

Recent trends in the management of status epilepticus

G. Rajshekher

Abstract

Status Epilepticus (SE) is a neurologic emergency associated with high morbidity and mortality. The etiology varies among the different age groups, and it has a U-shaped incidence curve, being more common at the extremes of ages. Mortality is rarely due to the status itself, and the outcome depends to a great extent on the underlying etiology and the presence of additional medical conditions. Outcome also depends on the rapidity of diagnosis and initiation of appropriate therapy. Anti-epileptic drug administration in appropriate doses should begin promptly after the suspicion of SE; intra-muscular midazolam and rectal diazepam administered by paramedical staff involved in transporting the patient also has been shown to shorten the duration of SE. Attention should be paid in the initial stages itself to airway patency, adequacy of breathing and ventilation, the circulatory status, securing intravenous access and identifying the underlying cause. The goals of therapy include rapid termination of clinical and electrical ictal activity, prevention of aspiration pneumonia, and treatment of complications in anticipation. Every hospital needs to manage SE on the basis of established protocols, and an early decision regarding artificial ventilation and midazolam or barbiturate anesthesia for refractory SE needs to be taken. With the existing protocols and available drugs, it is generally possible to control seizures and prevent complications and mortality.

Key Words: Status Epilepticus (SE), Refractory SE, Non-convulsive SE (NCSE), lorazepam, midazolam, barbiturate anesthesia

SE is a medical emergency in which the patient has continuous or rapidly repeating seizures.^[1] The ILAE defined SE as a seizure that "...persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur".^[2] This definition is a little difficult to use in clinical practice due to the lack of specific duration, and more recent publications have tried to remedy this by defining SE as a seizure that lasts for 20-30 minutes.^[3,4] This time frame is based on an estimate of duration necessary to cause damage

to cerebral neurons.^[3,4] However the practical experience of clinicians has been that seizures need to be controlled much earlier than 20 minutes, and therefore, an operational definition for SE has been proposed: either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness.^[5,6]

Clinical features

SE may be of convulsive type, when motor activity in the form of tonic, tonic-clonic, or clonic limb-jerking may be obvious to the observer. Patients are usually unresponsive during this stage if the seizures are generalized. Later on, the motor activity may become subtle, and may be missed, especially if the patient is seen for the first time in this phase. This is the non-convulsive phase of SE, and only upon careful observation one may

From:
Consultant Neurologist, Suite No. 16, A-Wing, Apollo Hospitals, Jubilee Hills,
Hyderabad - 500033, India

Correspondence:
Dr. G. Rajshekher,
Consultant Neurologist, Suite No. 16, A-Wing, Apollo Hospitals, Jubilee Hills,
Hyderabad - 500033, India. E-mail: drphaniraj@apollohospital.net

Free full text available from www.ijccm.org

notice small-amplitude twitching movements of the face, hands, or feet or nystagmoid jerking of the eyes.^[7] Sometimes, even these subtle manifestations may not be visible, and the diagnosis of ongoing seizure activity depends on electroencephalography.^[8] Electrographic seizures of this type are seen predominantly in the hospitalized, comatose patient, and may be more common than previously thought.^[9] In a study of 236 patients with coma and no seizure activity monitored with EEG as part of coma evaluation, 8% met the criteria for non-convulsive SE (NCSE).^[10] Electrographic SE or NCSE is mistakenly thought by many to be a benign condition; these patients are equally at risk for brain damage,^[11,12] even if they have been paralyzed and sedated for respiratory management. NCSE in adult animals too leads to widespread neuronal necrosis in vulnerable regions, although lesions develop more slowly than they would in the presence of convulsions or anoxia.^[13]

Incidence and prevalence of SE

SE is a common neurologic emergency; data emanating from the Rochester Epidemiology Project (Rochester, Minnesota, USA)^[14] indicate that the age-adjusted incidence of SE was 18.3 per 100,000 population in the decades 1965-84. It has a U-shaped incidence curve, peaking under 1 year and over 60 years of age.^[14-16] Cumulative incidence is 4 per 1,000 to age 75 and shows the greatest increase after 60 years of age.^[14] The incidence of SE is greater among males, in seizures related to acute symptomatic etiology, and for partial SE (than generalized SE). Based on the incidence of SE actually determined in Richmond, Virginia, it was projected that each year there would be 1,26,000 to 1,95,000 events of SE in the US, with 22,200 to 42,000 of these ending in death.^[17] Statistics for Indian population are scarce; 16 (3%) of 2531 patients followed over a 3-year period in a single center (Nizam's Institute of Medical Sciences, Hyderabad) developed SE.^[18] However, this is a gross underestimate of the incidence of SE, and a study involving multiple centers alone would give a correct estimate of the actual incidence.

Causes of SE

The single-most common cause of SE is non-compliance with AED drug prescription;^[19] of 98 patients over the age of 14 years, this accounted for the status in 53% of patients with previous seizures.^[19] Other patient-related factors include incomplete drug absorption, vomit-

ing, and drug-interactions.^[19] Other causes, especially in those without a past history of seizures, include alcohol-withdrawal, cerebrovascular disease, cerebral tumors or trauma (involving especially the frontal lobe), intracranial infection, metabolic disorders, drug overdose and cardiac arrest.^[19-21] Among Indian patients, infections of CNS and neurocysticercosis together account for 62.5% of the etiological factors for SE.^[18,22] The etiology of the status is frequently multi-factorial, and no specific cause can be found in 15 % of patients.^[19] In the San Francisco General Hospital, 154 patients were treated for SE in the decade between 1980 and 1989;^[23] of these 154 patients reviewed, the four leading etiologies for SE were anticonvulsant drug withdrawal (39), alcohol-related (39), drug toxicity (14), and CNS infection (12).^[23]

Outcome in SE

The most important factor deciding outcome in SE is the underlying etiology.^[24] In the San Francisco study, the best response to anticonvulsants occurred in patients with SE related to tumor, anticonvulsant drug withdrawal, or refractory epilepsy.^[23] The poor responders in this study had anoxia, drug toxicity, CNS infection, or other metabolic abnormalities. Aminoff et al found that the outcome of SE worsened with an increase in the duration of status.^[19] Towne et al also found that the group with SE lasting <1 h had a lower mortality as compared with seizure duration one hour or more.^[20] Hyperthermia, peripheral leucocytosis and CSF pleocytosis are common accompaniments of SE, and even systemic acidosis may occur in a few patients, without necessarily portending a worse outcome.^[19] The overall mortality among adults with SE is 20%, and those with first-time episodes of SE are at substantial risk for more such episodes and for the development of chronic epilepsy.^[17] When SE is related to an acute medical problem such as renal failure, sepsis, electrolyte abnormality, CNS infections, stroke, head trauma, drug toxicity, or hypoxia, seizures are especially difficult to control and associated with a higher mortality.^[20,23,25] The best example of this is the elderly patient who has survived an episode of cerebral hypoxia, and has developed myoclonic SE, which carries a grave prognosis. In a recent study evaluating variables affecting outcome in children with SE, no deaths were due to SE itself;^[26] symptomatic etiology (acute or remote) and refractory SE were associated with adverse outcomes, and age <12 months at development of SE, and duration of SE >60 minutes tended to be more frequent

among those who developed adverse outcome.^[26]

Pathophysiology

Isolated seizures occur due to the generation and spread of abnormal electrical activity among neuronal networks; the networks are probably abnormal to start with. But several mechanisms come into play with the onset of a seizure, which work to terminate the attack. SE is believed to be due to the failure of these seizure-abortive mechanisms.^[1]

In late 1987, following the consumption of mussels contaminated with domoic acid in Canada, there was an outbreak of gastrointestinal and neurological abnormalities;^[27] the latter included seizures, leading in a few cases to SE, and 4 of these who died underwent autopsy, which showed neuronal necrosis and loss, predominantly in the hippocampus and amygdala, in a pattern similar to that observed in the kainate model of epilepsy. Both Domoic acid and kainic acid are homologues of the excitatory amino acid glutamic acid. From these findings followed the hypothesis that SE occurs due to abnormally persistent excessive excitation.^[27] The other idea that there is ineffective recruitment of the inhibitory mechanisms springs from the observation of SE with penicillin and related compounds that antagonize the principal inhibitory amino acid in the brain, GABA.^[28] It is now believed that loss of GABA-mediated inhibitory synaptic transmission in the hippocampus is critical for the emergence of SE, and excitatory synaptic transmission is important in sustaining SE.^[29] Experimental studies in rats have shown that the sensitivity of GABA-A receptor to benzodiazepines, and other allosteric modulators decreases over time as SE continues.^[29,30] This may be one of the reasons for the failure of the inhibitory mechanisms.

Prolonged seizures produce CNS damage.^[31] The physiologic consequences of SE, such as elevation of body temperature, transient metabolic acidosis, and elevation of hormonal concentrations (such as epinephrine in the arrhythmic range) add to the injury.^[32]

Marked rise in pressure in the systemic as well as the pulmonary circulation may have deleterious effects, such as by causing pulmonary edema.^[31,33] Prolonged and repeated seizures themselves cause damage to limbic structures like the hippocampus.^[34] This damage is partly

due to glutamate-mediated excitotoxicity, and not merely because of increased metabolic demands of repetitive neuronal firing. Continued epileptic activity may lead to relative cerebral hypoxia and hypoglycemia.^[35] The seizures compromise cerebral vascular auto-regulation, which in turn compromises hypothalamic autonomic regulation, and intra-cranial hypertension may then supervene.^[36] Complications such as cardiovascular collapse, arrhythmias, aspiration pneumonia, acute lung injury, and pulmonary hypertension may further compromise cerebral oxygen delivery. Cerebral and systemic hypoxia and acidosis, hyperthermia, rhabdomyolysis, and DIC may then lead to multiple organ failure and death.

Management

The management of the patient with SE should normally occur at two levels:

1. Management of the seizures themselves
2. General medical management

Figure 1 provides the algorithm for the general management of SE presenting to the Emergency Room.

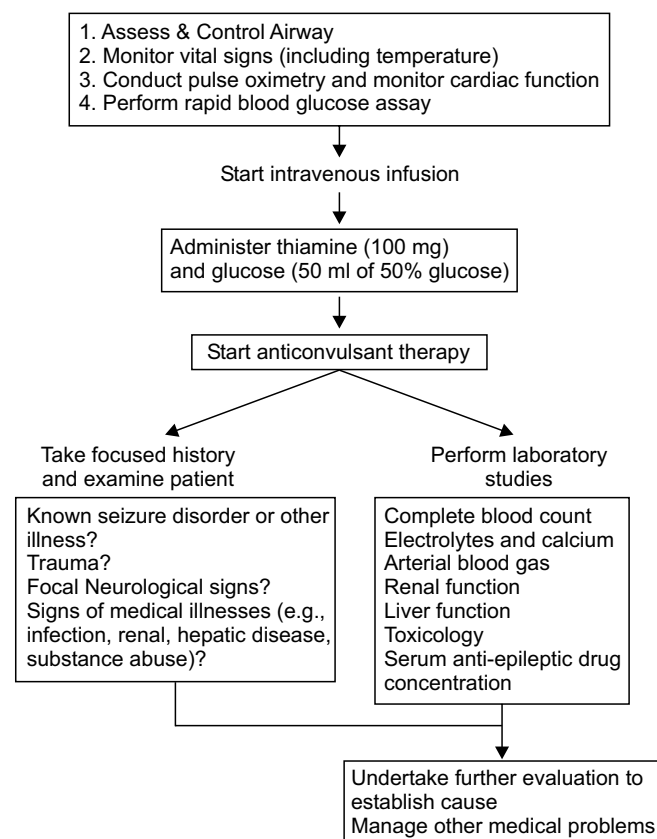


Figure 1: Algorithm for the general management of status epilepticus presenting to the Emergency Room

The patient should be placed in a position to minimize trauma to convulsing limbs from neighboring hard objects and surfaces. Frequent oro-pharyngeal suctioning may be required. Attempts to prevent tongue bites by placing handkerchiefs and other objects in the mouth between the teeth, have led to choking and death; a towel, folded cylindrically and placed sideways in the mouth may be far safer.

The immediate assessment of breathing and securing the airway is of paramount importance in the actively convulsing patients, as they are highly prone to develop aspiration and all the attendant complications. During the tonic-clonic phase of the convulsion, the patient may stop breathing and become cyanosed; however this is generally short-lasting, and does not create a problem, unless the airway is blocked. Administration of 100% oxygen is usually sufficient, but the airway patency should be secured with an oral or nasopharyngeal airway tube. If there is respiratory compromise, an emergent intubation may be called for; if neuromuscular blockade is deemed necessary to perform the procedure, then a short-acting agent like 0.1mg/kg of vecuronium should be employed, thereby ensuring that ongoing seizures are not missed by the attending physician.

Alcohol ingestion is a common cause of presentation in the emergency with SE;^[37] prompt administration of thiamine is therefore essential, often before it can be ascertained that alcohol has been consumed. Similarly, immediate blood sugar measurement is now routine, and even when initially normal, 100-200 ml of 25% glucose are administered in actively convulsing patients, as blood sugar levels tend to fall, and hypoglycemia can add to the complications.

Hyperthermia and metabolic acidosis occur relatively frequently in SE; together with the peripheral blood leucocytosis, they may suggest an infection and lead to the inappropriate use of antibiotics. Later on the patient may actually develop aspiration pneumonia, for which antibiotics may become necessary. On the other hand, the classical symptoms and signs of acute bacterial meningitis may be absent in convulsive SE with fever; a high index of suspicion for acute bacterial meningitis is therefore of paramount importance. The most appropriate management is early parenteral antibiotics and lumbar

puncture if there are no contraindications.^[38] Metabolic acidosis gets corrected once the seizures are controlled. Hyperthermia should be managed emergently with anti-pyretics and cooling blankets, as continued high fever can have deleterious effects on the central nervous system.

Control of seizures: Drug therapy

In the management of SE, the response to treatment and the ultimate outcome are very much dependent on the duration of the status before effective anti-epileptic medications are administered. This was amply demonstrated in the study in San Francisco in the 1980s,^[23] where the authors found that if the AED was administered within 30 minutes of the onset of SE, the response rate was as high as 80%, whereas in those treated after the 30 minute period, the response rate fell to 40%. Rapid functional plasticity of GABA_A receptors has been demonstrated to occur during SE in rats with a substantial reduction of diazepam potency for termination of the seizures,^[29] especially as the duration of electrographic seizures increases.^[39]

The ideal drug to control status should be easy to administer, should produce the effect immediately, have long-lasting effect, and at the same time should not depress cardio-respiratory function or the consciousness. Benzodiazepines like diazepam and barbiturates carry the risk of respiratory depression and also depress consciousness in a dose-dependant manner. Phenytoin and fosphenytoin can cause hypotension and cardiac arrhythmias if administered too fast; this can be a limiting factor when attempting rapid seizure control, though in practice this is seldom the reason for failing to control seizures. The Figure 2 gives an algorithm for the management of SE in adults and older children that is followed all over the world; the choice of drugs is based on the rapidity of action of the drugs and the duration of action. Lorazepam has an extremely rapid onset of action; in a retrospective analysis comparing the treatment of SE with diazepam and lorazepam, both were found to be equally effective, but there were fewer recurrences with lorazepam, and fewer repeat doses were required.^[40] Based on this the authors recommended that lorazepam should be the drug of first choice. Phenytoin has the advantages of the availability of an injectable preparation, and till recently was the only other

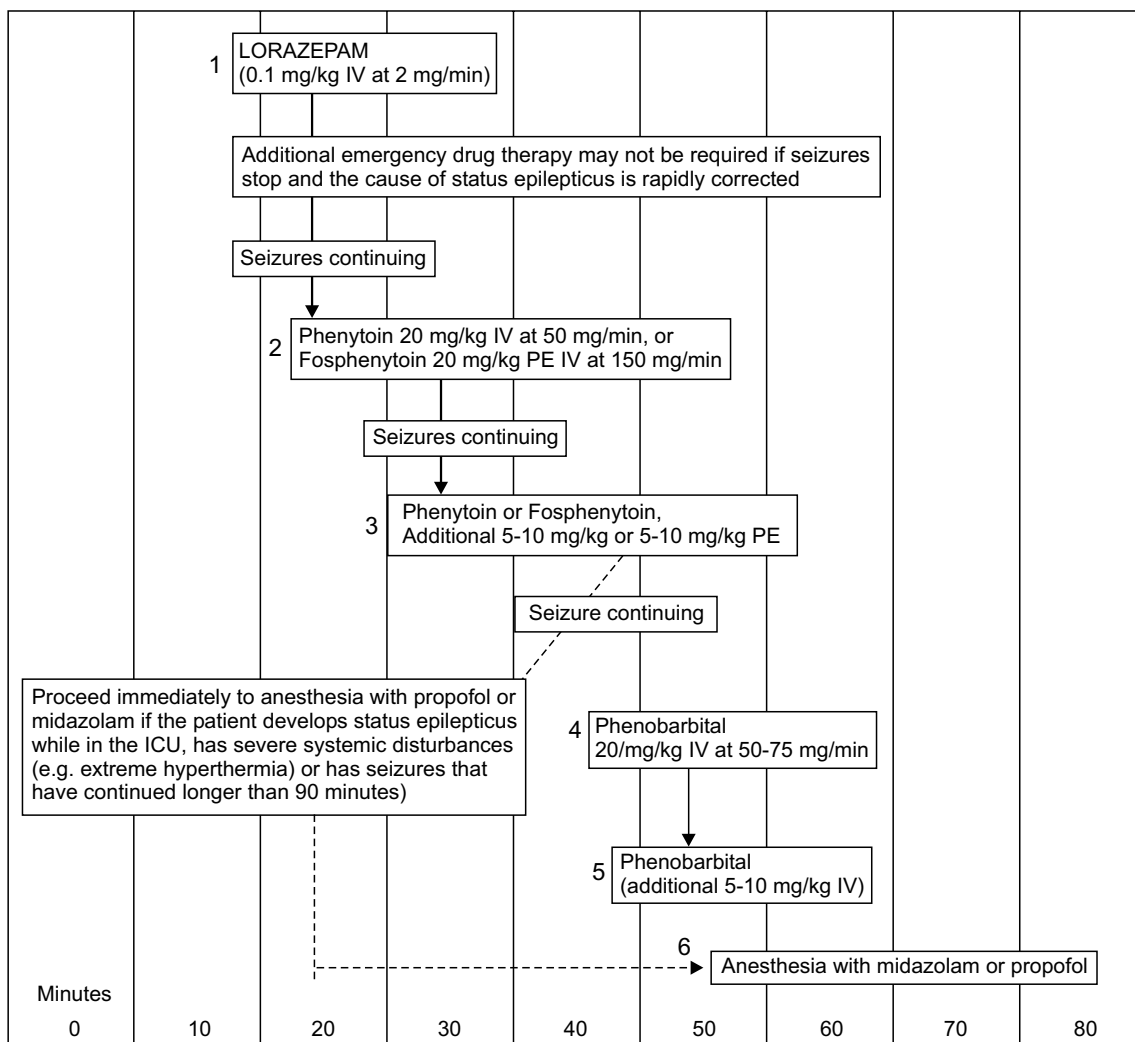


Figure 1 and 2: The figure gives an algorithm for the management of SE in adults and older children that is followed all over the world; the choice of drugs is based on the rapidity of action of the drugs and the duration of action

anti-epileptic drug whose plasma levels could be rapidly brought to the therapeutic range. In addition it has a long duration of action. In a five-year randomized, double-blind trial comparing the efficacy of lorazepam alone, phenytoin alone, diazepam with phenytoin, and phenobarbital alone for the treatment of generalized SE, the treatments were equally effective, except that lorazepam alone was more effective than phenytoin alone, when seizures were assessed 20 minutes after the administration began.^[41] In the algorithm, lorazepam is followed by Phenytoin if the seizures are not controlled, and this is preferred by neurologists and epileptologists the world over. When the cause of the SE is a reversible one, such as sub-therapeutic drug concentration or an acute metabolic process, then lorazepam alone may be sufficient and obviate the need for Phenytoin or Fosphenytoin.

Pharmacologic Therapy

Benzodiazepines

The benzodiazepines including diazepam, lorazepam, and midazolam are the preferred initial choice for therapy of SE, mainly because of their rapidity of onset of action, and high efficacy in aborting seizures; benzodiazepine-receptor-mediated enhancement of GABAergic transmission is their primary mode of action. In addition, they also block sustained repetitive neuronal firing in a manner similar to carbamazepine and phenytoin. All benzodiazepines rapidly enter CSF, with peak concentrations usually attained within 15 min of dosage.^[42] Though lorazepam is less lipid-soluble, and therefore its serum and CSF levels rise much more slowly than that of diazepam, it remains longer in brain than in the serum, leading to increasing brain: serum ratios over time.^[43] In a randomized, double-blind trial comparing

standard doses of diazepam and lorazepam, both were found to be equally effective, the median time to termination of seizure also being similar (two minutes for diazepam, three for lorazepam).^[44] Despite these similarities, the important difference between diazepam and lorazepam is their duration of actions (12 to 24 hours for lorazepam versus 15 to 20 minutes for diazepam), and it is this property which makes lorazepam superior in the acute treatment of SE.^[45] Adverse effects occur in 13% of the lorazepam-treated patients and in 12% of the diazepam-treated patients.^[44] These include respiratory depression in 3 to 10%, hypotension in <2%, and impaired consciousness in 20 to 60% patients.^[44,46,47] One problem with continued use of benzodiazepine in SE is that prolonged seizures of SE rapidly alter the functional properties of hippocampal dentate granule cell GABA(A) receptors leading to loss of sensitivity of the animals to diazepam during SE.^[29] Since this is not seen with barbiturates, they are preferred for refractory SE.

Phenytoin and Fosphenytoin

Phenytoin is ideally suited for rapid control of seizure as well as for prolonged effect, so much so that frequently, epilepsy treatment is equated with the administration of phenytoin. Even though many more alternatives are now available, phenytoin still has many advantages not offered by the other medications. Its use in the acute setting is most useful in three situations: (1) after rapid control of seizure with benzodiazepines, for prolonged effect; (2) as initial therapy for SE, and (3) when benzodiazepines fail to control seizures. The most common problem with its use in the emergency department is inadequate dose; at least 20 mg/kg is required, and an additional 5-10 mg/kg may occasionally be required.^[48] The maximum tolerated rate of administration is 50 mg/min; given at this rate it causes hypotension in 28-30% of patients, and cardiac arrhythmias (bradycardia or ectopic beats) in 2%, especially in those above 50 years age and those with pre-existing cardiac disease.^[49] These cardiovascular side-effects are attributed to phenytoin itself and to its propylene glycol diluent, and can be mitigated by slowing the rate of administration.^[50] This means that the shortest time in which a 1000 mg dose can be administered is 20 minutes; in practice, it is administered even more slowly, and this is occasionally the reason for its failure. In a known epileptic who is already on phenytoin, presenting with SE, a serum sample for estimation of phenytoin levels should be drawn

prior to administration of anti-epileptics; in this setting, the serum phenytoin level is likely to be sub-therapeutic but not zero, and that is why it is common practice to administer a half-loading dose of phenytoin. Though one should not wait for the serum levels to treat SE, this practice (of administering a half-loading dose) is at best an educated guess and the ER physician should not hesitate to administer additional phenytoin if the seizures remain uncontrolled. When a typical loading dose is given to an adult, it takes about 20-25 minutes for maximal effect.^[50] Fosphenytoin is the disodium phosphate ester pro-drug of phenytoin for parenteral use.^[51] It has significantly better water solubility, but little intrinsic pharmacologic activity. After parenteral administration, it is rapidly and completely converted by serum and tissue alkaline phosphatases to free phenytoin. The conversion half-life is approximately 8 to 15 minutes. Fosphenytoin has been recommended over conventional phenytoin for SE mainly for three reasons;^[52] (1) It has a pH of 8.5 as against 12 for phenytoin, (2) The vehicle does not contain propylene glycol or ethanol, thereby reducing the potential for cardiovascular or cutaneous side-effects, and (3) It can be administered much faster than phenytoin; Intravenous fosphenytoin is tolerated at infusion rates up to three times faster than those for phenytoin, and therapeutic concentrations are established within 10 minutes.^[53-56] No clinically significant hypotension or cardio-vascular side-effects have been reported with fosphenytoin, and injection-site-related problems like phlebitis and soft-tissue damage are less common with fosphenytoin. Another potential advantage of substituting fosphenytoin for phenytoin is the prevention of the "purple glove syndrome", which is reported in 6% of patients receiving intravenous phenytoin administration, characterized by progressive distal limb edema, discoloration, and pain.^[57]

Phenobarbital

Phenobarbital, 20 mg per kilogram at a rate of 50 to 75 mg per minute, has been used in the past when benzodiazepine and phenytoin fail; in a small, randomized, non-blinded trial involving 36 patients, phenobarbital was found to have shorter cumulative convulsion time and response latency when compared to benzodiazepine and phenytoin combined.^[58] However, Phenobarbital depresses respiratory drive, level of consciousness, and blood pressure, all effects are accentuated when it follows the administration of

benzodiazepine.^[59]

Treatment of Refractory SE

When SE does not respond to standard treatment with benzodiazepine, phenytoin, and phenobarbital, then it is considered to be refractory, requiring aggressive management. Patients generally need to be in the intensive care unit, and most require intubation to prevent aspiration and mechanical ventilation. This therapy requires a team approach, with the anesthetist and intensivist playing vital roles. Infusions with anesthetic doses of midazolam or propofol are usually required. EEG monitoring is generally necessary, and the aim is suppression of epileptic spikes; the end-point is burst-suppression, though occasionally, fall in BP becomes a limiting factor, especially when propofol is used. Midazolam is given in a bolus dose of 0.2 mg/kg slow intravenous push, followed by 0.75 to 10 µg/kg per minute.^[60,61] Alternatively, propofol at a dose of 1 to 2 mg per kilogram intravenous followed by 2 to 10 mg/kg/hr may be used.^[62] It directly activates GABA_A receptors. In addition, propofol inhibits the NMDA receptor and modulates calcium influx through slow calcium ion channels.^[63] Propofol has a rapid onset of action with a dose-related hypnotic effect, and recovery is rapid even after prolonged use. Propofol decreases cerebral oxygen consumption, reduces intracranial pressure and has potent anti-convulsant properties. It is a potent antioxidant, has anti-inflammatory properties and is a bronchodilator. As a consequence of these properties propofol is being increasingly used in the management of traumatic head injury, SE, delirium tremens, status asthmaticus and in critically ill septic patients.^[63] Propofol has a remarkable safety profile: dose dependent hypotension is the commonest complication, particularly in patients who are volume-depleted, or have limited cardiac reserve.^[64] Hypertriglyceridemia and pancreatitis are uncommon complications.^[63] High dose propofol infusions have been associated with the "propofol syndrome"; this is a potentially fatal complication characterized by severe metabolic acidosis and circulatory collapse.^[63] A smaller proportion of patients respond to propofol, than to barbiturates, but the response appears much earlier (2.6 min versus 123 min with barbiturate coma).^[65,66] The plasma concentrations of propofol associated with control of SE were 14 µM ± 4 (2.5 µg/ml). Recurrent seizures are common when propofol infusions are sud-

denly discontinued but not when the infusions are gradually tapered.^[67] Continuous electroencephalographic monitoring is necessary. The duration of such treatment is never certain, but usually, a seizure-free period of about 24 hours is sufficient, and the agent can be gradually tapered thereafter, unless further seizures supervene. Recovery usually takes a long time, depending on the duration of infusion, occasionally taking as long as 36-72 hours. More recently a meta-analysis of 22 studies with original data on the use of propofol in SE,^[68] has raised serious doubts about the safety of propofol in refractory SE, because two non-randomized studies and several case reports show an increased risk of mortality. The authors of this meta-analysis advise that guidelines should not recommend the use of propofol as a routine treatment in refractory SE before a proper randomized trial has been performed. Midazolam, on the other hand, appears safer; in a recent report of the treatment of 27 pediatric patients with refractory generalized convulsive SE, midazolam infusion at a rate of 3.1 µg/kg/min was found to be effective and safe in 26, without adverse effects such as hypotension, bradycardia or respiratory depression.^[69] In a randomized open-label study in children at the PGIMER, Chandigarh, comparing the efficacy of midazolam and diazepam in refractory SE, both were found to be equally effective, with median time to seizure control of 16 minutes; however in the midazolam group, seizures recurred in more children (57% versus 16% in diazepam group; $P < 0.05$) and the mortality was higher in the midazolam group (38%) as compared to the diazepam group (10.5%, $P < 0.1 > 0.05$).^[70] The maximum dose (mean ± SD) of midazolam and diazepam required was 5.3 ± 2.6 µg/kg/min and 0.04 ± 0.02 mg/kg/min, respectively. Thus the experience with midazolam also is varied and mixed, though overall it appears to be equally effective and marginally safer.

Benzodiazepines and barbiturates enhance GABA_A receptor-mediated inhibition. However, patients often become refractory to benzodiazepines when seizures are prolonged, and barbiturates are often then used for these refractory cases of SE.^[29] RSE has been treated conventionally with high-dose intravenous barbiturate coma;^[71] pentobarbital coma (PBC) was evaluated in a small series of 17 patients with RSE.^[72] Seizures were aborted in 16 of 17 patients, but vasopressors were re-

quired in 11 for severe hypotension; nine of them died, and among these, new-onset epilepsy, multiorgan failure before or during PBC, age >40 years, and hypotension requiring vasopressors during PBC were the causes identified. In a meta-analysis of twenty-eight studies describing a total of 193 patients comparing the efficacy of midazolam (MDL), propofol (PRO), and pentobarbital (PTB) for terminating seizures and improving outcome in RSE patients, PTB treatment was associated with a lower frequency of short-term treatment failure (8 vs. 23%; $P < 0.01$), breakthrough seizures (12 vs. 42%; $P < 0.001$), and changes to a different AED (3 vs. 21%; $P < 0.001$) and a higher frequency of hypotension (systolic blood pressure <100 mm Hg; 77 vs. 34%; $P < 0.001$).^[73] The conclusion is that though PB is more effective, midazolam is both safe and effective.

Sodium Valproate

Although sodium valproate is not approved by the US FDA for treatment of SE, it was found to have an overall efficacy of 63.3% in a study in which 63 patients were given a median dose of 31.5 mg/kg of IV valproate.^[74] In a multicenter, open-label, prospective, dose-escalation study of IV sodium valproate administered to patients with epilepsy, rates of infusion of up to 6 mg/kg/minute and doses of up to 30 mg/kg were well tolerated, with no clinically significant negative effects on blood pressure and pulse rate and caused only mild-to-moderate, reversible adverse events,^[75] even among unstable SE patients with hypotension.^[76]

Topiramate

Topiramate is an anticonvulsant with multiple activities at receptors and ion channels that may be more effective than conventional anticonvulsants in treating RSE. Like phenytoin, topiramate exhibits voltage-sensitive, use-dependent, sodium-channel blockade and may have an additive effect at this site.^[77] Topiramate potentiates GABA inhibition independently of the benzodiazepine site on the GABA_A receptor and significantly elevates brain GABA levels; this more likely underlies its effectiveness in RSE.^[78,79] Another action of topiramate is its ability to antagonize excitatory glutamatergic transmission, providing a mechanism for termination of seizure discharges in RSE.^[80] Topiramate has been shown to reduce neuronal injury after prolonged SE and may prevent delayed neuronal death.^[81] In a series of six cases, topiramate effectively terminated RSE in a variety of clinical set-

tings.^[82] In cases of RSE unresponsive to sequential trials of multiple agents, a suspension of topiramate administered via nasogastric tube was effective in aborting RSE; effective dosages range from 300 to 1,600 mg/d. Except for lethargy, no adverse events were reported.^[82]

Surgery for SE

Patients with RSE of focal origin may be potentially amenable to resective surgery.^[83] The literature is limited to isolated case reports or small case series involving multiple subpial transections, cortical resection, corpus callosotomy, or implantation of a vagus nerve stimulator.^[84,85] At the Jefferson Comprehensive Epilepsy Center, patients with medically intractable SE who fail to respond to three courses of cerebral suppressant therapy for approximately 2 weeks are considered for surgical treatment in the absence of any known remitting etiology. When structural or functional neuroimaging shows a focal lesion, or the EEG displays focal changes, they prefer focal resection and/or subpial transection. Corpus callosotomy is used for patients with generalized or non-localizable intractable SE.^[85] Bingaman and colleagues at the Cleveland Clinic performed resective surgery in the acute setting for refractory SE in 10 patients with focal epileptogenesis when High Dose Suppressant Therapy (HDST) failed; 7 (10%) became seizure-free, and 3 (30%) had significant improvement in epilepsy.^[84]

Pre-hospital treatment

SE frequently occurs or is identified in settings where it may not be feasible to administer intravenous drugs; in these settings, rectal diazepam, especially in children, and intramuscular midazolam can be used. Rectal diazepam is very easy to administer: a starting dose of 0.5 mg/kg is recommended, with a maximum of 20 mg per single dose;^[86] this is effective in 67% within 15 minutes. A gel formulation for rectal administration of diazepam is under study for rapid out-of-hospital control of SE.^[87] After intramuscular administration midazolam is rapidly absorbed (mean time to peak serum concentrations 25 min),^[88] and seizures are controlled within 10 minutes.^[89]

The mean absolute bioavailability of intramuscular midazolam is 87% and after intramuscular administration, sedation is slower (2-30 min versus less than 1-2

min with the intravenous preparation) and persists for a longer period (20-120 min versus 7-75 min).^[88]

Diazepam is administered to children in SE by paramedics in many Emergency Medical Services systems throughout the United States despite the lack of clear evidence that this therapy is safe and effective when employed in the pre-hospital environment. In a retrospective review, published in 1995,^[90] pre-hospital diazepam therapy was associated with SE of shorter duration (32 min vs. 60 min; $P=0.007$) and a reduced likelihood of recurrent seizures in the emergency department (58% vs. 85%; $P=0.045$). Though these data suggest that pre-hospital administration of diazepam may shorten the duration of SE in children and simplify the subsequent management of these patients in the emergency department, data concerning the safety of such treatment are scanty. Possibly, rectal diazepam or intramuscular midazolam may be considered relatively safe and effective in this setting.

Treatment after recovery from SE

Recovery in the post-SE phase is mainly dependent on the underlying cause of the SE, other medical problems, and complications related to the episode of SE, such as aspiration pneumonia. At this stage, the patient is likely to be on multiple AEDs, and this may be partly responsible for the morbidity. The aim at this stage is to minimize the number of drugs the patient has to take; optimizing anti-epileptic medication involves giving the appropriate drug in the lowest effective dose to minimize adverse effects. One problem that can arise while doing this is that of drug interactions. When the dose of an effective AED is decreased, and another interacting medication, such as an antibiotic, is withdrawn, the AED dose may become insufficient, and the patient may have breakthrough seizure. Careful titration at this stage may involve measurement of AED serum levels.

Conclusion

SE should be identified early and treatment initiated as soon as it is clear that a seizure has lasted 5-10 minutes; out-of-hospital administration of intramuscular midazolam or rectal diazepam by paramedics transporting the patient could shorten the duration of SE and hospital stay. Airway, breathing and circulation should be assessed in the emergency department and adequate steps initiated to correct any abnormalities. The appro-

priate drug in correct doses should be administered; every hospital needs to follow the treatment based on established protocols, and an early decision to paralyze and ventilate the patient in preparation for continuous midazolam or propofol administration should be taken. With the available drugs and the facilities to manage complications, the morbidity and mortality associated with SE can be minimized.

References

1. Daniel H. Lowenstein MD, Brian K. Alldredge. Status Epilepticus. *N Engl J Med* 1998;338:970-6.
2. Proposal for revised clinical and electroencephalographic classification of epileptic seizures: from the Commission on Classification and Terminology of the International League against Epilepsy. *Epilepsia* 1981;22:489-501.
3. Treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA* 1993;270:854-9.
4. Shorvon S. Status epilepticus: Its clinical features and treatment in children and adults. Cambridge, England: Cambridge University Press; 1994.
5. Bleck TP. Convulsive disorders: Status epilepticus. *Clin Neuropharmacol* 1991;14:191-8.
6. Gastaut H, Broughton R. Epileptic seizures: Clinical and electrographic features, diagnosis and treatment. Springfield, Ill.: Charles CT; 1972. p. 25-90.
7. Theodore WH, Porte RJ, Albert P, et al. The secondarily generalized tonic-clonic seizure: A videotape analysis *Neurology* 1994;44:1403-7.
8. Simon RP, Aminoff MJ. Electrographic status epilepticus in fatal anoxic coma. *Ann Neurol* 1986;20:351-5.
9. Lowenstein DH, Aminoff MJ. Clinical and EEG features of status epilepticus in comatose patients. *Neurology* 1992;42:100-4.
10. Jordan KG. Continuous EEG ad evoked potential monitoring in the neuroscience intensive care unit. *J Clin Neurophysiol* 1993;10:445-75.
11. Towne AR, Waterhouse EJ, Boggs JG, Garnett LK, Brown AJ, Smith JR, et al. Prevalence of non-convulsive status epilepticus in comatose patients. *Neurology* 2000;54:340.
12. Litt B, Wityk RJ, Hertz SH, Mullen PD, Weiss H, Ryan DD, et al. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998;39:1194-202.
13. Brenner RP. Is it status? *Epilepsia* 2002;43:S103-13.
14. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;34:S37.
15. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser

- WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology* 1998;50:735-41.
16. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med* 1980;69:657-66.
17. Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. *Eur J Neurol* 2004;11:800-10.
18. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia; *Neurology* 1996;46:1029-35.
19. Murthy JM, Yangala R. Acute symptomatic seizures - incidence and etiological spectrum: A hospital-based study from South India. *Seizure* 1999;8:162-5.
20. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med* 1980;69:657-66.
21. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994;35:27-34.
22. Vignatelli L, Tonon C, D'Alessandro R. Bologna Group for the Study of Status Epilepticus. Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* 2003;44:964-8.
23. Singhi S, Singhi P, Dass R. Status epilepticus: Emergency management. *Indian J Pediatr* 2003;70:S17-22.
24. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology* 1993;43:483-8.
25. Hui AC, Joynt GM, Li H, Wong KS. Status epilepticus in Hong Kong Chinese: Etiology, outcome and predictors of death and morbidity. *Seizure* 2003;12:478-82.
26. Kwong KL, Chang K, Lam SY. Features predicting adverse outcomes of status epilepticus in childhood. *Hong Kong Med J* 2004;10:156-9.
27. Teitelbaum JS, Zatorre RJ, Carpenter S, Gendron D, Evans AC, Gjedde A, et al. Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. *N Engl J Med* 1990;322:1781-7.
28. Lothman EW, Bertram EH III, Stringer JL. Functional anatomy of hippocampal seizures. *Prog Neurobiol* 1991;37:1-82.
29. Macdonald RL, Kapur J. Acute cellular alterations in the hippocampus after status epilepticus. *Epilepsia* 1999;40:S9-20; discussion S21-2.
30. Kapur J, Macdonald RL. Rapid Seizure-Induced Reduction of Benzodiazepine and Zn²⁺ Sensitivity of Hippocampal Dentate Granule Cell GABAA Receptors. *J Neurosciences* 1997;17:7532-40.
31. Simon RP. Physiologic consequences of status epilepticus. *Epilepsia* 1985;26:S58-66.
32. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;34:S37-53.
33. Meldrum BS, Vigouroux RA, Brierley JB. Systemic factors and epileptic brain damage: Prolonged seizures in paralyzed, artificially ventilated baboons. *Arch Neurol* 1973;29:82-7.
34. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: Ischemic cell change and its relation to ictal physiological events. *Arch Neurol* 1973;28:10-7.
35. Shorvon SD. Emergency treatment of status epilepticus. In: Shorvon SD, editor. *Status epilepticus: Its clinical features and treatment in children and adults*. Cambridge: Cambridge University Press; 1994. p. 175-292.
36. Heafield MTE. Managing status epilepticus New drug offers real advantages. *BMJ* 2000;320:953-4.
37. Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: Epidemiology, pathophysiology and management. *CNS. Drugs* 2003;17:1013-30.
38. Chin RFM, Neville BGR, Scott RC. Meningitis is a common cause of convulsive status epilepticus with fever. *Arch Dis Child* 2005;90:66-9.
39. Walton NY, Treiman DM. Response of status epilepticus induced by lithium and pilocarpine to treatment with diazepam. *Exp Neurol* 1988;101:267-75.
40. Cock HR, Schapira AHV. A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. *Q J Med* 2002;95:225-31.
41. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling CA, Rowan J, et al. For The Veterans Affairs Status Epilepticus Cooperative Study Group. A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. *N Engl J Med* 1998;339:792-8.
42. Arendt RM, Greenblatt DJ, deJong RH, Bonin JD, Abernethy DR, Ehrenberg BL, et al. In vitro correlates of benzodiazepine cerebrospinal fluid uptake, pharmacodynamic action and peripheral distribution. *J Pharmacol Exp Ther* 1983;227:98-106.
43. Walton NY, Treiman DM. Lorazepam treatment of experimental status epilepticus in the rat: Relevance to clinical practice. *Neurology* 1990;40:990-4.
44. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452-4.
45. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA* 1993;270.
46. Nicol CF, Tutton JC, Smith BH. Parenteral diazepam in status epilepticus. *Neurology* 1969;19:332-43.
47. George KA, Dundee JW. Relative amnesic actions of diazepam,

- flunitrazepam and lorazepam in man. *Br J Clin Pharmacol* 1977;4:45-50.
48. Osorio I, Reed RC. Treatment of refractory generalized tonic-clonic status epilepticus with pentobarbital anesthesia after high-dose phenytoin. *Epilepsia* 1989;30:464-71.
49. Wilder BJ. Efficacy of phenytoin in treatment of status epilepticus In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Advances in neurology Vol 34 Status epilepticus: Mechanisms of brain damage and treatment*. New York: Raven Press; 1983. p. 441-6.
50. Cranford RE, Leppik IE, Patrick B, Anderson CB, Kostick B. Intravenous phenytoin: Clinical and pharmacokinetic aspects. *Neurology* 1978;28:874-80.
51. Browne TR. Fosphenytoin (Cerebyx) *Clin Neuropharmacol* 1997;20:1-12.
52. Koul R, Deleu D. Subtherapeutic free phenytoin levels following fosphenytoin therapy in status epilepticus. *Neurology* 2002;58:147-8.
53. Jamerson BD, Dukes GE, Brouwer KL, Donn KH, Messenheimer JA, Powell JR. Venous irritation related to intravenous administration of phenytoin versus fosphenytoin. *Pharmacotherapy* 1994;14:47-52.
54. Elson MA, Loewn GR, Voightman RE, Koup JR, Holmes GB, Hunt AJ, et al. Pharmacokinetics and tolerance of fosphenytoin and phenytoin administered intravenously to health subjects. *Can J Neurol Sci* 1993;20:S180.
55. Ramsay RE, Philbrook B, Fischer JH, Sloan FB, Allen FH, Runge JW, et al. Safety and pharmacokinetics of fosphenytoin (Cerebyx) compared with Dilantin following rapid intravenous administration. *Neurology* 1996;46:A245.
56. Ramsay RE, DeToldo J. Intravenous administration of fosphenytoin: Options for the management of seizures. *Neurology* 1996;46:S17-9.
57. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology* 1998;51:1034-9.
58. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;38:202-7.
59. Goldberg MA, McIntyre HB. Barbiturates in the treatment of status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Advances in neurology Vol. 34 Status epilepticus: Mechanisms of brain damage and treatment*. New York: Raven Press; 1983. p. 499-503.
60. Kumar A, Bleck TP. Intravenous midazolam for the treatment of refractory status epilepticus. *Crit Care Med* 1992;20:483-8.
61. Bleck TP. Advances in the management of refractory status epilepticus. *Crit Care Med* 1993;21:955-7.
62. Stecker MM, Kramer TH, Raps EC, O'Meehan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: Clinical and pharmacokinetic findings. *Epilepsia* 1998;39:18-26.
63. Marik PE. Propofol: Therapeutic indications and side-effects. *Curr Pharm Des* 2004;10:3639-49.
64. Angelini G, Ketzler JT, Coursin DB. Use of propofol and other nonbenzodiazepine sedatives in the intensive care unit. *Crit Care Clin* 2001;17:863-80.
65. Stecker MM, Kramer TH, Raps EC, O'Meehan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: Clinical and pharmacokinetic findings. *Epilepsia* 1998;39:18-26.
66. Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J. Propofol treatment of refractory status epilepticus: A study of 31 episodes. *Epilepsia* 2004;45:757-63.
67. Stecker MM, Kramer TH, Raps EC, O'Meehan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: Clinical and pharmacokinetic findings. *Epilepsia* 1998;39:18-26.
68. Niermeijer JM, Uiterwaal CS, Van Donselaar CA. Propofol in status epilepticus: Little evidence, many dangers? *J Neurol* 2003;250:1237-40.
69. Ozdemir D, Gulez P, Uran N, Yendur G, Kavakli T, Aydin A. Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus. *Seizure* 2005;14:129-32.
70. Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. *J Child Neurol* 2002;17:106-10.
71. Jordan KG. Status epilepticus. A perspective from the neuroscience intensive care unit. *Neurosurg Clin N Am* 1994;5:671-86.
72. Yaffe K, Lowenstein DH. Prognostic factors of pentobarbital therapy for refractory generalized status epilepticus. *Neurology* 1993;43:895-900.
73. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. *Epilepsia* 2002;43:146-53.
74. Limdi NA, Shimpi AV, Faught E, Gomez CR, Burneo JG. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005;64:353-5.
75. Wheless JW, Vazquez BR, Kanner AM, Ramsay RE, Morton L, Pellock JM. Rapid infusion with valproate sodium is well tolerated in patients with epilepsy. *Neurology* 2004;63:1507-8.
76. Sinha S, Naritoku DK. Intravenous valproate is well tolerated in unstable patients with status epilepticus. *Neurology* 2000;55:722-4.
77. DeLorenzo RJ, Sombati S, Coulter DA. Effects of topiramate on sustained repetitive firing and spontaneous recurrent seizure

- discharges in cultured hippocampal neurons. *Epilepsia* 2000;41:S40-4.
78. White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. *Epilepsia* 2000;41:S17-20.
 79. Petroff OA, Hyder F, Rothman DL, Mattson RH. Topiramate rapidly raises brain GABA in epilepsy patients. *Epilepsia* 2001;42:543-8.
 80. Gibbs JW, Sombati S, DeLorenzo RJ, Coulter DA. Cellular actions of topiramate: Blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia* 2000;41:S10-6.
 81. Niebauer M, Gruenthal M. Topiramate reduces neuronal injury after experimental status epilepticus. *Brain Res* 1999;837:263-9.
 82. Towne AR, Garnett LK, Waterhouse EJ, Morton LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. *Neurology* 2003;60:332-4.
 83. Alexopoulos A, Lachwani DK, Gupta A, Kotagal P, Harrison AM, Bingaman W, et al. Resective surgery to treat refractory status epilepticus in children with focal epileptogenesis. *Neurology* 2005;64:567-70.
 84. Ma X, Liporace J, O'Connor MJ, Sperling MR. Neurosurgical treatment of medically intractable status epilepticus. *Epilepsy Res* 2001;46:33-82.
 85. Winston KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. *Pediatr Neurosurg* 2001;34:190-2.
 86. Hoppu K, Santavuori P. Diazepam rectal solution for home treatment of acute seizures in children. *Acta Paediatr Scand* 1981;70:369-72.
 87. Mitchell WG, Shellenberger K, Groves L, et al. Rectal diazepam gel (Diastat) for acute repetitive seizures: Results of a double-blind, placebo-controlled study in children and adults with epilepsy. *Epilepsia* 1996;37:154.
 88. Bell DM, Richards G, Dhillon S, Oxley JR, Cromarty J, Sander JW, et al. A comparative pharmacokinetic study of intravenous and intramuscular midazolam in patients with epilepsy. *Epilepsy Res* 1991;10:183-90.
 89. Lahat E, Aladjem M, Eshel G, Bistrizter T, Katz Y. Midazolam in treatment of epileptic seizures. *Pediatr Neurol* 1992;8:215-6.
 90. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. *Pediatr Neurol* 1995;12:213-6.

“HANSRAJ NAYYAR MEMORIAL AWARD”

A prestigious award, called the “**HANSRAJ NAYYAR MEMORIAL AWARD**” will be awarded annually to the best paper presented by a young scientist, below 40 years of age, at the National Conference in Critical Care organized by ISCCM. The winner will present this paper in a special session Called the **HANSRAJ NAYYAR MEMORIAL SESSION** to be held during the plenary Session. The award consists of a trophy, certificate, and a cash prize, which will be presented to the recipient of the award, at the Annual National Conference.

Last date for submission: 15th December