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Diagnostic and Therapeutic Approach in Pediatric Inflammatory Status Epilepticus: A Real-World Multicenter Experience

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SUMMARY

ABSTRACT

BACKGROUND: Inflammatory Status Epilepticus (ISE) is a neurological emergency, posing diagnostic and therapeutic challenges, particularly in the pediatric population. We aimed to analyze the clinical features and therapeutic approaches to pediatric ISE across multiple Italian centers. Moreover, we correlated these variables with the disease outcome in terms of SE duration and hospital Length of Stay (LOS).

METHODS: Children aged 1 month to 18 years old diagnosed with ISE were included. Data were retrospectively collected through a structured clinical sheet. Statistical analyses were conducted using either the unpaired Student's t-test for normally distributed data or the Mann-Whitney test for non-normally distributed data. Fisher's exact test was used for comparisons between categorical variables. Significance was set at p-value < 0.05.

RESULTS: 41 episodes of pediatric ISE were revised. The cohort included 30 patients (15 males) with a mean age of 8.12±3.97 years at ISE onset. ISE episodes lasting less than 30 minutes and more than 30 days accounted for 16.28% of the cases each. An average of 4.5 treatments per episode was reported, midazolam and diazepam being the most frequently used medications. Etiology-driven treatments (EDTs) accounted for 12.8% of all interventions. Patients receiving EDTs had significantly longer SE durations as compared to those conventionally treated (p<0.0001), though there was no significant difference in LOS. Patients with incomplete diagnostic workups had shorter LOS than those who underwent comprehensive evaluations (p = 0.022).

CONCLUSIONS: Our findings highlight the complexity of managing pediatric ISE. While EDTs show to be crucial in refractory cases, they are often delayed. Timely diagnostic and therapeutic approaches may reduce hospital stays without compromising care.

1. INTRODUCTION

1.1 Definition of Status Epilepticus

Status Epilepticus (SE) is one of the most common neurological emergencies in the pediatric population and can cause permanent neurological damage if not adequately addressed. Even when properly treated, survivors of SE often present with long-term sequelae, including cognitive and neurodevelopmental impairment, epilepsy, and recurrent SE. [1]

Over the years, the definition of SE has evolved significantly as the understanding of this condition improved; early definitions referred to SE as prolonged seizures but did not provide precise time references. [2] As the understanding of this condition grew over time, the duration of seizures became of pivotal importance in defining SE, although never reaching a universal consensus on the time frame in object, as this could space from 30 to 5 minutes. [3, 4]

In 2015 the Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have charged a Task Force to revise concepts, definition, and classification of SE. The proposed definition of SE states as follows: "*Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures."* [5] This definition is conceptual, encompassing two key operational aspects: the first is the duration of the seizure and the time point (t1) after which the seizure is considered "continuous seizure activity." The second time point (t2) marks the duration of the ongoing seizure, beyond which there is a risk of long-term effects. For convulsive (tonic-clonic) SE, both t1 (5 minutes) and t2 (30 minutes) are derived from animal studies and clinical research. While the evidence is incomplete and shows significant variability, these time points represent the best current estimates. Similar data for other forms of SE are not yet available, but as research progresses, time points for specific types of SE can be established based on

scientific evidence and integrated into the definition, while keeping the fundamental concepts intact. Figure 1 provides the two operational dimensions proposed by Trinka and al. for different types of SE. [5]

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.

Figure 1. *Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected [5]*

1.2 Epidemiology

Affecting approximately 17 to 23 per 100 000 children in the United States and Europe, SE constitutes one on the most frequent life-threatening emergencies. The short-term mortality ranges from 3% to 9%, and the long-term mortality rate is 7%. [1]

In earlier studies the overall mortality in children admitted to pediatric intensive care unit (PICU) was reported to be up to 17%, [6 - 8] although recent studies with prospective measurement in children estimate mortality at 3%. In fact, according to these studies, SE appears to be more common, have a different range of causes, and a lower risk of death in pediatric population compared to adults. [9]

Pediatric population exhibits distinct epidemiological features, including a relatively higher recurrence rate of SE, more frequent triggers like infections or remote symptomatic causes, and an increased likelihood of SE occurring in children without a previous epilepsy diagnosis. [10 -12]

The onset of epilepsy is described to be more common in the first 2 years of life rather than later in childhood. [13, 14]

In over 75% of cases, SE can represent the child's first seizure, [15] yet these children have only a 30% risk of later being diagnosed with epilepsy. [11]

To assess whether mortality and morbidity are directly related to SE or rather to the underlying cause of the seizures remains a challenging task. [16]

1.3 Classification

In 2015 Trinka and al. proposed a new diagnostic classification system for SE which relies

on 4 axes: 1) semiology, 2) etiology, 3) electroencephalography (EEG) correlates and 4) age. [5]

Axis 1 (semiology) refers to the clinical presentation of SE which can be categorized according to two main criteria: the presence or absence of prominent motor symptoms and the degree of impaired consciousness presented. The two main categories resulting from this partition are:

- *SE with prominent motor symptoms,* which encompasses Convulsive SE (CSE), Myoclonic SE, Focal motor SE, Tonic status and Hyperkinetic SE
- *SE without prominent motor symptoms, or Nonconvulsive SE (NCSE),* which includes NCSE with coma and NCSE without coma

Whereas the clinical manifestation of CSE appear overt, with the term *convulsive* designating *"episodes of excessive abnormal muscle contractions, usually bilateral, which may be sustained, or interrupted", [17]* defining NCSE can be more controversial.

The prevalent definition refers to NCSE as continuous EEG seizure activity for at least 30 minutes without visible convulsive movement. [18, 19] Whenever stupor or confusion is observed, if otherwise unexplained, a diagnosis of NCSE should be considered. [20]

Defining diagnostic criteria for NCSE can be controversial. [21, 22]

Since NCSE can be outlined as *"diminished level of consciousness or other neurologic deficit associated with epileptiform EEG of typical discrete seizures or continuous discharges" [20]* it is apparent that the use of EEG is of paramount importance in the diagnosis. The response to antiepileptic drugs (AEDs) can also be included in the diagnostic criteria, though always keeping in mind that many NCSEs show to be refractory to AEDs both on EEG and on clinical presentation. [20]

Axis 2 (etiology) divides the causes of SE into two different categories:

- *known* or *symptomatic*: SE caused by a known disorder, which can be structural, metabolic, inflammatory, infectious, toxic, or genetic. According

to its timing of onset, the subdivisions acute, remote, and progressive can be applied.

- *Unknown* or *cryptogenic*: SE of unknown cause, to assume that it is "presumably" symptomatic or genetic would be inappropriate. [5]

Axis 3 (EEG correlates) assigns the following terminology to EEG patterns in SE:

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

This review of terminology was proposed according to large descriptive series and consensus panels, [23 – 27] considered that none of the ictal EEG patterns of any type of SE is specific.

Axis 4 (age) provides five different age groups for SE stratification:

- *Neonatal* (0 to 30 days)
- *Infancy* (1 month to 2 years)
- *Childhood* (>2 to12 years)
- *Adolescence and adulthood* (> 12 to 59 years)
- *Elderly* (≥ 60 years)

Ideally, in this proposed classification, each patient should be categorized according to every axis, however it is acknowledged that this may not always be feasible; although the approximate age of the patient and the semiology may be immediately assessable at initial presentation, the etiology could be less apparent in early work-up and EEG recordings will not always be available. [5]

Based on its response to treatment, or rather on the lack thereof, SE can be further classified in Refractory SE (RSE) and Super Refractory SE (SRSE), where the former refers to a seizure activity that persists after administration of a first-line benzodiazepine (BZD) and a second line antiseizure medication (ASM), [28] and the latter occurs when continuous or intermittent seizures persist after at least 24 hours following the administration of general anesthesia or recur after its withdrawal. [29]

Both RSE and SRSE are neurological emergencies with limited treatment options. Encountered mainly in PICU settings, the causes for pediatric RSE and SRSE in literature vary, especially according to age groups and geographic location. In a study involving 151 refractory convulsive SE (RCSE) episodes, the most common etiology was acute symptomatic (28.5%) in neonates and infants; prolonged febrile convulsions (33.8%) in children 1–5 years; and remote symptomatic etiologies in 40% of patients between 5 and 10 years old, and in 36.8% patients between 10 and 16 years old. [30]

In RSE and particularly in SRSE, the mechanisms that typically halt seizures become ineffective, and additional pathophysiological processes arise, contributing to the persistence of SE. On a cellular level, SE enhances the internalization of synaptic γ-aminobutyric acid type A (GABA-A) receptors, while the function of extra-synaptic receptors remains intact. This synaptic "receptor trafficking" results in an overall decrease in the inhibitory effects of GABA, playing a significant role in the development of pharmacoresistance. [31] Furthermore, an increased presence of glutamatergic receptors on the neuronal surface may contribute to the continuation of seizures due to altered ion concentrations, such as chloride, within the cellular environment. The ongoing seizures and the development of SRSE might also be attributed to enhanced sensitivity to NMDA-mediated neuronal stimulation, [32] mitochondrial dysfunction, [33] blood-brain barrier disruption, and neuroinflammation (including pro-inflammatory cytokines and autoantibodies targeting neural components). [34] These factors collectively lead to excitotoxicity, [35] which directly causes neuronal injury, cell death, and ultimately poor clinical outcomes. Additionally, prior research underscores the importance of the time

between seizure onset and the initiation of treatment, [36, 37] with delayed or insufficient intervention leading to seizures becoming self-sustaining and resistant to the intrinsic mechanisms naturally involved in seizure termination. [38]

In recent years the definitions of New Onset RSE (NORSE) and Febrile Infection Related Epilepsy Syndrome (FIRES) have become increasingly noteworthy, particularly in the pediatric population.

NORSE is a clinical condition in which individuals without a history of epilepsy or any significant preexisting neurological disorder develop RSE with no apparent acute cause or active structural, toxic, or metabolic triggers. [39]

FIRES consists of a specific subcategory of NORSE that typically occurs in previously healthy, school-aged children. [40, 41] These cases are often preceded by a febrile illness, with fever appearing between two weeks and 24 hours before the onset of SE, at which the patient may or may not present with fever. [39]

Although NORSE and FIRES are relatively rare epilepsy syndromes in the general population, they are frequently observed in the SRSE population. Therefore, when the initial diagnostic evaluation yields negative results, these epilepsy syndromes should be included in the differential diagnosis. [29]

1.4 Management of SE

As it appears to be true for many critical conditions, it's well established that, in the management of SE, "time is brain". The temporal evolution of irreversible neuronal damage caused by epileptic seizures has been widely studied in animal models. As the duration of SE increases, it results in a progressively greater number of necrotic neurons and neuropil edema, along with an increasing number of brain regions with neuronal damage. [42]

It is now widely accepted that early recognition of SE and the prompt initiation of treatment significantly improve clinical outcomes. Therefore, it becomes crucial to note the start time of the seizure to accurately monitor its duration and the timing of medication administration. [43]

Effective treatment of SE is presently challenged by several factors, such as caregivers and pre-hospital healthcare providers administering insufficient doses of rescue medications, as well as the inadequate and poorly timed implementation of

established and shared treatment protocols once patients arrive at the emergency department. [44, 45]

One of the most recent studies proposes a treatment protocol for children presenting with prolonged convulsive seizures and SE divided into three phases. [46]

- PHASE I refers to stabilization and pre-hospital treatment, when general measures should be applied, such as: evaluating the level of consciousness, starting to measure the duration of the seizure episode, initiating pre-hospital treatment and calling emergency services, assessing and stabilizing vital functions following the ABC sequence of Basic Life Support (Airway, Breathing, Circulation).

  The ideal medication in this early phase should: 1) have a rapid and sustained action, 2) be easy to administer, 3) ensure an acceptable safety profile with limited adverse events 4) be socially acceptable, easy to store, transport, and use. In general, benzodiazepines are the preferred treatment at this stage [47] and they can be repeated a second time after about 5 minutes if the seizure persists. In the absence of intravenous access, buccal midazolam and rectal diazepam are the first-line treatments for prolonged seizures and convulsive SE during phase I. [48]
- PHASE II regards intra-hospital treatment at first and second level, that are summarized in the following stages, based on the main published algorithms for this condition: [48, 49]
  - STABILIZATION (0–5 minutes): Initial phase where general supportive measures are applied.
  - FIRST-LINE TREATMENT (5–20 minutes): Administration of benzodiazepines.
  - SECOND-LINE TREATMENT (20–40 minutes): Lack of response to benzodiazepines indicates the administration of ASMs belonging to different pharmacological classes.
  - THIRD-LINE TREATMENT (40–60 minutes): Refractoriness to at least two adequately dosed second-line ASMs leads to admission to the PICU for treatment with anesthetic drugs

In addition to their use in pre-hospital settings, benzodiazepines have also demonstrated efficacy in the Emergency Department in 40–80% of cases. [48] The intravenous route should be preferred if venous access is available. However, no more than two doses of intravenous benzodiazepines should be administered (including any pre-hospital dose), as the effectiveness of a third dose would be limited and would increase the risk of respiratory depression. If the seizure persists for more than 5 minutes after the last administration, the use of a second antiseizure medication (ASM) not belonging to the benzodiazepine class is indicated. Phenytoin and phenobarbital have specific indications and are included in most protocols. [48] However, in recent years, other drugs such as levetiracetam, valproic acid, lacosamide, and brivaracetam have become available, albeit off-label. [43]

If seizures persist 5 minutes after administration of the first second-line drug, a second-line drug with a different mechanism of action should be given, with attention to potential pharmacological interactions (e.g., phenytoin and valproic acid compete for the same protein binding sites). If seizures continue beyond this point, further treatments should be avoided as they are ineffective in over 85% of cases and may delay appropriate intensive care management.

- PHASE III involves intensive care management and third-level treatment**.** In this phase, continuous EEG monitoring is mandatory both for diagnostic purposes (identification of NCSE) and for treatment monitoring with continuous infusion of anesthetic medications. The medications most utilized for both children and adults at this stage are midazolam, thiopental, and ketamine. Propofol is not recommended for pediatric patients due to the risk of potentially fatal propofol infusion syndrome (characterized by rhabdomyolysis, acidosis, and cardiac arrhythmia). Additional pharmacological options include topiramate, isoflurane, lidocaine, valproic acid, high-dose phenobarbital, lacosamide, perampanel, zonisamide, and

brivaracetam. Adjunct therapies such as a ketogenic diet, hypothermia, and vagus nerve stimulation may also be considered. [46]

1.5 Neuroinflammation and SE

Recent studies have shown that neuroinflammation and status epilepticus are closely intertwined, with neuroinflammation both contributing to the onset and progression of SE and being a consequence of SE.

1.5.1 Neuroinflammatory mechanisms involved in SE

Two key factors should be considered when discussing the potential role of neuroimmunological mechanisms in SE: whether the epileptic activity itself triggers these mechanisms in the brain regions involved in the seizure network; and whether a pre-existing neuroimmunological condition contributes to the onset of SE and/or exacerbates its outcomes. [50]

This mutual relationship involves various molecular and cellular mechanisms that influence seizure activity and brain damage.

Several factors enhance the role of systemic and brain inflammation as a contributor to SE: firstly, the release of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, in the brain, which can lower the seizure threshold by altering neuronal excitability, making neurons more susceptible to hyperexcitability and seizures; secondly, microglial activation increases the release pro-inflammatory mediators and reactive oxygen species (ROS), which exacerbate neuronal hyperactivity and increase the likelihood of prolonged seizures, such as SE; lastly, astrocyte dysfunction may impair glutamate clearance, leading to excitotoxicity and promoting seizures.

On the other hand, evidence in both pre-clinical and clinical studies shows that SE can also act as a trigger of neuroinflammation: SE, in fact, induces significant neuronal injury, which releases molecules such as HMGB1 (High Mobility Group Box 1), which act as Damage-Associated Molecular Patterns DAMPs. These molecules activate immune receptors, like Toll-like receptors (TLRs), further promoting the neuroinflammatory response; other mechanisms involve disruption of the Blood-Brain Barrier (BBB) disruption caused by prolonged seizures,

allowing peripheral immune cells to infiltrate the brain, thus exacerbating neuroinflammation; ultimately, oxidative stress and excitotoxicity, induced by SE, lead to the activation of resident glial cells (microglia and astrocytes), which further release inflammatory cytokines, perpetuating the cycle of inflammation and neuronal damage.

The relationship between neuroinflammation and status epilepticus is cyclical and mutually reinforcing. Understanding this interplay is crucial for developing therapeutic strategies aimed at both controlling seizures and mitigating neuroinflammation to prevent long-term damage.

1.5.2 Current SE treatments and their effects on neuroinflammation

The American Epilepsy Society (AES) guidelines, published in 2016, recommend initiating the management of convulsive status epilepticus within the first 5 minutes with an early stabilization phase. [51] This phase includes basic seizure first aid using the "ABC" approach, followed by administering benzodiazepines. [52, 53]

- Benzodiazepines (BDZs) were shown to exert anti-inflammatory effects by binding to microglial cells in early studies, dating back to 1996.[54] Based on this, midazolam and diazepam may reduce the synthesis and release of proinflammatory and neurotoxic molecules produced by activated microglia and may inhibit microglial activation and proliferation. [55] Furthermore, diazepam appears to induce cellular inactivation, characterized by reduced transcription factor activity, lowered chemotactic potential, inhibition of Ca2+-mediated signaling, and decreased cytokine production. [56]

If seizures persist beyond 20 minutes, second-line therapy is recommended. With limited evidence to support any one approach, treatment choices are often influenced by local availability, cost, and patient-specific considerations. Options include intravenous (IV) phenytoin or fosphenytoin, valproic acid, or levetiracetam. [57] If these therapies are unavailable, IV phenobarbital may be considered. [58]

- Phenytoin has been shown to inhibit the mTOR pathway, decreasing levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. [59]

- Valproic acid (VPA) provides antioxidant benefits by reducing lipid peroxidation and oxidative DNA damage, as well as anti-inflammatory effects that lessen myeloperoxidase activity and microglial activation. Additionally, VPA reduces brain inflammation and degeneration through NF-κB pathway modulation and inhibits lipopolysaccharide-induced TNF-α and IL-6 production. [60-63]
- Recent findings suggest levetiracetam has neuroprotective properties through anti-inflammatory effects. It suppresses the expression of proinflammatory molecules like TNF-α, IL-6, and IL-1β and reduces mononuclear phagocyte-mediated phagocytosis. [64-66]

A third line of treatment should be considered when seizures persist for 40 minutes, as status epilepticus becomes refractory. Options include repeating second-line therapy or using an anesthetic agent. [67] Common anesthetics used in this context include midazolam, widely used due to its rapid onset and short duration of action, short-acting barbiturates (e.g., pentobarbital/thiopentone), and propofol.

- Recent studies suggest that midazolam may inhibit inflammation by regulating the RhoA/ROCK2 pathway, enhancing blood-brain barrier integrity against lipopolysaccharides (LPS). Additionally, midazolam may inhibit IL-1β-induced STAT3 phosphorylation and IL-6 release by reducing reactive oxygen species (ROS) production. [68-70]
- Preclinical research suggests that propofol may reduce the activation and secretion of proinflammatory cytokines. [71, 72] Lu and colleagues recently validated that propofol's benefits are mediated by the JAK1/STAT3 pathway, showing anti-neuroinflammatory effects through inhibition of proinflammatory mediators from microglial cells. [73]

As around one-third of patients continue seizing despite these treatment lines, leading to refractory status epilepticus and potentially super-refractory cases, further treatment options should be considered. [74]

- Ketamine has recently emerged as a promising alternative, offering favorable hemodynamic effects and a unique mechanism compared to conventional anesthetics. [29] Its high lipid solubility allows for rapid central

nervous system (CNS) uptake and onset of action. [75] Additionally, in the later stages of status epilepticus, the number of functional GABA-A receptors declines while NMDA receptor upregulation enhances ketamine's effectiveness. [76] Ketamine has also been shown to reduce neuroinflammation by decreasing microglia and active macrophages in the cerebral cortex and by lowering TNF-α production. [77, 78]

There's growing interest in the potential role of Ketamine in earlier lines of treatment for pediatric SE, due to its well-established safety profile in this population [111] and to the limited number of major drawbacks linked to its use in different emergency settings. [112-115]

In a recent review, Buratti and colleagues proposed ketamine as a valid option for advanced second-line treatment in SE. [116] In our experience at IRCCS G. Gaslini ketamine is already listed in the protocol for SE treatment as second-line ASM, after Levetiracetam, since 2019.

1.5.3 Etiology-driven treatments (EDTs)

When the autoimmune etiology of RSE or SRSE is confirmed or strongly suspected (based on clinical history and evolution, the presence of autoantibodies, oligoclonal bands in the cerebrospinal fluid, or typical MRI findings) coordinated care among specialists is of the essence to define further strategies, including the prompt initiation of immunomodulatory therapy. [79]

A range of immunomodulatory treatments, including corticosteroids, Intravenous immunoglobulin (IVIg), and plasmapheresis, have been proposed in recent years. Their use is supported by research on immunologic processes (antibodies against neural receptors like voltage-gated potassium channels and NMDA receptors) and inflammatory mechanisms (stimulation of pathways such as the interleukin-1 receptor/toll-like receptor pathway), which may play a role in the underlying pathophysiology. [80, 81]

Given its potential role in epilepsy pathophysiology, targeting the proconvulsant effect of inflammatory cytokines presents an innovative therapeutic option for drug-

resistant epilepsies, RSE and SRSE. This approach allows direct intervention on the disease mechanisms rather than just symptomatic relief. [82]

Various pharmacological studies on pathways involving IL-1β/IL-1R1, HMGB1/TLR4, COX-2/prostaglandins, and the complement system have shown how they contribute to the onset and recurrence of SE, making them viable targets for disease-modifying treatments. [83-87]

- IL-1β Blockade: the 2022 international guidelines for managing new-onset refractory status epilepticus endorse using the human recombinant IL-1 receptor antagonist *Anakinra* for refractory SE. [88] As aforementioned, IL-1β, released by glial cells, promotes neuroinflammation and increases neuronal excitability, contributing to seizure resistance. Recent studies suggest Anakinra's therapeutic potential in controlling seizure recurrence in inflammatory refractory epilepsy, positioning it as a suitable option for SE of unknown cause in its early stages. [89, 90]

  Additionally, inhibiting the IL-1β converting enzyme (ICE)/caspase-1, which blocks pro-IL-1β conversion to its proconvulsant form, is a promising strategy for drug-resistant epilepsies.[91] *Pralnacasan* and *Belnacasan*, inhibitors of ICE/caspase-1, are in phase III trials, with preliminary results showing significant seizure duration reduction in animal studies. [92, 93] Another trial with the selective ICE inhibitor VX765 showed promising response rates in seizure reduction. [94]
- HMGB1-TLR4 Axis: inhibiting the HMGB1 and TLR4 pathways represents another promising anticonvulsant strategy. [95, 96] *Resveratrol*, a natural phenol, has demonstrated anti-inflammatory and neuroprotective effects by suppressing TLR-induced NF-kB and INF-β expression. [97] It also reduces microglial activation and COX stimulation, both associated with epileptogenesis, and exerts antioxidant effects against seizure-induced oxidative stress. [98-100]
- ATP-P2X7R Signaling: The ATP-gated purinergic P2X7 receptor (P2X7R) on microglial cells is activated by ATP release during seizures, stimulating the NLRP3 inflammasome and leading to inflammatory molecule release. [101, 102] Decreased P2X7R expression in SE patients suggests that P2X7R

antagonists could aid in treating refractory SE. *Astaxanthin*, a carotenoid, has shown neuroprotective effects in SE by inhibiting P2X7R activation, lowering inflammatory cytokine gene expression, and providing antioxidant support. [103, 104]

- IL-6 Blockade: IL-6, an inflammatory cytokine critical in sustaining inflammation, is elevated in serum and cerebrospinal fluid (CSF) in patients with refractory epilepsy. [105, 106] *Tocilizumab*, an IL-6 receptor blocker, has shown efficacy in small studies for NORSE and FIRES. A 2018 study found that Tocilizumab resolved SE in six of seven patients after one or two doses without recurrence, with similar positive outcomes in pediatric cases. [107 – 109]

Further innovative treatments proposed in recent years include *Ketogenic Diet (KD)* and *Cannabidiol (CBD).* KD, characterized by low carbohydrate and high fat intake, sustains ketosis resembling a fasting metabolic state. While its anti-inflammatory properties are still under study, KD appears to impact neurotransmitter levels, increasing GABA activity and the epileptic threshold through multiple pathways. KD also promotes neuroprotective effects, reducing free radicals and altering gut microbiota diversity, potentially influencing seizure susceptibility. CBD has shown promise in reducing seizure frequency and duration, providing anti-inflammatory and neuroprotective effects. CBD is thought to work by downregulating ROS, TLR4-NFκB, and IFN-β-JAK-STAT pathways. Reports indicate CBD's efficacy in reducing seizures in FIRES and super-refractory SE, suggesting its potential role in SE treatment, although further studies are required to understand the exact mechanisms of action. [110]

1.5.4 Establishing inflammatory etiology of SE

There is currently no universally agreed-upon standard for diagnosing Inflammatory SE (ISE). The key features usually identified in ISE involve: prolonged seizure duration and treatment resistance to first and second-line AEDs, evidence of elevated inflammatory cytokines, chemokines, and other immune markers in serum and cerebrospinal fluid (CSF), a correlation to immune or infectious conditions or to systemic inflammatory responses, the causal role of

neuroinflammation in maintaining seizure activity and, lastly, the need for anti-inflammatory or immunomodulatory therapy.

ISE frequently presents as refractory SE, often unresponsive to standard AEDs, with elevated inflammatory markers in serum or CSF, suggesting a systemic or CNS inflammatory response and imaging findings on MRI that support the presence of inflammatory processes.

In a 2015 cohort study, Spatola et al. retrospectively analyzed 570 SE episodes occurring in 484 adult patients, of which 33 (6%) were attributable to an inflammatory etiology, furtherly divided into two subsets: infectious and autoimmune. This study outlined how patients with ISE appear to be younger compared to those with non-inflammatory SE, while also observing that ISE was significantly more refractory to initial antiepileptic treatment; additionally, functional prognosis was significantly different between autoimmune and infectious SE, the latter being more frequently associated with new handicap at discharge. [117]

Among the causes of ISE, acute encephalitis plays a significant role. It consists of a severe neurological condition characterized by rapidly progressing encephalopathy, typically developing in less than six weeks due to inflammation within the brain. [118] The estimated incidence of encephalitis in high-income countries is around 5–10 cases per 100,000 people annually, affecting individuals across all age groups and imposing a substantial impact on patients, families, and society. [119, 120]

Although encephalitis has traditionally been attributed to infectious causes, and diagnostic criteria have been established based on this assumption, [121-123] a growing number of non-infectious cases, primarily autoimmune in nature, have been recognized over the past decade.

A Position Paper published by Graus et al. in 2016 proposes the following diagnostic criteria for possible autoimmune encephalitis, according to which diagnosis can be made when all three of the following criteria have been met:

- Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
- At least one of the following:
  - New focal CNS findings
  - Seizures not explained by a previously known seizure disorder
  - CSF pleocytosis (WBC count of more than 5 cells per mm3)
  - MRI features suggestive of encephalitis
- Reasonable exclusion of alternative causes

These criteria intentionally do not rely on antibody testing and response to immunotherapy, as it appears difficult, if not unrealistic, for many centers to access antibody testing in the early diagnostic work-up and response to immunotherapy is not assessable at the time of symptom onset or early clinical evaluation. [124]

When available, specific autoantibody positivity can facilitate treatment strategy in an otherwise challenging clinical presentation.

The antigens most frequently targeted by autoantibodies and the typical age of presentation of the consistent forms of encephalitis are shown in **Table 1.** [125]

	Intracellular, onconeural antigen	**Intracellular, synaptic antigen**	**Cell surface or synaptic receptor**
Antigens	Hu, CRMP5, Ri, Yo, Ma2	GAD, amphiphysin	NMDAR, AMPAR, GABA(B)R, LGI1, Caspr2, GlyR
Age	Predominantly older individuals	Usually adults	All ages, some syndromes predominate in children

Table 1. *Intracellular and surface antigens commonly involved in autoimmune encephalitis*

In a recent study involving a 12-year single-center immunocompetent cohort of patients at IRCCS G. Gaslini, anti-NMDAR encephalitis was found to be the most frequent etiology for autoimmune encephalitis, reinforcing how a timely diagnostic classification in definite, probable, or possible autoimmune encephalitis can help the clinician in a successful therapeutic approach. [126]

2. AIMS OF THE STUDY

Despite increasing awareness in inflammation-related epilepsy, studies on ISE are still limited, especially in the pediatric population. As primary outcome we aimed to describe the clinical features and the diagnostic and therapeutic approach in pediatric patients presenting with ISE. Secondarily, we correlated the aforementioned variables with disease outcomes in terms of hospital Length of Stay (LOS) and ISE duration.

3. PATIENTS AND METHODS

3.1 Study design and population

This was a retrospective, observational, multicentric, cohort study. Children aged 1 month to 18 years old who experienced at least one SE of defined inflammatory etiology were included. Patients aged > 18 years old, and patients presenting with SE of other etiologies were excluded.

3.2 Data collection

The demographic, clinical, diagnostic and treatment data of each ISE episode occurred between October 2009 and July 2021 were retrospectively retrieved by the referring clinicians through a structured clinical sheet. Patients were recruited through a collaboration among Italian pediatric epilepsy centers as part of a multicenter study group known as the “IPSE Group” (Italian Pediatric Status Epilepticus Group), which includes specialists from various fields (Neurologists, Pediatric Neurologists, Child Neuropsychiatrists, Intensivists, and Pediatric Emergency Medicine Physicians). The group was formed in June 2022, building on a collaborative effort that began in 2014, with the development of a non-profit study on the treatment of SE in children. To date, this preliminary work has resulted in the collection of over a thousand SE events in pediatric patients, stored in a dedicated database.

The following variables were initially collected for each individual episode of ISE: the patient's gender and age at the time of the clinical condition under study, duration of SE, type of seizures, need for ICU admission, type of treatment, treatment efficacy, and outcome in terms of LOS and overall survival. Additional data on laboratory findings, neuroimaging results, treatment details, particularly regarding EDTs, were also retrieved through subsequent clinical case reviews.

Treatment efficacy was defined by EEG activity, namely: (1) the appearance of a burst-suppression pattern and/or (2) the appearance of diffuse β activity and/or (3) the appearance of slow activity without diffuse or lateralized, continuous or subcontinuous, and periodic epileptiform abnormalities.

Data were analyzed by calculating frequencies and percentages for categorical variables and using mean and standard deviation (SD) for normally distributed continuous variables or median for non-normally distributed variables. We provided a descriptive analysis of the demographic and clinical characteristics of the study subjects and the treatments administered.

For comparisons between groups, we used unpaired Student's t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Fisher's exact test was used for comparisons between categorical variables. Descriptive and statistical analysis were conducted using software GraphPad Prism 8.3.0 (San Diego, California, USA).

The threshold for statistical significance was set at 2-tailored p-value of < 0.05.

4. RESULTS

4.1 Demographic and clinical features of the cohort

A total of 41 ISE episodes were provided by 10 Italian centers: G. Salesi Pediatric Hospital in Ancona, S. Orsola-Malpighi University Hospital in Bologna, Anna Meyer University Hospital in Firenze, IRCCS Gaslini in Genova, Buzzi Hospital in Milano, Padova University Hospital, IRCCS Bambino Gesù Pediatric Hospital in Rome (OPBG), Agostino Gemelli University Hospital Foundation in Roma, Regina Margherita Children's Hospital in Torino, and the Integrated University Hospital of Verona.

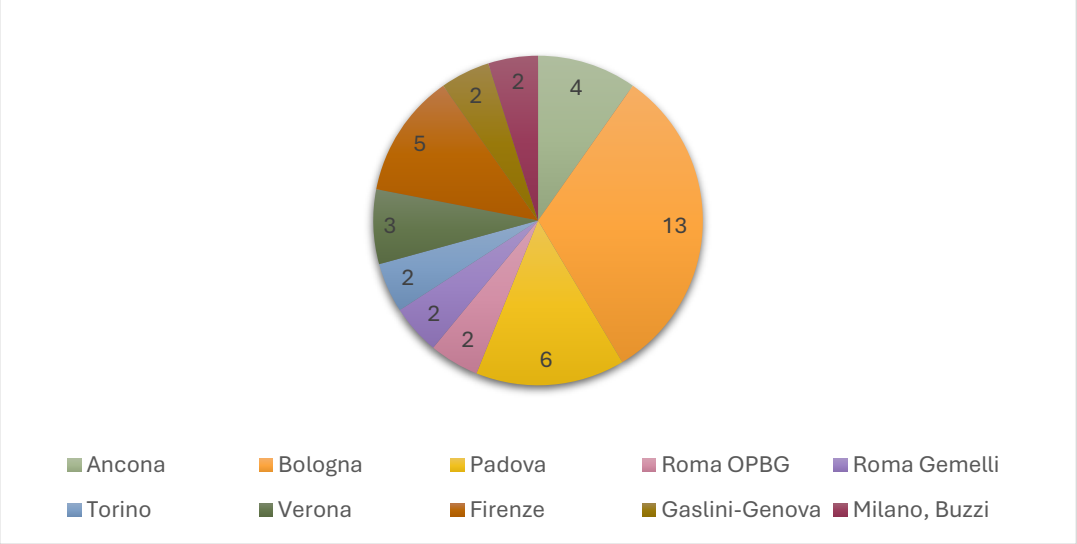

Figure 2. *Number of ISE provided by each center (41 total)*

Analysis of the geographical distribution of the population showed that 47% of the episodes were recruited in North-East Italy, 36% in Central Italy, and 17% in North-West Italy, lacking representation of data from Southern and Insular Italy. ***[Figure 3]***

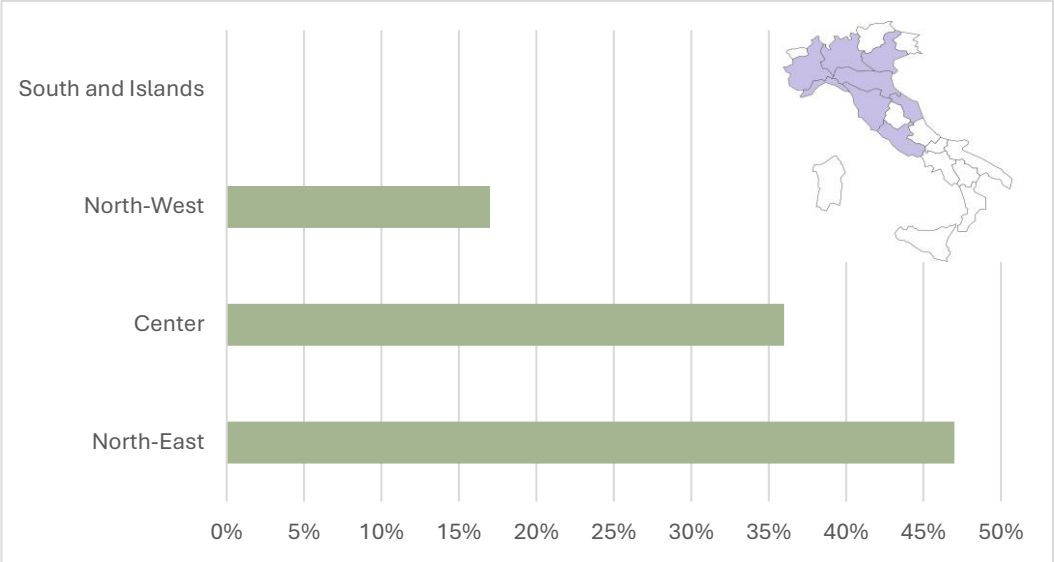

***Figure 3**. Geographical distribution of ISE provided*

The total number of patients was 30, with balanced gender ratio (15 males and 15 females). The mean ± SD age of patients at the onset of SE was 8.12 years ± 3.97, with a minimum age of 1.25 years and a maximum age of 16.71 years, with slightly older mean age at onset for the female subgroup (9.18 years) as compared to the male population (7.06 years).

	Mean age at SE onset (years)
FEMALE	9.18
MALE	7.06
TOTAL	8.12

***Table 2.** Mean age for each sex group and total population*

4.2 ISE characterization

The durations of the episodes were categorized into 10 specific time intervals. The most common duration was represented by less than 30 minutes and more than 30 days, each accounting for 16.28% of the cases. Other notable durations included 60-90 minutes and 120 minutes to 24 hours, comprising 11.63% and 13.95% of the cases. Durations between 30-60 minutes and 90-120 minutes represented about 6.98% of the total cases. Interestingly, there were no cases lasting between 24 to 48 hours. Durations of 2-7 days, 8-14 days, and 15-30 days accounted for 9.30% of the

total cases. This distribution indicates a significant variation in ISE duration, with notable peaks at both the shortest and longest ends of the spectrum.

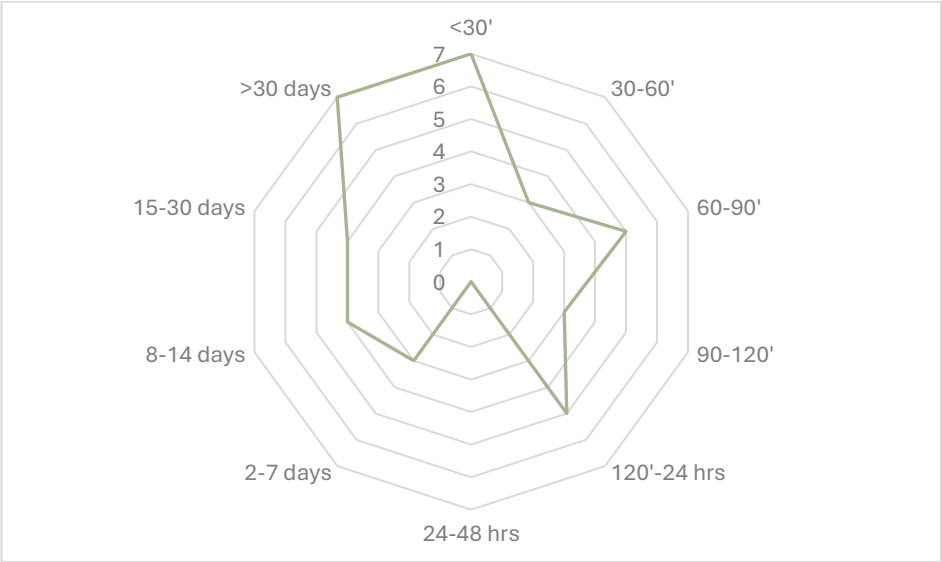

Figure 4. *Distribution of ISE duration*

Seizures semeiology varied among the group, with 27% (11/41) of the population presenting with focal-onset motor seizures, while 44% (18/41) showed focal to bilateral tonic-clonic SE. Twenty-four percent (10/41) patients had primarily generalized tonic-clonic SE, and 5% (2/41) had myoclonic SE.

TOTAL	**41**
Focal-onset motor seizures	11
Focal to bilateral tonic-clonic SE	18
Primarily generalized tonic-clonic SE	10
Myoclonic SE	2

Table 3. *Seizure types*

Non-Refractory SE and Refractory SE showed to be the most frequent, each accounting for 39% (16/41) of the total SE episodes; Super Refractory SE accounted for 22% (9/41) of the SE episodes.

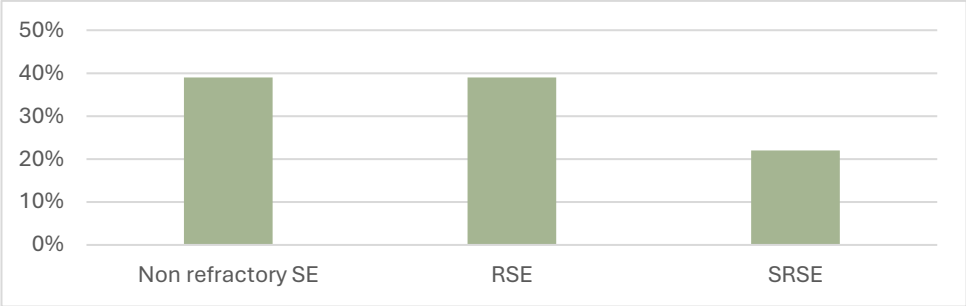

Figure 5. *SE stratification based on treatment response*

4.3 Diagnostic approach

Lumbar puncture was performed in 23/41 (56%) of SE episodes.

Brain MRI was performed in 27/41(66%) cases, showing pathological findings in 15 out of 27(55%) episodes.

CSF and/or serum antibodies were tested in 18/41 (44%) episodes, resulting in antibody positivity in 17% (3/18) cases. Specifically, anti-NMDAR antibodies were found in 2 cases and anti-GluR3 antibodies were found in 1 case.

Serum and/or CSF biomarkers profile was investigated in 6/41(15%) cases mostly in 3 centers (Padova, Bologna and Roma Gemelli), showing suggestive findings each time. ***[Table 4]***

CSF	SERUM
↑ IL-6, IL-8	↑ IL-8
↑ IL-8, Neopterin	n/a
↑ Neopterin, Biopterin	n/a
↑ Neopterin, Biopterin	n/a
↑ IL-6	↑ IL1a, IL1b
↑ IL-1a, IL-1b	n/a

Table 4. *inflammatory biomarkers profile results in CSF and serum*

4.4 Therapeutic approach

4.4.1 Treatment analysis

A total of 26 different medications were administered in various combinations and orders, with a total of 226 administrations. Treatment strategies were divided in first, second and third line, in accordance to evidence-based guidelines proposed by Glauser et al. [48] EDTs were considered as a separate line of treatment. ***[Table 5]***

On average, 4.5 orders of treatment were used per episode, with a minimum of 1 and a maximum of 20.

In the first line approach, midazolam (bolus) represented the most used treatment, with a total of 29 administrations, all within the first three orders of treatment. The second most used first line medication was diazepam (20 times) always within the fourth choice. Less commonly used BDZs were lorazepam and clobazam, used 2 times and 1 time, within the 8th choice.

Second line approach was mainly represented by phenytoin, used 21 times, followed by phenobarbital, levetiracetam and, less frequently, lacosamide, valproic acid, and carbamazepine.

The four most used medications in third line approach were midazolam continuous infusion (c.i.), thiopental, propofol and ketamine; less frequent treatments consisted in sevoflurane, lidocaine, vagus nerve stimulation, topiramate, cannabidiol, ketogenic diet and perampanel.

		ORDER OF TREATMENT																				
		1º	2º	3º	4º	5º	6º	7º	8º	9º	10º	11º	12º	13º	14º	15º	16º	17º	18º	19º	20º	TOTAL
1st line	Midazolam (bolus)	17	10	2																		29
	Diazepam	17	2		1																	20
	Lorazepam	2																				2
	Clobazam								1													1
2nd line	Phenytoin	1	5	4	8	1			1				1									21
	Phenobarbital		5	3		1	2	1	1										1			14
	Levetiracetam	1	3	5	3	2	1	1														16
	Lacosamide			1			1	2	1					1								6
	Valproic Acid	1		1	1	2	3	1														9
	Carbamazepine			1		1																2
EDT	IVIg			1		1	1		1	3	2	1	1									11
	IV Steroids			1		2		1	2		2	1	1									10
	Anakinra				1						1	1	1									4
	Plasmapheresis									2					1							3
	IVIg+MetilPDN+Bortezomib+Rituximab									1												1
3rd line	Midazolam (c.i.)	2	6	6	5	3	2		1													25
	Thiopental			2	1	3	2	2	2	1		1										14
	Propofol		2	2	1	3	2	1	1	1	1						1					15
	Ketamine				3		3	2		1	1											10
	Sevoflurane										1											1
	Lidocaine						1															1
	Vagus Nerve Stimulation																			1		1
	Topiramate							1		1								1				3
	Cannabidiol														1						1	2
	Ketogenic Diet							1		1				1		1						4
	Perampamel																1					1
TOTAL		41	33	29	24	19	18	13	11	11	8	4	4	2	2	1	2	1	1	1	1	226

Table 5. *Number of times each treatment was used in order of administration*

In total EDTs were administered 29 times out of 226 (12.8%). They were more frequently used from the third intervention onwards, on average as ninth choice. Specifically, intravenous immunoglobulin (IVIg) was used 11/226 (4.8%), intravenous (IV) steroids 10/226 (4.4%), anakinra 4/226 (1.7%), plasmapheresis 3/226 (1.3%). In only one case, at IRCCS G. Gaslini, a combined immunomodulatory treatment was administered, consisting of IVIg, MethylPDN, bortezomib and rituximab.

Single-center analysis of specific EDTs administered is provided in **Figure 6.**

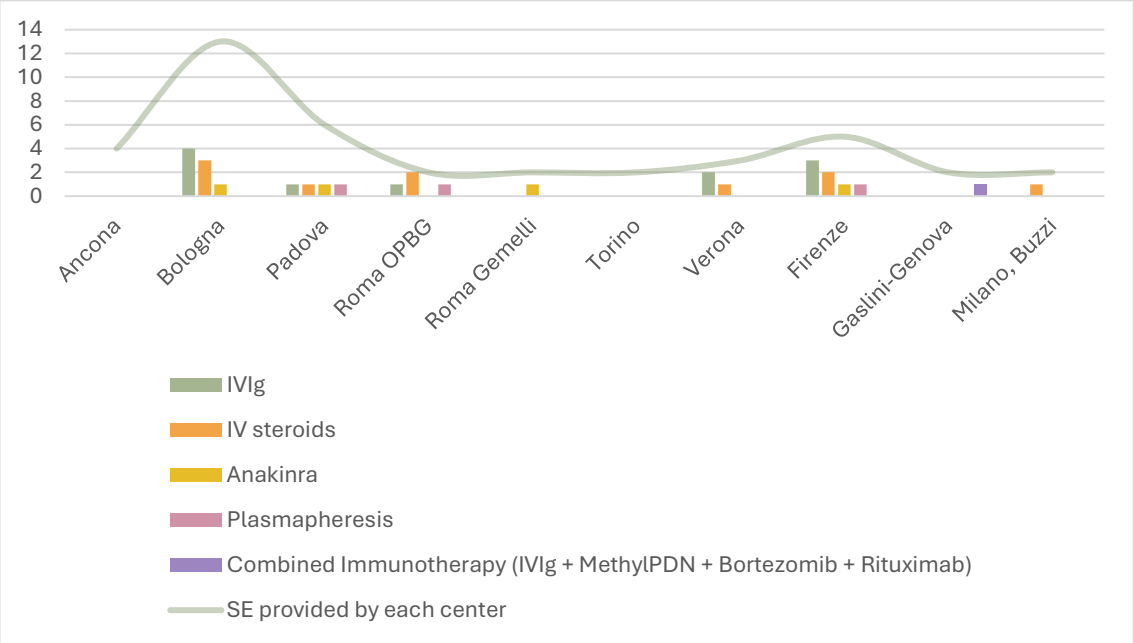

Figure 6. *EDT administered related to the number of SE provided by each center*

EDTs were used more frequently in absolute terms at S. Orsola-Malpighi University Hospital in Bologna (8 times), although, when compared to the number of SE episodes provided by each center, OPBG in Rome, Anna Meyer University Hospital in Firenze and Integrated University Hospital of Verona were the centers who most administered EDTs **[Figure 7]**. The earliest etiological interventions were recorded in Bologna and Verona. Specifically, in these hospitals, IV steroids and IVIG respectively, were used as the third-choice medication.

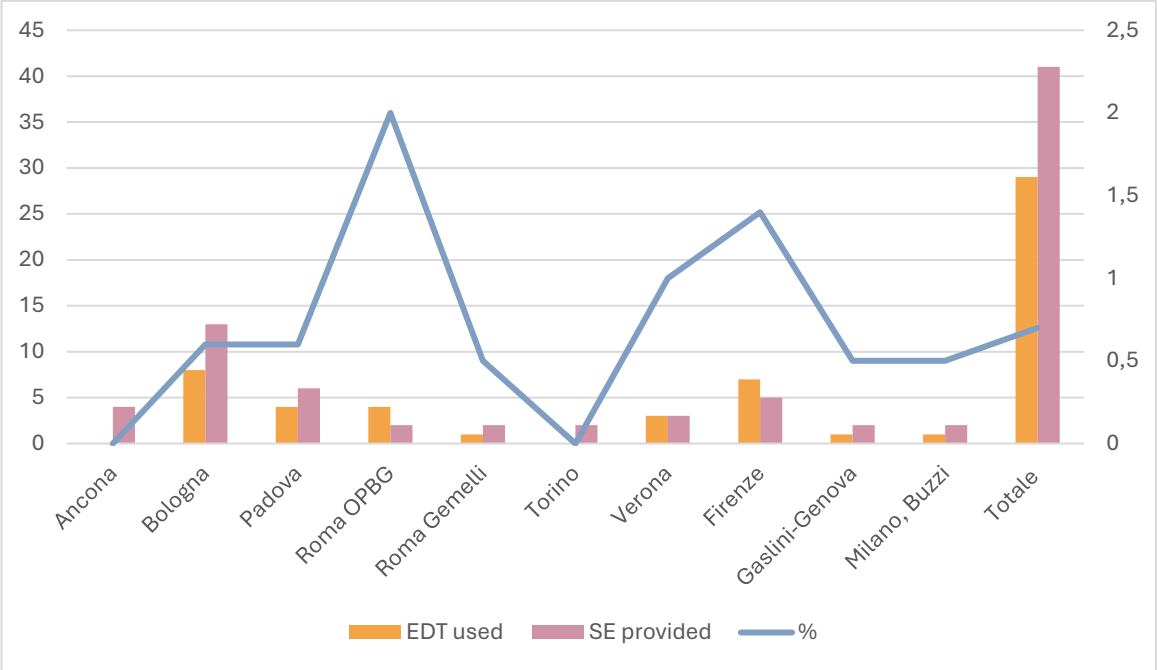

Figure 7. *Percentage of times each center used EDT compared to the number of SE provided*

4.4.2 Efficacy analysis

In terms of efficacy, midazolam (bolus) and diazepam were the most successful medications, being effective 6 and 5 times out of 41 (14.6% and 12.2%). The maximum number of drugs used per episode was 20. About 95% of the episodes were resolved within the 10th medication, only 2 cases required more than 10 treatments.

		ORDER OF ADMINISTRATION																			
	EFFECTIVE TREATMENT	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	Total
1st line	Midazolam (bolus)	2	4																			6
	Diazepam	4	1																			5
	Lorazepam	1																				1
	Clobazam								1													1
2nd line	Phenytoin		1		2																	3
	Phenobarbital		1					1														2
	Levetiracetam				2																	2
EDT	IVIg			1						1												2
	IV steroids										1											1
	IVIg + MetilPDN + Bortezomib + Rituximab									1												1
	Anakinra and ketogenic diet				1																	1
	Plasmapheresis									1												1
3rd line	Midazolam c.i.			1	1																	2
	Thiopental				1	1	1	1														4
	Propofol		1		1																	2
	Ketamine				1		1			1												3
	Sevoflurane										1											1
	Cannabidiol														1							1
	Lidocaine						1															1
	Vagus Nerve Stimulation+Cannabidiol+Phenobarbital																				1	1
	Total	7	8	2	9	1	3	2	1	4	2				1						1	41

Table 6. *Effective treatment and order of administration*

Although midazolam (bolus) and diazepam showed as the most effective treatments in absolute terms, when comparing with their frequency of use, the relative efficacy lowered to 20% and 25%, respectively.

Less frequent treatments, namely clobazam, sevoflurane, lidocaine, vagus nerve stimulation and combined immunotherapy (IVIg + MethylPDN + Bortezomib + Rituximab) were effective every time they were chosen.

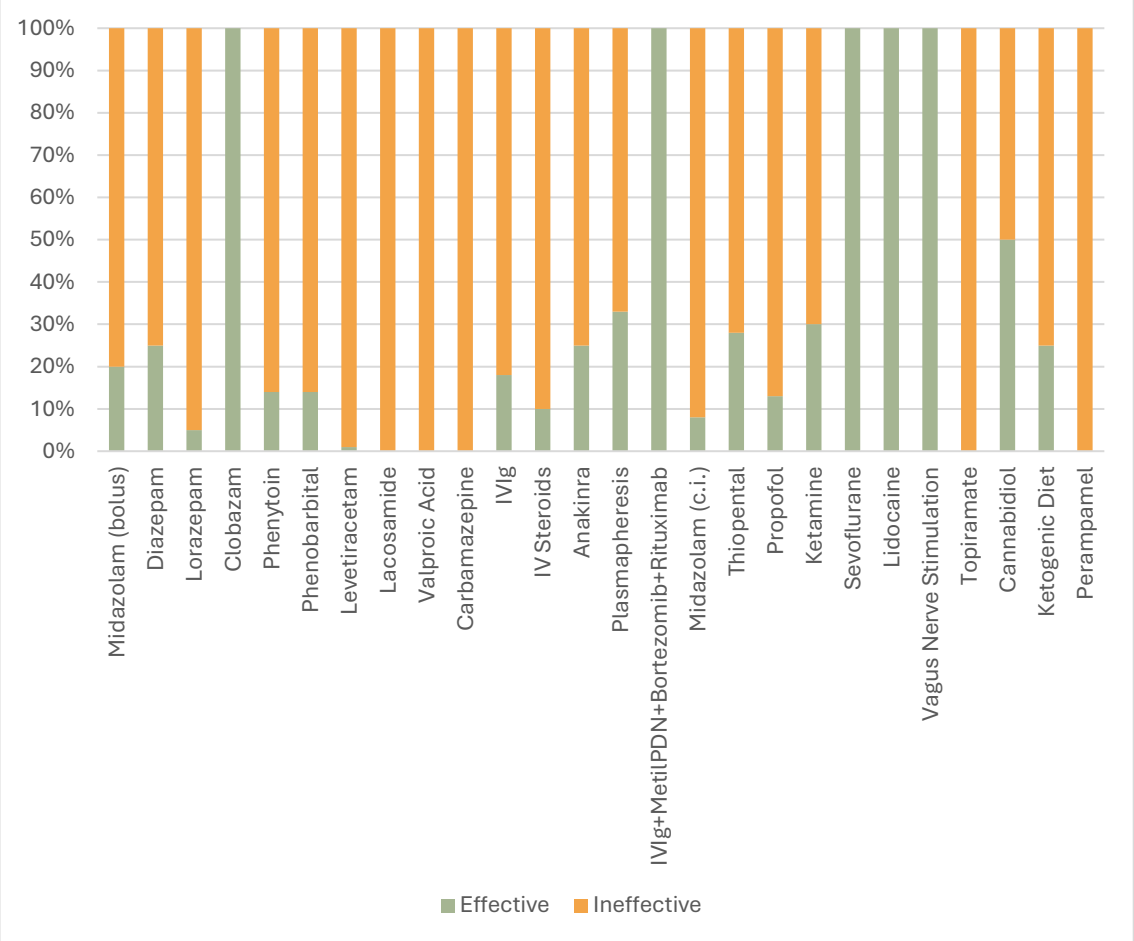

Figure 8. *Efficacy/Inefficacy ratio for each treatment*

As for EDTs, effective in 6 cases out of the 29 times they were used (20.7%). Particularly:

- IVIg 2/11 (18%)
- IV steroids 1/10 (10%)
- Anakinra 1/4 (25%)
- Plasmapheresis 1/3 (33%)

• Combined immunotherapy (IVIg + MethylPDN + Bortezomib + Rituximab) 1/1 (100%)

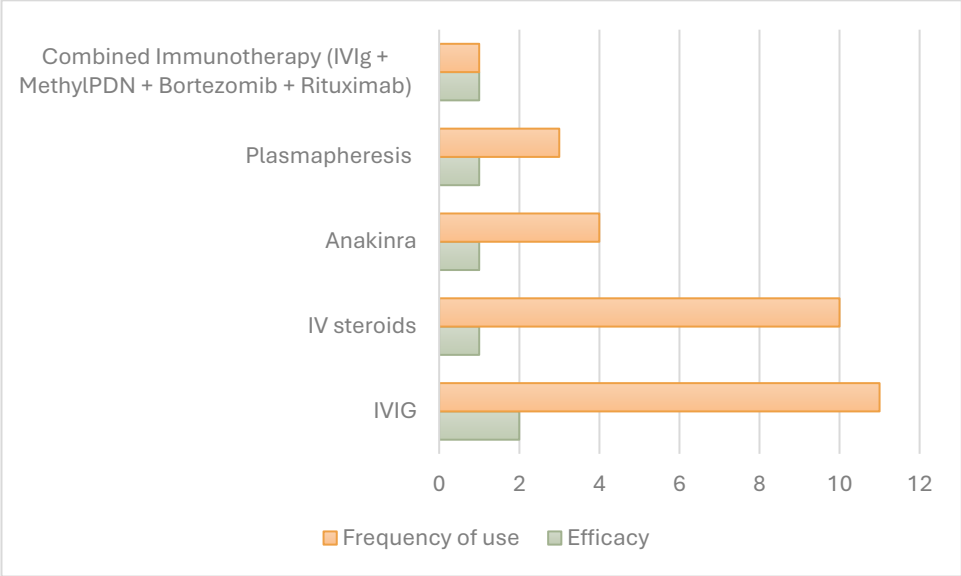

Figure 9. *Relative effectiveness of specific EDTs*

4.5 Final Diagnosis and outcome

Final diagnosis provided by each center was mostly represented by FIRES (46.3%), followed by Probable Seronegative Autoimmune Encephalitis (21.9%), Seronegative Limbic Encephalitis (17.1%), Autoimmune Encephalitis Anti-NMDAR+ (4.9%), Autoimmune Encephalitis Anti-GluR3+ and Acute Progressive Encephalitis of likely infectious-inflammatory origin accounting for 2.4% cases each. In 4.9% of the cases final diagnosis was not reached.

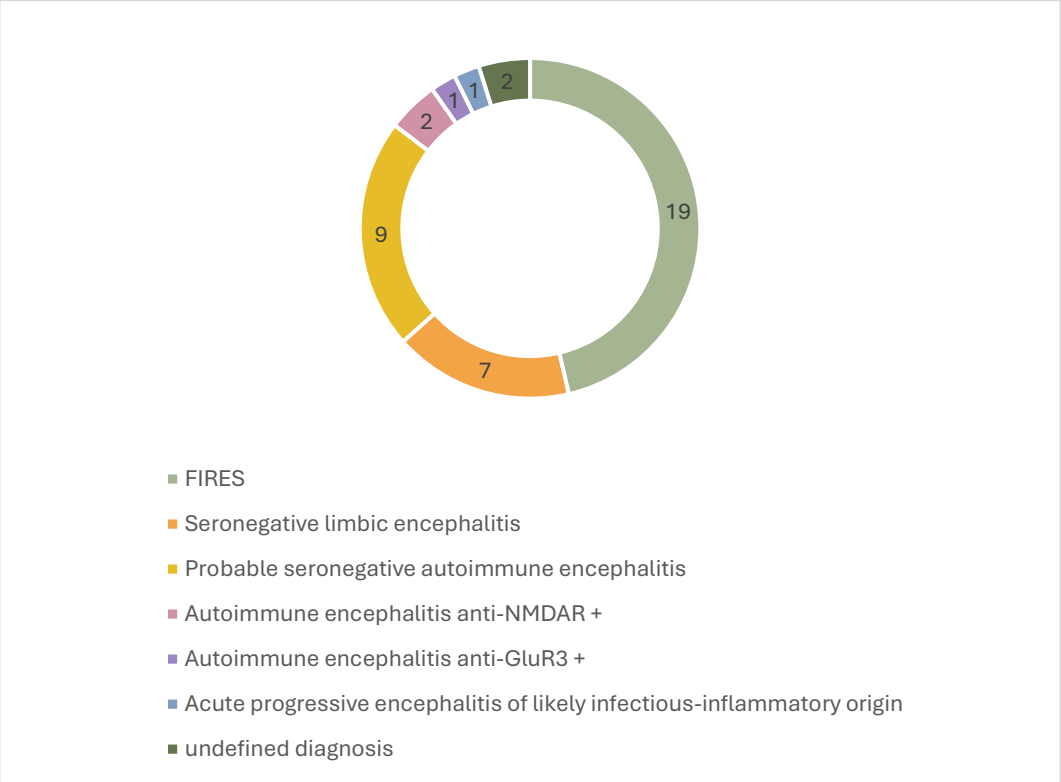

Figure 10. *Final diagnosis of each ISE*

ICU admission was required in most of the cases (39/41, 95%), mainly due to poor seizure control.

Mean hospital Length of Stay (LOS) was 59 days, with a minimum of 11 days and a maximum of 182 days.

Outcome in terms of overall survival was favorable for most of the cohort, with only 1/41 cases resulting in exitus.

4.6 Statistical Analysis

For statistical analysis we subdivided the population into two major groups. ***[Table 7]***

Group 1: patients who received incomplete diagnostic work-up, meaning that at least one diagnostic procedure among MRI, lumbar puncture and auto-antibody testing was not performed.

Group 2: patients who received thorough testing. MRI, lumbar puncture and auto-antibody testing were all performed.

These groups were analyzed based on the duration of SE (≤24 hours vs >24 hours):

- **Group 1** (n = 17): Of these patients, 13 (76%) experienced SE lasting ≤24 hours, while 4 (24%) had SE lasting more than 24 hours.
- **Group 2** (n = 11): Of these patients, 5 (45%) had SE duration ≤24 hours, and 6 (54%) had SE lasting more than 24 hours.

The overall *p*-value for group comparison was 0.125, suggesting no significant difference between Group 1 and Group 2 for SE duration.

In contrast, when the two groups were analyzed based on hospital Length of Stay (LOS), average LOS for **Group 1** was 43.29 days with a SD of 29.40, while **Group 2** had an average LOS of 73.64 days with a SD of 43.48.

The *p*-value for the comparison of LOS between the two groups was 0.022, indicating a statistically significant difference in LOS between Group 1 and Group 2 ($p < 0.05$).

		Group 1 (n = 17)	**Group 2** (n = 11)	***p*-value**
SE duration	*≤24h* *>24h*	13 (76%) 4 (24%)	5 (45%) 6 (54%)	0.125
Lenght of Stay (LOS)	*Days*	43.29 ± 29.40	73.64 ± 43.48	0.022*

Table 7. *Comparison of SE duration and LOS between group 1 and group 2*

Similarly, we analyzed SE duration and LOS comparing the group of patients who received EDTs (EDT+) and the group of patients who only received traditional treatments (EDT-).

- **EDT+ Group** (n=13): Of these patients, 1/13 (8%) had SE duration ≤24 hours while 12/13 (92%) had SE lasting more than 24 hours.
- **EDT- Group** (n=27): In contrast, 22/27 (81%) of these patients had SE duration ≤24 hours while 5/27 (19%) had SE lasting more than 24 hours.

The *p*-value for the comparison of SE duration between the two groups was <0.0001 indicating a statistically significant difference in SE duration between patients who received EDTs and patients who did not ($p < 0.05$).

Conversely, when analyzed based on LOS, the *p*-value for group comparison was 0.026, suggesting no significant difference between EDT+ and EDT - patients for LOS. ***[Table 8]***

		EDT + (n = 13)	**EDT -** (n = 27)	***p*-value**
SE duration				
	≤24h	1 (8%)	22 (81%)	<0.0001*
	>24h	12 (92%)	5 (19%)	
Lenght of stay (LOS)				
	Days	85.77 ± 54.43	47.00 ± 35.07	0.026

Table 8. *Comparison of SE duration and LOS between patients who received EDTs and patients who received traditional ASMs treatment*

DISCUSSION

This multicenter retrospective study analyzed 41 pediatric episodes of ISE across 10 Italian centers, yielding valuable insights into the demographic, clinical, and therapeutic profiles of ISE in children. Our findings highlight notable patterns in SE characteristics, variations in duration, treatment approaches, and outcomes, contributing to the understanding of SE within an inflammatory context in children.

Geographical and Demographic Distribution

The study's cohort comprised a balanced gender distribution of 30 pediatric patients with a mean age at SE onset of 8.12 years, slightly older for females (9.18 years) as compared to males (7.06 years). The geographical distribution of episodes showed an overwhelming predominance in North-East and Central Italy, with an underrepresentation from Southern and Insular regions, potentially affecting the generalizability of the findings to the broader Italian pediatric population. The age and gender balance are consistent with existing literature on pediatric SE, [127] but the regional bias underscores the need for future studies to include more diverse populations to capture regional variability in ISE.

Variability in SE Duration

The durations of SE episodes exhibited significant variation, with peaks at both short (<30 minutes) and extended (>30 days) ends of the spectrum. Notably, episodes lasted between 60–90 minutes and 120 minutes–24 hours in 11.63% and 13.95% of cases, but there were no cases lasting 24–48 hours. This distribution could suggest distinct ISE profiles in pediatric patients, with episodes either responding to initial treatments quickly or requiring extended, intensive management. This bimodal duration distribution aligns with previous findings on SE variability in pediatric populations, [128] although further research is needed to understand the factors contributing to these extremes and how they correlate with underlying inflammation.

Seizures Semeiology and SE Refractoriness

Focal-to-bilateral tonic-clonic SE was the most common semiology, followed by focal-onset motor and generalized tonic-clonic SE. The frequency of focal-to-

bilateral tonic-clonic SE (44%) is consistent with prior research on ISE, where focal onset is often prevalent. [129] Refractory and non-refractory SE were equally represented (39% each), with 22% of episodes progressing to SRSE. The high incidence of RSE and SRSE may reflect the challenges of managing ISE, especially in the presence of autoimmune and other neuroinflammatory conditions, where seizure control can be difficult. The findings suggest a potential need for rapid escalation to aggressive management strategies to prevent progression to SRSE.

Diagnostic Workup and Etiological Findings

Diagnostic procedures varied across cases, with lumbar punctures and CSF/serum antibody testing performed in 56% and 44% episodes. Only a minority (17%) of antibody tests were positive, identifying anti-NMDAR and anti-GluR3 antibodies, consistent with known markers in pediatric autoimmune encephalitis. Serum and/or CSF inflammatory markers profile, investigated in a limited subset, revealed inflammatory patterns, though data limitations hinder broader conclusions. Brain MRI, conducted in 66% of the cases, showed pathological findings 55% cases, indicating the relevance of neuroimaging in ISE. The variability in diagnostic workup could explain differences in treatment outcomes and underscores the importance of a comprehensive approach, including MRI, lumbar puncture, and antibody testing, for accurate diagnosis and treatment planning in ISE.

Therapeutic Approaches and Efficacy

Treatment patterns varied widely, with a total of 26 medications administered as first, second, and third-line strategies. Reflecting adherence to guidelines, treatments also included targeted anti-inflammatory interventions. Midazolam (bolus) and diazepam were the most frequently used first-line treatments, showing only moderate efficacy (20% and 25% relative effectiveness) consistent with the high RSE and SRSE prevalence in our cohort. Etiology-driven treatments (EDTs), such as IVIg, steroids, plasmapheresis and anakinra, were administered in 29 episodes, with a moderate efficacy rate of 20.7%. The different success rates of medications highlight the complexity of managing ISE and the need for individualized treatment plans, particularly as episodes become refractory.

Outcomes: SE Duration and Hospital Length of Stay

A significant finding was the impact of diagnostic completeness on hospital LOS. Patients with incomplete diagnostic workup (Group 1) had a significantly shorter LOS than those who underwent thorough diagnostic evaluations (Group 2). This suggests that comprehensive diagnostic workup is usually delayed and only resorted to when other approaches fail. Larger studies are needed to assess whether thorough initial diagnostic workup may facilitate targeted treatment, potentially reducing hospitalization.

Our analysis also indicated that the use of EDTs correlated with longer SE durations. Specifically, patients who received EDTs had a significantly higher proportion of SE episodes lasting over 24 hours, in contrast to patients managed with standard anti-seizure treatments. This likely reflects the more severe, refractory nature of SE cases that prompted the use of EDT. The prolonged duration in these cases underscores the challenges of managing SE when traditional treatments prove ineffective and inflammation persists.

Interestingly, the extended SE durations associated with EDT did not translate to significantly longer LOS as compared to patients who received only traditional SE treatments. This could suggest that while EDTs are typically reserved for prolonged SE episodes, they may facilitate stabilization and discharge once implemented, mitigating the overall impact on hospitalization time. These findings highlight the potential utility of EDTs in achieving seizure control, albeit at later stages in refractory cases, and call attention to the need for timely consideration of EDT in severe ISE.

Limitations

This study had several limitations. We faced challenges related to data collection due to the retrospective multicentric nature of the study. As previously stated, data were provided by referring clinicians through a structured clinical sheet, therefore we did not have direct access to clinical charts.

Selection bias also may have played a significant role, as we could only analyze data from the centers participating in IPSE Study Group, mainly located in North-central Italy, hence not fully representing the broader national patient population.

Furthermore, because the etiologic definition and workup were not standardized, we cannot formally exclude that some patients with inflammatory etiologies were left unrecognized.

Clinical Implications and Future Directions

This study offers important clinical insights. First, the observed difference in LOS between patients with complete and incomplete diagnostic workups raises questions about the impact of timeliness comprehensive diagnostics on hospital resources and patient experience. Streamlined protocols, prioritizing rapid initial testing for likely ISE markers, may offer a more efficient approach, ensuring that necessary evaluations are conducted without unduly prolonging hospital stays, ultimately improving patients' outcome.

Second, the association between EDT and prolonged SE underscores the need for a structured approach to escalation in SE management, especially when inflammatory or autoimmune etiologies are suspected. Future studies should explore the timing of EDT introduction and its impact on SE duration and patient outcomes, as early intervention with targeted therapies may offer benefits in controlling SE sooner, potentially reducing both SE duration and overall hospital stay.

CONCLUSIONS

This study provides valuable insights into the characteristics, management, and outcomes of pediatric ISE, highlighting the balance between diagnostic thoroughness and hospital efficiency, as well as the role of etiology-driven treatments in managing refractory cases. These findings underscore the importance of optimizing diagnostic and therapeutic strategies to improve outcomes in pediatric ISE, with further research needed to refine approaches that could minimize SE duration and hospitalization time. Continued collaboration across centers will be essential in advancing these goals and enhancing patient care in this challenging condition.

REFERENCES

[1] Gaínza-Lein M, Sánchez Fernández I, Jackson M, Abend NS, Arya R, Brenton JN, Carpenter JL, Chapman KE, Gaillard WD, Glauser TA, Goldstein JL, Goodkin HP, Kapur K, Mikati MA, Peariso K, Tasker RC, Tchapyjnikov D, Topjian AA, Wainwright MS, Wilfong A, Williams K, Loddenkemper T; Pediatric Status Epilepticus Research Group. Association of Time to Treatment With Short-term Outcomes for Pediatric Patients With Refractory Convulsive Status Epilepticus. JAMA Neurol. 2018 Apr 1;75(4):410-418. doi: 10.1001/jamaneurol.2017.4382. PMID: 29356811; PMCID: PMC5885266.

[2] Jackson, J.H. (1899). On a particular variety of epilepsy ('intellectual aura'), one case with symptoms of organic brain disease. Brain, 16(3): 179-207.

[3] International League Against Epilepsy (ILAE). (1993). Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia, 34(4), 453–458.

[4] Lowenstein, D.H., & Alldredge, B.K. (1998). Status epilepticus. The New England Journal of Medicine, 338(14), 970–976.

[5] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515-23. doi: 10.1111/epi.13121. Epub 2015 Sep 4. PMID: 26336950.

[6] Singh A, Stredny CM, Loddenkemper T. Pharmacotherapy for Pediatric Convulsive Status Epilepticus. CNS Drugs 2020;34(1):47-63.

[7] Stredny CM, Abend NS, Loddenkemper T. Towards acute pediatric sta tus epilepticus intervention teams: Do we need "Seizure Codes"? Sei zure 2018;58:133-140.

[8] Vasquez A, Gaínza-Lein M, Sánchez Fernández I, et al. Pediatric Status Epilepticus Research Group (pSERG). Hospital Emergency Treatment of Convulsive Status Epilepticus: Comparison of Pathways From Ten Pediatric Research Centers. Pediatr Neurol 2018 Sep;86:33-41.

[9] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC; NLSTEPSS Collaborative Group. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006 Jul 15;368(9531):222-9. doi: 10.1016/S0140-6736(06)69043-0. PMID: 16844492.

[10] DeLorenzo R.J., Hauser W.A., Towne A.R., Boggs J.G., Pellock J.M., Penberthy L., Garnett L., Fortner C.A., Ko D. A prospective, population-based epidemiologic study of

status epilepticus in Richmond, Virginia. Neurology. 1996;46:1029–1035. doi: 10.1212/WNL.46.4.1029.

[11] Maytal J., Shinnar S., Moshe S.L., Alvarez L.A. Low morbidity and mortality of status epilepticus in children. Pediatrics. 1989;83:323–331.

[12] Sillanpaa M., Shinnar S. Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. Ann Neurol. 2002;52:303–310. doi: 10.1002/ana.10286.

[13] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993 May-Jun;34(3):453-68. doi: 10.1111/j.1528-1157.1993.tb02586.x. PMID: 8504780.

[14] Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol. 2005 Oct;4(10):627-34. doi: 10.1016/S1474-4422(05)70172-1. PMID: 16168931.

[15] Aicardi J., Chevrie J.J. Convulsive status epilepticus in infants and children. A study of 239 cases. Epilepsia. 1970;11:187–197. doi: 10.1111/j.1528-1157.1970.tb03880.x.

[16] Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of Status Epilepticus in Children. J Clin Med. 2016 Apr 13;5(4):47. doi: 10.3390/jcm5040047. PMID: 27089373; PMCID: PMC4850470.

[17] Blume WT, Lüders HO, Mizrahi E, et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia 2001;42:1212–1218.

[18] Walker M, Cross H, Smith S, et al. Nonconvulsive status epilepticus: Epilepsy Research Foundation workshop reports. Epileptic Disord. 2005;7:253–96.

[19] Husain AM. Treatment of recurrent electrographic nonconvulsive seizures (TRENdS) study. Epilepsia. 2013;54(Suppl 6):84–8. doi: 10.1111/epi.12287.

[20] Lee SK. Diagnosis and Treatment of Status Epilepticus. J Epilepsy Res. 2020 Dec 31;10(2):45-54. doi: 10.14581/jer.20008. PMID: 33659195; PMCID: PMC7903042.

[21] Herman ST. The electroencephalogram of nonconvulsive status epilepticus. In: Kaplan PW, Drislane FW, editors. Nonconvulsive Status Epilepticus. New York: Demos Medical Publishing; 2009. pp. 41–62.

[22] Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology. 1996;47:83–9. doi: 10.1212/wnl.47.1.83.

[23] Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54 (Suppl. 6):28–29.

[24] Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neuro physiology Society's Standardized Critical Care EEG Terminology: 2012version. J Clin Neurophysiol 2013;30:1–27.

[25] Sutter R, Kaplan PW. The neurophysiologic types of nonconvulsive status epilepticus: EEG patterns of different phenotypes. Epilepsia 2013;54(Suppl. 6):23–27.

[26] Sutter R, Kaplan PW. Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia 2012;53(Suppl. 3):1–51.

[27] Kaplan PW. EEG criteria for nonconvulsive status epilepticus. Epilepsia 2007;48(Suppl. 8):39–41. Erratum in: Epilepsia. 2007;48:2383.

*[28] Falco-Walter, J.J.; Bleck, T. Treatment of Established Status Epilepticus. J. Clin. Med. **2016**, 5, 49. https://doi.org/10.3390/jcm5050049*

[29] Vasquez A, Farias-Moeller R, Tatum W. Pediatric refractory and super-refractory status epilepticus. Seizure. 2019 May;68:62-71. doi: 10.1016/j.seizure.2018.05.012. Epub 2018 May 19. PMID: 29941225.

[30] Tully I, Draper ES, Lamming CR, Mattison D, Thomas C, Martland T, et al. Admissions to paediatric intensive care units (PICU) with refractory convulsive status epilepticus (RCSE): a two-year multi-centre study. Seizure 2015;29:153–61.

[31] Macdonald RL, Kapur J. Acute cellular alterations in the hippocampus after status epilepticus. Epilepsia 1999;40(Supp. 1)S9–20 discussion S21-2.

[32] Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000;42:117–22.

[33] Cock H. The role of mitochondria in status epilepticus. Epilepsia 2007;48 (Suppl. 8):24–7.

[34] Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. Epilepsia 2011;52:.

[35] Fujikawa DG. Prolonged seizures and cellular injury: understanding the connection. Epilepsy Behav 2005;7(Suppl. 3):S3–11.

[36] Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, Ko D, et al. Prospective population-based study of intermittent and continuous convul sive status epilepticus in Richmond, Virginia. Epilepsia 1999;40:752–8.

[37] Sanchez Fernandez I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015;84:2304–11.

[38] Lado FA, Moshe SL. How do seizures stop. Epilepsia 2008;49:1651–64.

[39] Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018;59:739–44.

[40] Fox K, Wells ME, Tennison M, Vaughn B. Febrile infection-related epilepsy syndrome (FIRES): a literature review and case study. Neurodiagn J 2017;57:224 33.

[41] van Baalen A, Hausler M, Boor R, Rohr A, Sperner J, Kurlemann G, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalop athy in childhood. Epilepsia 2010;51:1323–8.

[42] Fujikawa DG. Starting ketamine for neuroprotection earlier than its current use as an anesthetic/antiepileptic drug late in refractory status epilepticus. Epilepsia. 2019 Mar;60(3):373-380. doi: 10.1111/epi.14676. Epub 2019 Feb 19. PMID: 30785224.

[43] B. Lawton, T. Davis, H. Goldstein, and A. Tagg, "An update in the initial management of paediatric status epilepticus," Current Opinion in Pediatrics, vol. 30, no. 3. Lippincott Williams and Wilkins, pp. 359–363, Jun. 01, 2018. doi: 10.1097/MOP.0000000000000616.

[44] Sathe AG, Underwood E, Coles LD, et al. Patterns of benzodiazepine underdosing in the established status epilepticus treatment trial. Epilepsia. 2021 Mar;62(3):795–806.

[45] Sánchez Fernández I, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology. 2015 Jun 9;84(23):2304–11. doi: 10.1212/WNL.0000000000001673

[46] Roberti R, Riva A, D'Onofrio G, Giacheri E, Amadori E, Vari MS, La Neve A, Vigevano F, Verrotti A, Cordelli DM, Romeo A, Palmieri A, Mancardi MM, Caglieris S, Varone A, Minetti C, Russo E, Buratti S, Striano P. A proposal for a shared therapeutic algorithm in children with prolonged convulsive seizures and status epilepticus. Expert Rev Neurother. 2024 Feb;24(2):133-138. doi: 10.1080/14737175.2024.2305813. Epub 2024 Feb 6. PMID: 38230547.

[47] Mctague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2018;2018(1). doi: 10.1002/14651858.CD001905.pub3

[48] Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American epilepsy society. Epilepsy Curr. 2016;16(1):48–61. doi: 10.5698/1535-7597-16.1.48

[49] Vasquez A, Gaínza-Lein M, Sánchez Fernández I, et al. Hospital emergency treatment of convulsive status epilepticus: comparison of pathways from Ten pediatric research centers. Pediatr Neurol. 2018;86:33–41. doi: 10.1016/j.pediatrneurol.2018.06.004

[50] Vezzani A, Di Sapia R, Kebede V, Balosso S, Ravizza T. Neuroimmunology of status epilepticus. Epilepsy Behav. 2023 Mar;140:109095. doi: 10.1016/j.yebeh.2023.109095. Epub 2023 Feb 6. PMID: 36753859.

[51] Samanta D, Garrity L, Arya R. Refractory and super-refractory Status epilepticus. Indian Pediatr. (2020) 57(3):239–253. 10.1007/s13312-020-1759-0

[52] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. (2012) 366:591–600. 10.1056/NEJMoa1107494

[53] Park CH, Carboni E, Wood PL, Gee KW. Characterization of peripheral benzodiazepine type sites in a cultured murine BV-2 microglial cell line. Glia. (1996) 16:65–70.

[54] Wilms H, Claasen J, Rohl C, Sievers J, Deuschl G, Lucius R. Involvement of benzodiazepine receptors in neuroinflammatory and neurodegenerative diseases: evidence from activated microglial cells in vitro. Neurobiol. Dis. (2003) 14:417–424. 10.1016/j.nbd.2003.07.002

[55] Lokensgard JR, Hu S, Hegg CC, Thayer SA, Gekker G, Peterson PK. Diazepam inhibits HIV-1 tat-induced migration of human microglia. J. Neurovirol. (2001) 7:481–486. 10.1080/135502801753170345

[56] Vossler DG, Bainbridge JL, Boggs JG, Novotny EJ, Loddenkemper T, Faught E, et al. Treatment of refractory convulsive status epilepticus: a comprehensive review by the American epilepsy society treatments committee. Epilepsy Curr. (2020) 20(5):245–264. 10.1177/1535759720928269

[57] Amengual-Gual M, Fischer SN, Gloss DS, Olson DM, Towne AR, Naritoku D, et al. Treatment of refractory convulsive Status epilepticus: a comprehensive review by the American epilepsy society treatments committee. Epilepsy Curr. (2020) 20(5):245–264. 10.1177/1535759720928269

[58] Crawshaw AA, Cock HR. Medical management of status epilepticus: emergency room to intensive care unit. Seizure. (2020) 75:145–152. (Erratum in: Seizure. 2020 Aug; 80:282). 10.1016/j.seizure.2019.10.006

[59] Pottoo FH, Salahuddin M, Khan FA, Alomar F, Al Dhamen MA, Alhashim AF, et al. Thymoquinone potentiates the effect of phenytoin against electroshock-induced convulsions in rats by reducing the hyperactivation of m-TOR pathway and

neuroinflammation: evidence from in vivo. In Vitro and Computational Studies. Pharmaceuticals (Basel). (2021) 14(11):1132. 10.3390/ph14111132

[60] Suda S, Katsura K, Kanamaru T, Saito M, Katayama Y. Valproic acid attenuates ischemia-reperfusion injury in the rat brain through inhibition of oxidative stress and inflammation. Eur J Pharmacol. (2013) 707(1–3):26–31. 10.1016/j.ejphar.2013.03.020

[61] Chang P, Williams AM, Bhatti UF, Biesterveld BE, Liu B, Nikolian VC, et al. Valproic acid and neural apoptosis, inflammation, and degeneration 30 days after traumatic brain injury, hemorrhagic shock, and polytrauma in a swine model. J Am Coll Surg. (2019) 228(3):265–275. 10.1016/j.jamcollsurg.2018.12.026

[62] Ichiyama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-alpha and IL-6 and activation of NF-kappaB. Brain Res. (2000) 857:246–251. 10.1016/s0006-8993(99)02439-7

[63] Peng GS, Li G, Tzeng NS, Chen PS, Chuang DM, Hsu YD, et al. Valproate pretreatment protects dopaminergic neurons from LPS- induced neurotoxicity in rat primary midbrain cultures: role of microglia. Brain Res Mol Brain Res. (2005) 134:162–169. 10.1016/j.molbrainres.2004.10.021

[64] Contreras-García IJ, Cárdenas-Rodríguez N, Romo-Mancillas A, Bandala C, Zamudio SR, Gómez-Manzo S, et al. Levetiracetam mechanisms of action: from molecules to systems. Pharmaceuticals (Basel). (2022) 15(4):475. 10.3390/ph15040475

[65] Itoh K, Ishihara Y, Komori R, Nochi H, Taniguchi R, Chiba Y, et al. Levetiracetam treatment influences blood-brain barrier failure associated with angiogenesis and inflammatory responses in the acute phase of epileptogenesis in post-status epilepticus mice. Brain Res. (2016) 1652:1–13. 10.1016/j.brainres.2016.09.038

[66] Itoh K, Taniguchi R, Matsuo T, Oguro A, Vogel CFA, Yamazaki T, et al. Suppressive effects of levetiracetam on neuroinflammation and phagocytic microglia: a comparative study of levetiracetam, valproate and carbamazepine. Neurosci Lett. (2019) 708:134363. 10.1016/j.neulet.2019.134363

[67] Samanta D, Garrity L, Arya R. Refractory and super-refractory Status epilepticus. Indian Pediatr. (2020) 57(3):239–253. 10.1007/s13312-020-1759-0

[68] Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol. (2008) 38:377–90. 10.1016/j.pediatrneurol.2008.01.001

[69] Zheng J, Zhang W, Kang P, Zheng X, He K, Bai H, et al. Midazolam ameliorates impairment of the blood-brain barrier (BBB) against LPS. Neurotox Res. (2022) 40(3):751–762. 10.1007/s12640-022-00508-4

[70] Tanabe K, Kozawa O, Iida H. Midazolam suppresses interleukin-1β-induced interleukin-6 release from rat glial cells. J Neuroinflamm. (2011) 8:68. 10.1186/1742-2094-8-68

[71] Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, et al. ATP mediates rapid microglial response to local brain injury in vivo. Nat. Neurosci. (2005) 8:752–758. 10.1038/nn1472

[72] Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. PLoS One. (2013) 8:e52887. 10.1371/journal.pone.0052887

[73] Lu Y, Gu Y, Ding X, Wang J, Chen J, Miao C. Intracellular Ca2 + homeostasis and JAK1/STAT3 pathway are involved in the protective effect of propofol on BV2 microglia against hypoxia-induced inflammation and apoptosis. PLoS One. (2017) 12:e0178098. 10.1371/journal.pone.0178098

[74] Vezzani A, Dingledine R, Rossetti AO. Immunity and inflammation in status epilepticus and its sequelae: possibilities for therapeutic application. Expert Rev Neurother. (2015) 15(9):1081–92. 10.1586/14737175.2015.1079130

[75] Bertrand HG, Ellen YC, O'Keefe S, Flecknell PA. Comparison of the effects of ketamine and fentanyl-midazolam-medetomidine for sedation of rhesus macaques (Macaca mulatta). BMC Vet. Res. (2016) 12:93. 10.1186/s12917-016-0721-9

[76] Keros S, Buraniqi E, Alex B, Antonetty A, Fialho H, Hafeez B, et al. Increasing ketamine use for refractory status epilepticus in US pediatric hospitals. J Child Neurol. (2017) 32:638–46. 10.1177/0883073817698629

[77] Chang EI, Zarate MA, Rabaglino MB, Richards EM, Arndt TJ, Keller-Wood M, et al. Ketamine decreases inflammatory and immune pathways after transient hypoxia in late gestation fetal cerebral cortex. Physiol. Rep. (2016) 4(6):e12741. 10.14814/phy2.12741

[78] Groetzinger LM, Rivosecchi RM, Bain W, Bahr M, Chin K, McVerry BJ, et al. Ketamine infusion for adjunct sedation in mechanically ventilated adults. Pharmacotherapy. (2018) 38:181–188. 10.1002/phar.2065

[79] F. J. Holzer, M. Seeck, and C. M. Korff, "Autoimmunity and inflammation in status epilepticus: From concepts to therapies," Expert Review of Neurotherapeutics, vol. 14, no. 10. Expert Reviews Ltd., pp. 1181–1202, Oct. 01, 2014. doi: 10.1586/14737175.2014.956457

[80] Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. (2011) 134(Pt 10):2802–18. 10.1093/brain/awr215

[81] Vezzani A, Balosso S, Aronica E, Ravizza T. Basic mechanisms of status epilepticus due to infection and inflammation. Epilepsia. (2009) 50(Suppl.12):56–7. 10.1111/j.1528-1167.2009.02370.x

[82] Matin N, Tabatabaie O, Falsaperla R, Lubrano R, Pavone P, Mahmood F, et al. Epilepsy and innate immune system: a possible immunogenic predisposition and related therapeutic implications. Hum Vaccin Immunother. (2015) 11(8):2021–9. 10.1080/21645515.2015.1034921

[83] Vezzani A, Maroso M, Balosso S, Sanchez MA, Bartfai T. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain Behav Immun. (2011) 25(7):1281–9. 10.1016/j.bbi.2011.03.018

[84] Rojas A, Jiang J, Ganesh T, Yang MS, Lelutiu N, Gueorguieva P, et al. Cyclooxygenase-2 in epilepsy. Epilepsia. (2014) 55(1):17–25. 10.1111/epi.12461

[85] Xiong ZQ, Qian W, Suzuki K, McNamara JO. Formation of complement membrane attack complex in mammalian cerebral cortex evokes seizures and neurodegeneration. J Neurosci. (2003) 23(3):955–60. 10.1523/JNEUROSCI.23-03-00955.2003

[86] Ravizza T, Balosso S, Aronica E, Vezzani A. Brain inflammation and epilepsy. In: Rho JM, Sankar R, Strafstrom CE, editors. Epilepsy: Mechanisms, models and translational perspectives. Boca Raton, FL, USA: CRC Press; (2010). p. 45–59.

[87] Kulkarni SK, Dhir A. Cyclooxygenase in epilepsy: from perception to application. Drugs Today (Barc). (2009) 45(2):135–54. 10.1358/dot.2009.45.2.1322481

[88] Wickstrom R, Taraschenko O, Dilena R, Payne ET, Specchio N, Nabbout R, et al. International consensus recommendations for management of new onset refractory Status epilepticus (NORSE) incl. Febrile infection-related epilepsy syndrome (FIRES): statements and supporting evidence. Epilepsia. (2022) 63(11):2840–64. 10.1111/epi.17397

[89] Dilena R, Mauri E, Aronica E, Bernasconi P, Bana C, Cappelletti C, et al. Therapeutic effect of anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. Epilepsia Open. (2019) 4(2):344–350. 10.1002/epi4.12317

[90] Westbrook C, Subramaniam T, Seagren RM, Tarula E, Co D, Furstenberg-K nauff M, et al. Febrile infection-related epilepsy syndrome treated successfully with anakinra in a 21- year- old woman. WMJ. (2019) 118:135–9.

[91] Randle JC, Harding MW, Ku G, Schonharting M, Kurrle R. ICE/Caspase-1 inhibitors as novel anti- inflammatory drugs. Expert Opin Invest Drugs. (2001) 10:1207–9. 10.1517/13543784.10.7.1207

[92] Wannamaker W, Davies R, Namchuk M, Pollard J, Ford P, Ku G, et al. (S)-1-((S)-2-{[1-(4-amino-3-chloro- phenyl)-methanoyl]-amino}-3, 3-dimethyl-butanoyl)- pyrrolidine-2-carboxylic acid ((2R, 3S)-2-ethoxy-5- oxo-tetrahydro-furan-3-yl)-amide (VX-765), an orally available selective interleukin (IL)-converting enzyme/ caspase-1 inhibitor, exhibits potent anti-inflammatory activities by inhibiting the release of IL-1b and IL-18. J Pharmacol Exp Ther. (2007) 321:509–16. 10.1124/jpet.106.111344

[93] Ravizza T, Lucas SM, Balosso S, Bernardino L, Ku G, Noe F, et al. Inactivation of caspase-1 in rodent brain: a novel anticonvulsive strategy. Epilepsia. (2006) 47:1160–8. 10.1111/j.1528-1167.2006.00590.x

[94] Incorporated VP. Study of VX-765 in subjects with treatment-resistant partial epilepsy. (Study code-clini-caltrials.gov identifier: NCT01048255).

[95] Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, Iyer AM, et al. Toll-like receptor 4 and high- mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. Nat Med. (2010) 16:413–9. 10.1038/nm.2127

[96] Zurolo E, Iyer A, Maroso M, Carbonell C, Anink JJ, Ravizza T, et al. Activation of toll-like receptor, RAGE and HMGB1 signalling in malformations of cortical development. Brain. (2011) 134:1015–32. 10.1093/brain/awr032

[97] Albani D, Polito L, Signorini A, Forloni G. Neuroprotective properties of resveratrol in different neurodegenerative disorders. Biofactors. (2010) 36:370–6. 10.1002/biof.118

[98] Youn HS, Lee JY, Fitzgerald KA, Young HA, Akira S, Hwang DH. Specific inhibition of MyD88-independent signaling pathways of TLR3 and TLR4 by resveratrol: molecular targets are TBK1 and RIP1 in TRIF complex. J Immunol. (2005) 175:3339–46. 10.4049/jimmunol.175.5.3339

[99] Zhang F, Liu J, Shi J-S. Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in micro-glial activation. Eur J Pharmacol. (2010) 636:1–7. 10.1016/j.ejphar.2010.03.043

[100] Bhat KP, Kosmeder JW, Pezzuto JM. Biological effects of resveratrol. Antioxid Redox Signal. (2001) 3:1041–64. 10.1089/152308601317203567

[101] Christian CA. Persistent protection against pathology and paroxysms by P2X7R antagonism. Epilepsy Currents. (2018) 18(1):42–44. 10.5698/1535-7597.18.1.42

[102] Beamer E, Fischer W, Engel T. The ATP-gated P2X7 receptor as a target for the treatment of drug-resistant epilepsy. Front Neurosci. (2017) 11:21. 10.3389/fnins.2017.00021

[103] Yu Y, Feng S, Wei S, Zhong Y, Yi G, Chen H, et al. Extracellular ATP activates P2X7R-NF -κB (p65) pathway to promote the maturation of bone marrow- derived dendritic cells of mice. Cytokine. (2019) 119:175–181. 10.1016/j.cyto.2019.03.019

[104] Wang M, Deng X, Xie Y, Chen Y. Astaxanthin attenuates neuroinflammation in Status epilepticus rats by regulating the ATP-P2X7R signal. Drug Des Devel Ther. (2020) 14:1651–1662. 10.2147/DDDT.S249162

[105] Li G, Bauer S, Nowak M, Norwood B, Tackemberg B, Rosenow F, et al. Cytokines and epilepsy. Seizure. (2011) 20:249–56. 10.1016/j.seizure.2010.12.005

[106] Lorigados Pedre L, Morales Chacón LM. Follow-up of peripheral IL-1β and IL-6 and relation with apoptotic death in drug-resistant temporal lobe epilepsy patients submitted to surgery. Behav Sci. (2018) 8:21. 10.3390/bs8020021

[107] Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. Ann Neurol. (2018) 84(6):940–945. 10.1002/ana.25374

[108] Cantarín-Extremera V, Jiménez-Legido M, Duat-Rodríguez A, García-Fernández M, Ortiz-Cabrera NV, Ruiz-Falcó-Rojas ML, et al. Tocilizumab in pediatric refractory status epilepticus and acute epilepsy: experience in two patients. J Neuroimmunol. (2020) 340:577142. 10.1016/j.jneuroim.2019.577142

[109] Stredny CM, Case S, Sansevere AJ, Son M, Henderson L, Gorman MP. Interleukin-6 blockade with tocilizumab in anakinra-refractory febrile infection-related epilepsy syndrome (FIRES). Child Neurol Open. (2020) 7:2329048X20979253. 10.1177/2329048X20979253

[110] Foiadelli T, Santangelo A, Costagliola G, Costa E, Scacciati M, Riva A, Volpedo G, Smaldone M, Bonuccelli A, Clemente AM, Ferretti A, Savasta S, Striano P, Orsini A. Neuroinflammation and status epilepticus: a narrative review unraveling a complex interplay. Front Pediatr. 2023 Nov 21;11:1251914. doi: 10.3389/fped.2023.1251914. PMID: 38078329; PMCID: PMC10703175.

[111] Bredmose PP, Grier G, Davies GE, Lockey DJ. Pre-hospital useof ketamine in pediatric trauma. Acta Anaesthesiol Scand.2009;53(4):543– 5

[112] lkhachroum A, Der-Nigoghossian CA, Mathews E, et al. Ketamine to treat super-refractory status epilepticus. Neurology.2020;95:e2286– 94.

[113] Chang L, Raty S, Ortiz J, et al. The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. CNSNeurosci Ther. 2013;19:390– 5.

[114] Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamineeffect on intra- cranial pressure in nontraumatic neurologicalillness. J Crit Care. 2014;29:1096–106.

[115] Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR,McCoy BM, et al. Intravenous ketamine for the treatment ofrefractory status epilepticus: a retrospective multicenter study.Epilepsia. 2013;54:1498– 503.

[116] Buratti S, Giacheri E, Palmieri A, Tibaldi J, Brisca G, Riva A, et al. Ketamine as advanced second-line treatment in benzodiazepine-refractory convulsive status epilepticus in children. Epilepsia. 2023; 64: 797–810. https://doi.org/10.1111/epi.17550

[117] Spatola M, Novy J, Du Pasquier R, Dalmau J, Rossetti AO. Status epilepticus of inflammatory etiology: a cohort study. Neurology. 2015 Aug 4;85(5):464-70. doi: 10.1212/WNL.0000000000001717. Epub 2015 Jun 19. PMID: 26092915; PMCID: PMC4534074.

[118] Venkatesan A, Tunkel AR, Bloch KC, et al. for the International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013; 57:1114–28. [PubMed: 23861361]

[119] Jmor F, Emsley HC, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. Virol J. 2008; 5:134–46. [PubMed: 18973679]

[120] Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitisassociated hospitalizations in the United States, 1998–2010. Neurology. 2014; 82:443–51. [PubMed: 24384647]

[121] Ball R, Halsey N, Braun MM, et al. for the VAERS Working Group. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the vaccine: Adverse Event Reporting System. J Clin Epidemiol. 2002; 55:819–24. [PubMed: 12384197]

[122] Sejvar JJ, Kohl KS, Bilynsky R, et al. for the Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25:5771–92. [PubMed: 17570566]

[123] Britton PN, Eastwood K, Paterson B, et al. for the Australasian Society of Infectious Diseases (ASID), the Australasian College of Emergency Medicine (ACEM), the Australian and New Zealand Association of Neurologists (ANZAN), and the Public Health Association of Australia (PHAA). Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J. 2015; 45:563–76. [PubMed: 25955462]

[124] Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr;15(4):391-404. doi: 10.1016/S1474-4422(15)00401-9. Epub 2016 Feb 20. PMID: 26906964; PMCID: PMC5066574.

[125] Rosenfeld MR, Titulaer MJ, Dalmau J. Paraneoplastic syndromes and autoimmune encephalitis: Five new things. Neurology. Clinical Practice. 2012 Sep;2(3):215-223. DOI: 10.1212/cpj.0b013e31826af23e. PMID: 23634368; PMCID: PMC3613202.

[126] Brisca G, Marini C, Buratti S, Mariani M, Tortora D, Morana G, Pirlo D, Romanengo M, Cannizzaro G, Cordani R, Canzoneri F, Calevo MG, Nobili L, Franciotta D, Castagnola E, Moscatelli A, Mancardi MM. Acute pediatric encephalitis: etiology, course, and outcome of a 12-year single-center immunocompetent cohort. J Neurol. 2023 Oct;270(10):5034-5047. doi: 10.1007/s00415-023-11847-3. Epub 2023 Jul 3. PMID: 37400659.

*[127] Shorvon S, THE MANAGEMENT OF STATUS EPILEPTICUS. Journal of Neurology, Neurosurgery & Psychiatry 2001;**70:**ii22-ii27.*

[128] Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol. 2001 May;49(5):659-64. PMID: 11357957.

[129] Jehan Suleiman, Sukhvir Wright, Deepak Gill, Fabienne Brilot, Patrick Waters, Ken Peacock, Peter Procopis, Anjan Nibber, Angela Vincent, Russell C. Dale, Bethan Lang. Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia, 54(12):2091–2100, 2013