Birmingham Women's and Children's NHS Foundation Trust

STATUS EPILEPTICUS MANAGEMENT IN PICU

Updated December 2022

K. Holliday et al on behalf of PICU NeuroCriticalCare Group

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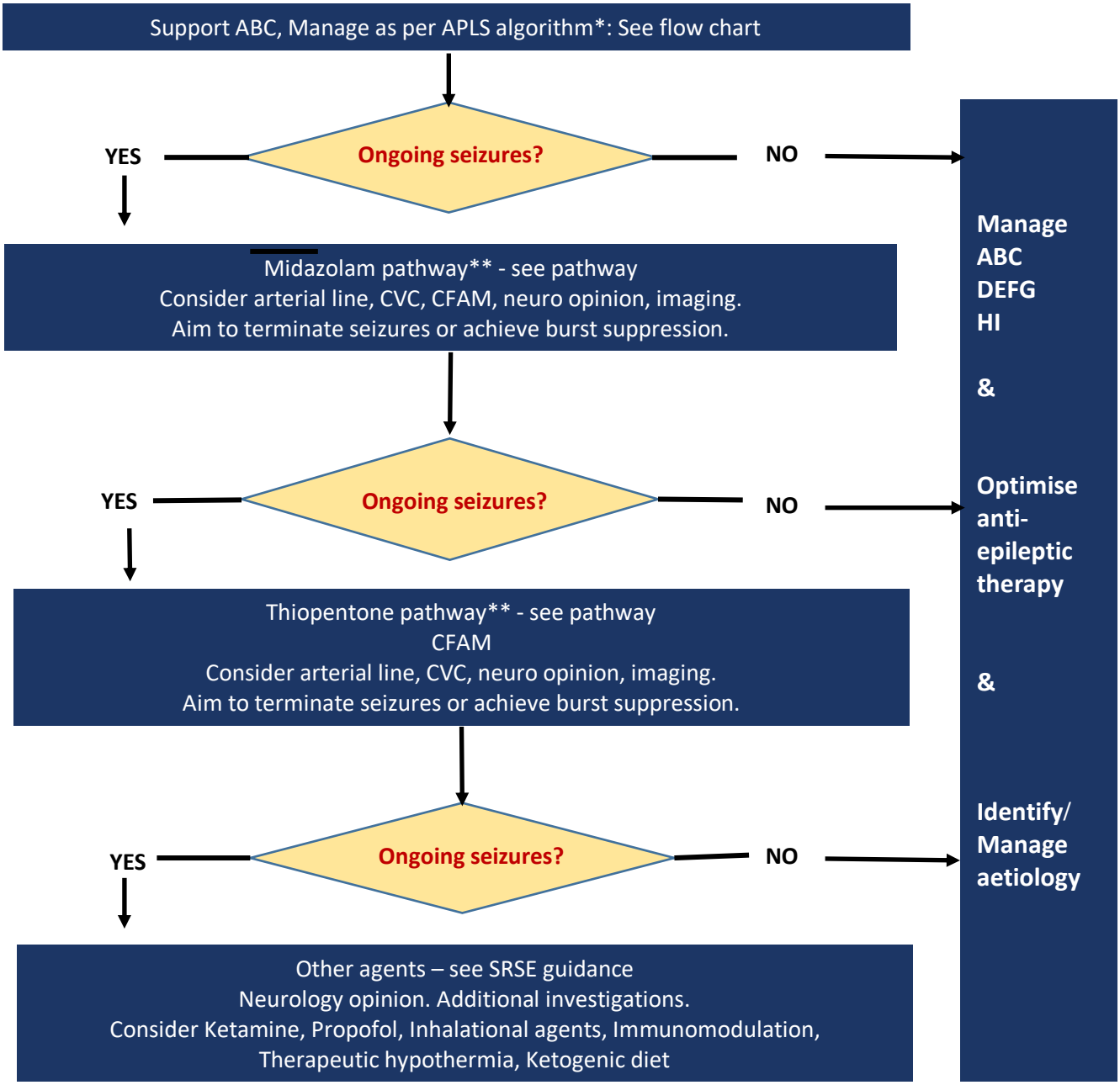
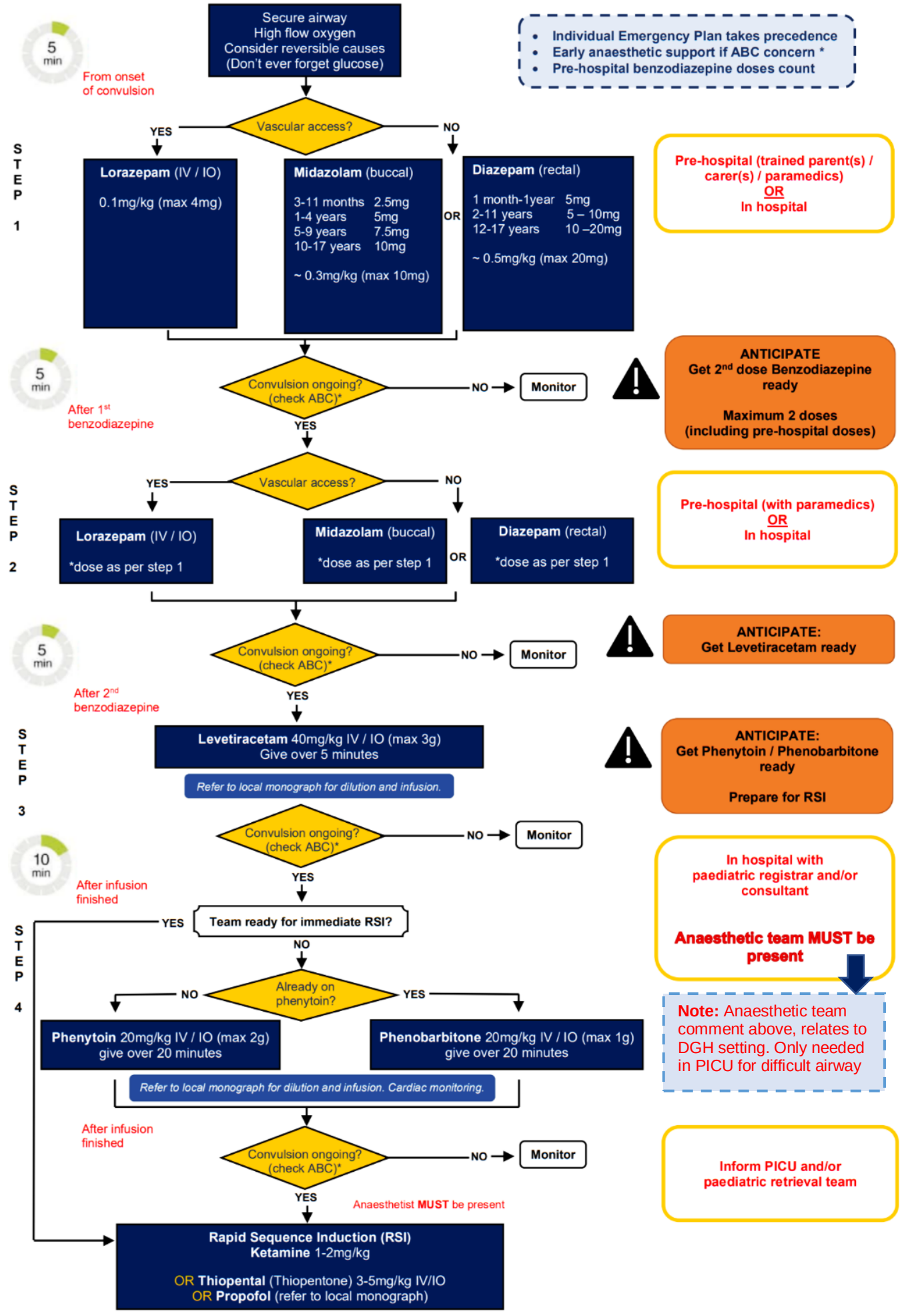
OVERVIEW OF STATUS EPILEPTICUS MANAGEMENT IN PICU



*** Individual Emergency plan takes precedence, if one exists.**
**** PICU Consultant must be informed**
Caution with Phenytoin – see additional guidance
Consider Pyridoxine in neonates with refractory seizures.
Alternative management strategies may apply for management of focal seizures or focal status [epilepsia partialis continua]-seek neuro advice

Author: K. Holliday et al on behalf of PICU NeuroCriticalCare team Dec 2022

APLS STATUS EPILEPTICUS GUIDELINE 2022



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CAUTION WITH PHENYTOIN

The following are advised when prescribing and administering phenytoin:

1) Side effects of arrhythmias & myocardial depression should be closely monitored with sufficient monitoring inclusive of ECG
2) Vigilance for other adverse effects such as nystagmus & ataxia should be maintained
3) Phenytoin is contra-indicated in patients with porphyria
4) When giving phenytoin to patients with pre-existing myocardial dysfunction or those high risk of arrhythmias, phenytoin should be given over 40 minutes
5) Patients must only be loaded with phenytoin ONCE. You must ensure from all previous hospital documentation & prescriptions that phenytoin has not been previously given. You must document this in the medical notes. Any verbal handovers that phenytoin has been given must be taken seriously and confirmed prior to administration.
6) Phenytoin levels may be used to avoid toxic phenytoin levels. A trough level could be considered after 8 hours of the first dose. The usual reference range is 10-20µg/ml.
7) Dosing advice should be taken from the PICU pharmacist if levels are high due to the need to consider other factors such as albumin levels
8) If a high level is reported out of normal pharmacy hours, then the dosing frequency should be extended, and reviewed the following day
9) Consider only a half-loading dose in patients with known low albumin levels, renal failure and/or cardiac arrhythmias.
10) If central line available, suggest central administration due to extravasation risk.

Purple Glove Syndrome (PGS) is characterised by pain, oedema and purple-blue discolouration of the limb distal to the site of phenytoin injection. It might evolve in three stages: initial stage, 2–12 h after injection, there is pain and purple-blue discolouration around the site of administration. The second stage involves development of oedema, varying degrees of discolouration, blister formation or necrosis. The third stage is the phase of resolution of pain, oedema and discolouration. Reasons, pathophysiology are unclear. Genetic susceptibility may be contributory. Use of higher than recommended concentrations, or extravasation may increase the risk.

Actions: The infusion should be discontinued immediately at the very first appearance of skin changes. The treatment of PGS involves elevation of the affected limb, avoiding further venous access through the limb, and preventing secondary infection through the site of initial access. Fasciotomy may be done to relieve the pressure if vascular compromise is evident. Contact plastic surgery team for review.

KEY UPDATES FROM APLS 2022

- Shorter time interval (5 minutes only) between benzodiazepine doses.
- Prehospital treatment with benzodiazepine doses given is counted. Maximum of two doses only.
- Second-line drug after benzodiazepines is Levetiracetam. It can be used in all patients including those on already on maintenance dose of levetiracetam.
- After Levetiracetam, if seizures persist AND if the team **is** ready, they should proceed to (modified) rapid sequence induction (RSI) with either Ketamine (if haemodynamically unstable), Thiopentone or Propofol (if haemodynamically stable).
- If the team is ***not*** ready either phenytoin or phenobarbitone (preferred in young infants or those already on maintenance Phenytoin) can be given.
- If immediately after completing this the child is still convulsing the team should then proceed to RSI.

STATUS EPILEPTICUS (SE)

- SE can be defined as a condition where there is continued generalised seizure activity for at least 30 minutes. This may include period of time without recovery of consciousness between episodes of seizures.

- Prolonged convulsions cause neuronal damage, but most fits stop within 5 minutes. If they do not, there is a significant chance of prolongation. The longer the duration of the fit, the longer it takes to stop it.

- **Medications should be used to stop fits that have been continued for longer than 5 minutes** (unless an alternative individual escalation plan exists). However, specific treatment can be started earlier than 5 minutes in most patients

Supportive management

- If seizure onset is witnessed, supportive care for up to 5 minutes may be appropriate. However, in most patients admitted to PICU without a pre-specified seizure management plan, administration of the first medication as soon as possible is recommended. i.e., there **is no need to wait for full 5 minutes** of seizures to administer a benzodiazepine.

- In all patients, consider **ABC-DEFG-HI**

A	Airway positioning	Consider naso (not in head injury) or oro-pharyngeal airway
B	Breathing	High flow oxygen via face mask (with a reservoir bag)
C	Circulation	Consider ECG, saturations, pulse volume, capillary refill time, blood pressure monitoring; assess and support
DEFG .	**D**on't **E**ver **F**orget **G**lucose	Check blood glucose in BM/blood gas. Obtain vascular access (IV/IO); Treat hypoglycaemia [Glu <3 mmol/L in neonate; <4 mmol/L others] with 2mL/kg glucose 10% and consider maintenance when possible
H	**H**ypo/**H**ypernatraemia, **H**ypocalcaemia, HypoMg, **H**yperammonaemia:	Consider, investigate, manage electrolyte imbalance especially if thought to be contributory to seizures.
I	**Infection**	Consider the need for antimicrobial(s) e.g., Cefotaxime, Aciclovir.
I	**I**ntracranial hypertension	Consider if pupillary asymmetry, sluggish/unreactive pupils, hypertension, bradycardia or supportive evidence on neuroimaging. 3mL/kg of 2.7% or 3% saline over 5-10min. Do **not** perform LP if intracranial hypertension is considered a possibility. Seek advice

REFRACTORY STATUS EPILEPTICUS (RSE)

- RSE has been defined as generalised seizures observed clinically or detected on EEG/CFAM after adequate doses of initial benzodiazepines and loading dose of an antiepileptic medication.

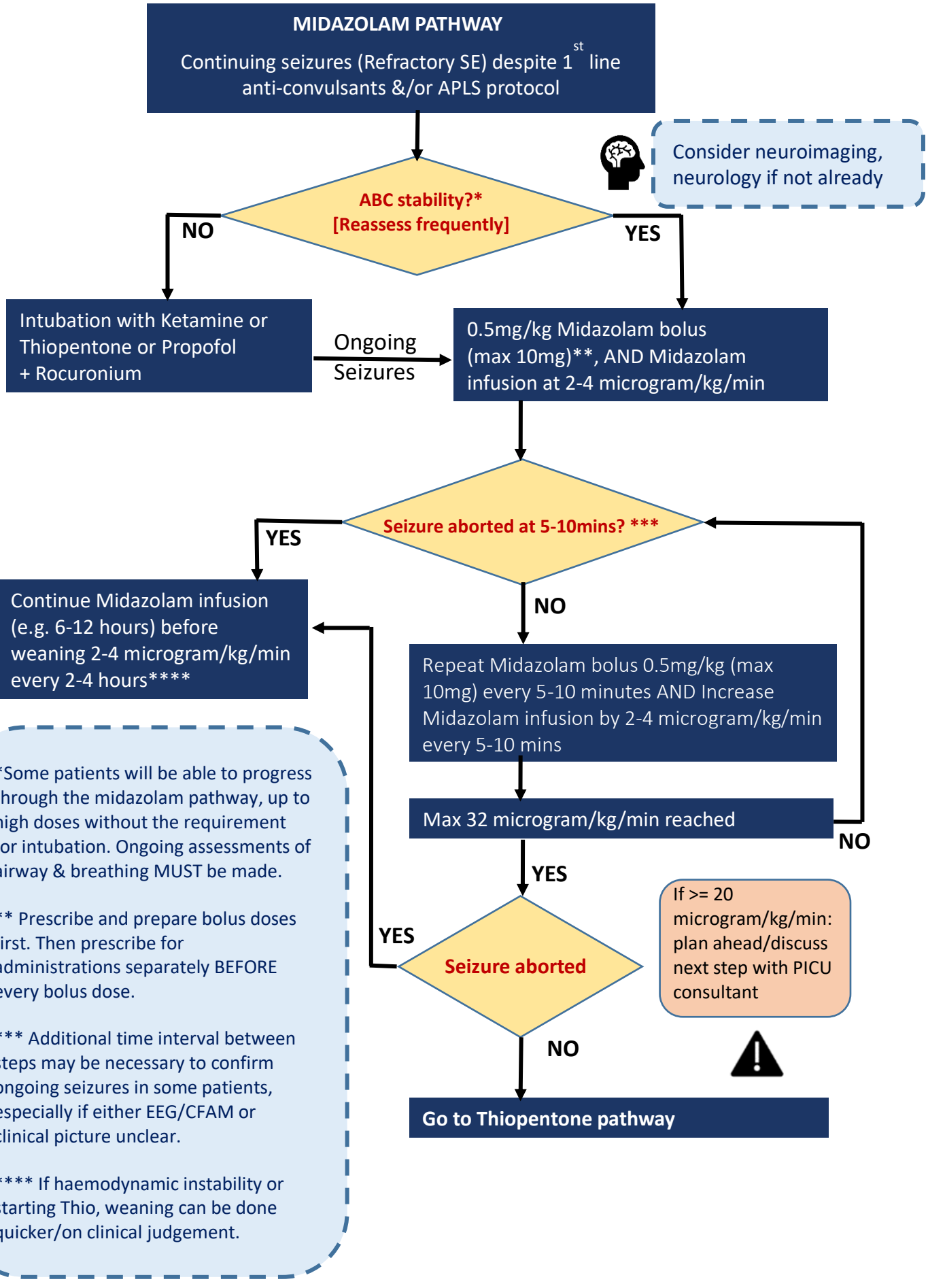
- In practice, this often refers to seizures that are ongoing for longer than an hour or two, despite appropriate antiepileptic therapy.

- Midazolam is the usual first-choice medication, with Thiopentone reserved for patients unresponsive to Midazolam infusion. [See below]

- Need for neuro-imaging, antimicrobials, neurology consult, administration of an additional anti-convulsant (if not already administered as a loading dose) such as levetiracetam, phenobarbitone, sodium valproate, phenytoin must be considered.

- **Generalised periodic discharges [GPD]** may mimic status epilepticus on CFAM/EEG. In post-cardiac arrest patients with persistent electrical seizure activity that does not show evolution in morphology or frequency, and usually 0.5-2.5Hz, consider GPDs. Seek neurophysiology/neurology advice. GPDs may not be amenable to usual RSE treatment pathways.

MIDAZOLAM PATHWAY



MIDAZOLAM PATHWAY

- Midazolam is first line continuous antiepileptic infusion of choice for patients with refractory status epilepticus.

- Can be entered by those spontaneously breathing [e.g. extubated after RSI in APLS algorithm prior to recurrence of ongoing seizure activity, or high risk intubation, or individual management plan] or those who are already intubated.

- Some patients may tolerate high doses of midazolam without intubation, however ongoing assessments of airway, breathing and circulation must be made, with consideration of haemodynamic effects and inotrope requirement.

- Keep NBM at least during the initial stages if not already intubated; patients can be fed when weaning/stability achieved.

- Consider CFAM in intubated patients if already muscle relaxed, or decision to muscle relax awaiting clarity.

- PICU Consultant [+/- ECLS consultant, for patients on ECLS] must be made aware, if not already when the pathway is triggered.

- Complete preparation and administration prescriptions on the separate prescription sheet (See Appendix 3).

- Bolus Midazolam 0.5mg/kg (max 10mg) IV and commence Midazolam @ 2-4 microgram/kg/min infusion

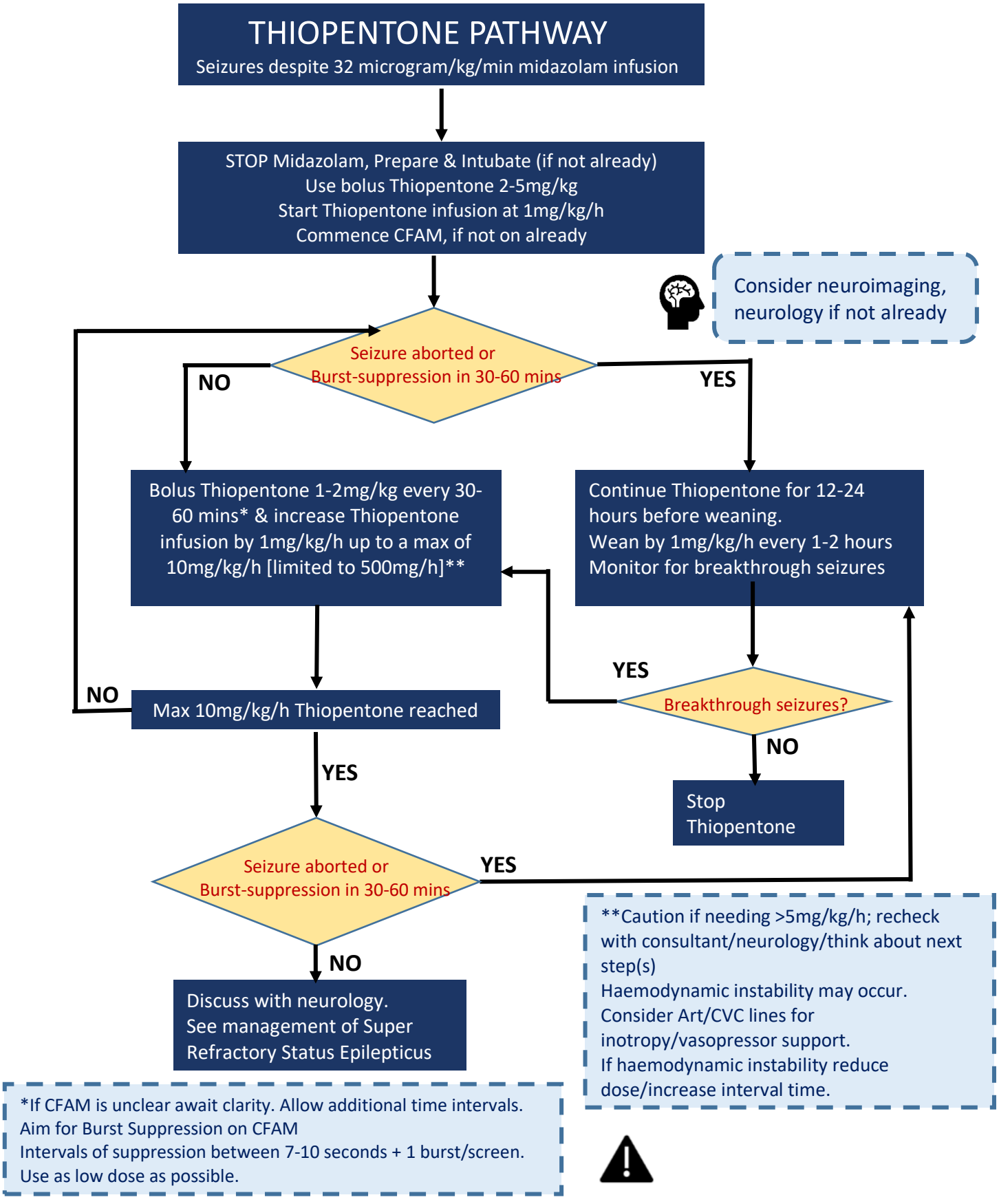
- <u>If seizure is aborted for 5-10 minutes</u>
    - Continue Midazolam at current dose
    - Continue Midazolam infusion for a minimum of 6-12 hours before weaning
    - If seizure re-occurs, recommence pathway

- <u>If seizure is not aborted or recurs</u>
    - Repeat 0.5 mg / kg (max 10mg) Midazolam bolus IV
    - Increase Midazolam infusion by 2-4 microgram/kg/min
    - If spontaneously breathing, assess airway integrity and INTUBATE if required
    - Consider EEG/CFAM monitoring if intubated.

- Repeat these steps until a dose of 32 microgram/kg/min is reached

- Recognition of continuing seizure activity either clinically or on CFAM may be challenging in some patients. Additional time interval between steps (beyond the usual 5-10mins) may be useful/necessary to confirm ongoing seizures, or in those with haemodynamic instability.

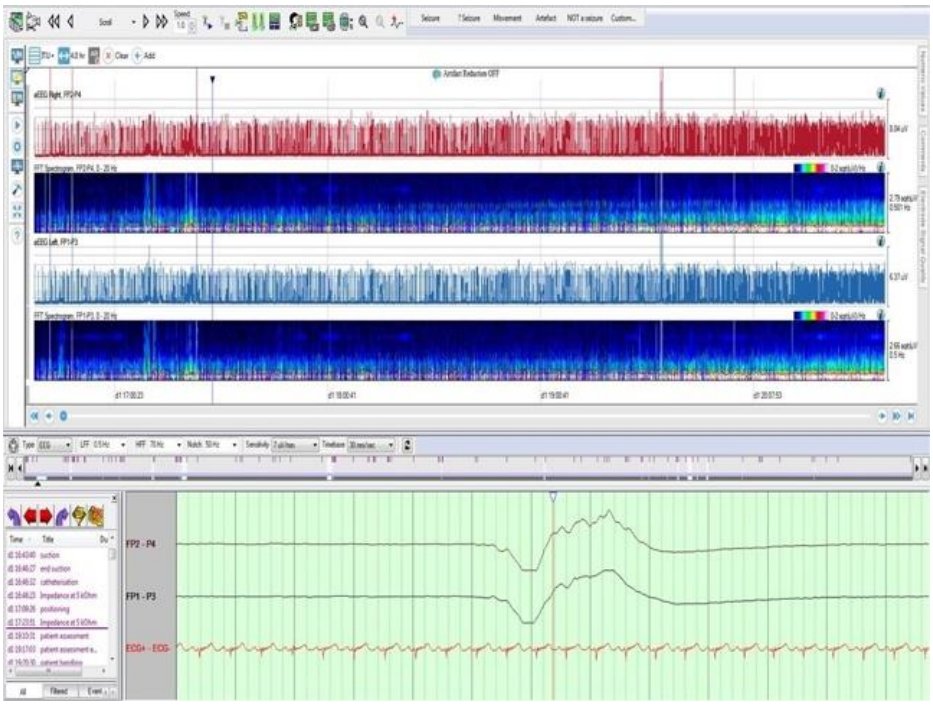
- Weaning can progress at a faster or slower rate than suggested on the midazolam pathway flowchart based on the clinical circumstances.


THIOPENTONE PATHWAY
Seizures despite 32 microgram/kg/min midazolam infusion
STOP Midazolam, Prepare & Intubate (if not already)
Use bolus Thiopentone 2-5mg/kg
Start Thiopentone infusion at 1mg/kg/h
Commence CFAM, if not on already
Consider neuroimaging, neurology if not already
Seizure aborted or Burst-suppression in 30-60 mins
NO
YES
Bolus Thiopentone 1-2mg/kg every 30-60 mins* & increase Thiopentone infusion by 1mg/kg/h up to a max of 10mg/kg/h [limited to 500mg/h]**
Continue Thiopentone for 12-24 hours before weaning.
Wean by 1mg/kg/h every 1-2 hours
Monitor for breakthrough seizures
YES
Breakthrough seizures?
NO
Stop Thiopentone
NO
Max 10mg/kg/h Thiopentone reached
YES
Seizure aborted or Burst-suppression in 30-60 mins
YES
NO
Discuss with neurology.
See management of Super Refractory Status Epilepticus
*If CFAM is unclear await clarity. Allow additional time intervals.
Aim for Burst Suppression on CFAM
Intervals of suppression between 7-10 seconds + 1 burst/screen.
Use as low dose as possible.
**Caution if needing >5mg/kg/h; recheck with consultant/neurology/think about next step(s)
Haemodynamic instability may occur.
Consider Art/CVC lines for inotropy/vasopressor support.
If haemodynamic instability reduce dose/increase interval time.

THIOPENTONE PATHWAY

- If seizures continue despite Midazolam at 32 microgram/kg/min, stop Midazolam and start Thiopentone pathway.
- All patients need to be intubated and mechanically ventilated prior to Thiopentone infusion pathway. Consider insertion of arterial and central venous lines.
- PICU Consultant [+/- ECLS consultant, for patients on ECLS] must be made aware, if not already when the pathway is triggered.
- An initial loading dose of Thiopentone 2-5 mg/kg IV [usually during intubation], followed by Thiopentone infusion at 1 mg/kg/h, if seizures continue or expected to continue despite the loading dose alone.
- Apply CFAM, if not already done – aim for termination of seizures or burst-suppression, if refractory seizures.
- If seizure recurs on EEG/CFAM, repeat boluses of 1-2 mg/kg AND increase Thiopentone infusion by 1 mg/kg/h (up to a maximum rate 10 mg/kg/h, usual maximum rate 500mg/h regardless of weight). Allow 30-60 minute intervals between each repeat bolus/stepwise increase in infusion rate.
- Recognition of continuing seizure activity either clinically or on CFAM may be challenging in some patients. Additional time interval between steps (beyond the usual 30-60mins) may be useful/necessary to confirm ongoing seizures, or in those with haemodynamic instability.
- In patients where burst-suppression is targeted, aim for intervals of suppression between 7-10 seconds and no less than 1 burst of EEG every 10-12 seconds.
- If seizures are controlled, or adequate burst-suppression achieved, continue Thiopentone infusion for at least 12-24 hours prior to weaning.
- Wean Thiopentone infusion rate by 1mg/kg/h every 1-2 hours, provided breakthrough seizures do not occur.
- Seek advice from Neurology, if seizures persist despite 10mg/kg/h of Thiopentone infusion

Example of an adequate burst suppression target →



SUPER-REFRACTORY STATUS EPILEPTICUS (SRSE)

- SRSE is essentially status epilepticus that continues for 24 hours or more after the onset of general anaesthesia, including recurrent seizures on weaning or withdrawal of anaesthesia. This is typically patients who are refractory to Midazolam and/or thiopentone infusions.

- SRSE has been associated with various new unexplained SE manifesting in people without pre-existing co-morbidities or identifiable aetiological factors, coined new onset RSE (NORSE), which include Febrile Infection-Related Epilepsy Syndrome (FIRES), Devastating Epilepsy In School-Age Children (DESC) and Acute Encephalitis with Refractory Repetitive Partial Seizures (AERRPS).

- SRSE is also associated with high morbidity and mortality.

Management strategies in SRSE

Due to the relatively infrequent incidence of SRSE, evidence for management strategies is scarce consisting mainly of case reports, case series and retrospective reviews. While SRSE treatment is ongoing, a combination of two or three anti-epileptic medications ought to be retained at high doses, without frequent alterations.

Management strategy is chosen in combination with neurologists and other experts.
A variety of management strategies have been suggested which include the following:

- **KETAMINE:**
  - **Mechanism:** As down-regulation in GABA receptors may occur in SRSE, the alternative NMDA-receptor blocking effect of ketamine has been successfully exploited. Several reports of successful resolution of SRSE using ketamine exist.
  - **Suggested dosing:** Bolus 2 mg/kg. Run infusion at 0.5-1mg/kg/h. If still seizures at 10 mins bolus 1.5mg/kg and increase infusion by 0.5mg/kg/h until Max 6mg/kg/h is reached.
  - **Cautions/Side effects:** Systemic hypertension, hypersalivation, avoid in patients with baseline diminished myocardial contractility and suspected catecholamine-depleted state.

- **PROPOFOL:**
  - **Mechanism**: activation of central GABA pathways and inhibition of NMDA pathways
  - **Suggested dosing**:
    - Bolus dose 2mg/kg then start infusion at 1mg/kg/h.
    - If continued seizures in 10 mins then bolus 0.5-1mg/kg dose and increase infusion by 0.5-1mg/kg/h unless a maximum dose 4mg/kg/h is reached.
    - Once seizures stopped keep on for 12-24 hours before weaning.
    - To minimise the chance of Propofol Infusion Syndrome, avoid dose of Propofol >4 mg/kg/h, and limit duration of Propofol to < 48 hours, where possible.
  - **Cautions/side effects**: Propofol infusion syndrome. Monitor Triglycerides, CK and ECG. Avoid in patients with inborn errors of metabolism.

- **INHALATIONAL ANAESTHETIC AGENTS** like **isoflurane**:
    - **Mechanism**: probably work on multiple receptors to provide good control of seizure activity in SRSE, but the logistics of delivering, monitoring and scavenging meant that their use is usually confined to the operating theatres and exceptional circumstances. The use of an anaesthetic conservation device such as 'AnaConDa' may facilitate the use of inhalational anaesthetics for SRSE in the PICU environment.
    - **Cautions/side effects:** While this strategy may be effective, significant morbidity associated with prolonged inhalational anaesthetics include hypotension, ileus and prolonged mechanical ventilation etc. Abrupt discontinuation after prolonged use of isoflurane may lead to extreme agitation and psychomotor disturbances.

- **IMMUNOMODULATION** using **steroids**, immunoglobulins, **plasma exchange**, cyclophosphamide and rituximab on their own or in combination, may be effective in treating SRSE where paraneoplastic syndromes or autoimmune encephalitis are suspected. **Rituximab** might be preferred agent when antibody mediated encephalitis is strongly suspected or confirmed. Whereas **Anakinra** or **Tocilizumab** might be used when antibodies are not available or absent. High IL1 (anakinra), IL6 (tocilizumab) levels might indicate preference for one rather than other. Access to **IVIG** requires a diagnosis on the supra-regional panel approved list or discussion with hospital DTC team. Seek advice from PICU pharmacist.

- **THERAPEUTIC HYPOTHERMIA:** The role of therapeutic hypothermia in SRSE is unclear. This method reduces cerebral metabolism and oxidative stress. A temperature target of 32 to 35ºC for 24 to 48 hours has been suggested for seizure control and neuroprotection in ICU for refractory epilepsy. However, clinical trials have not confirmed the effectiveness of therapeutic hypothermia in SE.

- **KETOGENIC DIET:** promotes formation of ketone bodies leading to increase in fatty acid levels that open ATP-sensitive potassium channels, thereby enhancing membrane hyperpolarisation to reduce seizure activity. This has been shown to be effective in cases of FIRES, immune-mediated encephalitis, non-ketotic hyperglycinaemia, and genetic epilepsy. This strategy is only suitable for those able to feed enterally, and input from an experienced dietician is required, with regular monitoring for severe hypoglycaemia and hypertriglyceridaemia

Tip: Search the intranet with word "Ketogenic" for **guidance document** and **monitoring sheet** for patients on Ketogenic diet

SUGGESTED NORSE/FIRES MANAGEMENT ALGORITHM

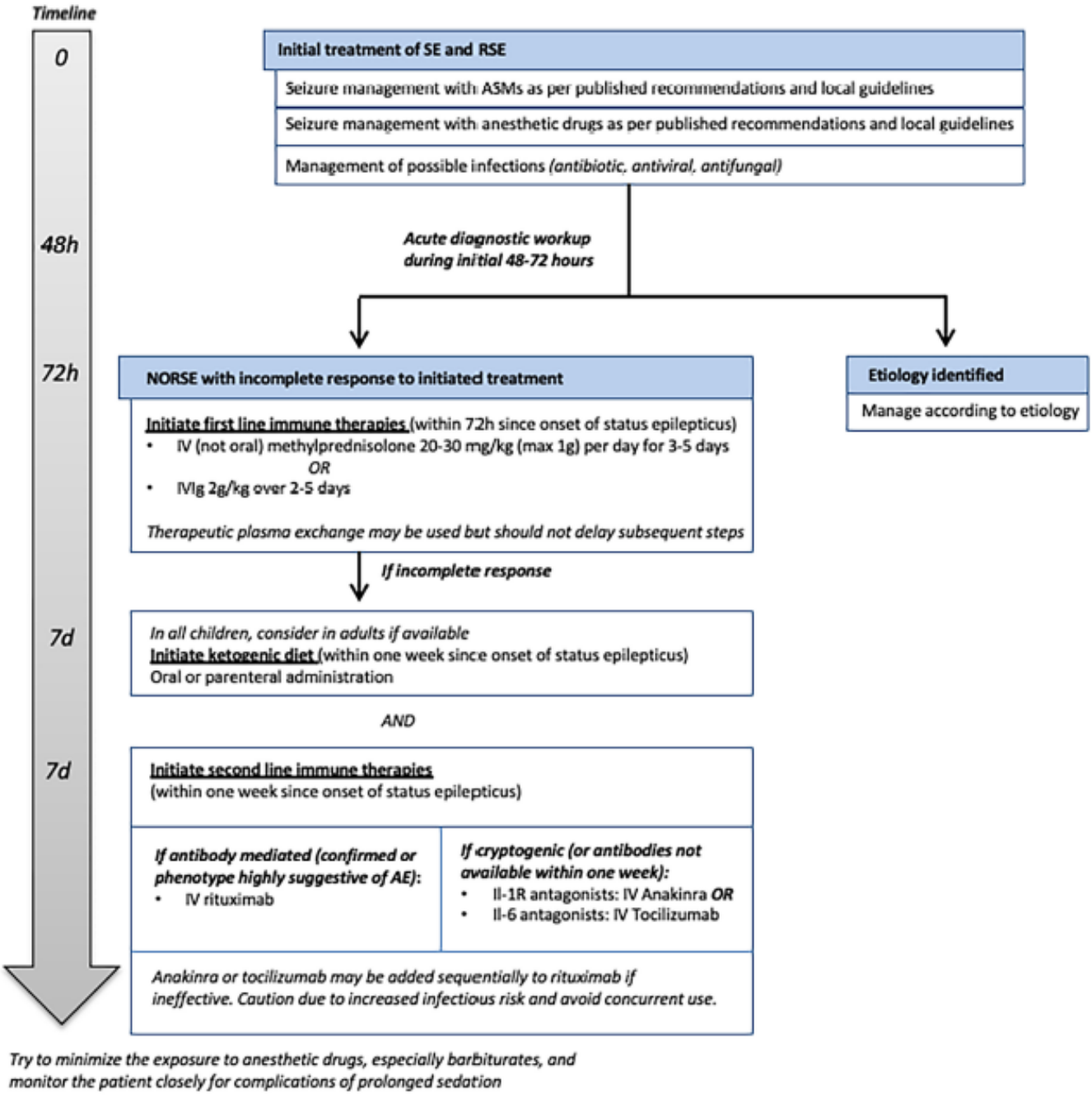


FIGURE 2 Suggested treatment algorithm for NORSE including FIRES (expert opinion). Adapted from Gaspard et al.[3] van Baalen et al.[10] and Sculier et al.[4] AE, autoimmune encephalitis; ASM, anti-seizure medication; IV, intravenous; IVIG, intravenous immunoglobulins; RSE, refractory status epilepticus; SE, status epilepticus.

Implementation and modification of suggested algorithm for SRSE will always include discussion with Neurology. Above is a suggested template only. Modifications will almost certainly be required

APPENDIX 1: INVESTIGATIONS TO CONSIDER IN PATIENTS WITH RSE/SRSE

The following is not an exhaustive list and will need to be tailored to the clinical history/ MRI findings in each individual case. Please **discuss** with neurology.

Investigation	Comment
BLOOD	
Plasma amino acids	Variety of metabolic conditions
Serum encephalitis antibodies	CSF must be sent as well as serum, as you can miss 20% of NMDA encephalitis on serum alone
MOG antibodies [request separately]	MOG antibody disease. Is not in encephalitis panel
Blood α-AASA	Pyridoxine-dependent epilepsy, particularly in neonates/infants
Serum cytokine signature	Send to immunology lab in GOSH- Il-1 and Il-6 are often raised in FIRES and might give some evidence to use Anakinra/ Tocilizumab
Plasma Uric acid in babies	Molybdenum co-factor deficiency
Plasma Sulphocysteine in babies	Sulfite oxidase deficiency
URINE	
Urine organic acids	Variety of metabolic conditions
Urine toxicology	Substance abuse, poisoning
α-AASA	Pyridoxine-dependent epilepsy, particularly in neonates/infants
CSF	
CSF MC+S/ virology	Infectious causes
CSF Lactate	Mitochondrial disease
CSF Oligoclonal bands	Multiple sclerosis; may be transiently present in ADEM
CSF encephalitis antibodies (ICE panel)	Autoimmune encephalitis
CSF neurotransmitters	Pterins might be raised in neuroinflammatory process, in neonates low pyridoxal-phosphate/ folate might diagnose a vitamin responsive epilepsy
CSF amino acids	In neonates high Glycine is diagnostic of Non-Ketotic Hyperglycinaemia. Can identify Serine deficiency.
CSF cytokines	Send to immunology lab in GOSH: IL-1 and IL-6 are often raised in FIRES and might give some evidence to use Anakinra/Tocilizumab
GENETICS	
R14	Rapid whole exome/genome sequencing
R299 and R300 (mitochondrial rearrangements and genome).	If unsuitable for WGS/WES, then request *POLG*
OTHER	
Muscle biopsy	Inborn errors of metabolism, mitochondrial disorders.

AASA: aminoadipic semialdehyde; CSF: cerebrospinal fluid; ADEM: acute disseminated encephalomyelitis; NMDA: N-methyl-D-aspartate

Note: CSF to be obtained when concerns about raised ICP have subsided. Speak to the metabolic lab before sending samples as special collection tubes may be needed.

APPENDIX 2: NEONATAL CONVLUSIONS

Neonatal seizures may manifest clinically as:

Subtle: (50%)

This is the most common seizure type in both preterm and term babies.

Subtle seizures can be difficult to recognise clinically.

Manifestations include:

- Ocular phenomena
- Oral phenomena
- Autonomic
- Fragmentary body movements

Clonic: (25%)

These may be multi-focal or focal

Myoclonic: (15-20%)

These are the least common and compromise synchronised jerking of limbs

These should be distinguished from jitteriness by grasping and gently flexing a limb (abates jitter but not myoclonus)

Tonic: (5%)

Common in preterm infants (may indicate severe cerebral damage)

Extension of the body with flexion or extension of the upper limbs, together with upward deviation of the eyes

CAUSES OF NEONATAL SEIZURES

➢ HYPOXIA	Hypoxic-ischemic encephalopathy
➢ HAEMORRHAGE	Intracranial hemorrhage: ▪ Subarachnoid hemorrhage ▪ Germinal matrix intraventricular hemorrhage ▪ Subdural hemorrhage (associated with cerebral contusion)
➢ METABOLIC	Hypoglycaemia, hypocalcaemia, hypomagnesaemia Inborn errors of metabolism (typically >72 hours of life) Pyridoxine dependent epilepsy
➢ INFECTION	Meningitis, encephalitis (including herpes encephalitis) Toxoplasmosis, Cytomegalovirus (CMV) infections Bacteria: especially Escherichia coli and Streptococcus pneumonia
➢ MALFORMATIONS	Cerebral malformations
➢ SEIZURE SYNDROMES	Benign neonatal seizure syndromes Benign idiopathic neonatal seizures (fifth day fits) Benign sleep myoclonus

Neonatal Network Guidelines has additional information related to neonatal seizures, investigation and management should it be required for education. Search PICU guidelines or intranet for “neonatal network guidelines” and click on “seizures” from the index from within the document

APPENDIX 3: MIDAZOLAM SEIZURE PATHWAY PRESCRIPTION

Patient name..... **Hospital Number**.....

MIDAZOLAM SEIZURE					**Route:** IV Central or Peripheral Diluents: G5W/G10W, NS, 1/2NS	
Standard fixed concentration: 100mg in 50ml		100 mg in 50 ml			*Non-standard strength instructions:* *(Only use in exceptional circumstances)* *..... mg in 50ml* *..... ml/hr = 1 microgram/kg/min*	
Drug Library = Midaz SEIZURE 100/50					**Extravasation Risk LOW**	
0.03ml/kg/hr = 1microgram/kg/min					*Start infusion at .....microgram/kg/min*	
Delete the above if a non-standard strength used & complete instructions in box top right					Pharm	
May be mixed at the terminal y-site with drugs listed on IV monograph Flush with 0.5ml-2ml sodium chloride 0.9% when infusion stopped						
Date/ time prepared						
Nurse 1 sign						
Nurse 2 sign						
Pump set by						
Pump checked by						

MIDAZOLAM Bolus *Preparation*					Seizure pathway dose = 0.5mg/kg (max 10mg) **Only give *after* Administration prescribed below**	**Bolus Dose** mg	**Extrav Risk LOW**
Prepare 4 separate bolus doses and assign 4 hour expiry to each labelled syringe					No bolus option in Drug Library		Pharm
Date prepared							
Time prepared							
Nurse 1 sign							
Nurse 2 sign							
Prescriber Name:			**GMC/Reg No.**	**Date**	**Note: Prescription is for infusion AND bolus *preparation* only**		
Prescriber Signature:							

MIDAZOLAM Bolus *Administration*						Seizure pathway bolus dose = 0.5mg/kg (max 10mg) **All doses must be prescribed below *before* Administration**	**Extrav Risk LOW**
IV Bolus Dose							
Prescriber Name:							
Prescriber Signature:							
GMC/Reg No.							
Date/time prescribed							
Date/ time prepared							
Nurse 1 sign							
Nurse 2 sign							

MIDAZOLAM Rate Changes						**Record all rate changes, both increases and decreases in rate** If bolus does not abort seizure within 10 mins, increase rate by 4microgram/kg/min Pathway maximum is 32microgram/kg/min Drug Library soft limit = 30microgram/kg/min, hard limit = 50microgram/kg/min	
Date changed							
Time changed							
New rate: microgram/kg/min							
Pump set by							
Pump checked by							

MIDAZOLAM Rate Changes						**Record all rate changes, both increases and decreases in rate** If bolus does not abort seizure within 10 mins, increase rate by 4microgram/kg/min Pathway maximum is 32microgram/kg/min Drug Library soft limit = 30microgram/kg/min, hard limit = 50microgram/kg/min	
Date changed							
Time changed							
New rate: microgram/kg/min							
Pump set by							
Pump checked by							

SEIZURE PATHWAY

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