Review Article

Refractory Seizures in the Emergency Department: Diagnostic Approach and Evidence-Based Therapeutic Strategies

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Abstract

Refractory seizures and status epilepticus represent critical neurological emergencies associated with high morbidity and mortality in the emergency department. Their pathophysiology is driven by maladaptive neurobiological mechanisms, including disruption of inhibitory gamma-aminobutyric acid signaling, upregulation of excitatory glutamatergic receptors, impaired chloride homeostasis mediated by KCC2 dysfunction, and progressive pharmacoresistance that worsens with seizure duration. These processes provide the biological basis for current operational definitions of refractory and super-refractory status epilepticus and reinforce the principle that seizure persistence directly influences neurological outcome. Etiologically, refractory seizures arise from a heterogeneous spectrum of acute symptomatic and chronic epilepsy-related causes. Acute triggers include structural brain injury, metabolic disturbances, infections, toxic exposures, and autoimmune disorders, while chronic epilepsy-related seizures are frequently linked to suboptimal seizure control or medication non-adherence. Certain populations, such as pediatric patients, individuals with autoimmune disease, and those with new-onset refractory status epilepticus, are particularly vulnerable and pose significant

diagnostic and therapeutic challenges. Management in the emergency department requires rapid stabilization, focused neurological assessment, and early identification of reversible causes. Laboratory testing, neuroimaging, and electroencephalographyespecially for detection of non-convulsive status epilepticuscare essential components of the diagnostic approach. Evidence-based treatment emphasizes timely benzodiazepine administration, followed by second-line antiepileptic drugs and escalation to anesthetic, immunomodulatory, or adjunctive therapies in refractory cases. Despite advances in pharmacological and supportive strategies, outcomes remain poor when seizure control is delayed or treatment sequences deviate from established guidelines. Coordinated multidisciplinary care and standardized clinical protocols are therefore crucial to optimize management. Ongoing research is needed to refine therapeutic pathways, improve implementation of evidence-based practices, and reduce the long-term neurological burden of refractory seizure disorders.

Key words

Pharmacoresistance; Nonconvulsive status epilepticus; KCC2 dysfunction; Emergency neurology; Multidisciplinary care; Treatment escalation.

Introduction

Refractory seizures represent a major clinical challenge in the emergency department because of their high potential to progress to status epilepticus, a life-threatening neurological emergency that demands prompt and decisive intervention [1, 2]. Their management extends beyond immediate seizure control and frequently requires a coordinated multidisciplinary approach involving emergency physicians, neurologists, and intensive care specialists, in order to address both acute stabilization and subsequent neurological care [3, 4].

From an epidemiological perspective, seizures account for approximately 1% of all emergency department visits, with a substantial proportion corresponding to refractory presentations [4]. The frequency of emergency medical service contacts related to seizures is comparable to that observed for stroke, illustrating the considerable burden these events impose on healthcare systems [1]. Among these cases, refractory status epilepticus is particularly associated with significant morbidity and mortality, with reported 30-day mortality rates of 8.5% and 1-year mortality rates reaching 25.1% in patients with new-onset status epilepticus. Poorer outcomes have been consistently linked to advanced age, acute symptomatic etiologies, and deviations from established treatment guidelines, further emphasizing the prognostic relevance of early and guideline-concordant management [2, 5].

The overarching objective of refractory seizure management in the emergency department is the rapid termination of ongoing seizure activity to prevent progression to status epilepticus and to minimize associated morbidity and mortality [6]. Current therapeutic frameworks prioritize benzodiazepines as first-line agents, while additional strategies, including immunotherapy and neuromodulatory approaches, are being explored for cases that remain resistant to conventional treatment [3, 7]. Parallel to these efforts, the development of novel rescue medications and alternative formulations, such as intranasal therapies, has emerged as a promising strategy to improve the management of seizure clusters and prolonged seizures [8]. Despite these advances, persistent gaps in evidence highlight the need for better adherence to clinical guidelines and for innovative clinical trial designs capable of addressing unresolved questions in the treatment of refractory status epilepticus [7].

The objective of this review is to summarize the evidence-based diagnostic and therapeutic strategies for the management of refractory seizures in the emergency department, emphasizing early recognition and timely intervention to reduce morbidity and mortality.

Methodology

The development of this manuscript was based on a narrative review approach focused on the diagnostic and therapeutic management of refractory seizures in the emergency department. The content was structured around the clinical challenges inherent to acute seizure care, emphasizing how rapid assessment, etiological evaluation, and timely therapeutic escalation are integrated in real-world emergency settings to optimize patient outcomes.

Key concepts were organized according to their relevance to emergency decision-making, prioritizing early recognition of refractory seizures, identification of precipitating factors, and progression through evidence-based treatment pathways. This organization allowed the discussion to evolve logically from initial clinical evaluation to advanced therapeutic strategies, rather than adhering to a rigid methodological sequence.

The scientific literature provided a contextual framework to support this clinical narrative. Peer-reviewed studies published between 2021 and 2026 and indexed in PubMed, Scopus, and Web of Science were selectively consulted, with preference given to sources addressing pathophysiological mechanisms of seizure refractoriness, diagnostic tools applicable to the emergency setting, and evidence-based pharmacological and adjunctive therapies. Publications lacking clinical relevance, methodological rigor, or direct applicability to acute care were excluded. Conceptual search terms related to pharmacoresistance; nonconvulsive status epilepticus; KCC2 dysfunction; emergency neurology; multidisciplinary care; treatment escalation

During manuscript preparation, artificial intelligence–based tools were used exclusively to assist with thematic organization and to ensure logical coherence and continuity across sections. This narrative, non-linear structure enabled the integration of diagnostic and therapeutic perspectives, resulting in a cohesive synthesis that highlights the importance of timely, structured, and evidence-based management of refractory seizures in the emergency department.

Pathophysiology and Definitions

Refractory seizures are driven by complex neurobiological mechanisms in which maladaptive alterations in inhibitory and excitatory signaling play a central role. At the synaptic level, inhibitory gamma-aminobutyric acid type A receptors undergo activity-dependent endocytosis, leading to a reduction in effective inhibitory neurotransmission. In parallel, excitatory glutamatergic receptors, including N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, are upregulated, promoting excessive excitatory drive. This imbalance favors sustained calcium influx, which in turn contributes to mitochondrial dysfunction and increased oxidative stress, thereby amplifying neuronal injury and cell death and reinforcing seizure refractoriness [9].

Within this pathophysiological framework, the potassium–chloride co-transporter KCC2 plays a critical role in maintaining intracellular chloride homeostasis and preserving effective gamma-aminobutyric acid–mediated inhibition. Impairment of KCC2 function has been closely linked to benzodiazepine-refractory status epilepticus, as disrupted chloride gradients diminish the hyperpolarizing effect of inhibitory signaling. Experimental evidence indicates that activation of KCC2 can reduce neuronal excitability and limit cell death, highlighting its relevance as a potential therapeutic target in refractory seizure states [10].

These neurobiological insights underpin the operational definitions used to classify refractory

seizure conditions in clinical practice. Refractory status epilepticus is defined as ongoing seizure activity that persists despite the administration of at least two appropriately dosed parenteral antiseizure medications, one of which must be a benzodiazepine [3]. In more severe cases, super-refractory status epilepticus is diagnosed when seizures continue for at least twenty-four hours after the initiation of continuous anesthetic therapy, reflecting a further escalation in pharmacoresistance and clinical severity. In contrast, drug-resistant epilepsy, as defined by the International League Against Epilepsy, refers to the failure of two adequately selected and tolerated antiepileptic drug regimens to achieve sustained seizure freedom, representing a chronic form of treatment resistance distinct from acute refractory states [3, 11].

The clinical relevance of these definitions is closely linked to the concept that seizure duration directly influences neurological outcome. Prolonged seizure activity is associated with progressive pharmacoresistance and cumulative neuronal injury, reinforcing the principle that "time is brain" in the context of status epilepticus. Delayed intervention increases the likelihood of irreversible brain damage, underscoring the need for rapid recognition and escalation of therapy. In this regard, the proposed "Stage 1 Plus" classification for prolonged convulsive status epilepticus emphasizes the early use of combined therapeutic strategies from the outset, aiming to counteract the rapid disruption of receptor homeostasis that characterizes evolving refractory seizures [12].

Etiology and Risk Factors

Acute symptomatic seizures and chronic epilepsy-related seizures represent two major etiological categories with distinct clinical implications in the emergency department. Acute symptomatic seizures are typically associated with a transient and identifiable insult to the central nervous system, including infections, metabolic derangements, or toxic exposures. Common acute triggers in the emergency setting include alcohol withdrawal and hemorrhagic stroke, both of which are frequently encountered and require prompt recognition [13]. In addition to these causes, acute symptomatic seizures have also been linked to systemic autoimmune disorders, in which immune-mediated mechanisms can enhance neuronal excitability and precipitate seizure activity [14].

In contrast, chronic epilepsy-related seizures occur in individuals with a known history of epilepsy and are most often related to suboptimal seizure control, medication non-adherence, or disease progression. These seizures constitute a significant proportion of emergency department visits, with many affected patients having a previously established epilepsy diagnosis, underscoring the ongoing burden of chronic seizure disorders on acute care services [1].

Beyond this broad etiological distinction, a wide range of specific triggers can precipitate seizures in the emergency setting. Structural causes, such as traumatic brain injury or acute cerebrovascular events, represent important precipitants by directly disrupting neuronal networks and lowering the seizure threshold. Metabolic abnormalities, including electrolyte disturbances and hypoglycemia, are also frequent and reversible contributors to acute symptomatic seizures and must be rapidly identified during initial evaluation [15]. Infectious etiologies are particularly relevant in pediatric populations, where seizures may arise in the context of systemic or central nervous system infections; febrile infection-related epilepsy syndrome exemplifies a severe infection-associated trigger with significant clinical consequences [16]. Toxic factors, especially substance use and withdrawal, play a prominent role, with alcohol-related seizures remaining among the most common toxic causes encountered in emergency practice [13]. More recently, autoimmune triggers, including autoimmune encephalitis, have gained increasing recognition as causes of refractory seizures, often necessitating

immunotherapy as part of the management strategy [17].

Patient-related and treatment-related factors further modulate seizure risk and outcomes. Male sex, absence of a prior epilepsy diagnosis, and generalized tonic–clonic seizure semiology have been associated with a higher likelihood of acute symptomatic seizures, highlighting the importance of demographic and clinical characteristics in risk stratification [13]. From a therapeutic standpoint, delays in diagnosis and initiation of appropriate treatment are associated with worse outcomes. Although antiseizure medications and immunotherapy are frequently employed, uncertainty regarding optimal treatment duration and escalation remains a significant clinical challenge [18].

Certain populations are particularly vulnerable in the emergency setting. Pediatric patients, especially those presenting with febrile illnesses, are at increased risk of acute symptomatic seizures and require age-specific diagnostic and therapeutic considerations [16]. Patients with systemic autoimmune disorders also constitute a high-risk group due to shared inflammatory and immunological mechanisms that predispose to seizure activity [14]. Additionally, individuals with new-onset refractory status epilepticus represent one of the most challenging populations, given the frequently cryptogenic nature of the condition and the high associated mortality, which complicates both diagnostic evaluation and therapeutic decision-making [19].

Initial Evaluation and Diagnostic Approach

The initial management of refractory seizures in the emergency department is centered on rapid stabilization and focused neurological assessment. Immediate attention to airway, breathing, and circulation is essential to prevent secondary neurological injury and to create a safe foundation for subsequent diagnostic and therapeutic interventions. Effective stabilization not only reduces the risk of hypoxia and hemodynamic compromise but also facilitates accurate clinical evaluation and timely escalation of care [1].

Once physiological stability is achieved, a structured neurological assessment becomes a priority. Careful evaluation of the level of consciousness and the presence of focal neurological deficits is crucial for distinguishing between ongoing convulsive activity and non-convulsive seizure states. This assessment guides further diagnostic steps and helps determine the urgency of advanced investigations, particularly in patients with persistent altered mental status [1].

Laboratory testing plays an important role in the early evaluation of patients with refractory seizures, primarily by identifying potentially reversible metabolic contributors. Routine laboratory studies commonly include blood glucose measurement, serum electrolytes, and assessment of renal function. Abnormalities in sodium and glucose levels are frequently observed in patients with recurrent seizures, with reported disturbances in sodium levels in approximately 19% of cases and glucose abnormalities in up to 50% of patients. Although these investigations are routinely obtained, their impact on immediate management is variable, as their greatest utility lies in the identification and correction of metabolic derangements rather than in the direct diagnosis of seizure activity itself [20].

Neuroimaging constitutes a key component of the diagnostic approach in the emergency setting. Computed tomography is commonly employed to rapidly exclude intracranial pathologies such as hemorrhage or mass lesions, with reported diagnostic yields ranging from 8% to 21% in patients presenting with recurrent seizures. Magnetic resonance imaging is used less frequently in the acute setting but may provide more detailed structural information in selected cases, particularly when computed tomography findings are inconclusive or when underlying

pathology is suspected [20]. Neuroimaging is especially indicated in patients experiencing a first seizure, those with prolonged alterations in consciousness, or individuals exhibiting focal neurological deficits, as these features increase the likelihood of an underlying structural cause [21].

Electroencephalography plays a pivotal role in the identification of non-convulsive seizures and non-convulsive status epilepticus, conditions that are frequently underrecognized in the emergency department. The implementation of rapid-response electroencephalography protocols has been shown to significantly enhance seizure detection, and the use of point-of-care electroencephalography devices allows for timely and reliable diagnosis in critically ill patients [22]. More recently, artificial intelligence–enhanced electroencephalography has demonstrated potential in improving diagnostic efficiency, although it may overestimate seizure burden. Reported sensitivity and specificity for seizure detection using these systems are 66.7% and 97.0%, respectively, highlighting both their promise and their limitations [23].

The clinical implications of early electroencephalographic assessment are substantial, as prompt identification of non-convulsive status epilepticus enables earlier initiation of targeted therapy and is associated with improved clinical outcomes. Maintaining a high index of suspicion for non-convulsive seizures is therefore essential, particularly in patients with unexplained or persistent alterations in mental status, where delayed diagnosis may result in ongoing neuronal injury and worse prognosis [24].

Evidence-Based Pharmacological Management

Benzodiazepines constitute the cornerstone of first-line therapy for status epilepticus; however, refractory cases emerge when seizure activity persists despite appropriate and timely administration. Early treatment failure may result from several factors, including delays in drug delivery, subtherapeutic dosing, or seizure etiologies that are inherently less responsive to benzodiazepine-mediated gamma-aminobutyric acid potentiation. In these contexts, ongoing seizure activity reflects not only pharmacokinetic limitations but also underlying pathophysiological mechanisms that diminish inhibitory responsiveness, thereby necessitating escalation of therapy beyond first-line agents [3].

When benzodiazepines fail to achieve seizure control, second-line antiepileptic drugs are introduced, with levetiracetam and fosphenytoin being among the most utilized options. Comparative studies have demonstrated that levetiracetam exhibits efficacy comparable to fosphenytoin while offering a more favorable safety profile, particularly with respect to respiratory depression and hemodynamic instability [25, 26]. These characteristics have supported its widespread adoption in emergency settings. In pediatric populations, levetiracetam has similarly shown efficacy equivalent to phenytoin or fosphenytoin, with a lower incidence of respiratory complications, positioning it as a particularly attractive option in cases of benzodiazepine-refractory status epilepticus [26].

In patients who progress to refractory or super-refractory status epilepticus, additional therapeutic strategies are required. Agents such as perampanel and ketamine have gained attention in this context due to their distinct mechanisms of action. Perampanel, a noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, has demonstrated effectiveness in both refractory and super-refractory status epilepticus, with reports indicating satisfactory seizure control and an acceptable safety profile when appropriately dosed [27]. Ketamine, which targets N-methyl-D-aspartate receptors, has also been associated with improved seizure control in refractory states, particularly in scenarios where

traditional gamma-aminobutyric acid–based therapies have failed, highlighting its role as a mechanistically complementary agent in advanced stages of treatment resistance [28].

The selection of antiseizure medications in refractory contexts must be individualized, considering the patient's clinical condition, comorbidities, and the adverse effect profiles of each agent. While perampanel has demonstrated efficacy, careful titration is required to minimize the risk of adverse outcomes [27]. Phenobarbital remains an option for super-refractory status epilepticus and has been associated with high rates of seizure control; however, its use is limited by significant complications, including hypotension and increased susceptibility to infections, necessitating close monitoring and supportive care [29]. In parallel, ganaxolone, a neuroactive steroid currently under investigation, represents a promising therapeutic alternative by modulating inhibitory signaling through a novel mechanism that may reduce reliance on intravenous anesthetics in refractory seizure management [30].

Advanced and Adjunctive Therapeutic Strategies

The management of refractory and super-refractory status epilepticus frequently requires the use of anesthetic agents within an intensive care setting, particularly when conventional antiseizure therapies fail to achieve adequate seizure control. Ketamine, an N-methyl-D-aspartate receptor antagonist, has emerged as a promising option in this context. Clinical studies have demonstrated that ketamine is associated with higher rates of seizure resolution within twenty-four hours compared with traditional anesthetic agents such as midazolam, propofol, and pentobarbital, without a corresponding increase in seizure relapse rates, supporting its utility as an effective and well-tolerated anesthetic strategy in refractory cases [38].

Phenobarbital remains another important anesthetic option for critically ill patients with refractory and super-refractory status epilepticus. Recent evidence suggests that optimizing phenobarbital dosing through population pharmacokinetic models may enhance both safety and efficacy, particularly given the substantial pharmacokinetic variability observed in this patient population. Individualized dosing strategies are therefore essential to balance seizure control with the risk of adverse effects in the intensive care environment [31].

In parallel with pharmacological approaches, non-pharmacological and immunomodulatory therapies have gained attention as adjunctive strategies in selected patients. Responsive neurostimulation has been explored as a treatment option for super-refractory status epilepticus, particularly in cases with well-defined seizure-onset zones. This approach allows for real-time electroencephalographic monitoring and the delivery of tailored stimulation patterns, offering a potential avenue for seizure resolution, although further research is required to refine patient selection and optimize therapeutic protocols [32]. Immunotherapy also plays a role when autoimmune mechanisms are suspected to contribute to ongoing seizure activity, with corticosteroids and other immunosuppressive agents being incorporated into management strategies for super-refractory status epilepticus in appropriate clinical contexts [3, 33].

The prevention and management of complications associated with prolonged seizure activity are integral components of care. Continuous electroencephalographic monitoring is essential in patients with refractory and super-refractory status epilepticus, as it enables accurate assessment of seizure burden and facilitates timely adjustments in therapeutic interventions [3]. In acute settings, the rapid administration of antiseizure medications remains a priority, and intravenous push administration of levetiracetam has been shown to be both safe and effective, allowing for

expedited seizure control during emergency management [34].

Alongside established therapies, several emerging and investigational treatment options are under active evaluation. Ganaxolone, a neuroactive steroid, is being developed as a potential therapy for refractory status epilepticus with the aim of achieving seizure control without escalation to continuous intravenous anesthetics. Ongoing studies are assessing its efficacy and safety profile in this challenging population [30]. Additional experimental approaches, including therapeutic hypothermia, ketogenic diet, pyridoxine infusion, and cerebrospinal fluid drainage, have also been explored; however, robust clinical data supporting their effectiveness remain limited, and their use is currently confined to highly selected cases or research settings [34].

Prognostic Factors and Outcomes

Short- and long-term neurological outcomes following refractory seizure states are frequently poor and are strongly influenced by the underlying etiology and duration of seizure activity. Patients with cryptogenic new-onset refractory status epilepticus often experience severe long-term consequences, including a high prevalence of active epilepsy, persistent cognitive impairment, and significant psychiatric comorbidities. Only a small proportion of these patients achieve favorable functional recovery, underscoring the profoundly life-altering impact of this condition [35]. Similarly, in cases of super-refractory status epilepticus, prolonged seizure duration and the extent of associated brain injury play a central role in determining the severity of subsequent neurological deficits and long-term functional limitations [34].

Several clinical and electroencephalographic factors have been identified as predictors of morbidity and mortality in status epilepticus. Adverse prognostic indicators include cardiac arrest, the presence of clinical seizures prior to initiation of continuous electroencephalogram monitoring, underlying brain neoplasms, and specific electroencephalographic patterns such as lateralized periodic discharges and generalized periodic discharges [36]. These features reflect both the severity of the underlying neurological insult and the extent of ongoing cortical dysfunction. The STEPPER study further demonstrated that failure to achieve resolution of status epilepticus is a strong predictor of thirty-day mortality and functional deterioration, highlighting the critical role of appropriate treatment sequencing and strict adherence to established clinical guidelines [37].

The timing and effectiveness of seizure control have a decisive impact on prognosis. Early and adequate termination of seizure activity is consistently associated with improved outcomes, whereas delays or incorrect therapeutic sequences contribute to treatment failure and worse survival. Data from the STEPPER study emphasize that inadequate use of benzodiazepines as first-line therapy is linked to higher rates of unresolved status epilepticus, which in turn translates into increased mortality and functional decline [37]. Beyond the acute setting, evidence from epilepsy surgery outcomes further supports the prognostic importance of seizure control, as achieving seizure freedom is associated with reduced overall mortality and a lower risk of sudden unexpected death in epilepsy [38].

Functional and cognitive sequelae represent a major source of long-term disability among survivors of severe seizure disorders. Posttraumatic epilepsy following severe traumatic brain injury is associated with particularly poor functional outcomes, with higher rates of severe disability and vegetative states compared with patients who do not develop epilepsy after trauma [39]. In a similar manner, survivors of cryptogenic new-onset refractory status epilepticus frequently face substantial vocational, cognitive, and psychiatric challenges. Many develop drug-resistant epilepsy and remain functionally impaired, reinforcing the

profound and persistent burden imposed by refractory seizure syndromes on patients and healthcare systems alike [35].

Multidisciplinary Management and Future Perspectives

Effective management of refractory seizures relies heavily on the coordinated efforts of multidisciplinary teams that integrate expertise from emergency medicine, neurology, and critical care. Collaboration among these specialties enables comprehensive patient care that spans initial stabilization, diagnostic evaluation, therapeutic escalation, and ongoing management in complex cases. Such coordinated approaches allow each discipline to contribute its specialized perspective, facilitating more efficient resource utilization and contributing to improved patient outcomes in the acute care setting [40, 41].

Within this collaborative framework, the use of standardized management protocols has emerged as an important strategy to optimize care delivery. Goal-directed care bundles and structured protocols have demonstrated benefits in neurological emergencies, including seizure management, by reducing treatment variability and promoting timely, evidence-based interventions [40]. Clinical pathways provide clear and actionable guidance for therapeutic decision-making, helping clinicians navigate complex scenarios and minimize delays in care that may adversely affect neurological outcomes [41].

Despite their potential advantages, the widespread implementation of standardized protocols remains challenging. Variability in available resources across emergency departments, differences in institutional infrastructure, and the need for ongoing training and adherence represent significant barriers to consistent application. Furthermore, the current evidence base comparing specific protocolized approaches with more generalized management strategies is still evolving, underscoring the need for additional research to define optimal practices and establish robust, evidence-driven standards of care [40].

Looking forward, future research efforts should prioritize the refinement of existing protocols to address these limitations and enhance their applicability across diverse healthcare environments. In parallel, strengthening the integration of multidisciplinary teams through improved communication strategies and the use of technological tools may further enhance coordination and efficiency in the management of refractory seizures, ultimately contributing to better clinical outcomes [40, 42].

Conclusions

Refractory seizures arise from progressive neurobiological mechanisms that promote pharmacoresistance and neuronal injury, underscoring the critical importance of early, mechanism-informed therapeutic intervention.

The heterogeneous etiologies and clinical presentations of refractory seizures require a structured and timely diagnostic approach in the emergency department, integrating rapid stabilization, targeted investigations, and early electroencephalographic assessment.

Patient outcomes are largely determined by prompt seizure control, adherence to evidence-based treatment sequences, and coordinated multidisciplinary management, highlighting the need for standardized protocols and ongoing research to improve prognosis.

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