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Epilepsy in Pakistan: national guidelines for clinicians (part 2)

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EPILEPSY IN PAKISTAN: NATIONAL GUIDELINES FOR CLINICIANS (PART 2)

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Advisors: Amir Arain (Vanderbilt University, Nashville, USA), Nizam Ahmed (University of Alberta, Edmonton, Canada)

Appendix A

Epilepsy in Pakistan: Classification and Diagnosis Guidelines for Clinicians:

QUESTIONS ADDRESSED

Q1-Definition of Epilepsy: Adapted from New definition of ILAE review statement 2104
Q2-Q5-Classification of seizures, Epilepsy and epilepsy syndromes and etiologic basis
Q5-Q10-Diagnosis (history, physical exam, relevant lab tests, EEG, Neuroimaging)

Definition of Epilepsy:
In 2013 an international taskforce of the ILAE shaped out a communal definition of Epilepsy. This definition is useful for all or most practical purposes, thus more helpful in management. Epilepsy was defined as recurrent unprovoked seizures i.e. 2 or more at least 24 hours apart. The revised practical definition implies that Epilepsy can be considered even after a single seizure in individuals who have other factors predictive of a second unprovoked seizure, a risk set at 60%. The factors include the diagnosis of an epilepsy syndrome, structural lesions like stroke, CNS infections, intraparenchymal contusions after trauma, as well as reflex seizures such as photosensitive seizures.

Table 1 (2)
A person is considered to have epilepsy if they meet any of the following conditions:
At least two unprovoked (or reflex) seizures occurring greater than 24 hours 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 or the diagnosis of an epilepsy syndrome is clear.

The Seizure:
A seizure is defined as a clinical manifestation of abnormal discharges of a group of cortical neurons. For the purpose of these guidelines seizures are divided into two main categories

Focal/Partial and Generalized.
Focal seizures or partial arise from a focal point in the brain that can be identified by history. An aura is always a sign of a focal seizure. Focal seizures can be simple partial or complex partial. Generalized seizures do not have an identifiable focal point and involve entire brain at the onset.

Simple Partial Seizures
- Locus
  - one site or lobe
- Manifestations
  - Duration: ~30secs
  - Involuntary muscle jerks, sensory (tastes or smells), psychic or emotional (fear)
  - Foul smell, metallic taste, light-headedness, bright light, rising sensation in stomach.
- Consciousness
  - Retained

Complex Partial Seizures
- Locus
  - One or multiple sites, TLE
- Manifestations
  - Duration: 1-3 min
  - Automatisms (picking at clothes, lip smacking, wandering, repeating words)
Clinical diagnosis of an epileptic seizure. A negative EEG and doubtful tracings to be sent to qualified having epilepsy.

Prospective recording of events, including video recording

Role of Home video’s and written discrptions

Patients should have at least 1 contrast enhanced scan in contrast scan may be higher if the entire procedure is to be done in all cases.

and tumors on low field strength machines (becoming a

Aga Khan University, Karachi.

1. MRI should be the imaging investigation of choice in

4. B12, vitamin D and serum iron, Mg, Ca, LFTs and

3. In children and young people, other investigations,

plasma electrolytes, glucose, calcium) to

SWI Axial

Axial DWI min b=1000

Axial TSE T2 5mm

below the age of 18 years.

FLAIR and High Resolution, thin section T2 sequences

5. If temporal lobe epilepsy is in the differential : Coronal

irrespective of whether contrast is given or not. If contrast

the course of their disease.

These guidelines will be revisited and modified on

initial stage of the disease can same much in long term

and classify it in the simplest possible form. These

concise practical plan which will help identify the seizure,

3. when an MRI has identified abnormalities in

considered in children, young people and adultin whom it

30 with suspected epilepsy.

• Refer to Pediatric Neurologist ASAP

• Correct transient metabolic disturbances

• Blood:  glucose, lytes, BUN, creatinine, lactate,

1. Pharmacological management of ABSENCE

10. Continued prophylaxix with AEDs is not recommended

diazepam  orClobazam 0.75mg/kg in two divided doses,

complex FF , febrile status epilepticus.

infection)

FEBRILE SEIZURES or FITS (FF)

5. Do not offer CBZ, gabapentin, OXC, pregabalin,

or vigabatrin is ineffective, offer a steroid (prednisolone or

syndrome.

5. Recommended myoclonic seizures,

vigabatrin is ineffective, offer a steroid (prednisolone or

or vigabatrin with VPA as first-line treatment to infants with

4. Progesterone pill should be avoided.

• There are problems with drug interactions, particularly

• Both AEDs and uncontrolled seizures can cause

• Every pregnancy is different.

CONTRACEPTION

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• There are problems with drug interactions, particularly

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• Every pregnancy is different.

CONTRA...
Neuroimaging should be used to identify structural changes in the brain that may indicate epilepsy. The role of neuroimaging in the diagnosis of epilepsy is to help differentiate between epileptic and non-epileptic events. A range of investigations, chiefly EEG and brain imaging, are used to assess for a neurological lesion or illness.

For the sake of brevity and practical applicability of these guidelines, the syndromes are simplified in few main categories.

Overall three categories in adults three more in children

1. Idiopathic Generalized Epilepsy (IGE) (Juvenile myoclonic epilepsy, absence, GTC, tonic, atonic)
2. Symptomatic localization related epilepsy(SLRE)
   - Temporal lobe epilepsy
   - Frontal lobe epilepsy
   - Occipital lobe epilepsies
3. Symptomatic Generalized Epilepsy eg Lennox- Gastaut syndrome
4. Other Epilepsies like Febrile seizures
5. West syndrome (Infantine spasms)
6. Benign rolandic epilepsy in children

Others like Reflex epilepsies and metabolic syndromes

A detailed list of Epilepsy syndromes is outlined in table 5.

**Table 5**

**EPILEPSY SYNDROMES:** (21-22)

Epilepsy syndromes arranged by age at onset

- **Neonatal period**
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- **Infancy**
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
- **Myoclonic Epilepsy in infancy (MEI)**

Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BECTS)
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Latter onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)

Adolescence – Adult
Juvenile absence epilepsy (JA E)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
Less specific age relationship
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
Distinctive constellations (lesion related symptomatic)
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Frontal lobe Epilepsy (FLE)
Occipital Lobe Epilepsy (OLE)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion–hemiplegia–epilepsy

Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal). Epilepsies attributed to and organized by structural-metabolic causes

Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Benign neonatal seizures (BNS)
Febrile seizures (FS) (22)
Childhood
Febrile seizures plus (FS+) (can start in infancy)
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures

DIAGNOSIS

Making the correct diagnosis is the key to all management. In PWE there are major health, educational and psycho-social implications. It is most important that the physician is sensitive to PWEs and their families when communicating the diagnosis of epilepsy. Epilepsy remains a clinical diagnosis and it can be difficult. Misdiagnosis is frequent about 25% of cases in developed countries, much higher particularly when made by non neurologists. This itself can cause social and financial losses due to the wrong label, not to mention the side effects of unnecessary treatment as well. Conversely, Individuals may die because diagnosis was not made. The diagnosis of Epilepsy remains a clinical diagnosis with all tests providing supplementary data.

History
• A detailed history should be taken from the child, young person or adult
• An eyewitness to the attack, where possible, to determine whether or not an epileptic seizure is likely to have occurred.
• The clinical decision as to whether an epileptic seizure has occurred should then be based on the combination of the description and the different symptoms.
• Diagnosis should not be based on the presence or absence of a single feature.

Physical Exam
PWE presenting with a seizure, a physical examination should be carried out. Vitals, inspection of skin, in children a general physical especially abdominal to r/o hepato-splenomegaly.
Include their cardiac, neurological and mental status and in case of children a developmental assessment where appropriate.[18]
Follow-up should always be arranged
Where non-epileptic attack disorder is suspected, first rule out organic cause then make suitable referral to psychological or psychiatric services for further investigation and treatment.

Epilepsy: Differential Diagnosis
• Many other conditions may be confused with epilepsy:
  – syncope - reflex, cardiac, postural
  – Psychogenic non epileptic seizures PNES
  – TIA
  – panic attacks
  – sleep disorders
  – hypo/hyperglycemia
  – migraine
  – Vertigo
  – intra ventricular colloid cyst,
  – cataplexy,
  – Acute symptomatic seizure secondary to hypoglycemia, alcohol intake, alcohol withdrawal, hyponatremia, eclampsia etc.

Differentiating seizures from syncope/LOC
Questions to ask and if “yes”, support a diagnosis of epileptic seizure:
• At times do you wake up with a cut tongue after your spells?
• At times do you have a sense of déjà vu or jamais vu before your spells?
• At times is emotional stress associated with losing consciousness?
• Has anyone noticed your head turning during a spell?
• Has anyone ever noted that you are unresponsive, have unusual posturing or have jerking limbs during your spells or have no memory of your spells afterwards?
• Has anyone noticed that you are confused after a spell?
• Have you had any episodes while lying down or during sleep?

Questions if “yes”, support a diagnosis of syncope:
• Have you ever had light-headed spells?
• Are all your attacks during the erect position?
• At times do you sweat before your spells?

Differentiating PNES with NES
Questions if “yes” support a diagnosis of PNES:
• Are all events during waking?
• Are you aware of the surroundings while you are unable to respond?
• Is there pelvic thrusting and bicycling that lasts for more usually longer than a couple of minutes.
• Do they always occur in the presence of someone or during an argument?
• Do they last for hours?
• Do they wax and wane over the span of hours with no stereotype?

Questions if “yes” support a diagnosis of ES:
• Are the episodes stereotyped and brief?
• Do they occur during sleep?
• Are they associated with incontinence?
• Is there tongue bite on lateral edges of the tongue?

In Children
Breath holding spells, febrile fits, syncope, parasomnias, behavioral issues should be differentiated.
Role of Home video’s and written discriptions

Prospective recording of events, including video recording and written descriptions, can be very helpful in reaching a diagnosis.

Investigations

A range of investigations, chiefly EEG and brain imaging, are available to assist the clinician in Classifying seizures and epilepsy syndromes of individuals suspected as having epilepsy.

Q. The role of EEG in making a diagnosis of epilepsy:
1. An EEG should be performed to support a diagnosis of epilepsy in PWE in whom the clinical history suggests that the seizure is likely to be epileptic in origin.
2. The normal EEG should not be used to exclude a diagnosis of epilepsy in PWE in whom the clinical presentation supports a diagnosis of a non-epileptic event.
3. The EEG should not be used in isolation to make a diagnosis of epilepsy.
4. The EEG should be reported by a qualified neurophysiologist to minimize over/under reporting. These not being available arrangements for workshops and doubtful tracings to be sent to qualified neurophysiologists be made.
5. The finding of interictal epileptiform activity on EEG can be used to help confirm the clinical diagnosis of an epileptic seizure. A negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure.
6. When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed. A sleep EEG is best achieved through sleep deprivation or the use of Melatonin.
7. A routine EEG should include activation procedures like photic stimulation and hyperventilation if not contraindicated due to state and condition of the patient.
8. Chloral hydrate, clonazepam (in children) and midazolam, diazepam or other benzodiazepines should not be used to sedate the patient prior to EEG.
9. When Temporal lobe Epilepsy is in the differential extra anterior temporal leads should be applied T1 and T2 preferably
10. When occipital lobe involvement is in the differential or occipital discharges are noted a posterior halo or headband montage should be used.
11. Longterm video EEG should be used in PWE who present with diagnostic difficulties after clinical assessment and standard EEG is not supportive or questionable as well as PNES suspected cases.

The role of neuroimaging in the diagnosis of epilepsy

Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies. It is recommended in patients with focal onset seizures or multifocal seizures or when there is an acute change in seizure semiology and frequency in a compliant previously controlled PWE.

1. MRI should be the imaging investigation of choice in children, young people and adults with epilepsy. (specified seizure protocol see appendix) MRI is particularly important in those:
   - who develop epilepsy before the age of 2 years or in adulthood
   - who have any suggestion of a focal onset on history, examination or EEG (unless clear evidence of benign focal epilepsy)
   - in whom seizures continue in spite of first-line medication.
2. Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalized epilepsy has been made.
3. CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children and young people in whom a general anaesthetic or sedation would be required for MRI but not CT. The CT should be at least 64 slice scanner and thin cuts with axial and coronal views.
4. In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness.

The Seizure Protocol MRI: Special Thanks to Dr. Zafar Sajjad, Professor, Department Of Radiology, Aga Khan University, Karachi.

Recommendations

- MRI request should say Seizure protocol
- Though a screening protocol has been put in the end it is important to reiterate that screening MRIs for strokes and tumors on low field strength machines (becoming a norm through Pakistan) is a false economy for Epilepsy.
- All MRI centers should have the protocol and guide the patient if they do not have the specifics.

Protocol Considerations

1. Axial T1 and T2 images standard SE/TSE 5mm should be done in all cases.
2. Fluid inversion (FLAIR) sequences in Coronal Plane in all PWE
3. Gadolinium contrast enhancement increases the cost further and is not necessary in routine cases but helpful in selected cases In patients where sedation or GA is required to enable the test the cost of not doing the contrast scan may be higher if the entire procedure is to be repeated.
Patients should have at least 1 contrast enhanced scan in
the course of their disease.

4. Coronal Flair and T2 images in all seizure protocols irrespective of whether contrast is given or not. If contrast is given post contrast coronal should also be taken.

5. If temporal lobe epilepsy is in the differential: Coronal FLAIR and High Resolution, thin section T2 sequences perpendicular to the long axis of the hippocampus, with and without contrast.

6. If cortical dysplasia is suspected: Sagittal T1 along with Axial T1, T2 FSE/TSE, Axial FLAIR, Axial DWI / ADC. Coronal T2, and 3D Volume GRE – T1, thin-section, whole brain but If there is a known EEG focus then do the coronal thin T2 and FLAIR (from the MTS protocol) in the suspicious EEG location. If any abnormality noticed, then give contrast. NOTE: This will apply only to the paediatric/adolescent population. In this a T1 GRE volume and a T1 IR sequence would be sufficient. DWI is now standard of care on all brain MRIs and should be acquired irrespective of indication.

7. T1 GRE volumes and T1 IR axial slices in all patients below the age of 18 years.

**Recommendation for a Standardized Seizure protocol MRI:**

Should only be carried out on a high field strength (1.5T or above) magnet

Axial TSE T2 5mm
Axial SE T1 5 mm
Coronal FLAIR 5mm
Coronal High Resolution T2 perpendicular to the hippocampus
Axial DWI min b=1000
Post contrast Axial T1 and FLAIR coronal

For the paediatric age group add:

T1 GRE volume. Primary acquisition in the coronal plain.
T1 IR Axial or coronal

For focal seizures or secondary generalization add SWI Axial

people (9)

Show details

**Laboratory tests**

1. Measurement of serum prolactin is not recommended for the diagnosis of epilepsy.

2. In adults, appropriate blood tests (for example, plasma electrolytes, glucose, calcium) to identify potential causes and/or to identify any significant co-morbidity should be considered.

3. In children and young people, other investigations, including blood and urine biochemistry should be undertaken at the discretion of the specialist to exclude other diagnoses, and to determine an underlying cause of the epilepsy.

4. B12, vitamin D and serum iron, Mg, Ca, LFTs and serum creatine kinase, complete blood count, creatinine should be checked especially when on AED’s.

**Cardiovascular tests as an aid to diagnosis**

1. A 12-lead ECG should be performed in adults over age 30 with suspected epilepsy.

2. In children and young people, a 12-lead ECG should be considered in cases of diagnostic uncertainty.

3. In cases of atypical attacks and strong possibility of syncope or any arrhythmia on EKG, a referral to a cardiologist should be considered.

**The role of neuropsychological assessment in the diagnosis and management of epilepsy?**

Neuropsychological deficits are commonly associated with epilepsy and its treatment. Awareness of these problems may facilitate education, social integration and employment.

1. Neuropsychological assessment should be considered in children, young people and adult in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory.

2. When a child, young person or adult with epilepsy is having educational or occupational difficulties.

3. When an MRI has identified abnormalities in cognitively important brain regions.

4. When a child, young person or adult complains of memory or other cognitive deficits and/or cognitive decline.

**Conclusion**

The primary scope of these guidelines is to provide a concise practical plan which will help identify the seizure, and classify it in the simplest possible form. These guidelines hope to provide the physicians treating epilepsy patients with a step wise approach to the diagnosis patient with epilepsy. Though some of these diagnostic tests are expensive making the correct diagnosis at an initial stage of the disease can save much in long term cost of morbidity and polypharmacy.

A health care structure needs to be created on the governmental level to provide subsidized AEDs and diagnostic facilities. These guidelines will be revisited and modified on applicability every four years. People with epilepsy remain at the centre of this guideline, and the need for services to consider the needs of each individual and their care givers have been focused.

**Appendix B**

**EPILEPSY IN CHILDREN AND NEONATES**

**Diagnosis:**

Making the correct diagnosis is extremely important in
children due to long term implications like educational, psychosocial, intelligence quotient, development, self esteem and the psychological impact on their parents. Misdiagnosis is more common in peads than in adults, particularly when diagnosis is made by non specialists. Recognizing and classifying seizures is different in neonates , infants and children as does the etiology and management.

**Classification:**
See Appendix A

**Treatment:**
The basic principles of AED treatment in children with epilepsy (CWE) remain the same as in adults. CWE should be encouraged to participate in normal activities with their peers, supervised where needed depending on the type of activity and seizure history. Parents of CWE should be advised not to be over protective.

**NEONATAL SEIZURES**
Diagnosis of neonatal seizures is essentially clinical and must be based on observation of repeated or rhythmic activity which is (subtle) for example orofacial twitching, (clonic) limb movements, jerking not stopped when held, autonomic disturbances, stiffening (tonic) or sustained posturing of limbs. Home video of events is helpful in diagnosis and further management of such neonates needs to be done under specialized care.

**Table 1: Causes of Neonatal seizures**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIE (32%)</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage (17%)</td>
<td></td>
</tr>
<tr>
<td>CNS infection (14%)</td>
<td></td>
</tr>
<tr>
<td>Infarction (7%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorders (6%)</td>
<td></td>
</tr>
<tr>
<td>Inborn errors (3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown (10%)</td>
<td></td>
</tr>
<tr>
<td>Drug withdrawal (1%)</td>
<td></td>
</tr>
</tbody>
</table>

**Ideal Metabolic Evaluation should include:**
- Blood: glucose, lytes, BUN, creatinine, lactate, pyruvate, ammonia, biotinidase, quantitative amino acids, very long chain fatty acids
- Urine: quantitative amino acids
- CSF: cell count, glucose, protein, pyruvate, lactate, quantitative amino acids, HSV PCR

Unfortunately these are very costly and some need to be sent abroad increasing cost.

**General Recommendations**
- All neonates with seizures should be given pyridoxine 50-100mg

**Table 2. Differential Diagnosis of Neonatal Seizures by Day of Presentation.**

<table>
<thead>
<tr>
<th>Day 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic brain injury (subdural, subarachnoid, or intraparenchymal hemorrhages)</td>
<td></td>
</tr>
<tr>
<td>Hypovolaemia and ischemia</td>
<td></td>
</tr>
<tr>
<td>Stroke (arterially more likely than venous)</td>
<td></td>
</tr>
<tr>
<td>Infection (bacterial or viral)</td>
<td></td>
</tr>
<tr>
<td>Severe refeedling metabolic disorder (e.g., deficiency of sulfite oxidase or non-ketotic hyperglycinemia)</td>
<td></td>
</tr>
<tr>
<td>Systemic hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbance (hypocalcemia or hypernatremia)</td>
<td></td>
</tr>
<tr>
<td>Intoxication (maternal substance abuse)</td>
<td></td>
</tr>
</tbody>
</table>

**Day 2**
- Strobe (especially venous thrombosis)
- Traumatic brain injury
- Inborn metabolic disorder (especially glucose transporter defect)

**Day 3**
- Partial defect is metabolism (e.g., organic acidemias or aminoacidopathies)
- Benign neonatal convulsions
- Strobe (either interal or venous)
- Withdrawal (from maternal substance abuse)
- Traumatic brain injury
- Inborn metabolic disorder

* This disorder requires medical or surgical intervention.

**Table 3. Oral AEDs that can be used in Neonatal seizures**

- Neonatal screening TSH,
- lactic acid, if acidosis biotin should be given and acidosis corrected.
- serum AA and urine organic acids if inborn errors suspected e.g, sibling history or consanguineous marriage.
- Stabilize vital signs and treat underlying hypotension
- Correct transient metabolic disturbances
- Phenobarbital is first line agent
- Lorazepam and Phenytoin second line
- Valporate and Levitiracetam if myoclonic fits.
- See table for oral AEDs that can be used
- Refer to Pediatric Neurologist ASAP

<table>
<thead>
<tr>
<th>AED</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primidone</td>
<td>15 to 25 mg/kg per day in 3 doses</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.1 mg/kg in 2 to 3 doses</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>10 mg/kg, then 15 to 20 mg/kg per day in 2 doses</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>10 to 25 mg/kg, then 20 mg/kg per day in 3 doses (avoid iv in neonates but can be given with L carnitine if refractory SI)</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>50 mg/kg per day in 2 doses, up to 200 mg/kg per day (caution visual field defects) Lamotrigine: 12.5 mg in 2 doses (care needed to titrate caution SJS, TE) Zonisamide: 2.5 mg/kg per day</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>10 mg/kg per day in 2 doses. I.V available can be used as add-on esp where myoclonus is prominent) 2012</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>2.5 mg BID, up to 4 mg/kg per day,</td>
</tr>
<tr>
<td>Folinic acid, biotin and pyridoxine trial in refractory cases prednisolone 1mg/kg if all else fails</td>
<td></td>
</tr>
</tbody>
</table>
Acute Therapy of Neonatal seizures:
If with hypoglycemia- Glucose 10%: 2ml/kg IV
If no hypoglycemia- Phenobarbital:20mg/kg IV loading dose
   If necessary : additional phenobarbital:
   5 mg/kg IV to a max of 20 mg/kg
   (omit if respiratory compromise)
Phenytoin: 20 mg/kg, IV (1 mg/kg/min)
   Lorazepam:0.05-0.10 mg/kg, IV
All neonates with intractable seizures should be given 50-100mg iv pyridoxine.

FEBRILE SEIZURES or FITS (FF)
1. Fits that occur in otherwise normal infants from age 6 months to 6 years on during high fever greater than 101°F or 38°C. (fever not caused by meningitis cerebral infection)
2. Single FF occurs in 3-5% of children. Recurrent FF occurs in one third of children with FF. Recurrence is higher if first FF within first year of life.
3. FF may be simple or complex and this helps prognosticate the FF. Simple is brief, generalized <1 min. Complex FF comprise only 15% of FF, usually partial onset, longer >15 minutes or multiple fits in the same illness. These are more likely to develop epilepsy in the future.
4. LP (lumbar puncture) should be done in children suspected of CNS infection
5. Recurrent simple FF do not warrant investigation and need parental counseling
6. EEG is not required in Simple FF, it should be done in complex FF, febrile status epilepticus.
7. FF is never focal
8. Neuroimaging has no role in simple FF
9. FF counseling should include lowering body temperature, acutely acting antiepileptic drugs like diazepam or Clobazam 0.75mg/kg in two divided doses, or phenobarbital prophylactically during fever only.
10. Continued prophylaxis with AEDs is not recommended in FF.
11. Parents need to be taught the use of rectal diazepam 0.5mg/kg and/or buccal midazolam (0.2-0.3mg/kg) for acute termination of seizure if lasts longer than 2 minutes.
12. Parents should be cautious not to let fever rise in such children.

CHILDHOOD Specific EPILEPSY SYNDROMES: (pharmacologic management)

Pharmacological management of ABSENCE SEIZURES
1. Ethosuximide or sodium valproate as frontline treatment to children, patients with absence seizures. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate. NOTE: Ethosuximide is not available in Pakistan.
2. Lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated.
3. If two firstline AEDs are ineffective in patients with absence seizures, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine, sodium valproate. Be aware of teratogenic risks of sodium valproate
4. If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide (not available in Pakistan)
5. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.
6. Avoid VPA with clonazepam in childhood absence it can induce absence status.

<table>
<thead>
<tr>
<th>Childhood Absence Epilepsy : Recommendations for Pakistan</th>
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<tbody>
<tr>
<td>1st Choice</td>
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<tr>
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<tr>
<td>VPA</td>
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Pharmacological management of myoclonic seizures
1. Offer VPA as first-line treatment to children, with newly diagnosed myoclonic seizures, unless it is unsuitable.
2. Offer LEV or TPM if VPA is not suitable or patient not responding (Be aware that TPM has a less favourable side effect profile than LEV and VPA)
3. Offer LEV, VPA or TPM as adjunctive treatment to children, with myoclonic seizures if frontline treatments are ineffective or not tolerated. Be aware of teratogenic risk of VPA
4. If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, epilepsy specialist and consider clobazam, clonazepam, piracetam or zonisamide or steroids.
5. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

Pharmacological management of INFANTILE SPASMS
1. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when an infant presents with infantile spasms. These children will need polytherapy.
2. Offer a steroid (prednisolone or tetracosactide or ACTH)
or vigabatrin with VPA as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. Carefully consider the risk-benefit when using vigabatrin or steroids.
3. Offer vigabatrin with VPA as first-line treatment to infants with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide). Carefully consider the risk-benefit when using vigabatrin or steroids.

**Pharmacological management of Dravet syndrome**
1. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Dravet syndrome.
2. Consider VPA or TPM as first-line treatment in children with Dravet syndrome.
3. If first-line treatments in patients with Dravets syndrome are ineffective or not tolerated try clobazam or stiripentol (* not available in Pakistan) as adjunctive treatment.
4. Do not offer CBZ, gabapentin, LTG, OXC, PHT, pregabalin, tiagabine or vigabatrin.

**Pharmacological management of LENNOX-GASTAUT SYNDROME**
1. Discuss with, or refer to, a tertiary paediatric/epilepsy specialist when a child presents with suspected Lennox–Gastaut syndrome. Most require poly-therapy.
2. Offer VPA as first-line treatment to children with Lennox–Gastaut syndrome.
3. Offer LTG, TPM as adjunctive treatment if first-line treatment with VPA is ineffective or not tolerated.
4. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate and polypharmacy with benzodiazepines, trial of steroids may also be considered.
5. Do not offer CBZ, gabapentin, OXC, pregabalin, tiagabine or vigabatrin.

**Pharmacological management of BENIGN EPILEPSY WITH CENTROTEMPORAL SPIKES (BECTS)**
1. Discuss with the child, and their family whether AED treatment for benign epilepsy with Centro-temporal spikes,
2. Offer LTG or CBZ* as first-line treatment.
3. Offer LEV, OXC*, or VPA (avoid in older girls) as 2nd line if above fail
(*Be aware that carbamazepine and oxcarbazepine may exacerbate or unmask continuous spike and wave during slow sleep, which may occur in some children with benign epilepsy with centrotemporal spikes. Be aware of teratogenic risks of VPA and rash with LTG.)
4. Consider adjunctive treatment if a second well-tolerated AED is ineffective.
5. Offer clobazam, gabapentin, LTG, LEV, OXC, VPA, TPM, LCM if first-line treatments fail.

**Refractory childhood epilepsy syndromes adjuvant AEDs**
Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, pregabalin, tiagabine, vigabatrin, LCM, and zonisamide, PB, PHT, TPM. Carefully consider the risk–benefit ratio when using vigabatrin due to irreversible visual field constriction in up to 30% Ketogenic diet, medical marijuana, methylprednisone, clobazam, nitrazepam, clonazepam, lorazepam are also recommended in refractory cases.

**Note**
- In children, the diagnosis and management of epilepsy within the first few years of life may be extremely challenging. For this reason, children with suspected epilepsy should be referred to tertiary services early, because of the profound developmental, behavioural and psychological effects that may be associated with continuing seizures.
- Behavioural or developmental regression or inability to identify the epilepsy syndrome requires immediate referral to tertiary services.
- Children, young people and adults with specific syndromes such as Sturge–Weber syndrome, the hemispheric syndromes, Rasmussen’s encephalitis and hypothalamic hamartoma should be referred to a tertiary epilepsy service.
- All PWE and learning disabilities should have a risk assessment including:
  - bathing and showering
  - preparing food
  - using electrical equipment
  - managing prolonged or serial seizures
  - the impact of epilepsy in social settings
  - SUDEP

**Annexure: RCT review and our modifications**

**Partial Seizures: Children Recommendations**
**Level A: OXC**
**Level B: None (RTC) LTG (NICE)**
**Level C: CBZ, PB, PHT, TPM, VPA, VGB**
**Level D: LTG, ZNS, CLB, CZP**
**Level E: Others**
**Level F: None**
**Recomendations: PB*, VPA, CBZ, OXC, LTG, VPA*
**Generalized Tonic Clonic Seizures: Children**

**Recommendations**
- Level A: None
- Level B: None
- Level C: CBZ*, PB, PHT*, TPM, VPA
- Level D: OXC* LEV, LTG, (considered first line NICE)
- Level E: Others
- Level F: None

*may aggravate tonic clonic seizures and more commonly other generalized seizure types, should be used with caution

**Women of childbearing age with epilepsy**

**Introduction**

Most women with epilepsy who are receiving optimal treatment for their epilepsy, and who are well-informed, supported and fully counselled have uncomplicated pregnancies, normal deliveries, and healthy children. However in Pakistan no such proper program or counseling or management plan is available. Thus number of complications and perinatal problems are high in WWE (women with epilepsy). A number of issues need to be considered

- Both the disease and its treatment may alter the menstrual cycle and fertility.
- There are problems with drug interactions, particularly with hormonal contraceptives. Some methods of hormonal contraception may not be as effective in women taking AEDs. The effectiveness will depend on which AED(s) are being taken. Effective contraception has an additional importance in women with epilepsy because of the risks associated with an unplanned pregnancy to the women and the developing fetus.
- AEDs are associated with teratogenic effects.
- Both AEDs and uncontrolled seizures can cause adverse effects during pregnancy.

Conversely, pregnancy and menses can affect seizure control due to hormonally induced alteration of the seizure threshold.
- Every pregnancy is different.

Management of Epilepsy in Women can be divided into 5 phases:
1. **COUNSELLING**
2. **CONTRACEPTION**
3. **PREGNANCY**
4. **LABOUR**
5. **POST PARTUM AND LACTATION**

**COUNSELLING**

- In order to enable informed decisions and choice, and to reduce misunderstandings, women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause.
- All healthcare professionals who treat, care for, or support women and girls with epilepsy should be familiar with relevant information and the availability of counseling the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child.
- Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of sodium valproate to the unbornchild, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. (see table drugs and teratogenicity)

**CONTRACEPTION**

1. CBZ, PHT, OXC, TPM and barbiturates reduce the effectiveness of oral contraceptives necessitating the use of alternative methods, or special highdose regimens of oral contraceptives. Even with this precaution, the effectiveness of the oral contraceptive is reduced. (Ia NICE)
2. Hormone-releasing IUDs are effective as a method of contraception in women taking AEDs.
3. There is limited evidence that progesterone implants (specifically levonorgestrel) are ineffective in women taking enzyme-inducing AEDs.
4. Progesterone pill should be avoided.
5. There is no evidence on the effectiveness of emergency contraception in women taking enzyme-inducing AEDs.
6. There needs to be a National Pregnancy registry.

**PREGNANCY**

7. AED’s should be continued in pregnancy. There is no benefit of stopping AED’s after 3-4 weeks of conception (nurial tube formed), and risk of seizures outweighs risk of continued AED exposure in vitro.

**Table 12: AED’s and Pregnancy Risk:**

<table>
<thead>
<tr>
<th>AED</th>
<th>Pregnancy Risk</th>
<th>Nonmalformal sodium</th>
<th>Omalformal sodium</th>
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<tbody>
<tr>
<td>Adduct</td>
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<tr>
<td>Carbamazepine</td>
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<td>Lamotriginate</td>
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<td>Ethosuximide</td>
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<td>Phenytoin</td>
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<td>Primidone</td>
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<td>Tiagabine</td>
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<tr>
<td>Topiramate</td>
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*Pregnancy risk codes:*
- Adduct: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Carbamazepine: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Ethosuximide: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Phenytoin: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Primidone: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Tiagabine: Studies in pregnant women show no increase in risk of fetal abnormalities.
- Topiramate: Studies in pregnant women show no increase in risk of fetal abnormalities.

8. When should screening for structural fetal anomalies be performed in pregnant women with epilepsy?
A recent NICE guideline reviewed the evidence on the detection of structural fetal abnormalities in healthy pregnant women. It is recommended that pregnant women should be offered an ultrasound scan to screen for structural anomalies, ideally between 18 to 20 weeks of gestation, by an appropriately trained sonographer and with equipment of an appropriate standard.
9. When should folic acid be started?
• All women on AEDs should be offered 5mg per day of folic acid before any possibility of pregnancy.
• There is limited evidence to show that folic acid supplementation reduces the risk of neural tube defects and other congenital malformations in women taking AEDs.
• Women who are planning pregnancy should be advised to take 400mcg of folic acid from when they begin trying to conceive until the 12th week of pregnancy and that those who suspect they are pregnant and who have not been taking supplements should start folic acid supplements 5mg immediately and continue until the 12th week of pregnancy.
10. Serum levels of AEDs are of help during pregnancy. The dose of AEDs should not be increased routinely if levels are low except if seizures start occurring, and at the time of delivery to avoid breakthrough seizures during the stress of labour.
11. If preterm labor is threatened in women taking enzyme-inducing AEDs, 48mg betamethasone (double the normal dose) should be given over 48 hours.
12. Vitamin K 10mg i.m. at 34 and 36 weeks is recommended for all women unless there is a contraindication.
13. Some counseling points:
What are the dangers of seizures in women who are pregnant or post-natal?
• Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women and girls who plan to stop AED therapy.
• Women and girls with generalised tonicclonic seizures should be informed that the fetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency.
• There is no evidence that simple focal, complex focal, absence and myoclonic seizures adversely affect the pregnancy or developing fetus.
• Generalized tonicclonic seizures are likely to result in more profound hypoxia than in the nongravid state due to increased maternal oxygen requirements. This may have adverse affects for the fetus.

POST-CONCEPTION
14. Counselling about safety during child rearing, like to keep baby in a crib next to the bed, care to avoid dropping the baby especially JME.
15. Breast Feeding guide: All mothers should be encouraged to breast feed.
16. The dosage of AEDs such as LTG, LEV, OXC may have to be reduced if they were raised during pregnancy but after 6 weeks post partum.
17. Spacing between pregnancies should be recommended and safe/ effective contraceptive methods should be offered to all WWE.

MANAGEMENT OF STATUS EPILEPTICUS Guidelines for Pakistan:
When a convulsive seizure continues for a prolonged period (longer than 5 minutes), or when convulsive seizures occur one after the other with no recovery in between patient is considered to be in Status Epilepticus. Convulsive status epilepticus is an emergency and requires immediate medical attention. TREAT HARD and TREAT FAST

APPENDIX : STATUS EPILEPTICUS PROTOCOL
Definition:
1. Convulsive Status Epilepticus (CSE): in adults and children older than 5 years is characterized by continuous convulsive seizures lasting more than 5 minutes or two or more seizures in 20 minutes without gaining consciousness in between.
2. Non-convulsive status epilepticus (NCSE) is mental status changes from baseline for at least 30 minutes associated with ictal discharges on EEG. It should be suspected in patient after convulsive seizure who is not regaining consciousness.
3. Refractory Status Epilepticus: (RSE) Seizure activity that continues after first and second line AED therapy have failed. This can be CSE and NCSE.

MANAGEMENT OF CONVULSIVE STATUS EPILEPTICUS: PRE-HOSPITAL STAGE: FIRST 5-10 MINUTES
• Children: Rectal diazepam 0.5mg /kg or buccal midazolam 0.2-0.3mg/kg ; adults: rectal diazepam 10mg or buccal midazolam 10mg (home)
• Maintain iv line as soon as possible and administer 5-10mg diazepam or 3-5 mg midazolam iv push followed by saline flush. (EMS)
• Secure airway, breathing and circulation

HOSPITAL STAGE: 5-20 MINUTES
• Diazepam 0.2mg /kg (maximum 10mg) over 1minute,OR midazolam 0.2mg/kg ivp or im, upto 10mg; wait 5 minutes for seizures to terminate. Order and prepare IV phentoin. If seizure terminates investigate cause of seizures further, if not repeat again in children
<2 years give neurobioniv to replace thiamine and biotin.
• Give Oxygen, stabilize airway, respiration and hemodynamic parameters, apply pulse oximetry.
• Send RBS, LFT, renal functions, electrolytes, BUN, and CT scan. LP and CSF analysis if CNS infection suspected.
• Start PHF infusion 15-20mg/kg at maximum rate of 50mg/min (1mg/kg/min in small children) AVOID dilution in glucose solution. Monitor heart rate and blood pressure, contraindicated in patients with heart block or hypotension SBP<95. (phosphorytin 15-18mg PE/kg/min at max rate of 150mg PE/min is internationally the drug of choice but unfortunately not available in Pakistan)

HOSPITAL STAGE : ESTABLISHED GSCE 20-60 minutes:
• If seizures continue 5-10 mins after PHF, reload 5-10mg/kg IV at same rates as above
• Seizures continue give Sodium Valproate 25-35mg/kg at a rate of 6mg/kg/hr
• Arrange for intubation, anaesthesia on board
• Seizures continue give iv levetiracetam loading 1000-3000mg (adults) at 2-5mg/kg/min
• Seizures continue next stage RCE.
• Start phenobarbitone 50-100mg/min IV loading dose, and if intubated can start infusion 0.5-5mg/kg/hr or skip to next stage RCE

HOSPITAL STAGE: Refractory Status Epilepticus (more than 60 mins)
• Prepare to intubate and transfer to ICU
• Start lacosamide 200-400mg IV 200 mg over 15 mins (adults only)
• Ideally obtain central venous access and continuous hemodynamic monitoring through arterial line and EEG monitoring
• Anaesthetic agents: Adults and children midazolam 0.2mg/kg IV bolus followed by 0.1-0.4mg/kg/hour continuous iv infusion OR propofol 2-5mg/kg IV bolus followed by 5-10mg/kg/hr IV infusion OR thiopental 10-20mg/kg IV bolus followed by 0.5-1mg/kg/hr IV infusion till EEG shows burst suppression (pharmacologic coma)
• Continue coma phase for 12 hours after last seizure
• Weaning phase: reduce infusion of anesthetic agent every 3 hours with EEG monitoring, if seizures recur re-institute coma with the same anesthetic to the dose where seizures were responsive.
• Add topiramate 200 mg bolus and 100 mg tid.
• Identify and treat medical complications correct acidosis if pH 7.2 or if symptomatic in the form of cardiac disturbances. Vigorously treat infections, avoid penicillin and quinolone group of antibiotics.
• If seizures continue and autoimmune or idiosyncratic modulation is suspected consider puse steroids and ivIG.

POST STATUS PHASE
• Maintenance therapy, all AEDs that were used to treat the status should be continued on maintenance dosage till patient remains seizure free for at least 3-7 days if patient awake, if GCS remains low gradually remove under EEG coverage.

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<tr>
<th>TIME IN MINUTES</th>
<th>STEPS</th>
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<tbody>
<tr>
<td>0-5</td>
<td>Thiamine 100mg iv 50% dextrose, along with Midazolam 5mg IV over 1 minute. Diazepam 5mg IV over 2 minutes and repeat in 5 minutes</td>
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<tr>
<td>6-10</td>
<td>Phenytoin 15 mg/kg IV at 50 min with Blood Pressure and ECG Monitoring — IF SEIZURES PERSIST If no seizures and patient not waking up EEG, if electrographic seizures continue as GSCE</td>
</tr>
<tr>
<td>10-20</td>
<td>IV Valproate-30 mg/kg OVER 10 minutes. Then give 20 mg/kg over 5 minutes — If patient on multiple medications or hepatic failure, give I/V Levitiracetam 1gm. over 15 minutes. IF SEIZURES PERSIST — Call Neurology/Epilepsy Service IN rbate If no clinical seizures but patient remains unconscious EEG if Electrographic seizures continuous EEG monitoring and IN rbate If PT. DNR or delay in intubation, give IV lacosamide 300 mg over 15 minutes.</td>
</tr>
<tr>
<td>30-60</td>
<td>IV Phenobarbital 20 mg/kg at 50-100 mg/min. IV lacosamide 300mg. Continuous EEG monitoring IF SEIZURES PERSIST 1. Continuous IV Midazolam load 0.2 mg/Kg; repeat 0.2 to 0.4 mg/Kg bolus every 5 min until seizures stop up to max of 2 mg/Kg. Initial clv rate 0.1 mg/kg/h (0.05-2mg/kg/hr) OR 2. clv Propofol Load 1 mg/Kg. Repeat 1-2 mg/kg boluses every 3-5 min max of 10mg/kg. Initial clv rate is 2 mg/kg (range 1-15 mg/kg/h) IF SEIZURES PERSIST</td>
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<tr>
<td>&gt; 60 min</td>
<td>1. c IV Pentobarbital Load 5-10 mg/kg up to 50mg/min. 2. Repeat 5 mg/kg boluses until seizures stop. Initial clv rate is 1 mg/kg/h (range 0.5-10mg/kg/h) till suppression-burst pattern on EEG monitoring 3. clv Continuous intravenous infusion</td>
</tr>
</tbody>
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Author’s Contribution:
Dr. Fozzia Siddiqi: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review
Dr. Shaukat Ali: Data collection, data analysis, manuscript writing, manuscript review
Dr. Mughis Sheerani: Data collection, data analysis, manuscript writing, manuscript review
Dr. Tipu Sultan: Data collection, data analysis, manuscript writing, manuscript review
Dr. Shahid Mustafa: Data collection, data analysis, manuscript writing, manuscript review
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