Consensus Guidelines on Management of Childhood Convulsive Status Epilepticus

*Devendra Mishra, #Suvasini Sharma, @Naveen Sankhyan, ^Ramesh Konanki, $Mahesh Kamate, °Sujata Kanhere and #Satinder Aneja; for the ‡Multi-disciplinary Group on Management of Status Epilepticus in Children in India

*From Departments of Pediatrics, *Maulana Azad Medical College and #Lady Hardinge Medical College, New Delhi; @Division of Pediatric Neurology, Department of Pediatrics, PGIMER, Chandigarh; ^Rainbow Hospital for Women and Children, Hyderabad; $Department of Pediatrics, KLE University's JN Medical College, Belgaum; °Department of Pediatrics and Neonatology, KJ Somaiya Medical College, Hospital and Research Centre, Mumbai; India.*

Correspondence to: Prof Satinder Aneja, Convener, Multi-disciplinary Group on Management of Status Epilepticus in Children in India; Director-Professor, Department of Pediatrics, Lady Hardinge Medical College, New Delhi 110 001, India. anejas52@gmail.com

Justification: Status epilepticus has a wide etiological spectrum, and significant morbidity and mortality. Management using a pre-determined uniform protocol leads to better outcomes. Multiple protocols for management of childhood status epilepticus are available, without much consensus.

Process: A 'Multi-disciplinary Consensus Development Workshop on Management of Status Epilepticus in Children in India' was organized. The invited experts included Pediatricians, Pediatric neurologists, Neurologists, Epileptologists, and Pediatric intensive care specialists from India, with experience in the relevant field. Experts had previously been divided into focus groups and had interacted on telephone and e-mail regarding their group recommendations, and developed consensus on the topic. During the meeting, each group presented their recommendations, which were deliberated upon by the house and a consensus was reached on various issues; the document was finalized after incorporating suggestions of experts on the draft document.

Objective: To provide consensus guidelines on evaluation and management of convulsive status epilepticus in children in India (excluding neonatal and super-refractory status epilepticus).

Recommendations: Each institution should use a pre-determined protocol for management of status epilepticus; pre-hospital management and early stabilization is the key to a satisfactory outcome of status epilepticus. Pharmacotherapy should not be delayed for any investigations; the initial management should consist of a parenteral benzodiazepine by any route feasible. Subsequent management has been detailed. The group also felt the need for more epidemiological research on status epilepticus from India, and identified certain research areas for the purpose.

Keywords: *Evaluation, Investigations, Multi-disciplinary, Pharmacotherapy, Seizure, Treatment.*

Status epilepticus (SE) is a life-threatening emergency that requires prompt recognition and management [1]. Immediate treatment of status epilepticus is crucial to prevent adverse neurologic and systemic consequences [2]. Multiple protocols for management of SE in children are available both internationally [3-5] and from India [6-8]. It has previously been demonstrated that use of a pre-determined protocol for management of SE leads to favorable outcomes [9]. A single protocol for management of SE in children, suitable for use in the Indian setting, taking in consideration the common etiologies of SE and the drugs available, is thus the need of the hour.

Process

A 'Multi-disciplinary Consensus Development Workshop on Management of Status Epilepticus in Children in India' was organized by the Association of Child Neurology on 17th November, 2013 in New Delhi. The invited experts included General pediatricians, Pediatric neurologists, Neurologists, Epileptologists, and Pediatric intensive care specialists from all over India with experience in the relevant field. This group was designated as the 'Multi-disciplinary Group on Management of Status Epilepticus in Children in India' (***Annexure* I**). In addition, consultants and residents in Pediatrics were invited as observers. Experts had previously been divided into focus groups, and had interacted on telephone and e-mail regarding their group recommendations. During the meeting, each group presented its recommendations, which were deliberated upon by the house and a consensus reached on various issues. At the end of the meeting, it was decided to bring out guidelines on evaluation and management of Status epilepticus in children in India, and a Writing group designated for the purpose. Due to the lack of country-

specific epidemiologic information and varying levels of care available at various centers, it was decided not to categorize the recommendations by either 'level of evidence' or 'strength of recommendation' [10]. The draft document was circulated by e-mail among all experts and suggestions received incorporated; the final document is presented here. It does not cover the management of neonatal SE and Super-refractory SE.

GUIDELINES

A. Definition and Epidemiology

The most widely used definition for SE is "a seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness" [11,12]. More recently, an operational definition has also been suggested for adults and children older than 5 years [13] (***Box* 1**). If we consider the duration for which most new-onset seizures in children last, once a seizure lasts for more than five to ten minutes, it is unlikely to stop spontaneously within the next few minutes, and intervention is indicated [14]. The use of the operational definition allows early treatment (starting at 5-10 min) [15]. However, in view of most previous studies on SE having been done using the 30-minute definition, the group suggests that for research purposes, both the definitions be considered and data provided with respect to both time durations.

SE in children is commonly due to cryptogenic or remote symptomatic causes in older children, and febrile or acute symptomatic cause in younger children [9,16]. Majority of childhood convulsive SE in a UK study (56%) occurred in previously neurologically healthy children, a quarter of SE were prolonged febrile seizures, and 17% were acute symptomatic [17]. Epidemiological data on SE in India is limited to a few single-center studies [18-20], with only one providing exclusive pediatric data [18]. The high proportion of acute symptomatic etiology, delayed presentation and poor outcome are the commonly reported findings. In an Indian pediatric intensive care unit (PICU) study over seven years, 53% had SE as their first seizure and only 60% had received any treatment prior to coming to the PICU [18]. A recent multi-centric study on SE in children across nine centers in India also reported similar findings: 82% acute symptomatic, <3% pre-hospital treatment, <20% deficit-free survival, and no uniform management protocol [unpublished data].

BOX 1 IMPORTANT DEFINITIONS

Status epilepticus (SE): A seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness .

**Operational definition:* Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to >5 min of (*i*) continuous seizures or (*ii*) two or more discrete seizures between which there is incomplete recovery of consciousness [13].

Refractory SE: Seizures persist despite the administration of two appropriate anticonvulsants at acceptable doses, with a minimum duration of status of 60 minutes (by history or on observation).

Super-refractory SE: SE that continues 24 hours or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia.

**For the purpose of initiating management.*

B. Pre-hospital Management

Treatment of SE needs to be initiated as early as possible since once seizures persist for 5 to 10 minutes, they are unlikely to stop on their own in the subsequent few minutes [21]. Moreover, the longer an episode of SE continues, the more refractory to treatment it becomes and the greater is the likelihood of complications [22]. Thus, the need for early treatment, preferably pre-hospital, is clear.

Pre-hospital management includes both first-aid during seizures, and pharmacotherapy. The initial care of a child with convulsions/coma is adequately described in Facility-based Integrated Management of Neonatal and Childhood Illnesses (F-IMNCI) guidelines of the Government of India [23] and will not be elucidated here further. Decision about pharmacotherapy must consider the drug and also the route of drug delivery (***Box* 2**).

Benzodiazepines are the drugs that are currently in use for pre-hospital therapy for SE and include diazepam, lorazepam and midazolam. Pre-hospital treatment with benzodiazepines has been shown to reduce seizure activity significantly compared with seizures that remain untreated until the patient reaches the emergency department [24]. The various routes employed include per-rectal (diazepam, lorazepam, paraldehyde), intranasal (midazolam), buccal (midazolam, lorazepam) and intramuscular (midazolam).

Rectal diazepam is an approved out-of-hospital treatment for acute repetitive seizures in children. Response rates have been demonstrated to be similar to intravenous diazepam [25]. Multiple randomized, double-blind, placebo controlled studies have demonstrated that rectal diazepam given by caregivers at home is an effective and safe treatment for acute recurrent seizures [26-28]. Rectal administration may be difficult with wheel-chair users and larger patients. It can be socially unacceptable, and there is increasing concern about risk

BOX 2 RECOMMENDATIONS FOR OUT-OF-HOSPITAL MANAGEMENT OF SEIZURES

Guiding Principles

- Acute treatment with anticonvulsants should be commenced after continuous seizures or serial seizures >5 min in an out-of-hospital setting, and efforts made to transfer the patient to the nearest health care facility.
- Prolonged seizures should be treated with either nasal or buccal midazolam or rectal diazepam when intravenous line is not available or in the community setting.
- Rectal diazepam is safe and effective as first-line treatment of prolonged seizures in community setting or when intravenous access is not available.
- Buccal or intranasal midazolam is as effective as rectal diazepam and can be considered as a preferable alternative in community setting.

At Home: Parents

- First aid
- Rectal diazepam OR buccal midazolam OR intranasal midazolam
- Inform doctor/shift to hospital if >5 min (or if more than 2 min longer than previous seizure duration)

At Home/Out of Hospital by Paramedics

- First aid - Airway, breathing, circulation, oxygen
- Supportive care
- Intranasal midazolam OR buccal midazolam OR rectal diazepam
- Shift to hospital

First-level Health Facility (Clinic/PHC/Nursing home)

- ABC, Oxygen
- *Intravenous access feasible*:
  - Intravenous lorazepam (if refrigeration & electric supply), diazepam, or midazolam
- *Intravenous access not feasible*:
  - Intramuscular injection can be given: IM midazolam
  - Intramuscular injection not feasible: Intranasal/buccal midazolam, rectal diazepam
- Shift to higher center, if required

of sexual abuse allegations [29,30]. Therefore, non-rectal routes are gradually gaining favor for use by relatives/ health workers in out-of-hospital settings. Rectal diazepam is the recommended drug for control of seizures in the F-IMNCI guidelines, in situations where intravenous access is not available [23].

In the past decade, research evidence has shown that buccal midazolam is more than or equally effective to rectal diazepam for children presenting to hospital with acute seizures, and is not associated with an increased incidence of respiratory depression [29,31,32]. Therefore, it may be considered as an acceptable alternative to rectal diazepam [30]. Intranasal midazolam has been shown to be as effective as intravenous diazepam in the treatment of prolonged febrile convulsions [4,33-35], and may also be an alternative. More recent data from the RAMPART study [36] of pre-hospital management of SE in children and adults has shown intramuscular midazolam to be as safe and effective as intravenous lorazepam for pre-hospital seizure cessation. This may therefore emerge to be the agent of choice for out-of-hospital management of seizure by trained personnel.

Rectal and intranasal lorazepam have also shown efficacy for termination of acute convulsive seizures in children [4,37]. However, non-availability of a commercial preparation in India precludes any firm guidance on non-parenteral use of lorazepam in India.

Parents of all children at risk of seizure recurrence should be counseled for appropriate home management for seizure [38].

C. Supportive Care and Stabilization

Although convulsive seizures are the most obvious manifestation, SE is in fact a multisystem phenomenon i.e. prolonged and ongoing SE affects multiple organ systems. Hence, apart from attempts to rapidly control seizures, important goals of therapy are neuro-protection,

and prevention and treatment of systemic complications associated with intravenous AEDs, anesthetic drugs and prolonged unconsciousness [39]. The supportive care should be tailored to the health care setting, the clinical presentations of SE, degree of encephalopathy, and degree of impairment of vital functions.

Airway, Breathing and Circulation

Assessment and care of vital functions is essential at all stages of managing any child with SE [40]. Adequate care of airway, breathing and circulaion takes precedence over any pharmacological therapy.

Airway: It is essential to maintain a patent airway during all stages of management of SE.

- In all children with brief seizures and altered sensorium, clearing the oral secretions (mouth, followed by nose) and keeping the child in recovery position is advisable to prevent aspiration. Cervical spine should be immobilized if trauma is suspected.
- In more severe degrees of altered sensorium, use an oral airway to prevent tongue from falling back.
- Endotracheal intubation in children whose airway is not maintainable with above measures.
- The airway compromise may occur at any stage; either as complication of prolonged or ongoing seizure, or due to respiratory depressant effect of medications.

Breathing: Hypoxemia may result from respiratory depression/apnea, aspiration, airway obstruction, and neurogenic pulmonary edema [41].

- All children with SE should have their breathing and SpO2 monitored continuously.
- All children with ongoing seizures should be given supplemental oxygen to ameliorate cerebral hypoxia, as it has been seen that the degree of hypoxia is often underestimated.
- Depending on the duration of SE and degree of altered sensorium, maintain oxygen saturation by: supplemental oxygen, AMBU bag, non-invasive continuous positive airway pressure (CPAP), and invasive ventilation by endotracheal intubation. Mechanical ventilation may also become necessary when children are started on continuous infusions of anesthetic agents.

Circulation: Continuous monitoring of pulse, blood pressure and perfusion should be done in all SE patients.

- Ensure good venous access (preferably have at least two venous lines); draw necessary blood samples, and start fluids and anti-epileptic drugs as necessary.
- Maintain blood pressure in the normal range with necessary measures including: intravenous fluids, fluid boluses, and inotropes. Invasive blood pressure monitoring should be considered, if feasible, in children with hypotension and poor peripheral perfusion either spontaneously or following infusion of continuous anesthetic agents.
- The choice of IV fluids depends on the metabolic and glycemic status. If there is hyperglycemia (especially initial phase of catecholamine excess) it is preferable to give either dextrose normal saline (DNS) or normal saline. However, in general, hypotonic fluid should be avoided for initial resuscitation.

Precipitating Factors and Ongoing Complications

The treating team should anticipate one or more of the below mentioned problems depending on the duration of SE, age, underlying etiology, and the associated systemic co-morbidities. The cerebral and systemic metabolism undergoes changes described as initial phase of 'compensation', and if SE is sufficiently prolonged, later phase of 'decompensation' [42,43]. During the initial phase, prolonged seizures result in increased cerebral blood flow and metabolism, excessive catecholaminergic activity and cardiovascular changes. These in turn result in hyperglycemia, hyperpyrexia, tachycardia, sweating, hypertension, incontinence, cardiac arrhythmias, and lactic acidosis [43-46]. If the SE is prolonged, the cerebral autoregulation progressively fails and cerebral perfusion becomes dependent on systemic blood pressure resulting in hypoxia, cerebral ischemia, hypoglycemia, and lactic acidosis [42,43]. Management of these conditions is detailed in ***Web Table* I**. Both hypernatremia (serum sodium >145 meq/L) and hyponatremia (<135 meq/L) are deleterious for the brain. The major risks associated with hypernatremia are intracranial hemorrhage (subdural, subarachnoid and intraparenchymal) and osmotic demyelination (pontine or extra-pontine) with rapid correction.

Risk of infections is greatly increased in those with SE, especially when the duration is prolonged. Ventilator-associated pneumonia, urinary tract infection, pseudomembranous colitis, oral candidiasis, and speticemia are the common infections [47,48]. Commonest organisms are *P. aeruginosa, A. spp, K. pneumoniae*, and Entero bacteriaceae [48]. Hyperpyrexia, rhabdomyolysis, and raised intracranial pressure are the other common accompaniments [43,49,50]. Rarely, SE is associated with ictal bradycardia, stress cardiomyopathy, neurogenic pulmonary edema, rhabdomyolysis and related renal failure, or bone fractures [46]. Hypotension is common due to prolonged seizures, IV benzo-diazepines, or

anesthetic agent infusions, and stress cardiomyopathy (Takotsubo cardiomyopathy) [47,51-53]. Cardiac arrhythmias are also common (up to 58%), with higher mortality in these patients [54,55]. Management depends on the cause of hypotension, hypovolemic shock, distributive shock, cardiomyopathy, or cardiac arrhythmias (***Web Table* I**).

Although in most cases it is mild, early identification and aggressive treatment of rhabdomyolysis prevents complications like renal failure and compartment syndrome. The initial fluids for resuscitation may include normal saline or 5% dextrose in water (approximately 2-3 times the daily maintenance). Sodium bicarbonate may be added to IV fluids, especially if there is associated metabolic acidosis and/or hyperkalemia [56,57].

D. Investigations

The clinical scenario, including the history and physical examination, is the most important factor guiding the specific evaluation that each child will require [58]. The investigations usually considered include blood chemistries, complete blood count, antiepileptic drug (AED) levels, toxicological studies, lumbar puncture, electroencephalography, and neuroimaging (Computed tomography [CT] scan and Magnetic resonance imaging [MRI]). The major part of evaluation can be performed after the child has been stabilized in an intensive care setting, and the seizures have been completely or partially controlled [58,59].

The investigations done are primarily to *(i)* determine the cause of status epilepticus, *(ii)* to look for complications of status epilepticus *per se*, and *(iii)* to identify the side-effects of drugs. Early identification of the etiology can result in aggressive specific management of cause. The investigations may vary depending on whether it is the first episode of SE in a normal child, or SE in a child with pre-existing epilepsy and already receiving AEDs [16,58]. The tests are detailed below (in no specific order), and listed in ***Table* I** in the order of importance.

Blood Chemistries

Electrolyte and glucose abnormalities have been reported to be present in 1-16% of children with SE, although it is unclear whether they were the etiology in all and did treatment lead to cessation of the SE [16].

Serum calcium: Hypocalcemia as a cause of seizures is common in our country [60,61], usually due to vitamin D deficiency, and presents as a cluster of seizures in infancy. Early recognition avoids unnecessary treatment with AEDs and other interventions. Ionic calcium is more reliable as a guide for treatment and levels are usually <0.8 μmol/L in symptomatic children. However, all children

TABLE I INVESTIGATIONS IN A CHILD WITH STATUS EPILEPTICUS

First Line	*Second Line**
SE in a child without history seizures	
Ionic/total calcium (especially <2yr)	MRI
Random blood sugar	EEG
Sodium (especially <6mo)	*If clinical suspicion*: Urine toxicology
Add, if febrile: Complete blood count; Lumbar puncture#	
SE in known epilepsy patient	
• Known non-compliance/Missed dose/Recent drug or dose changes	
Anti-epileptic drug level	Random blood sugar
Consider, if febrile	Ionic/total calcium (especially <2y)
Complete blood count	Sodium (especially <6mo)
Lumbar puncture#	*If clinical suspicion*: Urine toxicology
• No known precipitating event	
Ionic/total calcium (especially <2y)	*If clinical suspicion*: Urine toxicology
Random blood sugar	Anti-epileptic drug level (if feasible)
Sodium (especially <6mo)	
Add, if febrile: Complete blood count; Lumbar puncture#	
If refractory SE or Persistent encephalopathy: Video-EEG monitoring	

*SE: Status epilepticus; *EEG and Neuroimaging should be done later, after stabilization of the patient; #A central nervous system infection may be considered even in afebrile infants (<6 mo) and lumbar puncture done, based on clinical setting.*

with SE and subnormal ionized calcium levels (<1.2 µmol/L) should be treated. Total serum calcium, if done, should always be combined with estimation of phosphorous, serum alkaline phosphatase and serum albumin, for proper interpretation. Serum calcium estimation is an essential investigation for all children younger than 2 years with status epilepticus, irrespective of presence or absence of suggestive features.

Random blood sugar: Should be done in all children at presentation (especially in children less than 5 years) [58], as hypoglycemia may be responsible for seizures, and both hypo- or hyper-glycemia cause brain damage. When hypoglycemia is documented, urine ketones and reducing sugar should also be evaluated.

Serum sodium: Hyponatremia has been reported to be a cause in 1% of new-onset childhood convulsive SE [62]. However, most children with this abnormality were found to have suggestive features on history and clinical examination [63]. As this finding has important therapeutic implications [58], serum sodium estimation should be done in all, if feasible.

Metabolic disorders: Metabolic disorders are reportedly present in around 4.2% of children with SE [16], though their etiological significance is unclear. Routine metabolic workup therefore appears unwarranted. However, arterial blood gas estimation should be done in all children with established SE, if facilities are available; or when transferring to the Intensive Care Unit (ICU).

Workup for Infections

Blood counts: May be done routinely in children presenting with SE [16], especially those with associated fever. Infants with infection may not have fever and blood counts should be considered in them, even if afebrile.

Similarly, send blood cultures if the child is febrile (and above 6 months), or in a younger child, even if afebrile, if an infection is suspected.

Cerebrospinal fluid (CSF) examination: A central nervous system (CNS) infection is reported in 12.5% of pediatric convulsive SE [16]. CNS infections are also an important cause of SE in Indian children [18]. A CSF examination should be done by lumbar puncture in a febrile child, after stabilizing the child and excluding raised intracranial tension [16]. In infants younger than 6 months, signs of meningitis may not be clearly demonstrated and fever also may not be present. In such a situation, whenever there is a clinical suspicion of a CNS infection or sepsis, lumbar puncture should be done.

If done, CSF should be subjected at least to cell count (total and differential), biochemistry (protein, sugar, CSF: blood sugar ratio), bacterial culture, and gram stain. CSF pleocytosis, if present, should not be ascribed to a febrile SE [64]. Additional investigations on the CSF should be individualized. Systemic illness is a common trigger for convulsive SE in a patient who is already at risk, and, therefore, fever itself is not an indication to perform a lumbar puncture in a patient with epilepsy presenting with SE [58].

Antiepileptic Drug Levels

Inadequate AED drug levels (whether due to non-compliance, missed dose, or recent drug-dose alterations) are associated with a significant proportion of SE in children [9], although some studies found contradictory results [65]. Low AED levels were found in more than 30% childhood SE, although this was not necessarily the cause of SE [16].

AED levels should be done, if feasible, in all patients receiving AED and presenting with SE, as it has both etiologic (non-compliance/low drug-level as a cause) and therapeutic (loading dose of the previously effective drug for management) implications. However, availability of required facilities is likely to act as a bottleneck.

Electroencephalography (EEG)

While considering EEG in SE, two situations need to be considered *viz.*, an isolated, short-duration single EEG recording, or continuous EEG monitoring. No Indian studies on usefulness of EEG in pediatric SE are available. EEG abnormalities have been reported in ~90% children presenting with SE, though these were done hours to days later [16]. The information whether the seizure is focal or generalized is an important one when deciding chronic AED therapy for the patient.

EEG monitoring has been shown to be extremely useful, but under-utilized in SE management. After convulsive SE, one-third of children who undergo EEG monitoring are reported to have electrographic seizures, and among these, one-third experience entirely electrographic-only seizures [66,67].

An EEG should be considered in every child presenting with new-onset SE, although it can be delayed till the control of SE. An EEG should also be done if there is suspicion of non-convulsive SE (child not returning to the pre-SE state or remaining persistently encephalopathic even after the control of convulsive SE) or pseudostatus is suspected. Continuous EEG monitoring optimizes the management of SE and should be used, if feasible.

Neuroimaging

Neuroimaging can identify structural causes for SE,

especially to exclude the need for neurosurgical intervention in children with new-onset SE without a prior history of epilepsy, or in those with persistent SE despite appropriate treatment. MRI is more sensitive and specific than CT scanning, but CT is more widely available and quicker in an emergency setting.

A meta-analysis reported structural lesions in 7.8% of childhood SE, commonly CNS malformations, trauma, and stroke/hemorrhage [66]. In a more recent study [68], the yield of MRI to detect structural lesions in convulsive SE was 31%. In the Indian setting, where inflammatory granulomas are a common cause of seizures [69], neuroimaging is likely to provide a higher yield.

Neuroimaging should be done, if feasible, in all children with SE, in whom no definitive etiology has been found. It should only be done after the child is appropriately stabilized and the seizure activity controlled. Emergent neuroimaging may be considered if there are clinical indications (new-onset focal deficits, persistent altered awareness, fever, recent trauma, history of cancer, history of anticoagulation, or a suspicion of AIDS).

Special Tests

Metabolic and genetic testing: Inborn errors of metabolism account for about 4% of SE in children [59]. The common metabolic causes are listed at ***Table* II.** SE usually occurs during an inter-current illness or metabolic stress [16,70,71]. Pyridoxine dependency can present even after the neonatal period [72], and is reported in around 0.3% of pediatric SE [16]. This needs to be excluded by either getting the specific test done (elevated urinary α-aminoadipic semialdehyde or the mutations in the *ALDH7A1* gene), or giving a trial of intravenous pyridoxine [72].

Metabolic and genetic testing should be considered when no etiology is revealed in initial evaluation and/or the preceding history is suggestive of a metabolic disorder. The specific studies to be obtained should be guided by the history and the clinical examination.

Toxicology: Toxin or drug-ingestion is a cause of SE that requires urgent specific treatment. Specific serum toxicology testing should be considered if initial assessment does not yield the etiology and/or a suggestive history is elicited.

Work-up for autoimmune encephalitis: Patients of any age who develop rapidly progressing symptoms presenting or accompanied by seizures or status epilepticus, usually including behavioral change and memory deficits, with CSF lymphocytic pleocytosis and/or oligoclonal bands of unclear etiology, and EEG findings of encephalopathy and/or epileptic activity, should have serum and CSF studies for antibodies. In some of these disorders, the MRI is often normal. The diagnosis is established by demonstrating antibodies in serum and CSF, though occasionally antibodies are detectable only in the latter [73].

Investigations to detect SE complications and drug side-effects: The major complications are altered glucose metabolism, dyselectrolytemias, and metabolic acidosis [62]. Propylene glycol toxicity (vehicle in diazepam/lorazepam and barbiturates), Propofol infusion syndrome, immunosuppression due to barbiturate use, and liver toxicity due to AEDs [62,63] are the major drug side-effects seen. These are detailed in ***Web Table* II**.

E. Pharmacotherapy

The goal of treatment is the immediate termination of seizures. For this, drugs should be used in quick succession, and if possible, rapid institution of

TABLE II METABOLIC CONDITIONS ASSOCIATED WITH STATUS EPILEPTICUS

Group	*Disorders*
Mitochondrial diseases	Myoclonic epilepsy with red ragged fibers (MERRF), Alpers syndrome, pyruvate dehydrogenase complex deficiency
Lipid storage disorders	Tay Sachs-Sandhoff disease, Krabbe disease, neonatal adrenoleukodystrophy, Zellweger syndrome, infantile Refsum disease, punctuate rhyzomelic chondrodysplasia, Niemann-Pick disease type A and C, Neuronal ceroid lipofuscinosis
Amino-acidopathies	Serine metabolism disorders, hyperpolinemia type II, untreated phenylketonuria, Maple urine syrup diseases, congenital glutamine deficiency, Nonketotic hyperglycinemia
Organic acidopathies	Propionic, methylmalonic, D-2- hydroxyglutaric and isovaleric acidurias; 2-methyl-3-hydroxybutyril-CoA dehydrogenase deficiency
Other diseases	Vitamin-dependent epilepsies, creatine metabolism dysfunctions, Menkes disease, disorders of purine and pyrimidine metabolism

pharmacological coma should be done in refractory cases. In the acute setting, anticonvulsants are best administered by the intravenous route. Alternative routes can be employed, to avoid delay in institution of therapy, especially in the pre-hospital settings. Pharmacotherapy of SE includes drug-management in the hospital, and management of refractory and super-refractory SE. Before starting pharmacotherapy for SE in the hospital, the pre-hospital drugs and doses should be taken in consideration e.g., a child who has received one dose of midazolam during transfer should receive only one more dose of midazolam before moving on to the next drug. ***Table* III** provides the guidelines for using various AEDs for SE management, and ***Table* IV** shows the recommended protocol, with ***Box* 3** providing supplementary management options.

Status Epilepticus

A number of anticonvulsants are available and one can choose the drugs based on availability and cost, and the monitoring facilities available.

Benzodiazepines: Benzodiazepines are first line drugs for treatment of SE in children [4,74,75]. The choice within the benzodiazepines is based on side-effects and pharmacokinetic properties. Several RCTs and systematic reviews have concluded that lorazepam is the agent of choice among the benzodiazepines [4,74,75]. More recent data; however, suggests that the efficacy and side-effect profile of lorazepam and diazepam is similar in children, when efficacy is defined as cessation of status epilepticus by 10 minutes without recurrence within 30 minutes [76]. Children receiving lorazepam are less likely to: require additional doses of anticonvulsants to stop seizures, develop respiratory depression, and require admission to intensive care unit [77]. If lorazepam is not available, midazolam or diazepam can be used for aborting the seizure (***Table* IV**). These two drugs are shorter acting and thus need to be followed up with longer-acting non-benzodiazepine anticonvulsants. When using benzodiazepines, there is a risk of respiratory depression or arrest, which increases with repeated doses of the drug [78].

Pheytoin/Fosphenytoin: After using short-acting benzodiazepines, phenytoin is one of the preferred second-line anticonvulsant [74]. The loading dose of the drug offers long-duration seizure-suppression. Major precautions in its use are monitoring for hypotension and

TABLE III ANTICONVULSANT USAGE IN STATUS EPILEPTICUS

Drug	*Dosage and route*	*Comments*
Lorazepam	0.1 mg/Kg/IV (max 4 mg) @ 2 mg/min	Long acting benzodiazepine, Side effects: sedation, respiratory depression and hypotension.
Midazolam	0.15-0.2 mg/Kg;/IV or IM (Max 5 mg) Buccal/Nasal: 0.2 - 0.3 mg/Kg (Max 5 mg)	Can be used by IM route.
Diazepam	0.2-0.3 mg/Kg (Max 10 mg) IV 0.5 mg/Kg per rectal (Max 10 mg)	IV dose should be given slowly over 2-5 min under careful monitoring.
Phenytoin	20 mg/Kg (Max: 1000 mg) in NS @ 1 mg/Kg/min (Max 50 mg per min)	Must be diluted in saline. Side effects include; hypotension, cardiac arrythmias, 'purple glove syndrome', skin rashes. Contraindicated in severe hypotension and grade II AV block.
Fosphenytoin	20 PE/Kg, Rate: 3 PE/Kg/min	Fewer side effects compared with phenytoin. Can be given IM.
Valproate	20 mg/Kg-IV infusion over 15 min, max rate- 6 mg/Kg/min. Followed by an infusion of 1-2 mg/Kg/h	Avoid in presence of liver disease, coagulopathy, thrombocytopenia, suspected metabolic disease, and in infants.
Phenobarbitone	20 mg/Kg in NS @ 1.5 mg/Kg/min	Side effects: sedation, respiratory depression, and hypotension
Levetiracetam	20-30 mg/Kg, over 15 min	Considered safe in children with metabolic diseases, oncology patients, and in those with liver disease or coagulopathy.
Thiopentone	Induction: 3 mg/Kg bolus, repeated after 2 min, followed by maintenance 1-5 mg/Kg/hr (increasing 1 mg/Kg/hr every 2 min) to control seizures and/or to achieve "suppression-burst" EEG activity	Causes respiratory depression. Can also induce hypotension and heart failure, associated with an increased rate of nosocomial infections. Contraindicated in the presence of hypotension, cardiogenic shock and sepsis.
Topiramate	Initial dose: 5-10 mg/Kg/day orally, maintenance dose of 5 mg/Kg/day, if effective	Side effects: metabolic acidosis, decreased sweating and glaucoma.

NS- normal saline, PE: phenytoin equivalents, Max- maximum, IV –intravenous, IM- intramuscular, @- at the rate.

arrhythmias. In addition, local irritation and phlebitis are common with intravenous administration of phenytoin. Respiratory depression is exceedingly rare with its use and it does not cause sedation. In children, care has to be taken to adequately dilute it in normal saline and as far as possible use a large caliber vessel. As a second-line AED in SE after benzodiazepines, phenytoin has been evaluated against phenobarbitone, valproate and levetiracetam [74,79,80]. However, recent evidence [80] does not support the first line use of phenytoin.

Fosphenytoin is a water-soluble pro-drug of phenytoin which has a more favorable side-effect profile and can be given intramuscularly. It is preferred over phenytoin, when available, but its higher cost and limited availability precludes its widespread use.

Phenobarbitone

Intravenous phenobarbitone is an effective alternative to phenytoin in benzodiazepine unresponsive seizures. The perceived risk of higher rate of respiratory depression after its use has not been seen in randomized trials [74, 80]. Still, one needs caution in using it after two or more doses of benzodiazepines. It is particularly effective in infants younger than one year. When using this drug, personnel trained in intubation and resuscitation should be available. Hypotension, respiratory depression and sedation are the major side-effects. High dose phenobarbitone has also been used for refractory status epilepticus in intensive care setting [81].

Valproic Acid (Sodium valproate)

The efficacy of valproic acid is similar to phenytoin after failure of benzodiazepines [82], though a recent meta-analysis found it to have superior efficacy [80]. In a recent trial in children, intravenous valproic acid was shown to be equally effective as phenobarbitone with significant fewer adverse effects [83]. A recent systematic review of studies with mainly adult patients concluded that

TABLE IV DRUG MANAGEMENT OF STATUS EPILEPTICUS IN A HEALTH FACILITY*

Timeline	*Drug treatment*	
0 min	*IV Access available:* Inj Lorazepam- 0.1 mg/kg/IV (max 4 mg) @ 2 mg/min OR Inj Diazepam - 0.2 - 0.3 mg/Kg/IV (max 10 mg) Slow IV OR Inj Midazolam - 0.15 - 0.2 mg/kg/IV (max 5 mg)	
	IV access not available: Buccal/Nasal Midazolam 0.2 - 0.3 mg/kg (Max 5 mg) OR PR Diazepam 0.5 mg/kg (Max 10 mg) OR IM Midazolam 0.2 mg/kg (Max 5 mg)	
5 min	Repeat Benzodiazepine once	
10 min	IV Phenytoin 20 mg/kg (Max: 1000mg) in NS @ 1 mg/kg/min (Max 50 mg per min), OR Inj Fosphenytoin 20 mg PE/ kg, Rate: 3 mg PE/kg/min	
	PICU bed Available	
IV Midazolam infusion		
	PICU bed/PICU not-Available (following management may be done sequentially)	
Drug treatment		*Additional action*
IV Valproate 20 mg/kg-IV @ max 6 mg/kg/minute		Shift to PICU, if feasible
IV Phenobarbitone 20 mg/kg in NS @ 1.5 mg/kg/min		Shift to PICU, if feasible
Alternate drug: IV Levetiracetam (If Liver disease/Metabolic disease/ coagulopathy/on chemotherapy) - 20-30 mg/kg @ 5 mg/kg/min infusion		Shift to PICU, if feasible
IV Midazolam infusion		Shift to PICU, if feasible

**Details available in the text; #from the time child came to medical attention; AED- Anti epileptic drugs, PE- Phenytoin equivalent, NS- normal saline; Valproate and Levetiracetam can be interchangeably used in the sequence of drugs; Max- maximun dose; @- at the rate of.*

Special situations

- If the child is already on anti epileptic drugs (AED) : Give half the loading dose of the respective AED.
- IV Pyridoxine: To be used in children with Isoniazid overdose AND in children <2 years of age without a clear etiology for seizures (IV Pyridoxine 100 mg infusion); B6 trial may also be given to any child with super-refractory status and neonatal onset of seizures, who has not received pyridoxine before.
- Liver failure or Chronic liver disease: prefer levetiracetam, avoid valproate; Liver failure- Avoid long acting benzodiazepines, Phenobarbitone; preferred drugs- Phenytoin, Levetiracetam.
- Renal Failure: Levetiracetam accumulates in patients with renal failure; Valproate and benzodiazepines are better options.
- Suspected or proven neurometabolic disorder or Inborn error of metabolism: prefer- Levetiracetam.
- Porphyria: Check drug list for safe agents in prophyria, avoid Phenobarbitone.
- Child less than 2 years : Avoid Valproate.
- Child with severe PEM: consider deficiency states aggravating or causing seizures - Magnesium, Calcium, Vitamin- B6, Vitamin B1.
- Child with neuromuscular disease and respiratory or bulbar weakness: Caution in using respiratory depressants like Benzodiazepines, Phenobarbitone; Prefer Phenytoin, Valproate, Levetiracetam.

BOX 3 SUPPLEMENTARY MANAGEMENT OPTIONS IN SE

Indications for Mechanical Ventilation

- Glasgow coma scale score <8
- Respiratory depression (irregular jerky breathing or apnea) due to SE or anesthetic agents
- Fluid-refractory shock
- Raised intracranial pressure
- Difficult-to-maintain airway

Indications for Continuous EEG Monitoring

- Prolonged altered sensorium following cessation of clinical seizures*
- Clinical suspicion of non-convulsive status epilepticus^
- All children receiving IV anesthetic agents#

**No definite time cut-off for "prolonged"; #for titration of dosage till electroclinical seizure cessation is achieved; and to monitor for recurrence of electrographic seizures during tapering; ^Subtle twitching movements of eyelids, extremities, nystagmoid movements, unexplained tachycardia in the absence of pulmonary or cardiac pathology.*

intravenous valproate was as effective as intravenous phenytoin for SE control [84]. It has also been shown to be effective in children with status epilepticus refractory to phenytoin [85]. The major advantage of valproic acid is the relative lack of sedation, respiratory depression or adverse hemodynamic events. On the other hand, caution needs to be exercised in its use in infants, and in those with liver disease, bleeding diathesis and suspected metabolic disorders.

Levetiracetam

This is another emerging drug in the management of status epilepticus. Presently there are no randomized trials reporting its use in children. Data in adults suggest that it is as effective as valproic acid [80,84]. This drug too has the advantage of relative lack of sedation, respiratory depression or adverse hemodynamic events. Additionally, it can be used in liver failure and in presence of bleeding diathesis. It also has the advantage of relatively few drug-interactions.

An ongoing multi-centric trial is expected to clarify regarding the best drug (amongst valproate, fosphenytoin and levetiracetam) to be used after benzodiazepines [86].

Refractory Status Epilepticus

SE is considered refractory if seizures persist despite the administration of two appropriate anticonvulsants at acceptable doses [87]. Earlier definitions also mentioned duration of the status (60 min or 120 min) [88,89]. For the multi-centric Pediatric Status Epilepticus Research Group (pSERG) study, the definition described is prolonged seizures that fail to terminate after administration of two anti-epileptic drugs with different mechanisms of action or that require continuously administered medication to abort seizures, regardless of seizure duration [90]. These definitions highlight the concepts that the potential for neuronal injury is positively correlated with time, and pharmaco-resistance increases with time and is reflected in the number of drugs administered [87]. Refractory status epilepticus comprises around 10-40% of patients with status epilepticus [87,91]. Predictive factors for development of intractability in patients with SE include encephalitic etiology, severe impairment of consciousness at presentation, absence of a history of epilepsy, and low anticonvulsant levels (in patients with known epilepsy) [92,93].

EEG monitoring, if available, is important both to monitor for electroclinical seizures or non-convulsive electrographic seizures, and to titrate therapy and the depth of anesthesia, if necessary [87]. Additional investigations, other than those previously described, include a high resolution (3 Tesla) MRI to look for cortical dysplasias, metabolic work-up (blood Tandem mass spectrophotometry and/or blood/urine Gas chromatography mass spectrophotometry) in young children, and work-up for autoimmune encephalitis in patients with *de novo* status epilepticus associated with fever.

Refractory status epilepticus must be managed in the intensive care unit. These children require careful cardiorespiratory monitoring and may also require mechanical ventilation.

Agents available for treatment are anti-epileptic drugs (non-anesthetic agents) and intravenous anesthetic agents [87]. Non-anesthetic agents include phenobarbitone, valproic acid, levetiracetam, topiramate, and lacosamide. Intravenous preparations for all the above-mentioned drugs, except topiramate are available. Intravenous anesthetic agents include midazolam, pentobarbital, thiopental sodium, and propofol. Pentobarbital is not available in India. Propofol has been used extensively in adult status epilepticus. However, the risk of propofol infusion syndrome is high in children and hence propofol is not approved for the treatment of pediatric status epilepticus in many countries [94]. Given the absence of clear evidence, the decision to use one or other anesthetic medications must take into account the patient's general condition, weighing the benefits against the potential adverse effects of the medication, and the medical staff's experience in the use of these drugs and their ability to manage the side effects [95].

Second-line Anticonvulsants: After the failure of phenytoin/fosphenytoin, trial of any of the following: phenobarbitone, sodium valproate or levetiracetam may be given. In children below 2 years of age, pyridoxine (100 mg intravenously) may be tried. If the seizure continues despite this third agent, the patient must be shifted to the intensive care unit where facilities for mechanical ventilation and cardiorespiratory monitoring are available. If however, there is a delay in transfer or intensive care unit is not available, a fourth drug (phenobarbitone, sodium valproate or levetiracetam; whichever has not been tried earlier) may be tried before proceeding to midazolam infusion.

There are reports of use of topiramate in children with refractory SE leading to rapid resolution of status with no hemodynamic or sedative side effects. As intravenous preparation is not available, it should be administered through nasogastric tube [96]. Anecdotal reports of efficacy of Lacosamide in children with SE exist [97]; however, more data is needed before its use can be recommended.

Intravenous Anesthetic Agents: Midazolam infusion is the most preferred initial treatment in children with refractory status epilepticus, effective in seizure control in 76% of these patients [5]. Midazolam is a short-acting benzodiazepine that rapidly equilibrates across the blood-brain barrier and has a short elimination half-life. It has a favorable pharmacokinetic profile which allows for repeat bolus dosing, aggressive titration of the infusion, and relatively fast recovery time [98]. It causes little hypotension, and vasopressors are usually only needed when high doses of midazolam are used.

Initial effectiveness in terminating pediatric RSE has been shown in several studies with efficacy rates of approximately 80% to 90% [99,100]. Midazolam should be given as a 0.2 mg /kg bolus then infusion at the rate of 1 µg/kg/min, increasing 1 µg/kg/min, every 5-10 min, till seizures stop, up to a maximum of 12µg/kg/min [101]. Larger initial bolus doses (0.5 mg/kg) and more aggressive upward dose titration (up to 2 mg/kg/hour) may result in faster termination of status epilepticus [87,98,100]. Doses up to 36µg/kg/min have been used in previous studies, and may be tried provided it is being used in an ICU setting and appropriate monitoring and management facilities are available. Tapering should be started 24-48 hours after seizure stops at the rate of 1 µg/kg/min, every 3-4 hours. Although generally effective and well tolerated, a drawback of midazolam is the apparent increased propensity for seizure recurrence on tapering, compared with other intravenous anesthetic agents.

Thiopental sodium penetrates the central nervous system rapidly, allowing for rapid titration to EEG burst-suppression. It has multiple actions: activation of the GABA receptor; inhibition of N-methyl-D-aspartate (NMDA) receptors; and, alteration in the conductance of chloride, potassium, and calcium ion channels [5]. Its prolonged infusion results in a transition from the usual first-order elimination kinetics seen with bolus doses to the unpredictable zero-order kinetics and a prolonged elimination half-life because of distribution in lipid. This phenomenon makes recovery time prolonged and the drug effect can last days, even with short infusion periods of 12 to 24 hours.

Induction of barbiturate coma is done with bolus of 3 mg/kg, repeated after 2 min, followed by maintenance (1-5 mg/kg/hr) to control seizures and/or to achieve "suppression-burst" EEG activity (increasing 1 mg/kg/hr every 2 minutes) [95]. The subsequent maintenance infusion should continue for 12-48 hours. Thiopental usually causes respiratory depression. It can also induce hypotension and heart failure, and inotropic support is frequently needed. Thiopental is associated with an increased rate of nosocomial infection, especially pneumonia, and ileus [102]. It is contraindicated in the presence of hypotension, cardiogenic shock and sepsis [95]. It is reported to control seizures in 65% of the refractory SE patients not responding to midazolam [97].

Super-refractory Status Epilepticus

Around 15% of all those presenting to hospital in SE develop super-refractory status epilepticus and the mortality is 30-50% [102,103].

Therapies for this entity have not been well studied. Treatment modalities depend on the availability of resources, and experience and familiarity of the treating physicians with the various modalities. Other than the previously mentioned drugs; the agents and modalities that have been tried in super-refractory status epilepticus include ketamine [104], inhalational halogenated anesthetics [105], magnesium infusion [106], steroids and immunotherapy [103], ketogenic diet [107], hypothermia [108], electrical and magnetic stimulation therapies [103], electroconvulsive therapy [109], and CSF drainage [110]. Emergency neurosurgery may be considered in children in whom a lesion has been detected as the cause of status epilepticus, e.g. cortical dysplasia [111].

F. FEBRILE STATUS EPILEPTICUS

It is defined as status epilepticus in a child aged 1 month to 5 years that also meets the definition of a febrile seizure [112]. Thus it is clear that febrile central nervous system infections associated with status epilepticus will not be included in febrile SE. Febrile SE occur in 5% of febrile

KEY MESSAGES

- Each institution should use a uniform, written protocol for management of status epilepticus.
- Pre-hospital management and early stabilization is the key to a satisfactory outcome of status epilepticus.
- Initial management of status epilepticus consists of a parenteral benzodiazepine; any agent by any route may be used depending on the availability.
- Pharmacotherapy should not be delayed for any investigations.
- There is a need for more epidemiological research on status epilepticus from India.

seizures [113]. Western studies report febrile SE as the most common cause of status epilepticus in children (up to 50%) [114], although Indian studies have reported it to be less common (10%) [18], or have not characterized it separately [8]. Many of the issues related to investigations in febrile SE and its outcome are being explord by the FEBSTAT study [112].

CSF changes in Febrile SE: Pleocytosis due to SE or febrile SE has long been a controversial issue, and probably the definitive answer is now available with the results of the FEBSTAT study [112]. The CSF results from this large group of patients with prolonged febrile seizure were usually normal: 96% had ≤5 WBCs/ mm^3; CSF glucose and protein levels were also unremarkable [64]. Human herpesvirus-6B has been reported to be the most common cause of febrile SE [115].

Management of febrile SE is similar to that recommended for SE in these guidelines; however, there is evidence to show that phenytoin is less efficacious in this situation [116].

G. MANAGEMENT FOLLOWING STATUS EPILEPTICUS

It is well-established that the duration of the first seizure does not affect the risk of recurrence, whether it is a single seizure or a status epilepticus. Moreover, remission rates are also not different in those who present with an episode of SE [117]. Brief recommendations for follow-up management after control of SE are provided in ***Box* 4**.

H. RESEARCH NEEDS

During the deliberations, the group also tried to identify the areas requiring research in the Indian context. These are listed in ***Box* 5**, and are expected to provide guidance to the researchers about issues needing evidence-support.

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BOX 4 GUIDELINES FOR FOLLOW-UP MANAGEMENT OF CHILDREN WITH STATUS EPILEPTICUS

New-onset SE: Further treatment decisions should be similar to that for a First seizure.

Acute symptomatic seizures: Further treatment depends on the control of the precipitating event.

SE in known epilepsy:

- After control of SE for 24 hours, tapering of drugs should be started with 'last in, first out' as the guiding principle.
- All the AEDs should preferably be stopped during hospital stay and the child discharged on:
  - Augmented dose of the previous AED/s (if levels were sub-therapeutic or prescribed dose was less than maximum dose); and
  - Introduction of another appropriate AED (either replacement or addition), if previously receiving maximum doses of AED/s.

BOX 5 RESEARCH NEEDS FOR STATUS EPILEPTICUS IN CHILDREN

Epidemiology of SE in India

Role of hypocalcemia in SE, especially in infants

Role of phenobarbitone and phenytoin as the initial AED after benzodiazepine

Management of SE-associated with neuroinfections

Outcome of SE in Indian children

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ANNEXURE I

Participants of the Multi-disciplinary Consensus Development Workshop on Management of Status Epilepticus in Children in India

Experts (in alphabetical order)**:** Anju Aggarwal, UCMS, Delhi; Satinder Aneja, LHMC, Delhi (*Convener*); B Chakravarty, AIIMS, Delhi; A Chattopadhyay, Apollo hospital, Kolkata; JS Goraya, Dayanand Medical College, Ludhiana; Rahul Jain, Chacha Nehru Bal Chikitsalaya, Delhi; Sourabh Jain, SZ Hospital, Bhopal; Urmila Jhamb, MAMC, Delhi; Veena Kalra, Delhi; Mahesh Kamate, JNMC, Belgaum; Sujata Kanhere, KJ Somaiya Medical College, Mumbai; Praveen Khilnani, BLK Memorial hospital, Delhi; Ramesh Konanki, Hyderabad; Rashmi Kumar, KGMC, Lucknow; PAM Kunju, Thiruvanantpuram; Lokesh Lingappa, Hyderabad; MM Mehndiratta, JSSH, Delhi; Rekha Mittal, Max hospital, Delhi; D Mishra, MAMC, Delhi (*Co-convener*); V Murugan, Chennai; Rajniti Prasad, BHU, Varanasi; Ashalatha Radhakrishnan, SCTIMST, Trivandrum; Col. KS Rana, Military Hospital, Jabalpur; Naveen Sankhyan, PGIMER, Chandigarh; Suvasini Sharma, LHMC, Delhi; Sunit Singhi, PGIMER, Chandigarh; Sanjib Sinha, NIMHANS, Bangalore; Bibek Talukdar, CNBC, Delhi; Manjari Tripathi, AIIMS, Delhi; Vrajesh Udani, Hinduja Hospital, Mumbai; and Nitish Vora, Ahmedabad.

Rapporteur**:** Rachna Sehgal, Safdarjung Hospital, Delhi.

Observers: Puneet Jain, Bijoy Patra, Dinesh Raj and Harikishan Suthar (all Delhi); Neetu Sharma (Gwalior).

Invited but could not attend the meeting: CP Bansal, President, Indian Academy of Pediatrics; Virender Kumar, LHMC, Delhi; Sheffali Gulati, AIIMS, Delhi; Rakesh Lodha, AIIMS, Delhi; Pratibha Singhi, PGIMER, Chandigarh; Kalpana V, GMC, Thiruvanathapuram; and Jitendra Sahu, PGIMER, Chandigarh.