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Status Epilepticus and Acute Repetitive Seizures in Children, Adolescents, and Young Adults: Etiology, Outcome, and Treatment

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Summary: Status epilepticus (SE) is one of the most common neurologic emergencies in children, adolescents, and young adults. SE may be due to acute neurologic conditions such as meningitis, encephalitis, or stroke, complicated febrile seizures, intractable epilepsy, degenerative diseases, intoxication, or may be the first manifestation of epilepsy. Initial treatment of convulsive SE is usually with an intravenous benzodiazepine (BZD) [lorazepam (LZP) or diazepam (DZP)], phenobarbital (PB), or phenytoin (PHT). LZP is less likely to cause respiratory depression than DZP and is therefore preferred. Sequelae and risk for recurrence of SE are primarily related to the underlying cause. Refractory SE (RSE) is most often symptomatic of an acute neurologic condition or neurodegenerative disease. Treatment for RSE is difficult, usually requiring intensive support of vital functions. Reported treatments for RSE include very high dose PB, continuous infusions of pentobarbital or BZDs (DZP, midazolam), lidocaine, inhalation anesthesia, and propofol. Outcome is related to underlying cause. Nonconvulsive SE may present as confusion or may mimic psychiatric illness. Response to BZDs is usually rapid but may not be sustained. Rapid initiation of oral or rectal valproate may be useful. Epilepsia partialis continua (EPC) is almost always due to an acute or chronic destructive lesion. Surgical treatment may be the only effective modality in some children with EPC. Acute treatment of breakthrough seizures and clusters of seizures at home with rectal BZDs (usually DZP, 0.2–0.5 mg/kg) may prevent progression to SE in some children and adolescents and reduce the need for visits to emergency facilities. **Key Words:** Epilepsy—Seizures—Status epilepticus—Anticonvulsants—Treatment outcome—Adverse drug reaction—Brain diagnosis—Child—Adolescent—Adult.

Status epilepticus (SE) is one of the most common neurologic emergencies in children and adolescents. Initial treatment often occurs without the direct involvement of a neurologist, carried out by emergency room physicians, pediatricians and, in some communities, paramedical personnel before arrival at an emergency facility. Neurologists must recognize that their direct involvement in the treatment of SE often is limited to the patient with refractory or recurrent SE. Therefore, an important role of epileptologists is to provide guidelines for the initial management of the patient in SE.

Therapy for most episodes of SE is fairly straightforward. Many protocols have been developed, and multiple reviews of the topic are published each year. Fortunately, most patients respond to any of the commonly administered medications when appropriate doses are used, and most do not suffer major adverse effects of treatment. Newer benzodiazepines (BZDs) have been recently added to the list of first-line medications. Alternative routes of medication administration, such as rectal or intranasal, have been used in emergency rooms and by paramedics for prehospital treatment of SE (1). Documentation of safety and efficacy is scant.

A related issue is the prevention of SE in patients with known epilepsy. The neurologist is often faced with the need to treat a known epileptic person with acute repetitive seizures (seizure clusters). These are the patients whose caretakers call or come to emergency facilities when they recognize a change in the child's usual seizure pattern. Many variants are seen: either several seizures in a short time, increasingly frequent minor episodes, or partial sei-

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zures that are recognized by the family as generally preceding major convulsions. Treatment of these acute episodes of deterioration in seizure control has increasingly included short-term oral or rectal use of BZDs. The intent is to stop the progression from a cluster of seizures to SE. Careful definition of episodes that should be treated and instruction of parents or caretakers in giving additional medication and in monitoring the child for adverse effects both empowers the parents and reduces emergency room visits (2). Although treatment of acute repetitive seizures is not the same as that of SE, it should be included within the same context because similar pharmacologic concerns apply.

ETIOLOGY AND OUTCOME OF SE IN CHILDREN AND YOUNG ADULTS

Studies of SE in children and young adults differ in the distribution of etiologies, depending on the setting, population, and age (see Table 1 for summaries of three large studies). For example, a series of patients drawn solely from a pediatric intensive care unit (3) would be expected to report a different distribution of etiologies of episodes than a series from an urban hospital pediatric facility that includes emergency room, general ward admissions, and intensive care units (4). Series of adults with SE differ from reports from pediatric series (5). However, there is general agreement that four groups account for the majority of treated episodes: atypical febrile seizures presenting as SE; acute neurologic conditions such as meningitis, encephalitis, trauma, tumors, or stroke; known epileptic patients, either idiopathic or remote symptomatic, often with SE due to intercurrent illness or noncompliance with medication; and children with degenerative or progressive neurologic conditions. Occasionally, children who will ultimately meet diagnostic criteria for idiopathic or remote symptomatic epilepsy present with SE as their first unprovoked seizure. Intoxication and drug withdrawal, particularly involving alcohol, are relatively common precipitants of SE in adults but are rare in children (6). Adverse drug reactions or intoxications (e.g., isoniazid) may present with SE, especially in younger children.

Outcome is closely related to etiology, in terms both of acute neurologic deficits after the episode and risk for recurrent SE in the future (7). Population-based studies differ from a clinically based sample, generally suggesting a much more benign prognosis (8,9). Recurrent episodes of SE are seen primarily in children with degenerative diseases, and in multiply handicapped children with remote symptomatic epilepsy (10). Episodes of SE that are refractory to first-line treatment are most commonly seen in the setting of progressive neurologic diseases or acute symptomatic neurologic conditions. Outcome reflects the underlying etiology (10–12). New neurologic abnormalities are typically seen when both SE and the neurologic deficit are attributable to the underlying condition, such as meningitis, encephalitis, anoxic encephalopathy, or stroke. New neurologic abnormalities are relatively uncommon in children whose SE is attributed to epilepsy or atypical febrile seizures.

TREATMENT OF CONVULSIVE SE

Initial treatment of convulsive SE supports vital functions, followed by the halting of seizure activity. Definitions vary of how long a convulsion or serial convulsions must continue before it can be called SE. Most authors specify 20–30 min of continuous seizure activity or recurrent seizures with-

TABLE 1. *Comparison of etiology of status epilepticus in three studies*

Setting	Pediatric inpatients and emergency room (4)	Pediatric intensive care unit (3)	Adult, urban public hospital (5)
Age range	1 month–18 yr	0–16 yr	17–87 yr
Number (%)	193	153	154
Etiologies:			
Epilepsy, all	91 (47%)	49 (32%)	58 (38%)
Epilepsy subgroups			
Idiopathic	46 (24%)		
Remote symptomatic	45 (23%)		
AED discontinuation			48 (31%)
Other causes			
Febrile seizures	46 (24%)	21 (14%)	0
Acute symptomatic	45 (23%)	67 (44%)	46 (30%)
Progressive neurologic	11 (6%)	2 (1%)	0
Intoxication	0	8 (5%)	57 (37%)
Unknown/other		6 (4%)	8 (5%)

AED, antiepileptic drug.

out return of consciousness. However, most treating physicians do not wait 30 min before initiating antiepileptic drugs (AEDs). In addition, exact duration of seizure activity before arrival at an emergency facility is often difficult to determine. In general, patients who arrive at an emergency room with convulsions, or who have reportedly stopped having convulsions during transport and started again shortly after arrival, are assumed to be in SE. Patients who begin having convulsions under medical observation are commonly treated with i.v. AEDs very quickly, despite the fact that they are not technically in SE. Although neurologists often instruct pediatric housestaff and nursing staff to observe a child and provide supportive care for up to 10 min before initiating i.v. AEDs, this advice is rarely followed.

BZDs, phenobarbital (PB), and phenytoin (PHT) are the standard treatments for uncomplicated SE. Initial doses by age and weight are listed in Table 2. Among the BZDs, lorazepam (LZP) has generally replaced diazepam (DZP) as a first choice (13,14). The significant advantage of LZP is that it is not as rapidly distributed to fat stores and therefore has a much longer effective duration of action. Use of DZP to terminate SE usually requires the use of a second parenteral AED (often PHT) immediately afterward. The longer duration of action of LZP allows time for further evaluation of the etiology of SE, e.g., to measure serum levels of oral AEDs. In addition, in uncontrolled trials, LZP use is less often associated with the need for endotracheal intubation than DZP (13,15). We recommend i.v. LZP at an initial dose of 0.1 mg/kg (maximal first dose of 4 mg). A second dose may be given in 5–10 min if necessary, but a subsequent dose of LZP or another BZD is rarely helpful. The most common error in the use of BZD is use of inadequate fractional doses, which do not produce a peak blood level adequate to control seizures. Patients receiving chronic oral BZDs may be somewhat less sensitive to LZP and may need a higher dose (13).

PB for SE has the significant advantage of very prolonged duration of action, enabling continuation orally with conventional maintenance doses the next day if chronic AEDs will be administered. PB

TABLE 2. *Initial treatment of status epilepticus (SE)*

	Lorazepam	Diazepam	Phenobarbital	Phenytoin
Initial dose Age effects	0.05–0.1 mg/kg	0.3–0.5 mg/kg Under 3 yr, 0.5 mg/kg 3+ years, 0.3 mg/kg	8–30 mg/kg Neonate, 20–30 mg/kg; Infant, 15–20 mg/kg; Child, 10–15 mg/kg; Adolescent, 8–10 mg/kg	15–20 mg/kg
Maximum first dose	4 mg	10 mg	—	—
Repeat dose	Half to full dose in 5–10 min, once only	Half to full dose in 5–10 min, once only	5–10 mg/kg Additional dose at 10–15-min intervals	If SE is not controlled, check serum level in 1–2 h. An additional dose to achieve serum level of 25–30 mg/L may be given
Duration of action	Up to 24 h	15 min to 4 h	Up to 24 h	Up to 12 h
Delivery	i.v. push	i.v. push	i.v. slow push	i.v. into saline line, slowly (10–25 mg/min to start, maximum 50 mg/minute). NO GLUCOSE IN LINE
Notes	Rapid tolerance. Avoid repeating in less than 48 h; may need higher dose if taking chronic BDZ	Follow with phenytoin or other AED. Avoid immediate use of phenobarbital after diazepam except in RSE.	No maximum dose in RSE	Cardiac monitor and BP checks during infusion. Serum level in 12 h to predict chronic oral dose. Currently used parenteral formulation likely will be replaced by a water soluable preparation (fosphenytoin, phenytoin prodrug) when available.

BZD, benzodiazepine; AED, antiepileptic drug; RSE, refractory status epilepticus.

TABLE 3. *Treatment of refractory status epilepticus*

Phenobarbital
Dose: 10 mg/kg i.v. every 15–20 min until seizures are controlled
Maximum dose: there is *no* top dose
Monitor: vital signs—above total of 30–40 mg/kg intubation is often necessary. Pressors are occasionally needed
Respiratory depression more likely is due to seizure than to phenobarbital unless given rapidly
Pentobarbital
Dose: 6–8 mg/kg initial loading dose, then 1–4 mg/kg/h
Monitor EEG to assure burst–suppression or "flat" EEG
Escalating dose often necessary to maintain burst–suppression
Pressors are commonly needed
Intubation is always needed
Other agents
Intravenous lidocaine
Adult bolus dose of 100 mg or 1–2 mg/kg; follow by infusions of 1–3 mg/kg/h
Pediatric dose: 1–2 mg/kg bolus followed by 6 mg/kg/h (26,50,51)
Nasogastric tube or rectal dosing with carbamazepine to rapidly achieve therapeutic serum level (10 mg/kg bolus doses)
Nasogastric tube or rectal use of valproate (Depakene syrup) to rapidly achieve therapeutic serum level. (5–10 mg/kg bolus dose every 2–4 h)
Continuous infusions of diazepam: bolus, then continuous infusion; titrate to effective dose (may need 0.12–0.7 mg/h to maintain control) (52,53)
Continuous infusion of midazolam (200 μg/kg bolus, then continuous infusion, usually needing increasing dose to maintain control) (24)
Propofol: titrate dose to general anesthesia
Adult doses of 0.133–11.3 mg/kg/h reported (31)
Pediatric dose of 2.5–18 mg/kg/h reported (33)
Inhalation anesthesia
Paraldehyde: rectal or i.v. use is effective but no longer available in the United States

remains a frequently used oral maintenance medication for convulsive generalized epilepsy in children. However, i.v. PB used for uncomplicated SE frequently produces prolonged sedation. In a child who presents with SE with no prior seizure history, sedation may complicate the determination of etiology, raising concerns that the child has an acute encephalitis or encephalopathy and prolonging hospitalization. In general, older, larger children require lower doses of PB on a weight basis than infants (see Table 2). Use of i.v. PB immediately after i.v. BZD may increase the risk for respiratory depression.

PHT is more difficult to administer, particularly in infants and small children with limited venous access. Because of the highly irritating nature of the i.v. preparation and the potential for precipitating arrhythmias or hypotension, PHT must be given slowly, preferably into a large vein freely flushed with normal saline. It is not compatible with glucose-containing solutions. However, sedation after a loading dose of PHT is substantially less than after comparable doses of PB. For this reason, when serial evaluation of mental status is important for management, such as in the patient with head injury or suspected acute encephalitis, PHT may be preferable. Unlike PB, the PHT loading dose is 18–20 mg/kg for all ages and weights (16). (A new preparation of i.v. PHT will replace the currently marketed form and is expected to be available in 1996; see New Developments section.)

REFRACTORY STATUS EPILEPTICUS

Refractory SE (RSE) is defined as persistence of SE despite appropriate administration of at least two of the above first-line AEDs (Table 3). Most children with RSE either have suffered an acute neurologic insult (e.g., stroke, encephalitis) or have a progressive neurologic condition. Occasionally, children with intractable epilepsy have RSE without a demonstrable progressive lesion or metabolic disease.

The majority of children with RSE require admission to an intensive care unit for endotracheal intubation and further support of vital functions. Many are already in need of high-level care for their underlying condition. Outcome depends on etiology as well as on the duration of uncontrolled SE.

The control of RSE rests primarily on high-dose barbiturates, either PB or pentobarbital (11,12,17, 18). We prefer very high-dose PB to pentobarbital. Unlike pentobarbital coma, use of PB generally does not require continuous electroencephalographic (EEG) monitoring, as the goal is control of clinical seizure activity rather than a burst–suppression EEG (11). Hypotension requiring pres-

TABLE 4. *Rectal benzodiazepines for breakthrough seizures*

Absorption of rectal diazepam[a]
Healthy adult volunteers, single 10-mg dose (45)

	i.v.	i.m.	p.o. tab	Rectal solution	Rectal suppository
C_{max} (ng/ml)	650	375	383	369	272
T_{max} (min)	6	95	52	17	82

Neonates with seizures (46)
Doses of 0.5 mg/kg and 1 mg/kg using parenteral solution administered rectally produced serum levels of 150–300 ng/ml in 5 min. i.m. and oral administration did not. i.v. administration produced even higher serum levels

Infants with febrile seizures (47)
Serum levels of 150–300 ng/ml were obtained 4 ± 1 min after rectal solution of diazepam and 20–30 min after diazepam suppository

[a] Effective anticonvulsant levels of diazepam may be as low as 150–300 ng/ml, but some investigators suggest that effective serum level is as high as 500 ng/ml even in benzodiazepine-naive patients.

sor medications, which is very common with pentobarbital (19), is quite rare with PB (11). There are scattered reports of the successful use of continuous infusions of BZDs, usually DZP (20), midazolam (MDL) (21–24), or LZP (25) for RSE in children. This is particularly useful in the setting of allergies to multiple AEDs or documented barbiturate hypersensitivity. Whether or not continuous EEG monitoring is used in the treatment of RSE, routine follow-up EEGs are often helpful to differentiate appropriate drug-induced sedation from stupor due to continued electrical SE.

General inhalation anesthesia, advocated in the past, is rarely used today. A number of case reports and a small series of patients are reported to respond to i.v. lidocaine (26). Propofol, an anesthetic agent, has been studied in experimental SE and was effective in animals (27–30). There are several reports of RSE successfully treated with propofol. Dosage and modes of administration (bolus vs. infusion) differ (31–34). Ketamine, a general anesthetic that is a noncompetitive NMDA receptor antagonist, has been studied for its neuroprotective effect in animals with prolonged SE (35,36). Human use of ketamine for RSE has not been documented to date.

NONCONVULSIVE SE (ABSENCE STATUS, PARTIAL COMPLEX STATUS)

Absence SE may be the presenting feature in a child or adolescent with otherwise uncomplicated absence epilepsy, or may occur in a child with intractable mixed generalized epilepsy (i.e., Lennox–Gastaut syndrome) (37). Complex partial SE may be clinically indistinguishable from absence status until EEG clarifies the diagnosis. The usual complaint is persistent or fluctuating alteration in mental status without recognized seizure activity. Initial evaluation may be by a psychiatrist, and a few patients with absence SE are admitted to psychiatry units for suspected fugue states or psychosis. Occasionally, absence SE is subtle enough that it is detected only during a routine EEG performed to evaluate suspected encephalopathy (38). Most neurologists consider treatment of absence SE to be urgent but not emergent. Alterations in vital signs, acidosis, and hypoxia do not occur in nonconvulsive SE. BZDs, either LZP or DZP, are usually rapidly effective in terminating absence status. Conversely, nonconvulsive SE has been reported to be precipitated by use of BZDs and by BZD withdrawal (39,40). CBZ administration has also been reported to precipitate absence status (41). Recurrent episodes of absence SE may respond to rapid initiation of valproate (VPA) treatment. This may be achieved using a nasogastric tube or rectal instillation of VPA solution if the patient is too obtunded to swallow. Complex partial SE usually responds to a BZD, barbiturate, or PHT administered intravenously. In several children in whom complex partial SE recurred repeatedly, even after a period of barbiturate coma, we have initiated CBZ therapy rapidly via a nasogastric tube, successfully achieving therapeutic serum levels in 12–24 h.

EPILEPSIA PARTIALIS CONTINUA

Epilepsia partialis continua (EPC), ongoing or rapidly recurring simple partial seizures, is often very difficult to control. Acute therapy with a BZD or barbiturate may suppress the seizure activity temporarily, but seizures recur as soon as the sedation dissipates. EPC is often a symptom of an acute or progressive structural lesion: infarction, vascular malformation, Rasmussen encephalitis, or other inflammatory or destructive processes (42). Surgical therapy may be the only effective modality in refractory EPC, particularly for Rasmussen encephalitis (43). If a well-defined focal lesion is present or if there is a strong clinical suspicion of Rasmussen encephalitis, referral to a pediatric epilepsy surgery center should be considered. We have performed cortical resections for refractory EPC in infants as young as 12 weeks.

ACUTE REPETITIVE SEIZURES, "CLUSTERS", BREAKTHROUGH SEIZURES, AND OTHER ALARMING SITUATIONS

Some patients with epilepsy, well-controlled under ordinary circumstances, experience clusters of seizures under a variety of physiologic stresses, particularly fever, sleep deprivation, or other illness. Others with intractable epilepsy experience clusters of seizures, sometimes progressing to SE, without identifiable provocation. Physicians, caretakers, and patients can often identify particular seizure patterns that are alarming because progression to SE, serial seizures, or more severe seizures is likely. Acute intervention at home to abort seizure clusters is helpful, both to avoid progression to SE and to eliminate frequent visits to emergency facilities.

Clusters or breakthrough seizures may present with a variety of patterns. Examples include increasingly frequent auras or partial seizures, a convulsion of an increased length and severity, or increasing myoclonic jerks which the family recognizes as usually preceding a generalized convulsion.

Occasionally, a patient who has breakthrough seizures with every fever can be treated as soon as fever is detected. With careful selection of patients (and their families), definition of appropriate times to treat, and training of the caretakers in administration of the medication and monitoring, many children can safely be treated at home for clusters of seizures or breakthrough seizures. This does not extend to the treatment of SE.

Many patients take "an extra dose" of their usual medication in such circumstances, with or without the knowledge and direction of their physician. Recently, oral and rectal BZDs have been used to abort clusters of seizures (Table 4). A variety of specific medications and routes have been used. In patients not receiving chronic oral BZDs, a single oral dose of a BZD or administration of a BZD for a few days during a period of increased stress may abort clusters of seizures. DZP, LZP, clorazepate (CLZ), or clonazepam (CZP) are the antiepileptic BZDs readily available in the United States, and all have been tried, as have other BZDs, such as clobazam (CLB) and nitrazepam (NZP), available in Canada, Europe, and Asia.

Rectal DZP is widely used in Europe and Japan and has been increasingly used in the United States (2,44) despite the lack of an FDA-approved preparation for rectal use. The rectal mucosa allows drug absorption by passive diffusion, which is particularly efficient for lipid-soluble, nonionized compounds in solution. The extensive rectal venous plexus allows prompt distribution. Absorption of DZP via the rectal route is substantially faster and produces higher peak levels than oral or intramuscular administration of comparable doses. With a liquid solution of DZP, peak levels are achieved in about 10–15 min (45–47). DZP prepared as suppositories is more slowly absorbed. Rectally administered LZP solution is more slowly absorbed, producing peak concentrations in 30 min to 2 h (48). Peak levels of BZDs are achieved much more rapidly with i.v. administration, which is obviously preferable in convulsive SE. However, paramedics and emergency room personnel are already using rectal administration of DZP or LZP for children in SE in whom venous access is difficult, with or without approval of the neurologic community (1).

At present, DZP for rectal use is available in the United States by having the caretaker use a needle and syringe to draw up the appropriate dose of parenteral DZP solution, remove the needle, and either use a tuberculin syringe or a 3-ml syringe with a small feeding tube to place the medication in the rectum. A new preparation of DZP specifically formulated and packaged for rectal use is in the final stages of being tested and will presumably replace these cumbersome unofficial preparations.

NEW DEVELOPMENTS

The ideal AED for SE would be always effective, easily administered, lacking major or frequent adverse effects, and suitable for chronic administration without addition of a second AED. At present such an AED does not exist. However, several AEDs now on the horizon hold potential for improving the armamentarium. Fosphenytoin (or PHT prodrug) is rapidly converted to PHT after i.v. or i.m. administration (49). It is water-soluble and lacks the irritant properties of i.v. PHT. Unlike i.v. PHT, cardiovascular adverse effects have not been reported with fosphenytoin in clinical trials. Once approved, it will probably replace the current preparation of i.v. PHT for treatment of SE. An i.v. preparation of VPA is being developed, which will be useful in management of the child with refractory, nonconvulsive generalized seizures who cannot be given oral medication. Rectal DZP is in the final stages of testing, as noted above, and will be useful for serial seizures.

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