

Types of Status Epilepticus

Definitions and Classification

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What is status epilepticus? For all the criticisms leveled at the now-traditional definition accepted by the International League Against Epilepsy (ILAE) and based on the 1962 Marseilles conference, “a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition” (1), this definition *does* capture the concepts nearly everyone wants. The condition is necessarily epileptic, i.e., related to abnormal electrical activity in the brain with a clinical, and unhealthy, alteration in neurologic function. The patient in status epilepticus (SE) is clearly in a different and worse state than one who has an individual epileptic seizure only. Shorvon notes that SE is “not simply an iterative version of ordinary epilepsy” (2). Whether it is a more serious and fulminant etiology of seizures that produces their prolongation and repetition, or whether there is a fundamentally different failure of inhibition (more than occurs between a spike and a clinical seizure), the patient in status epilepticus has entered a new and worse condition. Discrete epileptic seizures come to an end, although there may be a prolonged postictal state. In SE, however, there is a definite clinical imperative to interrupt seizures because the patient may suffer grievous harm otherwise. Not only are there extensive physiologic, and sometimes pathologic, changes occurring during SE (3), but there is also a fundamentally different and urgent clinical problem for the patient and physician.

1. NATURE AND DIAGNOSIS OF STATUS EPILEPTICUS: WHAT ACTIVITY CONSTITUTES STATUS?

Extensive controversy persists over what type of clinical or electroencephalographic (EEG) activity constitutes status epilepticus. There are four primary components to the diagnosis: clinical manifestations (i.e., symptoms and signs), the duration of these events, EEG manifestations, and a response to anticonvulsant medication. Different components and criteria are more important, depending on the purpose of the definition, e.g., whether one is deciding to initiate treatment (in which case, clinical manifestations are primary, and a rather short duration should be

sufficient) or selecting cases for a clinical research review—in which case one might apply all the criteria, in what may be considered the neurologic equivalent of a medical diagnosis confirmed with tissue pathology.

1.1. Clinical Manifestations: Symptoms and Signs

Clinical manifestations of status epilepticus are primary. They are often sufficient and persuasive for diagnosis, such as with clinical motor activity, including ongoing rhythmic jerking activity or more dramatic tonic and clonic movements or intermittent generalized convulsions. Whatever the EEG findings or response to medication (or lack of either), all will accept these signs of ongoing epileptic seizures as diagnostic of SE. Those with motor manifestations, including automatisms or major alterations in behavior, are easier to diagnose. Nonconvulsive SE may be suggested clinically but often requires EEG to help make the diagnosis. The many different clinical forms of status epilepticus, their different definitions, methods of diagnostic determination, the many different clinical manifestations and consequences, and appropriate treatments, are the subjects of many chapters in this book.

1.2. Clinical Manifestations: Duration

Much dissatisfaction with the “fixed and lasting” definition results from its not specifying an exact time requirement. It often goes unacknowledged, however, that a precise temporal definition requires specification of the type of status epilepticus being timed. Most of the data brought to bear on such discussions involve generalized convulsive status epilepticus (GCSE); other types of SE are often not mentioned. The classic definition of SE captures the essence of the problem, but different durations should apply to different types of SE, i.e., whether one is referring to GCSE, focal motor status, or nonconvulsive status epilepticus (NCSE), and so on. Using a single duration as part of the definition for all forms of SE is no more possible or desirable than devising a single definition of “heart disease.”

For decades, clinicians faced with the temporal imprecision of the ILAE definition have imposed a 30-min criterion (4)—without international agreement or clear clinical or experimental support. This may represent a reasonable compromise between the time provoking neuropathologic consequences of SE in experimental animals on the one hand and clinical urgency in humans on the other.

Lothman and others have detailed the physiologic deterioration that occurs in human GCSE, often after about 30 min (3). Pathologic concomitants are speculated upon as occurring in parallel. While no experimental paradigm for SE in animals can capture all the features (from cellular to clinical) of human SE, the work of Meldrum and colleagues 30 yr ago provided a superb experimental model, at least for GCSE (5–7). In those experiments, baboons had SE induced by administration of bicuculline, and ensuing seizures included convulsions and prolonged, rapid epileptiform discharges, typically lasting hours. Even with the systemic factors of acidosis, hyperglycemia, and hypoxia prevented by paralysis and ventilation, animals with rapid, prolonged epileptiform discharges incurred neuronal damage and loss in the hippocampus and elsewhere. Most of these animals had SE for far longer

than 30 min. At some later point, damage appeared to accrue. Nevertheless, the *clinical* choice of 30 min was reasonable, especially in keeping with the physiologic deterioration (3). The timing with respect to pathologic changes is less certain, but a 30-min criterion shows prudent concern for the threshold of damage in humans.

For actual patients, however, there is clearly no reason to observe without intervening after frequent or continuous seizures short of 30 min. That criterion is often used retrospectively in describing patients with prolonged seizures or SE, but no reasonable physician would withhold treatment for 30 min. Accordingly, no *prospective* study of the treatment of SE can use the 30-min criterion derived from experimental (i.e., nonhuman animal) models.

Because of the clinical urgency in treating SE, durations required for diagnosis have been plummeting over the past few decades. The largest trial of different antiepileptic drugs (AEDs) for the treatment of GCSE covered 518 patients with clinical GCSE or “subtle” SE determined by EEG (8). In that trial, it was considered mandatory to begin treatment within 10 min—still retaining the label of SE. Patients with less obvious or “subtle” SE and those not responding to the initial treatment were particularly refractory and had a high mortality.

Subsequently, in a prospective, randomized trial covering 205 patients with repetitive or prolonged generalized seizures treated by San Francisco emergency medical technicians (EMTs) with diazepam, lorazepam, or placebo, “prolonged seizure” was defined as 5 min, and treatment was begun as soon as possible after that (9). The intent was to interrupt SE, but not to wait for 30 min to establish a traditional diagnosis. Beneficial effects were found for benzodiazepine treatments begun before emergency room arrival.

These clinical studies were randomized, prospective studies with human subjects. There was a clinical and ethical imperative to treat quickly. Such trials must define SE as diagnosable within several minutes. Consequently, there is a large difference in duration between the SE that led to neuronal damage experimentally and the shorter duration of SE now felt to warrant urgent treatment. Accordingly, Lowenstein, Bleck, and Macdonald proposed an “operational” definition of GCSE, i.e., 5 min, the time by which SE should be interrupted to avoid morbidity, mortality, or refractory SE (10).

An “operational” definition of status epilepticus is appropriate to guide clinical activity. In a National Institutes of Health (NIH) study of 120 secondarily generalized tonic-clonic seizures in 47 patients evaluated for refractory epilepsy, Theodore and colleagues found that the mean duration of a generalized convulsion (as reviewed on videotape) was 62 s; only one lasted longer than 2 min (11). They concluded that a duration of 2 min was outside the normal range for a discrete, individual seizure and that intravenous AEDs should be administered at that point. Certainly, seizures proceeding for at least 10 min appear much less likely to stop spontaneously (12,13). Some may do so, but the physician cannot rely on that in an individual patient. The situation calls for treatment, just as with conventionally defined status epilepticus.

Studies cited so far refer to GCSE, but there are necessarily several different, simultaneous, and reasonable definitions of status epilepticus for *different types* of SE. Definitions differ depending on whether one is diagnosing an individual patient in a clinical setting or reviewing a group's experience with patients with an ironclad diagnosis appropriate for clinical research. For GCSE in *retrospective* studies, 30 min should probably remain the standard definition, at least if it is desired to compare results from one study to another. As the "operational" and other shorter duration definitions become more readily applied clinically (as well they should be), it is very likely that outcomes will appear to improve. For example, in the study of DeLorenzo and colleagues, patients with shorter durations of ongoing, continuous, or repeated seizures without recovery, lasting 10 to 29 min (not quite long enough to warrant a classical diagnosis of SE), had a significant mortality but less than that for patients with SE diagnosed after 30 min (12). Presumably, patients treated after 5 to 10 min will do better than those treated after 30 min. This does not mean that short duration definitions are inappropriate or lead to inferior studies. Rather, definitions need to be stated clearly before reporting the outcome of any group of patients labeled as having status epilepticus.

1.3. EEG Manifestations

Often, the diagnosis of GCSE is made readily by clinical observation, but some forms of SE require EEG to help make the diagnosis. At the extreme of subtle or completely inevent clinical manifestations, the diagnosis may depend almost entirely on EEG. If clinical and "duration" components of SE definitions are controversial, they provide an island of relative tranquility in the stormy sea of debate over EEG criteria.

1.3.1. Discrete Seizures vs Continuous Discharges

More than 30 min of recurrent, discrete electrographic seizures on the EEG will satisfy almost all epileptologists as evidence of ongoing SE. In this case, the EEG is persuasive, even without any clinical manifestations during the intermittent electrographic seizures. The diagnosis holds even when the outcome can be attributed to the underlying disease rather than to recurrent seizures. Such discrete electrographic seizures occurred in 8 of 26 patients with depressed consciousness after subarachnoid hemorrhage (but without clinical seizures) who underwent prolonged continuous EEG monitoring; all died (14). Exclusive reliance on this recurrent, discrete electrographic seizure criterion, however, would certainly underestimate the problem of nonconvulsive SE. It establishes a diagnosis beyond question, but exclusion of more continuous discharges is more restrictive a definition than most clinicians will want to use.

There remains a controversy about *continuous* epileptiform discharges. Such discharges have been recorded extremely frequently in conditions that conform well to a reasonable understanding of the traditional definition of SE—which accommodates both continuous and repetitive seizures, as long as there is no recovery between them, i.e., the patient remains in a "fixed and lasting epileptic condition."

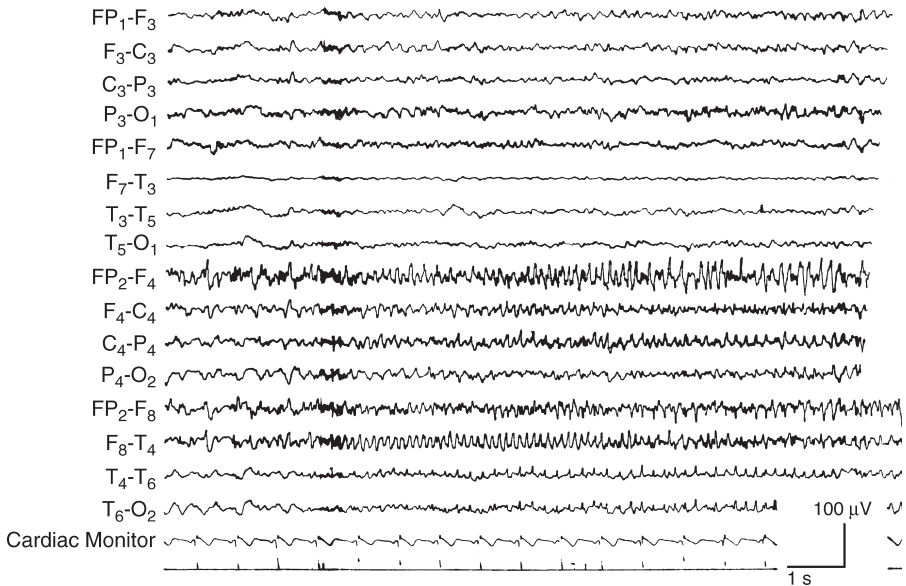


Fig. 1. EEG from a 48-yr-old woman with longstanding epilepsy admitted for cerebral artery aneurysm clipping. She had postoperative focal and complex partial seizures but was not thought to be having seizures at the time of the EEG; she was unresponsive. The EEG showed persistent right hemisphere slowing and three electrographic seizures beginning in the right frontocentral area, each lasting about 30 s. AEDs including pentobarbital were required to stop seizures (left facial twitching clinically), with subsequent excellent recovery.

There are several studies indicating that there is no important clinical difference between patients with intermittent electrographic seizures on the EEG and those with continuous discharges, at least when the discharges are rapid, e.g., ≥ 1 Hz. In one study of *focal SE* there was no significant clinical difference between patients with intermittent electrographic seizures and those with continuous discharges with a frequency of ≥ 1 Hz (Figs. 1 and 2) (15). In another series of patients with *clinical convulsions*, intermittent SE had a lower mortality than continuous SE (16). A third study of *all forms of SE* found no difference in outcome between those with continuous and intermittent seizures (17). Overall, continuous discharges may have a somewhat worse prognosis than discrete electrographic seizures and may be better correlated with structural and severe lesions. Nevertheless, the differences are modest, and both EEG patterns indicate serious illness and warrant a diagnosis of status epilepticus.

1.3.2. Characteristic EEG Features of Status Epilepticus

In GCSE, the clinical manifestations make the diagnosis clear. EEG features are detailed in Chapter 5. For nonconvulsive status, clinical features are often subtle and the EEG becomes more important for diagnosis, but the required characteristics are

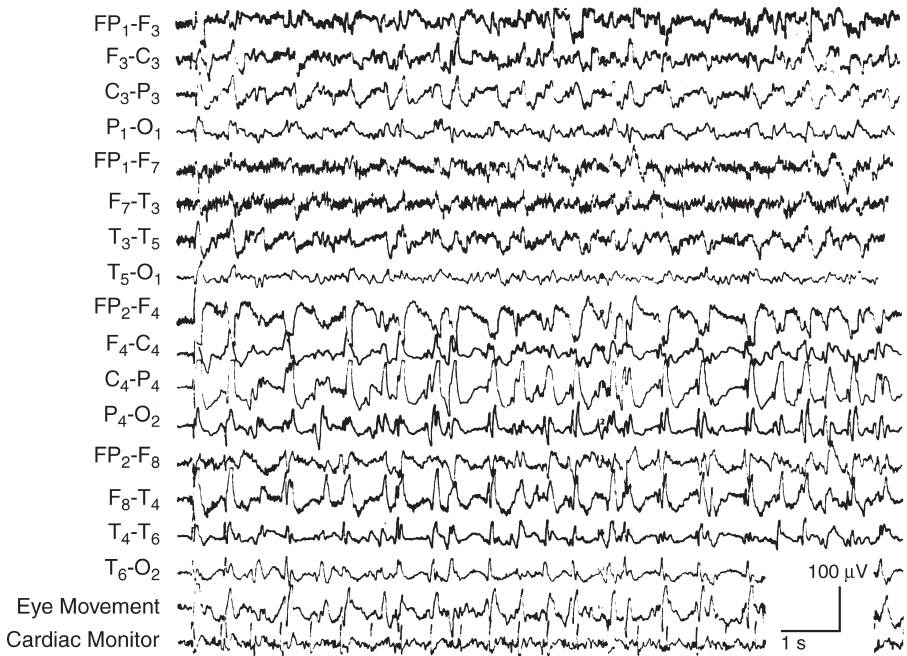


Fig. 2. EEG from a 71-yr-old woman with an old right hemisphere stroke, new infection, and possible theophylline toxicity. Left arm twitching was evident during the EEG. It shows continuous high voltage epileptiform discharges with a frequency of approx 1.8 Hz seen broadly over the right hemisphere. She recovered with AEDs and antibiotics.

more controversial. Common EEG features of almost all definitions of SE include epileptiform spike or sharp wave discharges or slowing, with a rapid, rhythmic appearance. These may be included within two or more electrographic seizures with a discrete onset of typical ictal discharges or with continuous discharges throughout the recording—and always in a patient with some clinical deficit.

Rather than debate what EEG findings *should* be seen with SE, one can be guided by the EEG patterns actually found in patients with a secure diagnosis. Granner and Lee reviewed EEGs from 85 episodes of NCSE in 78 patients with a clinical diagnosis confirmed by EEG and response to AEDs (18). EEG waveform morphologies were quite variable and included typical and atypical spike wave discharges, multiple or polyspike wave discharges, and rhythmic delta activity with intermixed spikes. Discharge frequency was always 1 to 3.5 Hz (mean 2.2 Hz), and only 4% were 3 Hz or faster. Two thirds were generalized and 13% focal, with another 18% generalized with a focal emphasis. In summary, the EEGs in a wide variety of cases of NCSE share three typical features: (1) epileptiform spike or sharp wave discharges or slowing with sharp features; (2) rhythmicity; and (3) recurrence frequencies of >1 Hz.

Logically, these guidelines do not apply to *long interval* periodic discharges, whether lateralized or generalized. Rather, they apply to EEGs with the more rapid

epileptiform discharges diagnosed as epileptic seizures in most clinical studies. Slower discharges constitute periodic lateralized epileptiform discharges (PLEDs) or generalized periodic epileptiform discharges (PEDs), usually not considered SE (see section 1.3.4.). Faster discharges would be read by most electroencephalographers as ongoing seizures.

Treiman and colleagues proposed that the EEG in GCSE typically evolves through five characteristic stages (19) (see Chapter 5). The last two stages are often unaccompanied by convulsions and could be considered either the later phases of GCSE or a type of NCSE. Frequently, there is subtle twitching, blinking, or jerking. Whether these later stages should be considered seizures, or SE, is controversial. Continuous, rapid generalized epileptiform discharges with occasional brief “flat” periods (Treiman's “stage 4”) are usually associated with a significant clinical deficit and will be considered NCSE or “subtle” SE by most. Some epileptologists argue that the subsequent, longer interval periodic discharges (PEDs; “stage 5”) constitute subtle status epilepticus as well (19,20), but this is not necessarily accepted as evidence of ongoing SE by all (21).

1.3.3. Clinical Correlates of Electrographic Status Epilepticus

Patients with ongoing electrographic seizure activity (continuous or in discrete seizures), usually with minimal or no motor activity, often following earlier generalized convulsions or GCSE or in the setting of severe medical illness (such as anoxia, sepsis, or severe metabolic derangements), have been given several different labels. They have been termed to be in “subtle” SE (19) or in electrographic status epilepticus (22). Figure 3 illustrates an example. Some refer to these patients as having “epileptic encephalopathies,” indicating that the underlying disease causing the encephalopathy is key and that the epileptic component is secondary and may not respond to AEDs. This term, however, is probably best reserved for certain, primarily pediatric, syndromes (see Chapter 16).

Such patients with ongoing discharges on EEG, with no obvious clinical manifestations except diminished consciousness, are not rare. Of 164 patients who had EEGs after apparent control of clinical SE in the large Virginia series, 42% had continued epileptiform discharges, and 14% were considered in NCSE (23). In the VA study of best drug treatments for convulsive SE, 20% of patients whose clinical SE had appeared to stop had evidence of ongoing SE on the EEG (8). Also, among 94 patients with severe head injury, 22% who underwent prolonged, continuous EEG monitoring had seizures, and 6% had SE, all without clinical signs, i.e., they were detected by EEG alone (24). Similarly, 8% of patients with coma of all causes and similar monitoring had NCSE without other clinical signs (25).

Often, it is not clear whether the ongoing repetitive epileptiform discharges are contributing to a clinical deficit or illness. As usual, the outcome is determined primarily by the etiology. Many of these patients have serious cerebrovascular disease or toxic and metabolic encephalopathies or both (22,26). Anoxia and sepsis are common causes, and patients are generally sicker than those with clinically obvious GCSE, in part because it takes time after the initial insult or deterioration to obtain



Fig. 3. EEG from an 83-yr-old woman found unresponsive after admission to the medical service with a urinary tract infection and “failure to thrive,” with no clinical seizures observed during the hospitalization.

an EEG. Patients who improve from SE quickly usually do not need or have EEGs; those still in SE when the EEG is done are usually the sicker patients.

In several series, these patients have had earlier seizures, were of markedly altered consciousness or comatose, had “subtle” presentations, and were usually unrecognized as being in SE when it was going on. SE often progressed for long durations and had a high mortality—often more than 50%. In one group who all had earlier, recognized clinical SE, EEGs picked up ongoing SE in 24 of 45 patients (27). This “subclinical” SE was far more difficult to treat than clinically evident status, and 24% died. Patients with SE in the setting of serious medical illness have a terrible prognosis, but it is not possible to dissect out that portion of the harm done by epileptiform discharges or NCSE from the damage caused by the underlying illness (8,22,26–28).

Electrographic status epilepticus (ESE; the typical appearance of SE on the EEG, without obvious clinical manifestations) should generally be considered “true” SE for several reasons. First, the EEG discharge appearance, frequency, and rhythmicity are characteristic for many clinical reports (16,17,22–25,27) and are similar to those from the study of Granner and Lee (above) (18). Continuous epileptiform discharges with a relatively high frequency (at least 1 Hz, and in some reports 1.5 Hz) have been the primary diagnostic evidence in nearly every case or series report of SE due to some new cause throughout the neurologic literature. As such, these EEGs help to define the usual experience of neurologists treating what they consider to be status epilepticus.

Second, the very large majority of patients with ESE have had clinical seizures recently, and most will have subsequent clinical seizures, indicating that this is not

simply a sign of “burnt out” seizures (22,26,27). For example, patients who develop electrographic SE upon emergence from continuous midazolam or pentobarbital infusions will usually go on to have clinically evident and important seizures (29,30).

Finally, while patients with ESE often have catastrophic neurologic and medical illness, and AED treatment may be unsuccessful in effecting a clinical improvement, a substantial number of patients (particularly those without anoxia) will have an EEG *and* clinical improvement on medication (27). In the end, it makes most sense to consider ESE as a manifestation of status epilepticus and treat accordingly rather than stating that something is not an epileptic seizure because it is difficult or impossible to fix.

Some neurologists are reluctant to diagnose SE in comatose patients with continuous rapid epileptiform discharges, perhaps because such conditions often have disastrous outcomes regardless of the treatment (8,28). The hesitancy discounts the possibility of a patient having two overlapping diagnoses, quite similar to those of cardiac arrhythmias and underlying coronary artery disease. For example, the anoxia that follows cardiac arrest is often devastating, and many such patients have focal or generalized repetitive discrete electrographic seizures without clinical manifestations or with subtle blinking or twitching. They have *both* anoxic brain injury and status epilepticus. The diagnosis of SE is not obviated by the devastation due to the underlying illness. Treatment or reversal of the SE may interrupt epileptic discharges and control subtle clinical motor abnormalities (or even clinical seizures) without improving the overall prognosis. Still, it is no more logical to suggest that these patients do not have SE because they are comatose and have a terrible prognosis than it would be to dispute a diagnosis of infection when antibiotics are not curative.

1.3.4. The Question of PLEDs

Most epileptologists do not consider periodic lateralized epileptiform discharges to be a manifestation of clinical seizures or SE, at least at the time of the EEG. Hundreds of such patients have been studied in several reports (31–34). Clinical seizures occurred in at least 80% before the EEG, and many had prior SE. PLEDs were usually associated with acute, serious focal neurologic illness such as stroke (the most common cause in many reports), tumors, and occasionally infections, metabolic disturbances, earlier epilepsy, and the like. The mortality is high—up to 50% within 2 mo (35). In the largest study to date, PLEDs were certainly a risk for more seizures; half the patients without prior epilepsy who survived the acute illness developed long-term epilepsy (34). Two thirds had SE before the PLEDs. The authors considered PLEDs to be “the terminal phase of status epilepticus,” and most epileptologists agree.

Almost all reports of PLEDs show illustrations of EEGs with epileptiform discharges at a frequency of 1 Hz or slower, often every 1 to 2 s and with intervals up to 10 s in some series. EEG features stay fairly constant over a given patient and EEG, but the discharge frequency may decline from one every 1.5 s in the first 2 d to half that frequency a week later, and most PLEDs will resolve after days to weeks

(31). Actual clinical seizures typically show more rapid epileptiform discharges on EEG. The discharge frequency may distinguish between PLEDs and seizures. Most electroencephalographers do not consider PLEDs to be clinical seizures, but most will read EEGs with more rapid discharges (at least >1 Hz and certainly >1.5 Hz) as indicative of ongoing seizures.

The frequency criterion cannot be absolute. One report of seven patients over the age of 60 described recurrent confusional episodes associated with PLEDs—with epileptiform discharge intervals as long as 4 s (36). The clinical deficit and confusion resolved with a slowing of the EEG discharges, whether spontaneous or in response to benzodiazepines. Carbamazepine appeared to prevent recurrences; patients relapsed when it was decreased. The authors considered PLEDs an “unusual status epilepticus of the elderly” in those cases. Another group found classic PLEDs during clinically well-defined SE (37). They demonstrated clearly that PLEDs could be an ictal EEG pattern, although they would not apply the term “status” to patients with longer interval discharges who had no clinical signs of seizures. Anecdotally, some have reported finding PLEDs on a surface EEG and clear rapid seizure discharges in deeper structures on invasive recordings in the same patient.

In summary, PLEDs are strongly associated with acute, severe, focal neurologic lesions. EEG discharges are generally slower than those in typical seizures and resolve with time. PLEDs are generally not considered seizures or SE themselves, but they may be seen during seizures or SE, and their clinical significance differs in individual cases. Clinicians must keep an open mind about rules specifying what is and what is not SE.

1.4. Diagnosis by AED Response

For some, a definition of SE, particularly NCSE, requires a beneficial response of the neurologic deficit to AEDs as a diagnostic criterion. Several papers demonstrate, however, that such a response may be delayed, even up to days (38–40). Many patients with SE and severe underlying medical and neurologic illnesses respond minimally to AEDs, although except in the setting of anoxia it is not possible to know which patients will respond (8,22). This slow (or minimal, or even nonexistent) response makes it difficult to use this criterion for diagnosis at the time of the clinical illness presentation. Many astute clinicians have made the diagnosis of NCSE and treated patients successfully—without waiting for an AED response (or EEG) to confirm the diagnosis. Such cases would be unsuitable for inclusion in many studies, but the right diagnosis was made at the time and appropriate treatment initiated. In the clinical setting one must often make the diagnosis (and persist in treatment for it) for hours or days before an improvement can be demonstrated. Kaplan notes, “Clinical response to treatment is best avoided in defining a syndrome” (41).

There are many ways to establish a diagnosis of status epilepticus. Patients with clear, prolonged clinical seizures and even those with questionable seizures but a definite response to AEDs warrant the diagnosis without much controversy. A response to AEDs may be an appropriate criterion for a retrospective clinical series. In other cases, response to AEDs may be delayed or questionable; the EEG may be

complementary or even the only clear indicator of SE, although it must be in a patient with some neurologic deficit or clinical abnormality.

2. REFRACTORY STATUS EPILEPTICUS

Finally, in terms of labels, refractory status epilepticus (RSE) may be considered the “status of status” or the truly ultimate expression of seizures. It has been defined differently in different settings, with two primary discriminating features. The first typical criterion is duration, variously chosen as 5, 30, or often 60 min of SE (42)—even 120 min in some cases (43). As noted earlier, seldom do seizures lasting longer than 10 min cease on their own (12,13,44). Of course, if shorter durations are used, almost all SE will be labeled as refractory. Secondly, some speak of refractory SE as that which continues despite adequate use of one or two (appropriately chosen and dosed) AEDs, usually including a benzodiazepine and at least one longer-acting agent such as phenytoin, fosphenytoin, or phenobarbital (46,56). Indeed, the temporal definitions described above should probably include the same requirement for adequate treatment before declaring refractoriness. Mayer and colleagues appropriately combine these temporal and treatment criteria to include 60 min of SE and inadequate response to a benzodiazepine and one other AED—in appropriate doses (47). The specification of adequate medication is pertinent because patients are frequently treated with insufficient doses, not really warranting a diagnosis of RSE but rather one of “inadequately treated” SE (48).

Refractory status epilepticus is a term usually describing GCSE, but a similar rationale is appropriate for other types of SE. Thirty to 60 min after treatment with two appropriate AEDs in adequate doses is usually reasonable. This is particularly the case for nonconvulsive forms of SE; it is often difficult to be confident about the diagnosis within a shorter time. Of course, if there are ongoing clinical manifestations of seizures (even nonconvulsive, such as blinking or interruption of normal behavior) or EEG evidence of seizures for more than a few minutes without recovery, there is an imperative to treat, long before one can establish a “research” criterion for the definition of SE, refractory or otherwise.

3. CLASSIFICATION

There are many ways to categorize the various types of status epilepticus. In discussing classification schemata, Wolf describes several methods (49). In part, a classification scheme depends on one’s goals. One can aim to understand the basic biology, including genetics, of individual syndromes and their relationship to one another. For this purpose, the age-related syndromes of SE described by Shorvon are appealing because presentations and types of seizures and status epilepticus and their biology change, somewhat coherently, with age, especially in the first few years of life (2). Ultimately, better genetic, anatomic, and developmental explanations of seizure disorders and SE will provide a richer intellectual understanding of SE. Neurologists also generally agree that a better biological understanding of a patient’s illness will eventually lead to better treatment and outcome.

Basic scientific information and insights, however, are often unavailable at the time of an individual patient's presentation. For more immediate clinical orientation, the organization of this volume parallels the types of status epilepticus differentiated by signs and symptoms seen in clinical practice and, whenever possible, EEG features. The approach to different manifestations of SE syndromes and their management will rely primarily on clinical presentation, with EEG features close behind.

These organizational approaches (biological-genetic and clinical syndromic) are not mutually exclusive, and both will be alluded to. Also, the clinical presentation correlates with the genetic and anatomic substrates and pathophysiology involved. The age and genetic background of the patient should be considered whenever possible. Neonatal and infantile forms of SE are remarkably varied and may have extremely subtle presentations, as covered in Chapters 16 and 17. After infancy, however, childhood and adult forms of SE often appear quite similar, at least in clinical presentations and EEG manifestations.

This book will not advance a comprehensive classification scheme for status epilepticus but rather will focus on the primary clinical and electrographic presentations as they appear to the clinician "in the field." An organization of SE concentrating on its recognition by clinical presentation, symptoms, signs, and seizure types proves convenient for diagnosis and initial treatment. Most of the presentation involves seizure type, but especially with nonconvulsive seizures, this is imprecise, and EEG is crucial in the diagnosis. The stereotyped patterns of clinical and EEG presentations will continue to guide management, treatment, and often, prognosis.

4. TYPES OF STATUS EPILEPTICUS

The largest categories of status epilepticus, and the initial approach to their recognition, involve a determination of focal versus generalized clinical and EEG patterns, and also a distinction between convulsive and nonconvulsive presentations (Table 1). The latter is evident to the examining physician's eye. The former (focal vs generalized) may also be obvious, but particularly with NCSE, focal and generalized presentations may appear identical at some point in the evolution of the status. This is still a useful distinction to make whenever possible because different types of NCSE may have different etiologies, courses, treatments, and prognoses (*see* Chapter 15). The correlation with pathophysiology is imprecise, however, and different etiologies may present with the same type of SE. After early childhood, these types of presentation do not depend substantially on the age of the patient.

4.1. *Convulsive Status Epilepticus*

Convulsive status epilepticus includes repetitive motor manifestations and comprises three major clinical groups (at least after infancy): generalized convulsive status epilepticus, focal motor status epilepticus, and myoclonic status epilepticus.

Generalized convulsive status epilepticus (GCSE) is the most dramatic, readily recognized, and dangerous form of status epilepticus. Indeed, until the last two decades, nearly all clinical reports of SE covered GCSE alone or did not allow a

Table 1
Different Forms of Status Epilepticus

Generalized	Focal
<i>Convulsive</i>	
Generalized convulsive SE (GCSE)	Focal motor SE
Primary generalized GTC	Epilepsia partialis continua
Secondarily generalized GCSE (focal onset)	
Myoclonic	
Tonic (may actually start as focal)	
Clonic (may actually start as focal)	
Atonic (very rare for SE; may also have focus)	
<i>Nonconvulsive</i>	
Absence (classic)	Other focal with nonmotor features:
Other generalized nonconvulsive seizures (often secondarily generalized)	aphasic, sensory SE
	Complex partial SE, with prolonged or repeated CP seizures

reader to determine whether other types of SE were included. Although characterized by its generalized convulsions, GCSE actually has some focal onset or focal lesion in most cases (4,50). This is largely because “acute symptomatic” status is often the result of a new stroke or other focal lesion, and “remote symptomatic” status frequently follows an earlier lesion.

Generalized convulsive status entails a significant mortality, typically about 3% from the status itself in adults but 25 to 30% overall because of the usual severity of the underlying illness causing the SE (4). The morbidity and mortality depend tremendously on the etiology. They also depend on age, but this may be a factor not independent of etiology (51) and possibly duration of SE (52)—although this may be true just for the first few hours of SE.

There is abundant experimental (and lesser clinical) evidence that GCSE can lead to neuronal damage, particularly when prolonged. Experiments by Meldrum and others (5–7,53,54) showed that prolonged generalized convulsions with continued electrographic spike discharges for more than 1 h caused neuronal damage in the neocortex, cerebellum, and hippocampus of animals with provoked SE (discussed further in Chapter 9).

Clinically, GCSE also involves substantial morbidity with all the attendant medical and hospitalization complications. Chronic epilepsy may present with an episode of GCSE (55). Thus, status is a risk factor for later epilepsy, but it is less clear that status is the *cause* of the later epilepsy (55). Finally, there is concern for cognitive loss and more lasting encephalopathy due to SE, but this is extremely difficult to be sure of in humans. Consequences of GCSE are detailed in Chapter 6. It is not clear that other forms of SE are as damaging and, accordingly, they may not require exactly the same treatment.

Focal status epilepticus has many manifestations, largely depending on the location of the epileptic discharges in the brain. Focal motor status epilepticus is the most

readily recognized. Nonmotor (or nonconvulsive) forms of focal SE include aphasic and sensory SE and are discussed further in Chapters 7, 10, and 11.

Because of the varied clinical presentations, it is much more difficult to know the incidence, duration, morbidity, and mortality of focal SE (compared to those of GCSE). Though its presentations may be more varied and even interesting, if somewhat less terrifying, than those of GCSE, some large series indicate that focal SE has a comparable mortality (52). In large part, this is due to the focal nature of many acquired lesions such as strokes, hemorrhages, and infections (56). Many of these cases progress from focal SE to involve an alteration of consciousness or even secondarily generalized convulsions. Simple partial SE alone has a lesser but nonnegligible mortality (57). Many other cases, such as SE in benign Rolandic epilepsy, should have a minimal risk of morbidity and mortality (58). As always, etiology is the chief contributor to prognosis.

One extreme form of focal motor status is *epilepsia partialis continua* (EPC), which may go on for years or even decades even without affecting consciousness or leading to generalized convulsions (59,60) (see Chapter 7). There is almost always a significant associated neurologic deficit and morbidity, but it is unclear whether the EPC itself causes additional morbidity.

As detailed earlier, few neurologists would consider PLEDs to signify clinical seizures or SE, at least at the time of the EEG recording (31–34). Nevertheless, clinical seizures precede PLEDs in the large majority of cases, and many patients had SE (often focal) earlier. There are some patients for whom it can be demonstrated that a clinical deficit associated with the PLEDs clears with AEDs (36) or that PLEDs are associated with definite motor manifestations of SE (37). These cases of PLEDs must be considered SE by virtue of the other criteria for making a diagnosis. When so, they fall under the category of focal status epilepticus.

Myoclonic status epilepticus (MSE) has obvious motor or movement components and cannot be considered nonconvulsive. (Most MSE results from generalized brain dysfunction, but there are cases of focal MSE, sometimes essentially myoclonic EPC.) Clinical presentations may suggest certain causes and preferred treatments, but presentations may also be quite similar over a range of etiologies. As with other types of SE, however, the outcome varies tremendously depending on the etiology (see Chapter 6).

The most important etiologic distinction is between those cases of MSE that are “symptomatic” or reflective of an acute and usually severe medical or neurologic illness on the one hand, and those that occur (remarkably infrequently) in more benign idiopathic syndromes such as benign childhood myoclonic epilepsies or juvenile myoclonic epilepsy on the other. Symptomatic MSE often has a grave prognosis, while the idiopathic syndromes are almost always treatable and lead to minimal morbidity or residua. Patients with myoclonic epilepsies of childhood almost always return to their baseline, but in some of these conditions the baseline is not normal (see Chapter 17). In yet another group of progressive neurologic illnesses, exemplified by storage diseases, the SE may cease but progression of the underlying disease causes major neurologic deficits and clinical deterioration (61).

Patients with symptomatic MSE tend to do very poorly. Many cases are particularly refractory to medication. Anoxic MSE has the worst prognosis. Many patients with anoxia have EEGs showing electrographic status epilepticus. The minimal or myoclonic clinical manifestations and EEG abnormalities may be suppressible with AEDs, but the underlying illness is determining and almost invariably fatal (62,63). Patients with MSE due to multiple medical problems, such as a combination of uremia and sepsis (a typical cause), also tend to have poor outcomes—certainly determined by the underlying illnesses.

EEG features can help to distinguish between the different etiologic groups of MSE. Some benign genetic childhood myoclonic epilepsy syndromes may include bursts of polyspikes with a relatively normal background. Cases with acute or remote symptomatic causes may show more of an encephalopathic EEG background, and those with the particularly ominous myoclonic status caused by anoxia may show a nearly flat background. The EEG backgrounds in MSE may correlate better with prognosis than do the clinical manifestations.

Infrequently, status epilepticus may assume a *tonic*, or a *clonic*, or an *atonic* form (the last is not actually convulsive, but often prompts falls and injuries). These are mostly neonatal and pediatric cases of SE.

4.2. Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus (NCSE) has usually been divided into generalized NCSE, characterized by generalized spike and slow wave discharges, and complex partial SE, usually including focal EEG abnormalities and considered the equivalent of prolonged or repetitive complex partial seizures (64).

Diagnostic criteria for NCSE status are frequent topics of debate. Traditionally, the diagnosis involves an abnormal mental status with diminished responsiveness, a supportive EEG, and often a response to anticonvulsant medication. For NCSE overall (without specifying generalized or CPSE), Tomson and colleagues required impaired consciousness for 1 h and an EEG with continuous seizure activity (64), whereas Kaplan sought impaired consciousness for 30 to 60 min with some form of EEG seizure activity (65). Neither required an immediate response to AEDs to make the diagnosis. As noted earlier, a clinical response to AEDs may be delayed up to days (38,39). Often, a diagnosis must be made sooner. When EEG is used to diagnose NCSE, certain features are required, but they can be controversial; almost all studies have in common epileptiform spike or sharp wave discharges or slowing, a rhythmic appearance, and a discharge frequency of at least 1 Hz (18).

Generalized NCSE has often been considered synonymous with absence SE, but this is not accurate. Clinical and EEG manifestations of absence and other forms of generalized SE may be similar (but not identical), and the term “absence status epilepticus” is best reserved for the several varieties of primary generalized NCSE, similar to “status epilepticus in petit mal” described by Schwab (66). It tends to occur in patients with earlier absence or other primary generalized epilepsy, has no features of focal seizures, and includes the typical 3 Hz generalized spike and slow wave discharges on the EEG. Cases of “*de novo* status” are typically generalized on

EEG but unrelated to adolescent absence SE (67). They may occur following medication (particularly benzodiazepine) withdrawal in older patients and appear very similar clinically. Primary generalized NCSE occurs in several idiopathic (usually genetic) syndromes with clinical spells often resembling absence seizures (68). Most forms of primary generalized NCSE are relatively easy to treat and have good prognoses. Unfortunately, there are probably many more cases of secondarily generalized SE. More ominous is the generalized SE diagnosed on EEG in patients with severe, underlying medical or neurologic illness—the patients with NCSE in coma or electrographic SE. Here, NCSE is generalized, but the underlying disease indicates a worsened prognosis.

Focal nonconvulsive status epilepticus, i.e., nonmotor focal SE, is almost certainly markedly underdiagnosed (see Chapter 7). The variety of causes, including encephalitis, stroke, mass lesions, trauma, even multiple sclerosis or mitochondrial and degenerative disorders, is matched by the number of clinical presentations, even including atonia (69), catatonia (70), and anarthria from opercular seizures (71).

Complex partial status epilepticus (CPSE) starts focally and involves enough of the brain to alter consciousness. It is the most common form of focal NCSE. It is often a series of prolonged or recurrent complex partial seizures altering consciousness or behavior. It may appear as an “epileptic twilight state” with confusion or bizarre and particularly fluctuating behavior (72–76). At times, there are automatisms. Cases include both prolonged repetitive complex partial seizures and continuous seizure activity. Clinical behavioral manifestations vary remarkably (77) (see Chapters 10 and 11).

Diagnosis of CPSE has been controversial, and criteria vary markedly from one paper to the next. Early definitions were particularly demanding. Mayeux and Lueders required prolonged complex partial seizures with continuous focal or secondarily generalized seizures on the EEG or repeated complex partial seizures with a focal EEG (78). Treiman and Delgado-Escueta required recurrent or persistent complex partial seizures, fluctuating neurologic signs, recurrent epileptiform EEG patterns, and a prompt clinical and EEG response to AEDs (75). Few patients in more recent surveys would meet these criteria. More recently, Cockerell and colleagues diagnosed CPSE in patients with confusion lasting at least 30 min, with persistent or continuous epileptiform discharges on the EEG, but with no definite requirement of medication responsiveness (76).

The clinical overlap of generalized NCSE and CPSE confuses the classification of NCSE and may explain why reported cases of “absence” (actually, generalized) SE outnumber those of CPSE, even though individual complex partial seizures are far more common than absence seizures in adult clinical practice. Both exhibit confusion or other altered mental status, along with minimal motor activity (except automatisms) and usually no systemic physiologic disturbance. A history of primary generalized epilepsy and rapid, rhythmic, generalized EEG discharges argue in favor of generalized NCSE while a history of focal seizures or other focal neurologic disease suggest CPSE. The key to understanding the overlap is almost certainly that an individual seizure may start focally and generalize rapidly. Cases considered as

“atypical” absence SE may well be complex partial seizures with generalization and prolongation.

The concepts of overlap and progression are buttressed by the correlation of clinical presentation and EEG. Tomson and colleagues studied 32 patients with NCSE, 14 with focal EEG changes (thus labeled CPSE), and 18 with generalized discharges, 6 of whom had primary generalized epilepsy (64). Patients could not be differentiated by clinical features. Similarly, Granner and Lee noted the predominance of generalized EEG discharges in NCSE, but many of their patients had focal discharges on interictal EEGs or after AED treatment (18).

To understand more completely the nature of the illness affecting one’s patient and to decide whether prolonged treatment is appropriate (and with what medications), it is helpful to categorize the patient’s NCSE precisely. Nevertheless, the clinical manifestations of different syndromes and even some EEG features may be quite similar at presentation, and the initial treatment is often with benzodiazepines for any type. It is important to diagnose NCSE, but it may not be so crucial to determine the NCSE type immediately.

4.3. Childhood and Neonatal Status Epilepticus

The general scheme of status epilepticus depicted in Table 1 applies best to patients after early childhood. Neonates and infants develop forms of SE that appear very different clinically and do not fit easily into the categories of focal, generalized, convulsive, or nonconvulsive used for older children and adults. They must be considered separately. Several childhood syndromes are covered in Chapters 16 and 17. The primarily pediatric syndrome of electrographic status epilepticus in sleep (ESES) serves as a useful example (79,80). The EEG patterns warrant a diagnosis of status epilepticus even though the clinical picture at the time may be dominated by sleep. It is clear that the electrographic pattern is related to a serious illness. Similarly, the epileptiform discharges, often rapid and even rhythmic, in an acquired epileptic aphasia, or Landau-Kleffner syndrome (LKS), may reach criteria for SE at times, but the role of repetitive discharges or SE in the progression of the disease is not at all clear. Thus, the diagnosis of SE does not necessarily mandate a particular treatment. The LKS discharges are related to the disease but may not necessitate AED treatment beyond that required to control clinically evident seizures (81,82). In the end, it is difficult to classify many of these infancy and childhood syndromes. An age-related approach may be best in this age group (2). The other SE category headings in this volume should be more useful and appropriate for patients beyond early childhood.

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