then 3 to 14 days of maintenance therapy. This randomized, double-blind, class III tolerability study in patients needing infusion and maintenance of phenytoin compared fosphenytoin (n = 88, 15.3 mg/kg, 37 mg PE/min) to phenytoin (n = 28, 15.0 mg/kg, 33 mg/min) and found pain at the infusion site was greater for phenytoin than fosphenytoin (17% vs 2%) (63). A third study was a single-dose, randomized, double-blind, class III tolerability study of fosphenytoin at 150 mg PE/min (n = 90) vs phenytoin at 50 mg/min (n = 22) (63). The infusion was slowed or discontinued more often with IV phenytoin compared with IV fosphenytoin; 63.6% of phenytoin patients experienced pain at site of infusion; 48.6% of fosphenytoin patients encountered pruritus; and the average blood pressure decrease with fosphenytoin was 13.7 mm Hg compared with 5.9 mm Hg with phenytoin.

The following conclusions were drawn. Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin (level U). Fosphenytoin is better tolerated compared with phenytoin (level B). When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative (level B).

Q5. When Does Anticonvulsant Efficacy Drop Significantly (i.e., After How Many Different Anticonvulsants Does Status Epilepticus Become Refractory)?

Only one class I RCT (the Veterans Affairs status epilepticus trial) (22) provides clear data to address this question. Treatment success was defined as status epilepticus stopping within 20 minutes after infusion started with no recurrence prior to 60 minutes after the start of the infusion. In this four-arm double-blind RCT, in order to maintain the blinding, if the first administered anticonvulsant was not successful, then the patient was randomized to another treatment arm; if the second anticonvulsant was not successful, then the patient was randomized to another treatment arm. In adults with overt status epilepticus, the overall success rate of the first administered therapy was 55.5%. If the first study drug did not succeed, the second study drug was able to stop the status epilepticus for an additional 7.0% of the total population; the third drug helped only an additional 2.3% of patients. It took intensive "non-study" therapy to stop the status epilepticus in 23.2% of the initial patient population, and no drug was successful within 12 hours in 11.7%. In this study, if the patient did not respond to lorazepam or phenytoin, the response rate to phenobarbital was 2.1% (D. Treiman, verbal communication).

Three other RCTs (31, 32, 58), detailed earlier, reported higher rates of second-therapy efficacy in adults and children after failure of initial benzodiazepine therapy. However, in each of these studies, initial therapy was not part of an RCT nor was it blinded. For second therapy, the class II RCTs reported success ranging from 77 percent to 90 percent, while the two class III RCTs reported success ranging from 50 percent to 88 percent.

The following conclusions were drawn. In adults, the second anticonvulsant administered is less effective than the first "standard" anticonvulsant, while the third anticonvulsant administered is substantially less effective than the first "standard" anticonvulsant (level A). In children, the second anticonvulsant appears less effective, and there are no data about third anticonvulsant efficacy (level C).

Recommendations and Algorithm

Based on the evidence-based answers to the above questions, a treatment algorithm is proposed for convulsive status epilepticus (Figure 1). As stated earlier, clinical trials have arbitrarily focused on either adults or children, and only three trials (24, 27, 30) included both. The guideline's treatment algorithm is not age specific because the disease pathophysiology of prolonged seizures/status epilepticus and anticonvulsant drug effects on neuronal receptors are the same from infants through adults, permitting a unified approach for all patients older than neonates.

The algorithm starts with a stabilization phase (0–5 minutes), which includes standard initial first aid for seizures. The initial therapy phase should begin when the seizure duration reaches 5 minutes and should conclude by the 20-minute mark when response (or lack of response) to initial therapy should be apparent. A benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability (level A, four class I RCTs). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy (level A, 1 class I RCT), its slower rate of administration, compared with the three recommended benzodiazepines above, positions it as an alternative initial therapy rather than a drug of first choice. For prehospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives (level B). Initial therapy should be administered as an adequate single full dose rather than broken into multiple smaller doses. Initial therapies should not be given twice except for IV lorazepam and diazepam that can be repeated at full doses once (level A, two class I, one class II RCT). Doses listed in the initial therapy phase are those used in class I trials. Note that some consensus guidelines list slightly different dosages; for example, phenobarbital is often recommended at 20 mg/kg (2).

The second-therapy phase should begin when the seizure duration reaches 20 minutes and should conclude by the 40-minute mark when response (or lack of response) to the second therapy should be apparent. Reasonable options include fosphenytoin (level U), valproic acid (level B, one class II study) and levetiracetam (level U). There is no clear evidence that any one of these options is better than the others. The ongoing Established Status Epilepticus Treatment Trial (ESETT) should provide the answer in the next few years (64). Because of adverse events, IV phenobarbital is a reasonable second-therapy alternative (level B, one class II study) if none of the three recommended therapies are available.

The third therapy phase should begin when the seizure duration reaches 40 minutes. There is no clear evidence to guide therapy in this phase (level U). Compared with initial therapy, second therapy is often less effective (adults—level A, one class I RCT; children—level C, two class III RCTs), and the third therapy is substantially less effective (adults—level