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缅甸联邦第一特区卫生部

The Union of Myanmar, SR(1) Department of Health

Epilepsy

Standard Operating Procedure (SOP)

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Epilepsy

Conventional Definition

- *Recurrent unprovoked seizures at least 24 hours apart*

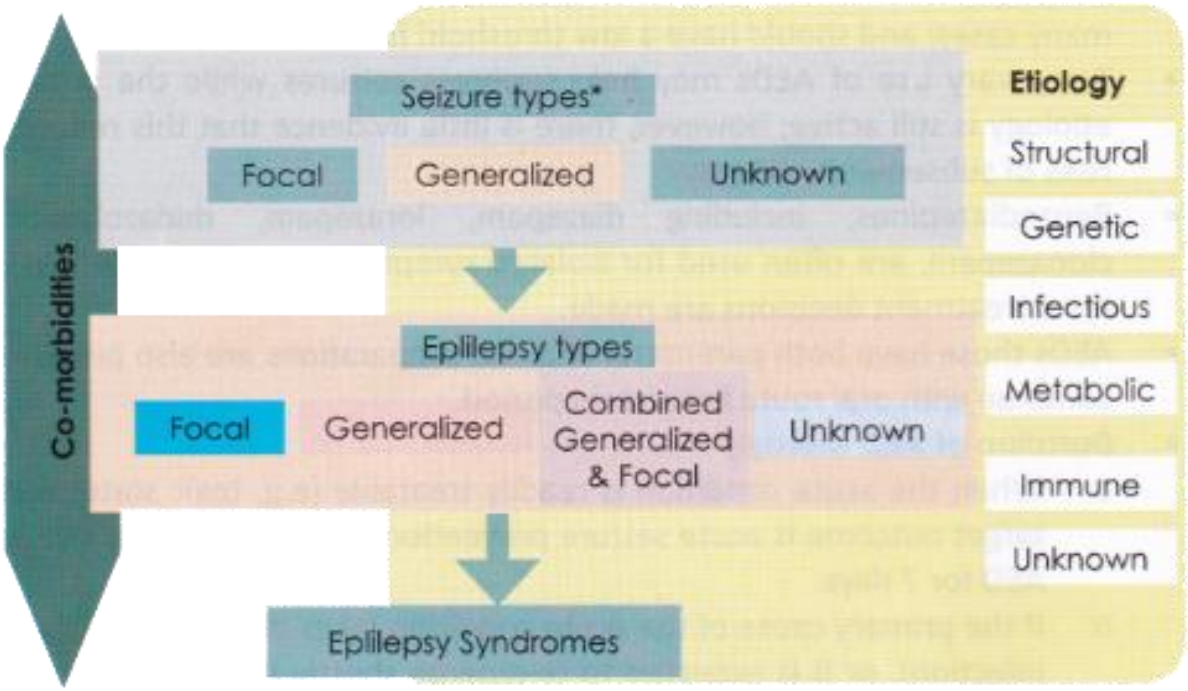
Operational (practical) Clinical Definition of Epilepsy (ILAE 2014)

Epilepsy is a disease of the brain defined by any of the following conditions:

- *At least two unprovoked (or reflex) seizures occurring >24 hour apart*
- *One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years*
- *Diagnosis of an epilepsy syndrome*
- *Epilepsy is considered to be resolved:*
- *If individual with age-dependent epilepsy syndrome, now past the applicable age (or)*
- *If remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.*

New ILAE Classification of Epilepsies (2017)

Framework for classification of the epilepsies



**Denotes onset of seizure.*

- *Classification of epilepsies includes 3 levels of diagnosis*
  - *Seizure type*

- *Epilepsy type*
- *Epilepsy syndrome*

- *All 3 levels might not always be possible to classify in certain setting e.g. if EEG is not available, seizure type can be the only classification.*
- *An etiologic diagnosis and comorbidities should be considered in each step along the diagnostic pathway.*
- *A patient's epilepsy may be classified into more than one etiological category*
- *Comorbidities include learning difficulties, intellectual disability, psychiatric features and mortality risk such as Sudden Unexpected Death in Epilepsy (SUDEP)*

Classification of Seizures Types

Focal Onset		Generalized Onset	Unknown Onset
Aware	Impaired awareness		
Motor Onset Automatisms Atonic Clonic Epileptic spasms Hyperkinetic Myoclonic Tonic **Nonmotor Onset** Autonomic Behavior arrest Cognitive Emotional Sensory		**Motor Onset** Tonic Tonic-clonic Clonic Myoclonic Myoclonic-tonic-clonic Myoclonic-atonic Atonic Epileptic spasms **Nonmotor (Absence)** Typical Atypical Myoclonic Eyelid myoclonia	**Motor** Tonic-clonic Epileptic spasms **Nonmotor** Behavior arrest **Unclassified**

Focal to bilateral tonic-clonic

- *Seizure type classification begins with determination of initial manifestations of seizures (Onset of seizure).*
- *If onset of seizure is missed or obscured, in which seizure is unknown onset.*

Focal onset seizure

- *Specification of level of awareness is optional.*
- *Awareness is knowledge of self or environment.*

- *'Focal aware seizure' means a seizure during which the person is aware of self and environment, even if immobile.*
- *'Focal impaired awareness seizure' means a seizure during which impaired awareness occurs during any part of the seizure.*
- *Any focal seizure optionally may be characterized by motor-onset or nonmotor onset symptoms, reflecting the first prominent sign or symptom in the seizure.*
- *When awareness is not applicable or unknown, classify the seizure directly by motor onset or nonmotor-onset*
- *'Focal to bilateral tonic clonic reflects a propagation pattern of seizure.*

Generalized Onset Seizure

- *'Generalized seizure' means seizure that engage bilateral network from onset (bilateral seizure foci generating epileptiform discharges simultaneously causing generalized type of seizure as initial manifestation)*

Unknown Onset Seizure

- *Unknown onset seizure means a seizure in which the onset is unknown whether focal or generalized.*
- *Unclassified seizure means a seizure in which not only the onset is unknown but also seizure type (motor or nonmotor) cannot be classified due to inadequate information.*

Following FOUR AXIS should be included in the diagnosis of epilepsy:

- *Seizure type*
- *Epilepsy syndrome*
- *Etiology-Genetic/metabolic/structural/infectious/immune/unknown*
- *Comorbidities*

MANAGEMENT OF NEWLY DIAGNOSED. EPILEPSY

Investigations

- *The same principles as first unprovoked seizure except following:*

EEG

- *EEG should be performed only to support a diagnosis of epilepsy*
- *EEG should be done in areas where expert interpretation is available*
- *EEG should be recorded after 3-4 days of last seizure to avoid post-ictal slowing and it can interfere with the interpretation*
- *EEG helps classify seizure type, epilepsy syndrome and predict recurrence*

- *Normal EEG doesn't rule out epilepsy*
- *Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear*
- *When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed*

Neuroimaging

- *MRI is preferred, but CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated*
- *Neuroimaging is indicated if:*
  - *Developed epilepsy during infancy*
  - *Focal seizures that are not typical for one of the benign focal epilepsies of childhood*
  - *History of significant developmental delay, arrest, or regression*
  - *Abnormal neurologic examination, including focal deficits, neurocutaneous stigmata, cerebral malformation syndrome*
  - *Difficult seizure control with first line drugs*

ECG – should be done in cases of diagnostic uncertainty

Other investigations – such as tests for metabolic diseases, genetic analysis are tailored to individual

Treatment

- *Long term AED treatment should be started after second unprovoked seizure*
- *Advise parents for possible side effects and first aid measures.*
- *The aim of treatment is complete seizure control without significant adverse effects.*
- *Choice of AED depends on:*
  - *Epilepsy syndrome if known*
  - *Seizure type if the exact syndromic diagnosis cannot be made*
  - *Etiology*
  - *Co-morbid conditions and*
  - *Availability of the drug*
- *Carbamazepine and valproate appear to be better tolerated and easily available than other first line anticonvulsants.*
- *All drugs are started in low doses and increased gradually (weekly or biweekly depending on severity and frequency) up to a maximum dose till seizure control is achieved or side effects appear.*
- *If no control is obtained with maximum doses of the first drug, then a second first line drug is initiated.*
- *Optimise second drug, then try to withdraw first drug (alternative monotherapy)*
- *If seizure is not controlled, review and check:*

  - *Diagnosis and investigations*
  - *Choice of AED*
  - *Drug dose, frequency and timing*
  - *Drug interactions*
  - *Compliance*
- *Rational combination (adjunctive) therapy should be considered:*
  - *After trying 2 drugs as monotherapy*
  - *In multiple seizure types*
  - *In poor prognostic epilepsy syndromes*
- *Advise for parents*
  - *Educate and counsel on epilepsy*
  - *Emphasize the drug compliance*
  - *Avoid triggers like poor sleep*
  - *Educate for first aid measures during seizure*
- *Withdrawal*
  - *Withdrawal of AED should be considered in patients who have been seizure free for at least 2 years.*
  - *Withdrawal should be carried out slowly at least over 2-3 months and one drug should be withdrawn at a time.*
  - *In case of phenobarbitone and benzodiazepines, withdrawal should be over 6 months or longer because of the possibility of drug-related withdrawal symptoms.*

Indication for referral to tertiary center

- *Management is unsuccessful after 2 drugs*
- *Children under 1 year*
- *If the diagnosis is uncertain*

Table 5.1 Seizure types and choice of AED

Seizure type	First line	Second line	Adjunctive	Others
Focal	CBZ, LTG	LEV, OXC, VPA	CBZ, CLB, LTG, LEV, OXC, VPA, TPM	LEV, OXC, VPA
GTCS	VPA, LTG		CLB, LTG, LEV, VPA, TPM	CBZ, OXC
Tonic or atonic	VPA		LTG	TPM
Absence	VPA	LTG	LTG, VPA	CLB, CZP, LEV, TPM, ZNS
Myoclonic	VPA, TPM, LEV		LEV, VPA, TPM,	CZP, CLB, ZNS

CBZ-Carbamazepine, CLB-Clobazam,
CZP-Clonazepam,
LTG-Lamotrigine, LEV-Levetiracetam,
NTZ-Nitrazepam, OXC-Oxcarbazepine,
PHB-Phenobarbitone, TPM-Topiramate,
VBT-Vigabatrin, VPA-Valporate, ZNS-Zonisamide.

Table 5.2 Dosage and side effects of AEDs – usually given twice daily

Drug	Initial dose	Titrated by	Maximum dose	Side effects/Remark
Carbamazepine	5 mg/kg/day	2.5-5 mg/kg every 3–7 days;	20 mg/kg/day	Stevens Johnson syndrome Hyponatremia Agranulocytosis
Clobazam	**1 month-6 year** 0.25 mg/kg/day	0.25 mg/kg Every 5 days	0.5-1 mg/kg/day (maximum-30 mg/day)	Sedation Constipation Drooling
	6–18 year 5 mg daily	5 mg every 5 days	0.5–1 mg/kg/day (max. 60 mg/day)	

Table 5.3 Dosage and side effects of AEDs – usually given twice daily (Continuum-1)

Drug	Initial dose	Titrated by	Maximum dose	Side effects/Remark
Clonazepam	**1 month-1 year** 250 µg at night for 4 nights **1-5 year** 250 µg at night for 4 nights **5-12 year** 500 µg at night for 4 nights,	Increased over 2-4 weeks	0.5-1 mg at night 1-3 mg at night 3-6 mg at night	Drowsiness Increased salivation, URTI May be given in 2 divided doses
Gabapentin	2-12 year 10 mg/kg (max- 300 mg) od on day 1, bd on day 2, then tds on day 3		30-70 mg/kg daily in 3 divided doses	GI disturbances Weight gain
Lamotrigine	0.15 mg/kg/day with valproate 0.3 mg/kg/day without valproate	Every 2 weeks	5 mg/kg/day 15 mg/kg/day	Drug rash Stevens-Johnson syndrome
Levetiracetam	**1-6 months** 7 mg/kg/day od/bd **6 month-18 years** 10 mg/kg/day od/bd	Increased by 7 mg/kg every 2 weeks; Increased by 10 mg/kg every 2 weeks;	40 mg/kg/day 60 mg/kg/day	Psychiatric and Behaviour problems
Nitrazepam	0.25 mg / kg / day bd/tds		1 mg/kg/day or 10 mg/day	Confusion Dependence Shaky movements, muscle weakness & loss of memory.
Oxcarbazepine	**6-18 year** 10 mg/kg/day (max. 300 mg)	10 mg/kg at weekly intervals	30 mg/kg/day	Hyponatremia

Table 5.3 Dosage and side effects of AEDs – usually given twice daily

Drug	Initial dose	Titrated by	Maximum dose	Side effects/Remark
Phenytoin	3-5 mg/kg/day		5-10 mg/kg/day (max. 15 mg/kg/ day or 500 mg/day)	Gum hypertrophy Hirsutism
Phenobarbitone	**Neonate** 20 mg/kg by slow IV stat dose **1 month-12 year** 2–3 mg/kg/day,	Increased by 2 mg/kg	2.5-5 mg/kg once daily either by slow IV or by mouth; 5-8 mg/kg/day od/bd	Drowsiness Hyperactivity
Prednisolone (Only for infantile spasm)	40 mg/day for 14 days	Increase to 60 mg/day if seizure not controlled at day 7	Gradual reduction over next 2 weeks (total 4 weeks)	Cushingoid features, Irritability, GI bleeding
Topiramate	0.5-1 mg/kg (max. 25 mg) at night for 1 week	increased in steps of 0.25-0.5 mg/kg (max. 25 mg) at intervals of 1–2 weeks;	15 mg/kg/day (max. 250 mg)	Loss of appetite, Weight loss Anhidrosis, Renal stone
Valproate	**Neonate** 20 mg/kg once daily; **1 month-12 year** 10-15 mg/kg/day		10 mg/kg twice daily 30 mg/kg/day (up to 60 mg/kg daily in 2 divided doses)	Weight gain Liver toxicity Teratogenicity
Vigabatrin (For Infantile spasm)	Neonate-2 years 30-50 mg/kg /day bd	Over 1 week	80-100 mg/kg/day bd (max. 150mg/kg/day)	Visual field defects

Drug Interactions

Interactions between antiepileptic drugs may increase toxicity without corresponding increase in antiepileptic effect. interactions are usually caused by hepatic enzyme induction or inhibition.

Enzyme inducers	*They can decrease the plasma concentration of some AEDs, oral anticoagulants, many psychotropic, immunosuppressant, antineoplastic, antimicrobial and cardiovascular drugs, as well as oral contraceptive steroids.*
Carbamazepine	
Phenobarbital	
Phenytoin	
Primidone	

Enzyme Inhibitors	*They can raise plasma concentration of lamotrigine, phenobarbital*
Valproic acid	
Felbamate	
Rufinamide	
Stiripentol	

- *Levetiracetam, gabapentin and pregabalin have not been reported to cause clinically relevant pharmacokinetic drug interactions.*
- *There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially during the first trimester and particularly if the patient takes two or more antiepileptic drugs).*
- *Caution is needed when an enzyme-inducing AED is discontinued, or substituted with a drug which does not have enzyme-inducing effects, because the serum concentration of the affected AEDs may increase, leading to potentially toxic concentrations if dose is not adjusted appropriately.*
- *When valproic acid is added to carbamazepine, inhibition of the enzyme epoxide hydrolase may cause an increase by up to 100% or even more in the serum concentration of the active epoxide metabolite of carbamazepine. potentially leading to CNS side effects*

Table 5.4 Pharmacokinetic interactions between AEDs

	Pre-Existing AED	First generation AEDs				Second generation AEDs			
		CBZ	CZP	PB	VPA	LEV	LTG	OXC	TPM
AED added									
CBZ		---	↓	NC	↓↓	↓	↓↓	↓	↓↓
CZP		NC	---	NC	NC	NC	NC	NC	NC
PB		↓↓	↓	---	↓↓	↓	↓↓	↓	↓↓
VPA				↑↑	---	NC	↑↑	NC	↓
LEV		NC	NC	NC	NC	---	NC	NC	NC
LTG		NC	↓	NC	↓		---	NC	NC
OXC				↑	NC	NC	↓	---	↓
TPM		NC		NC	NC				---

↑↑ – Marked increase in serum concentration
↑ – Mild-moderate increase
NC – Not Change
↓ – Mild-moderate decrease
↓↓ – Marked decrease

Abbreviations: CBZ: Carbamazepine; CZP: Clonazepam; PB: Phenobarbital; VPA: Valproic acid (Valproate); LEV: Levetiracetam; LTG: Lamotrigine; OXC: Oxcarbazepine; TPM: Topiramate

Monitoring

- *Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified but may be measured in children with worsening seizures status epilepticus, suspected noncompliance, or suspected toxicity.*
- *There is no evidence to recommend routine blood tests (blood counts and liver enzymes) either before or during AED treatment.*
- *In special circumstances depending on the clinical situations, blood tests may be considered.*

Examples of blood tests include:

- *Before surgery e.g. clotting studies in those on sodium valproate*
- *Full blood count, electrolytes, liver enzymes, Vitamin D levels, and other tests of bone metabolism (for example, serum calcium and alkaline phosphatase) every 2 years for those taking enzyme-inducing drugs (e.g. Phenytoin, Phenobarbital, Carbamazepine).*
- *liver function tests when there is concern of liver injury, particularly in the presence of comorbidities or other therapies that may affect liver.*