

Status epilepticus in children

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ABSTRACT

تعرف حالة الصرع بنوبات صرع مستمرة لمدة ٣٠ دقيقة على الأقل أو نوبات صرع متكررة تبقى لحوالي ٣٠ دقيقة، بدون استعادة الوعي. إن الإصابة المقدرة بالصرع في مرحلة الطفولة تقدر بحوالي ٢٠ لكل ١٠٠,٠٠٠ طفل في العام. إن الإصابة بالمرض عالية بين الأطفال الذين تقل أعمارهم عن عام واحد مع نسبة تقدر بحوالي ٥٠ حالة لكل ١٠٠,٠٠٠ طفل في العام. من بين عام إلى أربعة أعوام حوالي ٣٠ حالة لكل ١٠٠,٠٠٠ طفل في العام يتعرض لحالة صرع وفي أولئك الذين يبلغون من العمر من خمس إلى تسع سنوات تبلغ نسبة الإصابة حوالي ١٠ لكل ١٠٠,٠٠٠ طفل في العام. وأولئك الذين تبلغ أعمارهم ما بين عشرة أعوام إلى خمسة عشر عاماً لديهم أقل نسبة إصابة (حوالي حالتين لكل ١٠٠,٠٠٠ حالة في العام). تبلغ نسبة الوفيات المقدرة مع حالة الصرع بين الأطفال حوالي ٢,٥٪ إلى ٥٪ وهي مرتبطة بشكل أولي مع السبب الرئيسي لحالة الصرع. توجد الحالة المرضية العصبية في أقل من ١٥٪ من الأطفال المصابين. في معظم الحالات تكون حالة الصرع عبارة عن إما حالة مفردة أو أول ظهور للصرع. تظهر فقط نسبة ١٢٪ من الحالات في الأطفال الذين لديهم تشخيص أولي بالصرع. من الضروري أن تكون هنالك طريقة منظمة للتعامل مع حالة الصرع. هنالك بيانات قليلة أن هنالك نظام أفضل من نظام آخر. يوصى بأنه يجب على كل مركز أن يقرر على أي نظام بأنه نظام عقلائي وأنه قياسي للممارسة مع مرضاهم. تبادل معظم المراكز بالعلاج مع عقار بوكال أو عقار لورازيبام عبر الوريد. تشمل العلاجات البديلة عقار ديازيبام أو ميدازولام. يوصى بشكل عام بالمعالجة المبكرة على الرغم من أن لدى الإنسان دليل بسيط بأن طول نوبة الصرع تؤثر بشكل مباشر على النتيجة. ولكن هنالك دليل ذو عدد زائد في الحيوانات يشير إلى أن طول نوبات الصرع مؤلمة ونتائجها سيئة. التدخل المبكر يزيد من التحكم بنوبات الصرع لدى الإنسان. تتطلب المعالجة الأفضل للطفل المصاب بنوبات صرع منذ فترة طويلة فهم الأسباب الفعالة والفحوصات الملائمة والعلاج.

Status epilepticus is defined as a continuous seizure lasting for at least 30 minutes or recurrent seizures persisting for over 30 minutes, without recovery of consciousness. The estimated incidence in childhood is approximately 20 per 100,000 children per year. The incidence is higher in those under one year of age, with an incidence of approximately 50 per 100,000 per year. Among 1-4 year olds, approximately 30 per

100,000 per year will have an episode of status and in those aged 5-9 years, the incidence is approximately 10 per 100,000 per year. Those aged 10-15 years have the lowest incidence (approximately 2 per 100,000 per year). The mortality associated with status epilepticus in children is estimated at 2.5-5%, and is primarily related to the underlying cause of the episode of status. Neurological morbidity is seen in less than 15% of affected children. In most cases, the episode of status is either a single isolated event or is the first manifestation of epilepsy. Only 12% of cases occur in children with a prior diagnosis of epilepsy. It is essential to have an organized approach for dealing with status epilepticus. There is little data to support the contention that one protocol is better than another. It is recommended that each center should decide on a protocol that is rational and is standard practice for their patients. Most centers initiate therapy with either buccal or intravenous lorazepam. Alternate initial therapies include diazepam or midazolam. Early treatment is generally recommended although, in humans, there is minimal evidence that the length of seizure directly affects outcome. There is however, abundant evidence in animals, which indicates that longer seizures are harmful and result in poorer outcome. Early intervention does, however, increase the likelihood of attaining seizure control in humans. The optimal management of the child in a prolonged seizure therefore demands an understanding of the potential causes, appropriate investigations, and therapy.

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Status epilepticus is the most common neurologic emergency in childhood and therefore requires an organized approach to both its diagnosis and management. It is estimated that there are 42,000 deaths among the estimated 152,000 cases of status epilepticus in patients of all ages in the United States each year.¹

The annual associated societal cost is approximately \$3.8-7 billion in inpatient expenses.

Definitions. Convulsive status epilepticus (CSE).

Convulsive status epilepticus (CSE) is potentially life threatening and therefore requires emergency intervention. It is typically classified as either: 1) continuous or prolonged status and, 2) clustered or intermittent CSE. Continuous CSE is defined as a seizure lasting 30 minutes or longer while in intermittent CSE, seizures recur for ≥ 30 minutes, without interictal resumption of baseline CNS function. It is generally accepted that most children require intervention long before their seizure has persisted for 30 minutes. The definition of CSE as ≥ 30 minutes is arbitrary and in the past was defined as ≥ 60 minutes, until Meldrum² showed pathological changes in the brains of adult monkeys after 45 minutes of seizure activity. Lowenstein³ suggested that status epilepticus should be defined as seizures lasting longer than 5 minutes, as more than 90% of clinical seizures last less than 2 minutes. Most clinicians are uncomfortable with such a definition, which would include benign seizures, such as febrile seizures lasting 10 minutes. Regardless of the definition, seizures lasting longer than 5 minutes are prolonged and require intervention, as the chance of a seizure stopping spontaneously is significantly reduced after 5 minutes, and is unlikely if it has persisted for 15 minutes. Knudsen⁴ reported that more than 90% of seizures respond to treatment if initiated within 15 minutes compared to 60% if treatment is started after that time. In practice treatment after 5-10 minutes of seizure activity is recommended.⁵

Non-convulsive status epilepticus (NCSE). NCSE is defined by: 1) a persistent clinical change in behavior, which includes changes in cognition, memory, arousal, and motor behavior. 2) A change from previous level of functioning. 3) Continuous paroxysmal electrographic activity on EEG. 4) Absence of clonic, tonic, or tonic-clonic seizures.

Epidemiology. In a study from England, Chin et al⁶ studied a population of over 600,000 children aged 29 days to 15 years for CSE. They found 226 cases, of which 176 represented a first episode of seizure. The incidence of CSE in this study was between 17-23 episodes per 100,000/year. In a previous retrospective study⁷ the incidence was greater than 47.5 episodes per 100,000/year. In Chin's study⁶ the incidence was highest in those under one year of age (51 episodes per 100,000/year) with an incidence in the group aged 1-4 years of 29 per 100,000/year, 9 per 100,000/year in the 5-9 year-olds, and 2 per 100,000 in the 10-15 year olds.

Etiology. There may be a population of children who are susceptible to prolonged seizures. Of those, whose first febrile seizure lasts less than 10 minutes,

the chance of the second seizure also lasting less than 10 minutes was 91%.⁸ In contrast, if the initial febrile seizure lasted 10 minutes or longer the second seizure was similarly prolonged. Among a Finnish cohort⁹ the chance of having a second episode of status epilepticus was greater than 50%. A study from Connecticut¹⁰ found subsequent status occurred in 4.3% of those without and 19.6% of those with status epilepticus at first diagnosis. Therefore, having a history of prolonged seizure is a risk factor for further episodes. Other risk factors include a young age at onset of seizures, remote symptomatic etiology, neurologic abnormality, and having symptomatic epilepsy. The etiology of CSE varies depending on the age of the population studied. Overall febrile status epilepticus accounts for approximately one third of episodes of CSE in childhood, and idiopathic status epilepticus for a further 16-40%. Approximately 70% of episodes of CSE represent the initial seizure event for that child. Approximately half of all children with CSE are developmentally and neurologically normal before the first episode. Most of these children have a prolonged febrile convulsion with the remainder having acute symptomatic CSE. In a prospective study of 428 children with their first febrile seizure, 5% had a seizure that lasted 30 minutes or longer.¹¹ Acute symptomatic CSE accounts for 23-50% of cases overall, but represents 75% of cases in children younger than one year of age, and 28% of those older than 3 years. Acute symptomatic CSE occurs within a week of an acute illness affecting the CNS. Infection is most common, although hypoxic-ischemic damage, electrolyte disturbances, encephalopathy, cerebral vascular disease, metabolic disease, and exposure to toxins should all be considered. Acute symptomatic status epilepticus has the highest associated mortality, with up to 20% dying. It is therefore, essential to recognize that CSE in a child with a fever does not always indicate a prolonged febrile convulsion, but may reflect underlying CNS infection. In the North London study⁶ 12% (11 of 95) who had CSE associated with fever had acute bacterial meningitis, and a further 7 had viral meningitis. Most of these children did not have obvious signs of meningitis, and 3 died after an initial diagnosis of prolonged febrile seizure. Therefore, the risk of CNS infection in febrile CSE is much higher than the 1.2% risk of meningitis, which has been associated with a short febrile seizure. Remote symptomatic CSE (14-23%) occurs in children with prior neurological disorders, such as cortical dysplasia or epileptic encephalopathy. Most have a history of cerebral palsy, epilepsy or learning disabilities. The risk of CSE among children with epilepsy appears low, but when it does occur, 90% will happen within 2 years of diagnosis. In studies of children taking tiagabine, the risk of status epilepticus was 1% for those on the drug

and 1.5% for those on placebo. The risk was 20-fold higher, however, if there were a prior history of status epilepticus and is also increased in children with a history of seizure clusters.⁸ In Japan, benign infantile convulsions are reported, which do not respond to diazepam but readily respond to oral or nasogastric administration of carbamazepine (5 mg/Kg).¹² There is also evidence for a genetic component to CSE susceptibility, as monozygotic twins have a 19-fold increased risk if their twin has an episode of CSE. This increased risk is not seen for dizygotic twins. Data from long term video-EEG monitoring with refractory patients being evaluated for possible epilepsy surgery indicates that more than 90% of seizures in this group last less than 2 minutes.⁸

Pathogenesis. During status epilepticus, some GABA_A receptors move from the synaptic membrane into the cytoplasm and become inactive. This may partially explain why seizures self perpetuate and why they may become resistant to benzodiazepines. At the same time AMPA and NMDA receptors move from subsynaptic sites to the synaptic membrane and may cause further hyperexcitability. There is also a reduction of inhibitory peptides such as dynorphin, galanin, somatostatin, and neuropeptide Y and an increase in proconvulsant tachykinins, substance P, and neurokinin B.¹³

Diagnosis. The diagnosis of CSE is usually obvious although as many as 34% of cases of febrile status epilepticus were not recognized as such by hospital personnel. Similarly in *epilepsia partialis continua* the seizures may be very subtle with a prominent reduction in consciousness. In these patients, the failure of an initial trial of benzodiazepine may suggest a diagnosis other than status epilepticus. In most situations, however, the diagnosis is not difficult and the challenge is directed to appropriate investigations and management.

Investigations. The paucity of evidence on which investigations are appropriate for the child with status epilepticus led the American Academy of Neurology and the Child Neurology Society to publish practice parameters in 2006.¹⁴ The parameters are based on a review of the literature and subsequent consensus among a group of eminent child neurologists. The parameters concluded that there is insufficient evidence to either support or refute routine blood cultures or lumbar puncture for children with status epilepticus, as blood cultures are abnormal in only 2.5% of cases and CNS infection is found in approximately 10-15%. Obviously, those with suspected meningitis must receive the appropriate investigations. Approximately 12-15% of children with fever associated status have a CNS infection compared to 1-5% of children with fever associated short seizures. Alternatively some centers initiate antibiotic therapy or antiviral therapy

without a lumbar puncture in children with either focal neurological signs or in those who remain unconscious. Routine laboratory studies, such as electrolytes, calcium and glucose were abnormal in only 6%. Evidence of ingestion was found in 3.6% and tests for metabolic disease were positive in 4.2%,⁶ therefore suggesting that tests for metabolic or chromosomal abnormalities should only be undertaken if clinically indicated. Common toxins include tricyclic antidepressants or theophylline. In those with a prior history of epilepsy, anticonvulsant drug levels were low in approximately 20% of children who presented with CSE (range 3-63%) and anti epileptic drug (AED) levels should therefore be measured in all children in this category. This group of children constitutes only a small proportion of children with status epilepticus. There is insufficient evidence for the value of routine neuroimaging with CT or MRI, although imaging should be considered if there are clinical suspicions of underlying structural pathology or if the cause of the status epilepticus is unknown. Abnormalities on neuroimaging explain the cause of status in at least 8% of such cases. An MRI during or shortly after status epilepticus can show swelling and abnormal T2 or fluid attenuated inversion recovery signal, which may indicate cytotoxic or vasogenic edema and alteration of the blood brain barrier. An EEG can be helpful to distinguish focal from generalized CSE or to diagnose pseudo-seizures. Further research is needed on the value of 2 channel EEG in diagnosing NCSE.

Non-convulsive status epilepticus (NCSE). Non-convulsive status epilepticus, defined as seizures lasting longer than 30 minutes without convulsive activity, usually manifests as altered mental status or coma. It may follow CSE, or it may appear without any prior apparent seizures. The diagnosis usually requires EEG as the seizures are subclinical in more than 90%. As many as 16% of cases have their diagnosis delayed for more than 24 hours because of lack of recognition. Absence status is typically associated with confused and drowsy behavior although patients may be agitated with hallucinations and violent behavior. The impairment in alertness may be subtle, and patients may be able to continue some everyday activities. There may be associated automatisms or myoclonic jerks. The EEG may show 3 Hz spike and wave discharges, but may also show rhythmical slowing or slow spike and wave activity. Absence status occurs in patients with previously known generalized epilepsy, but does have a tendency to recur. Complex partial SE may be difficult to distinguish from absence status on clinical grounds. Symptoms include bizarre behavior, hemiparesis, amnesia, and aphasia. An EEG may be essential to make the correct diagnosis. Myoclonic status is usually generalized and may be seen in patients with Angelman syndrome. The

NCSE in coma may be extremely difficult to diagnose without EEG. A retrospective study in 19 children with NCSE.¹⁵ showed that 18 were in a comatose or stuporous state at the time of diagnosis. Electrical status epilepticus in sleep and atypical absence seizures must also be considered. Autonomic status epilepticus can be seen in Panayiotopoulos syndrome, with seizures usually characterized by nausea, vomiting, and pupillary abnormalities. These patients may also have abnormalities in cardiorespiratory and temperature regulation. The precipitants of NCSE are usually unclear, but include therapy with some anti-epileptic drugs, such as levetiracetam, lamotrigine, tiagabine, and valproic acid. NCSE may also be seen in specific syndromes, such as Dravet syndrome, Lennox-Gastaut syndrome, myoclonic astatic epilepsy, and West syndrome. In a recent study of 20 children with NCSE, the mean age was 6.8 years, but 30% were under one year of age.¹⁶ A prior history of epilepsy was present in 35%, congenital heart disease in 25% and no apparent previous illness in 40%. Immediately before the onset of NCSE, 20% had CSE, 55% had isolated clinical seizures, and 25% were preceded by only a change in mental status. The most common etiology was an exacerbation of epilepsy in 35%, ischemic stroke in 25%, infection in 20%, and hypoxic ischemic encephalopathy in 10%. Each of the following was found in one child: trauma, metabolic disease, and chronic static encephalopathy. In those less than one year of age, none had a history of epilepsy. The EEG demonstrated focal discharges in 40%, multifocal discharges in 25%, and generalized discharges in 35%. The NCSE lasted a mean of 56 hours, with a range of 3-120 hours. It was prolonged in the majority, and lasted more than 24 hours in 65%, and more than 72 hours in 25%. There were 2 deaths out of the 20 patients. One child had congenital heart disease with fungal sepsis and meningitis and the other had congenital heart disease and a cardiac arrest. The NCSE may follow CSE in as many as a third of patients, especially in neonates after asphyxia.

Treatment. Emergency therapy is most effective if started early and therefore should be initiated in the community before the child arrives at the hospital. Ideally treatment should both interfere with the epileptogenic process and stop the seizure. There is, however, little data to support the hypothesis that early treatment affects long-term outcome, although there is good evidence that seizures become more difficult to treat the longer they persist. In rats delaying treatment from 10-45 minutes increased the dose of diazepam needed to stop the seizure by 10-fold in half the rats. In humans the response to first-line therapy correlates with the time when the medication is given. Patients who received first-line therapy within 30 minutes had an

80% response rate to benzodiazepines and phenytoin compared to 75% of patients who received therapy within 60 minutes, 63% if treated within 90 minutes, 44% if treated within 120 minutes, and only 37% if treated after 120 minutes.¹⁷ Prehospital treatment with intravenous diazepam has been associated with a shorter duration of seizures (32 minutes versus 60 minutes). In addition, early treatment prior to arriving at the hospital has been associated with a decrease in number of visits to the emergency department, lower parental stress, and improved quality of life.⁸ Providing appropriate care for CSE within the community is challenging as only 35-40% of individuals feel that they know what to do if they encounter someone with a seizure.¹⁸ A US survey of 654 parents or guardians presenting to the emergency department in 2002¹⁹ found that 71% felt they knew basic first aid for somebody in a seizure. A survey of 216 parents of children with febrile convulsions in Taiwan,²⁰ however, found that many misconceptions persisted. For example many felt that it was appropriate to shake or attempt to wake a child during a convulsion and that one should prize the child's teeth apart to insert a protective object. Many school nurses also report that they are not comfortable when dealing with status epilepticus.¹⁸ Further public education is needed to optimize appropriate seizure care. When medication is provided prior to arrival at the hospital, the chosen drug should have a broad spectrum of action and low side effect profile. In general, a benzodiazepine is usually employed. A randomized double-blind placebo-controlled trial of 205 adults in seizure emergencies²¹ showed that IV lorazepam or diazepam given out of hospital by paramedics was significantly more effective than placebo in terminating status epilepticus before the patient arrived at the hospital and was also associated with a lower risk of being admitted to intensive care. The study was not powered sufficiently to compare one drug to the other.²¹ The benzodiazepines may all cause respiratory or cardiac depression and those who care for children in the community must be trained to deal with such an emergency. As discussed below, both lorazepam and midazolam are becoming more popular than diazepam primarily because of ease of administration. Within the emergency room we frequently send confusing messages to families. The administration of oxygen in the emergency room is almost universally the first step in the management of CSE, although it is very unlikely that oxygen administered through a face mask will significantly alter gas exchange in a seizure. Families are understandably confused when advised that there is no need for them to have oxygen at home while this seems such a key component of the management of status epilepticus in the ER. The initial management should ensure that the basic ABCs of care are met

(Figure 1). When the patient is stabilized, therapy with appropriate medications can begin. Most of the drugs used for treating refractory status epilepticus are associated with the risk of respiratory depression and hypotension and some of these children are best cared for within the intensive care unit as they may require both mechanical ventilation and vasopressor support.

Benzodiazepines. To date there have been no good trials of status epilepticus treatment in children. In the trials that have been completed, midazolam appears to stop seizures more quickly than diazepam. The time difference, however, is of questionable clinical significance. Generally, all 3 benzodiazepines appear well tolerated and effective and none have shown clear superiority. Rectal diazepam has been the standard therapy for many years, but is socially unacceptable in many situations. In contrast, buccal-sublingual administration is both safe and simple. Midazolam and diazepam redistribute more rapidly from the CNS to muscle and adipose tissues than does lorazepam because of their greater lipid solubility. One can therefore expect the AED effect of lorazepam to persist for longer. Rectal diazepam gel is approved for use in children and when used, the dose should be 0.5 mg/Kg for children aged 2-5 years, 0.3 mg/Kg for those aged 6-11 years, and 0.2 mg/Kg for patients older than 12 years of age. Overall,

the use of buccal lorazepam and midazolam is becoming increasingly popular. Although optimal midazolam absorption is difficult to achieve, as it requires a uniform spread of the liquid over the whole buccal pouch and retention in the buccal cavity, buccal midazolam is as effective and safe as rectal diazepam.²² When 0.5 mg/Kg midazolam was compared to a similar dose of diazepam, cessation of seizures occurred in 56% of patients receiving midazolam compared to 27% of those receiving rectal diazepam ($p < 0.001$).²³ The mean time to seizure cessation was 8 minutes for buccal midazolam and 15 minutes for rectal diazepam. Intranasal administration has potential advantages as a route of medication delivery, as patient cooperation is not necessary and administration is easy. Intranasal 0.2 mg/Kg midazolam was more effective than rectal diazepam prior to arriving at hospital.²⁴ Median seizure time was 11 minutes for the midazolam group compared to 30 minutes for those who received diazepam ($p = 0.003$). Those who received rectal diazepam were also more likely to have a seizure in the emergency room (odds ratio [OR] 8.4, confidence interval [CI]: 1.6-43.7), require intubation (OR, 12.2 CI: 2.0-75.4), need medication for seizures in hospital (OR, 12.1 CI: 2.2-67.8), need hospital admission (OR, 29.3, CI: 3.0-288.6) and require admission to the intensive care unit (OR 53.5, CI: 2.7-1046.8).²⁴ Intranasal lorazepam is unlikely to be as helpful because

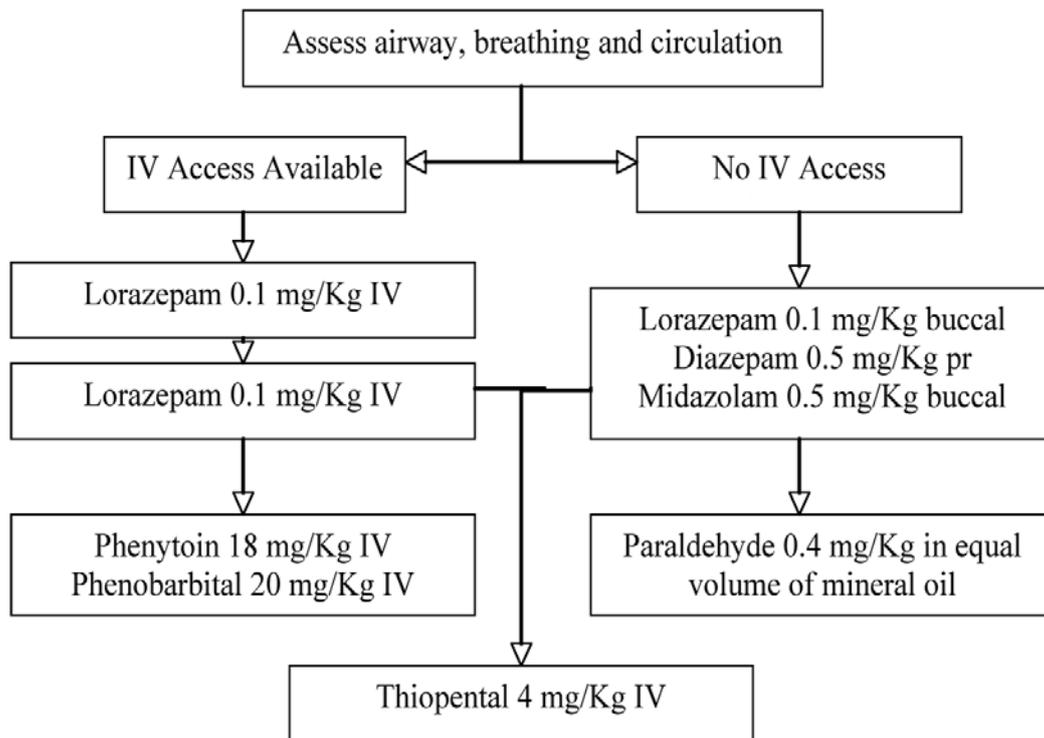


Figure 1 - Protocol for management of status epilepticus.

of its limited lipid solubility. Intranasal preparations of diazepam and midazolam will soon be commercially available. The choice of rectal administration is not only esthetically less acceptable, but is pharmacologically limited for benzodiazepines other than diazepam. The bioavailability of rectal lorazepam is limited, and absorption is slow. Rectal midazolam is rapidly absorbed but its bioavailability is erratic and low.

Longer acting medications. Many protocols suggest giving a longer acting drug in conjunction with the benzodiazepines. Phenytoin (18 mg/Kg) or fosphenytoin (a pro-drug formulation of phenytoin with 1.5 mg equivalent to 1 mg of phenytoin) are usually preferred. There are no studies comparing the 2 drugs in seizures lasting more than 5 minutes. In adults, however, IV phenytoin is more often associated with phlebitis, venous irritation, and need for slowing or discontinuing the infusion. If further treatment is necessary phenobarbital should be given. Failure to respond at this stage constitutes intractable status, and an infusion of diazepam, midazolam, thiopental, phenobarbital, pentobarbital, propofol, or sodium valproate should be considered. Children with refractory CSE should be referred to an intensive care unit as most of the above infusions potentially interfere with cardiorespiratory function. The evidence is accumulating that intravenous sodium valproate may be very beneficial. A recent study by Mehta et al²⁵ randomized 40 children with refractory status epilepticus to receive either intravenous sodium valproate or diazepam infusion. The CSE was controlled in 80% of valproate and 85% of diazepam patients with the median time to seizure control less for the valproate group (5 minutes) than the diazepam group (17 minutes, $p < 0.001$).²⁵ None of the patients in the valproate group required ventilation or developed hypotension compared to the diazepam group, where 60% required ventilation and 50% developed hypotension after starting the infusion. There were no adverse effects on liver function by valproate. Intravenous valproate was given as an initial loading dose of 30 mg/kg in an equal volume of normal saline. If the status was not controlled within 10 minutes a repeat bolus of 10 mg/kg was given. This was followed by an infusion at a rate of 5 mg/kg/hour, which was continued until the patient was seizure free for 6 hours. The rate was then reduced by one mg/kg/hr every 2 hours until the infusion ended, and a maintenance dose of 10 mg/kg was given every 8 hours until the child was able to take oral medication. If there was no response, a thiopental infusion was started. A study by Misra in 2006,²⁶ compared 30 mg/kg of valproic acid with 80 mg/kg of phenytoin for patients with generalized tonic clonic seizures lasting ≥ 10 minutes in 35 patients who received valproic acid and 33 who were treated with phenytoin. More patients stopped seizing with valproate than with phenytoin (66% versus

42%, $p = 0.046$). In general, medications should not be given intramuscularly (IM) because of slow absorption. Fosphenytoin can be given IM but the volume needed is quite large. Therapeutic levels of fosphenytoin are achieved as early as 5 minutes in approximately 15% of patients and in more than half at 30 minutes. Among the benzodiazepines only midazolam can be given by intramuscular injection and can be expected to work within 15 minutes of injection.

Other medications. Pyridoxine (100 mg) should be given to all infants with drug-resistant status epilepticus.

Non-convulsive status epilepticus. Absence status responds well to oral or intravenous benzodiazepines, with lorazepam usually the drug of choice. For atypical absence status epilepticus, oral benzodiazepines should be used, as intravenous benzodiazepines may aggravate the situation. Complex partial status epilepticus can be treated with oral clobazam over 2-3 days. When more emergent therapy is needed lorazepam, followed by phenytoin, or fosphenytoin if necessary, can be used. Alternatively valproate at a dose of 20-40 mg/Kg can be used. In patients with NCSE with learning difficulties, clobazam is effective. If this fails, steroids, either as oral prednisone or intravenous pulse methylprednisolone should be considered. Carbamazepine, phenytoin, and phenobarbital have all been shown to aggravate the seizures in these patients. Tonic status epilepticus may be worsened by benzodiazepines and should be treated with either steroids or immunoglobulins.

Prognosis. Adverse outcomes following CSE include death, cognitive impairment, permanent neurologic deficits, and epilepsy. In the North London study the recurrence rate for CSE in one year was 17% overall, but rose to 47% in the remote symptomatic group.⁶

Mortality. The risk of death in pediatric CSE (3-7%) is considerably lower than in adults (22%). Estimates usually range from 2.7-5.2%.²⁷ For children who are admitted to an intensive care unit, the mortality rises to 5-8%, which is still lower than the 13% mortality in young adults and 38% in the elderly. The lower mortality in children reflects the extremely low mortality and morbidity associated with prolonged febrile convulsions, which constitute a major part of pediatric CSE. Young children are, however, also more likely to have acute symptomatic CSE, which raises the mortality to 3-22.5%. Mortality is particularly high in those with CNS infection, trauma, or anoxia. There is controversy about whether these outcomes are related to the CSE itself or to the underlying cause. The mortality rate of 0-2% associated with CSE caused by febrile convulsions would suggest that the CSE itself seldom results in death.

Morbidity. Most studies report neurological sequelae following CSE in less than 15% of children, with a

range of 9-28%. As with mortality, the morbidity rate reflects the etiology of the CSE. Almost all children who have neurological sequelae have CSE, which is either acute symptomatic or remote symptomatic. Following symptomatic CSE, the morbidity is approximately 20%. In contrast, children with prolonged febrile seizures or idiopathic CSE have morbidity lower than 10%. There are few studies of the subsequent risk of epilepsy following CSE, although estimates have ranged from 13-74%. There is a strong correlation between the type of CSE and subsequent epilepsy. The risk is greater than 50% for those with acute symptomatic CSE or with a history of previous neurological abnormality. When epilepsy does follow CSE it is usually focal, although children may have infantile spasms or Lennox-Gastaut syndrome. Some children who appeared to have an initial episode of febrile CSE will go on to have Dravet syndrome. After a prolonged febrile convulsion the risk of epilepsy is approximately 10 times that of the general population. Epilepsy in this context is more often partial than generalized. Again, this data is controversial and is not supported by all studies. MRI studies have revealed that a prolonged febrile convulsion is associated with hippocampal edema when the MRI is performed within 48 hours of the episode of CSE. On follow-up studies carried out 4-8 months after a prolonged febrile convulsion there was an asymmetry in the hippocampal volumes. This may suggest neuronal loss, but it may also reflect the disappearance of edema and a return to previously pathologically small hippocampal state. In animals, however, CSE has been consistently associated with neuronal necrosis in vulnerable regions of the brain such as the hippocampus, amygdala, cerebellar cortex, thalamus, and cerebral cortex. The risk of epilepsy 2 years after the first unprovoked episode of CSE is 25-40%. This is similar to the risk after a brief unprovoked first seizure. The risk is probably highest during the year following the episode of CSE and there is no evidence that prophylactic anticonvulsant therapy would alter this risk. Similarly, the effect of CSE on IQ has been controversial. Although the studies have been small there is a suggestion of a correlation.

In conclusion, seizures therefore can be termed as brief if they last less than 5 minutes, prolonged if they last from 5-30 minutes, or status epilepticus if they persist for more than 30 minutes. If the cause of the status epilepticus is unexplained by the history, or if focal neurological signs are found, a CT scan or MRI should be carried out in young children, and an LP should be considered if the child has a fever. Defining a protocol that is widely used and accepted within each center will enhance the management of status epilepticus and will help reduce associated morbidity. Initial therapy with a benzodiazepine followed by phenytoin or fosphenytoin

for some children is currently the most widely accepted approach.

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