SEIZURES IN CHILDHOOD ***Definitions:-*** **Seizure** is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. It is generally divided into 2 large categories; Focal & Generalized

seizures. **Acute symptomatic seizures** occur secondary to an acute problem affecting brain excitability e.g. electrolyte disturbances or meningitis. **Remote symptomatic seizure** is thought to be secondary to a distant brain injury e.g. old stroke. **Unprovoked seizure** is not an acute symptomatic seizure, i.e. without a precipitating cause. **Epilepsy** is a disorder of brain characterized by enduring predisposition to generate seizures. It requires at least 1 unprovoked seizure with either

a second such seizure in >24 hr or enough EEG and clinical information to

convincingly demonstrate an enduring predisposition to develop

recurrences. **Epileptic syndrome** is a disorder that manifests one or more specific seizure types and has a specific age of onset and a specific prognosis. **Epileptic encephalopathy** is an epilepsy syndrome in which the severe EEG abnormality is thought to result in cognitive & other impairments. **Idiopathic epilepsy** is an epilepsy syndrome that is genetic (or

presumed genetic) and in which there is no underlying disorder affecting development or other neurologic function. **Symptomatic epilepsy** is an epilepsy syndrome caused by an underlying brain disorder. **Cryptogenic (or presumed symptomatic) epilepsy** is an epilepsy syndrome in which there is a presumed underlying brain disorder

causing the epilepsy and affecting neurologic function, but the underlying disorder is not known, hence also called (**unknown epilepsy**).

Seizure disorder is a general term that includes all the above conditions. **Epid.** About **30%** of patients who have a **first afebrile seizure** have later epilepsy, but the risk ↓ to **20**% if neurologic exam, EEG, and neuroimaging where **normal**.

About 4-10% of children experience at least 1 seizure in the first 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1%.

Path. The mechanism of epilepsy often passes into 4 sequential

processes:- 1. **Underlying etiology**; which is any process that can disrupt neuronal

function and connectivity, it includes any pathologic process or genetic

mutation. 2. **Epileptogenesis**; during which the brain turns excitable or epileptic. 3. **Epileptic state of increased excitability** which present in all patients with epilepsy. 4. **Seizure-related neuronal injury** after prolonged status epilepticus →

acute swelling of the **hippocampus** and long-term hippocampal atrophy with sclerosis (shown by MRI). **Types of Epileptic Seizures**

1. Self-Limited Seizure Types:- **Focal (Partial) Seizures** include: Focal sensory seizures (with elementary or experiential sensory symptoms), Focal motor seizures (with elementary clonic motor signs, asymmetrical tonic motor seizures, typical (temporal lobe) automatisms, hyperkinetic automatisms, focal

negative myoclonus or inhibitory motor seizures), Gelastic seizures, Hemiclonic seizures, Secondarily generalized seizures, & Reflex seizures in focal epilepsy syndromes. **Generalized Seizures** include: Tonic-clonic seizures, Clonic seizures +/_ tonic features, Typical absence seizures, Atypical absence seizures, Myoclonic absence seizures, Tonic seizures, Spasms, Myoclonic seizures, Eyelid myoclonia +/_ absences, Myoclonic atonic seizures, Negative

myoclonus, Atonic seizures, & Reflex seizures in generalized epilepsy syndromes. ***2. Continuous Seizure Types:-*** **Generalized Status Epilepticus** include: Generalized tonic-clonic, Clonic, Absence, Tonic, & Myoclonic status epilepticus. **Focal Status Epilepticus** include: Epilepsia partialis continua of *Kojevnikov*, Aura continua, Limbic status epilepticus (psychomotor status), & Hemiconvulsive status with hemiparesis. ***3. Precipitating Stimuli for Reflex Seizures:-*** Visual stimuli (e.g. flickering light, patterns & others), Thinking, Reading, Eating, Startle, Hot water, Music, Praxis, Somatosensory, & Proprioceptive.

Classification of Epilepsy Syndromes

Note: *Syndromes with (*) have a good prognosis.* ***Idiopathic Focal Epilepsies of Infancy and Childhood:-*** Benign infantile seizures (nonfamilial)*, Benign childhood epilepsy with centrotemporal spikes*, & Early and late onset idiopathic occipital

epilepsy*. ***Familial (Autosomal Dominant) Epilepsies:-*** Benign familial neonatal convulsions*, Benign familial infantile convulsions*, Autosomal dominant nocturnal frontal lobe epilepsy. Familial lateral temporal lobe epilepsy, & Generalized epilepsies with febrile seizures plus. ***Symptomatic (or probably symptomatic) Focal Epilepsies:-*** Mesial temporal lobe epilepsy with hippocampal sclerosis, Mesial

temporal lobe epilepsy defined by specific causes, Other types defined by location and causes, Rasmussen syndrome, Hemiconvulsion-

hemiplegia syndrome, Other types defined by location and cause, &

Migrating partial seizures of early infancy. ***Idiopathic Generalized Epilepsies:-*** Benign myoclonic epilepsy in infancy*, Epilepsy with myoclonic astatic seizures, Childhood absence epilepsy*, Epilepsy with myoclonic

absences, Juvenile absence epilepsy*, Juvenile myoclonic epilepsy*, &

Epilepsy with generalized tonic-clonic seizures only*. ***Reflex Epilepsies:-*** Idiopathic photosensitive occipital lobe epilepsy, Other visual sensitive

epilepsies, & Startle epilepsy. ***Epileptic Encephalopathies:-*** Early myoclonic encephalopathy and Ohtahara syndrome, West syndrome (infantile spasm), Dravet's syndrome (severe myoclonic epilepsy in infancy), Lennox-Gastaut syndrome, Landau-Kleffner synd, & Epilepsy with continuous spike waves during slow-wave sleep. ***Progressive Myoclonus Epilepsies:-*** Unverricht-Lundborg, Lafora, Ceroidolipofuscinoses...etc.

 Seizures not necessarily needing a diagnosis of Epilepsy:- Benign neonatal seizures*, Febrile seizures*, Reflex seizures, Drug or other chemically induced seizures, & Immediate and early post-

traumatic seizures.

 General approach to patient with any type of seizure:- ***First Aid*** management by A,B, C with assessment of vital signs. ***History;*** take a detailed hx of seizure by determining the following:- 1. **Trigger** factors for seizure *(see above)*.

2. **Aura & Automatisms** (if present) which precede the seizure (see

later). 3. **Onset** of seizure whether focal or generalized. 4. **Description** of posture of generalized seizure whether it is Tonic

(sustained contraction), Clonic (rhythmic contraction), Myoclonic

(rapid shock-like contraction), Atonic or Astatic (flaccidity which may be associated with fall), Absence (staring, unresponsiveness, and eye flutter for few sec). 5. **Duration** of the seizure.

6. **Postictal** state *(see later)*.

7. **Family** hx of epilepsy. 8. **Exclude** other conditions that mimic seizure. ***Examination;*** general exam (e.g. abnormal facies, skin rash of neurocutaneous syndromes) including growth parameters, & careful neurological exam including fundoscopy. ***Investigations*** are depending on whether the seizure is symptomatic, febrile, or unprovoked seizure. **Febrile Seizures** FS are the **most common** type of seizures that occur in **≈ 2-5%** of neurologically healthy infants and children. It usually occur between 6-60 mo (**0.5-5 yr**) of age with a **temp ≥ 380C** that is **not due to** CNS infection or metabolic disturbance, and in the absence of hx of prior afebrile

seizures. There are several identified **genetic mutations** that contribute for FS & manifested by positive family hx of FS. Although most FS are **polygenic**, in many families the disorder is inherited as **AD trait**.

Simple FS is a generalized (usually tonic-clonic) attack associated with fever, lasting for ≤ 15 min, and not recurrent within a 24-hour period. When any of these features are not met, it is called ***Complex FS*** & when the FS last >30 min, it is called ***Febrile status epilepticus***. ***Simple febrile seizure plus*** is used for those with recurrent febrile seizures within 24 hr.

Simple FS do not carry a risk of epilepsy or mortality, but it may recur in **≈30%** of infants & children after the first episode. However, there are several **risk factors that can predict recurrence of FS** including:- ▯ ***Major criteria;*** age <1 yr, fever 38-390C, & fever duration <24 hr (i.e. an infant with simple & short duration of fever). ▯ ***Minor criteria;*** family hx of FS or epilepsy, complex FS, male, day care, & hyponatremia!.

If patient has no risk factor, the recurrence rate is only 12%, but this

number is doubled or tripled with increasing risk factors. There are also **risk factors for subsequent epilepsy** including:- Simple FS (1%), Recurrent FS (4%), Complex FS (6%), Fever <1 hr before FS (11%), Family hx of epilepsy (18%), Focal complex FS (29%), Neurodevelopmental abnormalities (33%). Almost any type of epilepsy can be preceded as FS; whereas some types

are typically started as FS which called (FS plus) & mainly include:- ▯ **Generalized Epilepsy with Febrile Seizures Plus (GEFS+)** is an AD syndrome with highly variable phenotype, the onset is usually in early childhood and remit in mid-childhood. It is characterized by multiple FS & several types of afebrile generalized seizures. A focal febrile seizures plus epilepsy variant has also been described. ▯ **Severe Myoclonic Epilepsy of Infancy (SMEI)** (or ***Dravet syndrome***)

is considered to be the most severe of phenotypic spectrum of FS plus. It usually caused by new mutation, (although it is rarely inherited as AD). Its onset is in the 1st yr of life & is characterized by febrile and afebrile

unilateral clonic seizures recurring every 1 or 2 mo. ***Note:*** *Many patients with* ***Vaccine Encephalopathy****, i.e. seizures and*

psychomotor regression occurring after vaccination (which presumed to be caused by it) are found to have Dravet syndrome mutations!. ***Approach to patient with febrile seizure:-*** It is similar to the approach of patient with any type of seizure *(see above)*, but with some differences that include:- ▯ **Assess the cause of fever** by proper hx, general exam & investigations

e.g. CBP, blood glucose, serum electrolytes…etc

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Note: CSF exam *by LP should be done in any infant <6 mo with FS because*

seizure may be the only manifestation of meningitis, especially if patient

had received antibiotics which mask the other features of meningitis. **Assess the risk factors of recurrence** (according to the above criteria) with counseling of parents about taking prophylactic medications. **Assess the risk factors for later epilepsy** e.g. neurodevelopmental abnormalities or family hx of epilepsy as well as febrile status epilepticus. Hence EEG +/_ CT or MRI of brain should be taken. ***Note:*** *Early EEG after FS usually do* ***not*** *predict the future recurrence of FS or later epilepsy even if the result is abnormal, thus it should be deferred for at least* ***2 wk*** *after FS.* **Rx.** In case of **febrile status epilepticus**, IV benzodiazepines, phenobarbital, phenytoin, or valproate may be needed *(see later).*

In general, antiepileptic therapy, continuous or intermittent, is **not**

recommended for children with one or more simple FS, but if patient has risk factors for **recurrences**, parents should be educated about how to handle the seizure if it recur & last **>**5 min by rectal diazepam or

buccal/intranasal midazolam. **Management of the underlying illness** also an important part in the general Rx of FS. **Antipyretics** can reduce discomfort of child but, unfortunately, do not reduce the risk of having recurrent FS. **Iron deficiency** has been associated with ↑ risk of FS, and thus screening & Rx for it appears appropriate. **Pv.** If the parents are very anxious about their child's seizure, **intermittent oral diazepam** 0.33 mg/kg or **rectal suppository**

0.5 mg/kg every 8 hr can be given during febrile illnesses to prevent recurrence of FS. Other benzodiazepines, phenobarbital & valproate also can be used. **Chronic antiepileptic therapy** may be considered for

children with high risk of later epilepsy, although the possibility of future epilepsy does not change.

Generalized Seizures Absence Seizures *(Petit mal epilepsy)* can be divided into the following:-

 Typical Absence Seizures; it usually start at 5-8 yr of age & accompanied by flutter or upward rolling of the eyes. Owing to their brevity (usually last for only few seconds) & immediate resumption of what the patient was doing before the seizure, thus they often overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike complex partial seizures they neither have an aura nor associated with automatisms (although it may be accompanied by simple automatisms e.g. lip-smacking or picking at clothing). They also do not have postictal period. Hyperventilation for 3-5 min can precipitate the seizures and the

accompanying 3 Hz spike–and–slow wave discharges on EEG. Most children outgrow seizure before adulthood, although ≈ 25% may also develop generalized tonic-clonic seizures, half before and half after

the onset of absences. Ethosuximide is the drug of choice. Alternatives are valproate or

lamotrigine. ***Juvenile Absence Seizures*** are similar to typical absences but occur at

later age and are accompanied by 4-6 Hz spike–and–slow wave & polyspike–and–slow wave discharges. They are usually associated with juvenile myoclonic epilepsy. ***Atypical Absence Seizures*** have associated myoclonic components and

tone changes of the head and body. They are precipitated by drowsiness

and are usually accompanied by 1-2 Hz spike–and–slow wave

discharges. They are usually more difficult to treat. **Generalized Motor Seizure:-**

It is the **most common** type of seizures which can be either primary or secondarily generalized. If there is no partial component then the seizure usually starts with loss of consciousness or sometimes with a sudden cry, upward rolling of the eyes, and generalized tonic contraction with falling, apnea, and cyanosis. The tonic phase is followed by a clonic phase which slows until the seizure stops. Tongue biting, urinary and stool incontinence & vomiting (with risk of aspiration) are common.

Most such seizures last 1-2 min and the postictal period often follows which usually lasts for 30 min to several hours and associated with semicoma or obtundation with postictal sleepiness, ataxia, hyper- or

hyporeflexia, and headaches. Many patients have single ***idiopathic generalized tonic-clonic seizures***

that may be associated with intercurrent illness or with a cause that

cannot be ascertained. **First aid measures** include positioning the patient on his side, clearing the mouth (if it is open), loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway. The mouth should not be forcely open with a foreign object because this could

dislodge teeth causing aspiration, or with a finger as this could result in

serious injury to the examiner's finger. **Valproate** is the drug of choice for most generalized as well as unclassified epilepsies. Alternatives are lamotrigine, topiramate, or carbamazepine. ॐ ***Benign Generalized Epilepsies:-*** **Typical Absence Seizures** *(see above).*

Benign Myoclonic Epilepsy of Infancy consists of myoclonic and other seizures during the 1st yr of life. Rx by valproic acid, topiramate, or

levetiracetam. **Febrile Seizures Plus Syndrome** manifests as febrile seizures in the patient with multiple types of generalized seizures in multiple family members. Rx by valproic acid, ethosuximide, topiramate, or lamotrigine. **Juvenile Myoclonic Epilepsy *(Janz syndrome)*** is the most common generalized epilepsy in young adults (5% of all epilepsies). It has been

linked to many genes mutations. Typically, it starts in early adolescence

with one or more of the following manifestations: myoclonic jerks in the morning (often causing the patient to drop things), generalized tonic-

clonic, or clonic-tonic-clonic seizures upon awakening, or juvenile

absences. Rx by valproate, topiramate, or levetiracetam. **Photoparoxysmal Epilepsy;** in which the occipital, generalized tonic

clonic, absence, or myoclonic generalized seizures are precipitated by

photic stimuli e.g. flipping through TV channels or viewing video games. Valproic acid is the drug of choice. ***Severe Generalized Epilepsies:*** These are generally associated with intractable seizures and developmental delay.

 Early Myoclonic Infantile Encephalopathy; it usually starts during the first 2 mo of life due to inborn errors of metabolism as severe myoclonic

seizures with burst suppression pattern on EEG. Rx by phenobarbital, phenytoin, or others. **Early Epileptic Infantile Encephalopathy *(Ohtahara Syndrome)*** has similar age of onset and EEG of the above but manifests tonic seizures and usually caused by brain malformations or *syntaxin binding protein-1*

mutations. Rx by corticosteroids or phenobarbital. **Severe Myoclonic Epilepsy of Infancy *(Dravet syndrome)*** starts as focal febrile status epilepticus and later manifests as myoclonic and other seizure types. Rx by valproate, benzodiazepines (e.g. clonazepam), or topiramate. **West Syndrome *(Infantile Spasm)*** is usually starts between 2-12 mo of life and consists of a triad of: infantile spasms (usually occur in

clusters especially in drowsiness or upon arousal), developmental

regression, and typical EEG picture called ***"hypsarrhythmia"*** (high-

voltage, slow, chaotic background with multifocal spikes). These spasms are often overlooked by parents and by physicians, being mistaken for startles due to colic or for other benign paroxysmal

syndromes. Patients with cryptogenic (or idiopathic) disease have normal

development before onset, whereas symptomatic patients have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies e.g. gene mutations. Recognizing of West syndrome (especially cryptogenic), is a medical emergency because if diagnosis delayed ≥ 3 wk, it can affect the long-

term prognosis. **Rx** is usually by **ACTH** which is found to be better than corticosteroids

in management of West synd (although it has the same SE of

corticosteroids). The initial dose of ACTH is 150 IU/m2/day ÷ 2 IM

administered over a 2-wk period with a subsequent gradual taper over

a 2-wk period. Response is usually observed within the 1st wk of Rx

(especially in cryptogenic type), but relapse can occur during tapering (especially in symptomatic type) which entails resumption the protocol again. Another protocol involve low dose of ACTH e.g. 20 IU/day with tapering and discontinue therapy immediately once response is achieved. Another option for Rx is by antiepileptics e.g. vigabatrin (which is the drug of choice), ketogenic diet, or IVIG. **Lennox-Gastaut syndrome** typically starts between 2-10 yr of age and consists of a triad of developmental delay, multiple seizure types &

typical EEG findings. Seizures of LGS include: atypical absences, myoclonic, astatic, and tonic seizures. EEG findings are;1-2 Hz spike–

and-slow waves, polyspike bursts in sleep, and slow background in

wakefulness. Many patients start with Ohtahara syndrome, then develop West syndrome, and then progress to Lennox-Gastaut syndrome. Rx by valproate, lamotrigine, or topiramate. Alternative are IVIG or surgery. **Myoclonic Astatic Epilepsy** is a syndrome similar to but milder than Lennox-Gastaut syndrome that usually does not have tonic seizures or

polyspike bursts in sleep. It has better prognosis than LGS. Rx by valproic acid, ethosuximide or topiramate. **Progressive Myoclonic Epilepsies** are a group of epilepsies characterized by progressive dementia and worsening of myoclonic

(and other) seizures. ***Type I (Unvericht Lundborg disease)*** is secondary to a cystatin B mutation & is more slowly progressive than the other types and usually starts in adolescence. ***Type II (Lafora body disease)*** can have an early childhood onset but may starts in adolescence; it is more quickly progressive, and is usually fatal within the second or third decade. It is due to gene mutations & it manifests periodic acid-Schiff-positive Lafora inclusions on muscle or

skin biopsy; it also may be associated with photosensitivity. Other causes of progressive myoclonic epilepsy include: myoclonic epilepsy with ragged red fibers *(MERRF)*, sialidosis type I, neuronal

ceroid lipofuschinosis, juvenile neuropathic Gaucher disease, dentatorubral-pallidoluysian atrophy, and juvenile neuroaxonal

dystrophy. Rx by valproic acid or topiramate. **Myoclonic Encephalopathy in nonprogressive disorders** is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain e.g. Anglemann syndrome; it consists of almost continuous and difficult-to-treat myoclonic or other seizures. Rx by valproic acid. **Landau-Kleffner syndrome** is a rare condition of unknown cause. It is

characterized by loss of language skills in a previously normal child; at

least 70% have an associated seizure disorder of several types; it is

more common in boys with onset of ≈ 5.5 yr. It is often confused with autism because both conditions are associated with loss of language function. In LKS, **aphasia** may be primarily receptive or expressive, and auditory agnosia may be so severe that the child is oblivious (unaware) to the

everyday sounds. Hearing is normal, but behavioral problems, including irritability and poor attention span are common. Rx by valproic acid +/_ clobazam; alternatives are corticosteroids, IVIG, or surgery. ॐ ***Approach to patient with unprovoked seizure:-*** Hx & Ex are the same as in any type of seizure *(see above)*.

Inv. Blood glucose, serum electrolytes, toxicology screen, metabolic screen, LP, & genetic testing (the last 3 tests are usually done on individual circumstances rather than on routine base). It also should include:- **EEG** is useful in diagnosis of the event, prediction of recurrence risk, identification of specific focal abnormalities and/or epileptic syndromes. Unlike FS, EEG should not be deferred after 2 wk of unprovoked seizure. **Neuroimaging** is usually indicated to exclude organic lesions of brain. MRI is better than CT scan. **Rx.** Anticonvulsants are generally **not recommended** after the **1st** unprovoked seizure **unless** the patient has abnormal EEG, MRI, development, and/or abnormal neurologic exam and/or positive family

hx of epilepsy, because if the patient has normal neurodevelopmental

status, EEG, and MRI, the risk of recurrence is only ≈ 20%. Other considerations may include: type of employment in older patients

(e.g. motor vehicle driving) and the parents' ability to deal with recurrences or with antiepileptic therapy. If the unprovoked seizure is **recurs**, here the antiepileptic drug therapy

must be instituted **immediately**.

Treatment of Seizures & Epilepsy Counseling is an important part of management of a patient with epilepsy by **educating** the family and the child about the disease, its management, and the limitations it might impose and how to deal with them; this involve some **restrictions** on driving as well as some sport

participation e.g. gymnastics & swimming (unless with good supervision). **The mechanism of action of antiepileptic drugs** include: reduce excitability by interfering with sodium or calcium ion channels, by reducing glutamate induced excitatory function, or by enhancing GABAergic inhibition. ***Dose & SE of commonly used antiepileptic drugs:-*** **Valproate,** 15-40 mg/kg ÷ 2, 3 (up to 60 mg/kg with enzyme inducers).

SE; weight gain, tremor, alopecia, hyperammonemia, hepatic and

pancreatic toxicity. **Phenobarbital,** patient <5 yr, 3-5 mg/kg; patient >5 yr, 2-3 mg/kg ÷ 2, 3, or 4 (may be less dose with enzyme inhibitors). SE; insomnia, hyperactivity, fluctuation of mood, aggressive outbursts, liver toxicity, Stevens-Johnson syndrome. **Carbamazepine,** 10-20 mg/kg ÷ 3, 4 (usually start by 1/4 of dose then ↑ by 1/4 every 2-3 days to a full dose). SE; tics, weight gain, nausea, dizziness, transient leukopenia, agranulocytosis, aplastic anemia, liver toxicity, Stevens-Johnson syndrome, hyponatremia. **Oxcarbazepine,** 20-40 mg/kg ÷ 2 (starting dose same as carbamazepine). SE; somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia. **Phenytoin,** <3 yr, 8-10 mg/kg; >3 yr, 4-7 mg/kg ÷ 3, 4. SE; gingival hyperplasia, coarsening of facies, hirsutism, cerebello-

vestibular symptoms (nystagmus and ataxia), Stevens-Johnson

syndrome, liver toxicity. **Benzodiazepines** e.g. Clobazam, 10-20 mg/kg, Clonazepam, 0.01-0.02, Nitrazepam 0.25-1 & Lorazepam 0.03 ÷ 2, 3 (Clobazam & Clonazepam usually start by 1/4 of dose then ↑ by 1/4 every wk to a full dose).

SE; dose-related neurotoxicity (drowsiness, sedation, ataxia), apnea, hyperactivity, drooling. **Lamotrigine,** 1-5 mg/kg ÷ 2 (if patient on enzyme inhibitor), 5-15 mg/kg ÷ 3 (if patient on enzyme inducer). SE; CNS effects e.g. headache, ataxia, dizziness, tremor (but usually less than other antiepileptics), Stevens-Johnson syndrome, rarely liver

toxicity. **Topiramate,** 3-9 mg/kg ÷ 2, 3 (usually start by 1/4 of dose then ↑ by

1/4 every wk to full dose). SE; cognitive dysfunction, weight loss, renal calculi, hypohydrosis, fever, precipitation of glaucoma. **Ethosuximide,** 20-30 mg/kg ÷ 2, 3. SE; blood dyscrasias, GI upset, drowsiness, irritability. **Gabapentin,** 30-60 mg/kg ÷ 3 (usually start by 1/4 of dose then ↑ by 1/4 every day to full dose). SE; few e.g. acute aggression, hyperactivity. **Other antiepileptics** (including newer agents) include: Acetazolamide, Bromide, Diazepam, Methsuximide, Primidone, Tiagabine, Vigabatrin, Zonisamide, Felbamate, Levetiracetam, Rufinamide, Sulthiame. ***Note:*** *See the text for dose & SE of these drugs.* ***Initiation and Monitoring of Therapy:-*** In **non-emergency** situations or when loading is not necessary, the

maintenance dose of the antiepileptic drug can be started. Some may need to be started gradually to build tolerance to SE e.g. sedation. **Levels**

of many antiepileptics usually should be determined after initiation to ensure compliance and therapeutic concentrations. A **steady state** is not

reached until 5 half-lives have elapsed which, for most antiepileptics, is 2-

7 days, except in phenobarbital, it is 2-4 wk. Control with 1 drug ***(monotherapy)*** should be the goal, although some patients eventually need to take multiple drugs & hence consider drug interactions. After initiation of antiepileptics therapy, **EEG** should be monitored

during the 1st few weeks of Rx, then every few months to evaluate

changes of predisposition to seizures. It is also important upon discontinuation of therapy

To monitor SE of older antiepileptics, baseline laboratory studies e.g. CBP, LFTs, & RFTs may be done before initiation & repeated periodically after therapy, especially in the 1st few mo when SE are more likely to

occur. Some SEs are reversible e.g. dose-related leucopenia, whereas others e.g. idiosyncratic aplastic anemia or agranulocytosis are may be irreversable but much less common. There is increased risk of **liver toxicity with valproate therapy** in

children <2 yr of age, especially if they are on polytherapy, and/or with metabolic disorders. Thus, if metabolic disorders are suspected, it should be ruled out by checking amino acids, organic acids, acylcarnitine profile, lactate & pyruvate in addition to LFTs. Another SE is **rickets** induced by phenytoin, phenobarbital, primidone, and carbamazepine (which all are enzyme inducers) through ↓ 25-OH vit D level, thus skeletal monitoring is warranted in chronic therapy with

these agents & vit D supplementation may be recommended. ***Note:*** *Essentially all antiepileptics can cause CNS toxicity and potentially BM toxicity, rashes, and serious allergic reactions. There is also genetic predisposition to develop antiepileptics-induced SE e.g. in Chinese patients, there is a strong*

associated between certain HLA alleles & severe cutaneous reactions induced by some antiepileptics. ***Choice of drug & other considerations:-*** Because there are several options of antiepileptics for each patient, the choice of drug is depend on many considerations include:- **Comparative effectiveness & potential for paradoxical seizure aggravation** e.g. carbamazepine and tiagabine may precipitate absence

and myoclonic seizures; whereas lamotrigine may exacerbate seizures in *Dravet syndrome* and other myoclonic epilepsies. **Ease of initiation & use**; drugs that are started very slowly (e.g. lamotrigine and topiramate) may not be chosen in situations when there is need to achieve a therapeutic level quickly. Drugs that are palatable or given less frequently (e.g. once or twice daily) may ensure compliance. **Patient's and family's preferences** according to the comparative

tolerability of SE of each drug. Teratogenic effect of some antiepileptics should also be considered when they given to a girl in a child-bearing age.

 Ability to monitor the medication and adjust the dose; older medications (e.g. phenytoin) requiring frequent blood levels to gauge efficacy and avoid toxicity, whereas the newer antiepileptic are generally do not require monitoring of blood level. **Mechanism of drug actions**; it is better to avoid combining drugs with similar mechanisms of action e.g. phenytoin and carbamazepine (both work on sodium channels). **Drug interactions** and presence of background medications; a classical example is when use valproate (an enzyme inhibitor) with phenobarbital (an enzyme inducer), this entails either elevation of valproate dose or reduction of phenobarbital dose or both. **Cost and availability**; newer drugs are costy; because antiepileptics

have narrow therapeutic range, thus be careful when switching from one generic name to another which can result in changes of drug level

causing either breakthrough seizures or SE. **Hx of prior response** e.g. if a patient (or family member with the same

problem) had previously responded to a certain antiepileptic, it could be

a desirable choice. **Presence of coexisting seizures or comorbid conditions**; if both absence and generalized tonic-clonic seizures, a drug with broad spectrum of antiseizure effects should be used e.g. valproate or lamotrigine. If migraine is present, choose drug that effective against

both conditions e.g. valproate or topiramate.

 Discontinuation of Antiepileptic Therapy:- In general, discontinuation of antiepileptics usually indicated when

children are free of seizures for **at least 2 yr**. However, in **benign**

epilepsy syndromes, this duration can be as short as **6 mo**, whereas in **more-severe** syndromes e.g. Lennox-Gastaut syndrome, severe myoclonic epilepsy, or remote symptomatic epilepsy, the withdrawal of antiepileptics is usually **not attempted**, otherwise a **prolonged period**

(i.e. >2 yr) of seizure freedom is warranted before deciding withdrawal of antiepileptics. When deciding withdrawal of an antiepileptics, it should be

discontinued **gradually**, often over a period of **3-6 mo** because abrupt discontinuation can result in withdrawal seizures or status epilepticus

(which especially common with phenobarbital and benzodiazepines).

STATUS EPILEPTICUS S.E. is defined as **continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for >5 min**.

Refractory S.E. is S.E. that has failed to respond to therapy, usually with at least 2 medications. **New-Onset Refractory S.E.** (NORSE) can occur in a patient without prior epilepsy & can last several weeks or longer!, it often has a poor prognosis. About 30% of patients presenting with S.E. are having their first seizure, and ≈ 40% of these will develop epilepsy later on. S.E. can be divided clinically into convulsive & nonconvulsive:- **Convulsive S.E.** is the most common type, it include: generalized tonic, clonic, tonic-clonic, myoclonus, complex partial, absence or epilepsia partialis continua. **Nonconvulsive S.E.** include: confusional state, dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking (absence status), fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness

catatonia, and psychotic symptoms. **Path.** The mechanisms leading to the establishment of sustained seizure

activity appear to involve failure of desensitization of AMPA glutamate receptors, and reduction of GABA-mediated inhibition due to intracellular internalization of GABAA receptors. **Et. Febrile S.E. is the most common type** of S.E. in children. Other causes include: new-onset epilepsy of any type, drug wdrawal in patients

on antiepileptics, drug intoxication, hypoglycemia, electrolyte imbalance (hypocalcemia, hyponatremia, hypomagnesemia), acute head trauma, encephalitis, meningitis, postinfectious encephalitis, acute disseminated

encephalomyelitis, ischemic stroke, intracranial hemorrhage, inborn errors of metabolism, brain tumors, or any other disorder that can cause an ordinary epilepsy. Hemiconvulsion Hemiplegia Epilepsy (HHE) is a rare syndrome that

presumably due to focal acute encephalitis. Fever-induced refractory epileptic encephalopathy (FIRES) has been reported in older children. Epilepsia partialis continua can be caused by tumor, vascular etiologies, mitochondrial disease (e.g. MELAS), or Rasmussen encephalitis.

Inv. **Laboratory studies** include: serum glucose, sodium, calcium, or other electrolytes, blood and spinal fluid cultures, toxic screens, and tests for

inborn errors of metabolism. Antiepileptic drug levels need to be

determined if the patient is already on an antiepileptic. **EEG** is helpful in identifying the type of S.E., generalized versus focal, which can guide further testing for the underlying etiology and further therapy. It also can rule out *"pseudo–S.E."*, a psychological conversion reaction mimicking S.E. **Neuroimaging** needs to be considered after the child has been

stabilized. **Rx.** S.E. a medical emergency that is better managed in the **ICU** because

it requires initial and continuous attention to securing airway,

breathing, and circulation with continuous monitoring of vital signs

(including ECG) with attention to the systemic Cxs because some

develop multiorgan failure, as well as determination and management of the **underlying etiology** (e.g. hypoglycemia). Antiepileptic drugs are usually given parenterally in following sequential

steps:- 1. **Benzodiazepines** e.g. Lorazepam IV 0.05-0.1 mg/kg or Diazepam IV 0.2-0.5 mg/kg). If intravenous access is not available; use intranasal

lorazepam, rectal diazepam, or IM/intranasal/buccal Midazolam. ***Note:*** *In infants, a trial of pyridoxine is often warranted.* 2. **Phenytoin** (or fosphenytoin) IV, loading dose 15-20 mg/kg in a rate not >0.5-1 mg/kg/min. A level is usually taken 2 hr later to ensure achievement of therapeutic concentration & accordingly the maintenance dose 3-6 mg/24 hr can be started either soon or after 6 hr. 3. **Phenobarbital** IV loading dose in neonates is usually 20 mg/kg, but in infants and children the dose is 5-10 mg/kg (to avoid respiratory depression), the dose can be repeated if there is no adequate response. ***Note:*** *After the second or third medication is given, the patient may need to be intubated*

4. ***Valproate*** *IV loading 25 mg/kg, maintenance 30-60 mg/kg/24 hr. It also can be given as a third-line medication (instead of phenobarbital). 5.* ***For Refractory S.E.,*** *IV bolus of midazolam, propofol, pentobarbital, or*

thiopental are used with maintenance of corresponding continuous intravenous drip. Subsequent boluses and adjustment of the rate of infusion are usually made depending on the clinical and EEG response. Because most of these patients need to be intubated and paralyzed, the

EEG *becomes the method of choice to follow the seizure activity because*

the goal of Rx is to stop electrographic seizure activity before reducing therapy. Often, ***Barbiturate coma*** *and similar therapies are maintained for 1 or*

more days before it is possible to gradually taper the therapy over a few days. However, in some cases (including NORSE), such therapies need to

be maintained for several weeks or even months. Even though the prognosis in NORSE cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible. Occasionally, inhalational anesthetics (especially isoflorane) are useful. The approach to ***non-convulsive S.E. and epilepsia partialis continua****,*

therapy needs to be tailored according to the clinical manifestations and

often consists of trials of sequential ***oral*** *or sometimes parenteral antiepileptics; whereas the approach for complex partial S.E. is similar to that of convulsive S.E. or sometimes intermediate between convulsive*

and epilepsia partialis, depending on severity. ***Additional therapies*** *may be advocated for refractory S.E. in selected*

cases e.g. steroids, IVIG, surgery, & ketogenic diet; as well as induction of acidosis & hypothermia. ***Sudden Unexpected Death in Epilepsy (SUDEP)*** *is the most common epilepsy related mortality in patients with chronic epilepsy; the incidence is unknown but ranges from 1-5 per 1,000 people with epilepsy. Although the*

precise etiology is unknown, risk factors include polypharmacology, poorly

controlled generalized tonic–clonic seizures, male gender, age <16 yr, long duration of epilepsy, and frequent seizures.