

## Febrile Seizure and New Onset Afebrile Seizure

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### **Definition:**

Febrile seizures usually occur between three months and six years of age, associated with fever but without evidence of intracranial infection or defined cause. Febrile seizures are further divided into simple or complex, based on clinical features. Simple febrile seizures are the most common type, characterized by generalized seizures, last less than 15 minutes, and do not recur in a 24-hour period. Complex febrile seizures are characterized by episodes with a focal onset, last longer than 15 minutes, or occur more than once in 24-hours.<sup>(1-4)</sup>

### **Etiology:**

Nearly any insult to the cerebral cortex can cause a seizure, most are self-limited, and resolve with the inciting process. Febrile seizures are the most common seizure disorder in childhood, affecting 2% to 5% of children between the ages of three months and six years. Seizures can arise from any site in the brain but typically are localized to the neocortical gray matter and the limbic system, particularly the hippocampus and amygdala.

### **Genetic predisposition:**

- Monozygotic twins have a 70% concordance for febrile seizures, versus 20% in dizygotic twins.
- Having a first degree relative (sibling or parent) with febrile seizures increases the risk 4-5 times that of the general population.
- Four distinct loci have been nominated as candidate genes and multi-gene inheritance is suspected.

Various specific infectious agents have been more strongly associated with a risk of febrile seizures, particularly HHV-6.

### **Differential Diagnosis:**

Most concerning possibility is meningitis/encephalitis as cause of seizure in context of febrile illness

Children with a seizure predisposition might be triggered by an intercurrent illness, especially with fever, such as children with pre-existing neurological injury, autistic children, previously established epilepsy patients, and VP shunt patients

### **Guideline Inclusion Criteria:**

- Greater than 3 month of age
- Clinical findings of convulsive or nonconvulsive seizures

### **Guideline Exclusion Criteria:**

- Newborn to 3 months of age
- Greater than 18 years of age
- Prior neurological insult

### **Diagnostic Evaluation:**

#### **History: Assess for**

- Seizure onset
- Known seizure disorder
- Ingestion
- Fever
- Signs of serious infection
- Medications
  - Received prior to presentation (type, dose, dosage, route)
  - Current anticonvulsant medications
  - Use of psychopharmacologic medications
  - Toxic/subtherapeutic anticonvulsant levels
  - Nonadherence and/or recent change
- Vagus Nerve Stimulation
- Metabolic abnormalities
- Trauma
- Dietary therapies

#### **Physical Examination:**

- Careful examination for source of fever, especially ear, throat and lung exam
- Check for meningeal signs
- Exam for specific rashes
- Mental status assessment (after allowing post-ictal recovery) to look for signs of acute encephalopathy possibly indicative of meningitis or encephalitis
- Motor, reflex and gait assessment for focal motor deficit and/or ataxia

Seizure Classification: <sup>(13)</sup>

**Simple febrile seizures:**

- Age 6 months – 5 years (lower limit of age defined by clinical practice guidelines)
- Generalized convulsion (tonic-clonic)
- Duration <15 minutes
- No recurrence within 24 hours
- No evidence of acute symptomatic etiology (e.g. acute CNS infection, trauma, etc)
- Although neurologically impaired children qualify for a diagnosis of febrile seizures, the clinical practice guidelines specifically exclude this subpopulation from their recommendations

**Complex Febrile seizures:**

- Seizure behavior differs from GTC (e.g. focal onset, asymmetry, staring, collapse, etc)
- Duration > 15 minutes (prolonged)
- Recurrence within 24 hours

**Partial/Focal/Localization related:**

Initial Clinical or EEG changes originating within networks limited to a region of or one hemisphere

- **Focal** – Description of the seizure semiology without attempting to fit it into a specific category. Level of alertness should be a part of the description and documentation.

**Generalized:**

Both hemispheres involved at seizure onset (originating within and rapidly involving networks of both hemispheres)

- **Tonic – Clonic**
- **Absence**
  1. Typical
  2. Atypical
  3. Absence with special features
    - Myoclonic absence
    - Eyelid myoclonia
- **Myoclonic**
  1. Myoclonic
  2. Myoclonic atonic
  3. Myoclonic tonic
- **Clonic**
- **Tonic**
- **Atonic**

**Unknown:**

Unclear if Focal (Partial, Localization related) or Generalized

- **Epileptic Spasms** (Spasms may outlast or begin after infancy)

**Electroclinical Syndromes and other Epilepsies:**  
(Epilepsy and Epilepsy Syndromes)

Electroclinical Syndromes: A complex of clinical signs and symptoms that define a specific and recognizable clinical disorder.

Other Epilepsies are recognized based on clinical features and investigative findings (i.e. mesial temporal lobe epilepsy). These are sometimes coined **Constellations**.

Seizure type(s) are dependent on the specific Epilepsy Syndrome identified and may be:

1. Exclusively Focal
2. Exclusively Generalized
3. A mixture of both generalized and focal

- **Genetic** – Results from a genetic defect (Known or presumed based on a complex of specific clinical and investigative findings). i.e. **Juvenile Myoclonic Epilepsy**
- **Structural/Metabolic** – A specific associated structural or metabolic condition with a direct link to the Epilepsy or Epilepsy syndrome described.
- **Unknown** – The underlying cause is unknown. (No structural, Metabolic, or Genetic cause have been identified.)

Critical Points of Evidence

**Evidence Supports**

Use of lumbar puncture for febrile children with signs and symptoms of meningitis or encephalitis

**Evidence Lacking/Inconclusive**

Use of lumbar puncture for febrile children 6 to 12 months of age with deficient or unknown immunization history

Use of lumbar puncture for febrile children pretreated with antibiotics

**Evidence Against**

Use of electroencephalogram (EEG) in neurologically healthy children with simple febrile seizure

Use of neuroimaging in children with simple febrile seizure

**Practice Recommendations & Clinical Management**

*(for full recommendations see attached pathway and addendums)*

**Laboratory Testing**

Lumbar puncture should be performed in children with clinical signs or symptoms concerning for meningitis. <sup>(5)</sup>  
*(Strong recommendation; High quality evidence.)*

Lumbar puncture should be considered for infants between 6 and 12 months of age who present with a seizure and a fever when considered deficient or unknown immunization history. <sup>(5)</sup>  
*(Weak recommendation; Low quality evidence.)*

Lumbar puncture should be considered for any child who presents with seizure and fever and is pretreated with antibiotics. <sup>(5)</sup>  
*(Weak recommendation; Low quality evidence.)*

Additional laboratory tests may be indicated depending on clinical scenario. <sup>(5)</sup>  
*(Strong recommendation; Moderate quality evidence.)*

Consider Comprehensive Metabolic Panel in children of any age who present with afebrile seizures and any of the following:

- Dehydration
- Vomiting
- Diarrhea
- Persistent altered mental status

Consider toxicology screen in children of any age who present with afebrile seizures and suspected drug use or persistent altered mental status.

**Imaging**

Neuroimaging with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is not indicated for children with simple febrile seizures. <sup>(5,6,8)</sup>  
*(Strong recommendation; Moderate quality evidence.)*

Neuroimaging with CT or MRI of the brain w/wo contrast should be considered for children with complex febrile seizures presenting with focal motor onset, focal deficit, or abnormal focal exam. <sup>(6,8,9)</sup>  
*(Strong recommendation; Moderate quality evidence.)*

Neuroimaging with CT should be considered for children with complex febrile seizures presenting with focal motor onset, focal deficit, or abnormal focal exam **only** if emergent concerns and MRI is not available.

Neuroimaging with urgent MRI or CT should be considered in children of any age with afebrile seizure and any of the following:  
(Refer for consideration of outpatient brain MRI if none of the factors below apply.)

- Focal seizure
- Persistent encephalopathy
- Focal exam
- < 6 months of age
- Closed head injury
- Recent shunt revision
- Neurocutaneous disease
- Sickle cell disease
- AIDS
- Malignancy
- Travel to location endemic for cystercicosis

**Diagnosis**

Electroencephalogram (EEG) should not be performed in the evaluation of a neurologically healthy child with a simple febrile seizure. <sup>(5)</sup>  
*(Strong recommendation; Moderate quality evidence.)*

EEG should be performed in a child with complex febrile seizure presenting with complex focal motor seizure, abnormal focal exam, and persistent encephalopathy in house.

EEG should be performed in children of any age who presents with suspected, probable, or definite afebrile seizure, but can be performed in outpatient setting if patient returns to baseline.

**Consults/Referrals:**

All patients with afebrile seizures should be referred to neurology.

Febrile seizures should only be considered for referral if recurrent, persistent encephalopathy, or abnormal focal exam.

### Patient Disposition

#### **Admission Criteria**

##### Simple Febrile Seizure

Only indicated in ill appearing child, extreme parental anxiety or social concerns.

##### Complex Febrile Seizure

Admit for any of the following:

- Persistent encephalopathy
- Focal exam
- Ill-appearing

Consider observation for any of the following:

- Recurrence within 24 hours
- Extreme parental anxiety or social concerns

Consider outpatient neurology referral:

- Multiple recurrent febrile seizures (in different illnesses)
- Focal seizures without focal deficits
- Parental anxiety

#### **Prevention**

No routine treatment is recommended for prevention of recurrent simple febrile seizures in new onset patients.

Diastat should be prescribed for recurrent febrile seizures.

Prolonged febrile seizure patients should be prescribed Diastat for home use in the event of recurrence with prolonged febrile seizure of > 5 minutes duration.

Scheduled diazepam during febrile illnesses (0.33 mg/kg Q8 hours) is the recommended chronic anti-epileptic drug treatment for secondary prevention in patients with multiple recurrent febrile seizures.

##### Afebrile Seizure

Admit for any of the following:

- Recurrent seizures at onset
- Persistent encephalopathy
- Focal deficit
- Parental anxiety
- Concerns regarding follow-up

#### **Discharge Criteria**

Seizure cessation

Appropriate mental status; return to baseline mental status

Appropriate support system (e.g. primary care physician, caregiver/family)

#### **Follow-Up Care**

Children diagnosed with simple febrile seizures should follow up with their PCP

Children with referral should follow up with a Neurologist within 14 days.

#### **Addendums**

1. DCMC Seizure Diagnostic Evaluation
2. DCMC Status Epilepticus Acute Care & IMC Pathway
3. DCMC Seizure Clusters Acute Care & IMC Pathway

#### **Outcome Measures**

1. Readmission rate to the Emergency Department
2. Inpatient average length of stay
3. Time to outpatient Neurology clinic follow-up
4. Utilization of Computed Tomography
5. Utilization of Magnetic Resonance Imaging
6. Utilization of Electroencephalogram

# Seizure Diagnostic Evaluation

## Evidence Based Outcome Center

	Afebrile Seizure (New Onset)	Simple Febrile Seizure	Complex Febrile Seizure
Lumbar Puncture	<p>Not Indicated</p> <p><b>Exclusion criteria:</b> Patients less than 6 months of age</p>	<p><u>A lumbar puncture should be performed:</u></p> <ul style="list-style-type: none"> <li>Following a simple febrile seizure if the child is ill-appearing or if there are clinical signs or symptoms of concern</li> <li>Persistent altered mental status or neuro deficit</li> </ul> <p><u>A lumbar puncture should be considered:</u></p> <ul style="list-style-type: none"> <li>Child 6 to 12 months of age who is deficient in immunizations or for whom immunization status is unknown</li> <li>Child of any age who has been pretreated with antibiotics</li> </ul>	<p><u>A lumbar puncture should be performed:</u></p> <ul style="list-style-type: none"> <li>Following a complex febrile seizure if the child is ill-appearing or if there are clinical signs or symptoms of concern</li> <li>Persistent altered mental status or neuro deficit</li> </ul> <p><u>A lumbar puncture should be considered:</u></p> <ul style="list-style-type: none"> <li>Child 6 to 12 months of age who is deficient in immunizations or for whom immunization status is unknown</li> <li>Child of any age who has been pretreated with antibiotics</li> </ul>
Laboratory	<p><u>Consider CMP for any of the following:</u></p> <ul style="list-style-type: none"> <li>Dehydration</li> <li>Vomiting</li> <li>Diarrhea</li> <li>Persistent altered mental status</li> </ul> <p><u>Consider toxicology screen for any of the following:</u></p> <ul style="list-style-type: none"> <li>High risk population</li> <li>Persistent altered mental status</li> </ul>	<p>Patient's history and clinical condition will guide laboratory screening.</p>	<p>Patient's history and clinical condition will guide laboratory screening.</p>
EEG	<p><b>OUTPATIENT</b></p> <p>Obtain in all cases of suspected, probable or definite seizure.</p> <p>Neurology follow-up within 1 week.</p>	<p>Persistent encephalopathy</p>	<p><b>Not indicated if only prolonged or recurrent within 24 hours.</b></p> <p><u>Consider for focal motor seizure, persistent encephalopathy or abnormal focal exam.</u></p>
Neuroimaging	<p><u>Consider urgent MRI (if available) or CT for any of the following:</u></p> <ul style="list-style-type: none"> <li>Focal seizure</li> <li>Persistent encephalopathy</li> <li>Focal exam</li> <li>&lt; 6 months of age</li> <li>Closed head injury</li> <li>Recent shunt revision</li> <li>Existing comorbidities that increase likelihood of seizure activity</li> <li>High index for focal lesion</li> </ul> <p><b>Refer for consideration of outpatient brain MRI if none of the above factors apply.</b></p>	<p>Not Indicated</p>	<p><u>Consider for focal motor seizure onset, focal deficit or abnormal focal exam:</u></p> <p>MRI of the brain w/wo contrast</p> <p>Obtain CT <b>only if</b> emergent concerns <b>and</b> MRI is not available.</p>
Admission	<p>Admit for any of the following:</p> <ul style="list-style-type: none"> <li>Recurrent seizures at onset</li> <li>Persistent encephalopathy</li> <li>Focal deficit</li> <li>Parental anxiety</li> <li>Concerns regarding follow-up</li> <li>High index of seizure suspicion for patients less than 6 months</li> <li>Anti-Epileptic Medications required for seizure cessation</li> </ul> <p><b>Contact Neurologist on call if STAT EEG read is required.</b></p>	<p>Only indicated in ill appearing child, extreme parental anxiety or social concerns, or anti-epileptic medications required for seizure cessation.</p>	<p>Admit for any of the following:</p> <ul style="list-style-type: none"> <li>Persistent encephalopathy</li> <li>Focal exam</li> <li>Ill-appearing</li> </ul> <p><b>Contact Neurologist on call if STAT EEG read is required.</b></p> <p><u>Consider observation for any of the following:</u></p> <ul style="list-style-type: none"> <li>Recurrence within 24 hours</li> <li>Extreme parental anxiety or social concerns</li> <li>Anti-Epileptic Medications required for seizure cessation</li> </ul> <p><u>Consider outpatient neurology referral:</u></p> <ul style="list-style-type: none"> <li>Multiple recurrent febrile seizures (in different illnesses)</li> <li>Focal seizures without focal deficits</li> <li>Parental anxiety</li> </ul>
<p><b>For seizure exacerbation in known seizure patient please consult neurology.</b></p>			

**Inclusion Criteria**

- Age  $\geq$  3 months
- Convulsive seizure lasting  $\geq$  3 minutes
- Non-convulsive seizure lasting  $\geq$  3 minutes

**Exclusion Criteria**

- Age < than 3 months

**Step 1: First Dose Benzodiazepine**

If patient has received 2 or more doses of benzodiazepines before arrival to the hospital, move to second dose of benzodiazepine medication in the protocol

**IV Access:**

**Lorazepam**- 0.1 mg/kg/dose IV (max: 4 mg/dose)  
Dilute medication 1:1 with Normal Saline – IV push over 30 seconds

OR

**No IV Access:** Choose one of the following AND establish IV access

- Midazolam** – Use IV formulation
- Intranasal: 0.3 mg/kg (max: 10 mg/dose)  
Use 5 mg/mL concentration, if  $\geq$  1 mL give half in each nare
  - Buccal: 0.3 mg/kg (max: 10 mg/dose)
- Diazepam**- 0.5 mg/kg/dose per rectum (max: 20 mg/dose)

Prepare next step medication

Seizure continues 3 minutes more

YES

NO

**Step 2: Second Dose Benzodiazepine**

**Consult Neurologist**  
**Call for STAT continuous EEG**

**IV Access: Administer or Repeat**

**Lorazepam**- 0.1 mg/kg/dose IV (max: 4 mg/dose)

OR

**No IV Access:** Repeat one of the following AND establish IV access

- Midazolam** – Use IV formulation intranasal or buccal
- Diazepam**- 0.5 mg/kg/dose per rectum

Prepare next step medication

Seizure continues 3 minutes more

YES

NO

**Step 3: First Dose IV Anti-Epileptic Drug (AED)**

**CRT or Critical Care Consultation can be considered at this point**

**Primary:**

**Levetiracetam**- 30-60 mg/kg/dose IV (max: 3 g/dose)  
Infuse no faster than 5 mg/kg/min

**Other Medications to consider:**

- Fosphenytoin**- 20 mg/kg/dose IV with 1:1 Normal Saline or D5W  
Infuse no faster than 3 mg/kg/minute (max: 150 mg PE/min)
- Valproic Acid**- 20-40 mg/kg/dose IV (max: 2 g/dose)  
Infuse no faster than 10 mg/kg/min  
(For Valproic Acid- Do not use in patients with hepatic disorders or possible mitochondrial disorders)

Prepare next step medication

Seizure continues 10 minutes after infusion complete

YES

NO

**Step 4: Second Dose IV AED**

**CRT or Critical Care Consultation can be considered at this point**

**Primary:**

- Fosphenytoin**
- If not previously given: 20 mg/kg/dose IV  
If repeat dose: 5-10 mg/kg/dose IV  
Infuse no faster than 3 mg/kg/minute (max: 150 mg PE/min)

**Other Medications to consider:**

- Lacosamide**- 8-10 mg/kg IV infuse over 15 minutes
- Valproic Acid**- 20 mg/kg/dose IV (max: 2 g/dose)  
Infuse no faster than 10 mg/kg/min
- Phenobarbital**- 20 mg/kg IV (max 1 g/dose)  
Infuse no faster than 2 mg/kg/min (max: 60-100 mg/min)

Prepare next step medication

Seizure continues 10 minutes after infusion complete

YES

NO

Monitor blood pressure, electrocardiogram, and respiratory function  
Manage off Pathway

**Critical Care Management see next page**

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## Status Epilepticus: Critical Care Pathway

### Choose Midazolam or Pentobarbital for continuous infusion

#### Exclusion Criteria

Age < than 3 months

#### Midazolam (Preferred if not intubated)

1. **Midazolam** give 0.2 mg/kg IV bolus (max: 10 mg) followed by
2. **Midazolam** 0.2 mg/kg/hr IV continuous infusion
3. Establish a secure airway

If seizure persists >10 minutes after first Midazolam bolus:

1. Every 10 minutes, repeat Midazolam 0.2 mg/kg/dose IV bolus (max: 10 mg/dose) and
2. Increase Midazolam by 0.2 mg/kg/hr IV continuous infusion (max: 1.5 mg/kg/hr)

[Evidence suggests that if patient doesn't respond to 0.5 mg/kg/hr they are unlikely to respond to higher doses, consider moving to next agent]

**Consult neurology for titration goal to achieve seizure cessation, or until burst-suppression on EEG based on neurology recommendations, or until cardio-respiratory depression.**

If seizure persists on 1.5 mg/kg/hr for 10 min (total 70 min on Midazolam) max tolerated/allowed Midazolam infusion:

#### Pentobarbital

1. **Pentobarbital** 5-15 mg/kg IV bolus over 1-2 hours followed by
2. **Pentobarbital** IV infusion 1-3 mg/kg/hr IV (max: 5 mg/kg/hr) continuous infusion
3. Establish a secure airway

If not in burst suppression 1 hour after starting infusion:

1. Repeat bolus Pentobarbital 5 mg/kg IV over 1 hour and
2. Increase infusion by 1-2 mg/kg/hour

Maintain burst suppression with hourly boluses 5 mg/kg if needed over 1 hour

**Consult neurology for titration goal to achieve seizure cessation, or until burst-suppression on EEG based on neurology recommendations, or until cardio-respiratory depression.**

#### Ketamine

1. **Ketamine** 2-3 mg/kg IV bolus IV push over 60 seconds followed by
2. **Ketamine** 10 mcg/kg/min IV infusion

If seizure persists >10 min after first Ketamine bolus:

1. Every 10 minutes, repeat Ketamine bolus 1-2 mg/kg IV and
2. Increase Ketamine infusion by 5-10 mcg/kg/min to max dose 100 mcg/kg/min

#### Agents to consider for super refractory status epilepticus:

1. Ketogenic diet
2. Propofol [initial 1-2/mg/kg loading dose]
3. Anakinra [300mg subQ daily or See protocol for FIRES/autoimmune etiologies]
4. Verapamil [40mg/kg TID up to 120mg/kg TID]
5. High dose Topiramate via NG tube (start 5 mg/kg/day and increase by 5-10 mg/kg/day to max 25 mg/kg/day)

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