NEONATAL SEIZURES

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Introduction

- Mechanism of Seizures
  - Results from an excessive synchronous electrical discharge (depolarization) in the neurons

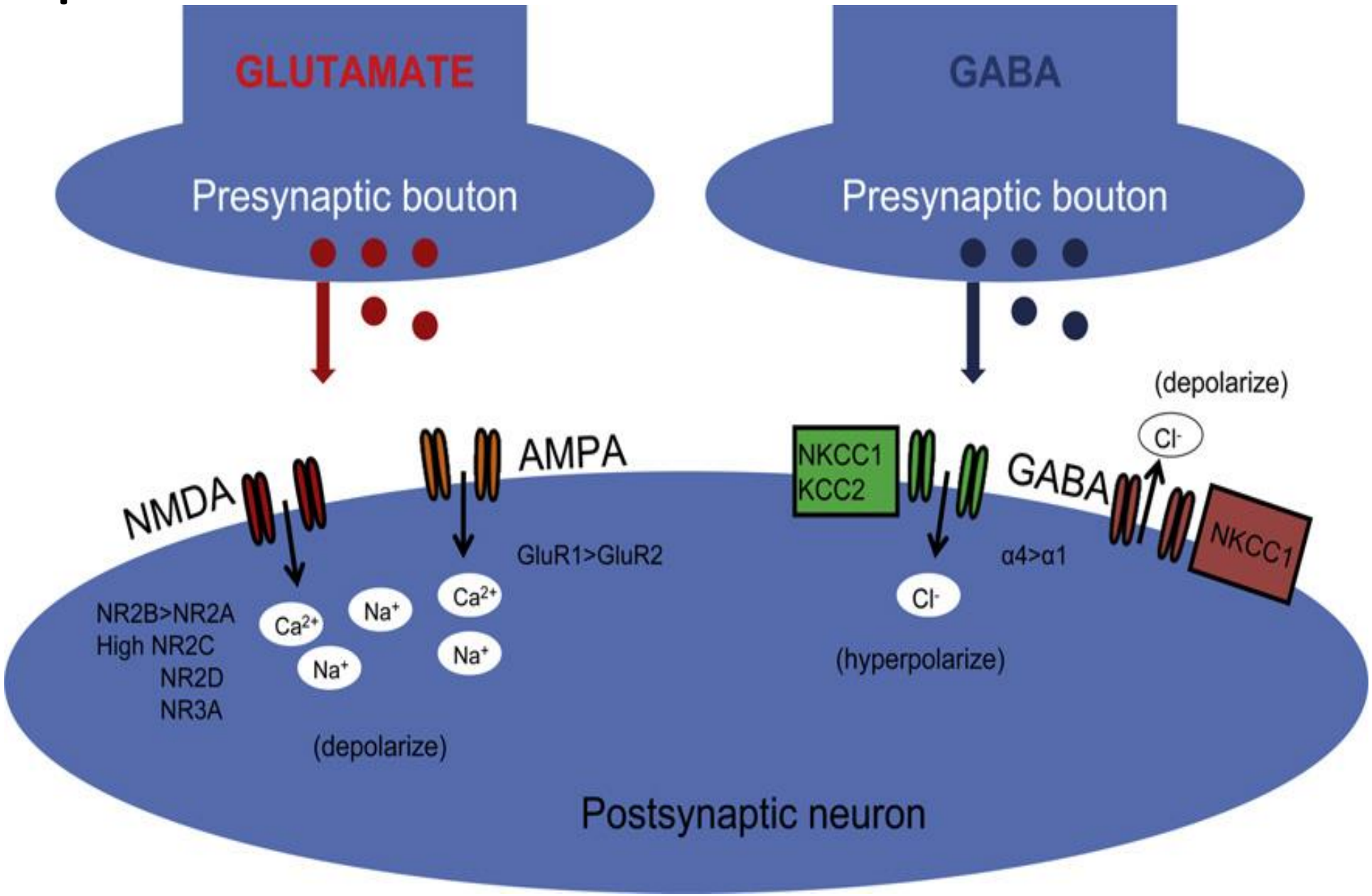
Physiology

- Basic Mechanisms
  - Maintenance of potential across membranes requires energy (ATP pump)- pushes out Na^+ in K^+
  - Depolarization- inward movement of Na^+
  - Repolarization- outward movement of K^+

Seizures Come From Depolarization

- Depolarization occurs because of imbalance of neuronal excitation and inhibition
- Mechanisms:
  - Failure of ATP-dependent pump (e.g. hypoxia, hypoglycaemia)
  - Excess of excitatory neurotransmitters especially glutamate (either increase release or decreased uptake) (e.g. hypoxia/ asphyxia)
  - Deficiency of inhibitory versus excitatory neurotransmitters (e.g. neonates are at risk of developing seizures compared to adults because of GABA is lower in newborns)
  - Increase sensitivity to depolarization- molecules interact with neuronal membrane and inhibit sodium movement (e.g. hypocalcaemia, hypomagnesaemia increase sodium influx and result in depolarization)

Synaptic Transmission in Neonates



Effects of Seizures

- Increased rate of energy dependent ion pumping- results in decrease in ATP
- Increased glucose utilization
- Elevated BP
- Increased CBF
- Hypoventilation (Low PaO_2, High $PaCO_2$)
- ===➔> BRAIN DAMAGE

Causes of Seizures

- Hypoxic Ischaemic Encephalopathy – 40-50%
  - Occurs during 1st 24 hours after birth, if TH then sometimes during rewarming
- Stroke – 10-15%
  - Usually after the first 12 hours of life
- Intraventricular haemorrhage – 10-20%
  - Usually first 72 hours of life
- Infection – 5%
  - Usually latter part of first week if GBS or E.coli,
  - could be earlier for CMV, after 7 days for Herpes
- Cerebral dysgenesis – 5%
- Other – 5-10%
  - Transient metabolic disorders (hypoglycaemia- 2nd day, hypocalcaemia- early (2-3d), late)
  - Inborn errors of metabolism
  - Drug withdrawal
  - Neonatal Epilepsy Syndromes

Diagnosis

- Clinical diagnosis
- Electroencephalograph

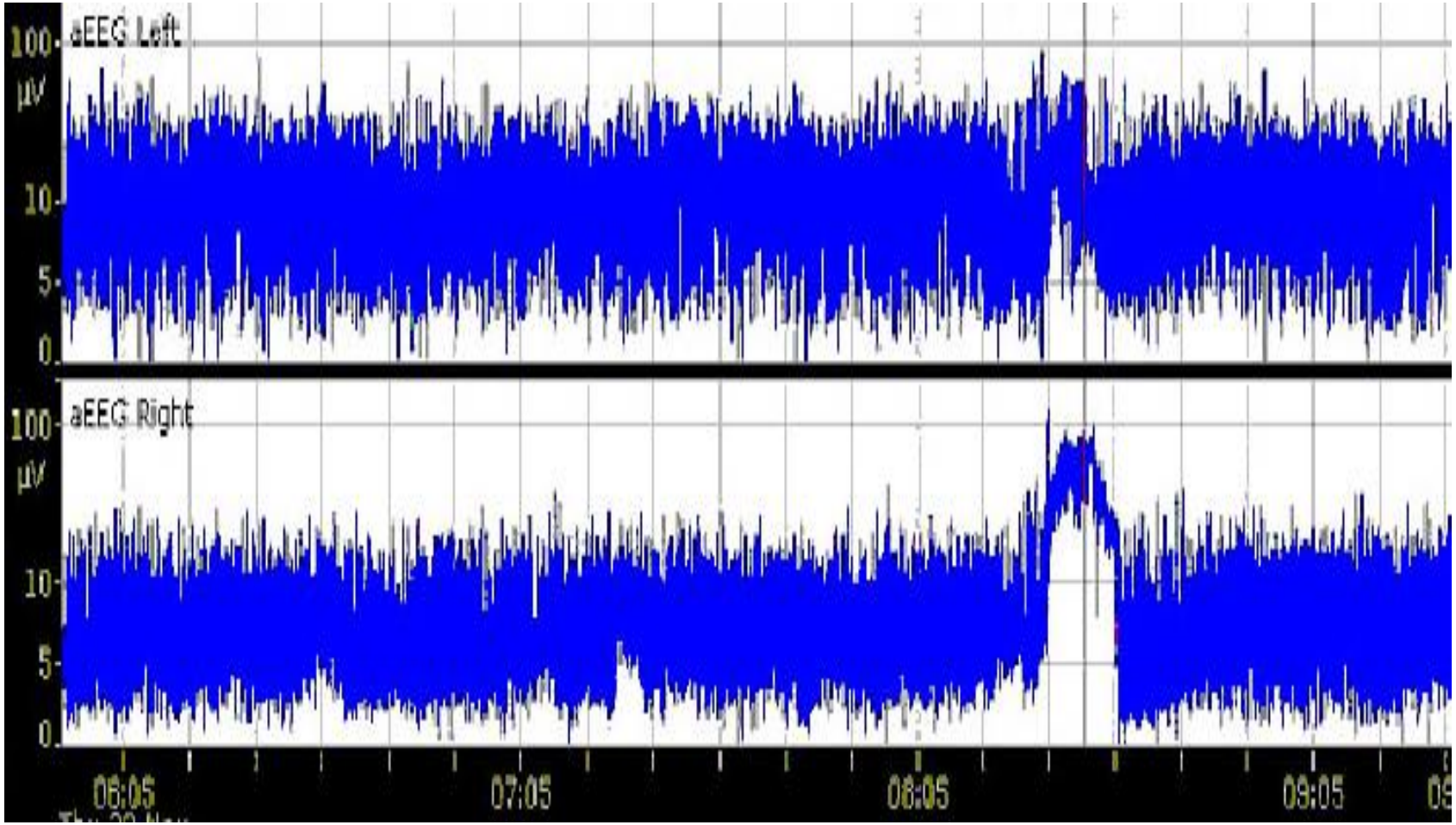
Clinical Diagnosis

	ELECTROENCEPHALOGRAPHIC SEIZURE CORRELATE
Subtle Ocular phenomena - horizontal deviation with/out eyes - sustained eye opening Oral-buccal-lingual - chewing, lip smacking Other manifestation - limb movements, autonomic phenomena, apnoeic episodes	Common
Clonic Focal Multifocal	 Common Common
Tonic Focal Generalized	 Common Uncommon
Myoclonic Focal multifocal Generalized	 Uncommon Common

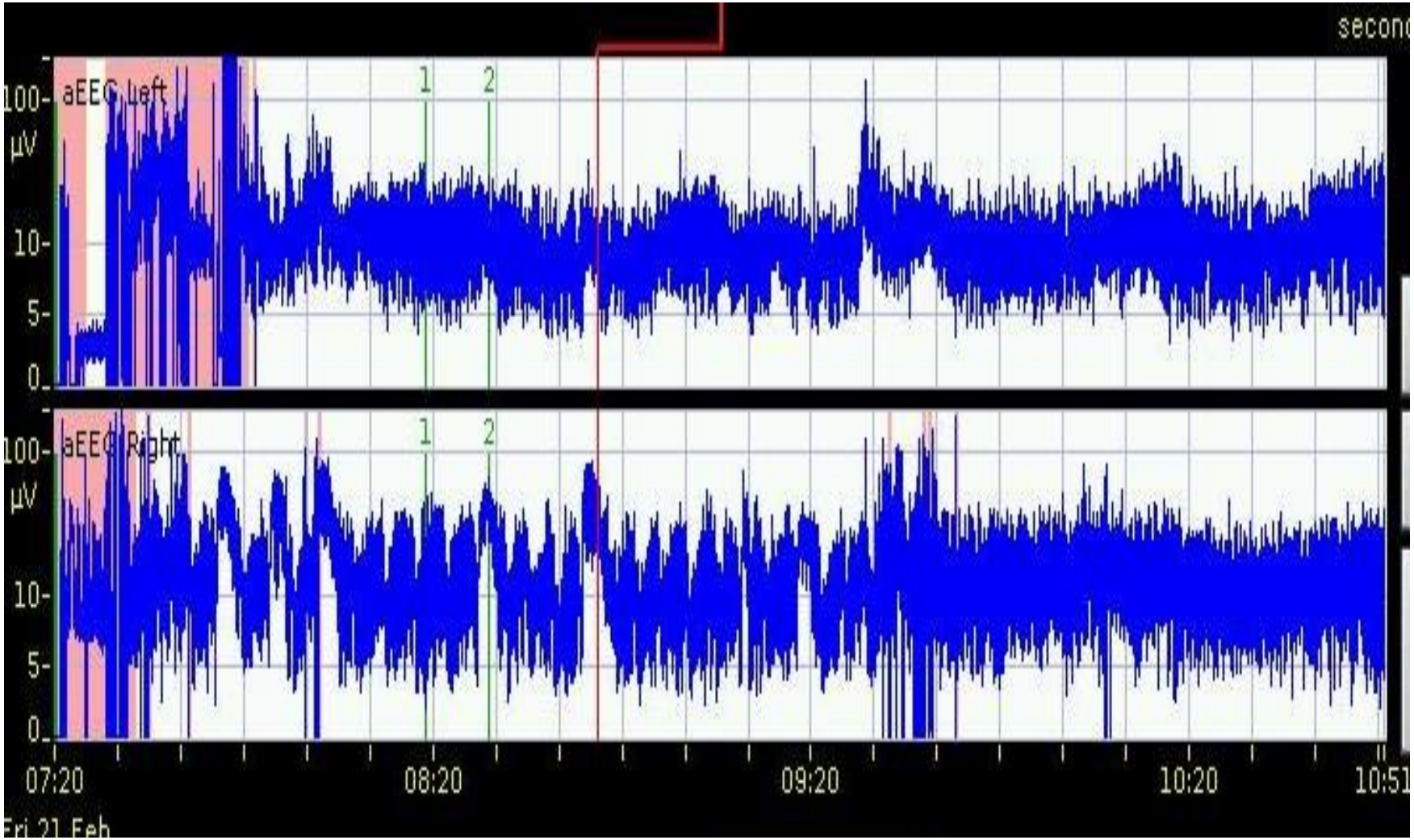
Electroencephalograph (EEG)

- Aim of an EEG:
  - Diagnosis
  - Prognosticate
- At least one hour of recording
- For high risk infants record for at least 24 hours
- If having seizures; continue with EEG for an additional 24 hours after the last electrographic seizure
- aEEG versus raw EEG
  - Sensitivity – 76% (71-85%)
  - Specificity- 85% (39-96%)

aEEG- Seizure



aEEG- Recurrent Seizures



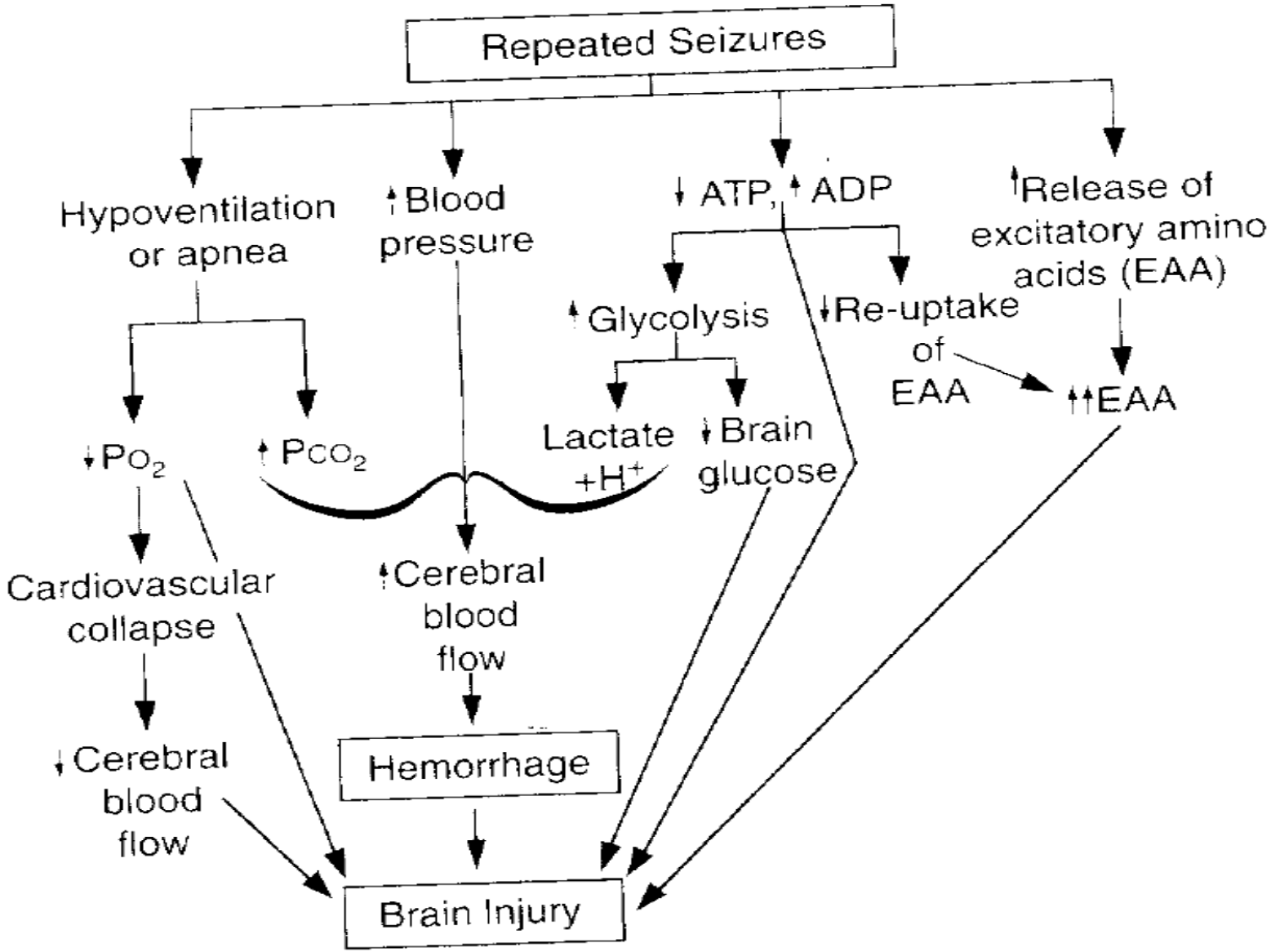
Investigation

- Target 2 disorders that are dangerous but readily treatable
  - Hypoglycaemia
  - Bacterial meningitis
- Electrolytes
- Calcium, phosphorus, magnesium
- Electro-encephalograph

Management

- Why to treat?
- Who to treat?
- Goal of therapy?
  - Eliminate electric seizure activity

Why to treat at all?



Who to treat?

- Treat all electrographic seizures
- Treat all clinical seizures
  - Challenge is that seizures might be difficult to distinguish from non-epileptic neonatal movements
    - Jitteriness
    - Tremors
    - Non-epileptic myoclonus
    - Hyperekplexia
    - Roving dysconjugate eye movements
    - Sucking puckering movements not accompanied by ocular fixation or deviation

Why have clinical seizures but no electrical activity?

- Seizures generated at a subcortical level
  - Deep limbic, diencephalic, brain stem levels
  - These might not always be propagated to cortex
  - EEG changes occur after clinical manifestations

Management

- Initial medical treatment
  - Adequate airway
  - Adequate ventilation
- Treatment of aetiological factors
- Anticonvulsant

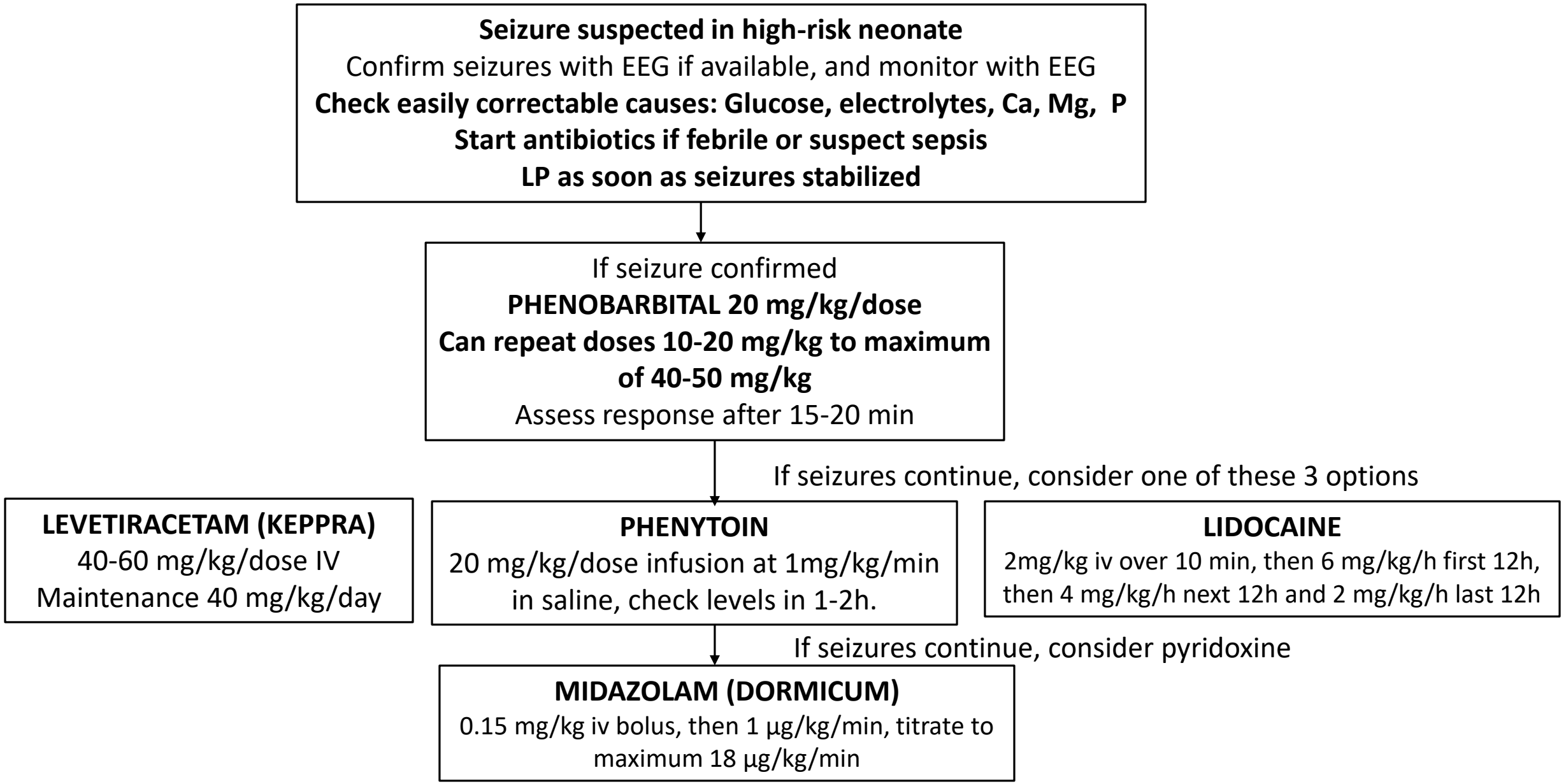
Acute Management: Anticonvulsant

- Phenobarbital 20 mg/kg/dose iv
- If no response
  - Repeat phenobarbital 10 mg/kg to max. 40-50 mg/kg
  - Phenytoin 20 mg/kg infusion (0.5-1mg/kg/min)
  - Lorazepam 0.05-0.1 mg/kg iv
  - Midazolam (Dormicum) 0.2 mg/kg iv, then 0.1-0.5 mg/kg/h

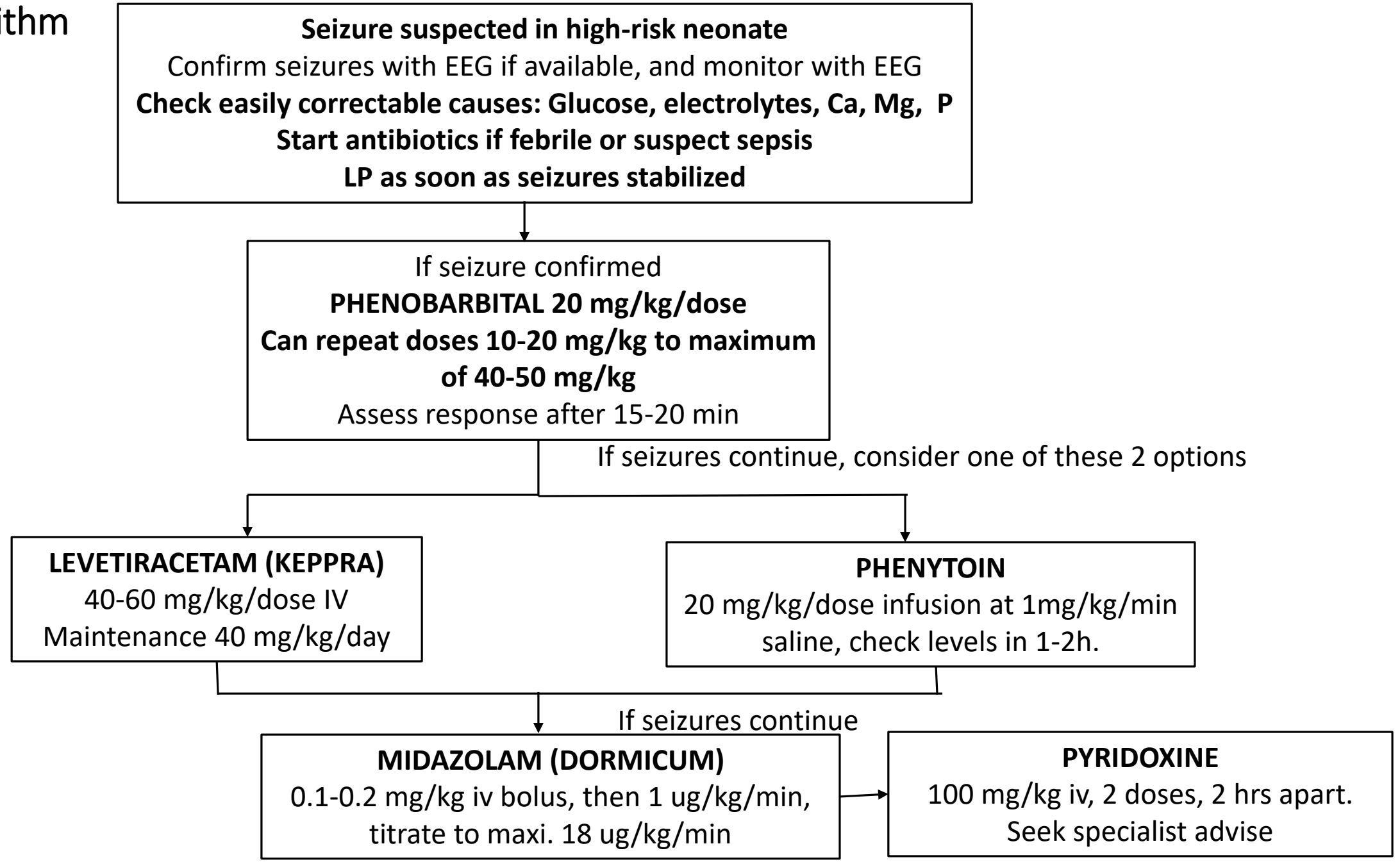
Management of Common Metabolic Disorders

- Hypoglycaemia
  - Give glucose 200 mg/kg i.v. (2mL/kg of a 10% solution)
- Hypocalcaemia
  - Give calcium 200 mg/kg i.v. (2ml/kg of 10% calcium gluconate)
- Hypomagnesaemia
  - Give magnesium 50-100 mg/kg i.m. (0.1-0.2 mL/kg of 50% magnesium sulphate)
- Pyridoxine deficiency
  - Pyridoxine: 50-100 mg, i.v.

Algorithm


Seizure suspected in high-risk neonate
Confirm seizures with EEG if available, and monitor with EEG
Check easily correctable causes: Glucose, electrolytes, Ca, Mg, P
Start antibiotics if febrile or suspect sepsis
LP as soon as seizures stabilized
If seizure confirmed
PHENOBARBITAL 20 mg/kg/dose
Can repeat doses 10-20 mg/kg to maximum of 40-50 mg/kg
Assess response after 15-20 min
If seizures continue, consider one of these 3 options
LEVETIRACETAM (KEPPRA)
40-60 mg/kg/dose IV
Maintenance 40 mg/kg/day
PHENYTOIN
20 mg/kg/dose infusion at 1mg/kg/min in saline, check levels in 1-2h.
LIDOCAINE
2mg/kg iv over 10 min, then 6 mg/kg/h first 12h, then 4 mg/kg/h next 12h and 2 mg/kg/h last 12h
If seizures continue, consider pyridoxine
MIDAZOLAM (DORMICUM)
0.15 mg/kg iv bolus, then 1 µg/kg/min, titrate to maximum 18 µg/kg/min

Algorithm


Seizure suspected in high-risk neonate
Confirm seizures with EEG if available, and monitor with EEG
Check easily correctable causes: Glucose, electrolytes, Ca, Mg, P
Start antibiotics if febrile or suspect sepsis
LP as soon as seizures stabilized
If seizure confirmed
PHENOBARBITAL 20 mg/kg/dose
Can repeat doses 10-20 mg/kg to maximum of 40-50 mg/kg
Assess response after 15-20 min
If seizures continue, consider one of these 2 options
LEVETIRACETAM (KEPPRA)
40-60 mg/kg/dose IV
Maintenance 40 mg/kg/day
PHENYTOIN
20 mg/kg/dose infusion at 1mg/kg/min
saline, check levels in 1-2h.
If seizures continue
MIDAZOLAM (DORMICUM)
0.1-0.2 mg/kg iv bolus, then 1 ug/kg/min,
titrate to maxi. 18 ug/kg/min
PYRIDOXINE
100 mg/kg iv, 2 doses, 2 hrs apart.
Seek specialist advise

Survey Results on Choice of Anticonvulsant in Term (Pediatr Neurol 2012)

	First	Second	Third
Phenobarbital	135 (72.2)	49 (26.2)	2 (1.1)
Lorazepam	41 (21.9)	26 (13.9)	23 (13.1)
Phenytoin	4 (2.1)	76 (40.6)	62 (35.2)
Levetiracetam	2 (1.1)	17 (9.1)	37 (21.0)
Midazolam	5 (2.7)	14 (7.5)	29 (16.5)
Topiramite	0	1 (0.5)	12 (6.8)
Lidocaine	0	4 (2.1)	7 (4.0)
Other	0	0	0

Survey Results on Choice of Anticonvulsant in Preterm (Pediatr Neurol 2012)

	First	Second	Third
Phenobarbital	120 (70.9)	49 (27.2)	3 (1.7)
Lorazepam	42 (23.1)	19 (10.6)	26 (14.9)
Phenytoin	4 (2.2)	77 (42.6)	61 (34.9)
Levetiracetam	2 (1.1)	16 (8.9	33 (18.9)
Midazolam	5 (2.7)	17 (9.4)	28 (16.0)
Topiramite	0	0	11 (6.3)
Lidocaine	0	2 (1.1)	11 (6.3)
Other	0	0	2 (1.1)

Expected Response of Seizures to Anticonvulsant (*Gilman, et al. Pediatrics 1989*)

Anticonvulsant (Cumulative Dose)	Cessation of Seizures (Cumulative Percentage) (%)
Phenobarbital 20mg/kg	40
Phenobarbital 40 mg/kg	70
Phenytoin 20 mg/kg	85
Lorazepam 0.05 – 0.10 mg/kg	95-100

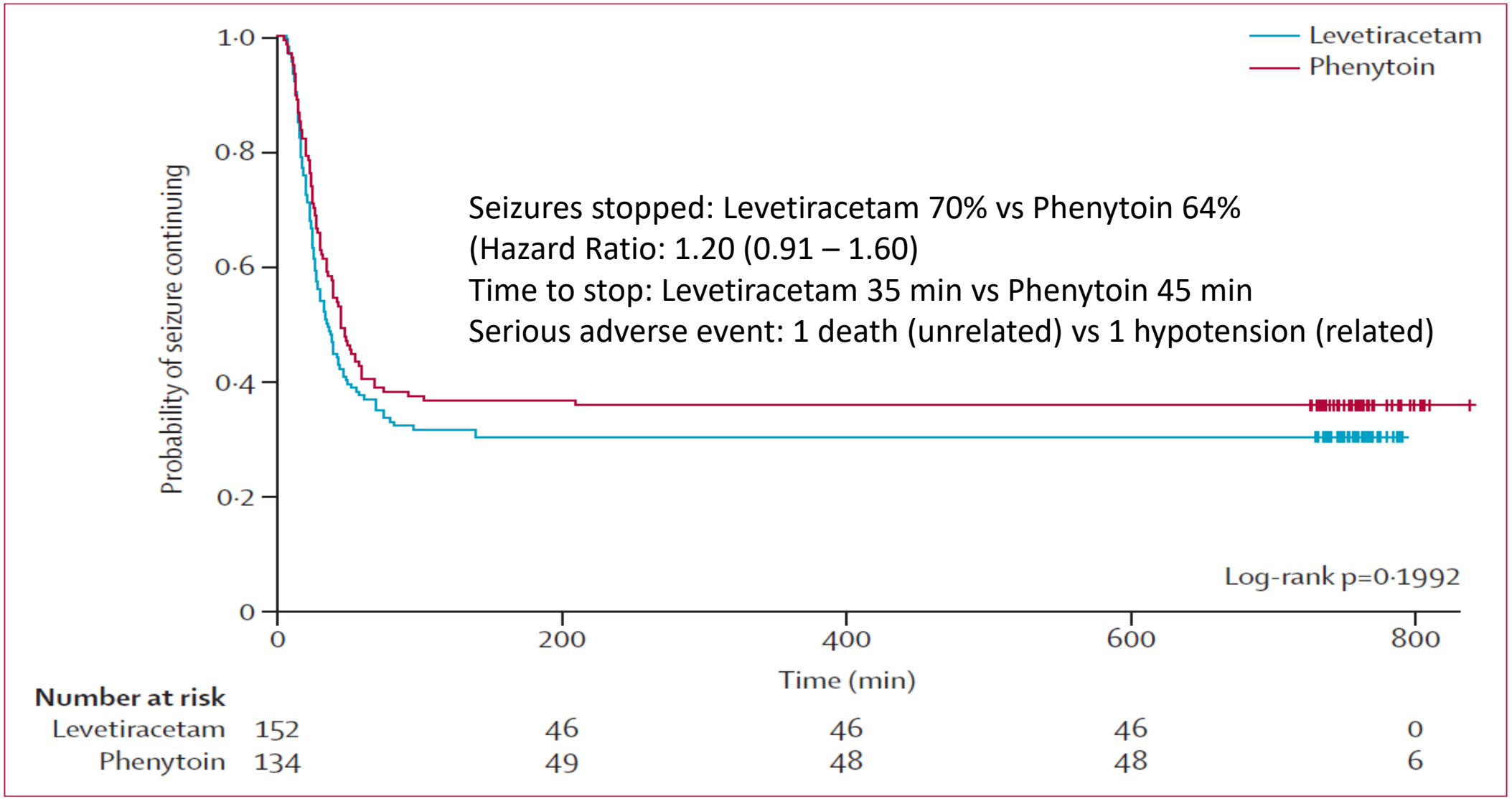
Response of Electrographic Seizures to Phenobarbital and Phenytoin (Painter, *et al. NEJM 1999*)

Anticonvulsant	Seizures Controlled (%)
Phenobarbital alone	43
Phenytoin alone	45
Phenobarbital + Phenytoin	57
Phenytoin + Phenobarbital	62

Mechanisms of Action

Drug	Mechanisms of Action
Phenobarbital	Activates gamma-aminobutyric acid (GABA) receptors
Benzodiazepines (e.g. Dormicum, Lorazepam)	Activates GABA receptors
Phenytoin	Blocks sodium channels
Levetiracetam	Prevents release of neurotransmitters by binding to presynaptic vesicle protein
Lidocaine	Unknown
Topiramate	Blocked AMPA type of glutamate receptor

Levetiracetam and Phenytoin (*Lyttle, et al. Lancet 2019*)



Seizures stopped: Levetiracetam 70% vs Phenytoin 64%
(Hazard Ratio: 1.20 (0.91 – 1.60)
Time to stop: Levetiracetam 35 min vs Phenytoin 45 min
Serious adverse event: 1 death (unrelated) vs 1 hypotension (related)

Maintenance Therapy

- If one or two loading doses stop seizures maintenance may not be required.
- If required:
  - Phenobarbital 2.5 – 5 mg/kg/day iv or oral daily
  - Phenytoin 5 mg/kg/day iv or oral divided 8-12 hourly
  - Levetiracetum (Keppra) 40 mg/kg/day iv or oral divided 8-12 hourly

Duration of Therapy

- If on infusion e.g. Dormicum/ Midazolum, consider weaning after 24 hours with no electrographic seizures
- Duration of therapy depends on likelihood of seizure recurrence or epilepsy if drugs are discontinued
  - Risk for subsequent seizures is 10-30%
  - This depends on 3 determinants
    - Abnormal neurological exam- risk of recurrence is 50%
    - Cause of seizures- risk is 30-50% if asphyxia, 100% if cerebral dysgenesis
    - Background EEG pattern- risk 40% if have marked suppression on EEG

WHO recommendation if examination and EEG normal

- Consider weaning after 72 hours if no seizures
- If required multiple drugs
  - Wean one at a time, starting with the last
  - Phenobarbital to be the last

Prognosis Related to Cause

Cause	Normal Development (%)
Hypoxic encephalopathy	50
Intraventricular haemorrhage	10
Primary subarachnoid haemorrhage	90
Hypocalcaemia - Early - Late	 50 100
Hypoglycaemia	50
Bacterial meningitis	50
Developmental defect	0

Prognosis Related to EEG

EEG Background	Neurological Sequelae (%)
Normal	≤10
Moderate abnormality	50
Severe abnormality	≥90

Prognosis Related to Number of Drugs Required to Control Seizures

(Maartens I. A., et al, 2012)

Outcome	≤2 Drugs	≥ 3 Drugs
Normal Development	50%	5%
Moderate disability	20%	27%
Severe disability	30%	68%

Prognosis Related to Gestational Age

Outcome	Term	Preterm
Mortality	42%	16%
Epilepsy	48%	29%
Cerebral Palsy	63%	25%
Intellectual Disability	52%	25%

I Thank you