When a person presents with status epilepticus (SE), as described in this case, there may be little indication of the diagnostic and treatment challenges ahead. The physician's initial goal is to stabilize and treat the patient, and then to evaluate the potential causes of SE, focusing first on acute or life-threatening etiologies. Initially, SE due to common causes may closely resemble SE due to rare causes. Common things being common, we consider fever and systemic infection in children. In young adults, head injury, infection, metabolic causes, or intoxication may be responsible. In older adults, we suspect stroke, anoxic or hypoxic injury, neoplasm, or metabolic disorder. Occasionally, the preliminary diagnostic studies are unrevealing; there is no history of pre-existing epilepsy and no acute or chronic cause of SE is evident. In these cases, less common causes of SE must be considered. In this article, we will review SE management and the investigation of infectious causes (relatively common) and autoimmune causes (relatively uncommon) of SE.

Initial Management
The first step in managing the SE patient is to assess and maintain airway, breathing, and circulation. An unconscious patient with seizures, like Ms. Q, will likely need endotracheal intubation for airway protection. Intubation is also appropriate if sedating or administering anesthetic doses of anti-epileptic drugs. Blood pressure, pulse, cardiac rhythm, and oxygen saturation should be continuously monitored, and intravenous access secured. Initial laboratory tests include toxic screen, alcohol level, complete blood count, comprehensive metabolic panel, urinalysis, and toxic screen—were normal. Head CT was normal. She remained stuporous.

EEG demonstrated waxing and waning electrographic ictal activity, and she was loaded with fosphenytoin. Intermittent electrographic seizure activity persisted, and a continuous infusion of intravenous propofol was administered. After 24 hr, propofol was weaned, but electrographic seizures recurred and it was restarted.
The electroencephalogram (EEG) plays an essential role in the diagnosis and management of SE. When obtained during the ictal event, it confirms seizures and rules out other entities such as rigor, panic attack, psychogenic spell, or dystonic reaction. EEG may offer useful information regarding localization of seizure onset. In Ms. Q’s case, its most important role is to monitor the response to treatment. After convulsive activity stops, almost half of patients with SE continue to have electrographic seizure activity, indicating the need for further treatment (1). If generalized or lateralized periodic discharges are present, they should also be closely monitored with continuous EEG. While periodic patterns are not usually treated as ictal activity, they may occur as a precursor to SE, as a very late stage of SE, or in between waning and waning seizures (2).

In febrile patients, lumbar puncture (LP) is warranted to evaluate for CNS infection, and empiric antibiotic coverage should be initiated. LP should also be performed in those patients for whom no SE etiology is identified in the preliminary workup. Cerebrospinal fluid (CSF) cell counts, differential, glucose, protein, gram stain, viral and bacterial cultures, VDRL, and HSV PCR are sent, with additional tests depending on exposure, season, geographic locale, travel, and presence of immunosuppression. In an immunosuppressed patient, CSF fungal cultures and acid fast bacillus stain and culture should be included.

Infection as a Cause of SE
Systemic infection not involving the central nervous system (CNS), with temperature elevation, is among the commonest causes of SE in children; in one series, over 50% of childhood cases of status epilepticus were the result of infection (3). However, infections restricted to the CNS are much rarer and, in the same study, accounted for fewer than 3% of all cases (3). However, it is not always clear how or whether CNS infections are differentiated from systemic infections. This perhaps explains the variation in the incidence of infective causes of convulsive status epilepticus between studies, which ranges from 1 to 12 percent (4).

A wide variety of CNS infections can result in SE (Table 1). SE in the setting of encephalitis has a worse prognosis than SE due to other etiologies, especially pre-existing epilepsy. In one study, encephalitis caused 22.2% of the cases of refractory SE and only 4.3% of the non-refractory SE cases (5). In contrast, the same study found that no patients with SE caused by low antiepileptic drug levels and a prior history of epilepsy progressed to refractory SE.

Autoimmune Causes of SE
Although encephalitis is a common cause of refractory SE, in many cases, an infective agent cannot be found. In one study, only 28% of people with encephalitis and refractory SE had a putative identifiable cause (7). In cases without an identified infectious organism, autoimmune encephalitis is an increasingly recognized cause of SE. Among the well-described syndromes are those that involve antibodies to the NMDA receptor or to the voltage-gated potassium channel (VGKC). In an analysis of 31 sequential patients with refractory SE who had an acute or subacute onset of encephalopathy/seizures with CSF pleocytosis and no infective cause found, 6 turned out to have antibodies to NMDA receptors (8). They all responded to immunosuppression, illustrating the importance of diagnosing this syndrome.

In addition to signaling the need for immunotherapy, a diagnosis of autoimmune encephalitis sometimes leads to the identification and treatment of a neoplasm. Between 20 and 57 percent of young women with encephalitis due to NMDA-receptor antibodies have an ovarian teratoma (9, 10). About 20% of cases of encephalitis due to VGKC antibodies are associated with thymoma. In some, but not all, cases, tumor removal leads to seizure control.

Not all autoimmune syndromes associated with encephalitis and SE are associated with tumors, but there are some that are almost always paraneoplastic. These include encephalitis caused by antibodies to Hu, collapsin response mediator protein-5 (CRMP5), Ma2, and amphiphysin (11). Each of these antibodies may be associated with small cell lung cancer. Anti-Hu antibodies are most frequently associated with seizures and SE (12, 13). Antibodies to Ma2 are associated with germ-cell tumors of the testis, and 30% of patients respond to tumor removal and immunotherapy. Antibodies to CRMP5 may occur in the setting of thymoma (14).

The number of autoantibodies that have been found to be associated with seizures and SE is growing (15), and it is likely that there are still, as yet, unidentified antibodies. Whether all these antibodies are pathogenic is unclear; some may be markers for autoimmune disease rather than the causative agent, as is likely to be the case with Hashimoto’s encephalopathy (16).

Several clinical scenarios should alert the physician to consider an autoimmune cause of SE. The occurrence of lymphocytic pleocytosis and oligoclonal bands in the cerebrospinal fluid, with no evidence of viral or bacterial infection, should lead to the suspicion of an antibody-mediated encephalitis (14). An autoimmune etiology should be considered if initial diagnostic studies fail to elucidate the cause of SE, especially if the SE is prolonged and refractory to treatments with conventional anti-epileptic drugs.

Ms. Q, the patient in our case, turned out to have NMDA-receptor antibodies. Are there clinical indicators that SE has an autoimmune cause? Certainly, patients with an NMDA-receptor-associated encephalopathy have a typical course, similar to that of Ms. Q. Early symptoms include a prodrome of headache and fever; followed by higher cognitive dysfunction (in > 90%), psychiatric symptoms (consisting of hallucinations, psychosis and agitation in 77%) and seizures; late features consist of reduced level of consciousness, SE, a movement disorder (mainly choreoathetosis), and dysautonomia (10). Nevertheless, with the availability of a diagnostic test (serum or CSF NMDA receptor antibodies), the spectrum of NMDA-receptor-associated encephalopathy is expanding, suggesting that if typical features are present, there should be a high suspicion; however, an absence of such features does not exclude this diagnosis. Moreover, whether there are specific features associated with other autoimmune syndromes that can help distinguish them from infective causes is unclear. Importantly, many of these antibodies (including NMDA receptor antibodies) are associated with neoplasms (15). Therefore, a whole-body PET scan should be considered.
in all patients without an infective cause for their refractory SE and encephalitis.

**Treatment of SE**

Generalized, convulsive SE is a neurological emergency that should be treated aggressively, regardless of the cause. However, it is reasonable to consider SE in the setting of acute encephalitis as a circumstance that requires especially aggressive treatment, given the increased likelihood that the seizures will be resistant to treatment relative to many other causes of SE (17, 18).

Initial management, in addition to careful attention to vital signs and treatment of the underlying condition, is the administration of an intravenous benzodiazepine (details of a suggested treatment protocol are provided in Figure 1). The preferred drug by most practitioners is lorazepam, given its sufficiently rapid onset of effect and longer duration of action compared to diazepam (19). Furthermore, although prospective, randomized, controlled trials have not shown statistically significant superiority of one benzodiazepine over another, a trend for superiority of lorazepam has been observed in some of the larger studies (20, 21). If the patient does not respond to the first dose, a second dose of lorazepam is given after 5 min following the end of the initial infusion.

If the patient has not responded to lorazepam or if SE recurs after two doses, the most common choice for second-line therapy is phenytoin or fosphenytoin (19). The effect of either drug should be seen within 20 minutes of the start of the infusion, and an additional 10 mg/kg is given if the SE fails to respond or recurs. In recent years, it appears that other options for second-line therapy are increasingly being used, depending on drug availability and local practice guidelines. Intravenous valproate has been shown to be at least as effective as phenytoin in a number of studies (22–24), and recent reports have suggested the effectiveness of intravenous levetiracetam and lacosamide for refractory status, leading to their use earlier in SE treatment protocols (especially levetiracetam given its relative lack of drug–drug interactions) (25–33). Unfortunately, there is no evidence in the literature to suggest that any one of these options—phenytoin, valproate, levetiracetam, or lacosamide—is superior to all of the others, emphasizing the need for a rigorous, controlled trial to guide practice.

When SE continues despite treatment with an initial benzodiazepine and a second-line agent, many authors consider this to be refractory status epilepticus (RSE), although there is not yet a universally accepted definition (34–37). However, it is worth emphasizing that the management of SE that fails to respond to appropriate initial doses of lorazepam alone

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**TABLE 1. Infections Reportedly Associated with Status Epilepticus. (after [3])**

<table>
<thead>
<tr>
<th>Common Causes</th>
<th>Uncommon Causes (&lt; 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>• Typical Bacterial Meningitis</td>
<td>• Herpes Simplex</td>
</tr>
<tr>
<td>• Tuberculosis</td>
<td>• Japanese encephalitis</td>
</tr>
<tr>
<td>• Tuberculosis</td>
<td>• Human Herpesvirus 6</td>
</tr>
<tr>
<td><strong>Protozoal</strong></td>
<td><strong>Fungal</strong></td>
</tr>
<tr>
<td>• Cerebral toxoplasmosis</td>
<td>• Coccidiodiomycosis</td>
</tr>
<tr>
<td>• Neurocysticercosis</td>
<td>• Paracoccidiodiomycosis</td>
</tr>
<tr>
<td>• Malaria</td>
<td>• Coccidiomycosis</td>
</tr>
<tr>
<td><strong>Prion</strong></td>
<td><strong>Protozoal</strong></td>
</tr>
<tr>
<td>• Creutzfeldt–Jakob disease</td>
<td>• Cerebral toxoplasmosis</td>
</tr>
</tbody>
</table>

| **Protozoal** | **Fungal**    |
| • Cerebral toxoplasmosis  | • Coccidioidiomycosis |
| • Neurocysticercosis     | • Paracoccidiomycosis |
| • Malaria              | • Coccidiomycosis      |
| **Prion** | **Protozoal**        |
| • Creutzfeldt–Jakob disease | • Cerebral toxoplasmosis |
Status Epilepticus in the Setting of Acute Encephalitis

has become increasingly controversial, with some authors arguing that patients with ongoing SE should be treated immediately with anesthetic agents (38). Part of the rationale for this strategy comes from the findings of the VA Cooperative Study (20), which showed that although 55% of all patients presenting in "overt" SE responded to treatment (lorazepam, diazepam followed by phenytoin, phenytoin, or phenobarbital), those who did not respond had only a 7% likelihood of responding to a second agent (39). Furthermore, for patients who presented in "subtle" SE, a proxy for more prolonged SE prior to treatment, only 15% responded to the first agent, 36% responded to any of the other options, and 50% were considered to be treatment failures. These observations, along with the consideration that a patient with SE due to encephalitis may be relatively resistant to treatment, suggest that immediate treatment with anesthetic agents may be a reasonable course of action when an appropriate level of intensive care is immediately available.

Patients in RSE are usually treated with midazolam, propofol, or pentobarbital (in Europe, thiopentone). No controlled trials of sufficient power have been done to guide the decision as to which drug should be used first, although a consensus opinion by the Neurocritical Care Society is being developed. A meta-analysis by Claassen et al. (40) looked at 28 reports published between 1980 and 2001 describing the use of these three agents in RSE in a total of 193 patients. Pentobarbital appeared to be superior to either midazolam and propofol in effectively controlling RSE (e.g., treatment failure was observed in only 3% of patients treated with pentobarbital compared to 21% with midazolam and 20% with propofol). However, pentobarbital was significantly more likely to lead to hypotension; for this reason, it should not be used as the primary agent for elderly patients or those with cardiovascular compromise. Many patients with acute encephalitis are young and otherwise healthy, so pentobarbital could still be considered a reasonable choice in this setting. Nonetheless, the meta-analysis showed no overall difference in mortality among the three treatment approaches.

Electroencephalography is obviously required to monitor patients in RSE, and it is typically used to establish an end-

**Figure 1.** Treatment algorithm for generalized status epilepticus in adults.

| **Lorazepam 4 mg IV over 2 minutes. If seizures persist, repeat in 5-10 minutes** |
| **Fosphenytoin 20 mg/kg IV at 150 mg/min. If seizures persist after 30 minutes, give additional 10 mg/kg IV repeat in 5-10 minutes** |
| **Alternatives:** Valproate Levetiracetam Phenobarbital |

**Choose One:**

- **Pentobarbital:** Load 5-10 mg/kg up to 50 mg/min; repeat 5 mg/kg boluses until seizures stop. cIV rate: 1 mg/kg/h; range 0.5-10 mg/kg/h
- **Propofol:** Load 1 mg/kg; repeat 1-2 mg/kg boluses every 3-5 minutes not to exceed a total of 4 doses or until seizures stop. cIV rate 25-150 mcg/kg/min
- **Midazolam:** Load 0.2 mg/kg; repeat 0.2-0.4 mg/kg boluses every 5 minutes until seizures stop. cIV rate 0.1 mg/kg/h; range 0.05-2 mg/kg/h

**Add (single or in combination):**
- Valproate Levetiracetam Phenobarbital Topiramate

**Consider:**
- Hypothermia Electroconvulsive Rx Inhalational Anesthetics
point for depth of anesthesia in this setting. A range of target EEG patterns has been suggested, including suppression of electrographic seizures, burst-suppression, or full or near-full suppression of all activity, but very little published data exist to guide this practice. Claassen et al. (40) noted in their meta-analysis that achievement of burst-suppression was associated with a lower frequency of breakthrough seizures compared to electrographic seizure suppression alone. However, not surprisingly, this lower depth of anesthesia was associated with a higher frequency of hypotension. Krishnamurthy and Drislane (41) analyzed depth of EEG suppression and outcome in pentobarbital treatment of RSE in 35 patients, suggesting that more profound suppression was associated with less likelihood of relapse of SE; however, but the study was underpowered to reach any firm conclusions.

The optimal duration of anesthesia in the treatment of RSE is also unknown, although common practice is to initially maintain coma for 24 hr, wean off the drug (which favors propofol and midazolam in terms of rapidity of clearance), assess the clinical and EEG response, and restart treatment if seizures are ongoing or recur (42). Beyond this, practice is extremely variable. A reasonable approach is to increase the duration to 48-hr intervals, and longer intervals after one week.

During anesthetic treatment of RSE, maintenance doses of the original second-line therapy (i.e., phenytoin, valproate, levetiracetam) should be administered, with the expectation that the patient will require long-term treatment with an oral antiepileptic drug (AED) if he or she recovers. If the patient has a recurrence of SE when the anesthesia is lightened, it is common practice to use combinations of these agents as well as drugs such as phenobarbital, topiramate, paraldehyde, or chlorpromazine, depending on availability and familiarity.

Special Treatment Considerations for SE of Infectious Etiology

In the setting of viral encephalitis, it is not uncommon to find that the patient is treatment resistant, even with progressively longer periods of anesthesia and AED polypharmacy. In these cases of “exceptionally refractory” SE, a variety of more aggressive therapies can be considered, including inhalational anesthetics (43), hypothermia (44), electroconvulsive therapy (45), and even surgery (46), although the likelihood of finding a resectable focus in the setting of viral encephalitis is extremely low. Ketamine has also been suggested as adjunctive therapy to protect secondary brain injury due to excitotoxicity, but there is very limited experience with its use for RSE (47). Nonetheless, it is important to emphasize that prolonged and aggressive treatment with a combination of approaches can be successful in some patients who remain in RSE for prolonged periods. Most practitioners with experience in the treatment of SE can describe anecdotal cases of non-elderly patients with viral encephalitis and RSE who have survived and made a significant neurological recovery after weeks or months of in-hospital treatment.

Additional Treatment Considerations

In addition to the treatment of SE itself, it is also necessary to treat the cause. Antiviral therapies are now well established in the treatment of at least some viral encephalopathies; however, the use of corticosteroids is more controversial (48). There is certainly evidence that varicella zoster viral encephalitis may be partly due to an associated cerebral vasculitis, supporting short-term use of steroids (49). Steroids have also been recommended in cases of acute viral encephalitis where there is evidence of progressive cerebral edema (48). The use of steroids is further supported by the observation that steroids may reduce viral replication (50). Corticosteroids have also been recommended in bacterial meningitis in high-income countries (51). Corticosteroids should therefore be used in many cases of CNS infections resulting in status epilepticus.

A diagnosis of autoimmune encephalitis has important implications for treatment. Removal of any neoplasm can often result in a resolution of the SE (15). If there is no systemic infection, then immunosuppressive therapy should be considered. Although dexamethasone is usually used in association with antiviral or antibiotic treatments for CNS infection, methylprednisolone is more commonly used for autoimmune conditions (52). Regardless of which steroid is chosen, high-dose therapy over a short period of time (e.g., 1 g methylprednisolone daily for 3–5 days) should be considered for all cases of refractory SE associated with encephalitis. Further immunosuppression should be administered only once CNS infection has been excluded. As with other autoimmune CNS conditions, intravenous immunoglobulin or plasma exchange should be tried (27). The effect of these treatments may not be evident until days after administration. In cases that have proved refractory to high-dose steroids, intravenous immunoglobulin, and plasma exchange, immunosuppression with agents such as rituximab or cyclophosphamide should be considered (8, 10, 15, 26, 27, 29, 31, 53).

What happened with Ms. Q? She had a prolonged course of SE, failing multiple attempts to wean propofol. After she was found to have NMDA-receptor antibodies, she was evaluated for ovarian teratoma (not present, in this case). She improved with steroid treatment, her anti-epileptic drugs were gradually tapered, and she eventually made a good recovery.

Summary

Because of the high mortality associated with SE, it is important to evaluate and treat SE patients thoroughly and expeditiously using an established protocol. Infections are a frequent cause of SE, and while most are readily diagnosed on the basis of routine testing, less common infectious agents and autoimmune etiologies should be considered when routine cultures are negative. Autoimmune encephalitis is a rare—but increasingly recognized—cause of SE and should be suspected if there is CSF pleocytosis without an identified infectious agent or if SE is refractory to treatment and no etiology has been identified. Testing for NMDA receptor antibodies is available. Treatment of SE begins with a benzodiazepine, followed by either a second drug or, if aggressive treatment is warranted, by a continuous infusion of an anesthetic agent. Establishing encephalitis as the cause of SE has important implications for additional diagnostic and treatment measures. In addition to antiepileptic drug therapy, immunotherapy may be effective. In the setting of autoimmune encephalitis, an associated neoplasm should be sought and treated. Prolonged and aggressive treatment may be necessary for refractory SE.
Status Epilepticus in the Setting of Acute Encephalitis

References


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