Seizures, Stroke, and Other Neurologic Emergencies

Thomas P. Bleck, MD, FCCP

Objectives:

- Improve the recognition, differential diagnosis, and management of seizures occurring in critically ill patients
- Understand the pharmacology and application of newer anticonvulsant drugs in the ICU
- Recognize and manage status epilepticus
- Understand the special diagnostic and management issues of refractory status epilepticus
- Improve recognition of patients with acute subarachnoid hemorrhage
- Recognize and manage the major CNS complications of subarachnoid hemorrhage
- Recognize the common systemic complications of subarachnoid hemorrhage
- Review the role of the critical care service in the management of stroke
- Briefly review other neurologic emergencies in the ICU setting

Key words: brain abscess; diazepam; encephalitis; Guillain-Barré syndrome; herpes simplex; ketamine; lorazepam; meningitis; myasthenia gravis; neurogenic respiratory failure; nonconvulsive status epilepticus; polymerase chain reaction; propofol; recombinant tissue-plasminogen activator; seizure; status epilepticus; stroke; subarachnoid hemorrhage

Seizures

Seizures complicate about 3% of adult ICU admissions for nonneurologic conditions. The medical and economic impact of these seizures confers importance on them out of proportion to their incidence. A seizure is often the first indication of a CNS complication; thus, their rapid etiologic diagnosis is mandatory. In addition, because epilepsy affects 2% of the population, patients with preexisting seizures occasionally enter the ICU for other problems. Because the initial treatment of these patients is the province of the intensivist, he or she must be familiar with seizure management as it affects the critically ill patient. Patients developing status epilepticus (SE) will often require the care of a critical care specialist in addition to a neurologist.

Seizures have been recognized at least since hippocratic times, their relatively high rate of occurrence in critically ill patients has only recently been recognized. Seizures complicating critical care treatments (*eg*, lidocaine) are also a recent phenomenon. Early attempts at treatment included bromide,[1] morphine,[2] and ice applications. Barbiturates were first employed in 1912, and phenytoin in the 1937.[3] Paraldehyde was popular in the next decades.[4] More recently, emphasis has shifted to the benzodiazepines, which were pioneered in the 1960s.[5]

Epidemiology

Limited data are available on the epidemiology of seizures the ICU. A 10-year retrospective study of all ICU patients with seizures at the Mayo Clinic found 7 patients per 1,000 ICU admissions.[6] Our 2-year prospective study of medical ICU patients identified 35 with seizures per 1,000 admissions.[7] These studies are not exactly comparable, as the patient populations and methods of detection differed. Seizures are probably even more frequent in pediatric ICUs.

Certain ICU patients are at higher risk for seizures, but the degree of that increase has not been quantified. Renal failure or an altered blood-brain barrier increases the seizure likelihood for patients receiving imipenem-cilastatin, but other patients receiving this antibiotic [or γ-aminobutyric acid (GABA) antagonists like penicillin] are also at risk. Transplant recipients, especially receiving cyclosporine, are also at increased risk, as are those who rapidly become hypo-osmolar from any etiology. Nonketotic hyperglycemia patients have an unusual predisposition toward partial seizures and partial SE.

Incidence estimates for generalized convulsive SE (GCSE) in the United States vary from 50,000 cases / yr[8] to 250,000 cases / yr.[9] Some portion of this difference derives from different definitions; the latter estimate represents the only population-based data available, however, and may be more accurate. Mortality estimates similarly vary from 1 to 2% in the former study to 22% in the latter. This disagreement follows from a conceptual discordance: the smaller number describes mortality that the authors

directly attributed to SE, while the larger figure estimates the overall mortality rate, even though the cause of death was frequently the underlying disease rather than SE itself. For example, the study by DeLorenzo et al[9] included SE due to anoxia in its SE mortality estimate. In many of the reports surveyed in the earlier review, such patients would not have been counted.

Many risk factors emerged from the Richmond study. SE lasting > 1 h carried a mortality of 32%, compared with 2.7% for a duration < 1 h. SE caused by anoxia resulted in 70% mortality in adults, but < 10% in children. The commonest cause of SE in adults was stroke, followed by withdrawal from antiepileptic drug therapy; cryptogenic SE; and SE related to alcohol withdrawal, anoxia, and metabolic disorders. Systemic infection was the commonest cause of childhood SE, followed by congenital anomalies, anoxia, metabolic problems, anticonvulsant withdrawal, CNS infections, and trauma.

The data in Table 1, based on 20 years of experience at the San Francisco General Hospital,[10-12] are of interest because almost all patients with SE in the city of San Francisco who begin to seize outside of a hospital are transported there. About 10% of epilepsy patients present with SE,[13] and nearly 20% of seizure patients experience an episode of SE within 5 years of their first seizure.[9]

Table 1. *Etiologies of SE at the San Francisco General Hospital**

	1970–1980 (%) (n = 98)		1980–1989 (%) (n = 152)	
Etiology	Prior Seizures	No Prior Seizures	Prior Seizures	No Prior Seizures
Ethanol-related	11	4	25	12
Anticonvulsant noncompliance	27	0	41	0
Drug toxicity	0	10	5	10
Refractory epilepsy	—	—	8	0
CNS infection†	0	4	2	10
Trauma	1	2	2	6
Tumor	0	4	2	7
Metabolic†	3	5	2	4
Stroke†	4	11	2	5
Anoxia†	0	4	0	6
Other	11	5	3	5

*Data from Lowenstein and Alldredge.[11].
†Indicates conditions most likely to result in ICU admission

Classification

The most frequently used classification schema is that of the International League Against Epilepsy[14] (Table 2). This allows classification based on clinical criteria without inferring etiology. *Simple partial seizures* start focally in the cerebral cortex, without invading other structures. The patient is aware throughout the episode, and appears otherwise unchanged. Bilateral limbic dysfunction produces a *complex partial seizure*; awareness and ability to interact are diminished (but may not be completely abolished). *Automatisms* (movements that the patient makes without awareness) may occur. *Secondary generalization* results from invasion of the other hemisphere or subcortical structures.

Primary generalized seizures arise from the cerebral cortex and diencephalon at the same time; no focal phenomena are visible, and consciousness is lost at the onset. *Absence seizures* are frequently confined to childhood, consisting of the abrupt

Table 2. *International Classification of Epileptic Seizures**

I. Partial seizures (seizures beginning locally)
  A. Simple partial seizures (SPS)—consciousness not impaired
    1. With motor symptoms
    2. With somatosensory or special sensory symptoms
    3. With autonomic symptoms
    4. With psychic symptoms
  B. Complex partial seizures—with impairment of consciousness
    1. Beginning as SPS and progressing to impairment of consciousness
      a. Without automatisms
      b. With automatisms
    2. With impairment of consciousness at onset
      a. With no other features
      b. With features of SPS
      c. With automatisms
  C. Partial seizures (simple or complex), secondarily generalized
II. Primary generalized seizures (bilaterally symmetric, without localized onset)
  A. Absence seizures
    1. True absence (*petit mal*)
    2. Atypical absence
  B. Myoclonic seizures
  C. Clonic seizures
  D. Tonic seizures
  E. Tonic-clonic seizures (grand mal; generalized tonic-clonic)
  F. Atonic seizures
III. Unclassified seizures

*Adapted from Bleck.[16]

onset of a blank stare, usually lasting 5 to 15 s, from which the patient abruptly returns to normal. Atypical absence occurs in children with the Lennox-Gastaut syndrome. *Myoclonic seizures* start with brief synchronous jerking without initially altered consciousness, followed by a generalized convulsion. They frequently occur in the genetic epilepsies; in the ICU, they commonly follow anoxia or metabolic disturbances.[15] *Tonic-clonic seizures* start with tonic extension and evolve to bilaterally synchronous clonus, and conclude with a postictal phase. Clinical judgment is required to apply this system in the ICU. In patients whose consciousness has already been altered by drugs, hypotension, sepsis, or intracranial pathology, the nature of their partial seizures may be difficult to classify.

SE is classified by a similar system, altered to match observable clinical phenomena (Table 3).[16] *Generalized convulsive SE* (GCSE) is the commonest type encountered in the ICU, and poses the greatest risk to the patient. It may either be primarily generalized, as in the drug-intoxicated patient, or secondarily generalized, as in the brain abscess patient in whom GCSE develops. *Nonconvulsive SE* (NCSE) in the ICU frequently follows partially treated GCSE. Some use the term for all SE involving altered consciousness without convulsive movements; this blurs the distinctions among absence SE, partially treated GCSE, and *complex partial SE* (CPSE), which have different etiologies and treatments. *Epilepsia partialis continua* (a special form of partial SE in which repetitive movements affect a small area of the body) sometimes lasts for months or years.

Table 3. *Clinical Classification of Status Epilepticus**

I. Generalized seizures
  A. Generalized convulsive SE (GCSE)
    1. Primary generalized SE
      a. Tonic-clonic SE
      b. Myoclonic SE
      c. Clonic-tonic-clonic SE
    2. Secondarily generalized SE
      a. Partial seizure with secondary generalization
      b. Tonic SE
  B. Nonconvulsive SE (NCSE)
    1. Absence SE (*petit mal* status)
    2. Atypical absence SE (*eg*, in the Lennox-Gastaut syndrome)
    3. Atonic SE
    4. NCSE as a sequel of partially treated GCSE
II. Partial SE
  A. Simple partial SE
    1. Typical
    2. Epilepsia partialis continua
  B. Complex partial SE (CPSE)
III. Neonatal SE

*Adapted from Lothman.[17]

Pathogenesis and Pathophysiology

The reported "causes" of SE can be divided into predispositions and precipitants. *Predispositions* are static conditions increasing the likelihood of SE in the presence of a precipitant. *Precipitants* are events that can produce SE in most, if not all, people, but tend to affect those with predispositions at lesser degrees of severity (*eg*, barbiturate withdrawal). The causes and effects of SE at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. Longer SE durations produce more profound alterations with an increasing likelihood of permanence, and of becoming refractory to treatment. The processes involved in a single seizure and the transition to SE have recently been reviewed.[17]

The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid (EAA) receptors. From the standpoint of the intensivist, three channels are particularly important because their activation may raise intracellular free calcium to toxic concentrations: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) channels, *N*-methyl-D-aspartate (NMDA) channels, and metabotropic channels. These EAA systems are crucial for learning and memory. Many drugs affect these systems but are too toxic for chronic use. The deleterious consequences of SE, and the brief period for which such agents would be needed, suggest that they may have a role in SE. Counterregulatory ionic events are triggered by the epileptiform discharge as well, such as the activation of inhibitory interneurons, which suppress excited neurons via GABA-A synapses.

The cellular effects of excessive EAA channel activity include (1) generating toxic concentrations of intracellular free calcium; (2) activating autolytic enzyme systems; (3) producing oxygen free radicals; (4) generating nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylating enzyme and receptor systems, making seizures likely; and (6) increasing intracellular osmolality, producing neuronal swelling.

If adenosine triphosphate production fails, membrane ion exchange ceases, and the neuron swells further. These events produce the neuronal damage associated with SE.

Many other biophysical and biochemical alterations occur during and after SE. The intense neuronal activity activates immediate-early genes and produces heat shock proteins, providing indications of the deleterious effects of SE and insight into the mechanisms of neuronal protection.[18] Wasterlain's group has summarized mechanisms by which SE damages the nervous system.[19] Absence SE is an exception among these conditions; it consists of rhythmically increased inhibition and does not produce clinical or pathologic abnormalities.

The mechanisms that terminate seizure activity are poorly understood. The leading candidates are inhibitory mechanisms, primarily GABAergic neuronal systems. Clinical observation supports the contention that human SE frequently follows withdrawal from GABA agonists (*eg*, benzodiazepines).

The electrical phenomena of SE at the whole brain level, as seen in the scalp EEG, reflect the seizure type that initiates SE, *eg*, absence SE begins with a 3-Hz wave-and-spike pattern. During SE, there is slowing of this rhythm, but the wave-and-spike characteristic remains. GCSE goes through a sequence of electrographic changes (Table 4).[20] The initial discharge becomes less well formed, implying that neuronal firing is losing synchrony. The sustained depolarizations that characterize SE alter the extracellular milieu, most importantly by raising extracellular potassium. The excess potassium ejected during SE exceeds the buffering ability of astrocytes. Raising extracellular potassium potentiates more seizures.

The increased cellular activity of SE elevates demand for oxygen and glucose, and blood flow initially increases. After about 20 min, however, energy supplies become exhausted. This causes local catabolism to support ion pumps (attempting to restore the internal milieu). This is a major cause of epileptic brain damage.

The brain contains systems to terminate seizure activity; GABAergic interneurons and inhibitory thalamic neurons are both important.

SE produces neuropathology even in patients who are paralyzed, ventilated, and maintained at normal temperature and blood pressure. The hippocampus, a crucial area for memory, contains the most susceptible neurons, but other regions are also vulnerable. In addition to damaging the CNS, GCSE produces life-threatening, systemic effects.[21] Systemic and pulmonary arterial pressures rise dramatically at seizure onset. Epinephrine and cortisol prompt further elevations and also produce hyperglycemia. Muscular work raises blood lactate. Breathing suffers from both airway obstruction and abnormal diaphragmatic contractions. CO_2 excretion falls while its production increases markedly. Muscular work accelerates heat production; skin blood flow falls concomitantly, sometimes raising core temperature dangerously.

After about 20 min, motor activity begins to diminish, and ventilation usually improves. Body temperature may rise further, however. Hyperglycemia diminishes; after 1 h, gluconeogenesis can fail, producing hypoglycemia. GCSE patients often aspirate oral or gastric contents, producing pneumonia. Rhabdomyolysis is common, and may lead to renal failure. Compression fractures, joint dislocations, and tendon avulsions are other sequelae.

Table 4. *Electrographic-Clinical Correlations in GCSE**

Stage	Typical Clinical Manifestations*	Electroencephalographic Features
1	Tonic-clonic convulsions; hypertension and hyperglycemia common	Discrete seizures with interictal slowing
2	Low- or medium-amplitude clonic activity, with rare convulsions	Waxing and waning of ictal discharges
3	Slight, but frequent, clonic activity, often confined to the eyes, face, or hands	Continuous ictal discharges
4	Rare episodes of slight clonic activity; hy≠potension and hypoglycemia become manifest	Continuous ictal discharges punctuated by flat periods
5	Coma without other manifestations of seizure activity	Periodic epileptiform discharges on a flat back≠ground

*Data from Treiman.[20]

Clinical Manifestations

Three problems occur in seizure recognition: (1) complex partial seizures in the setting of impaired awareness, (2) seizures in patients receiving pharmacologic paralysis, and (3) misinterpretation of other abnormal movements as seizures. ICU patients often have depressed consciousness in the absence of seizures, as a result of their disease, its complications (such as septic encephalopathy[22]), or drugs. A further decline in alertness may reflect a seizure; an EEG is required to diagnose one.

Patients receiving neuromuscular junction (NMJ) blocking agents do not manifest the usual signs of seizures. Because most such patients receive sedation with GABA agonists, the likelihood of seizures is small. Autonomic signs of seizures (hypertension, tachycardia, pupillary dilation) may also be the effects of pain or the response to inadequate sedation. Hence, in patients manifesting these findings who have a potential for seizures (*eg*, intracranial pathology), an EEG should be performed. The actual incidence of this problem is unknown.

Abnormal movements can occur in patients with metabolic disturbances or anoxia. Some can be distinguished from seizures by observation, but if doubt about their nature persists, an EEG should be performed. Psychiatric disturbances in the ICU occasionally resemble complex partial seizures. Prolonged EEG monitoring may be required if the problem is intermittent.

Manifestations of SE: The manifestations of SE depend on the type and, for partial SE, the cortical area of abnormality. Table 3 depicts the types of SE encountered. This focuses on those seen most in the ICU.

Primary GCSE begins as tonic extension of the trunk and extremities without preceding focal activity. No aura is reported and consciousness is immediately lost. After several seconds of tonic extension, the extremities start to vibrate, quickly giving way to clonic (rhythmic) extension of the extremities. This phase wanes in intensity over a few minutes. The patient may then repeat the cycle of tonus followed by clonic movements, or continue to have intermittent bursts of clonic activity without recovery. Less common forms of GCSE are *myoclonic SE* (bursts of myoclonic jerks increasing in intensity, leading to a convulsion) and *clonic-tonic-clonic SE* (clonic activity precedes the first tonic contraction). Myoclonic SE is usually seen in patients with anoxic encephalopathy or metabolic disturbances.

Secondarily generalized SE begins with a partial seizure and progresses to a convulsion. The initial focal clinical activity may be overlooked. This seizure type implies a structural lesion, so care must be taken to elicit evidence of lateralized movements.

Of the several forms of generalized *NCSE*, the one of greatest importance to intensivists is NCSE as a sequel of inadequately treated GCSE. When a patient with GCSE is treated with anticonvulsants (often in inadequate doses), visible convulsive activity may stop while the electrochemical seizure continues. Patients begin to awaken within 15 to 20 min after the successful termination of SE; many regain consciousness much faster. Patients who do not start to awaken after 20 min should be assumed to have entered NCSE. Careful observation may disclose slight clonic activity. NCSE is an extremely dangerous problem because the destructive effects of SE continue even without obvious motor activity. NCSE demands emergent treatment *under EEG monitoring* to prevent further cerebral damage, because there are no clinical criteria to indicate when therapy is effective.

Partial SE in ICU patients often follows a stroke or occurs with rapidly expanding brain masses. Clonic motor activity is most easily recognized, but the seizure takes on the characteristics of adjacent functional tissue. Therefore, somatosensory or special sensory manifestations occur, and the ICU patient may be unable to report such symptoms. Aphasic SE occurs when a seizure begins in a language area, and may resemble a stroke. *Epilepsia partialis continua* involves repetitive movements confined to a small region of the body. It may be seen with nonketotic hyperglycemia or with focal brain disease; anticonvulsant treatment is seldom useful. CPSE presents with diminished awareness. The diagnosis often comes as a surprise when an EEG is obtained.

Diagnostic Approach

When an ICU patient seizes, one has a natural tendency to try to stop the event. This leads to both diagnostic obscuration and iatrogenic complication. Beyond protecting the patient from harm, very little can be done rapidly enough to influence the course of the seizure. Padded tongue blades or similar items should not be placed in the mouth; they are

more likely to obstruct the airway than to preserve it. Most patients stop seizing before any medication can reach the brain in an effective concentration.

Observation is the most important activity during a single seizure. This is the time to collect evidence of a partial onset, in order to implicate structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure are evidence In the ICU patient, several potential seizure etiologies must be investigated. Drugs are a major cause of ICU seizures, especially in the setting of diminished renal or hepatic function, or when the blood-brain barrier is breached. Drug withdrawal is also a frequent offender. While ethanol withdrawal is common, discontinuing any hypnosedative agent may prompt convulsions 1 to 3 days later. A recent report suggests that narcotic withdrawal may produce seizures in the critically ill.[9]

The physical examination should emphasize the areas listed for the postictal examination. Evidence of cardiovascular disease or systemic infection should be sought, and the skin and fundi closely examined.

Illicit drug screening should be performed on patients with unexplained seizures. Cocaine is becoming a major cause of seizures.[23] Electrolytes and serum osmolality should also be measured. However, hypocalcemia rarely causes seizures beyond the neonatal period; its discovery must not end the diagnostic work-up. Hypomagnesemia has an equally unwarranted reputation as the cause of seizures in malnourished alcoholic patients.

The need for imaging studies in these patients has been an area of uncertainty. A prospective study of neurologic complications in medical ICU patients determined that 38 of 61 patients (62%) had a vascular, infectious, or neoplastic explanation for their fits. Hence, CT or MRI should be performed on most ICU patients with new seizures. Hypoglycemia and nonketotic hyperglycemia can produce seizures, and such patients might be treated for metabolic disturbances and observed if they lack other evidence of focal disease. With current technology, there are almost no patients who cannot undergo CT scanning. While MRI is preferable in most situations, the magnetic field precludes infusion pumps and other metallic devices. Whether to administer contrast for a CT depends on the clinical setting and on the appearance of the plain scan.

The EEG is a vital diagnostic tool for the seizure patient. Partial seizures usually have EEG abnormalities that begin in the area of cortex producing the seizures. Primary generalized seizures appear to start over the entire cortex simultaneously. Postictal slowing or depressed amplitude provide clues to the focal etiology of the seizures, and epileptiform activity helps to classify the type of seizure and guide treatment. In patients who do not begin to awaken soon after seizures have apparently been controlled, an emergent EEG is necessary to exclude NCSE.

Considering the etiologies of seizures in the ICU setting, patients who need cerebrospinal fluid (CSF) analysis usually require a CT scan first. When CNS infection is suspected, empiric antibiotic treatment should be started while these studies are being performed.

In contrast to the patient with a single seizure or a few seizures, the SE patient requires concomitant diagnostic and therapeutic efforts. Although 20 min of continuous or recurrent seizure activity usually define SE, one does not stand by waiting for this period to start treatment. Because most seizures stop within 2 to 3 min, it is reasonable to treat after 5 min of continuous seizure activity, or after the second or third seizure occurring without recovery between the spells.

GCSE can rarely be confused with decerebrate posturing, but observation usually makes the distinction straightforward. Tetanus patients are awake during their spasms, and flex their arms rather than extending them as seizure patients do.[18]

Treatment for SE should not be delayed to obtain an EEG. A variety of findings may be present on the EEG, depending on the type of SE and its duration (see Table 4). CPSE patients often lack such organized discharges of GCSE, but instead have waxing and waning rhythmic activity in one or several head regions. A diagnostic trial of an IV benzodiazepine is often necessary to diagnose CPSE. Patients developing refractory SE or having seizures during NMJ blockade require continuous EEG monitoring.

Management Approach

Deciding to administer anticonvulsants to an ICU patient who experiences one seizure or a few seizures requires a provisional etiology, estimation of the recurrence likelihood, and recognition of the

utility and limitations of anticonvulsants. For example, seizures during ethanol withdrawal do not indicate a need for chronic treatment, and giving phenytoin will not prevent more withdrawal convulsions. The patient may need prophylaxis against delirium tremens, but the few seizures themselves seldom require treatment. Patients who experience convulsions during barbiturate or benzodiazepine withdrawal, in contrast, should usually receive short-term treatment with lorazepam to prevent SE. Seizures related to drugs or metabolic disorders should also be treated briefly but not chronically.

The ICU patient with CNS disease who has even one seizure should usually start chronic anticonvulsant therapy, with review of this decision before discharge. Initiating this treatment after the first unprovoked seizure helps prevent subsequent epilepsy.[24] Starting after the first seizure in a critically ill patient at risk for seizure recurrence may be even more important, especially in conditions that would be seriously complicated by a convulsion. In the ICU setting, phenytoin is frequently selected for ease of administration and lack of sedation. The hypotension and arrhythmias that may complicate rapid administration can usually be prevented by slowing the infusion to < 25 mg/min. Because of the rare occurrence of third-degree AV block, an external pacemaker should be available when patients with conduction abnormalities receive IV phenytoin. Fosphenytoin is safer to administer from an extravasation standpoint, but still carries risks of hypotension and arrhythmias. The phenytoin concentration should be kept in the "therapeutic" range of 10 to 20 μg/mL unless further seizures occur; the level may then be increased until signs of toxicity occur. Failure to prevent seizures at a concentration of 25 μg/mL is usually an indication to add phenobarbital.

Phenytoin is usually 90% protein-bound. Patients with renal dysfunction have lower total phenytoin levels at a given dose because the drug is displaced from binding sites, but the unbound level is not affected. Thus, renal failure patients, and perhaps others who are receiving highly protein-bound drugs (which compete for binding), may benefit from free-phenytoin level determination. Only the free fraction is metabolized, so the dose is not altered with changing renal function. The clearance half-time with normal liver function varies from about 12 to 20 h (IV form) to > 24 h (extended-release capsules), so a new steady-state serum concentration occurs in 3 to 6 days. Phenytoin need not be given more frequently than every 12 h. Hepatic dysfunction mandates decreasing the maintenance dose.

Hypersensitivity is the major adverse effect of concern to the intensivist. This may manifest itself solely as fever, but commonly includes rash and eosinophilia. Adverse reactions to phenytoin and other anticonvulsants have been reviewed.[25]

Phenobarbital remains a useful anticonvulsant for those intolerant to phenytoin, or who have persistent seizures after adequate phenytoin. The target for phenobarbital in the ICU should be 20 to 40 μg/mL. Hepatic and renal dysfunction alter phenobarbital metabolism. Because its usual clearance half-time is about 96 h, give maintenance doses of this agent once a day. A steady-state level takes about 3 weeks to be established. Sedation is the major adverse effect; allergy occurs rarely.

Carbamazepine is seldom started in the ICU because its insolubility precludes parenteral formulation. Oral loading in conscious patients may produce coma lasting several days. This drug causes hyponatremia in patients receiving it chronically.

Management Issues in Acute Repetitive (Serial) Seizures

Despite the near-certainty that acute repetitive seizures not meeting a definition of SE must occur more frequently than SE itself, and that many cases of SE emerge from such a state, there has been little study of the issue of treatment. Although the use of IV benzodiazepines has become common in many inpatient settings, the choice of drug and the appropriate dose are uncertain. Many clinicians use IV diazepam, perhaps based more on tradition than pharmacokinetics. The anticonvulsant effect of a single dose of diazepam is very brief (about 20 min), while that of lorazepam is much longer (4 h or longer). Because the risk of serious adverse effects (*eg*, respiratory depression) is potentially greater for diazepam, lorazepam may represent a better choice.[26] If a shorter-acting agent is desired for diagnostic purposes when the diagnosis of a seizure is uncertain, midazolam may be a better choice. The role of other agents, such as intranasal or buccal midazolam or IV valproate, remain to be determined.[27]

Outside of the hospital setting, there is reasonably good evidence that rectal diazepam is effec-

tive and safe in the management of serial seizures, especially in children, at a dose of 0.2 to 0.5 mg/kg, with the dose repeated as necessary according to an age-based protocol.[28]

Management Issues in SE

Once the decision is made to treat the patient for SE, considerations for therapy should proceed on four fronts simultaneously (Table 5): (1) termination of SE; (2) prevention of seizure recurrence once SE is terminated; (3) management of potential precipitating causes for SE; and (4) management of the complications of SE and of underlying conditions.[29]

There is an implicit assumption here that the forms of SE that can produce neuronal damage should be terminated as rapidly as is safely possible. While there is no direct proof of this contention in humans, it appears to be the most reasonable approach.

The intensity of treatment for SE should reflect the risk that the patient experiences from the SE and its etiology. For example, GCSE puts the patient at risk for a panoply of neurologic, cardiac, respiratory,

Table 5. *Suggested Management Protocol for Status Epilepticus*

I. Establish an airway. Whether to perform endotracheal intubation emergently depends primarily on the safety with which the airway can be maintained during the control of SE. Should NMJ blockade be needed, one must assume that the patient is still in SE despite the appearance of relaxation, unless EEG monitoring is available to demonstrate the actual state of brain function. Use a nondepolarizing agent (*eg*, vecuronium).

II. Determine the blood pressure. If the patient is hypotensive, begin volume replacement and/or vasoactive agents as clinically indicated. GCSE patients who present with hypotension will usually require admission to a critical care unit. (Hypertension should not be treated until SE is controlled, as terminating SE will usually substantially correct it, and many of the agents used to terminate SE can produce hypotension).

III. Rapidly determine the blood glucose. Unless the patient is known to be normo- or hyperglycemic, administer dextrose (1 mg/kg) and thiamine (1 mg/kg).

IV. Terminate SE. We recommend the following sequence:
   - A. Lorazepam, 0.1 mg/kg at 0.04 mg/kg/min. This drug should be diluted in an equal volume of the solution being used for IV infusion, as it is quite viscous. Most adult patients who will respond will do so by a total dose of 8 mg. The latency of effect is debated, but lack of response after 5 min should be considered a failure.
   - B. If SE persists after lorazepam, begin phenytoin 20 mg/kg at 0.3 mg/kg/min. If the patient tolerates this infusion rate, it may be increased to a maximum of 50 mg/min. Alternatively, administer fosphenytoin at the same dose, but at a rate of up to 150 mg/min. Hypotension and arrhythmias are the major concern. Many investigators believe that an additional 5-mg/kg dose of phenytoin or fosphenytoin should be administered before advancing to the next line of therapy.
   - C. If SE persists, administer either midazolam or propofol. Midazolam can be given with a loading dose of 0.2 mg/kg, followed by an infusion of 0.1 to 2.0 mg/kg/h to achieve seizure control (as determined by EEG monitoring). Propofol can be given with a loading dose of 1 to 3 mg/kg, followed by an infusion of 1 to 15 mg/kg/h. We routinely intubate patients at this stage if this has not already been accomplished. Patients reaching this stage should be treated in a critical care unit.
   - D. Should the patient not be controlled with propofol or midazolam, administer pentobarbital 12 mg/kg at 0.2 to 0.4 mg/kg/min as tolerated, followed by an infusion of 0.25 to 2.0 mg/kg/h as determined by EEG monitoring (with a goal of seizure suppression). Most patients will require systemic and pulmonary arterial catheterization, with fluid and vasoactive therapy as indicated to maintain blood pressure.
   - E. Ketamine (1 mg/kg, followed by 10 to 50 μg/kg/min) is a potent NMDA antagonist[48] with intrinsic sympathomimetic properties that may be useful in patients who have become refractory to GABA-A agonists.

V. Prevent recurrence of SE. The choice of drugs depends greatly on the etiology of SE and the patient's medical and social situation. In general, patients not previously receiving anticonvulsants whose SE is easily controlled often respond well to chronic treatment with phenytoin or carbamazepine. In contrast, others (*eg*, patients with acute encephalitis) will require two or three anticonvulsants at "toxic" levels (*eg*, phenobarbital at greater than 100 μg/mL) to be weaned from midazolam or pentobarbital, and may still have occasional seizures.

VI. Treat complications.
   - A. Rhabdomyolysis should be treated with a vigorous saline diuresis to prevent acute renal failure; urinary alkalinization may be a useful adjunct.
   - B. Hyperthermia usually remits rapidly after termination of SE. External cooling usually suffices if the core temperature remains elevated. In rare instances, cool peritoneal lavage or extracorporeal blood cooling may be required. High-dose pentobarbital generally produces poikilothermia.
   - C. The treatment of cerebral edema secondary to SE has not been well studied. When substantial edema is present, one should suspect that SE and cerebral edema are both manifestations of the same underlying condition. Hyperventilation and mannitol may be valuable if edema is life-threatening. Edema due to SE is vasogenic, so steroids may be useful as well.

renal, hepatic, and orthopedic disorders, and should be terminated as rapidly one can safely accomplish the task, even if such termination requires the full support of a critical care unit. Typical absence SE, in contrast, probably poses a risk to the patient only if it occurs during a potentially dangerous activity (*eg*, driving an automobile), and initial attempts at its termination probably should not include agents likely to profoundly depress respiration and blood pressure. Treatment of CPSE, in which the risk of neurologic sequelae is considerable, should probably be similar to that recommended for GCSE. Simple partial SE appears to pose less risk to the patient than CPSE, and furthermore, attempts at therapy along the lines recommended for GCSE seldom result in prolonged seizure control. Therefore, therapy for simple partial SE is often pursued with somewhat less vigor that GCSE or CPSE.

The following recommendations were developed for patients in GCSE. There is very limited evidence regarding the optimal therapy for other types of SE. Because of the life-threatening nature of GCSE, and of the risks associated with its treatment, physicians caring for these patients must be constantly vigilant for respiratory and cardiovascular compromise, which may develop abruptly. Thus, neurologists and others caring for these patients should be adept at basic aspects of airway and blood pressure management. During the termination of SE, the patient should be constantly attended by personnel who can effectively perform bag-valve-mask ventilation, and plans for the rapid endotracheal intubation of such patients should be devised before intubation becomes necessary.

Termination of SE: The linchpin of treatment for SE is the rapid, safe termination of ictal activity. Numerous treatment modalities are available for this goal, and until recently there were few data to guide a decision among the various possible choices. The publication of the Veterans' Affairs (VA) cooperative trial allows a much greater degree of rational choice, and raises many new questions for study.[30]

Within the VA trial, patients were divided into the categories of "overt" and "subtle" SE. All patients were believed to have GCSE, which could be either primarily or secondarily generalized; the distinction between overt and subtle depended on the intensity of the clinically viewed convulsive activity. The subtle-SE patients were much more likely to have a serious underlying medical condition, and in general responded poorly to therapy. This discussion will concentrate on the overt-SE patients, because their results underlie the treatment paradigm developed herein.

In the study, 384 patients with overt SE were randomly divided into four treatment arms, which were chosen based on a survey of North American neurologists prior to the study's inception. These arms were (1) lorazepam, 0.1 mg/kg; (2) diazepam, 0.15 mg/kg, followed by phenytoin, 18 mg/kg; (3) phenytoin alone, 18 mg/kg; and (4) phenobarbital, 15 mg/kg. Successful treatment required both clinical and EEG termination of seizures within 20 min of the start of therapy, with noseizure recurrence within 60 min of the start of therapy. Patients in whom the first treatment failed received a second, and if necessary, a third study drug. These latter choices were not randomized, as this would have resulted in some patients receiving two loading doses of phenytoin, but the treating physician remained blinded to the treatments being given.

The overall success rates for patients whose diagnosis of overt SE was confirmed by subsequent review of clinical and EEG data are presented in Table 6. The results for patients with subtle SE are included for reference. Treatment with lorazepam demonstrated a statistically significant advantage over phenytoin ($p = 0.002$); there were no significant differences among the other agents. This differs from the intention-to-treat analysis, which showed similar trends but did not find a statistically significant difference among the treatment arms.

The results of this study may be compared to those of Leppik and colleagues,[31] who found lorazepam to be successful in about 85% of cases. However, this study used only clinical cessation of seizures as the criterion of success; preliminary data from the VA trial indicates that 20% of patients in whom SE appears to have been terminated actually remain in electrographic SE.

Table 6. *Treatment Results for First Agents in the VA Cooperative Study*[30]

Agent	Overt SE Success Rate (%)	Subtle SE Success Rate (%)
Lorazepam	64.9	17.9
Phenobarbital	58.2	24.2
Diazepam/phenytoin	55.8	8.3
Phenytoin alone	43.6	7.7

Preliminary analysis of the results of subsequent treatments in patients who did not respond to the first-line agents indicates that the aggregate response rate to the second-line drug regimen was 7.0%, and to the third-line treatment, 2.3% (Treiman DM; personal communication; 1998). These results call into question the common practice of using three conventional agents (*eg*, lorazepam, phenytoin, and phenobarbital) in the management of SE before using a more definitive approach.

Based on these results and the experience of many workers in the field, we recommend that treatment for GCSE begin with a single dose of lorazepam, 0.1 mg/kg. The limited data available do not suggest that administration of further conventional doses of lorazepam will be useful.[31] The drug should be administered after dilution with an equal volume of the IV solution through which it will be administered. If this fails to control SE within 5 to 7 min, a second agent should be chosen. The results of the VA trial suggest that a second conventional agent is unlikely to be successful. At this time, however, we still recommend the use of phenytoin (or fosphenytoin), 20 mg/kg, as the second drug. This approach carries the advantage that if it is effective, the patient may not require endotracheal intubation and extended critical care. However, it may delay the eventual termination of SE by more definitive treatment.

The introduction of the phenytoin prodrug fosphenytoin as a safer way of rapidly achieving an effective serum phenytoin concentration may prompt some reconsideration of the way in which this drug is used.[32] At its maximal rate of administration (150 mg phenytoin equivalent/min), and its 7-min half-time of conversion to phenytoin, a free-phenytoin level of about 2 μg/mL can be achieved with fosphenytoin in about 15 min, as opposed to about 25 min for phenytoin itself. Whether this greater speed of administration will produce a higher rate of SE control remains to be demonstrated. It is clear that fosphenytoin administration is safer, in that the risk of hypotension may be somewhat less, and the adverse effects of extravasation are nil with the newer drug. The much greater cost of fosphenytoin has discouraged many from using it, although pharmacoeconomic simulations suggest that its use may be cost-effective.[33]

Valproate is available in an IV form; its role in the termination of SE remains to be defined. Experimental data suggest that a serum valproate concentration of 250 μg/mL or greater may be necessary to control secondarily generalized SE.[34] We have limited experience using doses of 60 to 70 mg/kg to obtain such a concentration in patients, and have found the drug effective on occasion in situations where in was necessary to avoid the risks of hypotension and respiratory depression associated with other treatment modalities. However, more information is required before the role of this agent in SE becomes clear.

Patients who continue in SE after lorazepam and phenytoin have traditionally been treated with conventional doses of phenobarbital, but the results of the VA study suggest that this is very unlikely to result in the rapid termination of SE. At this point, we consider SE to be refractory, and go on to one of the more definitive forms of treatment.[35] These treatment modalities are very likely to result in termination of SE, but are also carry higher risks of respiratory depression, hypotension, and secondary complications such as infection. Patients who are to undergo one of these definitive therapies should be in a critical care unit and be endotracheally intubated if this has not yet been accomplished.

Discussion of the entire range of proposed definitive treatments for SE is beyond the scope of this paper. Three categories will be considered: high-dose barbiturates, high-dose benzodiazepines, and propofol.

It is our contention that patients reaching this stage in the treatment of SE should undergo continuous EEG monitoring. The technologic aspects of continuous EEG monitoring have been reviewed elsewhere.[36] What the goal regarding the activity on the EEG should be remains a matter of debate. There is no prospectively collected evidence that a burst-suppression EEG pattern is required for, or is efficacious for, the termination of SE. Many patients can achieve complete seizure control with a background of continuous slow activity, and do not thereby incur the greater risks associated with the higher doses of medication required to achieve a burst-suppression pattern. Conversely, a few patients will continue to have frequent seizures that emerge out of a burst-suppression background, and presumably need even higher doses of medication, which may result in very long periods of suppression or even a "flat" EEG. Without continuous EEG monitoring, one must rely on occasional samples of the EEG, which are thus associated with risks of under- and overtreatment.

Most of the published experience with high-dose barbiturates involves pentobarbital, although some of the earlier investigators used thiopental, and a few reports discuss phenobarbital. There are few data regarding efficacy rates and adverse effects of these drugs. Thiopental is the most rapidly acting of these drugs, but may produce more hypotension. Pentobarbital has emerged as one of the standard choices for refractory SE. A loading dose of 5 to 12 mg/kg is usually given IV, followed by an infusion of the drug at a dose chosen to achieve the desired effect on the EEG; this is usually in the range of 1 to 10 mg/kg/h. We usually increase the infusion rate, along with an additional 3- to 5-mg/kg loading dose, when a seizure occurs; almost all seizures at this stage of treatment are electrographic, probably as a consequence of the medications suppressing clinical seizure activity (twitchless electrical activity), and perhaps also as a consequence of the prolonged duration of SE by the time definitive treatment has commenced. After 12 h free of seizures, the pentobarbital infusion rate is decreased by 50%. If seizures recur, the patient again receives the smaller loading dose, and the infusion rate is raised to obtain another 12-h seizure-free period. Other medications (*eg*, phenytoin) are continued. Many patients reaching this point will require substantial maintenance anticonvulsant treatment in order to be weaned from the pentobarbital; we commonly maintain the serum phenytoin concentration in excess of 20 μg/mL, and load with phenobarbital to achieve a concentration in excess of 40 μg/mL (often, 100 μg/mL or an even higher concentration is required to successfully wean severely refractory patients, such as those with encephalitis, from their pentobarbital infusions). High doses of barbiturates are potently immunosuppressive, indicating extra care to avoid nosocomial infection and aggressive treatment if infection is suspected.

High-dose benzodiazepine strategies for SE usually employ either midazolam or lorazepam. Midazolam has the advantages of rapid onset of activity and greater water solubility, avoiding the problem of metabolic acidosis from the propylene glycol vehicle of the other benzodiazepines and the barbiturates. Its major disadvantage is tachyphylaxis; over 24 to 48 h, the dose of the drug must often be increased several-fold in order to maintain seizure control. A loading dose of 0.2 mg/kg is followed by an infusion of 0.1 to 2.0 mg/kg/h, titrated to produce seizure suppression by continuous EEG monitoring.[37] High-dose lorazepam, used in doses of up to 9 mg/h, was the subject of a report by Labar and colleagues.[38]

Propofol is a pharmacologically unique GABA-A agonist that may also have other mechanisms of anticonvulsant action. Soon after its introduction as a general anesthetic agent, concerns about a potential proconvulsant effect arose; this apparently represented myoclonus rather than seizure activity. At the doses used to control SE, it has a very potent anticonvulsant action. A loading dose of 3 to 5 mg/kg is frequently administered, followed by an infusion of 1 to 15 mg/kg/h,[39] titrated to EEG seizure suppression. After 12 h of seizure suppression, we taper the dose as outlined above for pentobarbital. There is evidence that rapid discontinuation of propofol can induce withdrawal seizures.

In our experience, propofol is more likely than midazolam to provide rapid control of refractory SE, exhibits less tachyphylaxis than midazolam, and produces less hypotension than pentobarbital for an equivalent degree of seizure control.[40] However, a recent retrospective analysis of our patients suggests that those with APACHE (acute physiology and chronic health evaluation) II scores > 20 may have better survival when treatment is started with midazolam.[41] There are few data addressing the immunosuppressive effects of the benzodiazepines or propofol[42]; clinically, these drugs appear associated with fewer nosocomial infections than high-dose pentobarbital. Although it is difficult to determine functionally equivalent doses of these agents because of differing rates of tachyphylaxis, in our institution the patient charge for midazolam appears to be about 10 times that for pentobarbital, and propofol about 2.5 times that for pentobarbital.

Many other agents have been employed for the control of refractory SE.[43] The information above represents a distillation of our experience; the available published data are inadequate to support more definite treatment recommendations.

Prevention of Seizure Recurrence Once SE Is Terminated: Once SE is controlled, attention turns to preventing its recurrence. The best regimen for an individual patient will depend on the cause of the patient's seizures and any previous history of anticonvulsant therapy. For example, a patient developing SE in the course of ethanol withdrawal may not need anticonvulsant therapy once the withdrawal phenomena have run their course. SE following changes in a previously effective anticon-

vulsant regimen will often mandate a return to the former successful mode of treatment. In contrast, patients with a new, ongoing epileptogenic stimulus (*eg*, encephalitis) may require extraordinarily high serum concentrations of anticonvulsant drugs to control their seizures as therapy for refractory SE is decreased.

Management of the Complications of SE and of Underlying Conditions: The major systemic complications of GCSE include rhabdomyolysis and hyperthermia. Patients presenting with GCSE should be screened at presentation for myoglobinuria (most effectively by a dipstick evaluation of the urine for occult blood; the reagent will react with myoglobin as well as hemoglobin, and if the reaction is present, a microscopic examination will determine whether red blood cells are present) and elevation of serum creatine kinase (CK). If myoglobinuria is present, or if the CK concentration is > 10 times the upper limit of normal, one should consider instituting a saline diuresis as well as urinary alkalinization.

If the patient's core temperature exceeds 40°C, the patient should be cooled. The techniques available for managing hyperthermic patients have been reviewed elsewhere.[44]

Cerebral edema may complicate SE. Vasogenic edema may develop as a consequence of the seizures themselves, and the underlying cause of SE may also produce either vasogenic or cytotoxic edema. The management of secondary cerebral edema with increased intracranial pressure (ICP) depends on the etiology; edema due solely to seizures rarely causes problems with ICP.

Prognosis

Wijdicks and Sharbrough[6] report that 34% of patients experiencing a seizure died during that hospitalization. Our prospective study of neurologic complications in medical ICU patients found that having even one seizure if in the unit for a nonneurologic reason doubled in-hospital mortality.[7] This effect on prognosis primarily reflected the etiology of the seizure.

Three major factors determine outcome in SE: the type of SE, its etiology, and its duration. GCSE has the worst prognosis for neurologic recovery; in contrast, myoclonic SE that follows an anoxic episode carries a very poor prognosis for survival. CPSE can produce limbic system damage, usually manifested as a memory disturbance. Most studies of outcome concentrate on GCSE mortality. Hauser,[8] summarizing data available in 1990, suggested that mortality rates vary from 1 to 53%. Those studies attempting to distinguish mortality due to SE from that of the underlying disease have attributed mortality rates of 1 to 7% to SE and 2 to 25% to its cause. Population-based studies in Richmond, VA showed the mortality of SE lasting > 1 h was increased 10-fold over SE lasting < 1 h. Etiologies associated with increased mortality included anoxia, intracranial hemorrhages, tumors, infections, and trauma.

Limited data are available concerning the functional abilities of GCSE survivors, and none reliably permit a distinction between the effects of SE and of its etiologies. One review concluded that intellectual ability declined as a consequence of SE.[45] Survivors of SE frequently seem to have memory and behavioral disorders out of proportion to structural damage produced by the etiology of their seizures. A wealth of experimental data support this observation, arguing strongly for rapid and effective control of SE. Case reports of severe memory deficits following prolonged CPSE have also been published.[46] Whether treatment of SE reduces the risk of subsequent epilepsy remains uncertain. Recent experimental studies indicate that SE lowers the threshold for subsequent seizures.[47]

Subarachnoid Hemorrhage

The management of patients with acute aneurysmal subarachnoid hemorrhage (SAH) has changed substantially in the past two decades. Previously, patients were typically put on bed rest for 2 weeks, until the periods of maximal risk for rebleeding and vasospasm had passed; if they survived, they were then given the option of surgical treatment. Current management strategies recognize (1) improvements in surgical technique that make early, definitive obliteration of the aneurysm more feasible and safer; (2) the consequent ability to use induced hypertension and hypervolemia to treat cerebral vasospasm; (3) the introduction of nitrendipine-class calcium channel blockers to relieve or ameliorate the effects of vasospasm; (4) the development of interventional neuroradiologic techniques (*eg*, angioplasty and intra-arterial papaverine infusion) to treat symptomatic vasospasm; (5) the use of ventricular drainage to treat communicating hydrocephalus; and (6) the introduction in several

countries, although not in North America, of a free-radical scavenger that appears to improve outcome in patients who present with high-grade SAH.

Future directions in the medical management of patients following SAH will probably depend primarily on the ability to recognize and manage cerebral vasospasm before it becomes symptomatic and before it produces cerebral infarction.

Epidemiology

The principal medical complications of aneurysmal SAH include rebleeding, cerebral vasospasm, and volume and osmolar disturbances. The risk of rebleeding from unsecured aneurysms varies with time after the initial hemorrhage: about 4% on the first postbleed day and about 1.5% per day up to day 28.[49] The mortality associated with rebleeding after the diagnosis of SAH exceeds 75%.[50] This complication is more frequent in patients with higher grades of SAH, in women, and in those with systolic blood pressures exceeding 170 mm Hg.[51] Cerebral vasospasm produces symptoms in up to 45% of patients,[52] but is noted angiographically in another 25% who appear asymptomatic.[53] Vasospasm usually starts to occur between postbleed days 4 and 6; the risk of its development is minimal after day 14. Volume and osmolar disturbances are reported in about 30% of patients.[54]

A number of other complications occur in this group of patients that are less directly related to the SAH itself.[52] Life-threatening cardiac arrhythmias are found 5%, with less ominous rhythm disturbances in 30%. Pulmonary edema is diagnosed in 23%, with 6% experiencing a severe form. Some degree of hepatic dysfunction is noted in 24% of patients, predominantly mild elevation of transaminase levels without symptoms; 4% experience severe hepatic dysfunction. Many of these patients are probably manifesting hepatic toxicity from anticonvulsants or other medications. Thrombocytopenia is reported in 4% of patients, usually related to sepsis or medications. Renal dysfunction is seen in 7%, but rarely requires dialysis.

Although this paper deals primarily with aneurysmal SAH, there are other causes of SAH, and their epidemiology is different. SAH following rupture of an arteriovenous malformation tends to occur at a younger age, with a peak incidence in the mid-20s. Traumatic SAH is a common accompaniment of severe head trauma, occurring in 15 to 40% of patients with severe head trauma. The incidence of the major complications of SAH in these patients appears to be lower than in patients with aneurysmal SAH, but data are scarce. After arteriovenous malformation rupture, the time course of angiographically diagnosable vasospasm is similar to that seen in aneurysmal SAH patients; it is usually asymptomatic,[55] except in rare cases.[56] The significance of vasospasm related to traumatic SAH continues to be debated, but in one series, 7 of 29 patients with large amounts of subarachnoid blood (detected by CT scanning) developed symptomatic vasospasm (detected angiographically) with subsequent infarction.[57] In patients with penetrating head trauma, the incidence (detected by transcranial Doppler [TCD] flow velocity measurements) may be as high as 40%.[58]

Pathophysiology

Rebleeding: Rebleeding of an aneurysm prior to its obliteration presumably reflects further leakage of blood at the site of the initial rupture. The tendency for this to occur appears to increase with arterial hypertension, which increases the stress on the aneurysm wall and the clot that occludes the original rupture site. Lowering the pressure in the subarachnoid space (*eg*, by lumbar puncture, or by allowing a ventriculostomy system to have a low pop-off pressure) similarly increases the pressure gradient across the aneurysm wall. Whether these procedures actually increase the risk of rebleeding is uncertain, and this theoretical concern does not militate against performing diagnostic lumbar punctures if needed either to prove the diagnosis of SAH or to exclude meningitis. Systemic factors that alter the balance between thrombosis and fibrinolysis (*eg*, disseminated intravascular coagulation) would presumably affect the risk of rebleeding as well.

Cerebral Vasospasm: Vasospasm appears to be a two-stage process, with an initial vasoconstrictive phase followed by a proliferative arteriopathy, associated with smooth-muscle-cell necrosis and fibrosis of the arterial wall.[59,60] Vasospasm appears to depend primarily on the presence of erythrocytes in the subarachnoid space,[61] but why it occurs more frequently and more symptomatically after aneurysmal SAH than after SAH due to other causes remains unexplained. The list of potential mediators contributing to the development of

vasospasm is substantial, but the vasoconstrictor peptide endothelin-1 appears to be one of the most important.[62] Endothelin antagonists are promising experimental agents for the prevention and treatment of this condition.[63]

The maximal risk for vasospasm occurs from day 4 through day 14 after SAH, although about 10% of patients may have some angiographic signs of vasospasm at the time of the initial angiogram.[64]

The risk of developing vasospasm is related to the amount of blood in the subarachnoid space. Fisher and colleagues[65] reported that patients with thick subarachnoid clots were much more likely to develop vasospasm than those without such clots. Antifibrinolytic agents (*eg*, ε-aminocaproic acid, tranexamic acid) used to prevent rebleeding raise the risk of symptomatic vasospasm and delayed ischemic deficits,[66] but whether there is an actual increase in the rate of vasospasm, or an increase in the rate of occlusion of already spastic vessels, is uncertain.

Hyperglycemia probably worsens outcome in stroke patients,[67] and therefore presumably in SAH patients developing delayed ischemia. Plasma glucose concentrations exceeding 120 mg / dL in the first postbleed week are associated with poor outcome.[68] All of these studies suffer from the confounding effect of severity of illness on intrinsic plasma glucose regulation, but they do suggest that maintenance of normoglycemia is a reasonable goal.

Volume and Osmolar Disturbances: Although earlier studies attributed the hyponatremia and hypo-osmolality occurring after SAH to the syndrome of inappropriate antidiuretic hormone secretion (SIADH),[69] most investigators now believe that these disturbances are the result of cerebral salt wasting.[70] The pathophysiology of this condition remains to be completely elucidated, but probably begins with the release of atrial, brain, and C-type natriuretic factors from the brain.[71] These peptides produce isotonic volume loss by their renal effects, resulting in hypovolemia. This hypovolemic state then prompts an appropriate antidiuretic hormone response, causing a fall in free water clearance and thereby producing hyponatremia and hypo-osmolality. Hypovolemia appears to increase the risk of cerebral infarction (delayed ischemic deficits) in patients with vasospasm, and should therefore be prevented with prophylactic volume replacement.[72]

Physical signs of hypovolemia are rare in SAH patients, who are usually kept flat in bed, and in whom a putative increase in adrenal catecholamine secretion and increased sympathetic nervous system activity often produce hypertension. Overly vigorous treatment of this hypertension after the aneurysm is secured appears to worsen outcome.[73]

Seizures: Following SAH, patients may experience any of four patterns of seizures. About 6% of patients appear to suffer a seizure at the time of the hemorrhage,[74] although the distinction between a generalized convulsion and an episode of decerebrate posturing may be difficult to establish from the reports of nonmedical observers. Postoperative seizures occur in about 1.5% of SAH patients despite anticonvulsant prophylaxis (usually phenytoin).[75] Patients developing delayed ischemia from vasospasm may seize following reperfusion by angioplasty.[76] Late seizures occur in about 3% of patients over several years of follow-up.[75]

SAH patients are somewhat more likely to have a seizure at the time of presentation than are patients with other types of stroke.[77]

The mechanisms producing seizures in SAH patients are uncertain. Patients in whom aneurysmal rupture produces a concomitant intracerebral hematoma probably have a direct epileptogenic stimulus. Irritation from the aneurysm clipping appears to account for some postoperative seizures. Reperfusion injury accounts for a small percentage.[76] Late seizures may reflect the epileptogenic effects of iron on the cerebral cortex.[78]

Cardiovascular Complications: Cardiac arrhythmias and ECG signs of ischemia are frequent in SAH patients.[79] In one series, all 61 patients had at least one such abnormal finding.[80] The most serious of such problems is the development of ventricular tachycardia, typically of the *torsades de pointes* form.[81]

ECG changes resembling acute myocardial infarction, and elevation of the MB isoenzyme of CK (and, by inference, elevation of troponins) occur without evidence of coronary arterial occlusion. About 10% of patients will have an ECG suggesting acute myocardial infarction during the first 3 days post-SAH.[82] In one study, elevation of CK was associated with left ventricular wall motion abnormalities.[83] Histopathologically, these findings correspond to myocardial contraction band necrosis, which resembles the cardiomyopathic changes associated with pheochromocytomas.

Pulmonary edema occurring in SAH patients may be either cardiogenic or noncardiogenic in

origin. Some patients have echocardiographic evidence of left ventricular dysfunction at the time their pulmonary edema is severe.[84] However, the majority of SAH patients have a defect in pulmonary gas exchange in the absence of evidence of cardiac dysfunction or aspiration, suggesting that neurogenic pulmonary edema is responsible.[85] This probably occurs as the consequence of a neurally mediated increase in extravascular lung water.[86]

CNS Infection: Excepting cases of ruptured mycotic aneurysms, CNS infections in SAH patients are almost always iatrogenic, either from organisms introduced during aneurysm clipping or, much more commonly, from ventriculostomy systems that become colonized with bacteria.

Other Infectious Complications: The non-CNS infectious complications of SAH patients vary with the severity of their illness. Patients remaining in Hunt and Hess grades 1 and 2 do not seem to be at particular risk for aspiration and may not need urinary catheters, feeding tubes, or central venous lines, which are the proximate causes of many ICU infections. Higher-grade patients are susceptible to the typical infectious complications of critical care. The contribution of corticosteroids in decreasing resistance to infection in these patients is unquantified. SAH patients in the trials of tirilazad mesylate,[87] a steroid free-radical scavenger without glucocorticoid effects, were not given glucocorticoids either before or after procedures to secure their aneurysms; they did not appear to suffer ICP problems. Although this question has not been formally tested, it raises the possibility that routine dexamethasone administration may not be necessary in this population. Withholding this agent would be expected to decrease both infectious and metabolic complications in these patients.

Higher-grade patients may need feeding tubes for nutritional support, or larger-bore gastric tubes should an ileus develop. Placing these tubes via the nasal route appears to increase the risk of nosocomial sinusitis, and probably of pneumonia as well.[88]

Deep Venous Thrombosis and Pulmonary Embolism: SAH patients are at risk for the development of deep venous thromboses and subsequent pulmonary embolism by virtue of immobilization. Whether the use of antifibrinolytic agents increases the risk of deep venous thrombosis has long been debated; the use of these agents for 2 weeks in patients undergoing late aneurysm surgery probably does increase these risks.[89] Brief use of these agents to decrease the risk of rebleeding prior to early surgery probably carries a lower risk.[90] Although the concentration of circulating fibrinogen complexes is increased in SAH patients (and other stroke patients) compared with controls,[91] the role of this finding in the genesis of venous thrombosis remains speculative.

Nutrition

Although standard critical care practice emphasizes the early institution of nutritional support to maintain muscle mass and gut integrity, the importance of nutritional support for SAH patients remains unproven. Starvation prior to experimental ischemia may result in a shift to the metabolism of fuels other than glucose, even in the brain, and potentially result in an improved outcome after delayed ischemia.[92] However, the balance between risks and benefits of this approach remains to be established. SAH patients are markedly catabolic, and may have a defect in the utilization of amino acids[93]; the mechanism of this defect is unknown.

Management

The higher-grade SAH patient may require all of the skills a critical care team can muster. The sickest of these patients can still attain a good functional outcome despite what appear to be overwhelming difficulties. Thus, attention to all of the details of care in these patients is essential. Guidelines for the care of SAH patients have recently been published by the American Heart Association[94] and the Canadian Neurosurgical Society.[95]

Rebleeding: Although aneurysm obliteration is the most important method of preventing rebleeding, antihypertensive drugs and antifibrinolytic agents may be valuable prior to surgery or interventional radiologic approaches. Preoperative blood pressures are typically elevated; we strive to maintain systolic pressures below 150 mm Hg and mean arterial pressures below 100 mm Hg in these patients. Nimodipine, which is used to try to prevent delayed ischemic deficits (see below), often lowers the blood pressure to a modest degree. Labetolol (see Table 7), which has both α- and β-adrenergic blocking effects when given IV, is commonly the first drug employed for blood pressure control. Hydralazine is also commonly used, although there is a theoretical concern about the use of pure vaso-

dilators in preoperative SAH patients (increasing pulse pressure may increase stress on the aneurysm wall). Enalaprilat may be useful for patients who do not respond to these agents. We tend to avoid nitrates because of the potential for increased ICP, but rarely nitroprusside may be the only effective drug. Pain relief with acetaminophen, codeine, or fentanyl is often necessary, and is frequently helpful in lowering blood pressure as well.

Postoperatively, the blood pressure may be allowed to rise to higher levels. Patients at risk for vasospasm may require higher blood pressures for adequate cerebral perfusion. In patients with more than one aneurysm, the risk of producing a new SAH from a previously unruptured aneurysm appears to be small (but not absent[96]) during the first few postbleed weeks.

Cerebral Vasospasm: Delayed ischemic deficits from vasospasm have emerged as the major cause of morbidity and mortality in patients undergoing early aneurysm obliteration. Management approaches attempt to prevent both spasm and its consequences, although it is not clear that any of the currently used techniques actually prevent vasospasm. Rather, most attempt to preserve either perfusion or neuronal survival in areas affected by vasospasm.

Vasospasm is definitively diagnosed angiographically, although spasm in vessels below the resolution of angiography probably occurs in patients whose symptoms suggest vasospasm. The initial symptom of vasospasm is typically decreased interaction with the unit staff and the patient's family and visitors. The patient may then progress to an abulic state, or appear to have bilateral frontal lobe dysfunction. The etiology of these symptoms is uncertain, as they do not appear to depend on the location of the aneurysm, the localization of subarachnoid blood, or the development of complications such as hydrocephalus. At this point, the TCD velocity measurements are usually elevated (*eg*, mean velocities > 120 cm/s). Xenon-CT blood flow studies suggest that TCD may underestimate the incidence and severity of vasospasm.[97] Lateralized motor findings suggest the development of delayed ischemic lesions.

Nimodipine, a voltage-sensitive calcium channel blocker, was introduced with the expectation that it would prevent vasospasm. Angiographic studies did not confirm this effect, at least in vessels visible by radiologic techniques, but clinical trials did confirm its utility in improving outcome.[98] Nicardipine, a related agent, does appear to decrease angiographically diagnosed vasospasm.[99] The outcome of patients treated with nicardipine did not differ statistically from that in patients receiving placebo, but the placebo patients received rescue hypertensive-hypervolemic therapy (HHT; see below) more frequently.

Volume replacement and expansion, usually practiced by attempts to maintain either a fixed, relatively high saline solution intake (*eg*, 3 to 6 L/d of normal or mildly hypertonic saline solution) or a positive fluid balance, is relatively standard in centers caring for SAH patients. While this usually prevents volume contraction due to cerebral salt wasting, it is unlikely that it prevents vasospasm *per se*. However, it appears to be very useful in preventing or decreasing the extent of symptomatic vasospasm and delayed ischemic deficits.

The free-radical scavenger tirilazad may be effective in improving outcome in SAH patients, primarily those in higher grades. A European-Australian trial showed efficacy at a dose of 6 mg/kg/d

Table 7. *Selected Drugs Useful in the Management of SAH Patients*

Agent	Dose	Comments
Enalaprilat	0.625 to 1.25 mg q6h	May decrease renal plasma flow and raise creatinine
Esmolol	250 to 500 μg/kg, then 50 to 200 μg/kg/min	May produce congestive heart failure
Hydralazine	10 to 20 mg q3-4h	Theoretical risk of increasing shear forces
Labetolol	10 mg q10min, up to 300 mg	Oral form lacks significant β-adrenergic blocking effect
Nicardipine	0.075 to 0.15 mg/kg/h	May produce congestive heart failure
Nimodipine	60 mg q4h for 14 to 21 days	Duration of therapy uncertain
Nitroprusside	0.25 to 10 μg/kg/min	Rarely necessary
Phenytoin	15 to 20 mg/kg loading dose, then 5 to 8 mg/kg/day maintenance (q12h for suspension, q24h for Dilantin* capsules	Duration of therapy uncertain; maintain serum concentration between 10 and 20 μg/mL. Hold tube feeding 1 h before and after dose.

*Dilantin; Parke-Davis; Morris Plains, NJ.

only in men,[100] presumably because the drug is more rapidly metabolized in women. A parallel North American trial did not achieve a statistically significant result.[87] This appears at least in part to reflect a higher percentage of North American patients receiving phenytoin, which accelerates the metabolism of tirilazad.[101] Higher-dose trials have been concluded, but the results have not yet been published. This agent has been licensed for SAH in men in 13 countries. The drug has poor blood-brain barrier penetration; more lipophilic derivatives have been synthesized,[102] and await clinical trials.

Treatment for Vasospasm: Two approaches are currently used for the management of vasospasm. The first is volume expansion, usually accompanied by induced hypertension (by means of HHT).[103] Although some consider hemodilution (to hemoglobin concentrations between 10 and 11 *g*/dL) to be part of this treatment as well, in the hope that decreasing blood viscosity will improve perfusion, this is the least consistently practiced part of this approach. HHT has not been subjected to a randomized clinical trial, and substantial debate persists regarding its utility.[104,105] If it is to be employed, careful patient monitoring is necessary, involving an arterial line and either a central venous line or, preferably, a pulmonary artery catheter to guide vasopressor and volume management. Angiographic confirmation of the diagnosis of vasospasm is usually obtained before instituting vasopressor therapy.

Because SAH patients appear to have low thresholds for the development of hydrostatic pulmonary edema, we try to maintain the pulmonary capillary wedge pressure (PCWP) between 15 and 18 mm Hg. In some patients, this volume expansion alone is adequate to produce an increase in cardiac index and mean arterial pressure. What mixture of colloid and crystalloid to use for volume expansion in this setting is the subject of endless debate and absent data. If the patient's examination does not improve, we next raise the mean arterial pressure using phenylephrine, dopamine, norepinephrine, epinephrine, or a combination of phenylephrine and dobutamine, as suggested by the patient's heart rate, the cardiac index produced, and evidence of ectopy, cardiac ischemia, or renal dysfunction. None of these medications has a proven advantage over the others in this setting, and each case provides individual challenges. Hypertensive encephalopathy can apparently complicate overly vigorous therapy.[106]

The second approach to vasospasm patient management involves interventional radiologic techniques, either angioplasty or papaverine infusion.[107] We use both hemodynamic and radiologic techniques. Intraventricular infusion of nitroprusside may be useful in the future.[108]

Volume and Osmolar Disturbances: Volume deficits are prevented or corrected as discussed above. If SAH patients receive adequate saline solution replacement, hypo-osmolality is an infrequent occurrence.

Evaluation of the SAH patient whose laboratory results indicate a low serum sodium concentration requires both clinical and laboratory evaluation. Prior to intervention, serum and urine osmolality measurements should be obtained. This will prevent the inadvertent treatment of the patient for hypo-osmolality when the real problem is, for example, a factitious hyponatremia due to hyperglycemia or pseudohyponatremia from hyperlipidemia. Truly hypo-osmolar SAH patients require careful thought, rather than just salt administration. Unless the patient has developed pulmonary edema or other signs suggesting congestive heart failure, one should not assume that hyponatremia is due to combined salt and water excess. The likely occurrence of cerebral salt wasting favors a diagnosis of salt loss with water retention. Osmolality measurements will usually indicate that the patient's urine is inappropriately concentrated for a patient with hypotonic serum. While this combination may suggest SIADH in many circumstances, this condition should rarely be diagnosed during the first 2 weeks postbleed. Attempts to treat the patient with volume restriction will likely lead to greater problems with delayed ischemic deficits. One potentially useful biochemical assay is the serum uric acid level, which tends to be low in SIADH but normal in cerebral salt wasting.

Management of hypo-osmolar states depends critically on their rate of development.[109] Rapidly developing (*eg*, over hours) hypo-osmolality produces neuronal swelling, and is associated with elevated ICP and seizures. More slowly developing (over days) hypo-osmolality is accompanied by solute shifts out of neurons, which prevent ICP increases and are unlikely to produce seizures; the patient may become confused, lethargic, and weak, but seldom experiences any life-threatening complications from the osmolality itself. However, these are the patients at risk for central and extrapontine myelinolysis if their osmolalities are raised too rapidly.

Patients who became rapidly hypo-osmolar may be treated with small doses of hypertonic saline solution (*eg*, 100 mL of 3N) to begin correcting this problem. They usually respond quickly with lower ICP and resolution of seizures. Those who became hypo-osmolar more slowly must be corrected more slowly; a goal of 6 milliosmols/L/day increases appears safe. Because these patients should not be allowed to become volume-depleted, this is best performed by replacement of their urine output and insensible loss by mildly hypertonic solutions, or, in patients receiving enteral feeding, addition of salt to their food. Attempts to decrease the urine osmolality with loop diuretics are seldom sufficiently successful to be useful.

Cardiovascular Complications: Prevention of electrolyte disturbances and magnesium replacement are probably useful for the prevention of arrhythmias. α- and β-adrenergic blockade may decrease or prevent myocardial contraction band necrosis, but this has not been tested.

Cardiac arrhythmias in SAH are seldom life-threatening. Sinus tachycardia and other supraventricular tachycardias should lead to a reassessment of electrolytes, volume status, pain control, infection, and endocrine (especially thyroid) function. Depending on the arrhythmia and its hemodynamic consequences, treatment with adenosine, calcium antagonists, β-blocking agents, or digoxin may be indicated. Ventricular arrhythmias frequently reflect adrenergic drug administration (*eg*, dopamine) or electrolyte disorders; alternatively, they may represent signs of myocardial ischemia. If possible, dopamine-induced rhythm disorders indicate switching to another agent. Lidocaine or procainamide may be required if runs of ventricular tachycardia appear. *Torsades de pointes* may respond to supplemental magnesium, or may require overdrive pacing.

SAH patients with heart failure who develop signs suggesting vasospasm will usually require pulmonary artery catheterization for volume and hemodynamic management.

CNS Infection: Infection is a major problem for SAH patients, because fever may increase the degree of damage produced by delayed ischemia. Another problem is the diagnosis of the etiology of fever in these patients. A preliminary analysis in our unit suggests that about 20% of SAH patients experience fever without evidence of infection on retrospective review, suggesting that they have developed "central fever."[110] These patients frequently receive antibiotics, putting them at risk for drug reactions and increasing expense, because it is difficult to prove that they do not have an infection. Drug-induced fevers are a major problem in all ICU patients, and SAH patients are no exception. Commonly implicated drugs include phenytoin, antibiotics, and, less frequently, agents such as histamine$_2$-antagonists and stool softeners.

Whether patients with ventriculostomies or lumbar drains should receive antibiotic prophylaxis is an open question. If prophylaxis is to be given, a cephalosporin with activity against *Staphylococcus aureus* (*eg*, cefazolin) is probably the most reasonable choice. Activity against coagulase-negative staphylococci does not seem important; nor do the brain or CSF penetration characteristics of the drug. A risk-benefit analysis suggests that ventriculostomy catheters probably should be changed every 5 days.[111]

Treatment of ventriculostomy infections should be based initially on a Gram stain of CSF. If staphylococcal infection is suspected, initial treatment with vancomycin is appropriate pending culture and sensitivity results. Patients with Gram-negative rods in the CSF should receive either a cephalosporin with antipseudomonal activity (*eg*, cefepime) or meropenem until microbiologic results are available. If the CSF contains increasing numbers of white cells but the Gram stain is negative, a combination of vancomycin and either meropenem or cefepime seems reasonable, although some of these patients will have an aseptic postoperative meningitis.

Other Infectious Complications: The question of routine changes of central venous catheters and pulmonary artery catheters is beyond the scope of this discussion. Whatever local practices control these policies for other critically ill patients should apply to SAH patients.

We attempt to place all tracheal and gastric tubes through the mouth, rather than the nose, to decrease the incidence of sinusitis[112] (see above).

Seizures: Because seizures in patients with unsecured aneurysms may promote rebleeding, it is a common, although by no means universal, practice to administer anticonvulsants to SAH patients.

The standard agent for prophylaxis in North America is phenytoin. Fosphenytoin, a water-soluble prodrug, is safer to administer IV, and may be given IM if necessary. An adequate loading dose should be given.

Should seizures occur in an SAH patient, one should obtain a CT scan to look for new intracranial pathology. At the same time, one should give an additional dose of phenytoin to raise the serum concentration. If seizures recur, and the phenytoin has been pushed to the point of symptomatic toxicity (in the responsive patient) or a level of about 24 μg/mL (in patients with impaired ability to respond), adding either phenobarbital or carbamazepine have been standard approaches. The recent introductions of gabapentin and an IV form of valproate increase the number of therapeutic options. This choice must be individualized.

Phenytoin is frequently implicated as a cause of drug-induced fever. When a rash and fever appear in a patient taking this drug, it is typically discontinued. Because of its long half-life, several days will elapse before it is cleared from the patient. Substitution of another anticonvulsant (*eg*, gabapentin) without sedative effects and without cross-sensitivity is a reasonable approach. Suspected allergy is the only circumstance in which most anticonvulsants should be stopped abruptly.

Deep Venous Thrombosis and Pulmonary Embolism: Before securing the aneurysm, many physicians are reluctant to give prophylactic doses of heparin, and instead rely on sequential compression devices to prevent deep venous thrombosis. These devices are effective in many circumstances, but have not been formally tested in SAH patients. Interestingly, sequential compression devices accelerate *in vitro* measurements of fibrinolysis,[113] and part of their effectiveness probably stems from this mechanism. We continue to use these devices for prophylaxis in bed-bound patients after the aneurysm has been secured.

Deep venous thrombosis or pulmonary embolism in patients with either unsecured aneurysms or fresh craniotomies pose difficult management problems. Our approach is usually to place an inferior vena cava filter, and not to give anticoagulant therapy until at least 1 week after surgery. The filter is generally held to be safer than immediate anticoagulation.[114]

Nutrition and GI Bleeding Prophylaxis: Despite strongly held opinions, there are few data on which to base recommendations for nutrition in SAH patients. In view of the likely deleterious effect of hyperglycemia on outcome after delayed ischemia, whatever nutritional approach is taken should include frequent measurements of blood glucose, and probably its tight control. So-called "trophic" feeding, in which a small volume (*eg*, 5 mL/h) of an enteral nutrition formula is constantly infused via a gastric or jejeunal feeding tube, may maintain the structure of the intestinal villi and help to prevent both bacterial translocation and the subsequent incidence of diarrhea when full feedings are instituted.

If patients are npo, some form of prophylaxis against GI bleeding seems reasonable. Clinically important GI bleeding occurs in up to 6% of SAH patients.[115] Histamine$_2$-blocking agents such as ranitidine or nizatidine are commonly used. These agents are occasionally associated with neutropenia or thromobocytopenia; in this circumstance, sucralfate or omeprazole may be substituted. The use of nonsteroidal anti-inflammatory agents appears to increase the risk of GI bleeding; we routinely administer misoprostol with these agents. Once patients are fully fed, these prophylactic agents may no longer be necessary.

When feedings begin, patients frequently develop diarrhea. Because a large percentage of patients are receiving antibiotics, the possibility of antibiotic-induced *Clostridium difficile* infection must be considered. After sending specimens for fecal leukocyte, cytotoxin, and *C difficile* cultures, we use kaolin and pectin to attempt to decrease the diarrhea. Some patients appear to have diarrhea induced by sorbitol, used in many solutions of drugs for tube administration.

Stroke

Stroke is the most common neurologic cause for hospital admission in the United States. About 80% of strokes are ischemic, with the remainder divided between intracerebral hemorrhage and SAH. The incidence of stroke is declining, coincident with and probably in part reflecting improvement in the treatment of hypertension. The association of stroke with hypertension, particularly intracerebral hemorrhage, has been slightly overstated in the past (blood pressures were often measured when the patient presented with the stroke, rather than seeking a documented history of hypertension; the same is true of many studies of hyperglycemia in stroke). Other risk factors include diabetes, cardiac disease, previous cerebrovascular disease (transient ischemic attack or stroke), age, sex, lipid disorders, excessive ethanol ingestion, elevated hematocrit,

elevated fibrinogen, and cigarette smoking. Smoking is the most powerful risk factor for aneurysmal SAH. In younger patients (usually defined as those < 55 years old), one should consider abnormalities of antithrombin III, protein S, protein C, or antiphospholipid antibodies. Young stroke patients with marfanoid habitus should be worked up for homocysteinuria; the heterozygous state is associated with stroke, and many patients respond to pyridoxine treatment.

The intensivist most commonly encounters potential stroke patients in the settings of (1) suspected carotid artery disease, and (2) cardiac disturbances that are potentially emboligenic. Patients with *asymptomatic* carotid bruits have approximately a 2% annual risk of stroke, but the side of the bruit does not predict the side of the stroke. There are no data on which to base the selection of patients for further work-up. I tend to start an aspirin regimen (80 to 325 mg / d) in these people, but not investigate them further. If studies (noninvasive or angiographic) have already been obtained, I would *consider* endarterectomy for *otherwise healthy* patients who have > 70% stenosis or a large area of ulceration. The common practice of "prophylactic" endarterectomy before other vascular surgical procedures lacks validation; from the poor data available, the risk of stroke related to such procedures does not seem to exceed the risks related to endarterectomy itself. The results of the Asymptomatic Carotid Artery Stenosis (ACAS) trial suggest that men with asymptomatic carotid stenosis of > 70% derive greater benefit from carotid endarteractomy than from medical therapy alone. Endarterectomy of the vertebral arteries and angioplasty of any cerebral vessel remain experimental techniques.

About 30% of untreated patients with new-onset transient ischemic attacks will suffer a stroke in the next 2 years. If the patient has 70 to 99% stenosis in the relevant carotid artery, endarterectomy reduces the risk of stroke or death to about 10%. Patients not appropriate candidates for surgery should probably receive ticlopidine 250 mg bid (with appropriate monitoring of the WBC count); this drug appears effective in both men and women (aspirin has not been universally efficacious in women).

If a cardiac source of embolism is suspected, anticoagulation with warfarin is usually indicated. For patients with nonvalvular atrial fibrillation, a prothrombin time of 1.3 to 1.7 times control (or an international normalized ratio of about 3.0; should be > 2.0 and < 5.0) is probably adequate and has few side effects (in three recent studies of prophylaxis, minor bleeding was more common in the warfarin groups than in the control group, but intracerebral hemorrhage or other major bleeding was not). One study suggested that aspirin also reduced stroke rates; it could be used in patients who are poor risks for warfarin. In patients with suspected embolism from other cardiac disorders (*eg*, cardiomyopathies, left ventricular aneurysms), low-dose warfarin has not been well studied. The aortic arch is a hitherto underrecognized source of emboli; management of this condition remains to be established.

Transesophageal echocardiography can detect clots and other lesions that escape detection by transthoracic echocardiography. In some series, the rate of detection of cardiac lesions is so high that their significance is uncertain.

In patients 6 h or more into acute ischemic stroke, no treatment has been proven useful. Heparin may be indicated to prevent subsequent embolic strokes, but does not affect either a completed stroke or so-called stroke-in-evolution. If the patient is to receive anticoagulant therapy because of a suspected source of embolism, some investigators feel that patients with large infarcts should not be given anticoagulants for several days because of a presumed risk of hemorrhage into the infarct. Other data suggest that the greatest risk of re-embolization occurs in the first few days after the initial stroke, which argues for early anticoagulation of this group. I favor the latter approach.

Patients who follow a stuttering course may benefit from induced hypertension to improve flow through stenotic vessels until collateral vessels can open. Spontaneous hypertension in these patients should be considered a compensatory response, and should not be treated in the first few poststroke days unless evidence of end-organ damage develops. We avoid treating blood pressure unless the *mean* pressure exceeds 160 mm Hg. After the patient has stabilized neurologically, a course of chronic antihypertensive treatment can be instituted.

The role of hyperglycemia in worsening stroke outcome seems established, but no studies have been done to determine whether tight control of blood sugar will improve prognosis.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS) trial[116] showed that thrombolysis was safe and ef-

fective if performed within 3 h of stroke onset (this does not mean 3 h after waking up with a new stroke; the time of stroke onset must be known). The recombinant tissue-plasminogen activator dose in this study was 0.9 mg/kg, with 10% of the dose as a bolus and the remainder over 1 h. The treated patients had a very significant improvement in functional outcome. There were more intracerebral hemorrhages in the treated group, but their mortality was actually lower (this did not reach statistical significance).

Patients who develop serious increases in ICP during the first 3 to 4 days poststroke are at risk for herniation and death. The earliest sign is usually diminished consciousness, often followed by an ipsilateral third-nerve palsy. Corticosteroids do not decrease the cytotoxic edema associated with strokes, and should not be used (unless the cause of the stroke is vasculitic). Although the routine use of hyperventilation in stroke patients is not indicated, this technique is appropriate to prevent herniation. Mannitol can also be used. If more drastic therapy is contemplated (*eg*, high-dose barbiturates), an ICP monitor should be inserted. We now use hemicraniectomy to reduce ICP in these patients, with surprisingly good functional outcomes; this has not become the standard of care. Experimental results suggest that the skull should be removed before swelling occurs, in order to protect the cortex from loss of pial collaterals.

Intracerebral hemorrhage produces much more rapid rises in ICP because of the volume of the hematoma. The major concerns for the internist are (1) exclusion or treatment of a bleeding diathesis, which should always be considered, and (2) management of ICP. Although the edema around an intracerebral hemorrhage is vasogenic, it does not respond to steroids. Three controlled studies have documented poorer outcome in steroid-treated patients, owing to the side effects of the steroids. In older patients, especially those with more than one episode of hemorrhage and without a history of hypertension, amyloid angiopathy becomes a diagnostic consideration (about 15% of all intracerebral hemorrhages). In younger patients, intracerebral hemorrhage related to sympathomimetic agents (including cocaine) is becoming an increasingly frequent problem.

Although neurogenic pulmonary edema may occur in any acute intracranial condition, SAH patients seem particularly prone to it; about 40% of our SAH patients have some degree of oxygenation difficulty not explained by other conditions. In neurogenic pulmonary edema, the PCWP is normal, and the edema fluid has a high protein content; this reflects the presumed pathogenic mechanism of pulmonary venoconstriction. One must then attempt to balance the need to expand volume in patients with the need to keep their lungs dry. We tend to keep the PCWP around 10 mm Hg, and use vasopressors to improve cerebral perfusion if necessary.

Nervous System Infections

Meningitis

The consensus of opinion seems to favor presumptive treatment for suspected meningitis in any situation in which lumbar puncture (LP) is delayed. This includes even delays to obtain CT scans, because the commonest causes of meningitis in adults (pneumococcal and meningococcal) can kill the patient while waiting for the scan. I believe that patients who are alert and have normal fundi and neurologic exams can undergo LP without scanning, because the possibility of a patient in that setting herniating soon after LP is infinitesimally small, but presumptive treatment is clearly more important than intellectual purity. With the increasing prevalence of penicillin-resistant pneumococci, cefotaxime (2 g q4h) or ceftriaxone (2 *g* q12h) should be used for empiric therapy. A few pneumococci with significant resistance to third-generation cephalosporins have emerged, prompting some to add vancomycin until results of sensitivity testing are available. Cefuroxime is inferior to these third-generation cephalosporins and should no longer be used. Because ampicillin-resistant *Haemophilus influenzae* infections are common, children should also receive the third-generation agents. Chloramphenicol is often recommended for truly penicillin-allergic (*eg*, anaphylactic) patients, although clinical failures have been reported in patients with penicillin-resistant pneumococci. In most cases, the initial dose of antibiotics will not sterilize the CSF within 30 to 60 min; even if this occurs, testing for bacterial antigens will reveal the etiology in the majority of cases. Blood cultures should be obtained before antibiotics are given. Further treatment decisions can be made based on the Gram stain and antigen results. If listeriosis is suspected

(immune-compromised host, or negative Gram stain and bacterial antigen tests), ampicillin or sulfamethoxazole-trimethoprim should be added until an organism is isolated or blood and CSF cultures have been negative for at least 3 days. Because of its epileptogenic effects, imipenem should usually be avoided in CNS infections.

In infants and children, pretreatment with steroids (dexamethasone, 0.15 mg/kg q6h for 4 days) appears to decrease neurologic dysfunction after recovery from meningitis (predominantly that due to *H influenzae*). This is presumed to reflect a decrease in inflammation from lysis of organisms, with the subsequent host elaboration of tumor necrosis factor and other inflammatory mediators. The use of steroids in adult meningitides remains controversial, but does not appear to be deleterious in the few patients so far studied. I think that the evidence favors its use in adults as well, but this is still debated. A recent study in children suggests that 2 days of dexamethasone is as useful as 4 days. The issue is clouded when vancomycin is used for potential penicillin-resistant pneumococci, because steroids may decrease vancomycin penetration into the CSF (this is debated in humans).

Increased ICP in meningitis patients is treated as described above. Cerebral edema in children appears to respond to steroids; it is probably appropriate to treat adults in the same fashion if elevated ICP is a problem. Hyponatremia is common, and may exacerbate vasogenic cerebral edema; it usually responds to fluid restriction. Whether this increases the rate of cerebral venous thrombosis is not clear. However, it is important not to let the cerebral perfusion pressure fall below about 60 mm Hg; this is more important that fluid restriction. Seizures are initially managed with benzodiazepines and phenytoin; the treatment of SE is covered above.

Encephalitis

As in meningitis, the weight of expert opinion is shifting (albeit more slowly) to the "shoot first and ask questions later" approach. When encephalitis is suspected, acyclovir (10 to 15 mg/kg q8h) is begun while the work-up is in progress; adequate hydration is necessary to prevent renal toxicity. The most sensitive test is CSF–polymerase chain reaction; MRI with gadolinium is second, with EEG third. Even though brain biopsy has a low rate of complications (3%, most of which are minor), the relative safety of acyclovir has encouraged many physicians to treat presumptively, and perform a biopsy only in patients who do not respond or in whom the work-up raises the possibility of another diagnosis. The commonly quoted list of "treatable disorders that mimic herpes simplex encephalitis" from the National Institute of Allergy and Infectious Diseases cooperative studies is not relevant in the MRI era. Seizures and elevated ICP are common.

Brain Abscess

Unless there is a strong suspicion of the etiology of a brain abscess (*eg*, the patient had a proven bacteremia prior to developing the abscess), empiric treatment for suspected brain abscess should include a third-generation cephalosporin, vancomycin, and metronidazole. Vancomycin is probably adequate treatment for Listeria, but if there is a reason to suspect this organism, one usually adds ampicillin or sulfamethoxazole-trimethoprim. Although some surgeons have tried to avoid aspiration, biopsy, or resection of these patients on the grounds that empiric medical treatment seems effective, this contention is based on small numbers of patients. Furthermore, it is often difficult to be certain that a particular lesion is an abscess and not a high-grade astrocytoma. Surgery also offers some direct relief of ICP problems. For these reasons, I recommend early aspiration of suspected abscesses, with possible later debulking or resection.

Neurogenic Respiratory Failure

Myasthenia Gravis

Although the standard teaching about myasthenia gravis stresses fatigability with exercise, this is rarely what brings the patient to medical attention. The usual complaints are diplopia, ptosis, difficulty with speech and secretions, proximal limb weakness, and ventilatory dysfunction. The condition preferentially affects young women and older men. There is overrepresentation of human leukocyte antigen-A1 (HLA-A1), HLA-B8, and HLA-DRw3 (another instance in which HLA testing is not clinically useful). This is a true autoimmune disease, in which antibodies directed at myoid cells in the thymus [which express acetylcholine receptors (AChR)] attack the NMJ. There is a greater than expected incidence of other autoimmune diseases,

including systemic lupus erythematosus, Sjögren's syndrome, polymyositis, and autoimmune thyroid disease. About 70% of patients have thymic hyperplasia, and 15% have thymomas. Anti-AChR antibodies are present in most patients with generalized myasthenia, and about 60% of those with ocular myasthenia. Antistriated muscle antibodies are a marker for thymoma.

Diagnostic studies include the edrophonium test (for which change in ptosis is the only truly objective bedside parameter to follow), measurement of anti-AChR antibodies, electromyography with repetitive stimulation, and chest CT to evaluate the thymus. Patients with generalized myasthenia who are developing ventilatory failure should be followed with vital capacity and negative inspiratory force (maximal inspiratory pressure) measurements; hypercapnia is a late finding. We usually intubate and ventilate patients when the vital capacity falls below about 12 mL/kg; some will require intubation because of upper airway problems but not need mechanical ventilation. Sometimes we will permit hypercapnia if the upper airway is intact and the patient is in the ICU. Edrophonium testing to distinguish myasthenic crisis from cholinergic crisis (too much anticholinesterase) is dangerous and should rarely be performed.

Treatment includes anticholinesterases (pyridostigmine), immunosuppressives (steroids, azathioprine, cyclophosphamide, sometimes cyclosporine), and thymectomy. Plasma exchange or IVIg can be dramatically effective, but each is only a short-term measure, primarily used for patients in crisis or to prepare them for thymectomy. Patients with purely ocular symptoms and normal thymic size on CT can be treated with anticholinesterases alone, but most other patients should be treated for the progressive autoimmune disease they have.

A large number of drugs have been reported to exacerbate myasthenia. The most important ones to remember are aminoglycosides, macrolides, lidocaine, propranolol, and quinidine. The effects of neuromuscular blocking agents is usually quite prolonged. Steroids often worsen the weakness before the patient improves.

Other Conditions

Respiratory failure due to diseases of the nervous system is predominantly hypercapnic, except in the case of neurogenic pulmonary edema. The diagnosis of neuromuscular respiratory failure is usually straightforward if one considers it as a possibility. Many of these conditions will be apparent at presentation, but on occasion a diagnosis of amyotrophic lateral sclerosis is made only when the patient has difficulty weaning from the ventilator. Critical illness polyneuropathy is a relatively recently described entity in which critically ill patients (most of whom have been septic) cannot be weaned from mechanical ventilation. Electromyographic studies show an axonal neuropathy; the prognosis for eventual recovery is very good, but these patients commonly require 4 to 6 months of mechanical ventilation.

Roelofs and coworkers,[117] Zochodne et al,[118] and others described a unique peripheral neuropathy in patients who fail to wean from mechanical ventilation after an episode of critical illness, usually involving bacteremia. In a prospective study, Witt et al[119] identified 43 patients with sepsis and multiple organ failure; electrophysiologic studies revealed sensorimotor axonal neuropathy in 70% of these patients, and 15 (35%) experienced difficulty in weaning from ventilatory support after improvement in their underlying conditions. Such patients display limb weakness on examination, with diminished or absent deep tendon reflexes. In the study by Witt et al,[119] 23 of the patients (53%) survived; although all of the neuropathic patients improved, three with very severe neuropathy made incomplete recoveries. The authors suggested that the decrements in peripheral nerve function were related to hyperglycemia and hypoalbuminemia. They speculated that the likely etiologies of this neuropathy include the metabolic stresses that accompany sepsis, as well as the microcirculatory abnormalities. A study of other neurologic causes of failure to wean from ventilatory support has been reported, and emphasizes the high frequency of neuromuscular diseases in ICU patients with respiratory failure.[120] Interestingly, in general ICU patients, failure to wean from a neurologic cause carries a better prognosis than does similar failure due to a pulmonary cause.[121]

Patients who have flaccid paralysis after the use of NMJ blockers have received considerable attention in recent years. One group, with a relatively brief duration of paralysis, represents patients who have accumulated large amounts of these agents and take days to clear them. A second group, most commonly including asthmatics and other patients

treated with steroids in addition to NMJ blockade, appears to have a myopathy, and the patients may take a very long time to recover. While earlier reports emphasized a relationship with the steroid-based NMJ-blocking drugs, this condition has been seen with atracurium as well.

Plasmapheresis is well established as a treatment for acute idiopathic polyneuritis (Guillain-Barré syndrome) if it is started in the first 2 weeks after onset. Usually, five treatments are given over 10 days. Ventilatory support is initiated as described above for myasthenia gravis. Autonomic instability may appear in the second week of the illness, and has become a leading cause of death. Thus, patients need careful observation until they are clearly improving. IVIg is also commonly used for both acute idiopathic polyneuritis and myasthenia gravis.

Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome (NMS) was recognized in the late 1950s.[122] It occurs in < 1% of patients exposed to these agents, but may be more frequent in patients requiring higher than normal doses or multiple agents.[123] Although some agents have been more frequently associated with NMS than others (most prominently haloperidol, fluphenazine, and the thioxanthines), it has been reported with almost every neuroleptic agent and mixed dopamine-serotonin agents. Long-acting forms of haloperidol may result in more cases in the next several years. It may also occur in parkinsonian patients from whom either dopaminergic agonists or anticholinergic agents are abruptly withdrawn,[124] although the epidemiology of this problem is uncertain. Early studies cite a mortality rate of up to 20%,[123] although more recent work suggests approximately 4% to be correct.[125]

The condition appears to stem from central dopaminergic blockade in the majority of cases;[126] the few reports of parkinsonian patients who develop the condition when dopaminergic therapy is terminated suggest that lack of dopamine effect alone, rather than some other effect on the receptor, is necessary and sufficient to produce NMS. Drugs with stronger D_2-receptor antagonist effects are more likely to produce NMS. A patient with a mutation in the D_2 receptor has been reported.[127] Dopaminergic blockade may also affect thermoregulation by altering the hypothalamic set-point for temperature.

Table 8. *Clinical Findings in NMS**

Feature	% Affected
Systemic findings	
Fever	100
Tachycardia	79
Diaphoresis	60
Labile blood pressure	54
Tachypnea	25
Movement-related findings	98
Tremor	56
Dystonia	33†
Chorea	15
Other neurologic findings	
Dysphagia	40
Akinetic mutism	38
Stupor	27
Coma	27

*Data from Kurlan et al.[128]
†Includes 6% with oculogyric crises.

Table 9. *Differential Diagnosis of Rhabdomyolysis in Association With Acute CNS Dysfunction**

Myofiber Metabolic Exhaustion
Seizures
Delirium
Tetanus
Strychnine intoxication
Extremes of environmental temperature
Malignant hyperthermia
Neuroleptic malignant syndrome
Diabetic ketoacidosis
Electric shock
Infectious Myositides
Influenza
HIV
Toxic shock
Clostridial myonecrosis (*Clostridium perfringens* bacteremia)
Toxins and Abused Drugs
Alcohol
Cocaine and other central stimulants
LSD
Narcotics
Phencyclidine
Envenomations (wasps, bees, spiders, snakes, etc.)
Medications
Salicylate overdose
Theophylline
Lithium
Fluid and Electrolyte Disturbances
Hyperosmolar states
Hypo-osmolar states
Severe hypophosphatemia
Trauma

Adapted from Bertorini.[44]

Most cases occur within a few weeks of either a dosage increase or, less commonly, the start of neuroleptic treatment.[128] Reported predispositions include strenuous exercise, dehydration, other CNS disorders, and the use of fluphenazine decanoate.[129] States of diminished osmolality may contribute to the pathogenesis of NMS.[130]

The major diagnostic findings of NMS include fever, severe rigidity (usually, but not always, accompanied by tremor), obtundation, and autonomic dysfunction (diaphoresis, pallor, unstable blood pressure, tachycardia, tachypnea, and pulmonary congestion).[131] Kurlan and colleagues[128] reviewed 52 published cases; their findings are summarized in Table 8.

NMS patients typically have a mild to marked leukocytosis.[132] The combination of sustained muscular contraction and immobility predisposes these patients to rhabdomyolysis; in combination with volume depletion, this often produces acute renal failure. The differential diagnosis of rhabdomyolysis in association with acute CNS dysfunction is extensive; Table 9 is adapted from the review by Bertorini.[44]

Other common systemic complications include disseminated intravascular coagulation and pulmonary embolism. Thrombocytopenia has recently been reported.[133]

The major differential diagnostic concerns are malignant hyperthermia (MH), the serotonin syndrome, and lethal catatonia (see below).

Once NMS is suspected, neuroleptic drugs should be withdrawn and the patient adequately hydrated. Whether to administer dopaminergic agonists (*eg*, bromocriptine) or a direct muscle relaxant[134] (dantrolene) remains the subject of debate. Dantrolene relaxes muscle contraction by decreasing Ca^{2+} release from the sarcoplasmic reticulum. Electroconvulsive therapy has also been proposed as a treatment,[135] blurring the distinction between NMS and lethal catatonia. Neuroleptic medications should not be resumed for at least 2 weeks because of the risk of recurrence.[136]

Malignant Hyperthermia

MH was recognized as an anesthetic complication in the 1960s.[137] It is an autosomal-dominant disorder that most typically follows exposure to anesthetic agents. A porcine model and several clinical studies have implicated abnormally high levels of Ca^{2+} release from a sarcoplasmic calcium channel (also known as the ryanodine receptor). This results in Ca^{2+}-induced Ca^{2+} release, which lowers the threshold for sustained muscle contracture.[138] (Most human cases are associated with a defect on chromosome 19, although a few cases are not associated with the defined ryanodine-receptor abnormality.[139]) The drugs that induce MH do so by triggering this Ca^{2+} release; the sustained contraction produced by Ca^{2+} release causes excessive oxygen consumption and heat production. High-energy phosphate stores are quickly depleted, resulting in failure of Ca^{2+} reuptake. As in other cells, sustained excessive elevation of free intracellular Ca^{2+} produces membrane lysis, and consequently myoglobin leaks from muscle cells.

MH begins with muscle contraction (classically, although not always, in the masseters) in response to a triggering agent (Table 10).

In a typical anesthetic-induced case, a rise in end-tidal CO_2 often signifies MH onset.[140] Quickly thereafter, rapidly rising temperature, metabolic acidosis, hypoxemia, and cardiac arrhythmias may follow. The combination of muscle breakdown and acidosis results in hyperkalemia. On rare occasions, the condition may not arise until after the operation is over, or may occur in other situations of metabolic stress, such as exercise.

Table 10. *Triggering Agents in Malignant Hyperthermia*

Recognized Agents	
Inhalational anesthetics	Desflurane
	Enflurane
	Halothane (most common)
	Isoflurane
	Sevoflurane
Depolarizing NMJ blockers	Decamethonium
	Succinylcholine (most common)
	Suxamethonium
Possible Agents	
Calcium	
Catecholamines	
Ketamine	
Monoamine oxidase inhibitors	
Phenothiazines	
Potassium	
"Safe Agents"	
Barbiturates	
β-Blockers	
Benzodiazepines	
Local anesthetics	
Nitrous oxide	
Nondepolarizing NMJ blockers	
Propofol	

A personal or appropriate family history of anesthetic complications is usually sufficient reason to suspect MH, and to consider *in vitro* muscle testing where it is available. A muscle biopsy specimen (obtained under local anesthesia) is electrically stimulated during exposure to varying concentrations of caffeine or halothane. Patients with other muscle diseases, such as central core disease, dystrophinopathies, and several others, may be at risk for MH-like reactions. Muscle biopsies from MH patients are frequently abnormal, but not specifically so.[44]

The major management issues in MH involve termination of exposure to the triggering agent and the use of dantrolene.

Serotonin Syndrome

In 1955, a patient died after taking a combination of iproniazid and meperidine.[141] By 1960, the serotonin syndrome (SS) was well described.[142] Most patients with SS are receiving more than one serotonergic agent (or a monoamine oxidase inhibitor, raising extracellular serotonin concentrations), although overdoses of single agents may trigger the syndrome.[143] The newer reversible monoamine oxidase inhibitors, such as moclobemide, may be less likely to precipitate SS[144] but are not devoid of this potential.[145] SS resembles NMS, but is frequently associated with myoclonus, and less frequently involves muscle rigidity.[146] Autonomic instability is common in both conditions.[147] The duration of SS is usually shorter than that of NMS. A case of SS also involving stroke in a young patient suggests that the spectrum of this disorder may involve precipitation of complicated migraine.[148] Treatment is supportive.

Lethal Catatonia

Lethal catatonia was described by Stauder in 1934, almost half a decade before the introduction of neuroleptic agents. The presentation of lethal catatonia is essentially indistinguishable from NMS, although published case reports of the two syndromes indicate differences in mode of onset, signs and symptoms, and outcome.[149] Lethal catatonia often begins with extreme psychotic excitement, which leads to fever, exhaustion, and death. In contrast, NMS begins with severe muscle rigidity. Lethal catatonia may require neuroleptic treatment, although electroconvulsive therapy is more commonly employed. Occasional reports of cases "requiring" treatment with both electroconvulsive therapy and dantrolene serve to blur the distinction between lethal catatonia and NMS.[150] The underlying pathophysiology of lethal catatonia remains unknown.

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Notes