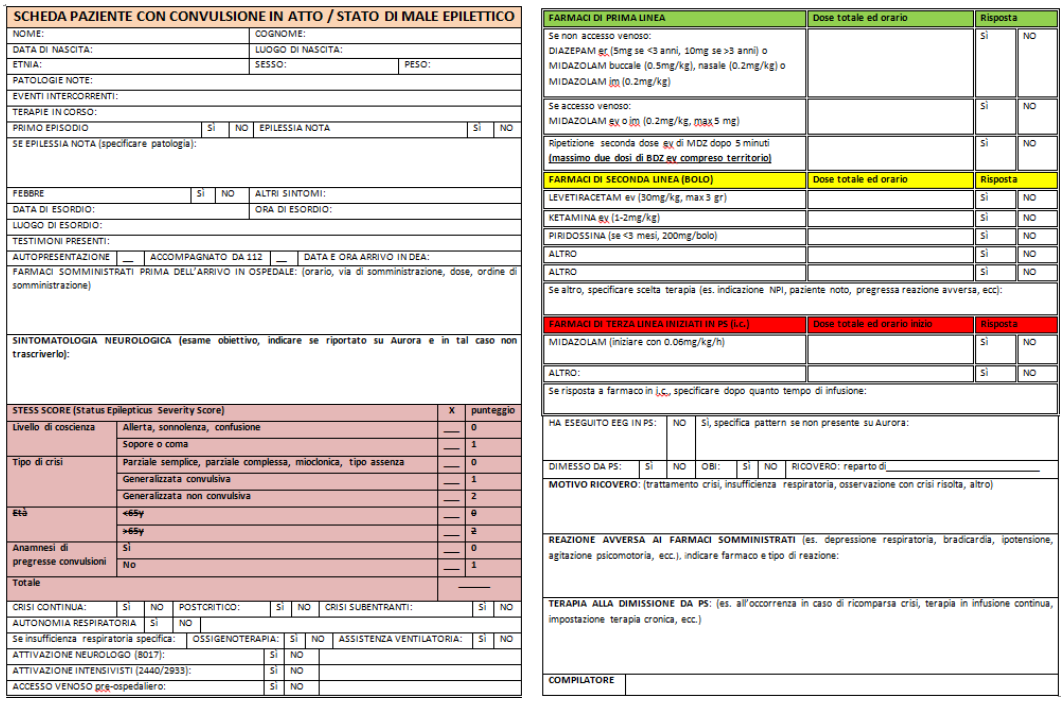
Study design

We conducted a prospective, single-center observational study at the Emergency Department of the Giannina Gaslini Institute (IGG) in Genoa. Patients were enrolled starting from 1 November 2022, when the new protocol regarding SE came into effect in the Emergency Department, with the main innovation being the introduction of ketamine as a second-line therapy. Enrollment ended on 30 September 2024.

Emergency Department physicians were asked to complete a paper Case Report Form (CRF) for each patient with SE, which includes the following data:

- Demographic and anthropometric data, including: sex, date of birth, age at the time of admission, ethnicity, and weight.

- Anamnestic data: any underlying conditions, ongoing events, home therapy, known epilepsy, previous convulsive episodes and/or SE.
- Pre-hospital data: clinical presentation, place of onset and witnesses of SE, mode of access to the ED, medications administered pre-hospital.
- Status Epilepticus Severity Score (STESS Score).
- Clinical data, including: type of seizure (continuous or evolving) or postictal state, respiratory autonomy or need for respiratory assistance, any evaluations performed (neurological and/or intensive care).
- Pharmacological therapy in the ED: method and timing of medication administration, response to therapy, and any adverse reactions.
- Discharge information: destination ward and therapy at discharge.



SCHEDA PAZIENTE CON CONVULSIONE IN ATTO / STATO DI MALE EPILETTICO

NOME:		COGNOME:	
DATA DI NASCITA:		LUOGO DI NASCITA:	
ETNIA:		SESSO:	PESO:
PATOLOGIE NOTE:			
EVENTI INTERCORRENTI:			
TERAPIE IN CORSO:			
PRIMO EPISODIO	SÌ / NO	EPILESSIA NOTA	SÌ / NO
SE EPILESSIA NOTA (specificare patologia):			
FEBBRE	SÌ / NO	ALTRI SINTOMI:	
DATA DI ESORDIO:		ORA DI ESORDIO:	
LUOGO DI ESORDIO:			
TESTIMONI PRESENTI:			
AUTOPRESENTAZIONE __	ACCOMPAGNATO DA 112 __	DATA E ORA ARRIVO IN DEA:	
FARMACI SOMMINISTRATI PRIMA DELL'ARRIVO IN OSPEDALE: (orario, via di somministrazione, dose, ordine di somministrazione)			
SINTOMATOLOGIA NEUROLOGICA (esame obiettivo, indicare se riportato su Aurora e in tal caso non trascriverlo):			

STESS SCORE (Status Epilepticus Severity Score)		X	punteggio
Livello di coscienza	Allerta, sonnolenza, confusione	__	0
	Sopore o coma	__	1
Tipo di crisi	Parziale semplice, parziale complessa, mioclonica, tipo assenza	__	0
	Generalizzata convulsiva	__	1
	Generalizzata non convulsiva	__	2
~~Età~~	~~<65y~~	__	~~0~~
	~~>65y~~	__	~~1~~
Anamnesi di pregresse convulsioni	Sì	__	0
	No	__	1
Totale			____

CRISI CONTINUA:	SÌ / NO	POSTCRITICO:	SÌ / NO	CRISI SUBENTRANTI:		SÌ	NO
AUTONOMIA RESPIRATORIA	SÌ / NO						
Se insufficienza respiratoria specifica:	OSSIGENOTERAPIA:	SÌ / NO	ASSISTENZA VENTILATORIA:			SÌ	NO
ATTIVAZIONE NEUROLOGO (8017):		SÌ / NO					
ATTIVAZIONE INTENSIVISTI (2440/2933):		SÌ / NO					
ACCESSO VENOSO pre-ospedaliero:		SÌ / NO					

FARMACI DI PRIMA LINEA	**Dose totale ed orario**	**Risposta**	
Se non accesso venoso: DIAZEPAM gr (5mg se <3 anni, 10mg se >3 anni) o MIDAZOLAM buccale (0.5mg/kg), nasale (0.2mg/kg) o MIDAZOLAM im (0.2mg/kg)		SÌ	NO
Se accesso venoso: MIDAZOLAM ev o im (0.2mg/kg, max 5 mg)		SÌ	NO
Ripetizione seconda dose ev di MDZ dopo 5 minuti **(massimo due dosi di BDZ ev compreso territorio)**		SÌ	NO
FARMACI DI SECONDA LINEA (BOLO)	**Dose totale ed orario**	**Risposta**	
LEVETIRACETAM ev (30mg/kg, max 3 gr)		SÌ	NO
KETAMINA ev (1-2mg/kg)		SÌ	NO
PIRIDOSSINA (se <3 mesi, 200mg/bolo)		SÌ	NO
ALTRO		SÌ	NO
ALTRO		SÌ	NO
Se altro, specificare scelta terapia (es. indicazione NPI, paziente noto, pregressa reazione avversa, ecc):			
FARMACI DI TERZA LINEA INIZIATI IN PS (i.c.)	**Dose totale ed orario inizio**	**Risposta**	
MIDAZOLAM (iniziare con 0.06mg/kg/h)		SÌ	NO
ALTRO:		SÌ	NO
Se risposta a farmaco in i.c., specificare dopo quanto tempo di infusione:			

HA ESEGUITO EEG IN PS:	NO	SÌ, specifica pattern se non presente su Aurora:					
DIMESSO DA PS:	SÌ / NO	OBI:	SÌ / NO	RICOVERO: reparto di_____			
MOTIVO RICOVERO: (trattamento crisi, insufficienza respiratoria, osservazione con crisi risolta, altro)							
REAZIONE AVVERSA AI FARMACI SOMMINISTRATI (es. depressione respiratoria, bradicardia, ipotensione, agitazione psicomotoria, ecc.), indicare farmaco e tipo di reazione:							
TERAPIA ALLA DIMISSIONE DA PS: (es. all'occorrenza in caso di ricomparsa crisi, terapia in infusione continua, impostazione terapia cronica, ecc.)							
COMPILATORE							

Figure 5. Case Report Form (CRF) for each patient with SE

A database was created using Microsoft Excel, followed by a descriptive and statistical analysis of the collected data. Appropriate statistical methodologies were applied to synthesize and interpret the information, highlighting the main characteristics of the data through measures of central tendency, dispersion, and frequency distributions.

Inclusion and exclusion criteria

Inclusion Criteria:

- Ongoing convulsive SE at the time of admission to the Emergency Department, defined according to the International League Against Epilepsy (ILAE) criteria as a seizure lasting ≥ 5 minutes, regardless of clinical history of epilepsy or previous episodes of status epilepticus.
- Age of patients greater than 3 months.
- Admission to the ED between 1 November 2022 and 30 September 2024.
- Patients not exposed to second-line therapies other than the IGG protocol (i.e., patients who have not received any hospital therapy or only benzodiazepines in the community from caregivers, the emergency service 118, or other hospitals).
- Adherence to the Gaslini Institute protocol for the treatment of SE, in terms of pharmacological sequence, timing of administration, and dosage.

Exclusion Criteria:

- SE resolved or postictal state upon arrival in the ED.
- Non-convulsive status epilepticus, diagnosed clinically or through EEG monitoring.
- Patients previously treated in pre-hospital settings or other hospitals with second-line therapies not compliant with the protocol.
- Non-adherence to the IGG protocol during treatment.

Results

In the study conducted on patients who accessed the ED between 1 November 2022 and 30 September 2024, and in accordance with the established inclusion criteria, a total of 16 patients were enrolled. Of these, 11 (69%) were male and 5 (31%) were female.

The demographic analysis of the enrolled population revealed a mean age of 74 months, with a median of 46 months. The standard deviation was high, at 70 months, while the interquartile range was 96 months. This wide variability is attributed to the extensive age range of participants, which spans from 3 months to 19 years and 1 month.

Regarding ethnicity, 13 patients (81%) were of Caucasian ethnicity, while 3 patients (19%) were of African ethnicity.

f

n. patients	**16**
Sex	Male 11/16 (69%)
Mean age (months)	74
Median age (months)	46
σ (months)	70
Q1 (months)	16
Q3 (months)	112
Interquartile range (months)	96
Ethnicity	Caucasian: 81% African: 19%

Table 2. Demographic analysis

Regarding the medical history of the enrolled patients, the distribution of conditions is as follows:

- 5 patients have a silent medical history;
- 1 patient has a history of febrile seizures;
- 2 patients have epilepsy (one in the diagnostic assessment phase, the other with epilepsy associated with Sturge-Weber syndrome);
- 3 patients have neurological conditions (one with White-Sutton syndrome and encephalopathy, one a former preterm infant with sequelae of intraventricular hemorrhage, and one with perinatal stroke);
- 4 patients have neurological conditions associated with epilepsy, all characterized by cerebral palsy;
- 1 patient has a cardiac condition.

Regarding pharmacological history, among the 6 patients with known epilepsy, 5 were receiving antiepileptic therapy. One patient was undergoing cardiological treatment, while another was following specific therapy for the underlying condition, which included adrenal insufficiency and spastic tetraparesis associated with White-Sutton syndrome.

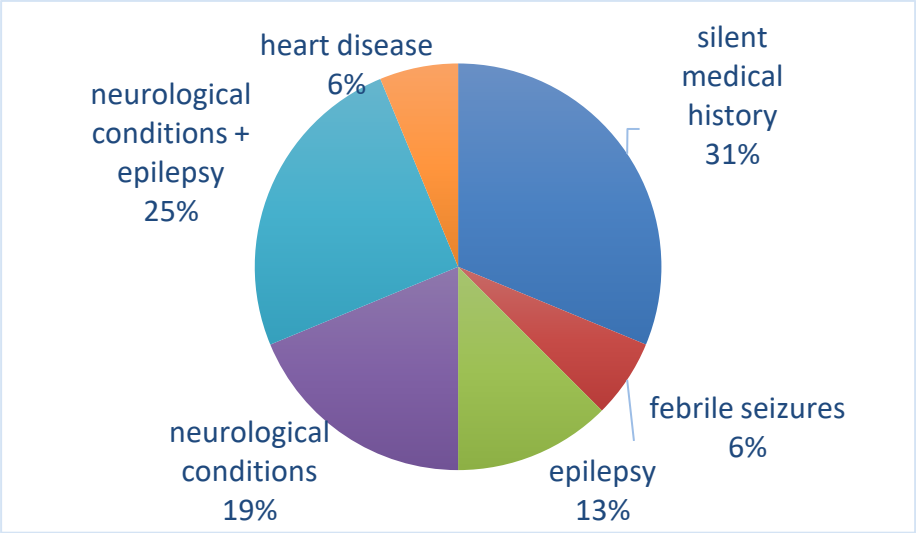


Figure 6. Medical history

In relation to the epileptological history, for 9 of the analyzed patients (56%), the episode in question represents the first convulsive episode. In contrast, 7 patients had previously experienced convulsive episodes, of which 1 was attributable to febrile seizures and 6 were related to pre-existing epilepsy. Additionally, for 14 patients (88%), the described episode was identified as the first episode of SE.

The analysis of pre-triage data revealed that 10 patients had a concomitant intercurrent event, with 9 associated with fever (56%). The mean age of the febrile patients was 56.1 months (with a median of 36 months), while the mean age of the non-febrile patients was higher, 93 months (with a median of 76.5 months).

One patient had a history of head trauma prior to the onset of SE.

Regarding the onset location, 13 patients were at home, as reported by their parents; 2 were at school, as confirmed by their teachers; and 1 patient was in the ED, as documented by the medical and nursing staff.

Concerning access to the ED, 11 patients were transported by the 118 ambulance service, while 4 presented independently.

The analysis of medications administered in the pre-hospital setting, both by caregivers and emergency service personnel (118), revealed that 50% of pediatric patients received at least one antiepileptic medication, particularly a benzodiazepine. In the examined sample, the data are as follows:

- Three patients received diazepam via rectal administration.
- Four patients received midazolam, of which three were administered nasally and one through a combined approach, initially via oromucosal and subsequently via nasal administration.
- One patient received diazepam rectally, followed by midazolam (first nasally and then intravenously).

Considering the number of benzodiazepines administered before hospital arrival, it was found that five patients received a single dose, one patient received two doses, and two patients received three doses

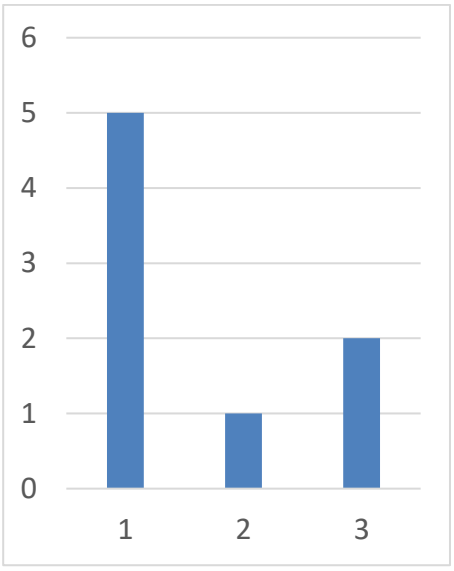


Figure 7. Number of benzodiazepines administered prior to arrival in the ED

For each patient, the Status Epilepticus Severity Score (STESS Score) was calculated, and the results are illustrated in the following figure. The total STESS Score indicated a value of 2 in 50% of the patients, while the remaining 50% scored 3.

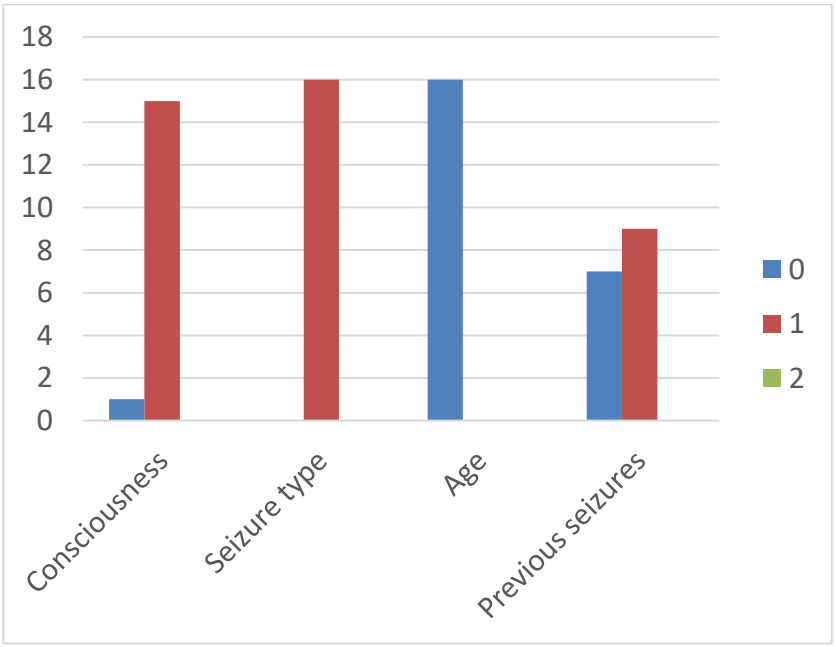


Figure 8. STESS score in our sample.

The analysis of the data collected during triage in our ED revealed the following distribution of color codes assigned: 13 patients were assigned a red code, 2 patients received an orange code (as they presented in a postictal state with subsequent resumption of seizures), and 1 patient was assigned a blue code (as the convulsive episode began while in the ED).

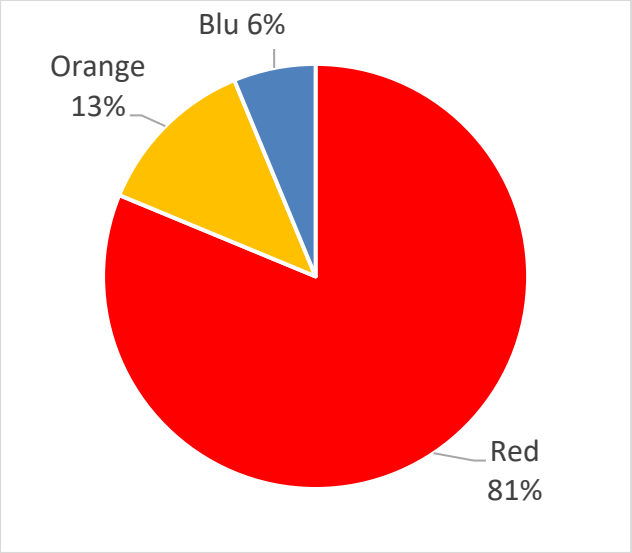


Figure 9. Color codes assigened at triage.

Regarding the type of epileptic seizure observed upon arrival in the ED, 9 patients presented with continuous seizures, while 7 patients exhibited evolving seizures, characterized by the absence of complete recovery of consciousness between episodes.

The body temperature, measured in 9 out of 16 patients, showed a mean of 38.0 °C (± 1.3 °C), with a median of 38.5 °C and an interquartile range of 2.45 °C.

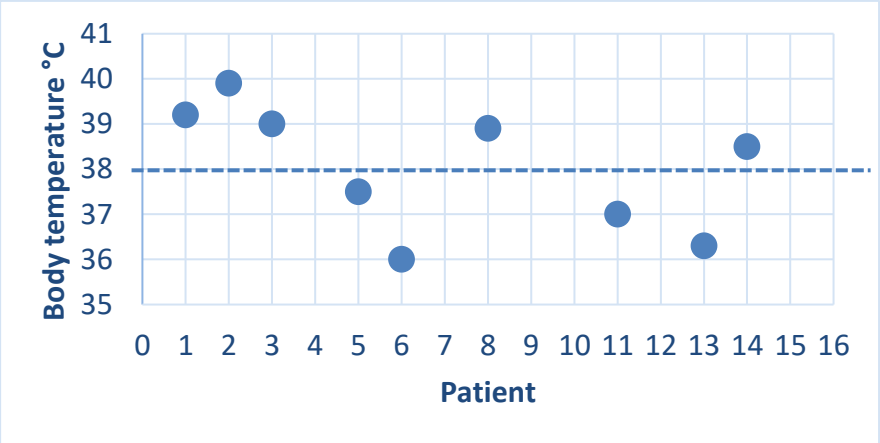


Figure 10. Body temperature in ED.

Only 6 patients were assigned a score on the Glasgow Coma Scale (GCS), which showed a mean value of 8 (± 2), a median of 9, and an interquartile range of 3.75.

Of the 16 patients enrolled in the study, 4 (25%) did not require respiratory support. For 6 patients (37.5%), low-flow oxygen therapy was administered due to episodes of desaturation, while 6 patients (37.5%) required respiratory assistance through mask ventilation; one of these patients was subsequently intubated for an MRI of the brain.

Additionally, during the observation period in the Emergency Department (ED), it was noted that:

- 2 patients already had a peripheral venous catheter inserted by the 118 medical staff;
- a consultation with a resuscitation colleague was requested for 11 patients;

- 4 patients received a neurological evaluation, of which 3 underwent an electroencephalogram (EEG) in the ED.

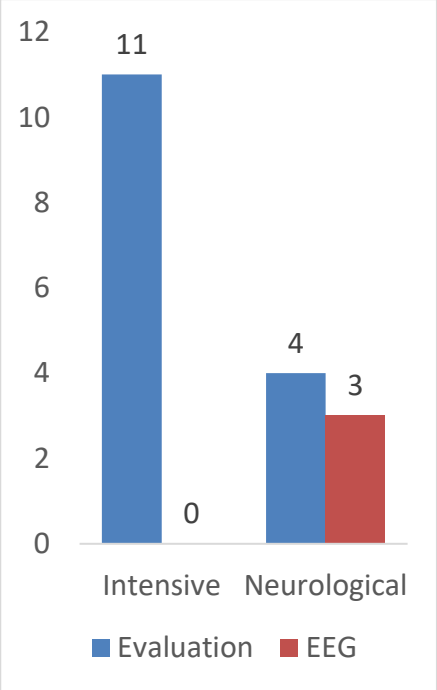


Figure 11. Evaluations in ED.

Regarding neuroimaging, one patient underwent a computed tomography (CT) scan of the brain, which yielded negative results, while three patients had an MRI of the brain: one with negative results, one with findings suggestive of posterior reversible encephalopathy syndrome (PRES), and another with a picture compatible with Menkes syndrome.

Analyzing the antiepileptic therapy administered in the ED, benzodiazepines were the first-line medication for 13 patients. The remaining 3 patients did not receive benzodiazepines for the following reasons: 2 patients had already received 2 or 3 doses of benzodiazepines in the pre-hospital setting, while 1

patient received propofol as the first medication for sedation to undergo a CT scan of the brain.

Among the 13 patients treated with benzodiazepines as first-line therapy, 6 received diazepam rectally, while 7 received midazolam intravenously. The average time from triage to the administration of the first benzodiazepine was 6.4 minutes (± 6, median 4).

The therapeutic response to the first dose of benzodiazepine in the ED was documented in 3 out of 13 patients. Of the 10 patients who were non-responsive, 6 continued with second-line treatment, while 4 received a second dose of benzodiazepines in the ED, specifically midazolam intravenously (mean dose of 0.29 mg/kg), administered on average 8.5 minutes after arrival in the ED (± 2.7, median 8.5). However, none of these 4 patients showed signs of response to the second dose of benzodiazepines.

Additionally, one patient received 3 doses of benzodiazepines in the ED, including diazepam rectally and two administrations of midazolam intravenously, without achieving any therapeutic benefit.

Twelve patients received second-line antiepileptic treatment with levetiracetam, three of whom had already received at least one dose of ketamine. The dosage of levetiracetam was 30 mg/kg for all patients, except for one who received a dose of 10 mg/kg. The therapeutic intervention occurred on average 28 minutes after triage (standard deviation ± 26, median 20 minutes).

Of these twelve patients, seven showed a positive response to levetiracetam, while the remaining five were subsequently treated with ketamine.

In total, nine patients received at least one dose of ketamine (five after receiving levetiracetam and three before, with one given immediately after the benzodiazepine dose) with a mean dose of 1.29 mg/kg, administered on average 35 minutes after arrival in the ED (standard deviation ± 34, median 22 minutes).

Six out of nine patients responded to ketamine treatment. The remaining three received a second dose of ketamine (mean dosage of 1.2 mg/kg), which was effective.

All patients terminated their seizures while in the ED.

In two cases, propofol was administered to induce sedation necessary for neuroimaging procedures (one CT scan and one MRI of the brain). No patients were discharged from the ED with third-line pharmacological therapy, i.e. with continuous infusion of antiepileptic treatment.

In our sample, three adverse drug events were recorded: one associated with the use of rectal diazepam, one with intravenous midazolam, and one with ketamine. All events were characterized by episodes of respiratory depression that required assisted ventilation via mask for a brief period. No further adverse events or cases of respiratory depression necessitating intubation were reported.

Regarding discharge procedures, all patients were admitted: 11 to the intermediate care unit (IMU) and 5 to pediatric intensive care unit(ICU).

Reasons for admission included diagnostic assessment for 3 patients and clinical observation for 13 patients, in whom the seizures had resolved.

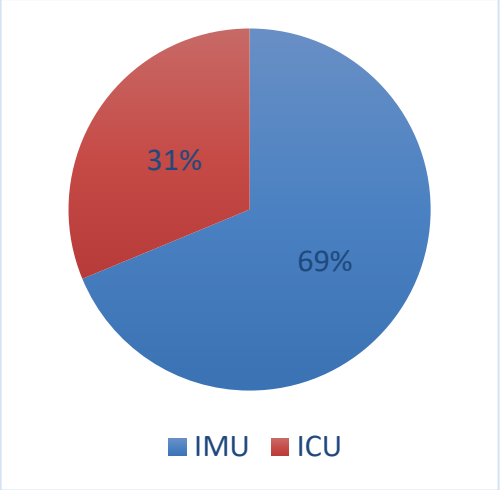


Figure 12. Admission from ER.

Therefore, the therapy prescribed at the time of discharge from the ED was "as needed" medication for 11 patients in case of seizure recurrence. For 4 patients, either the chronic therapy already in place was initiated or modified. Finally, one patient was discharged from the emergency department with a continuous infusion therapy (propofol and fentanyl) following sedation required for a brain MRI.

Discussion

It is now well-known that SE is a time-dependent condition, where the timeliness of administering appropriate medications is crucial to prevent long-term consequences, according to the principle of "time is brain." Early and aggressive treatment is key to preventing neuronal damage and the activation of receptor mechanisms that can lead to drug resistance. Based on these considerations, experts, scientific societies, and study groups have developed guidelines and step-by-step protocols, the main goal of which is to ensure a rapid intervention to interrupt critical epileptic activity as soon as possible.

Benzodiazepines are universally recognized as the first-line treatment for seizures in all protocols, with level A evidence and class I recommendation for their use in emergency, pre-hospital, and intra-hospital settings. In contrast, there are few clear indications to guide the treatment of benzodiazepine-refractory SE.

Numerous authors emphasize that, to address the rapid receptor changes characteristic of drug resistance, an immediate escalation from benzodiazepines to second-line medications is essential, as well as the early initiation of a targeted polytherapy aimed at both inhibitory GABA receptors and excitatory NMDA receptors. However, treatment protocols vary significantly among different centers. Phenytoin, valproate, and levetiracetam are often used interchangeably as second-line drugs, with similar efficacy rates (50-70%) and a relatively rare profile of serious adverse events.

Following the first London Meeting on Status Epilepticus, which recommended the adoption of written protocols for managing convulsive SE in all operational units, in collaboration with experts from other disciplines and potentially tailored to specific hospital realities, our Center also developed a management protocol for SE.

In light of the growing evidence of efficacy and safety, in 2019, ketamine was integrated into our treatment protocol as a second-line antiepileptic drug to be used after levetiracetam. This medication is applicable in the context of SE in all areas of the institute (emergency department, intensive care, semi-intensive care, and various wards).

This study examined the clinical and historical data, as well as the management of patients with SE in the Emergency Department of a Tertiary Care Center (IRCCS Istituto Gaslini in Genoa), involving a sample of 16 patients over a period of nearly two years (November 2022 - September 2024).

The age distribution in our sample was broad, ranging from 3 months to 19 years and 1 month. This highlights how SE can affect individuals of any age, associated with heterogeneous underlying etiologies.

In line with existing literature, pre-existing neurological conditions were found to be a significant risk factor for the development of SE, with 56% of patients presenting with pre-existing neurological abnormalities, while 31% were already receiving antiepileptic therapy at home. This demonstrates how often poor adherence to treatment, suboptimal therapy, the presence of

concomitant conditions (such as fever, stress, and other intercurrent events), and deterioration of the underlying neurological condition are factors that increase the risk of developing SE.

As is well known in the literature, febrile SE is the most common condition in pediatrics; indeed, in our study, fever was present in 56% of patients at the time of the episode, with a lower average age in febrile patients compared to those without fever (56 months vs. 93 months). These results are consistent with the evidence in the literature, indicating a stronger association between fever and SE in younger children, while in older age groups, SE is more commonly associated with pre-existing neurological conditions.

It is concerning to note that 19% of patients arrived at the Emergency Department on their own, accompanied by parents, without receiving any medical assistance; additionally, only 50% of all patients received antiepileptic therapy prior to admission to the Emergency Department.

Furthermore, considering the pre-hospital therapy administered, it is noteworthy that only one out of eight patients received two doses of benzodiazepines in accordance with the guidelines, while five patients received a single dose without showing any therapeutic benefit, and two patients received three doses, contrary to international recommendations.

It is therefore crucial to promote greater awareness among parents and ensure adequate therapeutic intervention by first responders through awareness campaigns aimed at parents, as well as providing continuous training and updates for community care providers.

In the Emergency Department, benzodiazepines were used as a first-line drug for 13 patients, with appropriate timing of administration. Two patients did not receive a dose of benzodiazepines as they had already been treated pre-hospitally, while another patient received propofol for sedation for neuroimaging.

Interestingly, only 23% of patients (3 out of 13) responded after the first dose of benzodiazepines administered in the Emergency Department. Additionally, among the 10 non-responsive patients, 4 received a second dose of benzodiazepines without any clinical benefit. One patient even received a third dose, which also had no positive effects.

These results further confirm that the efficacy of benzodiazepines is maximized when administered early, and that over time, due to the well-known receptor mechanisms described, there is a reduction in their effectiveness, necessitating a timely transition to second-line therapies according to a step-by-step approach.

Considering the time elapsed from the onset of the seizure (which occurred at home or at school) until arrival in the Emergency Department, it is likely that by the time of admission, patients were already in a state of refractoriness to benzodiazepines, which proved ineffective in 77% of the cases in which they were administered.

Regarding second-line therapy, among the 13 treated patients, 8 (62%) strictly followed our therapeutic algorithm, receiving ketamine after the failure of benzodiazepines and levetiracetam. All of these patients exhibited

complete resolution of seizures without side effects after one or two administrations of ketamine, confirming the efficacy and safety of this compound.

For the remaining 38% of patients, the algorithm was not strictly adhered to: specifically, 4 patients, due to their poor clinical conditions, received ketamine as the first second-line drug in agreement with the anesthesiologist, three of whom then received levetiracetam. An additional patient received propofol to allow for neuroimaging before being given levetiracetam and subsequently ketamine.

These five cases cannot be significantly evaluated as the correct sequence of therapies was not followed, making it difficult to attribute the clinical response to a single drug. However, patients who received ketamine in the early stages of SE and/or in combination with other medications (e.g., propofol) showed resolution of the episode, without recurrence of critical activity in the following hours. This suggests that, despite evaluation limitations, ketamine may play a positive role in managing SE in complex contexts.

These data also highlight how, in emergency settings, adherence to therapeutic protocols tends to diminish. We are implementing strategies to improve compliance with the treatment protocol both in the hospital and in community settings, but our preliminary experience suggests that applying a strict protocol across often very heterogeneous clinical scenarios, especially in an emergency setting, represents a significant challenge.

The analysis of the individual drugs administered reveals that levetiracetam was appropriately given in terms of dosage and timing, with the exception of a single case in which the drug was underdosed. This observation is particularly relevant in light of new recommendations suggesting an increase in the dosage of levetiracetam up to 60 mg/kg, considering its high safety and tolerability profile.(39)

Regarding ketamine, 56% of patients received this medication, with 5 patients treated after levetiracetam as per protocol and 4 patients immediately after benzodiazepines. All patients treated with ketamine experienced resolution of seizures (66% responding to the first dose, while the remainder responded to a second bolus), despite receiving an average dosage lower than the recommended amount (1.2 mg/kg).

In our sample, ketamine thus demonstrated an overall efficacy rate greater than those reported in the literature (60-70%). One might also wonder whether a second dose would have been necessary if the first had been administered at the full dose (i.e., 2 mg/kg).

In our sample, adverse events occurred in 19% of patients, corresponding to 3 cases.

Specifically, two patients exhibited signs of respiratory depression following the administration of benzodiazepines, both after a single dose given in the Emergency Department: the first patient received diazepam rectally, while the second received midazolam intravenously. Both patients required respiratory support with mask ventilation for a few minutes.

The third adverse event was documented after the administration of ketamine; in this case as well, mask ventilation was necessary for a few minutes, followed by the restoration of adequate oxygen saturation in the absence of respiratory support.

It is important to note that no adverse events were reported after the administration of levetiracetam, thereby confirming the safety profile of this drug in our sample as well.

These results highlight a good safety profile for the medications administered, with manageable adverse events, including for ketamine.

Finally, in accordance with the literature, all patients were admitted to departments with a high level of care to ensure adequate monitoring in case of seizure recurrence, allowing for potential adjustments to the underlying therapy and completing diagnostic assessments if necessary.

Regarding the interdisciplinary management of patients, an intensive care evaluation was requested in 69% of cases, while only 25% underwent a neurological assessment; among these, only three out of four patients had an electroencephalogram (EEG) performed.

Finally, the analysis of the STESS Score revealed that 50% of patients had scores of 2 and the other 50% had scores of 3, indicating a medium risk class. However, since the score assigns two points (out of a total of six) for being over 65 years of age, this suggests that the pediatric population will systematically have lower scores compared to adults, making the model less applicable to our pediatric sample.

It would be useful and interesting to develop similar assessment tools for the pediatric population, aimed at measuring the severity and risk of adverse outcomes. Such scores would allow for the stratification of the risk associated with each episode, thereby facilitating the optimization of therapeutic decisions.

Our study has limitations similar to those highlighted in the literature: a small sample size, lack of comparative data, limited EEG recordings performed, and variability in dosages, timing, and medications administered both pre-hospitally and in the hospital. These factors, along with the heterogeneity of patients and clinical cases, can complicate data interpretation.

However, the complete adherence to the protocol in 50% of patients resistant to benzodiazepines and the use of ketamine in 56% of cases demonstrate that the incorporation of this standardized, time-dependent flow chart within the Institute's protocol has been effective and well followed, promoting the adoption of this therapeutic approach.

Conclusions and future developments

Convulsive SE is a critical condition that requires rapid and effective treatment to prevent irreversible neuronal damage and avoid the onset of drug resistance mechanisms.

An effective approach to SE treatment should include timely intervention, early sequential polytherapy to address the dynamic synaptic changes during SE (targeting both inhibitory GABA receptors and excitatory NMDA receptors), and the selection of drugs with neuroprotective properties and limited side effects.

Additionally, it is well documented that there is often a delay from the onset of SE to the administration of antiepileptic drugs, as well as in transitioning from one class of antiepileptic drugs to another, both in pre-hospital and hospital settings. The only level I evidence for treating SE is represented by the use of short-acting benzodiazepines to interrupt early convulsive activity, but they are not always effective.

To date, there is no definitive evidence to guide the treatment of benzodiazepine-refractory SE. In this regard, ketamine emerges as a valid and promising therapeutic option for treating benzodiazepine-refractory SE, both in terms of efficacy and safety, in both hospital and community settings.

The methodological limitations of available studies on ketamine reflect the general issues of clinical research in the treatment of SE: the retrospective nature of the data; small sample sizes; heterogeneity of etiologies, ages, and study sample sizes; and variability in dosages and medications used prior to

or in conjunction with the study drug, as well as the timing, dosing, and duration of each drug.

It is therefore necessary to conduct further studies (preferably multicentric to increase the sample size) to confirm the results regarding ketamine and to establish standardized treatment protocols, given the need for a timely and uniform approach in critical situations.

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