Consensus Guideline on the Management of Epilepsy in Egypt: A National Delphi Consensus Study

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Abstract

In epilepsy, early diagnosis, accurate determination of epilepsy type, proper selection of anti-seizure treatment, and monitoring; all are essential. However, despite recent therapeutic advances and conceptual reconsiderations in the classification and management of epilepsy, serious gaps are still encountered in day-to-day practice in Egypt as well as several other limited resources countries. Premature mortality, poor quality of life, disabilities, diminished family function, cognitive problems, poor treatment outcomes, comorbidities, and significant economic burden are major challenges that impose urgent actions to be implemented at all levels. In recognition of this, a group of Egyptian epilepsy experts met through a series of consecutive meetings to specify main concepts and questions concerning the diagnosis, evaluation, and management of Epilepsy, with an ultimate goal of establishing a nationwide Egyptian consensus to guide health care professionals in the management of patients with epilepsy in general and to declare a pragmatic pathway for patients with drug-resistant epilepsy. The consensus was developed through a modified Delphi methodology. A thorough review of the most recent relevant literature and international guidelines was performed to evaluate their applicability to the Egyptian situation. Afterward, several remote and live rounds were scheduled to reach a final agreement for all listed statements. With the implementation of these unified recommendations, we believe this will bring about substantial improvements in both the quality of care and treatment outcomes for persons with epilepsy in Egypt.

1. Introduction

Epilepsy is a chronic disorder of the brain that is marked by episodes of seizures. It arises from various pathological insults and is considered heterogeneous rather than a specific disease [1]. The prevalence of epilepsy is around 50 million people worldwide as per the World Health Organization (WHO) figures, and the majority of them (almost 80%) reside in low- and middle-income countries. Moreover, the premature mortality risk is almost threefold in persons with epilepsy (PWE) compared to the general public [2]. The prevalence of epilepsy in Egypt was estimated to be 6.98/1000 [3]. The lifetime prevalence of epilepsy in children and adolescents in upper Egypt was estimated to be 9.7/1000, with a lower prevalence among adolescents than children below 12 years (7.2/1000 and 10.8/1000, respectively) [1].

Despite epilepsy being one of the oldest illnesses in history [4], serious difficulties and challenges are still encountered across the entire patient journey. Establishing the right epilepsy diagnosis and detecting the root cause are challenging tasks, particularly where cultural constraints are obstacles to acceptance of the disease [5]. Unlike other neurological disorders, epilepsy can develop due to different neuropathological alterations rather than a standalone disease [6]. For every five patients treated for epilepsy, one out of them does not really have the disease [7]. Further, a substantial increase in the number of anti-seizure medications (ASMs) has been notable in recent years, making the choice of the proper treatment more complex [8]. According to the WHO data, proper diagnosis and treatment of epilepsy can turn 70% of PWE into seizure-free [2]. What is more, epilepsy can be controlled pharmacologically in almost 70% of patients, and the remaining 30% presents a major challenge due to resistance and refractoriness to drugs [6].

In Egypt, inadequacies in the care of PWE (ex. misdiagnosis, inappropriate medication, sudden unexpected death that could have been avoided) are well recognized. This is now changing with the emergence of this nationwide consensus. With all the efforts that this initiative bears, it represents one of a series of efforts being devoted to creating a significant impact on the health of Egyptians in recent years. We believe that implementing these structured recommendations will substantially improve both the quality of care and treatment outcomes for PWE in Egypt. The goal of this gathering is to prepare a consensus/recommendation from Egyptian Epilepsy Experts about the definition, diagnosis, and management of epilepsy of different age groups in Egypt.

2. Methods

This initiative encompassed several consecutive steps **(**Fig. 1**).** Starting July 2020, a Delphi panel (DP) of 34 Egyptian experts; including 31 neurologists and 3 neurosurgeons who were representing 14 Egyptian university hospitals and health care institutions; met through a series of web-based meetings to specify main concepts and questions concerning the diagnosis, evaluation, and management of Epilepsy. Four main sections were identified to constitute the main sections for this consensus' recommendations, namely: (1) definition, classification, and diagnosis of epilepsy, (2) choice of ASMs, (3) status epilepticus, and (4) drug-resistant epilepsy (DRE). Once the broad lines were identified, a structured literature review was conducted to address the preliminary statements under each section. A thorough literature review was conducted across different databases, including Web of Science, Medline, PubMed, and the Cochrane Library.

The consensus was developed through a modified Delphi methodology [9]. For the draft statements of each section, 1 remote and 1 live voting rounds were scheduled. During the first round, each DP member anonymously voted on each statement using a 3-point scale (1 = agree, 2 = neutral, 3 = disagree). For each statement, if 80% or more of the DP members voted with an agreement, a consensus was considered achieved. During the second round, live discussion and refinement of the statements that didn't reach consensus took place, followed by final live voting. The final round of voting for the last section took place on April 2021.

3. Results

Section I: Definition, Classification, and Diagnosis of Epilepsy

I.1. Definition and classification of epilepsy

The Steering Committee (SC) consensus upon adopting the International League Against Epilepsy (ILAE) 2014 definition of epilepsy and 2017 classification of epilepsies and seizures [10–12]. The full voting results are presented in the **Supplementary file**.

I.2. General outlines for diagnosing epilepsy

The SC agreed upon adopting the following recommendations:

1. To determine whether the patient might have had an epileptic seizure, the patient's and eyewitness's (where possible) detailed histories should be taken.
2. A clinical examination that comprises a neurologic examination is crucial since recurrence can be predicted through an abnormal examination after a first seizure.
3. In children and young people, a specialist neurologist with training and expertise in epilepsy should establish the diagnosis of epilepsy.
4. Healthcare professionals should enable PWE and their carers and/or family members to be involved in all decisions as partners. Further, their culture, race, and any specific needs should be taken fully into consideration.
5. If the epilepsy diagnosis cannot be definitely confirmed, further investigations are recommended, and/or referral to a more specialized Epilepsy clinic should be done.
6. Where psychogenic non-epileptic seizures (PNES) are confirmed, suitable referrals to psychiatric services should be made for further investigation and treatment.

I.3. Electroencephalography for epilepsy diagnosis:

The SC agreed that electroencephalography (EEG) is a valuable tool for the confirmation and classification of seizure disorders. The SC highlighted the below recommendations:

1. Diagnosis of epilepsy should not be excluded by a normal EEG.
2. Epilepsy is a clinical diagnosis; however, EEG can be indicated in certain conditions[a].
3. When there is clinical doubt, EEG should be used to assist the classification of epileptic seizures and epilepsy syndromes.
4. In case of suspected epilepsy and non-epileptic attack disorder, short-term video-EEG should be available (preferably with a suggestion) to support the diagnosis.
5. In the case of patients who present diagnostic difficulties, inpatient video-EEG monitoring and other specialist investigations (including polysomnography with full EEG montages) should be available to support the diagnosis.
6. When findings of a standard EEG have not supported epilepsy diagnosis or classification, a sleep EEG should be performed.
7. The test should not be performed in patients with a typical history of other disorders (such as migraine and syncope) since the probability of epilepsy will be minor.
8. Increasing recording time to 60 minutes on conventional EEG is a more convenient and cost-effective method of enhancing the EEG diagnostic yield compared to multiple conventional EEGs.
9. In the case of patients with a likelihood of a non-convulsive epileptic seizure as suggested by the clinical history, the finding of epileptiform abnormalities is specific to assess the risk of seizure recurrence.

10. Video-EEG is the gold standard for the diagnosis of epilepsy and its mimics.
11. Recording attacks in the patient's usual setting is an advantage of the ambulatory EEG recording, but it is still inconvenient and costly.
12. All 21 electrodes and placements should be used (10-20 system) as recommended by the International Federation of Clinical Neurophysiology.
13. Periods when the eyes are closed and open, should be included in the recordings.
14. Photic stimulation, sleep deprivation, and hyperventilation can be used routinely (unless medical or other justifiable reasons).

I.4. Electrocardiography for epilepsy diagnosis:

The SC agreed upon adopting the following recommendations:

1. In all patients with blackouts, the 12-lead electrocardiography (ECG) has great importance in the assessment of those patients, especially in older age groups (since epilepsy can be stimulated by abnormal heart rhythm).
2. ECG must be a routine channel during EEG recording and should be performed as a baseline before starting ASM.

I.5. Magnetic resonance imaging:

The SC consensus to adopt the following recommendations:

1. Magnetic resonance imaging (MRI) protocol should follow the ILAE consensus on the "recommendations for the use of structural MRI in the care of PWE" [13].
2. MRI is mandatory for brain imaging in PWE (before 2 years or in adults).
3. Any patient with focal onset on history, EEG, or examination (unless clear evidence of benign focal epilepsy) is indicated for MRI.
4. Any patient with seizures that continue despite first-line ASM is indicated for MRI.
5. Loss of seizure control with ASMs or variation in the pattern of seizure that may suggest a progressive underlying lesion is an indication for MRI.
6. When the diagnosis of Genetically Generalized Epilepsy (GGE) is confirmed, there is no necessity for routine brain imaging. However, in case of suspicion of another diagnosis, an MRI epilepsy protocol is advised.
7. Computed Tomography (CT) has a role when there is an urgent need for assessment of seizures or when MRI is contraindicated.

I.6. Genetic testing:

New technologies for detecting different types of mutations have substantially improved understanding of epilepsy genetics, thus, allowing in some patients for more efficient genetic diagnosis. This new

approach can improve patient care, enhance prognosis, and support treatment decisions [14]. The SC agreed upon the following recommendations:

1. Expert advice on the genetics of epilepsy is still not available in Egypt.
2. For an accurate epilepsy syndromic diagnosis, the family history should be taken. Family history is also important to determine the risk of epilepsy development in children of parents with epilepsy.

I.7. Neuropsychological assessment:

The SC consensus upon adopting the following recommendations:

1. Access to specialist neuropsychological advice should be available, as deemed appropriate by the multidisciplinary team.
2. Referral for a neuropsychological assessment is indicated for:
   i. Any PWE who is suffering from learning or occupational hardness. Memory problems should be identified by a cognitive screen in the first instance since they can be distressing and/or disabling.
   ii. It is indicated as a part of the pre-surgical evaluation.

I.8. Laboratory studies:

The SC agreed upon adopting the following recommendations:

1. In adults, appropriate blood tests should be considered (complete blood count (CBC), glucose, calcium, thyroid-stimulating hormone (TSH), plasma electrolytes) to specify possible causes and/or any significant comorbidity.
2. In adolescents and adults, urine toxicology screening should be done according to individual considerations and circumstances.
3. Consider lumbar puncture (LP) for a child <6 months, a patient who fails to return to baseline /meningeal signs or suspect high intracranial pressure (imaging before LP is mandatory).
4. In children and young people, other investigations should be considered in special situations (including urine and blood biochemistry) to identify an underlying cause of epilepsy and exclude other diagnoses.

Section II: Choice of Anti-Seizure Medication

II.1. General Considerations:

The SC agreed upon adopting the following recommendations:

1. In case of failure of the initial ASM (due to continued seizures or adverse effects), initiation of an additional drug should take place and then escalate up to an adequate or maximum tolerated dose (this drug may be an alternative first-line or second-line drug). Afterward, slow tapering off the first drug should be done. Caution is needed during the changeover period.

2. In case the second drug is worthless, tapering of it or the first drug should be considered (this should be implemented considering efficacy, side effects, and tolerability of the drugs before starting another drug).
3. No available evidence shows whether alternative substitution or add-on therapy is more effective as a treatment strategy in the setting where the frequency of seizures after 1st medication reduced less than 50% or occurred on interval less than three-fold original seizures frequency.
4. A considerable proportion of patients who do not achieve seizure freedom on monotherapy can benefit from combination therapy with the newer antiepileptic drugs.
5. The decision to discontinue anti-seizure medication requires an individualized risk-benefit assessment by an epileptologist. In addition, the decision must be discussed with PWE and the patient's family/caregiver with explanation of all the benefits and risks of medication discontinuation.
6. Drug withdrawal can be considered after a minimum of 2-5 years without a seizure based on the risk of seizure recurrence. Gradual withdrawal over 2-6 months is recommended. If seizures recur, the effective well-tolerated drug previously used should be restarted using the last effective dose.

II.2. Choice of ASM According to Different Epileptic Syndromes in Different Age Groups (after excluding treatable metabolic causes):

The SC agreed upon adopting the recommendations depicted in **Table 1.**

II.3. Choice of ASM According to Different Epileptic Syndromes in Adolescents:

The SC agreed upon adopting the recommendations depicted in **Table 2.**

II.4. Choice of ASM According to Seizure Type:

The SC agreed upon adopting the recommendations depicted in **Table 3.**

II.5. The use of brand versus generic drugs

The SC agreed upon adopting the following recommendation:

1. A "brand" version of an ASM is not superior to a generic. What is important is finding a version of a drug that suits the patient and is taken consistently. "Consistency of supply" means getting the same drug version with every prescription.

Section III: Status Epilepticus

Status epilepticus (SE) is "a neurologic emergency characterized by prolonged seizure activity or multiple seizures without return to baseline, with substantial morbidity and mortality rates" [29]. The SC consensus to adopt the following recommendations for the definition, diagnosis, evaluation, and management of SE **(Figure 2)**:

III.1. Definition:

The SC agreed upon adopting the following definition:

1. SE is defined as “a seizure with 5 minutes or more of continuous clinical and/or convulsive seizure activity or recurrent seizure activity without recovery of consciousness between seizures” [30].

III.2. Diagnosis and Evaluation of SE:

The SC agreed upon adopting the following recommendations:

1. The diagnostic evaluation begins in parallel with Emergent Initial Therapy.
2. For diagnosis, finger stick glucose should be checked, pulse oximeter and cardiac monitoring should be started as soon as possible.
3. If intravenous (IV) access is already established, the IV diazepam should be preferentially used.
4. In case of the absence of IV access, intramuscular (IM) midazolam should be given as soon as possible.
5. Blood and serum laboratory evaluation typically includes CBC, basic metabolic panel, calcium, and magnesium determinations.
6. In several patients, some laboratory studies may be helpful such as liver enzymes, troponin, blood gas determinations, toxicology screen, pregnancy test, and ASM drug level.
7. If a myocardial injury or cardiac arrhythmia is doubtful, ECG should be performed as far as possible.
8. Non-contrast CT of the brain is the first imaging study to be considered in the Emergency Department (ED) if MRI is not feasible.
9. In the case of febrile patients or if there is a suspected subarachnoid hemorrhage or central nervous system infection, LP should be performed preferably after obtaining the CT scan.
10. In case of the patient does not return within 30 minutes to the normal consciousness level, EEG should be done to identify non-convulsive SE in those patients.
11. Non-epileptic spells simulating SE can be differentiated from SE by indicators such as poorly coordinated thrashing, preserved consciousness or purposeful movements, head rolling, eyes held shut, back-arching, and pelvic thrusting.

III.3. Emergent Treatment:

The SC agreed upon adopting the following recommendations:

1. Emergent prehospital treatment with benzodiazepines is needed; while assessing any abnormalities (hypoxia, hypoglycemia, or hypotension must be managed accordingly).
2. If benzodiazepines are not administered to the patient before ED arrival, and the patient is still seizing, IV benzodiazepines should be included in the initial dosing when IV access is immediately available.

3. When IV access is not available, IM, per rectum (PR), buccal, or intranasal benzodiazepines should be administered together with IV placement.
4. Unless IV access is immediately available, initiate IM. In adults or children over 40 kg, IM midazolam 10 mg, in children 13–40 kg, the IM midazolam dose is 5 mg, and in children<13 kg, the IM midazolam dose is 0.2 mg/ kg.
5. When two IV accesses are immediately available, one for diazepam 0.15 mg/kg IV (up to 10 mg/dose), and the second line for one of the ASMs would be better to start simultaneously with the initial benzodiazepine rather than waiting for a response for benzodiazepine.
6. Among second-line ASMs, the first-line choice will be either phenytoin or levetiracetam in their standard loading doses. Also, lacosamide can be used if the previous ASM failed or is unavailable.
7. If seizures have stopped after the initial ASM, and the patient had awakened, a maintenance dose of loading ASMs should be started if indicated. It can be given either orally or intravenously.

III.4. Treatment of Refractory Status Epilepticus:

The SC agreed upon adopting the following recommendations:

1. SE is considered refractory when the seizures continue despite urgent and emergent treatment.
2. Early (within one hour) drug-induced coma with continuous IV infusion of an anesthetic drug is recommended for refractory status epilepticus (RSE) with EEG target of burst suppression.
3. The recommended loading dose of IV midazolam* infusion is 0.2 mg/kg at 2 mg/min. Then, repeated boluses every 5 min of 0.2–0.4 mg/kg should be administered until the seizures stop, up to a maximum loading dose of 2 mg/kg. Then, a continuous infusion at 0.05–2 mg/kg/h should be started.
4. Propofol IV infusions are an alternative at 1–2 mg/kg IV over 3–5 min as a loading dose and then repeated boluses every 3–5 min of the same amount until the seizures stop. The propofol infusion rate of 30–200 mcg/kg/min should be maintained.
5. Pentobarbital at 5 mg/kg as a loading dose, followed by a maintenance infusion of 1–3 mg/ kg may be used in children with refractory SE more frequently because of adverse effects with propofol.
6. Continuous EEG monitoring is mandatory during drug-induced coma and weaning after 24 hours from starting the anesthetic drug. If not, we can perform EEG at least once every 24 hours for one hour while the patient is under the effect of anesthesia.
7. At least, second ASM* (phenytoin, sodium valproate, levetiracetam, lacosamide, and topiramate) must be added to the initial ASM in this stage before starting weaning of the anesthetic drug.
8. Occurrence of seizures during weaning of anesthetic drug categorize the patient as Super-Refractory SE (SRSE).

III.5. Treatment of Super-Refractory Status Epilepticus:

The SC agreed upon adopting the following recommendations:

1. Thiopental should be initiated in the recommended dose with progressive weaning of the previous anesthetic over the following 24 hours.
2. If a burst-suppression EEG pattern without epileptic activity has been achieved during 24 hours under thiopental and SE recurs after thiopental weaning, adding phenobarbital should be considered in therapeutic dose for at least 24 hours, after which weaning should again be tried.
3. If SRSE recurs after weaning of thiopental in association with phenobarbital or if it persists under thiopental anesthesia (epileptiform discharges), then ketamine in the recommended dose should be associated with thiopental.
4. If SRSE persists or recurs, progressively longer periods (>24 hours) of sedation should be considered.
5. Gradual weaning -over 24 hours- of each anesthetic should be done until complete suspension.
6. Simultaneous weaning of two anesthetics is not recommended.
7. In case of persistence or recurrence of SRSE despite the adoption of all previous recommendations; then the patient should be maintained in burst suppression under combined anesthesia with thiopental and ketamine, and all of the following therapeutics should be considered (according to availability and applicability); magnesium sulfate – intravenous bolus (4 g) followed by a continuous infusion (2 - 6 g/h) aiming for plasma levels of 3.5 mmol/L, pyridoxine 100 - 600mg daily oral dose, immunotherapy, therapeutic hypothermia if available, and a ketogenic diet.
8. In case of persistence or recurrence of SRSE despite the adoption of all previous recommendations; then the patient should be maintained in burst suppression under combined anesthesia with thiopental and ketamine, and all of the following therapeutics should be considered (according to availability and applicability); vagus nerve stimulation, epilepsy surgery, transcranial magnetic stimulation, trigeminal nerve stimulation, and electroconvulsive therapy.

Section IV: Drug-Resistant Epilepsy

There are still more than 30% of patients with epilepsy progressing to DRE despite the continuous development of antiepileptic drugs in the past few decades, with a considerable increase in morbidity and mortality. Currently, the only possible way to cure patients with DRE may be surgical treatment. However, it is always challenging to achieve a definitive effect with surgical treatment alone. It needs to be combined with other treatment methods due to the complicated etiology and unclear pathogenesis of DRE [31].

IV.1. Definition:

The SC agreed that the Egyptian Epilepsy consensus adopts the ILAE definition of DRE as “failure of adequate trials of two or three tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.

IV.2. Who and when to refer for evaluation in a specialized/tertiary epilepsy care facility:

The SC agreed upon adopting the following recommendations:

1. All PWE should have access to a tertiary service via their specialist whenever require it.
2. When one or more of the following criteria are present, referral should be considered:
   i. Uncontrolled epilepsy with medications within a maximum of 1 year.
   ii. Management is unsuccessful after two adequate trials.
   iii. Children < 2 years of age (due to the profound psychological, developmental, and behavioral effects that might be correlated to continuing seizures).
   iv. A PWE who is at risk of, or experiences, intolerable medication side effects.
   v. Presence of a unilateral structural lesion in patients with DRE.
   vi. Presence of a diagnostic doubt about the type of seizures and/or epilepsy syndrome.
   vii. 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.
   viii. Patients who require diet therapy for epilepsy.
   ix. Psychiatric comorbidity and/or negative baseline investigations should not be a contraindication for referral to a tertiary service.

IV.3. Characteristics of a specialized/tertiary epilepsy facility

The SC agreed upon adopting the following recommendations:

1. Multidisciplinary team, experienced in the assessment of patients with DRE, the expertise of multidisciplinary teams should include psychology, psychiatry, neuroradiology, social work, counseling, clinical nurse specialists, occupational therapy, neurology, neuroanesthesia, neurophysiology, and neurosurgery.
2. Investigations that must be available (i.e., as a minimal requirement) are; video EEG, MRI epilepsy protocol, functional imaging, ASMs drug level, and psychometric battery.
3. A specialized epilepsy facility should offer Basic and Advanced therapeutic Intervention(s).

IV.4. Once referred to a specialized/tertiary epilepsy facility, the patient should undergo:

The SC agreed upon adopting the following recommendations:

1. History in detail (to exclude causes of pseudo intractability): ex. PNES, cardiogenic (arrhythmias) and vasovagal events (syncope), Parasomnias, movement disorders, seizures triggers, drug-related problems: non-adherence, drug-drug interaction, or inappropriate choice or dose.
2. Review and order investigations, including routine labs such as CBC, liver, and kidney function tests, electrolytes (calcium, sodium, and magnesium), blood sugar, screening metabolic studies, genetic epilepsy panel is considered.
3. Video-EEG to characterize the epilepsy types and rule out PNES.
4. Imaging (MRI- HARNESS protocol) studies must be scrutinized once epilepsy diagnosis is confirmed to ascertain the presence of an epileptogenic focus and facilitate a possible surgical work-up.

5. In the presence of high suspicion of focal seizures; if no epileptogenic lesion is found on MRI, other ancillary tests include ictal single-photon emission computed tomography (SPECT) and positron emission tomography (PET) should be performed. In addition, eloquent regions of the brain can be studied using functional studies such as functional MRI.
6. Invasive testing can be considered in case of unclear localization or if a more precise definition of the relationship of the eloquent cortex to the epileptic cortex is needed.
7. Psychiatric evaluation and psychometric testing are usually warranted in the patients' pre-surgical evaluation.

IV.5. Epilepsy Surgery Referrals in Egypt:

The SC agreed upon adopting the following recommendations **(Figure 3)**:

1. Importance of Documentation: Documenting an attempt to titrate the dose of the appropriate medication to a target clinically effective dose range should be made to show the adequateness of the medication trial.
2. Sustained Seizure-Freedom: Seizure-free duration that is at least three times the longest interseizure interval prior to starting a new intervention (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer.
3. Treatment Failure: Recurrent seizure(s) after the intervention has been adequately applied.
4. Undetermined Seizure-Free Outcome: If a patient has been seizure-free for three times the pre-intervention inter-seizure interval but less than 12 months.
5. Patients who fulfill the criteria (regardless of age) for DRE should be referred to a Specialized Epilepsy Center (SEC) for reassessment to non-pharmacological management.
6. Specialized Epilepsy Center consists of an epilepsy monitoring unit (EMU), run by an epileptologist/neurophysiologist and functional neurosurgeon with infrastructure and a multidisciplinary team of healthcare professionals (psychologist, EEG technician, nurses, medical secretary, medical registry).
7. The Egyptian Epilepsy consensus recommends using the modified CASES Expert Panelists online tool [32] to identify patients who may benefit from an epilepsy surgery evaluation.
8. The Egyptian Epilepsy consensus recommends using the criteria for referral and evaluation of children for epilepsy surgery proposed by the Sub Commission for Pediatric Epilepsy Surgery of the ILAE.
9. Children with uncontrolled (i.e., failure of two or three appropriate drugs) and disabling epilepsy are also possible surgical candidates.
10. Children with lateralized seizures or other evidence of focality that cannot be attributed to idiopathic focal epilepsies or in whom the MRI reveals a lesion amenable to surgical removal should be referred to a pediatric SEC for evaluation.

11. In the pediatric surgical population, there are currently no preoperative clinical variables to predict seizure outcome; therefore, the presence of developmental delay, physical, and/ or psychiatric comorbidities should not be a contraindication for pediatric epilepsy surgery and/or epilepsy neuromodulation (ex. vagal nerve stimulation “VNS”).
12. The aim of testing for epilepsy surgery is to determine if a person can benefit from surgery to treat their seizures.
13. Pre-surgical evaluation tests are done in two phases. Phase 1 can be done in the outpatient setting. While in phase 2 tests, a hospital stay will be required.
14. The number of pre-surgical evaluation tests required depends on the person’s type of seizures and what information is needed to make the best decisions about moving forward with the pre-surgical evaluation and surgery.
15. Phase 1 (non-invasive) tests should include any of the following as required;

a. EEG

b. Continuous Video EEG Monitoring

c. High-Density EEG and Source Localization – OPTIONAL

d. Special Electrodes- OPTIONAL

e. CT Scan without/with IV contrast –OPTIONAL

f. MRI without/with IV contrast

g. PET – REQUIRED

h. MEG (Magnetoencephalography) – OPTIONAL

i. SPECT – OPTIONAL

j. SISCOM (Subtraction Ictal SPECT co-registered with MRI) – OPTIONAL

k. MRS (Magnetic Resonance Spectroscopy) – OPTIONAL

l. Neuropsychology Testing – REQUIRED

m. Wada

16. When imaging is used as part of the pre-surgical evaluation, strict standards for technique and interpretation must be used.

17. Imaging results must be placed in the context of other clinical and laboratory data, including clinical history, neurologic examination, video recordings of typical seizures, ictal and interictal EEG, and neuropsychometric evaluation.

18. Images should be reviewed by physicians experienced in the evaluation of patients with epilepsy and neuroradiologists.

19. Phase 2 tests include;

a.Intracranial Depth Electrodes (also called Stereo-EEG or SEEG)

b. Subdural Strip and Subdural Grid Electrodes

c. ECoG (Electrocorticography) or iEEG (intracranial Electroencephalography)

20. Surgical Decision Making is a multidisciplinary decision of the entire epilepsy team.

21. Pre-surgical evaluation should include:

a. Clinical semiology/Interictal EEG

b. Ictal video EEG

c. Neuroimaging: MRI epilepsy protocol: includes 3D FLAIR and volumetric studies

d. Neuroimaging: Interictal PET: for identifying the hypometabolic epileptogenic zone

e. Neuropsychometric assessment

22. Focal epilepsy:

a. Focal epilepsy should be classified into lesional or non-lesional subclasses based on the results of the MRI epilepsy protocol.

b. For lesional focal epilepsy not concordant with semiology and EEG, invasive monitoring should be applied.

c. For non-lesional focal epilepsy with a non-localized epileptogenic zone, invasive monitoring should be applied.

d. If cortical epileptogenic zone is suspected/or mapping is needed, subdural grids/strips invasive monitoring should be applied.

e. If a deep epileptogenic zone is suspected, SEEG invasive monitoring should be applied.

f. In case of the localized epileptogenic zone (i.e., for lesional focal epilepsy in concordance with semiology and EEG, or non-lesional focal epilepsy with the localized epileptogenic zone);

i. For non-eloquent extra-temporal lobe epilepsy, ECoG-guided resection should be applied.

ii. For extra-temporal lobe epilepsy related to eloquent areas but not included in the epileptogenic zone; awake craniotomy, mapping techniques, and ECoG-guided resection should be applied.

iii. For extra-temporal lobe epilepsy with eloquent areas included in the epileptogenic zone; implementation of procedures such as Multiple Subpial Transections (MST), VNS, or Responsive Neurostimulation (RNS) should be applied.

iv. For unilateral temporal lobe epilepsy with lateral temporal involvement, Anterior Temporal Lobectomy (ATL) should be applied.

v. For unilateral temporal lobe epilepsy with no lateral temporal involvement, either surgical procedures (ATL or Selective Amigdalo-Hippocampectomy “SAH”) or minimally invasive procedures (Laser Interstitial Thermal Therapy “LITT” or Stereotactic Radiosurgery “SRS”) should be applied.

vi. For bilateral temporal lobe epilepsy, either VNS or RNS should be applied.

23. Generalized or Multifocal Epilepsy:

a. In the case of hemispheric generalized or multifocal epilepsy, either hemispherectomy (anatomical or functional) or VNS should be applied.

b. In the case of generalized poorly localized epilepsy with mostly atonic attacks, palliative management with corpus callosotomy should be applied.

c. In case of generalized poorly localized epilepsy with minor atonic attacks, palliative management with VNS or Deep Brain Stimulation (DBS) of the anterior nucleus of the thalamus should be applied.

[a]Electrical status epilepticus during sleep (ESES) and Non-convulsive status epilepticus (NCSE).
* Check midazolam availability before starting continuous infusion
* Choices among different ASMs are determined according to comorbidities, availability, seizure types, and drug-drug interaction.

Abbreviations

ACTH: Adrenocorticotropic hormone; ASM: Anti-seizure medications; ATL: Anterior Temporal Lobectomy; CBC: Complete blood count; CT: Computed Tomography; DBS: Deep Brain Stimulation; DP: Delphi panel; DRE: Drug-Resistant Epilepsy; ECG: Electrocardiography; ECoG: Electrocorticography; ED: Emergency Department; EEG: Electroencephalography; EMU: Epilepsy monitoring unit; ESES: Electrical status epilepticus during sleep; EZ: Epileptogenic Zone; GGE: Genetically Generalized Epilepsy; iEEG: Intracranial

Electroencephalography; ILAE: International League Against Epilepsy; IM: Intramuscular; IV: Intravenous; JAE: Juvenile absence epilepsy; JME: Juvenile myoclonic epilepsy; LITT: Laser Interstitial Thermal Therapy; LP: Lumbar puncture; MEG: Magnetoencephalography; MRI: Magnetic resonance imaging; MRS: Magnetic Resonance Spectroscopy; MST: Multiple Subpial Transections; NCSE: Non-convulsive status epilepticus; NMDA: N-methyl-D-aspartate; PET: Positron emission tomography; PNES: Psychogenic non-epileptic seizures; PR: Per rectum; PWE: Persons with epilepsy; RNS: Responsive Neurostimulation; RSE: Refractory Status Epilepticus; SAH: Selective Amigdalo-Hippocampectomy; SC: Steering Committee; SD grids: Subdural grids; SE: Status epilepticus; SEC: Specialized Epilepsy Center; SEEG: Stereotactic Electroencephalography; SISCOM: Subtraction Ictal SPECT co-registered with MRI; SPECT: Single-photon emission computed tomography; SRS: Stereotactic Radiosurgery; SRSE: Super-Refractory Status Epilepticus**;** TSH: Thyroid-stimulating hormone; VNS: Vagal nerve stimulation; WHO: World Health Organization.

Declarations

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Authors' contributions

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Availability of data and materials

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Ethics approval and consent to participate

Not applicable

Consent for publication

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Competing interests

All authors listed have no conflict of interest, financial or otherwise.

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Tables

Table 1: Recommendations for choice of ASM according to different epileptic syndromes in different age groups (after excluding treatable metabolic causes)

No.	Recommendations	Contraindicated Medications
Self-limited epilepsy with centrotemporal spikes [15]		
1.	**First line;** carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, valproate. **Adjuvant therapy;** eslicarbazepine, lacosamide, lamotrigine, levetiracetam, zonisamide. **Other options;** carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin.	----
Self-limited epilepsy with autonomic seizures [15]		
2.	**First line;** carbamazepine, sodium valproate. **Adjuvant therapy;** eslicarbazepine, lacosamide, lamotrigine, levetiracetam, zonisamide. **Other options;** carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin.	----
Childhood occipital visual epilepsy [15]		
3.	**First line;** carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, valproate. **Adjuvant therapy;** eslicarbazepine, lacosamide, lamotrigine, levetiracetam, zonisamide. **Other options;** carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin.	----
Photosensitive occipital lobe epilepsy [16]		
4.	**First line;** avoid factors that provoke seizures, valproate. **Adjuvant therapy;** benzodiazepines, levetiracetam. **Other options;** carbamazepine, ethosuximide, lamotrigine, vigabatrin.	----
Childhood absence epilepsy [15]		
5.	**First line;** ethosuximide, valproic acid. **Adjuvant therapy;** a combination of ethosuximide and valproic acid. **Other options;** acetazolamide, clobazam, clonazepam, lamotrigine, levetiracetam, topiramate, zonisamide.	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, vigabatrin.
Epilepsy with myoclonic absence [17]		

6.	**First line;** ethosuximide, valproic acid. **Adjuvant therapy;** a combination of ethosuximide and valproic acid. **Other options;** benzodiazepines, lamotrigine, phenobarbitone, rufinamide.	Carbamazepine, phenytoin, vigabatrin.
Epilepsy with eyelid myoclonia [18]		
7.	**First line;** ethosuximide, valproic acid. **Adjuvant therapy;** clonazepam, ethosuximide, valproic acid. **Other options;** levetiracetam.	Carbamazepine, lamotrigine, oxcarbazepine, phenytoin.
Myoclonic atonic epilepsy [19]		
8.	**First line;** valproate in generalized tonic-clonic seizure, ethosuximide in absence seizures, steroids in the periods with multiple atonic seizures, and frequent prolonged episodes of nonconvulsive status. **Adjuvant therapy;** lamotrigine, ketogenic diet. **Other options;** clobazam, felbamate, lamotrigine, levetiracetam, rufinamide, topiramate, zonisamide, ketogenic diet.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, vigabatrin.
Lennox-gastaut syndrome [15, 20]		
9.	**First line;** lamotrigine, topiramate, valproate. **Adjuvant therapy;** lamotrigine, topiramate, valproate. **Other options;** felbamate, rufinamide, topiramate.	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, vigabatrin.
Developmental and/or epileptic encephalopathy with spike-wave activation during sleep [21]		
10.	**First line;** standard ASMs, valproate, benzodiazepines, ethosuximide, adrenocorticotropic hormone (ACTH) or prednisone, high-dose benzodiazepines, intravenous immunoglobulins, epilepsy surgery. **Adjuvant therapy;** ---- **Other options;** acetazolamide, clobazam, lacosamide, lamotrigine, levetiracetam.	----
Febrile infection-related epilepsy syndrome [22]		
11.	**First line;** benzodiazepines and barbiturates for treatment of the acute event. **Adjuvant therapy;** ketogenic diet. **Other options;** IVIG, cannabidiol, anakinra, immunomodulation such as tocilizumab or canakinumab, epilepsy surgery.	----
Hemiconvulsion, hemiplegia epilepsy syndrome [23-26]		

12.	**First line;** Steroids, N-methyl-D-aspartate (NMDA) receptor blocker as memantine, amantadine. **Adjuvant therapy;** carbamazepine, phenytoin in cases of persistent seizures. **Other options;** lamotrigine, perampanel, rufinamide, topiramate, valproate, epilepsy surgery.	----

Table 2: Recommendations for choice of ASM according to different epileptic syndromes in adolescents

No.	Recommendations	Contraindicated Medications
Juvenile absence epilepsy (JAE) [27, 28]		
1.	**First line;** ethosuximide, lamotrigine, sodium valproate*. **Adjuvant therapy;** a combination of any of the first lines. **Other options;** clobazam, clonazepam, levetiracetam, topiramate, zonisamide.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin.
Juvenile myoclonic epilepsy (JME) [27, 28]		
2.	**First line;** sodium valproate*, topiramate. **Adjuvant therapy;** acetazolamide, lamotrigine, levetiracetam, topiramate. **Other options;** clobazam, clonazepam, zonisamide.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin.
Idiopathic generalized tonic–clonic seizures [27, 28]		
3.	**First line;** lamotrigine, sodium valproate*. **Adjuvant therapy;** consider carbamazepine, oxcarbazepine (exacerbating myoclonic and absence seizures). **Other options;** clobazam, topiramate.	----
Other Idiopathic generalized seizures [27]		
4.	**First line;** lamotrigine, sodium valproate* (especially if photosensitive), topiramate. **Adjuvant therapy;** lamotrigine, levetiracetam, sodium valproate*, topiramate. **Other options;** clobazam, clonazepam, zonisamide.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin.
*Avoid valproate in adolescent females		

Table 3: Recommendations for choice of ASM according to seizure type

No.	Recommendations	Avoid/ Don't offer
Focal aware and impaired awareness seizures		
1.	**First line;** carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate*. **Adjuvant/ Add-on;** Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, sodium valproate*, topiramate, vigabatrin, zonisamide.	----
Focal to bilateral tonic-clonic seizure and generalized onset tonic-clonic seizure		
2.	**First line;** lamotrigine, sodium valproate*. **Adjuvant/ Add-on;** lamotrigine, levetiracetam, sodium valproate*, topiramate.	----
Generalized non-motor (Absence) seizures		
3.	**First line;** ethosuximide, sodium valproate*, if there is a high risk of generalized tonic-clonic seizures offer sodium valproate* or lamotrigine. **Adjuvant/ Add-on;** clonazepam, ethosuximide, lamotrigine, levetiracetam, sodium valproate*, topiramate, zonisamide.	Carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenytoin, pregabalin, vigabatrin.
Myoclonic seizures		
4.	**First line;** levetiracetam, sodium valproate*, topiramate. **Adjuvant/ Add-on;** clonazepam, levetiracetam, piracetam, sodium valproate*, topiramate, zonisamide.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, vigabatrin.
Tonic & atonic seizures		
5.	**First line;** sodium valproate*. **Adjuvant/ Add-on;** lamotrigine, topiramate.	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, vigabatrin.
*Avoid valproate in adolescent females		

Figures

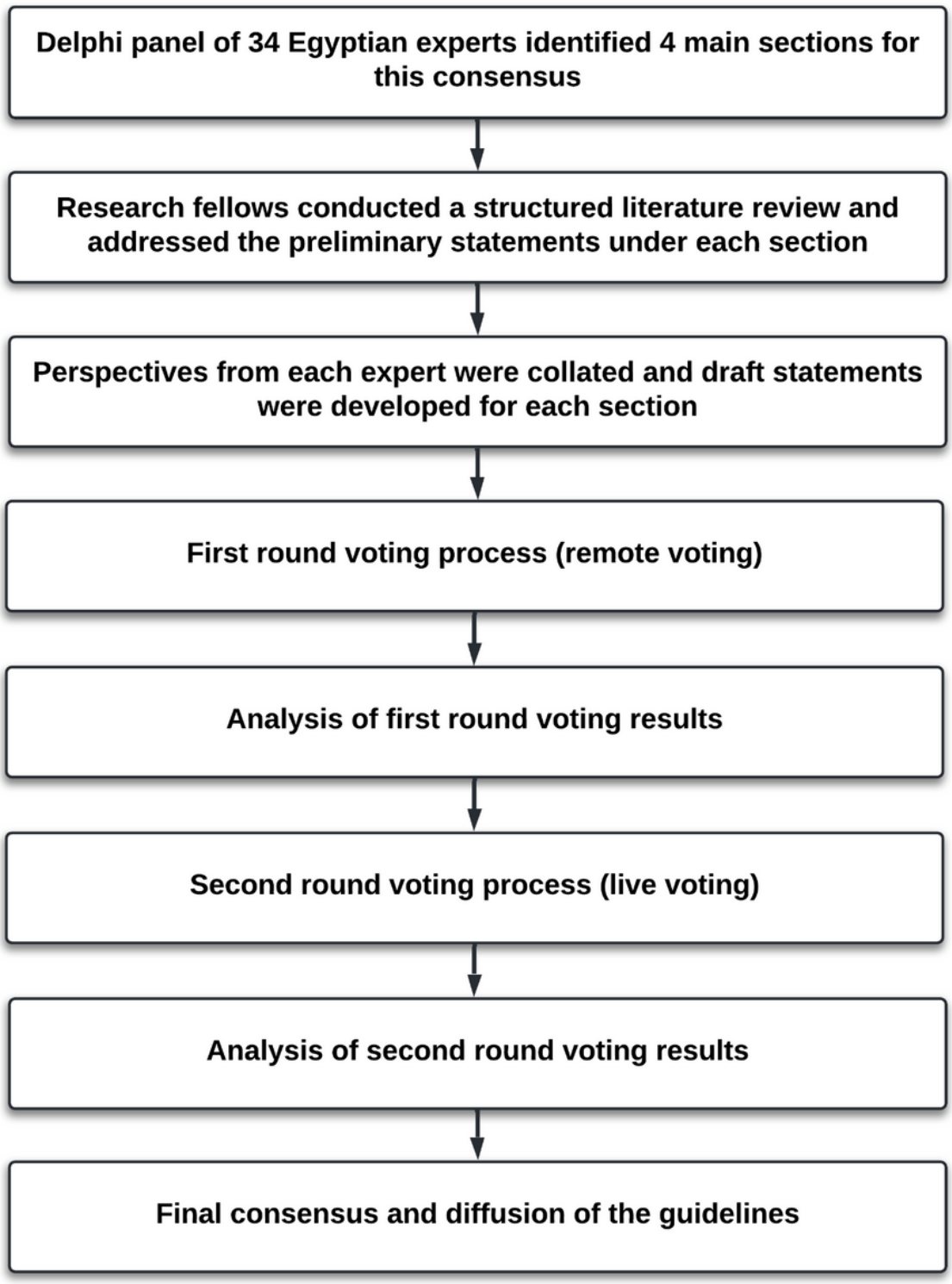

Figure 1

Consensus development by the modified Delphi methodology

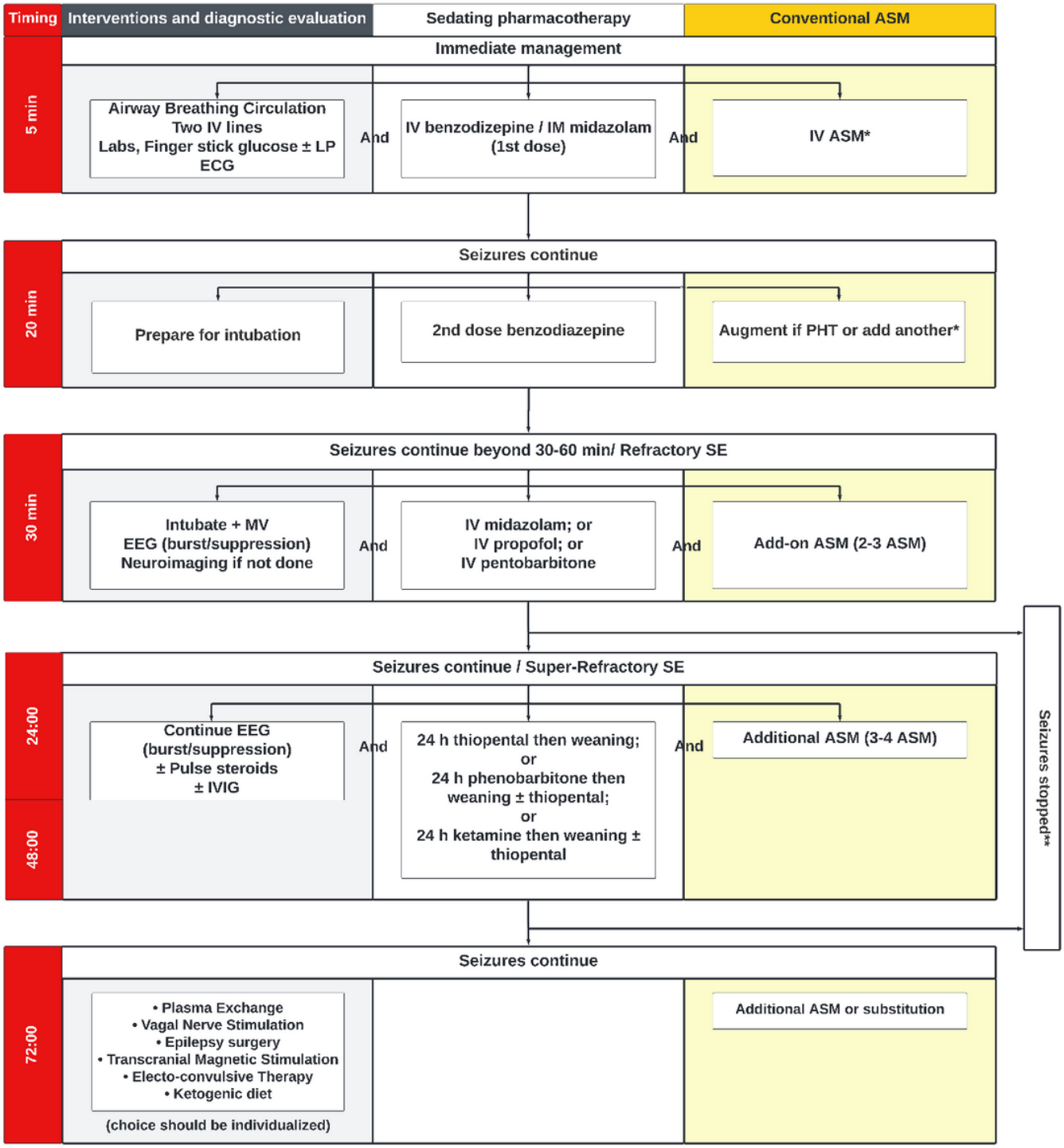

Figure 2

Status Epilepticus management algorithm

ASM: Anti-seizure medication; ECG: Electrocardiography; EEG: Electroencephalography; IM: Intramuscular; IV: Intravenous;

IVIG: Intravenous immune globulin; LP: Lumbar puncture; MV: Mechanical ventilation; PHT: Phenytoin; SE: Status Epilepticus.

*phynetoin, leviteracitam, lacosamide

**gradual weaning of anesthetic and continue on ASM

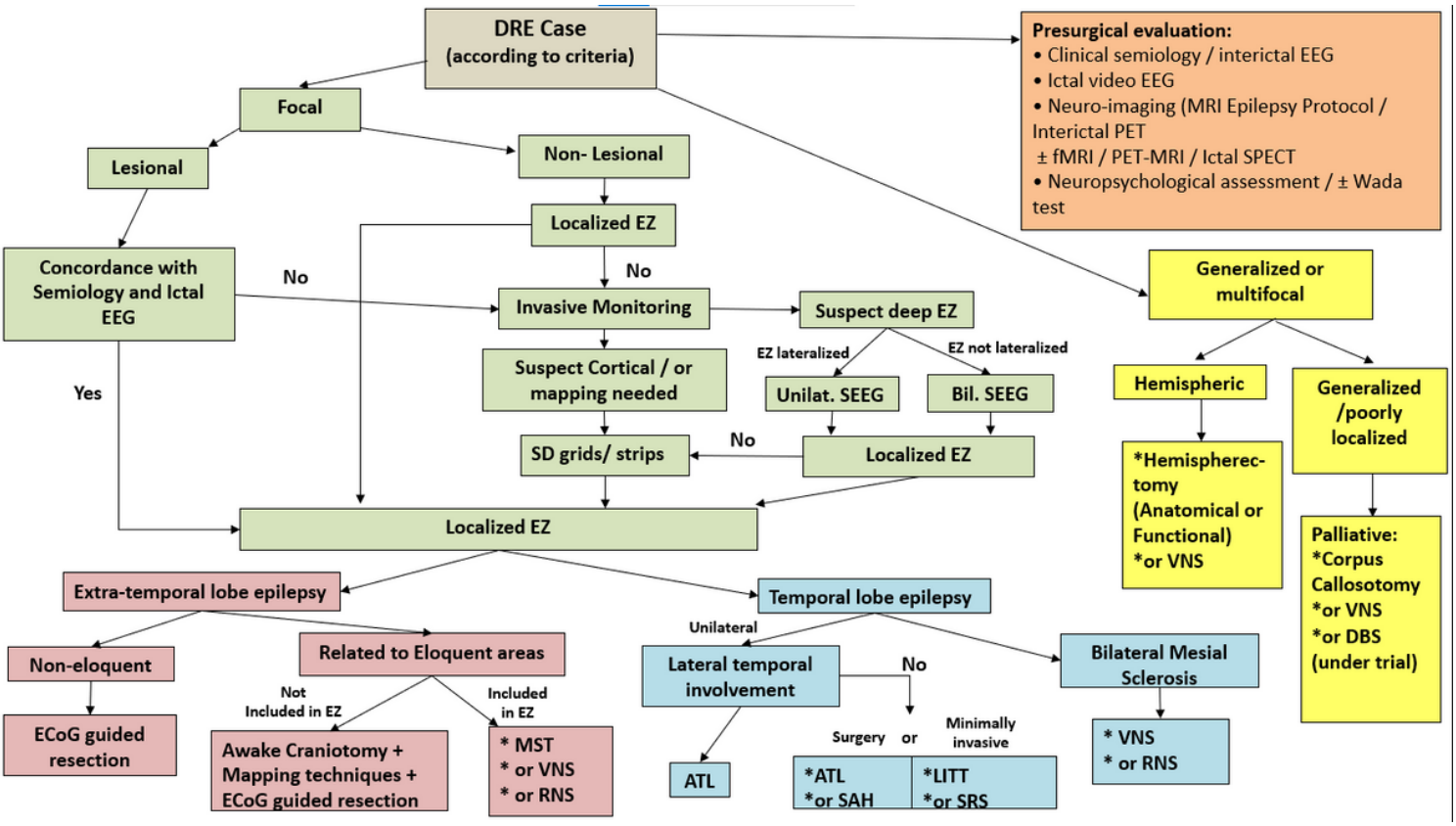

Figure 3

Epilepsy Surgery Algorithm

ATL: Anterior Temporal Lobectomy; DBS: Deep Brain Stimulation; DRE: Drug-Resistant Epilepsy; ECoG: Electrocorticography; EZ: Epileptogenic Zone; LITT: Laser Interstitial Thermal Therapy; MST: Multiple Subpial Transections; RNS: Responsive Neurostimulation; SAH: Selective Amigdalo-Hippocampectomy; SD grids: Subdural grids; SEEG: Stereotactic Electroencephalography; SRS: Stereotactic Radiosurgery; VNS: Vagal Nerve Stimulation.

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