Chapter 2
Management of Seizures in the ICU

2.1 Introduction

Seizures are common neurological emergencies in the intensive care unit (ICU), requiring immediate recognition and intervention to prevent significant morbidity and mortality. Status epilepticus (SE) is a particularly severe condition defined by the International League Against Epilepsy (ILAE) as a seizure lasting longer than five minutes (t_1), beyond which normal seizure termination mechanisms are unlikely, necessitating prompt treatment. Prolonged seizures beyond 30 minutes (t_2) can lead to long-term neurological consequences, including neuronal injury and death [1, 2].

SE is further classified into convulsive and nonconvulsive types, each requiring specific diagnostic and management strategies. Early and effective intervention is crucial, especially within the first five minutes of seizure onset to improve outcomes and reduce the risk of progression to refractory or super-refractory SE.

This chapter provides an evidence-based, systematic approach to the management of seizures in the ICU, emphasizing rapid stabilization, timely pharmacologic interventions, diagnostic evaluations, and consideration of underlying causes, including special populations and emerging therapies (Ref. Algorithm 2.1).

2.2 Definition and Classification of Status Epilepticus

- **Status Epilepticus (SE):** Seizure activity lasting longer than five minutes or recurrent seizures without recovery of consciousness between episodes.
- **Refractory Status Epilepticus (RSE):** SE that persists despite administration of adequate doses of at least two appropriate antiseizure medications, typically a benzodiazepine and a second-line agent.

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- **Super-Refractory Status Epilepticus (SRSE):** SE that continues or recurs 24 hours or more after the onset of anesthesia, including cases where SE recurs upon the reduction or withdrawal of anesthesia [3].

2.3 Initial Assessment and Stabilization (0–5 Min)

The first priority is rapid stabilization to ensure airway patency, adequate breathing, and circulation while initiating a focused neurologic assessment. Early treatment initiation within the first five minutes (t_1) is critical to prevent progression to prolonged SE [2].

1. **Airway, Breathing, Circulation (ABCs)**
   - Airway: Ensure airway patency. If the patient is unconscious or has impaired protective reflexes, consider endotracheal intubation to prevent aspiration. Position the patient in the lateral decubitus position if possible.
   - Breathing: Administer supplemental oxygen to maintain saturation above 94%. Monitor respiratory rate and effort continuously. Be prepared to provide ventilatory support in cases of hypoventilation or apnea.
   - Circulation: Establish intravenous (IV) access promptly for medication administration. Monitor blood pressure and heart rate continuously. Treat hypotension with isotonic fluids and vasopressors if necessary.
2. **Neurologic Assessment**
   Conduct a rapid neurologic examination:
   - Level of Consciousness: Assess using the Glasgow Coma Scale (GCS).
   - Pupillary Response: Evaluate for size, symmetry, and reactivity.
   - Motor Function: Check for focal neurological deficits or lateralizing signs.
   - Seizure Documentation: Note onset time, duration, type (convulsive vs. nonconvulsive), and characteristics to guide management and assess treatment response.
3. **Laboratory and Diagnostic Workup**
   - Blood Glucose: Check immediately; correct hypoglycemia with 50% dextrose IV if present.
   - Electrolytes: Obtain serum levels of sodium, calcium, and magnesium.
   - Renal and Liver Function Tests: Assess for metabolic derangements.
   - Complete Blood Count (CBC): Evaluate for infection or anemia.
   - Toxicology Screen: Consider in suspected overdose or poisoning.
   - Antiepileptic Drug Levels: If the patient is on maintenance therapy, check serum levels.
   - Continuous Monitoring: Initiate cardiac monitoring and obtain an electrocardiogram (ECG) to detect arrhythmias or conduction abnormalities [4].

4. **Diagnostic Evaluation**

- Electroencephalography (EEG): Early EEG is essential, especially to detect nonconvulsive SE, which may not have overt clinical signs but can cause significant morbidity.
- Neuroimaging: Obtain emergent brain imaging (CT or MRI) to identify structural causes such as hemorrhage, infarction, tumor, or cerebral edema.

5. **Consideration of Special Populations**

- Older Adults: Higher risk of SE due to comorbidities like stroke or neurodegenerative diseases. Adjust medication doses to avoid adverse effects and consider drug interactions.
- Pregnant Women: Be cautious with teratogenic medications like valproic acid. Balance maternal and fetal risks when selecting antiseizure medications. (Table 2.1).

Table 2.1 Pharmacological management of seizures: dosing, routes, and considerations for clinical practice

Drug	Dose	Route	Maximum dose	Considerations/ contraindications
Benzodiazepines				
Lorazepam	0.1 mg/kg	IV	Up to 4 mg/dose, may repeat once after 5–10 min	Preferred for initial control, monitor for respiratory depression
Diazepam	0.15–0.2 mg/kg	IV	Up to 10 mg/ dose, may repeat once	Quick onset but shorter duration, monitor for hypotension
Midazolam	0.2 mg/kg	IM, buccal intranasal	Up to 10 mg, single dose	Suitable for non-IV routes, watch for respiratory effects
Clonazepam	0.01–0.02 mg/ kg	IV	Up to 1 mg	For adjunctive use, caution in respiratory and liver diseases
Second-line anticonvulsants				
Phenytoin	20 mg/kg	IV	Max. Rate 50 mg/min	Avoid in cardiac arrhythmias, monitor for hypotension
Fosphenytoin	20 mg PE/kg	IV	Max. Rate 150 mg PE/min	Converted to phenytoin, safer for veins, same considerations
Valproic acid	40 mg/kg	IV	Up to 3000 mg	Caution in liver disease, can cause hyperammonemia
Levetiracetam	60 mg/kg	IV	Up to 4500 mg	Few drug interactions, adjust dose in renal impairment

(continued)

Table 2.1 (continued)

Drug	Dose	Route	Maximum dose	Considerations/ contraindications
Phenobarbital	15–20 mg/kg	IV	Up to 1000 mg	Long-acting, monitor for sedation and respiratory depression
Third-line anticonvulsants and sedatives				
Propofol	1–2 mg/kg loading	IV	Maintenance 2–10 mg/kg/hr	Risk of propofol infusion syndrome (PRIS), monitor hemodynamics
Ketamine	1–2 mg/kg loading	IV	Maintenance 1–2 mg/kg/hr	Useful for refractory cases, monitor for psychomimetic effects
Thiopental	3–5 mg/kg loading	IV	Maintenance 0.5–3 mg/kg/hr	Barbiturate, monitor for hypotension and prolonged sedation
Alternative antiepileptic drugs (AEDs)				
Lacosamide	200–400 mg loading	IV	Up to 600 mg	Avoid in severe cardiac conditions (e.g., AV block)
Topiramate	200 mg loading	Oral, NG tube	Up to 600 mg/kg	Slow titration needed, monitor for metabolic acidosis
Supportive and adjunctive therapies				
Magnesium sulfate	2–4 g loading	IV	Maintenance 1–2 g/hr	For seizures due to eclampsia, monitor for respiratory depression
Thiamine	100 mg	IV	–	For alcohol-related SE, give before glucose to prevent Wernicke's encephalopathy.
Dextrose	500 ml of 50% solution	IV	–	To correct hypoglycemia, monitor blood glucose levels

2.4 Initial Medication Administration (5–20 Min)

If seizure activity persists beyond five minutes, initiate pharmacologic treatment promptly with first-line agents. Early administration of benzodiazepines significantly improves outcomes [5].

1. **Benzodiazepines (First-Line Therapy)**
   - Intravenous Lorazepam: 0.1 mg/kg IV (maximum 4 mg per dose). Preferred for its longer duration of action. May repeat once after 5–10 min if seizures persist.
   - Intravenous Diazepam: 0.15–0.2 mg/kg IV (maximum 10 mg per dose). Rapid onset but shorter duration; may require repeated dosing.
   - Intramuscular Midazolam: 10 mg IM for adults if IV access is unavailable. Alternative routes include intranasal or buccal administration.
   - Reassessment: Monitor for seizure cessation and adverse effects. If seizures have stopped, proceed to maintenance therapy. If seizures continue, advance to second-line agents.

2.5 Second-Line Anticonvulsants (20–60 Min)

Administer second-line antiepileptic drugs if seizures are refractory to benzodiazepines. Choice of agent depends on availability, patient-specific factors, and contraindications.

1. Intravenous Levetiracetam
   - Levetiracetam: 60 mg/kg IV (maximum 4500 mg) over 15 min. Increasingly favored due to rapid administration, minimal drug interactions, and few side effects.
2. Intravenous Valproic Acid
   - Valproic Acid: 40 mg/kg IV (up to 3000 mg) over 10–15 min. Effective with minimal hemodynamic effects. Contraindicated in pregnant women and women of childbearing potential not using effective contraception due to teratogenicity.
3. Intravenous Phenytoin or Fosphenytoin
   - Fosphenytoin: 20 mg phenytoin equivalents (PE)/kg IV (maximum rate 150 mg PE/min). Preferred over phenytoin for safer infusion profile.
   - Phenytoin: 20 mg/kg IV (maximum rate 50 mg/min). Requires cardiac monitoring due to risk of hypotension and arrhythmias.
4. Intravenous Phenobarbital
   - Phenobarbital: 15–20 mg/kg IV (rate of 50–100 mg/min). Effective but may cause significant sedation and respiratory depression.

Check Table 2.2 for details on doses and other considerations.

Table 2.2 Seizure management in pregnancy: therapeutic approaches and special considerations

Aspect	Considerations for pregnant women
Medication selection	Prefer drugs with low teratogenic risk (e.g., Levetiracetam, lamotrigine) Avoid valproic acid and phenytoin if possible due to teratogenic risks. Use magnesium sulfate specifically for eclampsia-related seizures
Dosage adjustments	Adjust for altered pharmacokinetics (increased clearance, volume of distribution) Regularly monitor and adjust drug levels to maintain efficacy and safety
Monitoring	Continuous fetal monitoring to assess Well-being Monitor maternal drug levels more frequently to avoid fetal exposure to high doses
Supportive care	Position in left lateral decubitus to improve uteroplacental blood flow Avoid supine position to prevent compression of the inferior vena cava
Underlying causes	Manage pregnancy-specific conditions like eclampsia with magnesium sulfate Consider and treat pregnancy-related complications promptly
Delivery planning	Seizures alone are not an automatic indication for cesarean section Coordinate with obstetric care to plan for high-risk delivery if needed
Postpartum care	Adjust anticonvulsant therapy as pharmacokinetics change post-delivery Assess the safety of breastfeeding with current medications
Counseling and education	Provide detailed counseling on seizure management during pregnancy and postpartum Discuss the safety of anticonvulsants during breastfeeding

Reassessment: Monitor for seizure control and adverse effects. If seizures persist after adequate dosing of two appropriate medications (benzodiazepine and a second-line agent), the patient is considered to have refractory status epilepticus (RSE).

2.6 Third-Line Anticonvulsants and Sedatives (Beyond 60 Min)

In RSE, more aggressive treatment is required, including the use of anesthetic agents and advanced monitoring [5].

1. Refractory Status Epilepticus (RSE).
   - Definition: Seizures persisting after administration of a benzodiazepine and a second-line antiepileptic drug.
   - Management: Initiate continuous infusion of anesthetic agents and continuous EEG monitoring.
2. Anesthetic Agents
   Intravenous Midazolam
   - Dosage: Loading dose of 0.2 mg/kg IV, followed by maintenance infusion of 0.05–2 mg/kg/hr. Titrate to burst suppression or seizure cessation on EEG.

- Intravenous Propofol
- Dosage: Loading dose of 1–2 mg/kg IV, maintenance infusion of 2–10 mg/kg/hr. Monitor for hypotension and propofol infusion syndrome, especially with prolonged use.
- Intravenous Ketamine
- Dosage: Loading dose of 1–3 mg/kg IV, maintenance infusion of 1–5 mg/kg/hr. NMDA receptor antagonist beneficial in refractory cases, particularly when GABAergic agents fail [6, 7].
- Intravenous Thiopental/Pentobarbital
- Dosage: Loading dose of 3–5 mg/kg IV, maintenance infusion of 0.5–3 mg/kg/hr. Requires intensive hemodynamic and respiratory support due to profound sedation and hypotension.

3. **Super-Refractory Status Epilepticus (SRSE)** [6]

- Definition: SE that continues or recurs 24 hours or more after the onset of anesthetic therapy.
- Management: Consider additional therapies such as:
- Hypothermia: Therapeutic hypothermia may reduce metabolic demand and neuronal injury [8].
- Ketogenic Diet: High-fat, low-carbohydrate diet shown to reduce seizure frequency in some cases [9].
- Immunotherapy: In cases of suspected autoimmune encephalitis, consider steroids, intravenous immunoglobulin (IVIG), or plasmapheresis [10].

4. **Complications and Prognosis**

- Neuroinflammatory Conditions: Autoimmune encephalitis is a recognized cause of RSE and SRSE. Early identification and immunotherapy are crucial.
- Mortality: SRSE is associated with high mortality rates; early aggressive management may improve outcomes.

EEG Monitoring and Diagnostic Considerations

1. Continuous EEG Monitoring

- Purpose: Detect ongoing seizure activity, especially nonconvulsive seizures masked by sedation.
- Guidance: Adjust therapy based on EEG findings, aiming for seizure cessation or burst suppression patterns.

2. Neuroimaging

- CT/MRI: Essential to identify structural lesions, hemorrhages, infarctions, tumors, or cerebral edema contributing to seizures.

3. Additional Diagnostic Tests

- Lumbar Puncture: Perform if infection or autoimmune etiology is suspected.
- Autoimmune Panels: Consider testing for neuronal antibodies in cases of unexplained RSE or SRSE.

2.7 Maintenance Antiepileptics

After seizure control, transition to maintenance antiepileptic therapy to prevent recurrence. The choice depends on the underlying etiology, patient factors, and potential side effects [11].

Considerations

- Reversible Causes: If SE is due to reversible metabolic derangements, short-term therapy may suffice.
- Structural or Chronic Epilepsy: Patients with underlying brain abnormalities or chronic epilepsy may require long-term therapy.
- Drug Interactions: Consider potential interactions with other medications, especially in older adults with polypharmacy.

Common Maintenance AEDs

- Levetiracetam: Favorable side effect profile and minimal interactions. Dose adjustment may be needed in renal impairment.
- Phenytoin/Fosphenytoin: Requires monitoring of serum levels and attention to drug interactions.
- Valproic Acid: Broad-spectrum efficacy; avoid in women of childbearing potential unless no alternatives.
- Phenobarbital: Effective but associated with sedation and cognitive impairment.

Long-Term Management and Prognosis

1. Recurrence Risks
    - Structural Abnormalities: Higher risk of seizure recurrence in patients with stroke, tumors, or traumatic brain injuries [12].
    - Chronic Epilepsy: May require adjustment of maintenance therapy and close follow-up.
2. Special Populations
    - Older Adults: Monitor for cognitive side effects and adjust dosages accordingly.
    - Women of Childbearing Potential: Avoid teratogenic medications; provide counseling on contraception.
3. Rehabilitation and Support
    - Multidisciplinary Approach: Involve neurology, rehabilitation services, and social support for optimal recovery.
    - Education: Educate patients and families about seizure precautions, medication adherence, and follow-up care [13].

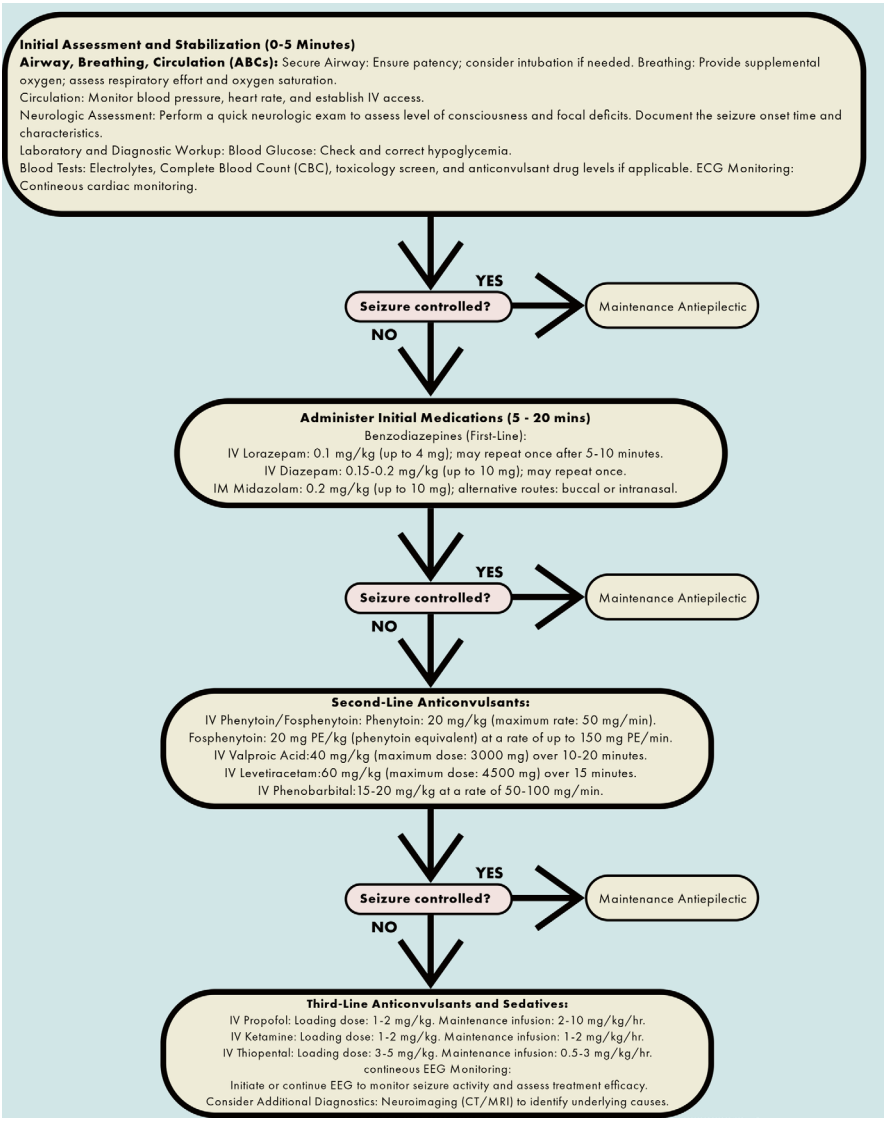
2.8 Conclusion

The management of seizures in the ICU is a time-sensitive, systematic process focusing on rapid stabilization, seizure termination, and prevention of complications. Early intervention within the first five minutes is critical to prevent progression to refractory stages. The use of benzodiazepines as first-line agents, followed by appropriate second-line antiepileptics, is supported by current evidence. In refractory cases, anesthetic agents and advanced therapies may be necessary.

Identifying and addressing underlying etiologies, including metabolic disturbances, structural lesions, infections, and autoimmune conditions, are essential components of care. Continuous EEG monitoring aids in guiding therapy, especially in nonconvulsive and refractory cases. Transitioning to appropriate maintenance therapy and considering patient-specific factors, such as age and comorbidities, are crucial for long-term management and improving patient outcomes.

Early and decisive intervention, coupled with comprehensive care, is paramount in preventing the severe consequences associated with prolonged seizure activity.

Algorithm 2.1: Management of seizures in the ICU



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