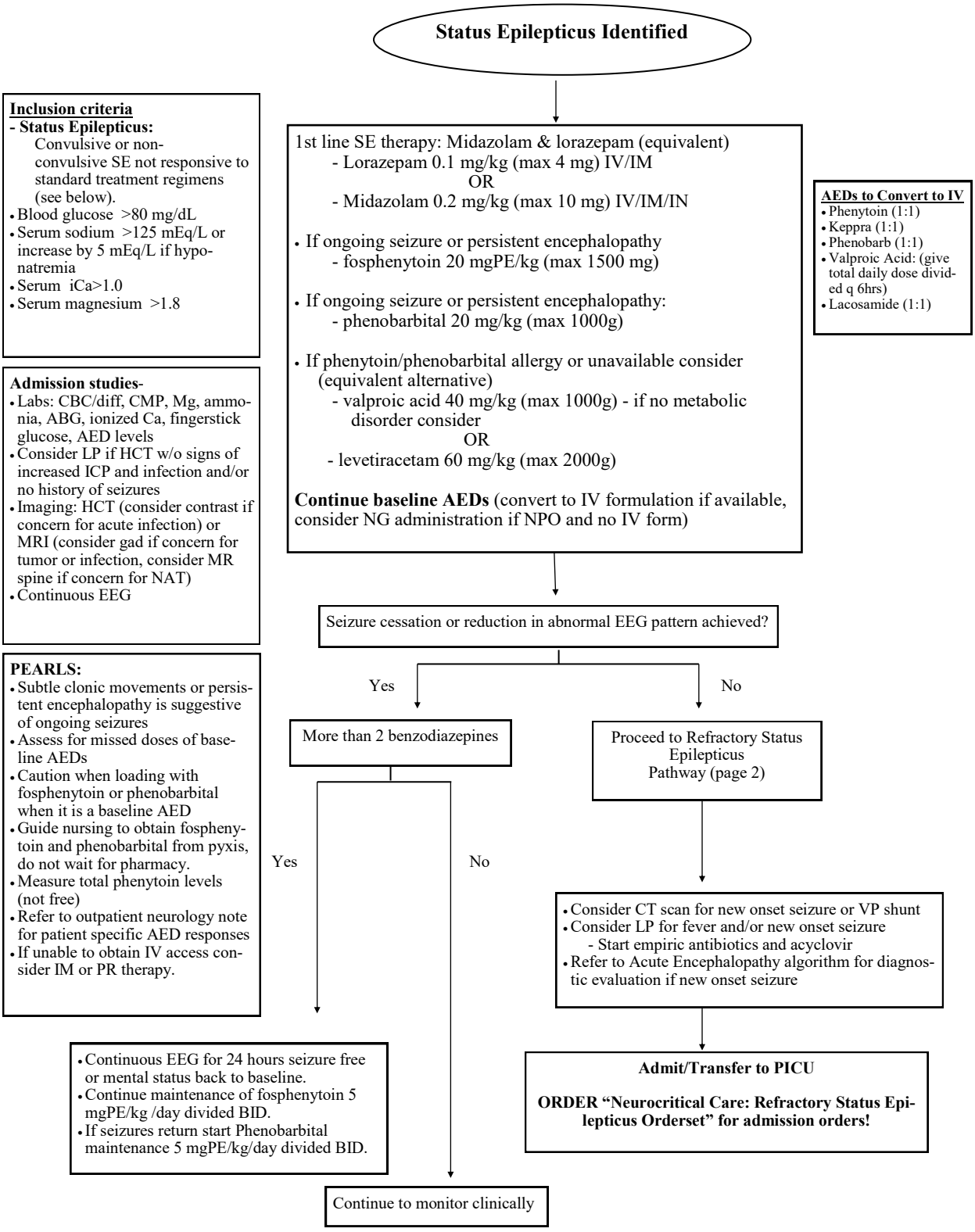
Status Epilepticus Pathway



Refractory Status Epilepticus Pathway

SUPPORTIVE CARE

- Aggressively manage sources of secondary insult
  - Fever
  - Hypotension
  - Hypoxemia
- Head of bed at 30° and midline
- Avoid hyponatremia, hypocalcemia, hypomagnesemia.
- Hourly neuro checks
- Continuous EEG (double distance after 48 hours)
- If on baseline AEDs are available, correction to therapeutic range

Respiratory
- Prophylactic intubation not indicated at lower versed infusion rates (≤0.4 mg/kg/hr)
- Monitor closely for impaired airway protection/ability to clear secretions
- Empiric intubation if goal EEG= burst suppression
- Maintain $PaCO_2$ 35-40 mmHg

Cardiovascular
- Versed and pentobarbital result in lowered SVR and depressed cardiac output
- Place arterial line if goal EEG= burst suppression or versed infusion rate ≥ 0.4 mg/kg/hr
- Maintain MAPs at 50%^{ile} for age
- Fluid bolus 20 mg/kg x2
- If still hypotensive
  - Dopamine 5-15 mcg/kg/min then
  - Epinephrine 0.1 mcg/kg/min if poor perfusion or
  - Norepinephrine 0.1 mcg/kg/min if well perfused

FEN/GI
- IVF fluids– 1st 48 hrs
  - Normal Saline
  - Add D5 if:
    - serum glucose <80 mg/dL
    - Age <6 mos
- Accu check glucose q 4-6 hrs while on IVF
- After 48 hrs consider TPN or enteral feeds
- Recommend TPN for patients in burst suppression
- Goal fluid balance 0 to +10 ml/kg/d
- Consider GI prophylaxis

Continued on next page

Refractory Status Epilepticus Identified

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Admit to PICU

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- Initiate midazolam infusion**. Goal: seizure cessation**
- Bolus 0.2 mg/kg, start infusion at 0.1 mg/kg/hour
- Increase infusion by 0.1 mg/kg/hr every 15 minutes until cessation of seizures (clinical and electrographic)
  -Max infusion dose 2 mg/kg/hour
- If little or no effect by 0.8 mg/kg/hr, consider pentobarbital infusion

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Seizure cessation or reduction in abnormal EEG pattern achieved?

Yes → **Maintain versed infusion x 48 hours**

If seizure occurs, up titrate to maintain cessation of seizures

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Once seizure cessation at least 24 hrs (prefer 48 hrs) begin weaning versed infusion, no faster than 0.05 mg/kg/hr q 6hrs

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Return of seizures?

No → Discontinue versed infusion; Adjust maintenance AEDs

Yes →
- Bolus versed equivalent to one hours worth of last effective dose and resume versed infusion at last effective dose
- Check levels of background AEDs
- Continue versed infusion for minimum of 24-48 hrs of goal seizure control
- Then resume wean at slower rate than previously attempted (ie– 0.05 mg/kg/hr every 12– 24 hrs)

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Return of seizures?

Yes → **Proceed to pentobarbital coma (page 3)**

No → Discontinue versed infusion; Adjust maintenance AEDs

No → **Proceed to pentobarbital coma (page 3)**

Refractory Status Epilepticus Pathway

Supportive Care (cont)

ID
- Refer to Acute Encephalopathy Algorithm if suspected infectious/inflammatory etiology
- Minimize risk for nosocomial infections
  - Daily assessment for need of foley or central access
  - Standard precautions against VAP
  - Absolute indications for central access:
    - + inotropic medications
    - + TPN
    - + goal EEG= Burst Suppression
  - Relative indications for central access:
    - Frequent lab draws
    - Difficulty obtaining peripheral IV acess
    - Versed infusion $\geq$ 0.4 mg/kg/hr

Heme
- DVT prophylaxis w/ venodynes if past puberty

Musculoskeletal/Skin
- Specialty care bed and close monitoring for decubitus ulcers
- Physical therapy consult for splints and range of motion exercises

ORDER pentobarbital infusion to achieve seizure cessation

- Discontinue versed infusion
- Order bolus of 10 mg/kg of pentobarbital. Give first 5 mg/kg over 15 minutes. Bolus additional 5 mg/kg over 15 minutes.

- If no burst suppression with interburst interval (IBI) of 5-7 seconds after first pentobarbital bolus.
  - Repeat boluses should **immediately** follow prior bolus until burst suppression is achieved
- Place order requesting bedside RN to notify MD prior to end of bolus infusion to review EEG pattern
- Review EEG q 15 min until burst suppression achieved
- Once burst suppressed, start infusion at 1 mg/kg/hr
- Consider immune modulating therapies (e.g. IVIG)

- Titrate pentobarbital infusion to maintain BS with IBI of 5-7 seconds
- Increase infusion by 0.5 mg/kg/hr (max 3 mg/kg/hr) if IBI < 5 sec or seizure

- If IBI becomes too long, hold infusion until IBI is <20s, then resume infusion at dose 0.5 mg/kg/hr less than previous dose
- Continue burst suppression for minimum of 24 hrs
- Wean no faster than 0.5 mg/kg every 6hrs

Return of seizures upon weaning?

No

- Adjust maintenance AEDs
- For new onset seizure continue to explore diagnostic evaluation
- Consult PM&R

Yes

- Bolus pentobarbital 10 mg/kg
- Repeat bolus until 5-7 s burst suppression is achieved
- Resume pentobarbital infusion at last effective dose
- Continue burst suppression for min 24-48 hrs and then wean infusion no faster than 0.5 mg/kg q12-24 hrs
- Consider medications that may lower seizure threshold

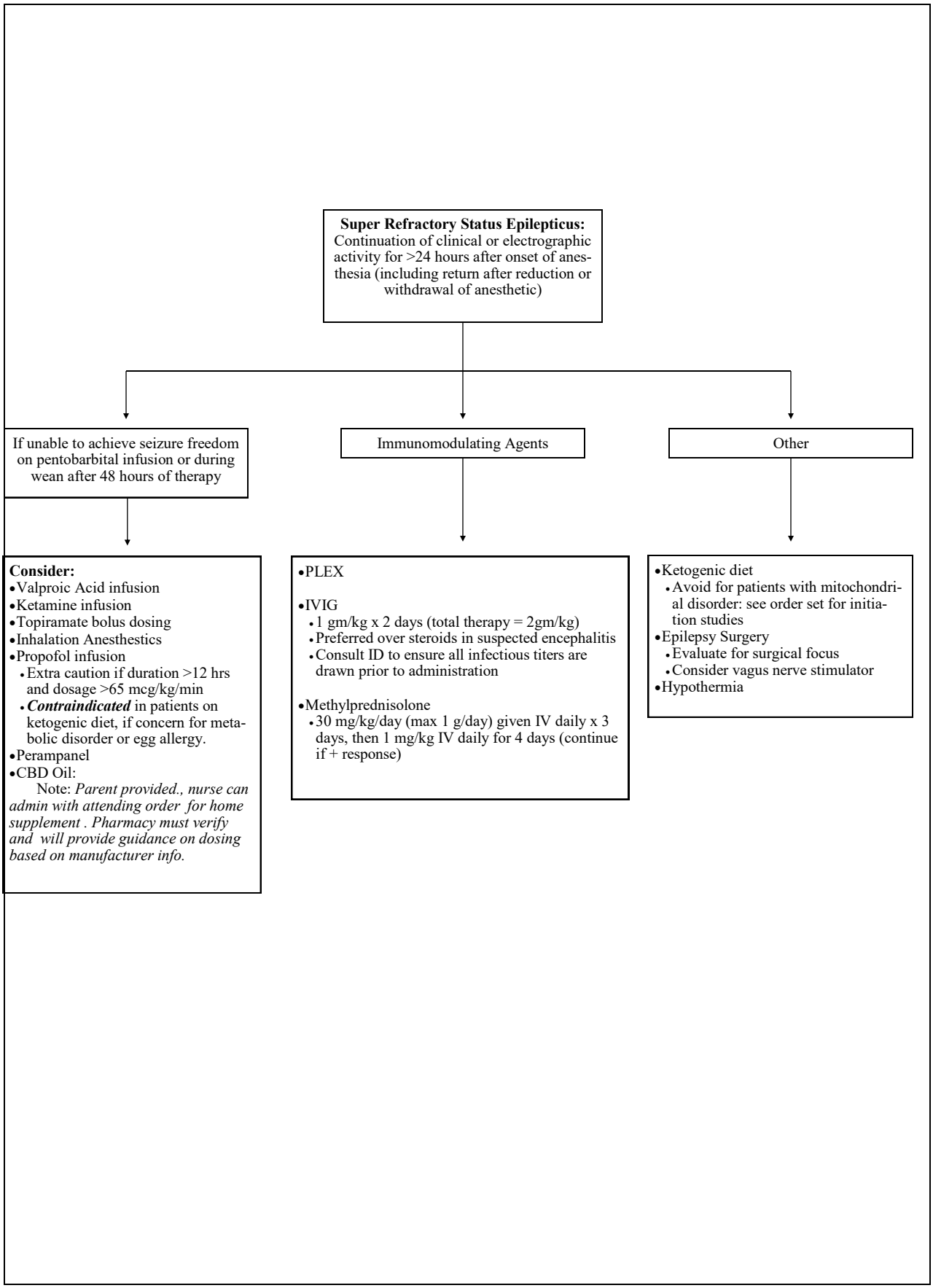
Return of seizures?

No

Yes

Refer to Super Refractory Status Epilepticus treatment options on Page 4

Refractory Status Epilepticus Pathway



Status Epilepticus Timeline

Time	Intervention Category	Specific Intervention
0-5 minutes	Monitoring	Clinical recognition of seizure
	Therapeutic	LORazepam 0.1 mg/kg (max 4 mg/dose) IV, may repeat X 1 for ongoing seizure (midazolam 0.2 mg/kg, max 10 mg IV/IM is equivalent) **ORDER** fosphenytoin 20 mgPE/kg (max 1500mg/dose) IV/IM upon administration of 2nd LORazepam dose independent of seizure cessation
	Diagnostic	r/o hypoglycemia or electrolyte disturbance AED levels if on chronic AEDs
	Goal	Complete cessation of Seizure
Continued encephalopathy or concern for clinical seizures		
5-30 minutes	Monitoring	Clinical monitoring Look for small clonic movements, vital sign changes (e.g. hypertension and tachycardia) suggestive of ongoing seizure Assess for fever and airway protection
	Therapeutic	Verify fosphenytoin dose was received **ORDER** PHENobarbital 20 mg/kg (max 1000 mg/dose) IV *If on chronic phenytoin or PHENobarbital will need to modify*
	Diagnostic	CT scan if new onset seizure or if patient has VP shunt LP if fever or new onset seizure (exclude if hx of febrile seizure) Obtain 10-20 ml CSF Begin empiric IV acyclovir and antibiotics for possible meningitis **ORDER** EEG and call x7962 (EEG techs) for placement in ICU or ED if PICU bed not readily available
	Goal	Cessation of seizure
Continued encephalopathy (not explained by post-ictal state) or concern for clinical seizures		
30-60 minutes	Monitoring	Clinical monitoring Consult Neurology Transfer to PICU Continuous EEG placed upon transfer to ICU (coordinate with imaging, if image delay monitor EEG with double distance lead placement)
	Therapeutic	PHENobarbital dose was received, consider additional 10 mg/kg bolus (max 1000 mg) of PHENobarbital Midazolam bolus 0.2 mg/kg (max 10mg/dose) followed by continuous infusion of 0.1 mg/kg/hr Bolus midazolam until infusion arrives If inadequate seizure control, titrate midazolam infusion every 15-30 minutes Bolus new hourly rate every other titration See RSE pathway for more details
	Diagnostic	See Encephalitis/Encephalopathy Pathway Metabolic work up
	Goal	Seizure cessation

Continued encephalopathy or concern for clinical seizures		
1-3 hours	Monitoring	Continuous EEG in place Monitor for hypotension – consider central access
	Therapeutic	Titration of midazolam continuous infusion every 15-30 minutes Bolus new hourly rate every other titration See RSE pathway for more details
	Diagnostic	MRI once seizures controlled AED levels if bolus provided earlier Follow up with EEG for read
	Goal	Seizure cessation (100% clinical and electrographic) Consider burst suppression
3- 12 hours	Monitoring	Continuous EEG in place Monitor for hypotension and respiratory failure
	Therapeutic	If seizure control: maintain infusion If no seizure control: continue to rapidly increase midazolam infusion to maximum 2 mg/kg/hr (refer to pathway for more details) Consider other AED options
	Diagnostic	ID Consult if concern for encephalitis, f/u on labs and LP
	Goal	Seizure cessation or transition off midazolam to 2nd agent
12-24 hours	Monitoring	Continuous EEG
	Therapeutic	If seizure control: maintain midazolam infusion for additional 24 hours If no or poor seizure control: discontinue midazolam infusion and start PENTobarbital, propofol or ketamine infusion (refer to pathway for more details). **PENTobarbital**: Bolus 10 mg/kg à Give first 5 mg/kg over 15 minutes, bolus additional 5 mg/kg over 15 minutes. If no burst suppression with IBI of 5-7 seconds repeat boluses should immediately follow until burst suppression is achieved. Start maintenance at 1-3 mg/kg/hr. Adv: historical first line agent Disadv: hypotension, ileus, increased infection risk, drug interactions **Propofol**: 3-5 mg/ kg load, maintenance at 75-150 mcg/kg/min Adv: fewer drug interactions Disadv: hypotension, prolonged use associated with propofol infusion syndrome *CONTRAINDICATED* in patients on ketogenic diet, if concern for metabolic disorder (especially mitochondrial disorder), egg allergy **Ketamine**: 1-3 mg/kg load, maintenance at 2-5 mg/kg/hr Adv: less hemodynamic compromise, non-GABA mechanism of action, fewer drug interactions Disadv: potential neurotoxin, newer agent
	Diagnostic	f/u ID consult, LP results, and EEG read Call lab and request storage of CSF for 14 days Consideration of autoimmune/paraneoplastic process
	Goal	Seizure cessation or titration of 2nd agent Normal hemodynamics, monitor for infections, consider nutritional support

48 hours	Monitoring	Continuous EEG Monitor skin carefully for breakdown/irritation
	Therapeutic	Once seizures are under control for 48hrs, begin to wean (per protocol) If poor control: optimize current drip to ensure burst suppression Consider IVIG for non-epilepsy patients, refer to encephalitis pathway
	Diagnostic	Completion of ID work up/autoimmune work up Call outside labs to confirm receipt
	Goal	Titration to burst suppression for duration of 48 hours
If Seizures return upon weaning		
>48 hours	Monitoring	Continuous EEG Monitor skin carefully for breakdown/irritation (consider double distance lead placement)
	Therapeutic	Consider slower wean (q12 instead of q6/q8 or q24 instead of q12) Consider change in general anesthetic approach Consider manipulation of chronic AEDs (valproic, phenobarb, topiramate, fosphenytoin) Consider methylprednisolone 30 mg/kg (max 1 gm/dose) IV daily x 3 days, then 1 mg/kg IV daily for 4 days (continue if + response) Determine acyclovir course
	Diagnostic	Consider repeat MRI (with contrast) Consider repeat LP, discuss with ID
	Goal	Seizure cessation or transition to 3rd continuous infusion for 48 hours of burst suppression
	Other	Family Meeting with Neurology and CCM if return of epileptic activity at time weaning
Continued seizures		
>5-7 days	Monitoring	Consider EEG break
	Therapeutic	Consider nutritional support unless preexisting malnutrition Consider: Plasma exchange Hypothermia Ketogenic diet Inhaled Anesthetics
	Diagnostic	Consider brain biopsy

FIRES Management

FIRES criteria

SRSE (must have failed wean of 3rd line agent)
Age 3-17
Seizures preceded by febrile illness
No alternative diagnosis despite comprehensive evaluation for infectious and inflammatory causes of seizures

Strategies for weaning infusion medications

Phenobarbital with goal levels ~ 100
Felbamate with goal levels > 50 *(fosphenytoin drives level down)*
Avoid propofol (due to concerns for secondary mitochondrial injury and propofol infusion syndrome)
Start metabolic supplements *(see page 8)*
Start ketogenic diet
Start aggressive bowel regimen (if being fed enterally).
* ILEUS IS NOT COMPATIBLE WITH ENTERAL AED ADMINISTRATION
Attend to parental inquiries regarding cannabadiols.
Bolus ketamine 1 mg/kg and begin infusion 1 mg/kg/hr (titrate to max of 10 mg/kg/hr)
Avoid polypharmacy, limit background AEDs to 4

Strategies for reducing inflammation

Begin pulse dose steroids (see page 8 for dosing)
Begin IVIG 2g/kg div 2 days as soon as labs sent (must confirm they are received in the lab and being processed)
Begin Anakinra (5 mg/kg/dose BID) once FIRES suspected
Consider PLEX if hemodynamically stable (will need to get AED labs post PLEX and bolus immediately after infusion) - anticipate timing for line placement and transfusion team preparation.
Consider Cytoxan if seizures continue to be refractory beyond week 3

Monitoring

Switch EEG to double distance once burst suppressed
Scalp breaks should be given every 4 days (minimum 4 hours)
Daily am trough for AED levels (phenobarbital, phenytoin, VPA)
Felbamate and Topiramate levels Monday and Thursday
High index of suspicion for DRESS (monitor for rash), HLH (multiorgan failure, increased TG and ferritin), dysautonomia (including gut dysmotility)
MRI brain every 2-4 weeks during initial PICU admission